SUNDAY, AUGUST 6, 2017
3:00 pm  Registration and Check-In
Moderator: Robert B. Baron, MD, MS
5:00  Welcome and Course Overview
5:10  G  Cancer Screening 2017: New Recommendations, New Controversies
Judith M.E. Walsh, MD, MPH
6:00  G  Modern Management of Hypertension: Where Do We Draw the Line
Robert B. Baron, MD, MS
6:50 pm  Adjourn

MONDAY, AUGUST 7, 2017
7:00 am  Continental Breakfast
Moderator: Robert B. Baron, MD, MS
7:30  RxG  Management of Lipid Disorders: Maximizing Benefits and Minimizing Harms
Robert B. Baron, MD, MS
8:20  RxG  Management of Coronary Artery Disease: a Primary Care Perspective
Michael G. Shlipak, MD, MPH
9:10  Coffee Break
9:30  RxG  Understanding Dementia and Cognitive Assessment
Anna Chodos, MD
10:20  G  Common Dermatologic Problems: What the Primary Care Physician Needs to Know
Toby A. Maurer, MD
11:10 am  Adjourn

TUESDAY, AUGUST 8, 2017
7:00 am  Continental Breakfast
Moderator: Carlin Senter, MD
7:30  G  Common Disorders of the Knee
Carlin Senter, MD
8:20  RxG  Management of Diabetes Mellitus: Which Drugs for Which Patients?
Robert B. Baron, MD, MS
9:10  G  Promoting Functional Independence and Activity in Older Adults
Anna Chodos, MD
10:00  Coffee Break
10:20  Concurrent Workshops (select one):
A: Mastering the Musculoskeletal Exam
Carlin Senter, MD
B: Nutrition and Weight Management in Office Practice
Henry Crevensten, MD
Robert B. Baron, MD, MS
11:50 am  Adjourn

WEDNESDAY, AUGUST 9, 2017
7:00 am  Continental Breakfast
Moderator: Toby A. Maurer, MD
7:30  G  Skin Diseases in the Aging Patient
Toby A. Maurer, MD
8:20  Rx  Updated Guidelines for Managing Menopausal Symptoms
Judith M.E. Walsh, MD, MPH
9:10  G  Chronic Kidney Disease: What the Generalist Needs to Know
Michael G. Shlipak, MD, MPH
10:00  Coffee Break
10:20  Concurrent Workshops (select one):
C: Dermatologic Procedures in Primary Care
Toby A. Maurer, MD
D: Advances in Primary Care: a Critical Review of the Year’s Most Important Papers
Michael G. Shlipak, MD, MPH
11:50 am  Adjourn

THURSDAY, AUGUST 10, 2017
7:00 am  Continental Breakfast
Moderator: Judith M.E. Walsh, MD, MPH
7:30  RxG  New Developments in Osteoporosis: Screening, Prevention, and Treatment
Judith M.E. Walsh, MD, MPH
8:20  G  Updates in Preoperative Evaluation and Perioperative Care
Henry Crevensten, MD
9:10  G  Diagnosis and Management of Common Shoulder and Hip Complaints
Carlin Senter, MD
10:00  Coffee Break
10:20  Concurrent Workshops (select one):
E: Clinical Pearls in Caring for Older Adults
Anna Chodos, MD
F: Advances in Women’s Health: a Critical Review of the Year’s Most Important Papers
Judith M.E. Walsh, MD, MPH
11:50 am  Adjourn

FRIDAY, AUGUST 11, 2017
7:00 am  Continental Breakfast
Moderator: Michael G. Shlipak, MD, MPH
7:30  RxG  Congestive Heart Failure: Effective Diagnosis, Treatment, and Monitoring
Michael G. Shlipak, MD, MPH
8:20  RxG  Dermatologic Infectious Disease: Viral, Fungal, and Bacterial Skin Diseases
Toby A. Maurer, MD
9:10  Coffee Break
9:30  G  Best Practices in Palliative Care: What Works, What Doesn’t
Anna Chodos, MD
10:20  Sports Concussion: What the Clinician Needs to Know
Carlin Senter, MD
11:10 am  Adjourn
G  Geriatric Credit  Rx  Meets Requirements for Pharmacotherapeutics
CEUs for NPs/Nurses
Cancer Screening 2017

New Recommendations, New Controversies

Judith M.E. Walsh, MD, MPH
Division of General Internal Medicine
Women’s Health Center of Excellence
University of California, San Francisco

Disclosures

• I have no conflicts of interest

Selected Controversies

• Breast Cancer Screening
  – Guideline confusion
  – Implications of “dense breasts”
  – New screening technologies
• Colorectal Cancer
  – What test and how often?
  – New options?

• Lung Cancer
  – Why not Chest X Ray?
  – Who should we screen?
• Prostate Cancer
  – The ongoing question- should we screen?
Principles of screening

• Detection while patient is asymptomatic
  – High sensitivity
• Early detection reduces the risk of death
  from the cancer – randomized trials
• The number of false positives is acceptably low
  – High specificity
  – Reasonably high prevalence of disease
• Ideally few harms

USPSTF

• Rigorous review of existing peer-reviewed evidence
• Ratings reflect the strength of the evidence on the benefits and harms of a preventive service
• No consideration of costs
• ACA: Must cover A or B ratings

Breast Cancer Screening

• Breast cancer is the most common cancer in women and the second leading cause of cancer death
• Screening mammography reduces breast cancer mortality
• Risk increases with age
• Pre-menopausal breast tissue is dense
  – Decreased sensitivity
Breast Cancer Screening

• Maggie Graham is a 50 year old woman with no family history of breast cancer. She has been reading news articles about the “increased accuracy” of screening ultrasound or MRI in women with dense breasts.

• You perform a clinical breast examination, which is normal.

U.S. screening guidelines: no agreement

<table>
<thead>
<tr>
<th>Organization</th>
<th>Starting age</th>
<th>Stopping age</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Preventive Services Task Force (USPSTF)</td>
<td>50</td>
<td>74</td>
<td>Biennial</td>
<td>Screening for age 40–49 = Grade C recommendation. Continue screening as long as good health, life expectancy &gt; 10 years.</td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td>45</td>
<td>As appropriate based on life expectancy</td>
<td>Annually, then biennially once age ≥55</td>
<td></td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists (ACOG)</td>
<td>40</td>
<td>As appropriate based on life expectancy</td>
<td>Annually</td>
<td>Consider cessation of screening at age 75.</td>
</tr>
</tbody>
</table>

USPSTF vs American Cancer Society Recommendations

<table>
<thead>
<tr>
<th>Age</th>
<th>USPSTF 2015</th>
<th>ACS 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>None (or biennial)</td>
<td>None</td>
</tr>
<tr>
<td>45–49</td>
<td>None (or biennial)</td>
<td>Annual</td>
</tr>
<tr>
<td>50–54</td>
<td>Biennial</td>
<td>Annual</td>
</tr>
<tr>
<td>55–74</td>
<td>Biennial</td>
<td>Biennial</td>
</tr>
<tr>
<td>75+</td>
<td>Insufficient evidence for or against</td>
<td>Biennial if good health and life expectancy ≥10 yrs</td>
</tr>
</tbody>
</table>

American Cancer Society Guidelines. JAMA 2015;314(15):1599-1614

Breast Cancer Screening

• What do you recommend to Maggie?
  – Add ultrasound
  – Add breast MRI
  – Mammogram alone
  – Add ultrasound and MRI
Harms Of Screening

- Over-diagnosis
  - Cancers diagnosed that never would cause symptoms: patients receive all the costs and harms of treatment
    - Estimates: 10% to 30% of invasive breast cancers plus much of DCIS
- False positives
  - Anxiety
  - Additional tests including biopsies
    - One-third of total screening cost
- Radiation exposure
  - One breast cancer for 3000 women screened annually for 10 years

Jørgensen, BMJ, 2009

Impact of mammographic screening in U.S.

Screening has also led to large increase in detection of ductal carcinoma in situ (DCIS)

Bottom line: Greatest screening benefit in women aged 60-69; smaller, and possibly no, screening benefit in women aged 40-49

Breast Cancer Deaths
Randomized Trials, all ages

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Deaths Averted Screening 1,000 Women Over 10 Years</th>
<th>95% confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 49</td>
<td>0.3</td>
<td>0 to 0.9</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.8</td>
<td>0.2 to 1.7</td>
</tr>
<tr>
<td>60 to 69</td>
<td>2.1</td>
<td>1.1 to 3.2</td>
</tr>
<tr>
<td>70 to 74</td>
<td>1.3</td>
<td>0 to 3.2</td>
</tr>
<tr>
<td>75+</td>
<td>Unknown</td>
<td>--</td>
</tr>
<tr>
<td>50 to 69</td>
<td>1.3</td>
<td>0.6 to 0.2</td>
</tr>
</tbody>
</table>

Bottom line: Greatest screening benefit in women aged 60-69; smaller, and possibly no, screening benefit in women aged 40-49
False-Positive Results and Breast Biopsies per 1000 women

<table>
<thead>
<tr>
<th>Outcome</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-74</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive mammogram</td>
<td>121 (12%)</td>
<td>93 (9%)</td>
<td>81 (8%)</td>
<td>70 (7%)</td>
</tr>
<tr>
<td>Breast biopsies recommended</td>
<td>16 (1.6%)</td>
<td>16 (1.6%)</td>
<td>17 (1.7%)</td>
<td>18 (1.8%)</td>
</tr>
<tr>
<td>Biopsies per cancer diagnosed</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Harms of One-Time Mammography Screening, by age

Estimated annual mammography screening costs in the US

Screening the 40 million women in the US aged 50-74 costs $4.72 billion per year

Screening the 22 million women in the US aged 40-49 costs an additional $1.32 billion per year


State breast density legislation

- Requires notification of women with heterogeneously dense or extremely dense breasts
- Exact wording specified by law: decreased sensitivity and increased risk for BC
- No mandate for insurance coverage of supplemental screening in most states

New Breast Technologies

- Digital Mammography
- Digital Breast Tomosynthesis
- Breast MRI
- Breast Ultrasound
Digital mammography

- Higher sensitivity, same specificity in women < 50 years old, dense breasts
  - Sensitivity 78% versus 51% film
  - Specificity 90%
- Worse in women 65 and older
  - Sensitivity 53% versus 69% film

Digital Breast Tomosynthesis

- Digital Breast Tomosynthesis (DBT) as a primary screening strategy

USPSTF: DBT

- Digital Breast Tomosynthesis (DBT) as a primary screening strategy
  - Benefit: Reduces recall rate and increases cancer detection rates compared to conventional mammography
  - Harm: twice as much radiation; unknown rate of over diagnosis. May increase biopsy rates
- No evidence on mortality, morbidity, or QOL
- “Insufficient evidence to fully assess benefits and harms

MRI Screening

- Does MRI have a role for screening in high risk women?
  - MRI is a very sensitive method of breast imaging and has been used as a diagnostic tool in women with breast cancer
  - Not influenced by breast density
  - Specificity is variable
  - Expensive
Sensitivity And Specificity Of Breast Cancer Screening Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>77%</td>
<td>95%</td>
</tr>
<tr>
<td>Mammography</td>
<td>36%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>33%</td>
<td>96%</td>
</tr>
</tbody>
</table>

Supplemental screening: better outcomes?

<table>
<thead>
<tr>
<th>Test</th>
<th>MRI</th>
<th>Ultrasound (US)</th>
<th>Tomosynthesis (DBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Most sensitive</td>
<td>Well-tolerated</td>
<td>Similar cancer</td>
</tr>
<tr>
<td></td>
<td>No radiation</td>
<td>Relatively</td>
<td>detection rate,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>inexpensive</td>
<td>fewer false</td>
</tr>
<tr>
<td>Limitations</td>
<td>High false positive rate</td>
<td>High false</td>
<td>Not as sensitive</td>
</tr>
<tr>
<td></td>
<td>Overdiagnosis</td>
<td>positive rate</td>
<td>as MRI</td>
</tr>
<tr>
<td></td>
<td>IV contrast</td>
<td>low PPV</td>
<td>Limited evidence</td>
</tr>
<tr>
<td></td>
<td>Claustrophobia</td>
<td>Operator-</td>
<td>base (newer)</td>
</tr>
<tr>
<td></td>
<td>Expensive</td>
<td>dependent</td>
<td>Limited availability</td>
</tr>
</tbody>
</table>

Impact For Clinical Practice

- MRI may be useful in screening high risk women
- The effect of MRI screening on mortality is not known
- MRI is not currently recommended for screening average risk women
- Ultrasound adds little to mammography
- Tomosynthesis is promising

Bottom Line: Breast Cancer

- 40-49 informed consent
  - Digital if decide to screen: now standard
- 50-74 screen every 2 years
- 75+ informed consent - don’t if life expectancy less than 10 years
- Don’t promote SBE, promote breast awareness
- BRCA risk equivalent: MRI
Lung Cancer Screening

Question?

- Mr. Nico Teen is a 69 year old man with a 50 pack-year history of smoking and COPD. You have previously been unsuccessful in encouraging him to quit smoking. He comes in for a check-up, is worried about developing lung cancer and wants to know what test you think he should have. What do you recommend?
  - Chest X ray
  - Sputum cytology
  - LDCT
  - None of these tests

Lung Cancer Screening: Systematic Review of Chest X-rays

- 7 trials of lung cancer screening
- Frequent screening with chest x-rays was associated with an increase in mortality
  - RR 1.11 (95% C.I. 1.00-1.23)
- No difference in chest X-ray plus cytology versus chest X-ray alone

Manser, Thorax, 2003

PLCO: Lung Cancer Screening

- PCLO randomly assigned 154,901 adults aged 55 through 74 to annual CXR for 4 years vs. usual care
- Followed for 13 years
- Cumulative lung cancer mortality
  - 14.0/10,000 py screening group vs. 14.2/10,000 py control group
  - Rate ratio: 0.99 (95% CI 0.87-1.22)

Oken MM. JAMA 2011;306:1865
Low Dose Spiral Computed Tomography

- Scans lung in < 20 seconds (single breath)
- No IV contrast
- More radiation exposure than CXR but less than conventional CT
- Can detect much smaller lesions than chest X-ray

The National Lung Screening Trial (NLST)

53,454 participants randomized to CT or CXR
- Current or former heavy smokers: ≥ 30 pack-years
- Ages 55 to 74
- Annual CT scans x 3 years. 6.5 years follow-up

RR (95% CI)

- Lung cancer death: 0.80 (0.73–0.93)
- Any death: 0.93 (0.86–0.98)

20% reduction in lung cancer death; 7% all deaths!

Number needed to invite to screen

- NNI to prevent one lung cancer death in 6.5 years = 320
- NNI to prevent one death from any cause in 6.5 years = 218

Summary from NLST

<table>
<thead>
<tr>
<th>Benefit: How did CT scans help compared to chest X-ray?</th>
<th>Low-dose CT</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 in 1,000 never died from lung cancer</td>
<td>12 in 1,000</td>
<td>17 in 1,000</td>
</tr>
<tr>
<td>5 in 1,000 never died from all causes</td>
<td>70 in 1,000</td>
<td>75 in 1,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Harm: What problems did CT scans cause compared to chest X-ray?</th>
</tr>
</thead>
<tbody>
<tr>
<td>223 in 1,000 never had at least one false alarm</td>
</tr>
<tr>
<td>16 in 1,000 never had a false alarm leading to an invasive procedure</td>
</tr>
<tr>
<td>3 in 1,000 never had a major complication from invasive procedures</td>
</tr>
</tbody>
</table>
NLST Harms

- False positives
  - At least 1 positive test in 39% CT
- Possible over diagnosis
  - Higher cancer incidence with CT
    - 1060 vs. 941 cancers
    - Rate ratio 1.13 (95% CI 1.03-1.23)
- Radiation exposure
- Incidental findings

Guidelines and recommendations

- Recommend for those meeting NLST entry criteria at specialized centers
  - ACCP / ASCP / ATS
  - ACS
  - ALA
  - NCCN
  - AATS

The NLST Setting

- 76% of sites were NCI designated cancer centers
- 82% were large academic medical centers
- All likely to have specialized thoracic radiologists and board certified thoracic surgeons on site
- CT scanners extensive quality control
- Nodule management algorithm but not mandated
USPSTF Recommendation

- USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in persons at high risk for lung cancer based on age and smoking history
  - Grade B recommendation
  - Published December 31, 2013

USPSTF

- Age
  - 55-79
- Total exposure to tobacco smoke
  - 30 pack years or more
- Years since quitting
  - Those who have smoked within the past 15 years are at highest risk
- Consider other comorbidities

Medicare Coverage Decision

- Annual lung cancer screening with LDCT for age 55-77, asymptomatic, at least 30 pack year history and currently smoking or quit within past 15 years
- Written order for lung cancer screening written during lung cancer screening shared decision making visit furnished by physician or certified non-physician practitioner
  - February, 2015

Primary Prevention Of Lung Cancer

- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation!!!!!
Implications

- Smoking cessation
- Strict adherence to guidelines
  - 55-79 years, 30+ pack years
- Use experienced centers / demonstration projects to ensure quality and effectiveness

Colorectal Cancer

Question

- What do you most commonly recommend for colorectal cancer screening?
  - Fecal occult blood test (FOBT)
  - Fecal immunochemical Test (FIT)
  - Sigmoidoscopy
  - Colonoscopy
  - Virtual Colonoscopy
  - Fecal DNA

Guidelines
Guidelines, Guidelines
**Joint Guideline: ACS, ACR,…**

- FOBT annually
- Fecal immunochemical test annually
- Flexible sigmoidoscopy every 5 years
- DCBE every 5 years
- CT colonography every 5 years
- Colonoscopy every 10 years
- Stool DNA testing (interval uncertain)

Levin, Gastroenterology, 2008

---

**Joint Guideline Recommendation**

- Clinicians should make patients aware of the full range of screening options
- Offer patients a choice between a screening test that is effective at both early cancer detection and cancer prevention through the detection and removal of polyps and a test that is primarily effective at cancer detection
- CRC prevention should be the primary goal of screening

---

**American College of Gastroenterology**

- American College of Gastroenterology guidelines for colorectal cancer screening
  - Colonoscopy… remains the preferred CRC screening strategy

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**American College of Physicians 2015**

- Annual high sensitivity gFOBT or FIT
- Flex sigmoidoscopy every 5 years
- High sensitivity gFOBT or FIT every 4 years plus flex sigmoidoscopy every 5 years
- Colonoscopy every 10 years

« Ann Int Med 2015 »
**USPSTF 2016**

- USPSTF: "A" recommendation (2016)
  - Routine screening from age 50 until 75
- USPSTF "C" recommendation (2016)
  - Individualized decisions age 75 to 85
    - Greater benefit in those not previously screened
  - No screening after 85

**USPSTF 2016**

- Screening for CRC in average risk patients age 50-75 is of substantial net benefit
- Multiple screening strategies available
  - Different levels of evidence
  - Strategies reviewed include colonoscopy, FOBT, FIT, flex sig, CT colonography, fecal DNA and methylated SEPT9DNA test
  - No evidence that any strategy provides greater net benefit

**Colonoscopy: RCTs in progress**

- VA
  - Colonoscopy versus fecal immunochemical test in reducing mortality from colorectal cancer
- Spain
  - Colorectal cancer screening in average-risk population: immunochemical fecal occult blood testing versus colonoscopy
- Netherlands
  - Colonoscopy or colonography for screening

**Newer Tests**

- Virtual Colonoscopy
- Stool based molecular testing
  - Fecal DNA
- Combined FIT and Stool DNA
- Septin-9
### Computed Tomographic Colonography (Virtual Colonoscopy)

- Non-invasive radiological technique
  - Radiation dose similar to barium enema
- Bowel preparation similar to colonoscopy
  - Prep-less technique is being evaluated
- Does not require sedation
- Colon distended with carbon dioxide or air
- Breath holding for 20-50 seconds
- Colonoscopy to remove polyps

### Laxative-Free CT Colonography

- Low fiber diet, orally ingested contrast material and specialized processing software “electronic cleansing”
- 605 adults underwent CTC and OC
- CTC was more accurate in detecting adenomas 10 mm or larger and less so for smaller lesions
  - 91% sensitivity vs 70% for adenoma 8 mm or larger
- Patients preferred it

### Potential Harms

- Radiation Exposure
  - 1/1000 could develop solid cancer or leukemia
- Procedure related harms
  - Perforation rate low
- Extra-colonic findings

### Extra-colonic Findings

- Extra-colonic findings common: 27 – 69%
- “High” clinical significance require surgical or medical treatment or intervention or further investigation
  - 5 - 11%
- 7-16% of individuals need additional evaluation for extra-colonic findings, but very few abnormalities ultimately required definitive treatment
Fecal DNA Testing

- PCR test for DNA mutations in the stool
- Potential advantages
  - Non-invasive
  - No preparation
  - Detection along entire length of the colon

Multi-target Stool DNA Testing

- Multi-target DNA test (and hemoglobin), FIT, and colonoscopy in 9989 average risk adults in multiple centers
- Fecal DNA detects more neoplasms than FIT, but with more false positive results
  - Sensitivity for CRC 92.3% vs 73.8%
  - Specificity for CRC 86.6% vs 94.9%
- Problems with sample collection or assay application greater with DNA test
  - 6.3% vs 0.3%

Fecal Immunochemical Testing (FIT)

- Uses labeled antibodies that attach to antigens of any human globin present in the stool
- Globin does not survive passage of the upper GI tract
- No dietary restrictions (easier than FOBT)

Fecal Immunochemical Testing

- FIT is more sensitive in detecting CRC and large adenomas (>1 cm) than FOBT
- FIT is a little less specific than FOBT
Combined FIT-Stool DNA

- Cologuard is the only combined stool DNA with FIT available in the U.S.
- Colorectal cancer detection
  - Sensitivity 92%
  - Specificity 84%
- More sensitive than FIT but less specific
  - More false positives

Septin 9

- Second generation serum assay to detect circulating Septin 9
  - Septin 9 hypermethylated in CRC
  - FDA approved 2016
- Use for those refusing guideline recommended strategies?

Colorectal Cancer Screening: Choices

- Randomized trial offering colonoscopy, FOBT, or choice of colonoscopy/FOBT
- 997 subjects ages 50 to 79
- 12-month follow up
  - (Inadomi JM. Arch Intern Med 2012;172:575)
- Recommending only colonoscopy led to lower adherence

Screening Completion

Inadomi JM. Arch Intern Med 2012;172:575
Colorectal Cancer Screening: Conclusions

- Offer testing
- Any screening is better than no screening for reducing colorectal cancer mortality
- Increase awareness of the importance of colorectal cancer screening

Implications for Practice

- Recognize importance of patient preferences
  - “The best test is the one that gets done”
- Positive fecal blood tests must be evaluated with diagnostic colonoscopy

QUESTION

- What is your usual practice for PSA screening for men aged 50-70?
  - Usually order PSA
  - Sometimes order PSA
  - Rarely order PSA
  - Never order PSA
Prostate Cancer: Should We Screen?

• Disease has high prevalence
  – 10% lifetime risk
  – 30% of men have prostate cancer at autopsy
• Disease has serious consequences
  – Sometimes but may be a benign disease for many men
• Detectable preclinical phase?? PSA
• Treatment for preclinical disease is more effective?
  – Complications of prostate cancer treatment
    • 8.4% incontinence
    • 60% impotence
  – Prostate Cancer Outcomes Study 24 month follow up Screening
• Screening reduces cancer mortality?

SCREENING TESTS: PSA

• PSA testing has increased dramatically since 1988
• Observational studies have had conflicting findings about the benefits of screening
• Two large randomized controlled trials of PSA screening and mortality
  – PLCO Cancer Screening Trial
    • 76,693 men randomized to annual PSA for 6 years plus rectal examination for four years vs usual care
    • High rates of screening in the control group
    • No significant difference in death between the two groups at 7 year follow-up
      – 2.0 deaths per 10,000 person years in the screening group
      – 1.7 deaths per 10,000 person years in the controls
    • Similar results after 10 years
      [details, MJH 2009]
  – European Randomized Study of Screening for Prostate Cancer (ERSPC)
    • 182,160 men aged 50-74 in eight European countries
    • PSA screening at least once every four years vs no screening
    • Mortality lower in the screened group at 9 year follow up
      – 7 fewer prostate cancers per 10,000 screened men
    • To prevent one prostate cancer death at 11 year follow up
      – 1,410 men needed to be screened
      – 48 additional prostate cancers treated
    • To prevent one prostate cancer death at 13 year follow up
      – 781 men screened
PSA Screening: Conclusions

- PSA screening may lead to a modest reduction in mortality
- To achieve this mortality reduction, there is a substantial amount of over-diagnosis and over-treatment

USPSTF Recommendations 2012

- Recommended against PSA based screening for prostate cancer
  - PSA can detect early prostate cancer, but inconclusive evidence about whether early detection improves health outcomes.
  - Harms include frequent false positives and unnecessary anxiety, biopsies and potential complications of treatment of some cases of cancer that may never have affected a patient’s health.
  - Grade “D” recommendation

USPSTF Draft Recommendations 2017

- Clinicians should inform men age 55-69 about the potential benefits and harms of PSA screening
  - Grade C
- Decision to screen should be individualized
- No screening in men aged 70 and over
  - Grade D

USPSTF

- Persistent mortality reduction and new evidence to suggest decrease in metastatic prostate cancer with screening
  - 3 fewer cases per 1000 men over 13 years
- No specific recommendations for high risk men
  - Family history, African American
- Public commentary period closed in May, 2017
American Cancer Society

- Men with at least a 10 year life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened
- Screening should not occur without an informed decision making process
- Men at average risk should receive the information beginning at age 50
- Information should be provided at age 45 for men at higher risk and age 40 for very high risk
  - American Cancer Society, 2016

- For men unable to decide, the decision can be left to the discretion of the health care provider
- Men with less than a 10 year life expectancy should not be offered screening
  - At age 75, only half of men have a life expectancy of 10 years or more
- Men without access to regular care should be tested only if high quality informed decision making is available through community based programs
  - ACS 2016

- For those who choose to be screened
  - PSA with or without DRE
  - Screening yearly for men whose PSA is 2.5 ng/ml or greater
  - If PSA <2.5 ng/ml, screening can be extended to every 2 years
  - PSA of 4.0 ng/ml or greater: referral
  - PSA of 2.5-4.0 ng/ml: individualized risk assessment
  - Age, African American, family history, previous negative biopsy
  - ACS, 2016

American Urological Association Guidelines

- The decision to use PSA testing should be individualized
  - Inform men of the potential benefits and risks
- No routine screening for men aged 40-54
- Shared decision making for men aged 55-69
- No routine screening for men aged 70 and over
- Screening intervals can be individualized based on baseline PSA level
  - American Urological Association, 2013
ACP Guidance Statement

- Derived from an appraisal of available guidelines
  - ACPM, ACS, AUA, USPSTF
- Inform men aged 50-69 about limited potential benefits and substantial harms of screening for PSA
  - Base decision on risk for prostate CA, discussion of benefits and harms, health and life expectancy and preferences
  - Do not screen in those who do not have a clear preference for screening

ACP Guidance Statement

- Do not screen average risk men under age 50, over age 69 or with a life expectancy of less than 10-15 years

Prostate Cancer Screening: Summary

- PSA testing may reduce prostate cancer mortality but the benefit is small
- Risks of early detection and treatment
- Shared decision making is key

Summary Of Recommendations

- Women aged 50 to 74 should undergo mammography every 2 years
- Screening decisions for women in their forties and for women and for women aged 75 and older should be individualized
- All men and women aged 50-75 should be screened for colorectal cancer
  - Any screening is better than no screening
Summary Of Recommendations

• Screening for lung cancer with low-dose CT reduces mortality
  – USPSTF Recommends screening high risk individuals

• A shared decision making approach is recommended for prostate cancer screening

Questions?

“Today I ate two bowls of dog food, a sandwich crust, some spaghetti that fell on the floor, half of your cat food, a wet tea bag, three bugs and the inside of a tomato. How many grams of fat is that?”
Blood Pressure and Risk

- Risk of cardiovascular disease (CVD) is linear to systolic blood pressure (SBP) level. Starts at relatively low BP’s (118 mm Hg)
- Risk doubles for every 20/10 mm Hg
- 120-139/80-89 is “pre-hypertension” and merits lifestyle modifications

Current Status of Hypertension

- Prevalence 29.1%; Blacks 42.1%
- About 75.6% treated; 51.8% controlled (<140/90)
- Risk for poor control: Latinos, Blacks, age 18-44 and ≥80, <300% poverty, < college degree
- Better control: Any insurance, ≥2 visits, and a usual source of care
46 yo woman, annual visit. BP 148/88. No diabetes, kidney normal. Otherwise well. The next best step is:

1) Recheck office BP
2) Discuss home monitoring
3) Order ambulatory BP monitor
4) Begin non-drug therapy
5) Begin hydrochlorothiazide or ACE I

Accurate BP Measurement

1) Seated for 5 minutes in chair
2) Arms bared and supported
3) No cigs, coffee; no talking
4) Correct fitting cuff for arm (small cuff results in elevated BP)
5) First appearance of sound is SBP; disappearance is DBP
6) Two or more reading in 2 minutes averaged
7) Two visits to define HTN

Treatment Based on What Blood Pressure Measurement?

Office clinician measures are standard, used in trials

Home BP measurement leads to less intensive drug Rx & BP control. Identifies “white-coat” HTN

Ambulatory monitor measures higher correlation with CVD

Lifestyle Modifications for BP Control

- Weight loss if overweight: 5-20 mm Hg/10-kg weight loss
- Limit alcohol to ≤ 1 oz/day: 2-4 mm Hg
- Reduce sodium intake to ≤100 meq/d (2.4 g Na): 2-8 mm Hg in SBP
- DASH Diet: 6 mm alone; 14 mm plus Na
- Physical activity 30 min/day: 4-9 mm Hg
- Habitual caffeine consumption not associated with risk of HTN
46 yo woman, annual visit. BP 148/88. No diabetes, kidney normal. Otherwise well. The next best step is:

1) Recheck office BP (my preference)
2) Discuss home monitoring
3) Order ambulatory BP monitor
4) Begin non-drug therapy
5) Begin hydrochlorothiazide or ACE I

73 yo woman. BP 148/88. No diabetes, kidney normal. Lipids normal. Otherwise well. On non-drug therapy. The next best step is:

1) Continue current therapy
2) Begin hydrochlorothiazide
3) Begin ace inhibitor
4) Begin calcium channel blocker
5) Begin beta blocker

NHLBI Panel on BP (aka Joint National Commission 8)

Three questions:
1) Does Rx at specific BP thresholds improve outcomes?
2) Does Rx to a specific BP goal improve outcomes?
3) Do various meds differ on outcomes?

Nine recommendations

Recommendations for Management of Hypertension

Recommendation 1
≥60 years:
- Lower BP at SBP ≥150 mm Hg or DBP ≥90 mm Hg
- Treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg.

Strong Recommendation – Grade A (but not unanimous)
Recommendations for Management of Hypertension

Corollary Recommendation
≥60 years:
❖ If treatment results in lower SBP (eg, <140 mm Hg) and is well tolerated treatment does not need to be adjusted.

Expert Opinion – Grade E

Recommendation 2
<60 years:
❖ Treat to lower BP at DBP ≥90 mm Hg
❖ Treat to a goal DBP <90 mm Hg.

30-59 years, Strong Recommendation – Grade A
18-29 years, Expert Opinion – Grade E

Recommendation 3
<60 years:
❖ Treat to lower BP at SBP ≥140 mm Hg
❖ Treat to a goal SBP <140 mm Hg.
(Expert Opinion – Grade E)

Recommendation 4
≥18 years with chronic kidney disease (CKD) (GFR < 60 or proteinuria > 30 mg alb/g creat):
❖ Treat to lower SBP ≥140 mm Hg or DBP ≥90 mm Hg
❖ Treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg.

Expert Opinion – Grade E
Recommendations for Management of Hypertension

Recommendation 5

❖ ≥18 years with diabetes, treat to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg
❖ Treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg.

Expert Opinion – Grade E

Recommendation 6

Nonblack population, including diabetes:

Initial treatment:
✓ Thiazide-type diuretic
✓ Calcium channel blocker (CCB)
✓ Angiotensin-converting enzyme inhibitor (ACEI)
✓ Angiotensin receptor blocker (ARB).

(Moderate Recommendation – Grade B)

Recommendation 7

Black population, including diabetes:

Initial treatment:
✓ Thiazide-type diuretic
✓ Calcium Channel Blocker (CCB)

General black population: Moderate Rec – Grade B
Black patients with diabetes: Weak Rec – Grade C

53 yo African-American woman, BP 148/88. Has diabetes, kidney normal. Otherwise well. On non-drug therapy. The next best step is:

1) Continue current therapy
2) Begin hydrochlorothiazide
3) Begin ace inhibitor
4) Begin calcium channel blocker
5) Begin angiotensin receptor blocker
53 yo African-American woman, BP 148/88. Has diabetes, kidney normal. Otherwise well. On non-drug therapy. The next best step is:

1) Continue current therapy
2) Begin hydrochlorothiazide
3) Begin ace inhibitor
4) Begin calcium channel blocker
5) Begin angiotensin receptor blocker

Recommendations for Management of Hypertension

Recommendation 8
≥18 years with CKD, initial (or add-on) treatment:

✧ ACEI or ARB to improve kidney outcomes.
✧ For all CKD patients with HTN regardless of race or diabetes

Moderate Recommendation – Grade B

Recommendations for Management of Hypertension

Recommendation 9

✧ If goal BP not reached within 1 month, increase the dose of the initial drug or add a second drug (thiazide, CCB, ACEI, or ARB).
✧ Assess BP and adjust the treatment regimen until goal is reached.
✧ If goal cannot be reached with 2 drugs, add and titrate a third drug from the list provided.

✧ Do not use and ACE and an ARB in the same patient.
✧ If goal cannot be reached using the drugs in rec 6 drugs from other classes can be used.
✧ Referral to a specialist may be indicated
✧ Expert Opinion – Grade E
**Evidence-based Medications**

**ACE inhibitors**
- Captopril
- Enalapril
- Lisinopril

**Angiotensin receptor blockers**
- Eprosartan
- Candesartan
- Losartan
- Valsartan
- Irbesartan

**Beta blockers**
- Atenolol
- Metoprolol

**Calcium channel blockers**
- Amlodipine
- Diltiazem ER
- Nitrendipine

**Thiazide-type diuretics**
- Bendroflumethiazide
- Chlorthalidone
- Hydrocholorthiazide
- Indapamide

**Medications in Pregnancy and in Women of Reproductive Age**

**Beta blockers**
- Labetalol

**Calcium channel blockers**
- Nifedipine

**Others**
- Methyldopa

**± Thiazide-type diuretics**
- Hydrocholorthiazide

**Strategies to Dose BP Meds**

1) One drug, titrate to max, add second (my preference)

2) One drug, add second before max of initial

3) Two drugs at same time, separate or as combo
**Key Points of JNC 8**

1) ≥60 yo: goal ≤150
2) Others <140/<90 (including DM, CKD, race/ethnicity)
3) Non blacks: thiazide, CCB, ACEI, ARB
4) Blacks: thiazide, CCB
5) CKD: ACEI or ARB

**Resistant Hypertension**

- Not reaching goal BP despite three medications from different classes (including one diuretic)
- Adherence is number one cause
- Avoid NSAID, decongestants, speed
- Other causes not common

**What About Other Drugs?**

- Spironolactone
- Beta blockers
- CNS sympatholytics: Clonidine
- Methyldopa: Little reason to use
- Alpha-1 blockers: OK but inferior as single drug and tachyphylaxis
- Labetalol good 5th or 6th choice
- Direct vasodilators - hydralazine or minoxidil - need more diuretics
- Peripheral adrenergic antagonists

**Are the Guidelines Already Out of Date?**

- USPSTF: Screening for HTN 2015
- Begin at age 18
- Measure carefully
- Obtain measurements outside of the clinical setting before starting treatment
Measuring BP Out of the Office

- Ambulatory monitoring is the best method (the “reference standard”)
  - Independent prediction of risk of stroke and MI
  - Fewer patients will need treatment
- Home BP monitoring may also be acceptable (but there is less data)

Are the Guidelines Out of Date?

- SPRINT: NIH-funded RCT
  - 9,361 men and women 50 and over (30% over age 75)
  - SBP > 130 mm Hg
  - Increased CV risk (but no DM)
  - Design <120 mm Hg vs <140 mm Hg
    - 2.7 meds vs. 1.8 meds
    - Actual 121.4 mm Hg vs 136.2

SPRINT: Results

- Composite outcome
  - 243 events (1.65% per year) vs 319 (2.19% per year)
  - HR 0.75 (0.64 – 0.89)

- All cause mortality
  - 155 (1.03% per year) vs. 210 (1.40% per year)
  - HR 0.73 (0.60 – 0.90)

SPRINT: Adverse Events

- Hypotension: HR= 1.67 (p=0.001)
- Syncope: HR 1.33 (p=0.05)
- Electrolyte abnormality: HR 1.35 (p=0.02)
- Acute kidney injury: HR 1.66 (p=<.001)
NNT and NNH from SPRINT

<table>
<thead>
<tr>
<th>Over 3.26 years of trial...</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary aggregate outcome</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>Death from any Cause</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>Death from CVD</td>
<td>172</td>
<td>-</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>-</td>
<td>45</td>
</tr>
<tr>
<td>Hypotension</td>
<td>-</td>
<td>72</td>
</tr>
<tr>
<td>Syncope</td>
<td>-</td>
<td>93</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>-</td>
<td>56</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td>-</td>
<td>97</td>
</tr>
</tbody>
</table>

SPRINT Reflections

- SPRINT showed that SBP 120 had better CVD/mortality benefit than SBP 140 (NNT 61)...
- But there were notable adverse effects with a NNH 45.
- Generalizability: would only apply 1/6 of current patients treated for HTN

SPRINT Reflections

- No DM, no stroke, > age 50
- No frail older patients, nursing home patients, patients with very high BP
- Framingham risk: >15% ten year risk (actual 20%)

SPRINT Reflections

- Free care, carefully measured BP
- More meds, more combo meds, more monitoring, more frequent visits
Modern Management of Hypertension

**1000 people treated 3.2 years to an SBP goal <120 compared to <140**

![](image)

16 Benefit 22 Harmed

**SPRINT Reflections**

“This strategy would represent a big shift in the approach to screening and treatment, and in my view, the findings need replication before intensive treatment can be pushed as the standard of care.”

Harlan Krumholz, MD

**ACP/AAFP Guidelines**

- Over age 60:
  - Goal <150 mm Hg

- For patients over age 60 with stroke/TIA, high CV risk:
  - Goal < 140 mm Hg

**USPSTF: Screening For Preeclampsia**

- USPSTF recommends screening for preeclampsia in pregnant women with BP measurements throughout pregnancy (B)

Annals IM, March 2017

JAMA, April 2017
73 yo woman. BP 148/88. No diabetes, Kidney normal. Lipids normal. Otherwise well. On non-drug therapy. The next best step is:

1) Continue current therapy (my preference)
2) Begin hydrochlorothiazide
3) Begin ace inhibitor
4) Begin calcium channel blocker
5) Begin beta blocker

Final Thoughts on Hypertension

- Take the BP accurately yourself and record it in the medical record
- Consider ambulatory BP monitoring before making major treatment decisions
- Control requires motivated patients who trust their clinician(s)

Final Thoughts on Hypertension

- In 2017, treatment decisions must be individualized. JNC 8 still a useful construct.
- But...consider a lower BP treatment for some motivated patients (>age 50, increased CV risk, no DM, no stroke, no other exclusions)
- Begin to use CV risk equations for HTN decisions, too

baron@medicine.ucsf.edu
EXPLAINING THE DECREASE IN DEATHS FROM CVD

1980 to 2000: death rate fell by approximately 50% in both men and women

2000 to 2010: Death still falling: down 31%

- About 1/2 from acute treatments, 1/2 from risk factor modification:
  - Predominantly cholesterol (1/4), BP, smoking

Placebo-Controlled Statin Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reduction in Major Coronary Events Relative to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>simva 20-40 mg</td>
<td>20%</td>
</tr>
<tr>
<td>prava 40 mg</td>
<td>20%</td>
</tr>
<tr>
<td>prava 40 mg</td>
<td>20%</td>
</tr>
<tr>
<td>simva 40 mg</td>
<td>27%</td>
</tr>
<tr>
<td>prava 80 mg</td>
<td>31%</td>
</tr>
<tr>
<td>simva 80 mg</td>
<td>30%</td>
</tr>
</tbody>
</table>
Management of Hyperlipidemia and Cardiovascular Risk

Robert Baron MD, MS

A RISK-BASED APPROACH

The benefit from any given intervention is a function of:
1) The relative risk reduction conferred by the intervention, and
2) The native risk of the patient

ACC/AHA Guidelines

- 4 groups of patients who benefit from statins
- Identifies high and moderate intensity statins
- No LDL treatment targets
- Non-statin therapies do not provide acceptable risk reduction
- Estimate 10-year ASCVD risk with new equation

Heart Protection Study: Vascular Events by Baseline LDL-C

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>No. Events</th>
<th>Statin (10,269)</th>
<th>Placebo (10,267)</th>
<th>Risk Ratio and 95% CI</th>
<th>Statin better</th>
<th>Statin worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>285</td>
<td>360</td>
<td></td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>≥100 &lt;130</td>
<td>670</td>
<td>881</td>
<td></td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>≥130</td>
<td>1087</td>
<td>1365</td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042</td>
<td>2606</td>
<td>2606</td>
<td>0.75</td>
<td></td>
<td>0.83</td>
</tr>
</tbody>
</table>

24% reduction (p<0.00001)

ACC/AHA Guidelines

Four Groups of Patients Who Benefit From Statins

- Individuals with clinical ASCVD
- Individuals with primary elevations of LDL ≥190
- Individuals age 40-75 with diabetes and LDL ≥70
- Individuals without ASCVD or diabetes, age 40-75, with LDL ≥70, and 10 year risk 7.5% or higher
Management of Hyperlipidemia and Cardiovascular Risk

**ACC/AHA Guidelines**

**Importance of Lifestyle Recommendations**
- Heart healthy diet
- Regular aerobic exercise
- Desirable body weight
- Avoidance of tobacco

**Heart Healthy Diet 2017**
- Two dietary factors increase LDL:
  - Saturated fat
  - Total Calories
- Restriction of dietary cholesterol is no longer recommended (Dietary Guidelines 2015)

**Saturated Fat 2017**
- Observational studies: no association between sat fat and CVD
- But: RCTs that replace sat fat with unsat fat reduce total and LDL cholesterol and CVD events and mortality
- And: replacing sat fat with carb reduces total and LDL cholesterol but increases triglycerides and HDL and does not lower CVD events

**ACC/AHA Guidelines**

**What Statin for Each Group?**
- Individuals with clinical ASCVD:
  - Treat with: high intensity statin, or moderate intensity statin if > age 75
- Individuals with primary elevations of LDL ≥190:
  - Treat with: high intensity statin
Management of Hyperlipidemia and Cardiovascular Risk

ACC/AHA Guidelines
What Statin for Each Group?
- Individuals 40-75 with diabetes and LDL ≥ 70:
  - Treat with: moderate intensity statin, or high intensity statin if risk over 7.5%
- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  - Treat with: moderate-to-high intensity statin

High Intensity vs. Moderate Intensity Statin
- High Intensity: lowers LDL by >50%
  - Atorvastatin 40 - 80
  - Rosuvastatin 20 - 40
- Moderate Intensity: lowers LDL by 30-50%
  - Atorvastatin 10 - 20
  - Rosuvastatin 5 – 10
  - Simvastatin 20 - 40
  - Pravastatin 40 – 80
  - Lovastatin 40

How Best To Calculate 10 Year Risk?

Pooled Cohort Risk Assessment Equations: hard CHD events and stroke
- http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

Pooled Cohort Risk Assessment Equations
- Age
- Gender
- Race (White/African American)
- Total cholesterol (170 mg/dl)
- HDL cholesterol (50 mg/dl)
- Systolic BP (110 mmHg)
- Yes/no meds for BP
- Yes/no DM
- Yes/no cigs
Outcome: 10-year risk of total CVD (fatal and non-fatal MI and stroke)
Management of Hyperlipidemia and Cardiovascular Risk

Robert Baron MD, MS

Do the Pooled Cohort Risk Assessment Equations Overestimate Risk?

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention, According to Set of Guidelines and Age Group:

How Best To Calculate 10 Year Risk?
Baron Approach 2017

- Use both CHD (hard end points) calculator and new CV risk calculator
- Include both in shared decision-making discussion

How Best To Calculate 10 Year Risk?
Mayo Clinic Statin Choice Decision Aid:

- http://statindecisionaid.mayoclinic.org/index.php/statin/index?PHPSESSID=0khk8nm14h9vubjm3423e6h6b2
63 yo woman; s/p MI

LDL  115
HDL  45
TG   160

The best next step in lipid management is:

1. Atorvastatin 40 mg
2. Rosuvastatin 10 mg
3. Pravastatin 40 mg
4. Simvastatin 40 mg
5. Lovastatin 40 mg
6. Whatever works to get her LDL below 70 mg/dl

2013 ACC/AHA Guidelines
What Statin for Each Group?

- Individuals with clinical ASCVD:
  - Treat with: high intensity statin, or moderate intensity statin if > age 75

The best next step in lipid management is:

1. Atorvastatin 40 mg
2. Rosuvastatin 10 mg
3. Pravastatin 40 mg
4. Simvastatin 40 mg
5. Lovastatin 40 mg
6. Whatever works to get her LDL below 70 mg/dl
63 yo woman; s/p MI. On atorvastatin 80.

LDL  95
HDL  40
TG   200

The best next step in lipid management is:

1. Continue current therapy
2. Switch to rosuvastatin 40 mg
3. Add fenofibrate
4. Add fish oil
5. Add niacin
6. Add ezetimibe

Summary Lipid-Lowering Drugs

- Statins are treatment of choice based on RCT to decrease risk
- No evidence to support adding niacin or fibrates to statins
- If completely statin-intolerant, niacin may reduce CVD risk (weak evidence)
- Fibrates appear to lower MI risk, but no other CVD endpoints

Summary Lipid-Lowering Drugs

- Ezetimibe study: (IMPROVE-IT)
  18,000 ACS patients (40% from North America)
  RCT: Simvastatin vs simvastatin + ezetimibe. Took 7 years. Death, MI, Stroke
  Simvastatin: 34.7% vs Simva/ezetimibe 32.7% (270 fewer events over 7 years)
PCSK9 Inhibitors
- Evolocumab (Repatha) and alirocumab (Praluent)—monoclonal antibodies that reduce liver LDL-receptor degradation
- Reduce LDL by 50%. Injectable Q2 – 4 weeks
- Approved for FH or patients with CVD “who need additional LDL lowering.”

FOURIER TRIAL
- 27,564 patients, CV disease, on statin, LDL >70, 2.2 years
- Evolocumab vs placebo (SQ injections)
- Primary composite CV endpoint: death, MI, stroke, ACS revascularization
- Secondary endpoint: CV death, MI, stroke

- LDL reduced 59% (92 mmol/L to 30)
- Primary composite endpoint:
  - 1344 (9.8%) vs 1563 (11.3%)
  - 15% reduction
- Secondary endpoint: CV death, MI, stroke
  - 816 (5.9%) vs 1013 (7.4%)
  - 20% reduction

Reflections:
- Evolocumab reduces risk
- Risk reduction less than hoped/thought
- $14,000 per year
The best next step in lipid management is:

1. Continue current therapy
2. Switch to rosuvastatin 40 mg (Also potentially correct, but medication still on patent)
3. Add fenofibrate
4. Add fish oil
5. Add niacin
6. Add ezetimibe

63 yo woman, no traditional risk factors

LDL 155
HDL 55
TG 160
SBP 120
No BP meds
No DM
Nonsmoker

The best next step in lipid management is to calculate 10 year risk and:

1. Continue current therapy (no meds)
2. Begin atorvastatin 40
3. Begin atorvastatin 10
4. Begin simvastatin 20
5. Begin sustained release niacin
6. Begin red yeast rice

63 yo woman, no risks

LDL 155, HDL 55, TG 160
SBP 120, No BP meds
Nonsmoker, No DM

10 yr CHD risk (old calculator): 2%...
10 yr CV risk (new calculator): 4.5%...

Therefore no medication recommended
63 yo man, no traditional risk factors

LDL 155
HDL 55
TG 160
SBP 120
No BP meds
No DM
Nonsmoker

The best next step in lipid management is to calculate 10 year risk and:

1. Continue current therapy (no meds)
2. Begin atorvastatin 40
3. Begin atorvastatin 10
4. Begin simvastatin 20
5. Begin sustained release niacin
6. Begin red yeast rice

63 yo man, no risks

LDL 155, HDL 55, TG 160
SBP 120, No BP meds
Nonsmoker, No DM

10 yr CHD risk (old calculator): 10%...
10 yr CV risk (new calculator): 10.8%...

“Toss-up.” Shared decision making. If start statin (per new guidelines), can start with moderate intensity statin
Management of Hyperlipidemia and Cardiovascular Risk

Robert Baron MD, MS

The best next step in lipid management is to calculate 10 year risk and:

1. Continue current therapy (no meds) - old (but toss-up)
2. Begin atorvastatin 40 - new (but still close call)
3. Begin atorvastatin 10 - new (but still close call)
4. Begin simvastatin 20 - new (but still close call)
5. Begin sustained release niacin
6. Begin red yeast rice

Key is shared decision-making

Other Factors That Could Affect Treatment Decisions

- LDL ≥ 160 mg/dl or evidence of genetic disorder
- Family history of premature ASCVD (<55 in first degree male relative, <65 in first degree woman)
- hs-CRP ≥2 mg/dl
- CAC score ≥ 300 (or ≥75% for age, sex, ethnicity)
- Ankle brachial index <0.9
- Elevated lifetime risk of ASCVD

The Good and The Controversial of the ACC/AHA Cholesterol Guidelines

- Focus on healthy lifestyle is good
- Focus to use statins (and not other agents) is good
- Focus to treat patients at high risk is good
- Focus to treat all patients with LDL <190 mg/dl and treat patients with DM/existing CV disease is good
- Not having target LDL is controversial
- Adults with no DM or heart disease and 10-year calculated risk >7.5% (using new risk calculator) to be treated – controversial

Statin Use for Primary Prevention of CVD: USPSTF

- Age 40 – 75, no CVD, 1 or more CVD risk factor* and calculated risk of and 10% or greater

USPSTF B: Prescribe if no contraindications

- Treat with low to moderate dose statin

*Risk: dyslipidemia, diabetes, HTN, smoking

USPSTF 2016
### Statin Use for Primary Prevention of CVD: USPSTF

- Age 40 – 75, no CVD, 1 or more CVD risk factor and calculated risk of and 7.5 – 10%
- **USPSTF C**: Individualized decision
- Age 76 and older: **USPSTF I**

**USPSTF 2016**

### USPSTF vs. ACA/AHA

- Recommendations modeled in NHANES primary prevention population.
- 3416 adults, 40-75. 21.5% already on statins.
- **USPSTF**: 15.8% additional
- **ACA/AHA**: 24.3% additional
- 55% of extra ACC/AHA group 40-59 years old.

Pagidipati, *JAMA* 2017

### NSAIDS and CVD

- Danish national study, 97,698 patients with prior MI. 44% received NSAIDS.
- NSAIDS associated with 42% increase in CV death (CI 1.36 – 1.49)
- Diclofenac 96% and rofecoxib 66% increase
- Ibuprofen 34% and naproxen 27% increase

### Competing Risks

- Example: women with 10-year risk 10%
- Reduce risk by 30% with statins. Risk now 7%.
- Add NSAID. Increase risk by 50%
- Total risk now back to 10%.
Aspirin and CVD

- Aspirin reduces nonfatal MI by about 20%; no benefit on non-fatal stroke.
- Also reduces incidence of colorectal cancer.
- Has definable off-setting harms: GI bleed, hemorrhagic stroke)

Aspirin and CVD

- Age 50 – 59 and 10% 10-yr risk: USPSTF B (Prescribe if no contraindications)
- Age 60 – 69 and 10% 10-yr risk: USPSTF C (Individualized decision)
- Less than age 50, over age 70: USPSTF I (Insufficient evidence)

USPSTF 2016

Conclusions I

- Statins are effective and cost effective in selected groups of patients
- Optimal screening age not known.
  - ACC/AHA age 21 (to identify those > LDL 190)
  - USPSTF age 35 men and 45 women for most, age 20 if increased risk.
- Use statins in patients with ASCVD, LDL ≥190 and diabetes

Conclusions II

- For those without ASCVD and diabetes, calculate 10 year risk, and treat those with risk greater than 7.5% (or 10% or maybe even 15%). Use shared decision making.
- Use appropriate intensity statin (high and moderate)
- Monitor adherence, but do not treat to specific LDL goal
Conclusions III

- Do not treat those over age 75 (unless ASCVD),

- Do not treat with other lipid-modifying drugs in addition to statins (but may need if truly statin intolerant)

- Avoid other factors that raise risk (i.e. NSAIDS) and use those that lower it (i.e. aspirin)
OUTPATIENT MANAGEMENT OF CAD- A PRIMARY CARE PERSPECTIVE

Michael G. Shlipak, MD, MPH
Professor of Medicine, UCSF
Chief, Division of General Internal Medicine, SFVA Medical Center
Scientific Director, Kidney Health Research Collaborative, UCSF

DISCLOSURES
I am on the Scientific Advisory Boards with stock option compensation for the following companies:
- TAI Diagnostics
- Cricket Health, Inc.

FEATURES OF THIS TALK
- Covers a broad array of topics
- Greatest attention to common challenges in decision making
- All recommendations supported by the following Guideline: AHA Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease (Circulation, 2012)
  - Class 1 indication: we should do this
  - Class 2 indication: it’s reasonable to do this

QUESTION #1
Your patient is a 62yo man with history of controlled hypertension, mild overweight (BMI 29), and untreated LDL of 137mg/dL. He reports to you that for about 2 months he has experienced left-sided chest tightness after working up 2 flights of stairs. It is relieved by rest and is not progressing noticeably. The symptoms have not occurred at any other times. What is the probability that the patient's symptoms are caused by CAD?

a) <50%
b) 60%
c) 80%
d) >90%
**Pretest Probability of Coronary Heart Disease in Patients with Chest Pain According to Age, Gender, and Symptoms**

<table>
<thead>
<tr>
<th>Age</th>
<th>Nonanginal Chest Pain</th>
<th>Atypical angina</th>
<th>Typical angina</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>40-49</td>
<td>13</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>50-59</td>
<td>20</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>60-69</td>
<td>27</td>
<td>14</td>
<td>72</td>
</tr>
</tbody>
</table>

AHA definitions:
- low risk = ~10% or less
- high risk = ~90% or higher
- intermediate risk = anything in between

Diamond GA et al., N Engl J Med 1979
Weiner DA et al., N Engl J Med 1979

**Question #2: Your patient is capable of walking and has a normal resting ECG. Which of the following tests should you order next?**

- a) Exercise only stress test
- b) Exercise with perfusion imaging
- c) Exercise echo
- d) Coronary angiography
- e) None of the above

**Non Invasive Testing for Diagnosis of Ischemic Heart Disease**

AHA recommendation is to limit testing to intermediate risk patients
- If patient can exercise and has normal resting ECG, then exercise only stress test
- If abnormal ECG, then exercise/imaging or exercise echo
- If patient cannot exercise, then pharmacologic stress with imaging/echo

**Why do we only test patients with intermediate probability of CAD?**

- Exercise only:
  - LR+ = 3.0
  - LR- = 0.42

- Exercise echo:
  - LR+ = 3.7
  - LR- = 0.19
  (Fleischmann KE. et al. JAMA 1998)

- Exercise imaging:
  - LR+ = 2.4
  - LR- = 0.20
  (Fleischmann KE. et al. JAMA 1988)
**PROMISE Trial**

Is coronary CT angio the best tests for evaluation of intermediate risk patients with chest pain?


---

**TRIAL DESIGN**

- 10,000 participants in North America
- 193 sites
- NIH-funded
- Randomization:
  - CTA- coronary computed tomographic angiography
  - Functional Testing- (one of the 3 options)
    - Exercise EGG
    - Nuclear stress
    - Stress echo
- Composite: death, MI, UA hospital procedure complication
- Median follow-up 25 months

---

**PATIENT CHARACTERISTICS**

- **Age**: 60±8
- **Women**: 53%
- **Mean**: 2.4 risk factors
- **Typical angina**: 17%
- **Atypical angina**: 78%
- **Non-anginal symptoms**: 10%
- **Individual predicted CAD risk**: mean 0.53

---

**QUESTION 3**

Among these intermediate risk patients, what percentage would you guess had the primary outcome (death or MI) within 2 years?

a) <5%
b) 5-10%
c) 10-20%
d) >20%
CT ANGIO IS NO BETTER THAN FUNCTIONAL TESTING

Incidences of death or MI was only 1%/year in each group

SUMMARY
- A lot of testing with very low yield
- “Intermediate risk” is actually low risk
- “…reflects an excellent prognosis for patients with similar, new-onset, stable chest pain in real-world settings.”

QUESTION #4
Based on his symptoms of typical angina, you inform your patient that he has CAD. You explain the proven value of “optimal medical therapy”

Which of the following is not considered part of optimal medical therapy for a patient with anginal symptoms?

- a) ACE inhibitors (ARBs)
- b) Aspirin
- c) Beta blockers
- d) Statins

ASPIRIN
- All patients with CAD should use 81-162mg of aspirin (class 1)
- Clopidigrel (plavix) should be offered to patients who cannot tolerate aspirin (class 1)
- Aspirin + clopidigrel for severe patients is reasonable (class 2B)
**Beta Blockers**
- Improved survival in patients with prior MI
  - If patient has prior MI, BB is class 1
  - If MI >3 years ago, BB is class 2A
- Best choice for angina symptoms

**Statins (More on this topic later)**
- LDL target <100 mg/dL - class 1
- LDL target <70 mg/dL - class 2A
- “No evidence to suggest LDL targets of 70 vs. 100 mg/dL in patients with ASCVD”

**Ace Inhibitors**
- Not clearly indicated in patients with angina because no effect on symptoms
- Considered a “reasonable choice” (2A)
- ACE inhibitors (Class I) must be used for patients with:
  - Reduced ejection fraction
  - CKD with albuminuria

**Case Continued**
- Your patient worries that something bad might happen with his heart. He asks you to assess the likelihood of him having a heart attack or dying from his heart disease. How do you determine risk in the secondary prevention setting?
**Risk Prediction in CAD**

- **Primary prevention:**
  - Patients without CAD or CVD
  - CVD risk calculator

- **Secondary prevention:**
  - Patients who have CAD
  - No risk score for ambulatory patients with established CAD
  - CVD risk calculators do not work

**Risk Factors for Adverse Outcomes in Patients with CAD**

- Feared adverse outcomes in CAD patients:
  - Recurrent MI
  - Heart failure
  - Sudden death

- Traditional CVD risk factors are still important:
  - Blood pressure control
  - Smoking cessation
  - Weight loss
  - Diabetes control
  - Lipid management
  - Encourage exercise

- Although important, cardiac status matters more for prognosis than metabolic risk factors

**Cardiac-Specific Risk Factors in Patients with CAD**

1. Exercise capacity
2. Number and size of MIs
3. Reduced ejection fraction
4. HF symptoms
5. BNP/NT-pro-BNP
6. High sensitivity troponins

**Treatments of Anginal Symptoms**

*Ranking Anti-Ischemic Agents (Per AHA Guidelines)*

1. BBs: top choice
2. CCBs or long acting nitrites (if BB intolerant)
3. Use combinations if necessary
4. NTG (sl or spray) for immediate relief
5. Ranolozine as lesser alternative (class 2A)
**FOLLOW UP IN CAD PATIENTS**

**Routine**
- Assess anginal symptoms and physical function
- Assess signs of heart failure or arrhythmia
- Risk factor management
- Lifestyle

**Situational**
- If heart failure signs or repeat MI → echo
- If new or worsening angina → exercise testing or coronary angiography

**CASE STUDY FOLLOW UP**

Your patient is still frustrated by the concept of medical management and concerned that his symptoms indicate an impending heart attack. He asks you “why can’t I just get a stent and fix this problem?”

This seems logical—why not proceed to PCI?

**INTERVENTIONS IN STABLE ANGINA**

- Interventions should be limited to patients who fail optimal medical therapy
- Currently, 85% of all percutaneous coronary intervention (PCI) procedures are elective in patients with stable angina
- The COURAGE trial demonstrated that PCI does not improve outcomes

**COURAGE TRIAL**

- Conducted to compare OMT with and without PCI in 2,287 patients with stable angina
- Funded by the US VA R&D/Canadian Institutes of Health Research
- Outcome:
  - All-cause mortality
  - Non-fatal MI
- Initial trial: mean of 4.6 years
  - Boden et al. *NEJM* 2007
- Extended follow-up: 12 years
  - Sedlis et al. *NEJM* 2015
Your patient insists on talking with a specialist
You refer to a cardiologist
The patient returns to your office 8 weeks later for a follow-up visit...

...after having received a stent.

What happened?

What are cardiologists thinking?

- Design: focus groups of cardiologists in N. Cal
- Research Question: Why do cardiologists ignore COURAGE results?
- Reasons given for performing PCI in stable angina:
  - Belief in the benefits of treating ischemia and in the open artery hypothesis
  - Potential regret (psychological and legal) for not intervening if a cardiac event could be averted
  - Alleviation of patient anxiety
  - Belief that referring PCP expects a procedure

Lin et al. Arch Intern Med. 2007
WHY STATINS ARE BETTER THAN STENTS

- Severity of stenosis ≠ MI risk
- Stents are small (1-2 cm) relative to length of 3 major coronary arteries (~30cm) and their branches (~30cm)
- Statins stabilize all the plaques

CONCLUSIONS

- We need to fully implement OMT (β-blocker, statin, aspirin) first, before referring to cardiologists
- We need to resist the urge to “fix” patients’ angina by stenting
- We need to educate patients that stents do not prevent adverse outcomes
- We need to be clear about our expectations prior to referring patients to cardiologists

QUESTION 5

- Your patient returns for follow up. He has been taking 20mg simvastatin. LDL is 110mg, HDL 25mg. Which is the best next step?
  - a) ↑ simvastatin
  - b) Change to pravastatin
  - c) Change to atorvastatin
  - d) Add gemfibrozil
  - e) Add niacin

NEW RECOMMENDATIONS FOR LIPID MANAGEMENT IN PERSONS WITH CVD

- “High intensity statin therapy should be first line in persons with clinical ASCVD, aged ≤ 75, unless contraindicated”
  - High- atorvastatin 40-80, rosuvastatin 20-40
  - Moderate- simvastatin 20-40, pravastatin 40, lovastatin 40
  - Low- simvastatin 10, pravastatin 10-20, lovastatin 20
- Our patient should be on atorvastatin or rosuvastatin
**SHOULD WE STILL USE SIMVASTATIN?**

- June 8, 2011: FDA restricts use of 80mg simvastatin because of increased risk of myopathy
- FDA recommends:
  - No new patients on simvastatin 80mg
  - Okay to maintain patients on 80mg if >1 year without symptoms of muscle toxicity
  - Beware of drug interactions
- Based on the SEARCH Trial (Lancet, 2010)
  - Simvastatin 80mg vs. 20mg in RCT of 12,000 with CAD

**SEARCH TRIAL RESULTS**

- Difference in myopathy risk:
  - **Myopathy** (muscle weakness + CK >10x ULN)
    - 80 mg: 52 patients (0.9%)
    - 20 mg: 1 patient (0.02%)
  - **Rhabdomyolysis** (muscle weakness + CK>40x ULN)
    - 80 mg: 22 patients (0.4%)
    - 20 mg: 0 patients
- Risk 5-fold higher in year 1 compared with subsequent years
- Key drug interactions noted
  - Calcium channel blockers, Amiodarone, Ranolazine, and others

**WHY IS NIACIN IN DISFAVOR?**

- **AIM-HIGH trial** (NEJM 2011)
  - AIM HIGH Investigators, NEJM 2011
- **HPS2-THRIVE trial** (NEJM, July 17, 2014)
  - [http://www.ctsu.ox.ac.uk/hps2-thrive/](http://www.ctsu.ox.ac.uk/hps2-thrive/)
  - HPS2-THRIVE Investigators, NEJM 2014

**QUESTION 6**

You decide your patient should switch to atorvastatin. However, he has now stopped his statin due to adverse publicity and will not restart. He tells you that he is now taking niacin because it is “a natural option.”

You recheck his lipids; his HDL is 50mg/dL and his LDL is 140 mg/dL.

Your best management option is:

a) Reinforce to the patient that statins are by far the best treatment for lipid disorders.

b) Congratulate him on his choice because niacin has made his HDL go up beautifully

c) Offer a fibrate (e.g. gemfibrozil), as it is an evidence-based treatment for patients like him

d) Any of the above approaches is fine.
AIM-HIGH TRIAL (NIH, ABBVIE)
- Participants: N=3,414 in US and Canada
- Inclusion criteria:
  - Prior CVD
  - On a statin
  - Low HDL and high TG
- Design: Placebo-controlled RCT
- Intervention: Niaspan – 2 g/day or placebo
- Outcomes: CVD death, MI, CVA, ACS, revascularization
- Follow-up: 3 years

AIM-HIGH FINDINGS
- Trial stopped early
- Event rate was same in both groups

HPS2-THRIVE TRIAL (MERCK)
- Participants: N=25,673 in UK, Scandinavia, and China
- Inclusion criteria:
  - Prior CVD
  - On a statin
- Design: Placebo-controlled RCT
- Intervention: 2g ext-release niacin + 40mg laropiprant vs. placebo
- Outcomes: CVD death, MI, CVA, and revascularization
- Follow-up: 4 years

HPS2-THRIVE FINDINGS
- Primary outcome RR= 0.96 (0.90-1.03)
- All-cause mortality RR= 1.09 (0.99 to 1.21)

But, there is more to the story…
Niacin Increases Risk for Serious Adverse Events and Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate Ratio (95% CI)</th>
<th>Extra Events/100 Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event</td>
<td>1.28 (1.13-1.44)</td>
<td>1.0</td>
</tr>
<tr>
<td>G.I. Event</td>
<td>1.26 (1.10-1.44)</td>
<td>0.7</td>
</tr>
<tr>
<td>Musculoskeletal event</td>
<td>1.67 (1.20-2.34)</td>
<td>0.3</td>
</tr>
<tr>
<td>Skin-related event</td>
<td>1.22 (1.12-1.34)</td>
<td>1.4</td>
</tr>
<tr>
<td>Infection event</td>
<td>1.28 (1.17-1.62)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.32 (1.16-1.51)</td>
<td>1.3</td>
</tr>
<tr>
<td>New-onset</td>
<td>1.55 (1.34-1.78)</td>
<td>3.7</td>
</tr>
</tbody>
</table>

“On the basis of the weight of available evidence showing net clinical harm, niacin must be considered to have an unacceptable toxicity profile for the majority of patients, and it should not be used routinely.”

“...[the study] lends further evidence to the notion that HDL cholesterol is unlikely to be causal.”

Do fibrates improve clinical outcomes?

Effects of Fibrates on Cardiovascular Outcomes

- **Design:** systematic review and meta-analysis
- **Analysis:** 18 RCTs from 1950-2010
- **Participants:** N=45,058

Jun et al. The Lancet 2010
FIBRATE VS. PLACEBO AND CVD RISK

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal coronary events</td>
<td>0.81</td>
<td>0.75-0.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total stroke</td>
<td>1.03</td>
<td>0.91-1.16</td>
<td>0.69</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.97</td>
<td>0.88-1.07</td>
<td>0.59</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.00</td>
<td>0.98-1.08</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Jun et al. *The Lancet* 2010

DATA SUMMARY

- **For patients with low HDL:**
  - Statins are treatment of choice to decrease CVD risk, regardless of LDL
  - Do not add either niacin or fibrates to statin treatment
- **For patients who cannot tolerate statins:**
  - Fibrates appear to lower MI risk, but no other CVD endpoints
  - Niacin has clear harmful effects and uncertain benefits among statin non-users.
  - AHA guidelines state that for statin untreated patients fibrates are a “reasonable choice” (2A)

CASE STUDY FOLLOW UP

- Now that your patient with stable CAD is on OMT, he has increased exercise, as you recommended.
- However, he has developed persistent knee pain and wants to take “prescription-strength” ibuprofen. The label says to ask a doctor before use if you have heart disease.
- Is the risk real?

NSAIDS IN CAD PATIENTS

- Meta-analysis demonstrated increased risk for incident CAD (Trelle et al. BMJ 2011)
- Are they clinically harmful in patients with established CAD?
- No RCT evidence in CAD patients
BEST EVIDENCE FROM DENMARK
- National registry of MI patients and pharmacy data
- Patients with first MI (2002-2011); N= 61,971
- 34% received NSAIDS; average age = 68, 63% men
- Follow-up for MI/CHD death
- Follow-up for bleeding risk

Olsen AM et al. JAMA 2015

NSAID ASSOCIATION WITH CVD RISK
- Outcome: CVD death, MI, stroke
- No NSAID: 8.3%/year
- NSAID: 11.2%
- Adjusted HR: 1.40 (1.3-1.5)
- Risks similar across NSAIDS; naproxen rarely used

Olsen AM et al. JAMA 2015

NSAID ASSOCIATION WITH BLEEDING RISK
- Outcome: Intra-cranial, GI, respiratory, or urinary bleeding
- No NSAID: 2.2%/year
- NSAID: 4.2%
- Adjusted HR: 2.0 (1.8-2.3)
- Risks similar across NSAIDS

Olsen AM et al. JAMA 2015

NSAID CONCLUSIONS
- MI risk from NSAIDs appears real
- NSAIDs should be used at most for short-term in CAD patients
- Evidence supports FDA’s “Black Box” warning (FDA update 7-9-2015):
  - NSAIDs cause MI and stroke, even in first weeks
  - Increased risk with higher dose and duration
  - Uncertain whether risk varies by particular NSAID
  - NSAIDs also cause HF
THANK YOU!  ANY QUESTIONS?
Understanding Dementia and Cognitive Assessment

ANNA H. CHODOS, MD, MPH
DIVISION OF GERIATRICS
DIVISION OF GENERAL INTERNAL MEDICINE, ZSFG
CO-PI, OPTIMIZING AGING COLLABORATIVE
GERIATRICS WORKFORCE ENHANCEMENT PROGRAM

The Optimizing Aging Collaborative at UCSF is supported by the UCSF Geriatrics Workforce Enhancement Program: Health Resources and Services Administration (HRSA) Grant Number U1QHP28727.

Disclosures
I have nothing to disclose.

Outline

Dementia overview
  • Definition
  • Assessment

Behavioral issues in dementia

Dementia
Dementia (Major Neurocognitive Disorder):
Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains:
- Learning and memory
- Language
- Executive function
- Complex attention
- Perceptual-motor
- Social cognition = behavior

Dementia (Major Neurocognitive Disorder), cont’d:
The cognitive deficits interfere with independence in everyday activities.
The cognitive deficits do not occur exclusively in the context of a delirium.
The cognitive deficits are not better explained by another mental disorder (e.g. major depressive disorder, schizophrenia)

Diagnosis of dementia = acquired cognitive impairment + acquired functional impairment

DSM-V (2013)
A Case
88 yo man, here for follow-up.
No complaints.
PMH: hypertension, glaucoma, depression
Meds: HCTZ, eye drops
Says he takes the medicines. “You have my list.”

Our Case
Mr. H’s probability is high given his age.
- Early warning signs present?
- Sparse details during conversation and no memory for current news events.

Red flags for Dementia
Repetition (not normal in span of a clinic visit)
Losing track of conversation
Frequently deferring to caregiver/family
Unexplained medical decompensation
Unexplained weight loss
Missing appointments
Inattentive to appearance, behavioral changes
Falls or injury, hospitalizations
Paucity of content, detail

Dementia Assessment: Part I
Cognitive:
- History and trajectory of:
  - Memory
  - Executive Function
  - Visuospatial
  - Language
  - Motor
  - Psychiatric/Behavioral
Dementia Assessment: Part I
Neurologic exam: MS, motor, balance

Cognitive Testing
- What tools are you familiar with?
- What do you have time to do?

Screening Method: Mini-Cog
1-2 min
3 item recall (3 points)
+ CLOCK DRAW (2 points)

Negative screen ≥3
Positive screen <3, consider DELIRIUM vs. DEMENTIA
http://www.alz.org/documents_custom/minicog.pdf

MOCA Test
10-20 min
Montreal Cognitive Assessment (MOCA)

- Positives: Many languages, Many cognitive domains
- Negatives: +1 education < HS, unclear if this is enough
- USE THE INSTRUCTIONS the first few times you use it
  www.mocatest.org (need to register)

GP-COG
5-8 min

GPCOG Screening Test
Step 1: Patient Examination
Unless specified, each question should only be asked once

Part 2- Informant (function)
Available in Spanish, Chinese, Korean.

Our Case
Neurologic exam normal.

Mr H’s MOCA test: 14/30

What is his education?
What is normal for 88yo?

Dementia Assessment: Part II

Function:
- Activities of Daily Living (ADLs), Instrumental Activities of Daily Living (IADLs)

How the person is doing is the most important part of this diagnosis.

Assessing Function

Our Case
Function: He reports no problems with ADLs or IADLs
- In the clear?
Dementia Assessment: Part II

Collateral- family, caregiver/s
- Memory
- Executive fxn
- Language
- Visuospatial
- Motor
- Behavior
- FUNCTION

Our Case
Collateral-
- His wife's children - unaware anything serious was going on, says he drives daily.
- Wife says he is more forgetful, forgets bills.

Dementia assessment: Part III
R/o reversible causes:
- Delirium: acute, fluctuating, inattentive
- Substance Use
- Depression
- Labs: TSH, B12, RPR and HIV
- Medication review

Medications Causing Cognitive Symptoms
- Benzodiazepines
- Anti-cholinergics: diphenhydramine, hydroxyzine, chlorpheniramine
  - Including OTC combination meds- tylenol PM
- Sleep medications: Z-drugs
- Muscle relaxants (cyclobenzaprine, carisoprodol)
- Antispasmotics: oxybutynin, tolterodine
- TCA anti-depressants
- Anti-psychotics
When should I order head imaging?

- <65
- Rapid onset
- Other diagnoses: cancer, HIV
- Head injury
- Focal neurologic findings
- Meds: anti-coagulants

Our case

Labs wnl

Diagnosed mild/moderate dementia—Informed patient and CDPH (mandated reporter) -> they will inform DMV

Dementia: the take home

Suspect it—Recognize red flags and symptoms

Diagnosis it:
- **Part I Cognitive history**
- **Part II Functional history**
  - Get collateral
- **Part III R/o reversible causes**

Get specialist help when you are not sure

Types

- Alzheimer disease
- Vascular dementia
- Dementia with Lewy Bodies
- Parkinson’s disease with dementia
- Frontotemporal dementia
- Normal pressure hydrocephalus
- Alcohol-related dementia
- HIV-related dementia
- Syphilis-related dementia
- Progressive supranuclear palsy
- Corticobasal degeneration
- Primary progressive aphasia
- Creutzfeldt-Jakob disease
- Huntington disease
Types of Dementia

<table>
<thead>
<tr>
<th>Type</th>
<th>MCI</th>
<th>Alzheimer's</th>
<th>Vascular</th>
<th>Lewy Body</th>
<th>PTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Sudden, or stepwise</td>
<td>Gradual</td>
<td>Insidious, younger</td>
</tr>
<tr>
<td>Cognitive Features</td>
<td>Memory</td>
<td>Memory</td>
<td>Language</td>
<td>Depends on injury</td>
<td>Memory</td>
</tr>
<tr>
<td>Motor Features</td>
<td>Rare early</td>
<td>Rare early</td>
<td>Apraxia-late</td>
<td>Depends on injury</td>
<td>Parkinsonian</td>
</tr>
<tr>
<td>Other</td>
<td>May progress to AD</td>
<td>Gradual Decline</td>
<td>Stepwise decline</td>
<td>Caution with antipsychotics</td>
<td></td>
</tr>
</tbody>
</table>

Preserving cognition

- Intellectually engaging activities
- Physical Activity
- Social Engagement

Behavioral symptoms of dementia

“Agitation” (nonspecific), aggression, arguing, irritability, delusions, hallucinations, wandering, depression, apathy, disinhibition, repetitive behaviors, sleep disturbances

Most patients have some NPS.
- ~80% at some point, especially later in disease course

Neuropsychiatric symptoms of dementia


NPS

Why are they important?
- Worse daily function
- Worse quality of life
- Burden on caregivers
- Behavioral symptoms > physical needs
- More institutionalization

Torti FM, Alzheimer Disease & Associated Disorders 200418(2), pp 99-109

A Case: Neuropsychiatric Symptoms in Dementia

Ms. L who lives in a board and care, spends many afternoons banging on the chairs causing a lot of noise.

Her daughter is asking if there is “anything we can give her to calm her down” so the staff will stop calling her?

Example: www.teepasnow.com-- “About Videos”: Challenging Behaviors

An Approach to NPS

Identify and describe the behavior
Identify triggers
Identify if it’s a problem and if it is leading to potential harm
### Identify the behavior

**Ms. L—Behavior:** repetitive behavior, argumentative

Examples:
- Yelling, vocalizing
- Repetitive behaviors—cleaning, reorganizing
- Hitting

### Identify triggers

**Needs:** thirst/hunger, pain, toileting, boredom, tired, comfort

**Environment:** Attendant gender, bathing, undressing

**Over or understimulated**
- Isolation and loneliness
- Unwanted interaction, fear

**Depression, anxiety**

### Our Case: NPS in dementia

Ms. L was a housekeeper prior to retirement.

In reviewing her needs, staff noticed she was not taken to the toilet enough during the afternoon because she was resistant.

### Identify if it’s a problem

What is the consequence of this behavior?

- Caregiver stress
- Harm to others/self

What has been tried?
Identify the behavior to identify solutions

<table>
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<tr>
<th>Common NPS</th>
<th>Interpretations/solutions</th>
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<tr>
<td>Toileting issues</td>
<td>Timed voiding</td>
</tr>
<tr>
<td>Agitated, upset, restless</td>
<td>Overstimulation, unrealistic expectations, delirium?</td>
</tr>
<tr>
<td></td>
<td>Provide structure, calm, pets, music</td>
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<tr>
<td>Repetitive behavior</td>
<td>Give outlet for activity, safe environment, substitutions</td>
</tr>
<tr>
<td>Argumentativeness</td>
<td>Agree, avoid debates, calm environment</td>
</tr>
</tbody>
</table>

Adapted from Kathryn Eubanks, MD

Educate caregivers

- Alzheimer's Association
- Family Caregiver Alliance
- Companies/programs, e.g. teepasnow.com
- UCSF Memory and Aging Center videos (Alz Dis)

Choosing Wisely Campaign
Geriatrics Rec #2 (2013)

Don’t use antipsychotics as first choice to treat behavioral and psychological symptoms of dementia
Treatment with antipsychotics

Are modestly effective.
- Agitation, aggression, psychosis

1 in 3 nursing home residents and 1 in 7 community-dwelling adults with dementia
- Use goes up with age

GAO Antipsychotic Drugs and Older Adults 2012

CATIE-AD RCT

421 outpatients
- Risp (1mg) > olanz (5mg) > quet (50mg)
- Affected: Paranoia, hostility, aggression, mistrust, psychosis
- No change in function, care needs, QOL
- Withdrawal from treatment high
- Olanz: worsening ADL function


Side effects of anti-psychotics for NPS

1.5-1.7x increased risk of mortality
- risk of death occurs as early as <6mo
2-3x increased stroke risk
- CV and metabolic effects (obesity, glucose)
Extrapyramidal symptoms
Worsening cognition and falls
Hospitalizations


Approach for NPS: Medication

Try dementia medications and antidepressants first.

Consider an antipsychotic if it’s a severe problem:
- Quetiapine > risperidone > olanzapine
- Record target symptom
- Schedule it, lowest dose possible
- Record response, trial off after 3-6 months
Our Case
For Ms. L, staff put cleaning cloths in easy reach and would clean next to her. This would get her to use cloths to clean the chairs instead of hitting them and so no one would have to try to get her to stop.
Staff started to regularly offer her bathroom trips. She seemed more comfortable afterward and would spend less time cleaning the chairs and “annoying” the staff.

NPS: the take home
Identify the behavior, triggers, if it’s a problem.
NONPHARMACOLOGIC approaches first
Educate caregivers
If decided, plan a medication trial carefully.
https://www.healthcare.uiowa.edu/igec/iaadapt/

Thank you
Helen Kao, MD
Kathryn Eubank, MD
Stephanie Rogers, MD
Stefanie Bonigut, LCSW, Alz Association
Kirby Lee, PharmD
Kate Radcliffe
EXTRA SLIDES

Questions you can ask to elicit history about cognitive impairment in the various cognitive domains

Cognitive Symptoms: Memory

Problems with recent events – Trouble remembering conversations, repeating things
Remote events (generally remain intact until later in disease)
Misplacing objects
Repetitive Questions
Missing appointments
Objective findings: Repeats complaint stated earlier in visit, unable to do short-term recall exercise

Cognitive Symptoms: Executive Function

Difficulty with planning or organization
Multi-tasking
Concentration/attention span
Problem Solving
Impulsivity (acting without thinking)
Mental rigidity/inflexibility
Objective findings: Difficulty following complex instructions, difficulty with clock draw or trails

Cognitive Symptoms: Language

Word finding trouble
Poor articulation
Impaired comprehension
Impoverished speech (e.g. "thingie" instead of specific word)
Impaired reading/writing/spelling
Mutism/ Decreased speech output
Objective findings: Can name <11 words in 1 minute, poor score on Boston Naming Test (doesn’t know names of high frequency words)
Cognitive Symptoms:
Visuospatial

Lost in familiar environments
Difficulty recognizing faces
Difficulty driving
Difficulty parking
Objective finding: Trouble drawing a cube

Cognitive Symptoms:
Behavioral

Changes in emotional expression (blunting/labile)
Changes in personality/behavior
Apathy/decreased motivation
Obsessive/compulsive behaviors
Agitation/aggression
Depression
Delusions/Hallucinations
Impaired Hygiene/eating
Changes in sleep

Cognitive Symptoms:
Motor

Difficulty with walking or balance
Trouble using utensils (apraxia)
Change in handwriting
Tremor
Weakness
Involuntary movements
Trouble Swallowing
Objective findings: Falls, cannot demonstrate how to brush teeth or hair (apraxia)

EXTRA SLIDES

Management of Dementia
Pharmacological Management

Depends on the type of dementia

Treatment of risk factors for stroke and cardiovascular disease

Tailor to patient’s goals of care

Setting realistic expectations
  * Most treatments don’t have a big effect on cognition or function

PHARMACOLOGICAL MANAGEMENT

CHOLINESTERASE INHIBITORS

MILD/MODERATE DEMENTIA

- Donepezil
- Rivastigmine
- Galantamine

General side effects: nausea, diarrhea, anorexia, insomnia

NMDA RECEPTOR ANTAGONIST

MODERATE/SEVERE DEMENTIA

- Memantine

Minimal impact on function and quality of life. Do not really change the disease course.

What works?

<table>
<thead>
<tr>
<th></th>
<th>Physical Function</th>
<th>Cognitive Function</th>
<th>Quality of Life</th>
<th>Mood/Behavior</th>
<th>Caregiver Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>0.68</td>
<td>0.31 - 0.55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social/Cog</td>
<td></td>
<td>0.41</td>
<td>0.44</td>
<td></td>
<td></td>
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<tr>
<td>Music</td>
<td></td>
<td></td>
<td>0.49 - 0.64</td>
<td></td>
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<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Cholinesterase Inhibitors</td>
<td>0.25 - 0.29</td>
<td>0.15 - 0.28</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Memantine</td>
<td>0.11</td>
<td>0.33</td>
<td>0.22*</td>
<td></td>
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</tr>
</tbody>
</table>

Effect sizes are: small = 0.2; moderate= 0.5; large= 0.8

Address the environmental, social factors and engage caregivers

Future Drug Therapies

Anti-beta amyloid
  * Solanezumab & bapineuzumab- no improvement in cognition or function in Phase 3 study

Many other still in early phase studies
  * Beta-secretase (BACE) inhibitors- prevents formation of beta-amyloid
  * Preservation of tau protein- maintain neuronal structures
  * Anti-inflammatory medication
What the primary needs to know in the world of increased access

Toby Maurer, MD
University of California, San Francisco

Teledermatology
- In the world of dermatology-teledermatology is powering many processes of medicine
- Direct to consumer-losing weight
- Contracted derms reading pictures sent from PCP’s and providing triage advice—works best when there is the option of follow-up in dermatology

Objectives
- Review most common diseases seen in telederm
- Strengthen the partnership between the PCP and derm to provide the best care to the pt?

Acne
Primary care provider:
Pt has recent onset of bumps on face. What is this and how do I treat? Has used “proactive “with minimal change.
Topicals

- BP 5% gel (10% - more drying)
- Retin A 0.025% - 0.1% (vehicle determines strength - start with crème)
- Cleocin T or erythromycin topically
  -- Use 1 qam and 1qhs
  -- If NO success after 8 weeks, go to p.o.’s

Primary Care Provider:
Pt with acne –used Retin -A but very irritating. What is the next step?

Pt has cystic/scarring acne-topicals won’t work and in Asians-Retin A is very irritating.
- Start p.o. antibiotics

P.O. Antibiotics

- TCN - 500 bid x 8 weeks
- Doxycycline - 100 bid x 8 weeks
- Minocycline - 100 bid x 8 weeks
- Taper - Do NOT STOP ABRUPTLY. Once pt’s skin is clear, taper the dose in ½ for another month and then stop the medication
Scarring, keloidal, cystic acne

• Record treatments
• If failed 2 or more systemic meds, consider Accutane
• Check depression history, CBC, LFT’s, TG, Chol and pregnancy counselling

Acne Rosacea

• Rosacea-if just red-laser or makeup
• If papules-start doxy 100 bid x 8 wks then topical flagyl daily for maintenance
• Seb derm: topical HC 1% oint plus econazole crème bid and seb derm shampoo (tar, ketoconazole, selenium, zinc)

Acne Keloidalis Nuchae

• Never buzz cut hair again
• Topical clobetasol qam and topical retin a 0.1% crème/gel qhs x 3 months
• If very inflamed, add doxycyline 100 bid x 2 months
• See pt back in 3 months
• If no change, send back another consult-we can book him in clinic for intralesional kenalog
• New association with metabolic syndrome (especially HTN)

Primary Care Provider:
Pt told he has psoriasis-used some crème in Mexico-can’t remember name. Worried that his grandchildren could catch this.
Psoriasis is fast growing skin—can’t get it from anyone and can’t give it to anyone

What meds is he on? Certain meds might unmask this like atenolol, lithium, NSAIDS

Start Clobetasol oint and dovonex crème together. Apply M-F bid-weekends off

Primary see pt again in 6 weeks. If not better—send another telederm consult and we will readvise or book pt in derm clinic

Pt did not get better......

New pictures show increased total body surface area involvement

Dermatology triage: I see that pt has liver disease (seen on EMR). First choice systemic drug is acitretin. Please order up baseline LFT’s, fasting TG and cholesterol.

We will book pt for derm clinic in 3 weeks—please order baseline labs and start him on acitretin 25 qd

Psoriasis—when topicals don’t work

Acitretin—safer to use in liver disease—monitor TG, Chol

Methotrexate—titrate dose, follow LFT’s and CBC, needs liver biopsy after 1.5 gm—great drug if there is psoriatic arthritis

Biologics—good drugs, expensive, subcu injections except for ompremilast, presecreen for TB and Hep B and cancer risk

Ultraviolet light—is pt able to spend the time; is it accessible to pt?

Psoriasis and Metabolic Syndrome

associated with HTN and cardiac disease

associated with renal disease

Chronic inflammation—no evidence that the TNF blockers or aicretin are helpful in down regulating systemic inflammatory markers

Did not check against MTX
LOTS of BIOLOGICS

- Personalized medicine
- Starting to look at tissue flow cytometry to identify specific markers in an individual and then use the most specific targeted biologic
- Especially useful in folks who have failed multiple different biologics

NO PREDNISONE

Atopic Dermatitis Body Treatment

- Topical steroids and antihistamines still mainstay of treatment
- Avoid prednisone (oral and injectable)
- Clobetasol ointment qd for 5 days when severe then
- Fluocinidine (lidex) oint bid for 2 weeks then
- Triamcinolone 0.1 % oint bid maintenance
- FACE: HC or aclometasone oint bid

Gentle Skin Care discussion

- Steroids are okay to use-not going to thin out the skin BUT give limited amts of potent steroids
- Use steroids with grease-bid when disease is active
- Otherwise JUST GREASE
- Bathing or showering 1-2x/wk and don’t even dry off after bathing
- Grease up immediately
- Antihistamine (benadryl, atarax, doxepin) at night so pt can sleep and break the itch/scratch cycle
Dupilumab

- Anti-IL4 receptor
- Expensive
- SEVERE atopic dermatitis

Scabies: Classic treatment

- Permethrin 5% crème—2 applications 1 week apart
- Must treat all intimates
- Clothing instructions essential—wash 3 days of clothing and linens, then apply permethrin—start using clean clothes next morning
- Everything else goes into garbage bags—tie off for 3 days

Primary Care Provider:
Pt notes changing mole—also itchy. Worried she has melanoma

Seborrheic keratosis—OBSERVE over time—Alert to pt if bleeds or grows rapidly—return to you ASAP!

- You can apply cryotherapy 2 x 15 sec thaw cycles or
- Private derms in your county will do this for a fee
• Primary Care Provider:
  24 year old with new black bump
  No others noted

• Teledermatology Response:
  Looks like seb keratosis but that is unusual in pt under the age of 29. I want to biopsy this
  We will contact pt for next live derm clinic
  Cc scheduler-book for live derm in 1 week

• Pt notes these get caught on shirt-sometimes get inflamed

• Skin tags-benign
  Primary can snip them off-services not covered by county
New red/brown bump

- Dermatofibroma—often on arms and legs of women
- Banal—reaction to bug bite or trauma
- Resolves in 20 yrs
- Don’t excise

Primary Care Provider:
30 yr old with multiple previous biopsies to rule out melanoma. Here for skin check.
- No recent changes in moles
- No family history of melanoma
- Please see in live derm clinic
- Teledermatology response:
  Agree and will book within 1-2 months

Melanoma

- Melanoma may be INHERITED or occur SPORADICALLY
- 10% of melanomas are of the INHERITED type Familial Atypical Multiple Mole-Melanoma Syndrome (FAMMM)

Ask these questions:
1) Personal or family history of melanoma?
2) History of atypical nevus that has been removed?
3) Presence of new or changing mole—i.e. change in size or color?
<table>
<thead>
<tr>
<th>Risk Factors for Sporadic (Nonhereditary) Melanoma</th>
<th>Clinical Features of FAMMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Numerous normal nevi, some atypical nevi</td>
<td>- Often numerous nevi (30-100+)</td>
</tr>
<tr>
<td>- Sun sensitivity, excessive sun exposure</td>
<td>- Nevi &gt; 6mm in diameter</td>
</tr>
<tr>
<td></td>
<td>- New nevi appear throughout life (after age 30)</td>
</tr>
<tr>
<td></td>
<td>- Nevi in sun-protected areas (buttocks, breasts of females)</td>
</tr>
<tr>
<td></td>
<td>- Family history of atypical nevi and melanoma</td>
</tr>
</tbody>
</table>

**Prevention**
- Self examination/spousal exam for low-risk individuals
- Self examination/spousal exam and regular physician examination (yearly to every several years) for intermediate risk individuals
- Self examination and examination by a dermatologist every 3-12 months for FAMMM kindred

**If not sure:**
- Measure and see pt back in 3-6 months for reevaluation!!

Teledermatology Response:
- Have pt come back-take another picture and let’s compare
• Primary Care Provider:
  On pts back-Sometimes wife squeezes out smelly cheese–like material. Advice?

• Epidermoid cyst-not inflamed. Does not need to be excised unless repeatedly inflamed.
  • Wife should stop squeezing this–could cause cyst contents to be released into surrounding tissue–causing inflammation
  • If pt wants this excised–please send to surgery for excision–may not be covered by insurance

• Primary Care Provider:
  Pt came in with 2 day history of enlarging lesion and increasing pain.
  • Started doxycyline

• Inflamed Epidermoid Cysts
  • Antibiotics–USELESS–this is abscessed–6 papers and metanalysis shows that antibiotics will not help where an I and D should be done
  • If just starting to become inflamed and cyst is small (< 1 cm), can try intralesional Kenalog injection but see them back in few days–you can exacerbate the inflammation
  • This cyst is bigger than 1 cm
  • INCISE and DRAIN and PACK–send to surgery or ER today
  • 6 weeks later, inspect for residual cyst and send pt for excision to surgery
### Keloids
- These are keloids
- Did they come from acne-if so-look for other acneiform lesions and let me know-I can discuss systemic acne treatment so that pt does not get new keloids after every acne breakout.
- Will need intralesional kenalog-will book with derm clinic for monthly injections-book within next two months

### Vitiligo
- Immune system hyperactive
- Thyroid disease (19%) and other autoimmune diseases-screen for thyroid dz every 3 yrs
- Trial of clobetasol oint qd x 3 months; if not working tacrolimus bid x 3 months then leave it alone
- Makeup, counselling

### Alopecia areata
- Non-scarring alopecia-we have no idea why it starts and we don’t have preventive treatment in terms of halting future episodes
- Inject with intralesional kenalog 10mg/cc q month for at least 6 months to see if there is hair regrowth
- For widespread areas :Trying to understand the immune pathway-opremilast and JAK inhibitors

### Pthas actinic keratosis
- Pt has actinic keratosis
- Can I freeze it with liquid nitrogen?
• Yes-2 x 15 sec thaws –appropriate treatment. Please make sure that you have looked at all sun-exposed areas to rule out non-melanoma skin cancers
• We can book pt for exam
• ARE ANY SPOTS BLEEDING?

Teledermatology as part of Dermatology
• Increased efficiency and access
• Total cost of specialty service is less
• Pt outcomes and satisfaction appear to be better
• Over next few days-hope to develop skills to make dermatology a better partnership specialty with primary care!
Common Disorders of the Knee

Carlin Senter, MD
Associate Professor
Primary Care Sports Medicine
UCSF Medicine and Orthopaedics

Disclosures

I have nothing to disclose.

Knee: Top 3 referral diagnoses from primary care IM to ortho (at UCSF in 2011)

1. Osteoarthritis (OA)
2. Anterior knee pain
   - Patellofemoral pain syndrome
   - Chondromalacia patella
   - Patellar tendinopathy
3. Meniscus tear

Objectives

Upon completion of this session, participants should be able to:

1. List 4 exam maneuvers for meniscus tear
2. List the diagnostic criteria for knee OA
3. Identify 5 non operative treatment options for knee OA
4. Identify indications for surgery for patient with meniscus tear
   - Without knee OA
   - With knee OA
5. Generate a differential diagnosis for chronic anterior knee pain
Case #1

25 y/o man with medial-sided pain and swelling of the R knee for 6 weeks since he twisted the knee playing soccer. No locking, no instability.

All of the following tests, if positive, would raise concern for a meniscus tear except...

A. Joint line tenderness
B. Pain when he stands and pivots on the knee
C. Pain when you axially load and rotate the knee
D. Pain when you flex the R knee and extend the R hip with the patient lying on his left side.
E. Pain when he squats

4 tests for meniscus tear

1. Isolated joint line tenderness
2. McMurray
3. Thessaly
4. Squat

Joint line tenderness

Medial: Sensitivity 83%, Specificity 76%
Lateral: Sensitivity 68%, Specificity 97%
(Konan et al. Knee Surg Traumatol Arthrosc. 2009)

Meniscus: McMurray

Sensitivity medial 65%, Specificity medial 93%

Video used with permission from Anthony Luke, MD

Meniscus: Thessaly

Sensitivity 90%, Specificity 98% (Harrison BK et al. CJSM, 2009)
Sensitivity 51-67%, Specificity 38-44% (Snoeker BAM et al. JOSPT, 2015)

Video used with permission from Anthony Luke, MD

Meniscus: squat

Sensitivity 75-77%, Specificity 36-42%
(Snoeker BAM et al. JOSPT, 2015)

Ober’s Test for tight IT Band

Passive hip abduction and extension.
Hip extension ➔ ITB positioned over greater trochanter of femur.
Case #1 Management

- Exclude bucket handle meniscus tear
  - Locked knee, large effusion, acute injury
  - Crutches, non weight bearing, urgent MRI and surgery
  - MRI to evaluate for medial meniscus tear
  - Refer for knee arthroscopy
  - Meniscus repair vs debridement
  - If no bucket handle tear and patient prefers non surgical treatment, also okay to try physical therapy first and monitor.

Case #2

- 65 y/o man with h/o medial meniscus surgery R knee years ago.
  - Moderate medial-sided pain and generalized swelling of the R knee since hiking last week.
  - No locking, no instability, no stiffness > 30 min in AM
  - Exam:
    - Moderate effusion, no warmth
    - Crepitus with range of motion
    - Tenderness of medial joint line and above/below medial joint line on the medial femoral condyle and medial tibial plateau.
    - (-) McMurray, knee feels tight with squat, unable to perform complete squat, unable to perform Thessaly due to pain.
    - No ligamentous laxity

Diagnosis?

A. Medial meniscus tear
B. ACL tear
C. Medial compartment osteoarthritis
D. Gout
E. Septic arthritis
F. Medial meniscus tear and medial compartment osteoarthritis

Clinical criteria for diagnosis of knee OA

Case #2

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- No locking, no instability, no stiffness > 30 min in AM
- Exam:
  - Moderate effusion, no warmth
  - Crepitus with range of motion
  - Tender medial joint line and above/below medial joint line on the medial femoral condyle and medial tibial plateau.
  - (-) McMurray, knee feels tight with squat, unable to perform complete squat, unable to perform Thessaly due to pain.
  - No ligamentous laxity

What do you recommend?

A. Refer for arthroscopic debridement of cartilage and lavage
B. Nonoperative knee OA program
C. Refer for total knee arthroplasty

Interventions

- Control
  - PT: 1 hour/week x 12 weeks
  - Home ex program 2x/day
  - Instruction on ADLS
  - Self management arthritis education reading + videotape
  - Medications (APAP, NSAIDs, hyaluronic acid injections)

- Arthroscopic surgery
  - Irrigation with saline
  - 1 or more of the following:
    - Debridement or excision of degenerative meniscal tears
    - Removal loose bodies, chondral flaps, bone spurs
  - Medical and physical therapy like controls

Corticosteroid injections for knee osteoarthritis

- Anti-inflammatory
- Probably inhibit COX-2 and phospholipase-A2, both inflammatory mediators

Published 22 October 2015.
2-year RCT
- Patients with knee OA (mild-moderate)
- Q3 month triamcinolone or saline knee injection under ultrasound x 2 years
- Annual knee MRI, WOMAC q 3 months

140 randomized patients
- Mean age 58 years
- 54% women
- Sig more cartilage loss in triamcinolone group compared to saline group
- No sig difference in pain between groups

Intra-articular corticosteroid injections: take home points
- Short-term pain relief (6 weeks average)
- Small effect on function
- No evidence for long-term pain relief
- Clinical effect independent of degree of inflammation present
  - Don’t need to restrict injection just to those with effusion
  - Frequency: general practice once every 3-4 months max
  - Concern for cartilage toxicity if given q 3 months x 2 years

Hyaluronic acid injections for knee OA
- No data for 1 brand name over another
- Can provide pain relief for longer than steroid (5-13 weeks)
- Evidence is heterogeneous
- Significant placebo response
- Risk = 1-3% pseudoseptic reaction
- Less likely to benefit
  - > 65 yrs old
  - Severe joint space narrowing
  - “Uncertain” recommendation from OARSI 2014
  - “Cannot recommend” (strength of recommendation = strong) from AAOS 2013

OA: disease modifying treatment?

- Surgical repair of cartilage
  - Efficacious for isolated cartilage lesions
  - Less useful for global cartilage wear in OA
- Injections: some promise, more data needed
  - Platelet rich plasma (PRP)
  - Mesenchymal stem cells


Case #3

60 y/o woman presents with 3 months of medial knee pain, (+) swelling, and instability. No frank locking. Pain is worse with weight bearing. Better with rest, ice, and NSAIDs.

Exam: Neutral knee alignment when standing. Knee is not warm. There is tenderness of the medial joint line + medial femoral condyle + medial tibial plateau. Small effusion. ROM 0-120, limited by pain. (+) crepitus. (+) medial McMurray, medial knee pain with squat and Thessaly tests. No ligamentous laxity.

Diagnosis?

A. Medial meniscus tear
B. ACL tear
C. Medial compartment osteoarthritis
D. Gout
E. Septic arthritis
F. Medial meniscus tear and medial compartment osteoarthritis
What do you recommend?

A. Refer for arthroscopic debridement of cartilage and meniscus
B. Nonoperative knee OA program
C. Refer for total knee arthroplasty

Surgery vs PT for meniscal tear and OA

- Multicenter RCT
- 351 patients with meniscal tear + mild-moderate OA
- Meniscal sx (clicking, popping, catching, giving way, joint line pain, pain with twisting)
- Avg. age 60 years
- 50% men, 50% women
- Primary outcome = change in WOMAC physical-function score between groups at 6 mo

Results


Conclusions

- 30% crossed over from PT to APM at 6 mo
  - These people had WOMACs that didn’t improve until crossover
- No sig difference in adverse events
- PT and APM are reasonable options with similar outcomes for these patients (with allowed cross over if not achieving relief with PT)
- Starting with conservative approach is reasonable

What if this same patient had an isolated degenerative meniscus tear and no clinical signs or symptoms of knee OA?
Degenerative meniscus tear, no OA

- FIDELITY studies suggest no benefit from arthroscopic partial meniscectomy, even with mechanical symptoms (locking/catching), over sham arthroscopic surgery.
- Limitations
  - Definition of degenerative meniscus tear?
  - No radiographic OA but these patients had some mild cartilage wear

Osteoarthritis with meniscus tear

- Degenerative meniscus tear is part of the natural history of osteoarthritis
- Treat as osteoarthritis initially
- Imaging: Start with x-ray. Consider referral vs MRI if exam c/w meniscus tear and not improving with PT
- Could consider arthroscopic meniscus surgery if weight loss, PT, medications, injections not helping or if patient prefers surgical treatment.
Who to refer for knee arthroscopy?

- Younger patients (case #1)
- Traumatic onset of symptoms
- Bucket handle meniscus tears
  - Knee locked due to meniscus blocking joint movement
- Locking (knee stuck, cannot move it) → Loose body
- Not improving despite conservative treatment
- Patient prefers surgery to conservative treatment

Case #4

40 y/o woman with sharp anterior knee pain x 1 month. Might have some swelling. No locking but the knee is popping. Feels unstable when walking down stairs. Pain worse up/down stairs. Painless when gets up from sitting. Exercise: started a walking program for New Year’s resolution, walking more hills than usual. No squats/lunges. Doesn’t wear orthotics.

Ddx subacute-chronic anterior knee pain

1. Patellofemoral pain syndrome
2. Patellar chondromalacia
3. Osteochondral lesion
4. Osteoarthritis of patellofemoral joint
5. Patellar or quadriceps tendinitis or tendinopathy
6. Pes anserine bursitis

Case #4: Inspection

[Image of labeled anatomical diagram of the knee]
Patellofemoral pain syndrome: miserable malalignment syndrome

- Femoral anteversion (inward rotation of femur)
- Squinting patella (inward patellar rotation)
- Patella alta
- Increased Q-angle
- Excessive outward tibial rotation


Case #4: Other tests identify tightness and weakness

- Ober (too tight?)
- Hip abduction strength (weak?)
- One-legged standing squat (weak? Pain?)

Ober's Test for tight IT Band

*Passive hip abduction and extension.*

*Hip extension ➔ ITB positioned over greater trochanter of femur.*

http://www.youtube.com/watch?v=9ly-QrcuGno&feature=player_detailpage

Hip abduction strength

http://www.youtube.com/watch?v=9ly-QrcuGno&feature=player_detailpage
One-legged standing squat

- Patient standing on unaffected leg
- Do 3 slow 1-legged squats
- Watch for stability, valgus angulation of knee, ask about pain
- Switch and perform on affected leg
- Sign of weak hip abductors, weak core
- Can bring out pain of patellofemoral pain

Case #4: Physical exam

- Valgus knees while standing
- No effusion
- Tender lateral patellar facet
- Nontender joint lines
- ROM 0-135
- Meniscus testing (-)
- No ligamentous laxity
- (+) Ober bilaterally
- 4/5 hip abductor strength bilaterally
- Unstable 1-legged squat with valgus knee angulation

http://www.kneeguru.co.uk/KNEEnotes/node/763
Case #4 diagnosis

A. Patellofemoral pain syndrome
B. Patellar chondromalacia
C. Osteochondral lesion
D. Osteoarthritis

Case #4 treatment

- Physical therapy rx
  - Strengthen hip abductors
  - Strengthen quadriceps
  - Stretch ITB, quads, hamstrings
- Correct alignment: consider OTC orthotics with arch support if pes planus
- Activity: avoid running, squats, lunges, stair-running, downhill hiking until improved.
- If not improved with above → x-rays and if those normal then MRI (or refer to sports medicine)

Take home points

1. 4 tests for meniscus tear
2. Joint line tenderness
3. McMurray
4. Squat
5. Thessaly

Take home points

2. Diagnostic criteria for knee OA

<table>
<thead>
<tr>
<th>Clinical and laboratory</th>
<th>Clinical and radiographic</th>
<th>Clinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee pain at least 3 of 6</td>
<td>Knee pain at least 3 of 6</td>
<td>Knee pain at least 3 of 6</td>
<td>Knee pain at least 3 of 6</td>
</tr>
<tr>
<td>Age ≥ 50 yrs</td>
<td>Age ≥ 50 yrs</td>
<td>Age ≥ 50 yrs</td>
<td>Age ≥ 50 yrs</td>
</tr>
<tr>
<td>Meniscal tear</td>
<td>Meniscal tear</td>
<td>Meniscal tear</td>
<td>Meniscal tear</td>
</tr>
<tr>
<td>Chondrolysis</td>
<td>Chondrolysis</td>
<td>Chondrolysis</td>
<td>Chondrolysis</td>
</tr>
<tr>
<td>No tear</td>
<td>No tear</td>
<td>No tear</td>
<td>No tear</td>
</tr>
<tr>
<td>MRI</td>
<td>MRI</td>
<td>MRI</td>
<td>MRI</td>
</tr>
</tbody>
</table>

- MRI or arthroscopic confirmation with/or magnetic resonance imaging (MRI) vs. Meniscal tear.
- Love the fluid signs of OA. Other imaging on order based on clinic. (Latto’s)
- Alternative is the diagnosis might be 4 of 6, which is MRI sensitive and MRI specific.
Take home points

3. 5 options for non operative treatment for knee OA
   • Weight loss
   • Acetaminophen
   • NSAIDs: oral or topical
   • Cane
   • Corticosteroid injection

4. Identify indications for surgery for patient with meniscus tear
   • Without knee OA
     – Degenerative tear → try non operative treatment first
     – Acute tear → refer for surgical consult
     – Bucket handle tear → urgent MRI, surgical consult, NWB
   • With knee OA → non operative treatment first

Take home points

5. Differential diagnosis for anterior knee pain
   • Patellofemoral pain syndrome
   • Patellofemoral chondromalacia
   • Osteochondral lesion
   • Osteoarthritis of patellofemoral joint
   • Patellar or quadriceps tendinitis or tendinopathy

Thank you!

Carlin Senter, MD
Carlin.Senter@ucsf.edu
Management of Diabetes Mellitus: Which Drugs for Which Patients?

Robert B. Baron MD MS
Professor and Associate Dean
UCSF School of Medicine
baron@medicine.ucsf.edu

Disclosure
No relevant financial relationships

Presentation Outline
- Updates in prevention of complications (other than glycemic control)
- Controversies in glycemic control
- Updates/controversies with diabetes medications

Screening for Diabetes 2017
- BMI ≥25 (or ≥23 in Asian Americans) plus other risk factors
  - Inactivity
  - High-risk ethnicity
  - PCOS
  - Acanthosis nigricans
  - Gestational DM
  - Hx CVD
  - HTN
  - Age 45
  - Repeat Q3 years

ADA Diabetes Care, 2017
Management of Diabetes

USPSTF Screening for Diabetes 2015

- Screen as part of cardiovascular risk assessment in adults 40 - 70 who are overweight or obese

USPSTF 2015

Diagnosis of Diabetes 2017

- A1C ≥ 6.5%
- FPG ≥ 126 mg/dl (7.0 mmol/L)
- 2-h plasma glucose ≥ 200 during OGTT
- Symptoms and random plasma glucose ≥ 200 mg/dl (11.1 mmol/L)
- Need two separate measurements

ADA Diabetes Care, 2017

Diagnosis of Pre-Diabetes 2017

- A1C 5.7 – 6.4%
- FPG 100 - 125 mg/dl (5.6mmol/L - 6.9 mmol/L)
- 2-h plasma glucose 140 mg/dl – 199 mg/dl during OGTT (7.8mmol/L – 11.0 mmol/L)

ADA Diabetes Care, 2017

2017 Practice Guidelines: ASA

- Use in all patients with DM and CVD
- ASA: For primary prevention - only use in those at increased CV risk (10 year risk >10%).
  - Typically men over 50, women over 60 with other risk factors.

ADA Diabetes Care, 2017
Management of Diabetes

2017 Practice Guidelines: HTN and Tobacco
- BP: Goal < 140 and <90
  - But not <130 (no evidence) and not <70 (higher mortality)
  - Still prefer ACEI or ARB
- Don’t forget tobacco.
  - Recommend against e-cigarettes

2017 Practice Guidelines: Lipids
- Mostly consistent with ACC/AHA
- CVD: High intensity statin
- 40-75: moderate or high intensity statin
- Differences with ACC/AHA
  - <40 with other risks: consider statin
  - >75: consider statin

2017 Practice Guidelines: Bariatric Surgery
- Bariatric (Metabolic) Surgery should be recommended for adults with BMI > 35 and type 2 DM, especially if diabetes and comorbidities are difficult to control with lifestyle and meds
- Bariatric (Metabolic) Surgery should be considered for adults with BMI < 35 and type 2 DM, especially if diabetes and comorbidities are difficult to control with lifestyle and meds

Case 1
74 year old woman with type 2 diabetes, hypertension, coronary heart disease (s/p MI in 2010), GERD, and osteoarthritis.
Meds: Metformin, glipizide, aspirin, lisinopril, metoprolol, atorvastatin, omeprazole, tylenol, topical diclofenac
Exam: BP 132/80, BMI 29 kg/m²
Normal exam
Case 1
Her glycemic goal should be:
1. HbA1c <6.5%
2. HbA1c <7.0%
3. HbA1c <7.5%
4. HbA1c <8.0%
5. HbA1c <9.0%

Glycemic Control Update
- 3 important newer trials
  - ADVANCE
  - ACCORD
  - VA Diabetes Trial

ACCORD Trial
- NIH RCT in DM 2, 10,251 patients, known CVD or risk factors, mean A1c 8.1%
- Intensive vs. standard BP (120 v. 140)
- Lipid control (statins v. statins + fibrates)
- Normalization v. standard BS control (A1c 6 v. 7-7.9)
- Outcomes: CV events. Also microvascular events, quality of life, others

ACCORD trial
<table>
<thead>
<tr>
<th></th>
<th>Intensive n=5,128</th>
<th>Standard n=5,123</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c achieved:</td>
<td>6.5%</td>
<td>7.5%</td>
<td></td>
</tr>
<tr>
<td>1* outcome:</td>
<td>352</td>
<td>371</td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>5.0%</td>
<td>3.1%</td>
<td>1.22 (1.01-1.46)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>2.6%</td>
<td>1.8%</td>
<td>1.35 (1.04-1.76)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10.5%</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Wt. gain&gt;10 kg</td>
<td>27.8%</td>
<td>14.1%</td>
<td></td>
</tr>
</tbody>
</table>
Management of Diabetes

**ACCORD Trial**

<table>
<thead>
<tr>
<th>Standard</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td></td>
</tr>
<tr>
<td>203</td>
<td>257</td>
</tr>
<tr>
<td>11/1000/y</td>
<td>14/1000/y</td>
</tr>
</tbody>
</table>

Number Needed to Harm: 333

February 2008 (after 3.5 years): NIH stops this arm of study

---

**Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials**

- **Study**
  - UKPDS
  - DCCT / EDIC*
  - ACCORD
  - ADVANCE
  - VADT

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>←</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
</tbody>
</table>

---

**Glycemic Control Summary**

- No consistent evidence that tight glycemic control reduces risk of CVD in DM 2
- Possible subgroups with benefit:
  - shorter diabetes duration, no CVD
- Strong evidence of decrease in microvascular disease outcomes with more intensive glucose control
- More hypoglycemia and weight gain with more intensive regimens

---

**2017 ADA Practice Guidelines: Glucose Control**

- Goal A1C ≤7 for most
- Goal A1C <6.5 for some: short duration, long life expectancy, and no CVD
- Goal less stringent (<8) for history of hypoglycemia, limited life expectancy, advanced micro or macrovascular complications, extensive comorbid conditions, and longstanding DM in whom the goal is difficult to achieve.
Glycemic Control in Older Adults

- For majority of adults older than 65, the harms of HgA1c <7.5 or >9 are likely to outweigh the benefits.
- Optimal targets depend on patient factors, meds, life expectancy, and patient preferences.
- For example: if only need metformin, lower target may be preferred; if need insulin or finger sticks a higher target may be preferred.


2016 AACE Practice Guidelines: Glucose Control

- A1C ≤6.5 is optimal if it can be achieved in a safe and affordable manner.
- Higher targets (>6.5) may be appropriate for certain individuals (patients with concurrent serious illness and risk of hypoglycemia) and may change over time

Case 1

Her glycemic goal should be:

1. HbA1c <6.5%
2. HbA1c <7.0%
3. HbA1c <7.5%
4. HbA1c <8.0%
5. HbA1c <9.0%
Management of Diabetes

Case 2: 48 yo woman with DM, BMI 33, on diet and exercise and max dose metformin. HbA1C is now 8.5. Your next best step is:

1. Continue current therapy
2. Begin a sulfonylurea
3. Begin pioglitizone
4. Begin NPH insulin or long-acting insulin analogue
5. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™), saxagliptin (Onglyza™)
6. Begin canagliflozin (Invokana™), dapaglifozin (Farxiga™), empaglifozin (Jardiance™)

**Generic Oral Hypoglycemic Slide**

---

**Metformin**

- Lowers A1C 1.5-2%
- Weight loss (0-2 kg)
- Lowers triglyceride and LDL; increases HDL
- No hypoglycemia
- No self monitoring
- Inexpensive
- Disadvantages: GI side effects, decreased B12 absorption, (very low) risk of lactic acidosis

**Thiazolidinediones (TZD)**

- Lowers A1C 0.4-1.5%
- No hypoglycemia when used alone
- Other risks: osteoporosis, bladder cancer with pioglitazone, weight gain edema
- FDA lifted restrictions on rosiglitazone in November 2013
- No hypoglycemia
- No self monitoring
- Preference for pioglitazone
Management of Diabetes

Oral Agent “Failure” Why does this occur?

- Changing HbA1c goals
- Compliance, side effects
- Wrong diagnosis (LADA—latent autoimmune diabetes in adults 10%)
- Stress, diabetogenic medications
- Postprandial hyperglycemia
- Natural progression of the disease

Natural History of Type 2 Diabetes

Insulin

Introduction of insulin
- Bedtime
- Intermediate/Long-acting insulins
  - NPH, glargine, levmir
  - 10 units
- Self-monitoring of blood glucose
  (hypoglycemia education)
**When to go to > 1 shot per day**
- HgA1c >7
- Glucose in AM at goal but glucose before dinner >140

**Options**
- Add premeal lispro/aspart
- Add bid premixed insulin – 70/30, 75/25

**Questions**
- Continue metformin
- ? Sulfonylurea, ? Thiazolidinedione (mostly not)

---

**Function of Insulin in Regimens**

**Basal insulin**

**Meal coverage (carbohydrates)**

**Correction of high blood sugar**

---

**INCRETINS**

Gut factors that promote insulin secretion in response to nutrients

Major incretins: GLP-1, CCK, GIP

---

**Oral Glucose Promotes More Insulin Release than IV Glucose - Indicating a Role for Incretins**
Management of Diabetes

Incretin Drugs

GLP Agonists
- Exenatide (2005/2012)
- Liraglutide (2010)
- Dulaglutide (2014)
- Albiglutide (2014)
- Taspoglutide
- Lixisenatide
- Semaglutide

DPP IV Inhibitors
- Sitagliptin (2006)
- Saxagliptin (2009)
- Alogliptin (2013)
- Linagliptin (2011)
- Vildagliptin
- Dutagliptin
- Metagliptin
- Gemigliptin

A1C (%) Effect (change from baseline)

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>5 mcg exenatide BID</th>
<th>10 mcg exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>0.1</td>
<td>-0.4</td>
<td>-0.8</td>
</tr>
<tr>
<td>SFU</td>
<td>0.1</td>
<td>-0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>MET+SFU</td>
<td>0.2</td>
<td>-0.6</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

Changes in A1C from baseline vs placebo statistically significant

Weight (change from baseline) & Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>5 mcg exenatide BID</th>
<th>10 mcg exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>-1.4</td>
<td>-3.1</td>
<td>-4.2</td>
</tr>
<tr>
<td>SFU</td>
<td>5.3</td>
<td>4.5</td>
<td>35.7</td>
</tr>
<tr>
<td>MET + SFU</td>
<td>3.3</td>
<td>14.4</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Open-label extension study to 90 weeks: persistence in weight loss and ↓A1C.
Management of Diabetes

Side Effects

GI
- Nausea (44% vs 18% with placebo); incidence lessens over time; 3% dropout rate due to nausea
- Vomiting (13% vs 4%)
- Diarrhea (13% vs 6%)

Headache (9% vs 6%)
Hypoglycemia (see previous slide)

Improvements in HbA1C With Initial Co-administration of Sitagliptin and Metformin

<table>
<thead>
<tr>
<th></th>
<th>HbA1C (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-2.5</td>
</tr>
<tr>
<td>Sit 100 mg OD</td>
<td>-2.0</td>
</tr>
<tr>
<td>Met 500 mg BID</td>
<td>-2.0</td>
</tr>
<tr>
<td>Sit 100 mg OD + Met 500 mg BID</td>
<td>-1.5</td>
</tr>
<tr>
<td>Met 500 mg BID</td>
<td>-1.5</td>
</tr>
<tr>
<td>Sit 100 mg OD + Met 1000 mg BID</td>
<td>-1.0</td>
</tr>
<tr>
<td>Met 1000 mg BID</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

Mean Baseline HbA1C = 8.8%
N=1091

* Placebo-subtracted LS mean change from baseline at Week 24.
Sita=sitagliptin; Met=metformin.

Sitagliptin – Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>n = 443</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>23 (5.2)</td>
</tr>
<tr>
<td>+ pioglitazone</td>
<td>n = 175</td>
</tr>
<tr>
<td>Upper resp. infection</td>
<td>11 (6.3)</td>
</tr>
</tbody>
</table>

Small increase in neutrophil count
No nausea or vomiting
No weight loss

Two Newer Studies of DPP-4 Meds

- Saxagliptin not inferior (nor superior) to placebo for CV outcomes.
  - But statistically significant increase in CHF admissions
  - A1C 0.2% lower

- Sitagliptin not inferior (nor superior) to placebo for CV outcomes.
  - No increase in CHF
  - A1C 0.3% lower

Sax, NEJM 2013; Green, NEJM 2015
Management of Diabetes

CV outcomes with Liraglutide
- RCT, 9340 patients, high CV risk, 3.8 years
  - A1C 0.2% lower
- Fewer events with liraglutide: 13.0% vs. 14.9%
- Few deaths with liraglutide: 8.2% vs. 9.6%

Marso SP, NEJM 2016

SGLT2 Inhibitors
- Sodium-glucose cotransporter 2 Inhibitors
  - Inhibit glucose reabsorption in renal proximal tubule (Canagliflozin, Dapagliflozin, Empagliflozin)
  - Potential advantages
    - Weight loss (2.5-4kg), low risk of hypoglycemia, reduced BP, lowers A1C about 1%
  - Potential disadvantages
    - Polyuria, electrolyte disorders, UTI, fungal genital infections, syncope, increased Cr, expensive

Empagliflozin, CV Outcomes, and Mortality
- RCT 7020 patients, high risk CV disease, 3.1 years
- Minimal changes in A1C (0.24% lower)
- Reduced combined CV outcome (10.5% vs. 12.1%) and reduced CV (3.7% vs. 5.9%) and all cause mortality (5.7% vs. 8.3%)
  - No difference in stroke or MI
  - No difference when secondary outcomes (unstable angina) included
  - Increased genital infections


Natural History of Type 2 Diabetes
Pharmacological Therapy for Type 2 Diabetes

- Metformin is the preferred agent
- In patients with new DM2, marked symptoms, or marked BS or A1C, consider initiating insulin (with or without other agents).
- If monotherapy not to goal, add second oral agent, GLP-1 agonist, or basal insulin

A patient-centered approach should guide selection: efficacy, cost, side effects, weight, comorbidities, hypoglycemia, and patient preference.

Insulin therapy is eventually indicated for many patients with DM2

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1C</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1-2%</td>
<td>$4</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1-2%</td>
<td>$5</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.5-1.5%</td>
<td>$20</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>0.5-0.8%</td>
<td>$320</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5-1.5%</td>
<td>$450</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>0.5-1.5%</td>
<td>$330</td>
</tr>
<tr>
<td>Acarbose</td>
<td>0.5-0.8%</td>
<td>$30</td>
</tr>
<tr>
<td>Test strips</td>
<td>0.4% (?)</td>
<td>$20-$60</td>
</tr>
<tr>
<td>Glargine 45 U</td>
<td></td>
<td>$150</td>
</tr>
<tr>
<td>YMCA</td>
<td></td>
<td>$65</td>
</tr>
</tbody>
</table>

ADA Diabetes Care, 2016
Case 2: 48 yo woman with DM, BMI 33, on diet and exercise and max dose metformin. HbA1C is now 8.5. Your next best step is:

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6. Begin canagliflozin (Invokana™), dapaglifozin (Farxiga™), empaglifozin (Jardiance™)

Conclusions

- Tight glycemic control not effective in lowering total mortality or CV mortality (but is effective at preventing microvascular complications)
- Many newer diabetes agents available, all with some side effects and higher costs...few with hard outcome data. (But hard outcome data coming...)

Conclusions

- Glucose control may be more important early in diabetes
- Good BP, lipid control, smoking cessation, and aspirin use is important throughout the course of diabetes

Conclusions

The best way to treat DM in the long term...

...is to not develop it in the first place.
Promoting Functional Independence and Activity in Older Adults

Anna H. Chodos, MD, MPH
Assistant Professor
Division of Geriatrics
UCSF

What is mobility?
Mobility is broadly defined as the ability to move oneself...within community environments that expand from one’s home, to the neighborhood, and to regions beyond.

“Optimal mobility, defined simply as being able to safely and reliably go where you want to go, when you want to go, and how you want to get there, is a key component of healthy aging.”

Mobility Disability

The gap between an individual’s physical ability and environmental challenges.

- Ability, examples: strength, balance, sensation
- Environment, examples: uneven surface, hill, indoor vs. outdoor

How do we measure Mobility?

For health or physical reasons, do you have difficulty climbing up 10 steps or walking one-quarter of a mile?

Because of underlying health or physical reasons, have you modified the way you climb 10 steps or walk a quarter of a mile?

Measuring mobility

Neurologic exam
- Gait speed = 10 feet at a comfortable pace ≤3 sec
- Balance

Short Physical Performance Battery
- Chair stands
- Semitandem and tandem stand
- 8 ft. walk

Mobility Limitations are Common

Of adults ≥65 NOT in long term care, 27% have “difficulty walking or climbing stairs”

CDC report, July 31, 2015, 64(29):777-783.
Risk factors for Mobility Impairment

- Older age
- Low physical activity
- Obesity
- Strength or balance impairment
- Chronic disease burden (example, diabetes, heart failure, arthritis)


Mobility Disability and Health

Physical:
- An early predictor of physical disability and mortality (2-3x risk)
- Linked to lower health status, quality of life

Psychological and Social:
- Linked to depression, isolation, loneliness

Increase risk of nursing home placement.

JAGS 2000;48:493-498

Requirements to maintain mobility

- Sensation  ◦ Hearing, vision, feeling
- Balance
- Strength
- Flexibility

Early signs of mobility disability

Report of difficulty with walking
- First signs typically walking longer distances or running

Early: changes in method, frequency, or time used in a mobility task

Activity and Older Adults

Physical activity decrease with age
Decreasing physiologic capacity in many organ systems with age

Activity is Possible and Beneficial at Any Ability Level

Benefits of Activity in Older Adults

Improved disease management
Improved brain health
Prevention of disability and loss of independence
Improved quality of life
Lower mortality risk
Mobility and Activity are Linked

Low levels of physical activity are linked to mobility limitations

- In 12 years, about ½ of adults over 70 developed walking disability in one study.
- Lower physical activity was linked to ~40% increased chance of walking disability.

*walking disability= needing help walking ¼ mile

Recommendations: health.gov

Physical Activity Guidelines for ALL ADULTS
Avoid inactivity
At least 150 minutes of moderate-intensity/week OR 75 minutes of vigorous-intensity/week
Muscle-strengthening 2 days or more/week

Recommendations: health.gov

Physical Activity Guidelines for OLDER ADULTS
Do it as abilities and conditions allow
Exercises that maintain or improve balance if at risk of falling
Determine level of effort based on level of fitness
Understand how any chronic conditions might affect ability to do regular activity

https://health.gov/paguidelines/guidelines/chapter5.aspx
Background: function

• Physiologic age incorporates many factors
  – Age
  – Genetics (family history)
  – Lifestyle factors (smoking, alcohol, diet, fitness)
  – Comorbidities
  – Functional loss

• Physiologic age is more important than chronologic age in determining health outcomes and prognosis

Assessing Function

Activities of Daily Living
- Bathing
- Dressing
- Toileting
- Transferring
- Feeding

Instrumental Activities of Daily Living
- Driving/transportation
- Using phone
- Shopping for food
- Finances
- Cooking
- Housework
- Taking meds

Needs 24 hour care
Needs help intermittently

Gill TM, Assessment of Function and Disability in Longitudinal Studies. JAGS 2010;58(Suppl 2):S308-S312


“The defining feature of geriatric medicine is the intense focus on the preservation and restoration of function.”

Gill TM, Assessment of Function and Disability in Longitudinal Studies. JAGS 2010;58(Suppl 2):S308-S312
**Risk Factors: Functional Decline**

- Environment: Social, Financial, Living Supports
- Genes
- Medications: Appropriate, Inappropriate
- Age-related changes
- Hospitalizations, Medical Conditions, Falls

**Lower function associated with shorter life expectancy**

<table>
<thead>
<tr>
<th>Age</th>
<th>Independent</th>
<th>Mobility disabled</th>
<th>ADL disabled</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>16.7</td>
<td>15.7</td>
<td>11.5</td>
</tr>
<tr>
<td>85</td>
<td>8</td>
<td>6.9</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*Mobility disabled = inability to walk half a mile and/or walk up and down stairs to the second floor without help.*


**Hospitalization-Associated Disability**

> 1/3 of older patients are discharged with worse functional status than baseline

1/2 of these patients acquire their deficits during their hospitalization

Covinsky KE et al. JAGS 2003;51:451-58

**Slippery slope**

Covinsky KE et al. JAGS 2003;51:451-58
Impact of functional disability

- Worse function with hospitalization
- Longer hospital stays
- Higher rate of institutionalization
- Higher risk for readmission
- Higher mortality rate

Preventing Functional Decline

- Disease-specific health promotion
- Individualized home assessment and rehabilitation plan
- Preventing falls
- Interventions during hospitalization
  - 50% of new ADL disability is acquired during hospitalization
  - Hospital at home, Acute Care for Elders units

Sensory Function

- Hearing impairment
  - 50% of 65+ have hearing impairment
  - Assoc with falls, social isolation, cognitive impairment
  - Whisper test
- Vision impairment
  - At least 1/5 of 60+ have some vision loss
  - Assoc with falls, social isolation, cognitive impairment, reduced QOL
  - Snellen chart

Take away: Ask about function

<table>
<thead>
<tr>
<th>ADL/IADLs</th>
<th>Can you get out of bed, dress, prepare meals, and shop on your own without help?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing</td>
<td>Do you have difficulty hearing? Do you stay at home rather than be with family or friends because of hearing difficulty? Do others comment to you about your hearing?</td>
</tr>
<tr>
<td>Vision</td>
<td>Any changes in your vision? Do you wear glasses? Do you need a new prescription? Any trouble driving due to vision?</td>
</tr>
<tr>
<td>Gait</td>
<td>Timed up and go (rise from seat, walk 10ft, turn around, return to seat)</td>
</tr>
<tr>
<td>Cognition</td>
<td>Mini-cog: 3 item re-call and Clock Draw Test</td>
</tr>
</tbody>
</table>
Definition of falls

Unintentionally ending up on the ground or other lower level

Not because of:
- Fainting
- Sudden illness (e.g. stroke)
- Act of man (e.g. car crash)
- Act of nature (e.g. earthquake)

Falls are common

25-30% of adults over age 65 fall each year

Half of adults over age 80 fall each year

JAMA. 2010 Jan 20; 303(3): 258–266.
CDC Fall Injury Data, 2015.

• Every 11 seconds an older adult is in the ER because of a fall
• Every 19 minutes an older adult DIES because of a fall

NCOA: Fall Prevention, Get the Facts
Falls are a critical medical event

A top ten causes of death for adults 65+

10% of falls → major injury
- Fractures
- Brain trauma
- Hospitalization

JAMA. 2010 Jan 20; 303(3): 258–266.

Falls take away what matters most

Fallers experience decline in function (~35%)
Decrease in physical and social activity (~15%)
Fear of falling leads to social isolation, depression and further decline
3-10x increases risk of needing a nursing home not related to rehabilitation

NEJM 1997;337:1279-1284

Falls are Multifactorial

**Intrinsic Factors**
- Medical conditions
- Vision and hearing impairments
- Age, age-related changes
- Prior fall

**Extrinsic Factors**
- Medications
- Improper use of assistive devices
- Environment

**FALLS**

Fall Risk

People at highest risk for falls
- Have fallen before
- Older
- Have problems with strength, balance, mobility, vision
- Use certain medications (including alcohol/drugs) and 4+ medications

http://nihseniorhealth.gov/falls/causesandriskfactors/01.html
Medications and Fall Risk

- Benzodiazepines – 60% incr risk
- Non-benzodiazepine hypnotics
- Tricyclic antidepressants
- Anticholinergics
- Anticonvulsants
- Antihypertensives

More risk factors =
Greater chance of falling in 1 yr

What can we do?

- Environmental modifications
- Strength and balance exercises
- Assess and correct vision and hearing impairments
- Rule out low blood pressure or drops in blood pressure with standing
- Minimize medications
- Vitamin D especially if “high risk”

Vitamin D

Vitamin D may reduce falls

Meta-analysis of double blind RCTs (2004) suggested Vitamin D decreases falls

More recent studies less convincing

Doses <800 IU do not appear to be effective

Low risk of harm of 800 IU daily and possible benefit in falls and injury reduction in high risk, so Vitamin D is recommended by USPSTF

BMJ 2009; 339: 63692
**Functional Assessment and Goal Setting**

**Function vs Fun**

| Get out of bed | Get up and dance! |
| Get up from a chair | Get to a cross court shot in tennis |
| Get up from the floor | |
| Get out and go shopping | |

**Motivation: Make it Personal**

- Travel goals
- Enjoy time with friends and family
- Be Independent
- Competition
- Health goals
- Be able to care for loved ones

**Mobility Research in the News**

Health education vs physical activity

- Activity: 150 min/week of walking, plus strength, flexibility & balance
- Able to walk 400 m (~1/4 mile)
Assessing Gait Speed

5 meter walk
Almost 5.5 yards
16.4 feet
Comfortable pace
Average time of 3 trials

Walking speed Linked to Independence

Walking speed Linked to Independence

Walking speed
metres per second (m/s)

Dependent in ADLs & IADLs
Independent in ADLs
More likely to be hospitalized
Less likely to be hospitalized
Need intervention to reduce falls risk
Less likely to have adverse event

D/C: D/C to home more likely
Household Walker
Limited Community Ambulator
Community Ambulator
Cross Street

Goals for Gait Speed

If walking speed is not normal, a gain of 0.1 m/s predicts well-being.
Purser (2005), Hardy, Perera (2007)

Increased speed
Consistent trials
Varied environments
Assessing Functional Mobility

Standard test with multiple actions

Timed Up & Go: TUG

Used to assess:
- Gait
- Memory
- Speed
- Accuracy
- Safety
- Fall Risk

TUG: Timed Up & Go

Start: seated comfortably
Stand up
Walk at a comfortable pace: 3 meters
Turn around and return to chair
Sit down

Ok to use assistive device
Score recorded in seconds

Other Assessments

Sit to Stand
- Time for 5x to complete movement
- Repetitions completed in 30 sec

Stand up from Cross-Legged position on floor
- Timed
- Without Hands

Strength: Lower Extremities

HIPS
- Squat
- Sit to stand
- Walk stairs
- Sideways walk
- Sideways kicks
- Bridges

ANKLES
- Calf raise
- Toe Tap
- Walk on balls of feet
- Walk on heels
- Sideways walk
Flexibility Goals

Hips
- Knee to chest (flexion)
- Standing extension stretch

Knees
- Prone knee bend with strap
- Knee to chest

Ankles:
- Dorsiflexion
- Calf stretch
- Squat with heel down
- Step down
- Plantarflexion
- Toe point

Fear of Falling

Independent risk factor for falls

Education
- Have a plan to prevent falls
- Recognize when situations deviate

Exercise for Confidence
- Physical training
- Practice, practice, practice

Assessing Fear of Falls

Activities-Specific Balance Confidence Scale (ABC)
Measures over and under confidence
Identifies
- Safety Risk
- Risk of Decreased Mobility

ABC Assessment

Sample Items:
- Walk around the house
- Walk down stairs
- Pick up item from the floor
- Reach for something on tip toes
- In & out of car
- Getting bumped while walking
- Escalator holding rail or holding parcels
Assessing Other Factors

<table>
<thead>
<tr>
<th>Vision</th>
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<tbody>
<tr>
<td>Pain</td>
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<td>Environment</td>
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<td>Nutrition</td>
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<td>Community</td>
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<tr>
<td>Medications</td>
<td>Support</td>
</tr>
</tbody>
</table>

Making an Activity Plan

GETTING STARTED

What issues do you feel you need help with to your activity and mobility goals? (For example, vision improvement, pain control, etc)

Making an Activity Plan

What is 1 shortterm (1-2 weeks) goal around incorporating or increasing activity into your life? (For example, walk 30 more min/week, etc.)

What is 1 longterm (3-6 months) goal around incorporating or increasing activity into your life? (For example, be able to dance at my niece’s wedding in 4 months, etc)

Recommendations for Activity

Health.gov
https://health.gov/paguidelines/
NIH Senior Health
https://nhseniorhealth.gov/exerciseforolderadults/healthbenefits/01.html
NIA Go 4 Life
https://go4life.nia.nih.gov/
Resources for Falls Prevention


Optimize Aging Collaborative at UCSF - Geriatric Workforce Enhancement Program

Resources for Falls Prevention

CDC: http://www.cdc.gov/steadi/patient.html

Thank you
Lowen Cattolico, PT
Helen Kao, MD

For reference: Normal Gait Speeds
For Community Dwelling Adults from Lusardi 2003

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Group</th>
<th>Mean (m/s)</th>
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<td></td>
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<td>Overall</td>
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For reference: Timed Up & Go

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<th>n</th>
<th>Mean</th>
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<td>9</td>
<td>2</td>
<td>8-10</td>
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<td>80-89</td>
<td>Male</td>
<td>8</td>
<td>10</td>
<td>1</td>
<td>9.11</td>
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<tr>
<td></td>
<td>Female</td>
<td>15</td>
<td>11</td>
<td>3</td>
<td>9.12</td>
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</table>
Mastering the Musculoskeletal Exam
UCSF Essentials of Primary Care
August 8, 2017
Carlin Senter, M.D.
Henry Crevensten, M.D.

WE HAVE NOTHING TO DISCLOSE

Outline

• Knee exam
• Shoulder exam

Knee Anatomy
The quadriceps muscles extend the knee

The quadriceps muscles merge to form the quadriceps tendon...

The hamstrings flex the knee

Pes anserine bursa

http://thefitcoach.wordpress.com/2012/04/07/267/

http://scientia.wikispaces.com/Thigh+and+Leg+-+Lecture+Notes

http://meded.ucsd.edu/clinicalmed/joints.htm
There are 4 main ligaments in the knee

Meniscus

Knee exam

Musculoskeletal work-up

- History
- Inspection
- Palpation
- Range of motion
- Other Tests
### Common Causes of Knee Pain by Location of Symptoms

- **Anterior:**
  - Patellofemoral syndrome
  - Quadriceps tendinitis
  - Patellar tendinitis

- **Lateral:**
  - Lateral jointline: meniscus tear or OA
  - IT band syndrome
  - LCL sprain (rare)
  - Fibular head: fracture (rare)

- **Medial:**
  - Medial joint-line: meniscus tear or OA
  - MCL sprain
  - Pes anserine bursitis

- **Posterior:**
  - Hamstring tendinitis
  - Gastrocnemius strain
  - OA, meniscus tears, effusion, popliteal cyst….

### Diagnosis of Knee Osteoarthritis

#### Table 8: Criteria for classification of osteoarthritis (OA) of the knee

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Clinical and Laboratory</th>
<th>Clinical and radiographic</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Knee pain</td>
<td>Knee pain + at least 2 of 3:</td>
<td>Knee pain + at least 2 of 3:</td>
<td>Knee pain + at least 2 of 3:</td>
</tr>
<tr>
<td>Age ≥ 30 years</td>
<td>Age ≥ 30 years</td>
<td>Age ≥ 30 years</td>
<td>Age ≥ 30 years</td>
</tr>
<tr>
<td>SFMOL *</td>
<td>SFMOL *</td>
<td>SFMOL *</td>
<td>SFMOL *</td>
</tr>
<tr>
<td>Knee effusion</td>
<td>Knee effusion</td>
<td>Knee effusion</td>
<td>Knee effusion</td>
</tr>
<tr>
<td>Cartilage loss</td>
<td>Cartilage loss</td>
<td>Cartilage loss</td>
<td>Cartilage loss</td>
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<tr>
<td>Bone abnormalities</td>
<td>Bone abnormalities</td>
<td>Bone abnormalities</td>
<td>Bone abnormalities</td>
</tr>
<tr>
<td>OA</td>
<td>OA</td>
<td>OA</td>
<td>OA</td>
</tr>
</tbody>
</table>

* SFMOL = synovitis - effusion - malalignment - OA

**References:**

Palpation of patella - supine

Ballottement

Palpation of patellar facet

Knee range of motion

• ROM: normal 0-135
  – Determine if knee is locking or if ROM is limited due to effusion
  – Locking: think bucket handle meniscus.
    • Urgent x-rays, MRI
    • Urgent referral to sports surgeon for arthroscopy

Other Tests: Lachman to evaluate ACL

Sensitivity 75-100% Specificity 95-100%

PCL: Posterior Drawer

MCL and LCL

MCL and LCL grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Injury</th>
<th>Translation compared to unaffected side</th>
<th>Patient response</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Strain</td>
<td>Minimal laxity, firm endpoint</td>
<td>Pain</td>
</tr>
<tr>
<td>II</td>
<td>Partial tear</td>
<td>Some laxity, firm endpoint</td>
<td>Pain, may feel loose</td>
</tr>
<tr>
<td>III</td>
<td>Complete tear</td>
<td>Obvious laxity, no endpoint</td>
<td>Minimal pain, may feel very loose</td>
</tr>
</tbody>
</table>

4 tests for meniscus tear

1. Isolated joint line tenderness
2. McMurray
3. Thessaly
4. Squat

*These tests not needed in patients with knee OA. Do these tests in patients < 50 with isolated joint line tenderness.*
Meniscus: McMurray

Sensitivity medial 65%, Specificity medial 93%


Meniscus: Thessaly

Meniscus: Squat

Knee exam practice

• Standing: inspection
  – Varus or valgus
• Sitting: palpation
  – Joint line
  – Femoral condyles
  – Tibial plateau
  – Fibular head

• Supine
  – Patellar facets
  – Patellar grind
  – ROM
• Special tests
  • Lachman
  • Posterior drawer
  • Varus 0 and 30
  • Valgus 0 and 30
  • McMurray medial and lateral
  • Thessaly
  • Squat
Shoulder anatomy

- Humerus
- Scapula
  - Glenoid
  - Acromion
  - Coracoid
  - Scapular body
- Clavicle
- Sternum

Underlying Anatomy - Bones

- Humerus
- Scapula
  - Glenoid
  - Acromion
  - Coracoid
  - Scapular body
- Clavicle
- Sternum

LABRUM: The LABRUM is a fibrocartilaginous ring of tissue that attaches to the glenoid rim & deepens the glenoid fossa.

Glenoid Labrum

Acromion

Spine of scapula is at the level of T3

Bottom of scapula is at level of T7
The tendons of the rotator cuff muscles reinforce the capsule of the glenohumeral joint.

Subscapularis (Internal Rotation)

The Rotator Cuff Muscles (SITS)

Anterior View

Lesser Tuberosity

Greater Tuberosity

Infraspinatus (External rotation)

Posterior View

Teres Minor

The Biceps Muscle

• #1 Supination of the elbow (screwing, twisting)
• #2 Flexion of the elbow

Shoulder exam
Shoulder examination

Key Components of the Shoulder Exam:
- Neck
- Shoulder
- Inspection
- Palpation
- Range of Motion:
  - abduction, flexion, ER, IR
- Strength
- Neurovascular

Special Tests:
- Hawkins impingement sign
- Neer's impingement sign
- Painful arc (rotator cuff dx)
- Jobe's, aka Empty-can (supraspinatus)
- Drop arm test (rotator cuff)
- External rotation lag test (rotator cuff tear)
- Internal rotation lag test (rotator cuff tear)
- Speeds (biceps)
- Yergason's (biceps)
- O'Brien's (SLAP tear)
- AC crossover (AC joint OA or sprain)

Neck examination

- Inspection
- Palpate CS
- FF and extension
- Spurlings

Cervical Spine
Spurling’s Maneuver

- Neck extended
- Head rotated toward affected shoulder
- Axial load placed on the cervical spine
- Reproduction of patient’s shoulder/arm pain indicates possible nerve root compression

http://meded.ucsd.edu/clinicalmed/joints 2.htm, permission granted by Dr. Charles Goldberg, UCSD SOM
Inspection

- Presence of infraspinatus atrophy increases likelihood of rotator cuff disease
- Positive LR 2.0
- Negative LR 0.61


Shoulder examination

- Inspection
- Palpation
- ROM
- Strength
  - Supraspinatus
  - Infraspinatus & Teres minor
  - Subscapularis
- Other tests

Range of motion

Abduction
Flexion

Range of motion

External rotation
Internal rotation
Supine shoulder PROM

Passive range of motion

- If limited AROM in any direction
- Follow up by testing passive motion in that direction
- If limited active and passive ROM think
  - Frozen shoulder
  - Glenohumeral joint arthritis

Shoulder exam practice

- Neck: palpation, ROM and Spurling’s maneuver
- Inspection
- Palpation
- AROM
  - Abduction
  - Flexion
  - External rotation (ER)
  - Internal rotation (IR)
- PROM

Shoulder: diagnosis driven exam

1. Active ROM
   - Normal
   - Decreased

2. Passive ROM
   - Normal
   - Decreased

3. X-ray
   - Normal
   - Abnormal

Frozen shoulder

Weak = Rotator cuff tear
Limited by pain = Other rotator cuff dz
Labral tear
Biceps tendinitis
AC joint OA

GH joint OA
Other tests

- Rotator cuff disease (RCD)
  - Bursitis or impingement
  - Tendinitis/tendinopathy
  - Partial tear
  - Full thickness tear
- Biceps tendinitis/tendinopathy
- Labral tear
- AC joint osteoarthritis

Rotator cuff disease exam

- Pain provocation tests
- Pain and strength tests
- Often the pain radiates to lateral shoulder/proximal arm ("deltoid")

Pain test: Impingement signs

Hawkin’s
Neer’s

Pain test: Painful arc

If painful, positive LR 3.7 for RCD.
If not painful, negative LR 0.36 for RCD.

Photos from Dr. Christina Allen
Exam practice: pain provocation tests in RCD

- Hawkins impingement sign
- Neers impingement sign
- Painful arc (rotator cuff dz)

Pain & Strength test: Supraspinatus = abduction

- 71% sensitivity
- 41% specificity for rotator cuff disease. (+) LR 1.3

Pain/strength test: Drop arm test

- Positive LR 3.3, negative LR 0.82 for rotator cuff disease.

Physical exam maneuvers that increase likelihood of full thickness rotator cuff tear

1. External rotation lag test
2. Internal rotation lag test

https://www.healthbase.com/hb/images/cm/procedures/orthopedics/rotator_cuff_tear.jpg

JAMA. Rational clinical exam: Does this patient have rotator cuff disease? Aug 2013.
Strength test: 
External rotation lag test

Positive LR 7.2, 
Negative LR 0.57 
for full thickness 
rotator cuff tear

Exam practice: 
Rotator cuff strength and tear

• Jobe’s, aka Empty-can (rotator cuff disease)
• Drop arm (rotator cuff disease)
• External rotation lag test (rotator cuff tear)
• Internal rotation lag test aka Lift-off test (rotator cuff tear)

Pain & Strength test: 
Subscapularis = internal rotation lag test

Positive LR 5.6, 
negative LR 
0.04 for full 
thickness 
rotator cuff 
tear

Biceps Tests: Speeds

Tests for biceps pathology 
tendinitis, tendinopathy, 
tear

Palms up, patient pushes 
up against resistance 
(resisted elbow flexion)

+Test is pain at proximal 
biceps tendon 
Sens = 54%, Spec = 81%
Biceps Tests: Yergasons

Tests for biceps pathology (tendinitis, tendinopathy, tear)

Patient supinates (twists out) against resistance

+Test is pain at proximal biceps tendon
Also tests for biceps strength

Sens = 41%, Spec = 79%

O'Brien's Test
To r/o Labral Tear

• Arm forward flexed to 90°
• Elbow fully extended
• Arm adducted 10° to 15° with thumb down
• Downward pressure
• Repeat with thumb up
• Suggestive of labral tear if more pain with thumb down

Sens = 59-94%, Spec = 28-92%

Testing the AC Joint: AC Crossover

• Tests for AC joint osteoarthritis or sprain
• Can be done passively by patient or physician
• +Test is pain at AC joint

Exam practice:

biceps tendinitis, labral tear, AC OA

• Speeds (biceps)
• Yergason's (biceps)
• O'briens (SLAP tear)
• AC crossover (AC joint OA or sprain)
Shoulder examination

Key Components of the Shoulder Exam:
- Neck
- Shoulder
- Inspection
- Palpation
- Range of Motion:
  - abduction, flexion, ER, IR
- Strength
- Neurovascular

Special Tests:
- Hawkins impingement sign
- Neer impingement sign
- Painful arc (rotator cuff)
- Jobe's, aka Empty-can (supraspinatus)
- Drop arm test (rotator cuff)
- External rotation lag test (rotator cuff tear)
- Internal rotation lag test (rotator cuff tear)
- Speeds (biceps)
- Yergason's (biceps)
- O'Brien's (Glenohumeral)
- AC crossover (AC joint OA or sprain)

Questions?
Carlin.Senter@ucsf.edu
Why Do We Care About What We Eat?

US Leading Causes of Death, CDC

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>1</td>
<td>Heart Disease</td>
<td>32.6%</td>
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<tr>
<td>2</td>
<td>Cancer</td>
<td>30.9%</td>
</tr>
<tr>
<td>3</td>
<td>Chronic lower respiratory disease</td>
<td>7.5%</td>
</tr>
<tr>
<td>4</td>
<td>Stroke</td>
<td>7.0%</td>
</tr>
<tr>
<td>5</td>
<td>Accidents</td>
<td>6.4%</td>
</tr>
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<td>6</td>
<td>Alzheimer’s disease</td>
<td>4.3%</td>
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<td>7</td>
<td>Diabetes</td>
<td>3.7%</td>
</tr>
<tr>
<td>8</td>
<td>Influenza and pneumonia</td>
<td>2.9%</td>
</tr>
<tr>
<td>9</td>
<td>Nephritis, nephrotic syndrome &amp; nephrosis</td>
<td>2.7%</td>
</tr>
<tr>
<td>10</td>
<td>Intentional self-harm (suicide)</td>
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Lifestyle and Disease

- 1/3 of premature deaths in the U.S. are attributable to poor nutrition and physical inactivity.
- Well over 50% of American adults do not get the recommended amount of physical activity.
- Only 10% of Americans eat a diet consistent with current nutrition recommendations.

Question for Discussion

- How would you describe your own diet?

Question for Discussion

- How do you ask patients about their diets?

Topics

- Total calories and macronutrient balance
- Weight Loss Diets
- Dietary Fiber
- Dietary Guidelines
- Sodium

- Vegetarian Diets
- Mediterranean Diets
- Other Micronutrients
- Final Recommendations
Nutrition and Weight Management

**U.S. Calorie Intake**

- Calorie consumption in the U.S. has increased 30% over the past 4 decades.

<table>
<thead>
<tr>
<th>Year</th>
<th>Average calories consumed</th>
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</thead>
<tbody>
<tr>
<td>1970</td>
<td>2,057</td>
</tr>
<tr>
<td>2008</td>
<td>2,674</td>
</tr>
</tbody>
</table>

**Top calorie sources in U.S.**

1. Grain-based desserts
2. Yeast breads
3. Chicken and chicken-mixed dishes
4. Soda, energy drinks, and sports drinks
5. Pizza
6. Alcoholic beverages
7. Pasta and pasta dishes
8. Mexican mixed dishes
9. Beef and beef dishes
10. Dairy desserts

**Extra Calories From Eating Away From Home**

<table>
<thead>
<tr>
<th></th>
<th>Calories/meal at home</th>
<th>Calories/meal at a restaurant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Weight</td>
<td>550</td>
<td>825</td>
</tr>
<tr>
<td>Overweight/Obese</td>
<td>625</td>
<td>900</td>
</tr>
</tbody>
</table>

**Macronutrient Composition**

- Macronutrient composition: the relative proportions of fat, carbohydrate, and protein in the diet

- **Bottom line:**
  - A wide range of macronutrient composition is consistent with a healthy diet
  - In most clinical circumstances, total calories “trump” macronutrient composition
  - Achieving desired calorie intake will achieve most clinical goals
COMPARISON OF WEIGHT LOSS DIETS WITH DIFFERENT MACRONUTRIENTS

RCT of 811 patients, 4 diets: fat/protein/carbs 20/15/65; 20/25/55; 40/15/45; 40/25/35

- 6 months: 6 kg, 7% weight;
- 2 years: completers lost 4 kg. 15% lost 10% of weight
- Results similar for:
  - 15% pro v. 25% pro
  - 20% fat v. 40% fat
  - 35% carbs v. 65% carbs
- Weight loss highly correlated with adherence; satiety, hunger, lipids, insulin all equal

Principles of Weight Management

- Be as fit as you can be at your current weight
- Don’t gain any more weight
- If highly motivated, attempt weight loss

Dietary Fiber

- Plant matter
  - Not digested by human digestive enzymes
  - Some can be digested by gut bacteria
- Includes
  - Cellulose, hemicellulose, pectins, gums, and mucilages, lignins
- Classified as soluble or insoluble
- IOM: Men 30-38 g/day. Women 21-25 g/day.

Dietary Fiber: The Most Important Nutrient?

- Heart: Lowers LDL, lowers triglycerides
- Diabetes: Reduces blood sugar
- Gut: Prevents constipation, hemorrhoids, diverticular disease
- Weight: Promotes satiety
Nutrition and Weight Management

**Dietary Fiber: The Most Important Nutrient?**

- Meta-analysis of 22 cohort studies:
- Every 7 grams of fiber associated with a 9% decrease in CV events
- One portion of whole grains and one portion of legumes, or from two to four servings of fruits and vegetables.

Threapleton DE, BMJ, 2013

**Quantifying Dietary Fiber (per serving)**

<table>
<thead>
<tr>
<th>Food</th>
<th>Fiber (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>4.4</td>
</tr>
<tr>
<td>Blueberries</td>
<td>3.6</td>
</tr>
<tr>
<td>Orange</td>
<td>3.0</td>
</tr>
<tr>
<td>Grapes</td>
<td>0.8</td>
</tr>
<tr>
<td>Pear</td>
<td>5.5</td>
</tr>
<tr>
<td>Raspberries</td>
<td>8.0</td>
</tr>
<tr>
<td>White bread</td>
<td>0.7</td>
</tr>
<tr>
<td>Wheat bread</td>
<td>1.9</td>
</tr>
<tr>
<td>Brown rice</td>
<td>1.5</td>
</tr>
<tr>
<td>White rice</td>
<td>0.3</td>
</tr>
<tr>
<td>Wheat bran cereal</td>
<td>7.4</td>
</tr>
<tr>
<td>Oatmeal</td>
<td>4.8</td>
</tr>
<tr>
<td>Shredded wheat</td>
<td>6.1</td>
</tr>
<tr>
<td>Cornflakes</td>
<td>0.9</td>
</tr>
<tr>
<td>Peanuts</td>
<td>9.1</td>
</tr>
<tr>
<td>Kidney beans</td>
<td>6.8</td>
</tr>
<tr>
<td>Asparagus</td>
<td>1.4</td>
</tr>
<tr>
<td>Broccoli</td>
<td>1.1</td>
</tr>
<tr>
<td>Carrot</td>
<td>1.7</td>
</tr>
<tr>
<td>Spinach</td>
<td>3.5</td>
</tr>
<tr>
<td>Powdered psyllium</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**Principles of a Healthy Diet**

- Wide variety of foods
- High food quality
- Moderation (right quantity)

**Dietary Guidelines 2015**

- Limitations on dietary cholesterol have been removed
- Consume a diet rich in fruits and vegetables, whole grains, low-fat dairy, seafood, legumes, and nuts
- Consume a diet low in red or processed meats, sugar sweetened foods and beverages, and refined grains
Nutrition and Weight Management

**Dietary Guidelines 2015**

- Limit daily consumption of added sugars (<10% of calories), saturated fat (<10% of calories), and dietary sodium (2300 mg)
- Half of all grain intake should come from whole grains
- Moderate alcohol is fine in most (non-pregnant) adults
- Up to five cups of coffee per day is not associated with adverse effects in most adults

**MyPlate**

- Guidelines recommend six, 1-ounce servings per day for a 2000 calorie diet, and half should be whole grain.

- The average person eats 8 servings of grains per day, and 7 of the 8 are refined.
**What is a serving of grain?**
- 1/2 cup cooked rice or other cooked grain
- 1/2 cup cooked pasta
- 1/2 cup cooked hot cereal, such as oatmeal
- 1 six inch tortilla
- 1 slice of bread (1 oz.); ½ bun
- 1 very small (1 oz.) muffin
- ½-1 cup ready-to-eat cereal

(½ cup = ½ a baseball)

**Select whole grains**
- Look for “whole” in the first ingredient on the label.
- Aim for total carbs/fiber = <10 for bread and <5 for cereals.
- Whole grains: wheat (spelt, farro, durum, bulgur, others), barley, buckwheat, com, millet, oats, quinoa, rice, rye

---

**Way Too Much Added Sugar**

The average person in US consumes 30 teaspoons of sugar and sweeteners per day (up to 600 calories)

(Includes cane and beet sugar, high fructose corn syrup, com syrup, dextrose, honey)

- The Dietary Guidelines recommend <10 teaspoons (200 calories) of added sugar per day for women.
  Am. Heart Association says <6 teaspoons (120 calories)
- A 20 oz. soda has 240 calories from sugar

**Salt and Public Policy**

- Coronary Heart Disease Policy Model to quantify benefits of modest salt reduction in U.S.
- Benefit through a reduction in systolic blood pressure from 1-9 mm Hg in selected populations
- New cases of CHD decrease by 4.7 - 8.3 and stroke by 2.4 to 3.9 /10,000
- Regulatory change leads to wide benefit and is cost-effective

Bibbins-Domingo K, et al. NEJM 2010
**Sodium**

- Average current intake 3,400 mg per day (1.5 teaspoon salt)

- **Institute of Medicine, 2013**
  - Limit everyone to 2,300 mg per day (1 teaspoon)
  - Evidence doesn’t support lower recommendations

- **Dietary Guidelines, 2015**
  - Limit everyone to 2,300 mg per day

---

**Top sodium sources in U.S.**

1. Yeast breads
2. Chicken and chicken-mixed dishes
3. Pizza
4. Soda, energy drinks, and sports drinks
5. Cold cuts
6. Condiments
7. Mexican mixed dishes
8. Sausage, franks, bacon and ribs
9. Regular cheese
10. Grain-based desserts

---

**Classification of Dietary Fat**

- **Saturated Fat**
  - Dairy
  - Meat

- **Mono-unsaturated Fat**
  - Olive oil
  - Canola oil

- **Poly-unsaturated Fat**
  - Omega-3
    - Fish, walnuts, flaxseed, soybean
  - Omega-6
    - Safflower oil, corn oil, peanuts, soybean

- **Trans Fat**
  - Hydrogenated oils (Processed foods)
Saturated Fat and Cardiovascular Disease (CVD)

- Two recent meta-analyses of observational studies: no association between higher saturated fat and CVD.
- But strong evidence from randomized trials: replacing saturated fat with unsaturated fat reduces total and LDL cholesterol.
- Replacing sat fat with carbohydrates: reduces total and LDL cholesterol but increases triglycerides and lowers HDL.

Current recs: Limit saturated fat, but be careful what replaces it.

Use oils (soy, com, olive, canola) to replace animal fats (butter, cream, lard) or tropical oils (palm, coconut).

Mediterranean Diet:
Healthy fats and good carbs with a big side of fruits and vegetables.

Use healthy oils (like olive and canola oil): for cooking, on salads, and at the table. Avoid trans fats.

- Whole grains—like brown rice, whole wheat bread, and whole-grain pasta: limit refined grains like white rice and white bread.

Choose fish, poultry, beans, and nuts, lentil red meat, avocados, cold cuts, and other processed meats.

HEALTHY EATING PLATE

- Whole grains
- Fruits
- Vegetables
- Protein
- Healthy oils
- Water
**Primary Prevention of Cardiovascular Disease with a Mediterranean Diet**

7447 Men and women, type 2 diabetes or at least 3 CV risk factors. 4.8 years

Compared 1) Mediterranean diet supplemented with 4 Tbsp/day of olive oil or 2) with 1 ounce of nuts/day; vs. 3) a low fat diet (the control)

**Results:** 288 cardiovascular events occurred: 3.8% in the olive oil group, 3.4% in the nut group, and 4.4% in the control group. (P=0.015)

*NEJM, 2013*

---

**Eat about 1 ounce of nuts most days**

- 1 ounce of nuts=1/4 cup or a small handful

- But be aware of the calories...
  - 1 ounce=160-200 calories

---

**Vegetarian Diets**

- Vegans
- Fruitarians
- Lacto-vegetarians
- Lacto-ovo vegetarians
- Pesco-vegetarians
- Pollo-vegetarians
- Flexitarians (Semi-vegetarians)

---

**Vegetarian Diets: Observational Study**

- Adventist Health Study 2
  - 73,000 participants; 2570 deaths
  - 5.8 years follow-up

- Compare: vegans, pesco-; lacto-ovo-; and semi-vegetarians to non-vegetarians

- Outcome: lowest mortality in pesco-vegetarians and vegans (15-20%).

*Orlich, JAMA IM, 2013*

*Baron, JAMA IM, 2013*
Micronutrients in Brief

- Beta-carotene
  - Discourage - harmful
- Vitamin E
  - Discourage - harmful
- Folate
  - Women of child-bearing age - prevent neural tube defects

Micronutrients in Brief

- Omega-3 fatty acids
  - Discourage - no benefit
- Vitamin D and calcium
  - Older, frail patients to prevent falls
  - Use with bisphosphonates
  - 800 IU of vitamin D3 per day is sufficient
  - Ensure adequate calcium intake
    - 1000 mg under 50; 1200 mg over 50

Dietary Calcium

- Dairy
  - Plain Yogurt 8 oz 448
  - Mozzarella 1.5 oz 333
  - Cheddar 1.5 oz 307
  - 2% milk 1 cup 293
  - Cottage cheese 1 cup 206
- Fruits and vegetables
  - Fortified OJ 6 oz 261
  - Kale 1 cup 100
  - Bok Choy 1 cup 74
  - Broccoli 1 cup 43

Dietary Calcium

- Canned fish
  - Sardines 3 oz 325
  - Salmon 3 oz 183
- Grains
  - Fortified cereals 1 cup 100-1333
  - Fortified cooked oats 1 cup 187
- Commercial breads 1 slice 30-73
Michael Pollan’s Three Rules

- Eat food
- Not too much
- Mostly plants

Baron’s Rules

- Eat unprocessed foods
- Eat the right amount to maintain your weight
- Eat something colorful at every meal (and every snack)
- Don’t drink calories
- If can’t make the “best” choice, make a better choice
- Be as fit as you can be: exercise daily
- Eat with your children; eat at home

The “Generic” Diet

- Continued debate: macronutrient balance, amounts of meat/fish/fowl, other specific foods
- But almost all agree:
  - Limit sugar, refined grains, large amounts of saturated and trans fat
  - Eat fruits and vegetables, healthy oils, whole grains, legumes and nuts
- Bottom line: Master a “generic” diet for patients and self

Baron’s Rules

- Exercise is “biblical”
  - 6 days of exercise, one day of rest
  - Never go to sleep without knowing exercise plan for tomorrow (and back-up plan)
  - Morning exercise is best (to do it when energy is highest)
  - Home machines help with adherence
- Focus on cardiovascular fitness, strength, balance, and flexibility
Nutrition and Weight Management

For More Information

- Dietary Guidelines for Americans, 2015
  http://health.gov/dietaryguidelines/2015,

- USDA’s Food & Nutrition Information Center:

- CDC Division of Nutrition, Physical Activity & Obesity:
  http://www.cdc.gov/nccdphp/dnpao/index.html

- USDA National Agricultural Library:
  http://www.nutrition.gov/

- Center for Science in the Public Interest (CSPI):
  http://www.cspinet.org/

- ChooseMyPlate.gov: http://www.choosemyplate.gov/

For More Information

- FDA: How to Understand and Use the Nutrition Facts Label:
  http://www.fda.gov/Food/ResourcesForYou/Consumers/NFPM/ucm274593.htm

- FDA: Label Man – Make Your Calories Count:
  http://www.accessdata.fda.gov/videos/CFSAN/HWM/hwminro.cfm

- Nutrition.gov: Shopping, Cooking & Meal Planning:
  http://www.nutrition.gov/shopping-cooking-meal-planning

- Healthy Eating Plate (Harvard):
  http://www.hsph.harvard.edu/nutritionsource/what-should-you-eat/pyramid/
Common Dermatologic Conditions in Aging Skin

Toby Maurer, MD
University of California, San Francisco

The Aging Skin

Normal maturation and sun exposure

- Too much-
  Tumors, lentigenes, seborrheic keratoses, leg veins, hair, muscle tone
- Too little-
  Collagen, fat and elastic tissue

Tanning Beds

- International Agency for Research on Cancer
- Comprehensive metaanalysis found that risk of melanoma (skin and eye) increases by 75% when tanning begins before age 30.
- Cite this to your young patients
  Even though tanners knew the risk, they still used tanning beds—prohibit tanning beds—Finley J Surg Onc 2015

- Sunscreens - Australian study randomized residents to daily use vs discretionary use between 1992 and 1996
- Risk for developing any melanoma reduced by 50% and invasive melanoma risk reduced by 73%
- Same trial also showed reduction of risk of developing squamous cell cancer
“I’m Here for a Skin Check”

- Can screening by Primary MD reduce morbidity/mortality from skin cancer?
- Hard to do study-need to follow 800,000 persons over long period of time to determine this-studies not done

Bottom line:

- Not enough evidence for or against to advise that patients have routine full body exams BUT
- Know risk factors and incorporate exam into full physical and teach patients what to look for

Actinic Keratosis (AK)

- Who is at risk?
  - Over age 35-40
  - Fair-skinned persons
  - Sun-exposed sites
    - Face, forearms, hands, upper trunk
  - History of chronic sun exposure

Clinical Features of AK

- Red, adherent, scaly lesions, usually < 5mm
- Sandpapery, rough texture
- Tender when touched or shaved
- Thick, warty character (cutaneous horn)
Diagnosis of AK

- Diagnosis
  - Clinical features
  - Shave or punch biopsy

Treatment of AK

- Cryotherapy-goal is 2x15 sec thaws
- Topical chemotherapy/chemical peel
  - Efudex (5FU crème) 2x/day x 6 wks or Imiquimod-3X’s /wk and 3 mos.
  - Photodynamic therapy

Photodynamic Therapy

- Apply paint that increases photosensitivity/absorbance so that laser can destroy AK’s. Doing it with sunlight and even greenhouse light in developing countries.

Diagnosis of BCC: Shave or Punch Biopsy
Recommended Treatment of BCC

• Surgical excision (head and neck)
• Curettage and desiccation (trunk)
• Radiation therapy (debilitated patient)
• Microscopically controlled surgery (Mohs)
  – Recurrent/sclerotic BCC’s
  – BCC’s on eyelid and nasal tip
  – Recurrent widespread BCC-oral

Vismodegib

Aldara (Imiquimod)

• Topical therapy designed for wart treatment
• Upregulates interferon/ down regulates tumor necrosis factor/works on toll like receptors
• Seems to have efficacy in superficial BCC’s
• Do Not use in BCC’s that are nodular or invasive
• Biopsy to confirm diagnosis BEFORE treatment

Squamous Cell Carcinoma (SCC)

• Who is at risk?
  – Age 50+
  – Chronic sun exposure
    • Head, neck, lower lip, ears, dorsal hands, trunk
  – Special circumstances
    • Immunosuppression (organ transplant)
    • Radiation therapy

Clinical Features of SCC

• Papule, nodule or tumor
• Non-healing erosion or ulcer
• Cutaneous horn (wart-like lesion)
• Fixed, red, scaling patch/plaque (Bowen’s-SCC-in-situ)
How to Diagnose

- Punch or excisional/incisional biopsy
- Shave biopsy for flat, non-elevated lesion

Treatment of SCC

- Recommended treatment
  - Excision
  - Radiation therapy (in debilitated patient)

METASTATIC Disease:
Cetuximab/EGFR blockers
PD-1 inhibitors

Melasma

- Hyperpigmentation of cheeks, chin, forehead
- Seen in pregnancy and in hormone replacement
- Also seen in females and males without hormone treatment
- Treatment - Hydroquinone 4%, (Solaquin forte) sunscreen, Trilumina (retinoid, hydroquinone and steroid)
- 4 months on; 4 months off to avoid ochreosis

Follow-up for SCC-1-3 months for 2 yrs then q 4-6 months for 5 yrs
**Perioral Dermatitis**

- Characterized by small papules and pustules
- In 30-40 year olds, centered around mouth and eyes (perioral/orbital dermatitis)
- These patients may never have had history of acne as teens
- Tx: oral antibiotics (doxycycline) 100 bid x 6-8 wks

**Lichen simplex chronica**

- Often seen on the labia
- Pts have had multiple anticandidal treatment
- Stop itch /scratch cycle with potent topical steroids
- Stop the washing/cleaning habits

**Dry skin on feet**

- Keratoderma climacterum-seen in menopause/post-menopause
- Often present with deep fissures
- Urea 40% /topical steroid

**Pruritus and Xerosis**

- Aging skin loses it’s barrier functions and gets drier and itchier
- New onset dryness and itchiness in the elderly - CBC, TSH, LFT’s and renal function
- Lubrication is key
- Decrease water use, NO soap
  - Sedating antihistamines such as benadryl, atarax, doxepin are useful
Treatment

- ACV 800 mg 5 x’s/day
- Famvir 500mg tid
- Valacyclovir 1000 tid
- begin within 48 hrs of onset of blister. Any time in immunosuppressed host
- Pain control
  – NSAIDS/Tylenol
  – Neurontin: 100 mg tid
  – Elavil: 25 mg qhs or q 8 hrs
- Prednisone: no role

Herpes Zoster

- Zoster vaccine available –boosts older person’s cell-mediated immunity to VZV
- Study done on 38,000 persons 60 yrs and older (Kimberlin et al NEJM March 2007)
- Incidence of zoster was 51% lower in those that received vaccine vs placebo
- Post-herpetic neuralgia was 67% lower in vaccinated group
- Worked best in 60-69 yr olds

- Can it be used in pts with previous zoster-yes
- How about use in younger age groups? 50 and above now being looked at
- Needs to be give within ½ hour of reconstitution
- $190.00 for injection (ave)

-uptake in most communities is only around 30%
- recommended now before giving patients immunosuppressive drugs like MTX or TNF blockers.
### Blistering Diseases
- Most common in the elderly is **BULLOUS PEMPHIGOID**
- Can be localized or widespread blistering
- Biopsy
- Start prednisone 60-80 mg daily and taper over months
- Add steroid sparing drugs like mycophenolate or azathioprine
- Always keep pt on at least low dose prednisone

### Too Much Hair
- **Vaniqa**
  - topical cream that breaks the chemical bond of hair
  - apply 2x’s/day forever
  - 30% effective
  - $30/month

### Hair Removal
- pigment of hair absorbs the light and gets destroyed
- dark hair responds
- hair is always in different growth phases, so treatment has to be repeated several times to catch the phase(expensive)
- pigment changes of surrounding skin and scarring
- fast and minimal scarring

### Hair Loss
- If not scarring and diffuse:
  - Check recent surgeries/illness, nutrition, anemia, TSH, estrogen replacement, medication history, VDRL.
  - If hirsute with scalp hair loss-DHEAS and free testosterone
  - If lactating- check prolactin
If all negative

- Androgenetic Alopecia—Minoxidil 5% bid topically (even in women)
  Can make hair oily—may want to start with minoxidil 2% or use
  2% by day and 5% at night
  Minoxidil foam—once at night
  Use for at least 6 months for results and what you see after 1
  yr. is the effect you can expect.

What about finasteride (propecia)?—Does not work in women—in
men the dose is 1 mg qd.

Stop the Motion

- Botulinum Toxin
  – FDA approved (two types available)
  – paralyzes muscles so that the wrinkles relax
  – excellent for crow’s feet, glabellar wrinkles, and
  nasolabial fold
  – ptosis and necrosis if not done right
  – lasts for 3 months

Androgenetic Alopecia

- Men
- Women

- Also being used for hyperhydrosis in palms and
  axilla
- anal fissures
- migraine headaches
- tics/dysphonia
- muscle spasm in stroke victims
Build up the understructure

- Can you build collagen with creme?
- Retinoids (topical): with daily use over long periods of time, may increase the thickness of collagen
- Retin A- 0.025-0.1 %. Start with crème and move to gel

To Fill and Create Understructure

- Collagen
- Hyaluronic Acid (Restalyne)
- Silicone
- Poly-L-lactic Acid (Sculptra)
- Polymethacralate (Artefill)
- Fat Transfer-pts own material

Points to consider

- Allergy testing
- Pain on injection-some of these have preservatives
- Overcorrection vs undercorrection-pts are happier after they leave office overcorrected with non-permanents

Cautionary points

- Technique important-send to practitioners in the know-nonpermanent fillers are more forgiving; permanent fillers, technique is everything
- Expensive
- May need touch-ups
- Can form granulomas
Ablative Therapy

- Involves wounding the skin with chemicals or light (laser)
- Take into account skin type and amount of damage from sun and aging

What can primary provider do to help?

- If pt has h/o orolabial HSV-prophylax with ACV
- If pt has been on accutane-no procedure for at least 6 months after stopping
- If pt has psoriasis-reconsider so as not to have psoriasis spread to face after a procedure
- No bacterial antibiotic prophylaxis is needed
- Sunscreen before and after procedure

Economics

- Most providers using these techniques will use a combination - i.e. they will fill in some cracks, ablate tumors and stop the motion
- Costly and NOT covered by insurance
- Expectations are often high-many providers who are good will spend time understanding expectations and discuss reality and cost
- Lawsuits are very common
- Addiction to procedures not uncommon

Body Dysmorphic Syndrome

- Patients complain of ugliness/physical flaws
- Thinking about this consumes many hours of their day
- Mirror-looking/ changing clothes/ picking of skin-often associated
- Can be associated with psychosis but does not have to be, drug use not uncommon
- Pts often do their own surgery
• Seek dermatologic and surgical care
• Very dissatisfied with results-onus is on doctor to figure it out
• Recognition by providers is helpful although patients often deny situation
• Conveying to patient that treatment (other than cosmetic) will help with functionality i.e. recognizing that hours of thinking of this gets in the way with other aspects of life-help patients get beyond the pain of their disease

• SSRI’s have been helpful in some studies-usually high dose for at least 12 weeks
• Cognitive behavioral therapy has also been helpful in small studies-time consuming and expensive-pts keep journals of their behavior, substitute pleasurable behaviors, keep track of lapses and what made them lapse
Guidelines for Managing Menopausal Symptoms

Judith M.E. Walsh, MD, MPH
Professor of Medicine
UCSF Women’s Health Center of Excellence

Conflicts of Interest: None

Overview

• Natural history of menopause
• Hormone therapy: Risks and Benefits
• Menopausal symptoms
• Current role of hormone therapy for menopausal symptoms
• Non-hormonal treatment of menopausal symptoms

MENOPAUSE IS NOT A DISEASE

“Feminine Forever”

• Dr. Robert Wilson, 1966
• Replacing estrogen is like diabetics replacing insulin
• Women “will be much more pleasant to live with and will not become dull and unattractive.”
• Wyeth-Ayerst funded all expenses
Menopause Is A Positive Step

- Gallup poll 1997: Most middle aged American women “welcome menopause as a new and fulfilling life stage.”
- Goal: Support women in achieving a successful transition

Natural History of Menopause

- Average age is 51
- Predictors of age at menopause
  - Genetics
  - Family history
  - Ethnicity
    - Earlier in Latino and later in Japanese American compared to Caucasians
  - Smoking: about two years earlier
  - Reproductive history
    - Earlier menopause in women never having children and with shorter cycle length

Menopausal Symptoms: Prevalence

- Hot flushes (50% or more)
  - Often with perspiration
- Night sweats (50% or more)
- Sleep disturbance (40-60%)

OTHER SYMPTOMS

- Other symptoms happen at the time of menopause but are less clearly related to menopause
  - Mood changes
  - Cognition
  - Changes in sexual function
  - Urinary complaints
  - Joint pain
Vasomotor Symptoms

- Minnie Pause is a 53 year old woman who had her last menstrual period 18 months ago. She is still having hot flashes and awakens at least twice a night with them. She is considering taking estrogen but wants to know how much longer this will last. What do you tell her?

What do you tell her about when they will go away?

- Average duration is about 2 years and so they should be gone in about 6 months.
- Average duration is about 4 years
- Average duration is about 7 years
- They will never go away

Background

- Treatment for menopausal symptoms is based on their transitory nature
- Many clinical guidelines suggest that symptom duration is approximately 2 years
  - Many studies do not follow women more than 2 years
- Risks and benefits of hormone therapy depend on duration of use
  - “Use lowest dose for shortest duration”
Duration of Vasomotor Symptoms

- Objective: to estimate the natural progression of menopausal symptoms

Vasomotor symptoms

- Rigorous meta-analysis included 10 studies with over 35,000 participants
- Clear definition of vasomotor symptoms
- Assessed prevalence of symptoms and “bothersome symptoms”

Results

- Percent of women with symptoms increased in the two years before the final menstrual period (FMP), peaked one year after the FMP and did not return to premenopausal levels until 8 years after the FMP
- 50% of women had symptoms during the 4 years after FMP
- 10% of women had symptoms up to 12 years after FMP
Results: Bothersome Symptoms

Avis NE et al. Duration of menopausal vasomotor symptoms over the menopause transition.

Objective: to determine total duration of frequent vasomotor symptoms (VMS) during menopause transition, to determine how long frequent VMS persist and to identify risk factors for longer VMS duration

JAMA Int Med 2015

Duration of Vasomotor Symptoms

SWAN Study

- Multi-ethnic, multi-racial observational study of menopausal transition in 3302 women at 7 sites
  - 13 visits over 17 years
  - Analyses of 1449 women with frequent VMS
- Assessed VMS duration and persistence after FMP

Results

- Median duration of VMS was 7.4 years
  - FMP persistence 4.5 years
- Longer VMS duration in women who were pre or perimenopausal when symptoms began
  - Median 11.8 years
- Women who were postmenopausal when symptoms began had shortest duration
  - Median 3.4 years
- Longer VMS duration
  - African American, younger age, lower educational level, greater perceived stress and symptom sensitivity and higher depressive symptoms and anxiety
Impact

- Frequent VMS lasted more than 7 years for more than half of women
- The earlier VMS started the longer they were likely to last
- This can be included in decision making about menopausal symptom management

Minnie Pause….continued

- Now that Minnie knows that the symptoms could last for a while more, she definitely wants to do something about her intolerable hot flashes. Her only medical history is hypertension well controlled on lisinopril. She would like to hear your thoughts on hormones and whether they are a safe option for her.
- What do you tell her?

What do you tell her?

- Why don’t you try black cohosh- that will work just as well
- Venlafaxine is as effective as hormones and it is a lot safer
- Hormone therapy is probably ok, if you don’t take it for too long
- Absolutely not- no one takes hormones any more

Should I use hormones?

- Ok, so they may help my symptoms……but are they safe?
Background

- WHI trials designed to determine benefit/risk of hormone therapy when taken for chronic disease prevention
  - Primary efficacy outcome: CHD
  - Primary safety outcome: invasive breast cancer
- Combination trial stopped early due to increased breast cancer risk and unfavorable risk-to-benefit ratio

The News

- Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Post-stopping Phases of the Women’s Health Initiative Randomized Trials
- Aims:
  - Provide a comprehensive, integrated overview of findings from the 2 WHI hormone therapy trials with extended post-intervention follow-up and stratification by age and other important variables

Methods

- Post-intervention follow up through Sept 30, 2010 based on 81% surviving participants
- Utilized time to event methods based on intention-to-treat, global index calculated
  - CHD, invasive breast cancer, stroke, PE, colorectal cancer, endometrial cancer, hip fracture, and death
## Results

### CEE + MPA

<table>
<thead>
<tr>
<th>Post-intervention</th>
<th>Diff/10,000 PY</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>2</td>
<td>1.04 (0.89-1.23)</td>
<td>0.61</td>
</tr>
<tr>
<td>Breast CA</td>
<td>10</td>
<td>1.32 (1.08-1.61)</td>
<td>0.007</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0</td>
<td>1.01 (0.91-1.11)</td>
<td>0.90</td>
</tr>
<tr>
<td>Global index</td>
<td>4</td>
<td>1.03 (0.95-1.11)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Global index HR was not modified by age (p>0.99 for trend)*

- Absolute risks of adverse events were lower in younger than older women

### CEE Alone

<table>
<thead>
<tr>
<th>Post-intervention</th>
<th>Diff/10,000 PY</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>-4</td>
<td>0.96 (0.77-1.19)</td>
<td>0.70</td>
</tr>
<tr>
<td>Breast CA</td>
<td>-7</td>
<td>0.80 (0.58-1.11)</td>
<td>0.19</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>-7</td>
<td>0.96 (0.84-1.10)</td>
<td>0.54</td>
</tr>
<tr>
<td>Global index</td>
<td>-6</td>
<td>1.00 (0.90-1.12)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Women in 50s had fewer events per 10,000 PY compared with women in 70s (p for trend, 0.02)*

## Conclusions

- Neither CEE + MPA nor CEE alone significantly affected all-cause mortality during or after the intervention phase
  - HT has a harmful effect on CHD risk among older women, results in younger women are inconclusive
- Risk–benefit ratio of HT is most favorable when initiated in younger menopausal women
  - Most risks and benefits from hormone therapy dissipate after stopping

## Take Home Messages

- For women early in menopause, risks are lowest for hormone therapy and once therapy is stopped these risks wane
- Minnie is young and healthy and would be a candidate for hormone therapy for her vasomotor symptoms; would recommend revisiting the use of hormones annually
ACOG Recommendations

- Management of Menopausal Symptoms, ACOG Practice Bulletin #141, January 2014
  - ACOG. Obstet Gyne. 2014
- Level A Evidence:
  - Systemic HT is the most effective therapy for vasomotor symptoms, low dose has better side effect profile
  - Risks of combined systemic HT include VTE and breast cancer
  - It is recommended that providers individualize care and treat women with lowest effective dose for the shortest duration needed to relieve vasomotor symptoms

Minnie, continued...

- Minnie decides she wants to use hormone therapy and asks what she should start. You have heard that transdermal methods might be safer, but are not entirely sure what to recommend beyond that...

Transdermal Estrogen

- Avoids hepatic first pass metabolism
  - Decreased effect on serum coagulation factors, triglycerides, CRP
- Associated with a lower VTE risk
  - Canonico, 2007
- Associated with a lower risk of stroke
  - Renoux BMJ 2010
- No RCT comparisons of differing HT regimens and clinical CVD outcomes

Key Article

- ACOG Committee Opinion: Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism
  - ACOG Committee Opinion #556, April 2013
- Prothrombotic effect of estrogen is possibly related to high concentrations of estrogen in the liver due to first pass effect
- Transdermally administered estrogen has little or no effect in elevating prothrombotic substances
Take home messages
- Transdermal estrogen has been associated with decreased risks of VTE compared with oral forms
- For Minnie, transdermal estrogen is safest, and it may be better to recommend it
  - And she needs a progestin as she still has a uterus

HT for Symptomatic Relief
- Any form of estrogen is highly effective
- Generally can be taken for a few years and gradually stopped
- A progestin should be added for women with a uterus
- Therapy can be tailored to a woman’s preference
  - “Lowest dose for shortest duration”

Effective Dose Equivalents
- Dose that stops hot flashes in 80% of women
  - 1 mg micronized 17 beta estradiol
  - 50mcg/day transdermal 17 beta-estradiol
  - 0.625 mg conjugated equine estrogens
  - 1.25 mg piperazine estrone sulfate

Lower dose hormone therapy
- Effective in some trials
- Estimates of efficacy after 12 weeks
  - 38% placebo
  - 63% low dose estrogen
  - 83% standard dose estrogen
- Lower doses may take longer for maximal symptom relief
  - 12 weeks vs 4-8 weeks
- Less bleeding and breast tenderness and may require less progestin
Adding Progestins

- Medroxyprogesterone acetate
  - 2.5 mg daily
- Micronized progesterone
  - "Natural"
  - 200 mg for 12 days or 100 mg a day
- Safer for heart and breast?
  - Not proven
- Cyclic vs continuous?
- Levonorgestrel containing IUD?
  - Off label

Bazedoxifene/conjugated estrogen

- Duavee® approved for treatment of menopausal symptoms and prevention of osteoporosis
  - CEE 0.45 mg
  - Bazedoxifene 20 mg
- Bazedoxifene has estrogen agonist effects on bone and antagonist effects on uterine tissue
- Theoretic advantage
  - Relieve estrogen deficiency symptoms while possibly avoiding increased risks of endometrial and breast cancer

Bazedoxifene/conjugated estrogen

- Medication improved indices of vaginal atrophy and reduced daily number of hot flashes compared with placebo
  - (-9 vs -2.4)
- Similar incidence of VTE between groups
- May be useful for women who can’t tolerate progestin

Estee Jenn

- Estee Jenn is a 60 year old woman who has been on HT for 10 years. You have been trying to encourage her to stop it for a while but she has not wanted to do it. Her best friend has recently developed breast cancer; she has now decided to stop, and wants your advice on the best way to do it. What do you recommend?
**QUESTION**

- Taper by decreasing the daily dose over 6-12 months
- Taper by decreasing the number of days a week HT is used over 6-12 months
- Just stop

**Discontinuing hormone therapy**

- Symptoms will recur in up to 25% of women with stopping therapy
- Unclear if it is best to stop “cold turkey” or to taper
- Taper can be by daily dose or number of days per week or strength of transdermal estrogen
- Taper until mild symptoms
  - Maintain that dose until symptoms resolve

**Factors Associated with Successful Discontinuation of HT**

- 2,328 women participated in a survey about HT practices
  - 802/2090 attempted HT discontinuation
- 75% experienced hot flushes after discontinuation
- Factors associated with successful discontinuation: MD advice, lack of symptom relief, vaginal bleeding and learning to cope with symptoms
- Factors associated with unsuccessful discontinuation: trouble sleeping, mood swings or depression

*Newton; J Woman’s Health 2014*

**QUESTION**

- Estee has a resumption of her hot flashes after she stops her estrogen. What pharmacologic alternative do you suggest?
  - Paroxetine
  - Escitalopram
  - Venlafaxine
  - Clonidine
  - Gabapentin
OTHER DRUG TREATMENTS

- SSRIs
- Venlafaxine
- Desvenlafaxine
- Clonidine
- Gabapentin

- Overall efficacy:
  - 50-67% reduction in hot flash frequency with these regimens
  - Placebo effects generally large

Paroxitene

- Paroxitene CR led to a significant decrease in hot flash score
  - 62% in 12.5 mg group
  - 65% in 25 mg group
  - 38% in placebo group

- Avoid in women receiving tamoxifen
  - Decreases active metabolite of tamoxifen
  - Cytochrome P450 CYP2D6

Brisdelle

- First non-hormonal treatment approved for treatment of menopausal symptoms
  - Paroxitene Salt 7.5 mg

- “Efficacy”
  - Reduced hot flashes/severe hot flashes compared with placebo
  - 1 to 1.7 fewer severe hot flashes per day at different time points
  - Proportion with >50% reduction in moderate to severe hot flashes at 24 weeks
    - 48% vs 36%

Escitalopram

- Reduction in hot flash frequency
  - 55% in escitalopram group
  - 36% in placebo group

- Effective in African American and Caucasian women

- Effective regardless of coexisting anxiety or depression
  - Freeman, JAMA 2011
Venlafaxine

- Significant reduction in hot flashes
  - 61% vs 27% in placebo (p<0.01)
- 150 mg no more effective than 75 mg
  - Lopinzi, Lancet 2000

Venlafaxine vs low dose estrogen

- MsFLASH
- 339 peri and post-menopausal women with at least 2 bothersome VMS per day
  - Low dose estrogen (0.5 mg estradiol)
  - Venlafaxine extended release (75 mg)
  - Placebo
- Mean VMS frequency after 8 weeks
  - Joffe et al JAMA 2014

Results

- Number of VMS per day at 8 weeks
  - Estradiol 3.9 (2.9-4.9)
  - Venlafaxine 4.4 (3.5-5.3)
  - Placebo 5.5 (4.7-6.3)
- Treatment satisfaction highest for estradiol
- Both interventions well tolerated

Impact

- Both low dose estrogen and venlafaxine reduced symptoms more than placebo
  - No higher dose estrogen comparison
- Treatment satisfaction with estradiol somewhat higher but clinical significance unclear
Desvenlafaxine

- Industry sponsored trial of metabolite of venlafaxine
  - 700 women with severe hot flashes
- 64% reduction in hot flashes at 12 weeks
  - Vs 51% with placebo
- Hot flashes less severe in desvenlafaxine group
- Not currently FDA approved for this indication
  - Speroff, 2008

Clonidine and Gabapentin

- Clonidine
  - Start with 0.1 mg/day transdermal patch
  - 40% reduction in hot flashes
  - Side effects can be limiting
- Gabapentin
  - 45% reduction in hot flashes vs placebo (29%)
  - 900 mg a day more effective than placebo
  - 300-600 mg at bedtime may help with hot flashes that awaken patients from sleep

“Bioidentical” hormone therapy

- Custom-compounded, multi-hormone regimens
  - Dose adjustments based on serial serum or saliva hormone monitoring
  - No evidence that monitoring is useful
- No evidence it is better than conventional HT
  - Safety not established
- FDA has published statement that the claims are false and misleading
- Endocrine Society states that there is no scientific evidence for bioidenticals

Question

- Estee is tired of medications and would like to try an herbal therapy for treatment of her hot flashes. What treatment do you recommend?
  - Black Cohosh
  - Evening primrose
  - Ginseng
  - Dietary soy
  - Wild yam
  - None of the above
The News

  – Menopause, 2015

• Objective
  – To update and expand the NAMS evidence-based position on nonhormonal management of menopause-associated vasomotor symptoms

Methods

• Systematic review of nonhormonal menopause treatments
• Costs, time, effort and adverse effects weighed against potential effectiveness
• Divided into categories
  – Recommended
  – Recommend with caution
  – Do not recommend at this time

Results

• Recommended
  – Cognitive behavioral therapy and hypnosis
  – Paroxetine is the only FDA-approved non-hormonal treatment
  – Other SSRIs, SNRIs, gabapentin and clonidine have shown efficacy

• Recommend with caution
  – Weight loss
  – Mindfulness-based stress reduction
  – Sesquiol derivatives of soy isoflavones
  – Stellate ganglion block

• Do not recommend at this time
  – Cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, OTC supplements and herbal remedies, acupuncture, chiropractic, calibration of neural oscillations

Impact for practice

• When recommending nonhormonal treatments for menopause, clinicians should be aware of the limited evidence supporting them
• Although many proposed menopause treatments may not have been proven to be beneficial for VMS treatment, some may be relatively benign (e.g. cooling techniques) or have other benefits (e.g. yoga and exercise)
Guidelines for Hormone Therapy Use

Recommendations

• USPSTF: Harmful effects are likely to exceed the chronic disease prevention benefits in most women

• ACOG, AHA, and Canadian Task Force recommend against use of HT for prevention of chronic disease

• NAMS 2012: When alternative therapies not appropriate, extended use of HT appropriate for women at high risk of fracture

NAMS 2012

• Focuses on emerging differences between ET and EPT as varying ages and time intervals since menopause

• Individualization in decision to use HT: consider individual health, personal risk factors and quality of life priorities

• ET has a more favorable risk benefit profile which allows for more flexibility in duration of use

• EPT associated with an increased risk of breast cancer incidence and mortality after 3-5 years

• Premature menopause: HT until median age of natural menopause and then reassess

NAMS Recommendations for Older Women (2015)

• Statement:
  – Provided that the woman has been advised of the increase in risks associated with continuing HT beyond age 60 and has clinical supervision, extending HT use with the lowest effective dose is acceptable under some circumstances, such as for the woman who has persistent bothersome menopausal symptoms and for whom her clinician has determined that the benefits of menopause symptom relief outweigh the risks.
  – Use of HT should be individualized and not discontinued solely based on a woman’s age.
  – Decision to continue or discontinue should be made jointly.
Donna

- Donna is a 67 year old woman with significant vaginal atrophy. She has not been sexually active for some time and when asked if this is bothersome to her she admits it causes difficulties in her relationship with her husband. She is very hesitant to use hormones in any form because she reads a lot of articles about them and doesn’t think they are safe. She has significant pain with intercourse, no other major symptoms.

- What recommendations do you have?

What do you tell her?

- Vaginal moisturizers
- Estrogen crème will work and it is safer than the pills
- Why don’t you try an estrogen vaginal ring? It’s safer than the crème
- There is a new medication called ospemifene that could help

Background

- VVA is associated with physical discomfort, sexual dysfunction, emotional distress, and reduced quality of life
- Incidence of VVA can be ~60%
- Current treatment options are only estrogen or vaginal moisturizer

Treatment Options

- Vaginal moisturizers are used several times a week and vaginal lubricants are used for sexual intercourse
  - Moisturizers: Replens, Vagisil
  - Lubricants: Astroglide, K-Y Jelly, Elegance Women’s
- Can improve symptoms of vaginal dryness or coital comfort but do not reduce vaginal atrophy
Local Estrogen

- Most effective treatment for moderate to severe symptoms of vaginal atrophy
- Can also reduce UTIs and symptoms of overactive bladder
- Typically given daily initially and then twice a week

Local Estrogen Preparations

- **Creams**
  - Estradiol (100 µg/g) or CEE (0.625 mg/g)
  - 1 applicator qd for 7 days
  - Then ¼ to ½ applicator twice a week
- **Tablet**
  - Vagifem (10 µg estradiol)
  - 1 tab vaginally for two weeks then one tab twice a week
- **Ring**
  - Estrin
  - Releases 7.5 µg estrogen daily for 90 days

Ospemifene

- Novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy
- Trial in over 600 women with moderate to severe dyspareunia
- Severity of vaginal pain improved by 2-3 levels in 52.8% of ospemifene, 38.8% of placebo
- Hot flushes were the most common AE
  - Only 4.6% in treatment group discontinuing due to AE

Key Article

  - NAMS. Menopause, 2013.
- <10% of women report their provider initiated a conversation about VVA
- 1st line therapy: lubricant with intercourse and vaginal moisturizer [Level A]
- Mod-severe VVA: low dose vaginal estrogen or ospemifene [Level A]
Take Home Messages

• Screen women for dyspareunia and VVA—it’s common and distressing for women

• Ospemifene is a SERM with apparent positive effects on VVA without endometrial or VTE events
  – Vasomotor symptoms are the most common side effect
  – Not for use in women with a history of breast cancer
  – FDA approved for moderate-severe dyspareunia

Treatment of Vaginal Atrophy

• Regular sexual activity helps maintain vaginal health
• Start with moisturizers and lubricants
• Vaginal Estrogen if moisturizers and lubricants are insufficient
  – Type of estrogen dependent on patient preference
• Ospemifene if a woman can’t (arthritis, obesity, vulvodynia) or prefers not to use vaginal product

Women with Breast Cancer

• Topical estrogen has minimal systemic absorption but it is not zero
• Start with non-hormonal options
• Women on aromatase inhibitors
  – Probably best to avoid
• Women with low risk of recurrence
  – Probably ok
  – In concert with oncologist and with discussion of pros and cons

Summary

• Average duration of menopausal symptoms is approximately 4-7 years but seems to be longer in younger women
• Estrogen either alone or with a progestin is not recommended for chronic disease prevention in postmenopausal women
• Risks and benefits of estrogen treatment may differ in older and younger women
Summary

- Estrogen works best for symptoms
  - Use lowest dose for shortest duration
- Best method for discontinuation is not known
- Start with lifestyle modifications and nonprescription remedies
- Drug alternatives include SSRIs, SNRIs, gabapentin, clonidine and combined estrogen/SSRI

Vaginal Atrophy

- Regular sexual activity, moisturizers and lubricants
- Topical estrogen: start with higher dose and then decrease to maintenance dose
- Ospemifene: for women who can’t or won’t use estrogen
- Women with breast cancer individualized decision

Questions?

“Having nine lives is cool, but if I have to go through menopause again, forget it!”
CHRONIC KIDNEY DISEASE
UPDATE: WHAT THE
GENERALIST NEEDS TO KNOW

MICHAEL G. SHLIPAK, MD, MPH
CHIEF-GENERAL INTERNAL MEDICINE,
SAN FRANCISCO VA MEDICAL CENTER
PROFESSOR OF MEDICINE, EPIDEMIOLOGY AND
BIOSTATISTICS, UCSF

Disclosures

- I am on the Scientific Advisory Boards with stock option compensation for the following companies:
  - TAI Diagnostics
  - Cricket Health, Inc.

Outline

- Definition and Complications
- New CKD Staging 2013
- Screening for CKD
- Introduction to Cystatin C
- Treatment of CKD
- Hyperkalemia

Outline

- Definition and Complications
- New CKD Staging 2013
- Screening for CKD
- Introduction to Cystatin C
- Treatment of CKD
- Hyperkalemia
Question 1: Which of these patients has CKD?

- A. Heart failure patient in ED with creatinine of 2.0
- B. Diabetes patient with albumin/creatinine of 100 mg/g, creatinine = 1.0 mg/dL
- C. 35 year old African American man with creatinine of 1.5
- D. All of the above

---

**Introduction**

- **Chronic Kidney Disease (CKD):**
  - Defined in 2002 with original CKD staging
  - Replaced earlier terms "chronic renal insufficiency", "chronic renal failure", or "high creatinine"
  - Previous 5 CKD stages were developed by an expert panel
  - Most CKD epidemiology research has been conducted since the 5 stages were defined

---

**Definition and Complications**

- Overall CKD definition unchanged
- **Chronic kidney disease:** >3 month duration of either:
  - Decreased kidney function (GFR<60)
  - Injury/damage to the kidney (e.g. albuminuria, cysts, stones)
- **Etiology of CKD:**
  - Common diseases treated by generalists: diabetes, hypertension, cardiovascular disease, heart failure
  - Other systemic diseases typically treated by specialists: systemic lupus erythematosus, HIV, urological diseases
  - **Primary kidney disease:** polycystic kidney disease, glomerular disease

---

**DEFINITION & CLASSIFICATION OF CHRONIC KIDNEY DISEASE**

KDIGO 2012 Clinical Practice Guideline (CPG) for the Evaluation and Management of Chronic Kidney Disease
Complications of CKD

- Kidney failure (end-stage renal disease)
- Death
- Other chronic disease:
  - Atherosclerotic Cardiovascular Disease
  - Heart failure
  - Osteoporosis/fracture
  - Cognitive impairment/dementia
  - Frailty
- Treatment Complications:
  - Medications
  - Procedures

Prognosis by eGFR and Albuminuria

- Key meta-analysis published in 2010 in Lancet
- Evaluated prognosis by eGFR and albuminuria
- 21 studies, 1.2 million patients
- Predictor:
  - eGFR categories
  - Albuminuria (ACR categories)
- Outcome: mortality risk

### Albuminuria and eGFR grid


<table>
<thead>
<tr>
<th>Albuminuria Classes (mg/g)</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-300</th>
<th>&gt;300</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;105</td>
<td>1.0</td>
<td>1.4</td>
<td>2.0</td>
<td>4.4</td>
<td>1.2</td>
</tr>
<tr>
<td>90-104</td>
<td>1.0</td>
<td>1.3</td>
<td>1.5</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>75-90</td>
<td>0.9</td>
<td>1.2</td>
<td>1.7</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>60-74</td>
<td>0.9</td>
<td>1.1</td>
<td>1.6</td>
<td>1.0</td>
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<tr>
<td>55-59</td>
<td>1.0</td>
<td>1.4</td>
<td>1.6</td>
<td>2.6</td>
<td>1.9</td>
</tr>
<tr>
<td>50-44</td>
<td>1.7</td>
<td>2.3</td>
<td>3.0</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>30-44</td>
<td>2.0</td>
<td>3.5</td>
<td>4.2</td>
<td>6.0</td>
<td>3.6</td>
</tr>
<tr>
<td>15-29</td>
<td>4.0</td>
<td>4.2</td>
<td>5.0</td>
<td>6.0</td>
<td>3.6</td>
</tr>
</tbody>
</table>

*P<0.05

### ESRD Risk


<table>
<thead>
<tr>
<th>Albuminuria Classes (mg/g)</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-300</th>
<th>&gt;300</th>
<th>All</th>
</tr>
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<td>eGFR (mL/min/1.73m²)</td>
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<td></td>
</tr>
<tr>
<td>&gt;105</td>
<td>0.1</td>
<td></td>
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</tr>
<tr>
<td>90-104</td>
<td>0.3</td>
<td></td>
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<td>0.3</td>
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<tr>
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<td>0.4</td>
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<tr>
<td>60-74</td>
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<tr>
<td>55-59</td>
<td>1.0</td>
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<td></td>
<td>1.0</td>
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<tr>
<td>50-44</td>
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<td>15-29</td>
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<td>4.0</td>
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</tbody>
</table>

*P<0.05
Outline

- Definition and Complications
- New CKD Staging 2013
- Screening for CKD
- Introduction to Cystatin C
- Treatment of CKD
- Hyperkalemia

CKD Stages and Prevalence

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Estimated GFR (mL/min per 1.73 m²)</th>
<th>U.S. Prevalence N (1000's) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 1</td>
<td>90**</td>
<td>3,200 (1.4)</td>
</tr>
<tr>
<td>CKD Stage 2</td>
<td>60-89*</td>
<td>6,500 (3.2)</td>
</tr>
<tr>
<td>CKD Stage 3</td>
<td>30–59</td>
<td>15,500 (7.7)</td>
</tr>
<tr>
<td>CKD Stage 4</td>
<td>15–29</td>
<td>700 (0.4)</td>
</tr>
<tr>
<td>CKD Stage 5</td>
<td>&lt;15 (or dialysis)</td>
<td>400 (0.2)</td>
</tr>
</tbody>
</table>

*With evidence of kidney damage, e.g. albuminuria

Problems with Old Staging

- Stages 1 and 2 were the same
- Stage 3 (30-60) was too broad; eGFR of 30-45 is very different from 45-60
- Did not address levels of albuminuria; and only used albuminuria for Stages 1 and 2

From Old to New Staging

- KDOQI Guidelines, AJKD, Feb. 2002
- "CKD" is an inadequate descriptor (like diabetes)
- Hypertensive with eGFR= 50, ACR= 10
- Diabetic CKD with eGFR= 75, ACR= 500
- Polycystic Disease
- GN
- G4 (15–29)
- G5 (< 15)
It is recommended that CKD be classified by:
- Cause
- GFR category
- Albuminuria category


International CKD guidelines do not address when or how to screen
- No RCT evidence for or against
- Relative costs of screening vary by region
- Hypertension, Diabetes, and CVD guidelines all recommend some form of CKD screening.
- The following are my suggestions for primary care:

Primary prevention screens:
- Diabetes- annual
- Hypertension
- Elderly

CKD Staging:
- Urine albumin is now important part of CKD staging
- Should be measured and documented in all CKD patients
  - Repeat annually in diabetics
  - every 2-3 years in non-diabetics
How to Measure Urine Albumin

- Often listed as “microalbumin panel”
- Focus on albumin/creatinine ratio (ACR):
  
<table>
<thead>
<tr>
<th>ACR (mg/g)</th>
<th>OLD</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>Normal</td>
<td>Normal or mildly elevated</td>
</tr>
<tr>
<td>30-300</td>
<td>Microalbuminuria</td>
<td>Moderately elevated</td>
</tr>
<tr>
<td>&gt;300</td>
<td>Macroalbuminuria</td>
<td>Severely elevated</td>
</tr>
</tbody>
</table>

- Dipstick: “trace” is abnormal
- If dipstick is abnormal, quantify ACR

Who and When to Check Creatinine?

- Begin screening:
  - Age >40 lower-risk populations
  - Age >30 Blacks, Native Americans
- Diagnosis of hypertension, diabetes, cardiovascular disease, heart failure
- Frequency of creatinine monitoring (no evidence)
  - No risk factors: 3-5 years
  - Risk factors: 1-2 years
- Creatinine cost: $0.20

Question 2: Which of the following is true about creatinine GFR estimates?

A. More accurate in older populations than middle-aged because prevalence of kidney disease is higher
B. They have been validated in most ethnic groups
C. They are more likely to be accurate in healthy persons than in persons with chronic illness
D. All of the above

GFR Estimation from Creatinine

- Estimated GFR:
  - Automatic reporting by most labs
  - Equations are rough
  - <60 concerning for kidney disease, but not specific
  - >60- so imprecise, its considered just “>60”

3 equations in current use:

- Cockcroft-Gault (Nephron, 1976)- used by FDA and pharmacies
- MDRD (Annals, 1999)- used for most automated reporting
- CKD-EPI (Annals, 2009)- favored by researchers
Pros and Cons of Estimated GFR

- **Pros:**
  - Indexes creatinine for demographic characteristics
  - Forces us to think in terms of GFR and kidney function

- **Cons:**
  - Mostly validated in younger patients with kidney disease
  - Huge assumption that demographic characteristics alone can define muscle mass
  - Only developed in Whites and Blacks
  - Estimated GFR ≠ GFR

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Question 3: Which of the following is true of cystatin C?

A. Better marker of GFR than creatinine
B. Better marker of glomerular injury than albumin
C. Has not been studied in African Americans, but approved for use in Whites
D. Only used outside the U.S.
E. All of the above

Cystatin C

- Cystatin C is a blood test of kidney function that is an alternative better version of creatinine
- Because cystatin C is not related to muscle mass (or age, sex, and race), it has major advantages over creatinine
- Cystatin C is a reliable, standardized, and automated measure that is available for clinical use.
“Cystatin C versus Creatinine in Determining Risk based on Kidney Function”
Shlipak et al. New England Journal of Medicine, 2013

- Meta-analysis of all available observational studies and clinical trials with creatinine and cystatin C
- 16 studies, 90,750 persons
- Compared associations of eGFRcr, eGFRcys, and eGFRcr-cys with mortality risk
- Determined proportions reclassified by cystatin C in each eGFRcr subgroup and impact on risk associations

Comparisons of eGFR Using Creatinine, Cystatin C, or both with All-Cause Mortality

Reclassification by eGFRcys and associated risk
# International Guidelines Support Use of Cystatin C


## KDIGO Suggestion #1 (2B)

**Estimating GFR:**

1. Use creatinine eGFR
2. Are you confident that this is accurate?
3. If not, use either:
   - Cystatin C
   - Direct measure GFR

## KDIGO Suggestion #2 (2C)

**Confirming CKD:**

Your patient’s eGFRcr is 45–60 and is not known to have kidney disease:

- Measure cystatin C
- If cystatin C eGFR <60, patient has CKD
- If cystatin C eGFR >60, patient does NOT have CKD

## KDIGO Recommendation (1C)

- For medical dosing of potentially toxic agents, use cystatin C or direct measure GFR
- Potential examples – novel, oral anti-coagulants, chemotherapeutics, metformin
- Major challenge – FDA has dosing based on creatinine clearance
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CKD Treatment

- Goals:
  - Prevent progression to ESRD
  - Prevent CKD complications

- Treatments:
  - ACE/ARB therapy
  - Blood Pressure Control
  - Glucose Control in Diabetes
  - Statins

ACE/ARB's in Diabetic and Non-Diabetic CKD

- Diabetic CKD- nearly always has albuminuria
- Diabetic CKD- ACE/ARB essential for:
  - Moderate albuminuria (ACR 30-300)
  - Severe albuminuria (ACR > 300)
- ACE/ARB’s do not appear to be helpful to prevent onset of albuminuria
- In non-diabetic CKD, ACE benefit limited to persons with proteinuria
  - Rahman M, Arch Intern Med, 2005

  Conclusion: For patients with reduced eGFR but normal levels of albuminuria - choice of blood pressure agent probably does not matter

Two Guidelines, Two Opinions

- The new JNC-8 Guideline: ACE/ARB should be used in all patients with CKD (eGFR<60)
  - James PA et al. JAMA 2014
- KDIGO-CKD Hypertension Guideline: ACE/ARB only necessary if ACR > 30
Frequently Asked ACE/ARB Questions

- **Question 1:** How much increase in creatinine is safe?
  - **Answer 1:** ↑ of creatinine >30% is common; worry about the potassium

- **Question 2:** Do we stop the ACE in advanced CKD?
  - **Answer 2:** Only if the potassium is un-manageable
    - RCT: Hou FF et al. NEJM 2006; 354: 131-140

- **Question 3:** Is there a reason to combine ACE + ARB?
  - **Answer 3:** No, might decrease proteinuria, but increased potassium risks too high

Blood Pressure Target Uncertain in CKD

- Modern RCTs HAVE NOT proven that tighter BP control reduces CKD PROGRESSION

- Current guidelines on blood pressure control in CKD:
  - JNC-7 target < 130 (contrast with <140)
  - KDIGO-CKD HTN guideline: <140, though <130 considered optimal.
  - JNC-8 target < 140 (contrast with < 150)

- **Does SPRINT apply to CKD patients?**
  - SPRINT Trial: SBP <120 (Intensive) vs. <140 (Standard)
  - Primary Outcome (CVD composite): HR 0.75 (0.64 – 0.89)
  - CKD subset (N = 2,646)
    - Primary CVD outcome: 0.82 (0.63-1.07) (interaction p=0.36)
    - Composite renal outcome: 14 vs. 15 events
    - Impact on kidney injury – TBD
  - **Summary:** Impact of intensive BP lowering appear similar in persons with or without CKD.
    - Participants without CKD at baseline had higher incidence of incident CKD (<60 ml/min and 30% decline)
    - 127 vs. 37 events; HR = 3.49 (2.44 – 5.10)

- **Glycemic Control in Diabetic CKD**
  - **Type I Diabetes**— tight glucose control slows kidney disease progression: OR= 0.34 (0.20-0.58)
  - **Type II Diabetes**— ADVANCE trial (NEJM, 2008, 2560-72)
    - Tight glucose control (HbA1c 6.5 vs. 7.3): 20% lower risk of “new or worsening nephropathy”(RR 0.80; p=0.006)
    - Low rates: 4.1 vs. 5.2%
  - In Type II Diabetes, risks of tight glucose control probably offset kidney benefits in older patients.
Statins in CKD- beneficial for CVD

- CKD patients have very high CVD Risk
- Statins lower CVD risk in CKD patients:
  - Meta-analysis of 20 early studies (N=18,746 patients) found RR 0.80 (95% CI: 0.70,0.90)
  - SHARP RCT: (N=9,500) simvastatin/ezetimide vs placebo RR= 0.83 (95% CI: 0.74-0.94)
- No effect on CKD progression
- No benefits of statins in patients with ESRD

Question 4

In a stable patient on an ACE or ARB, I will tolerate K levels up to the following without stopping the ACE/ARB:

A. 5.1
B. 5.3
C. 5.5
D. 5.9

Question 5

Your patient with diabetic nephropathy (eGFR<40, ACR 150) has serum K of 5.3 on repeat measures over 6 months. She is asymptomatic and has a normal physical exam except for symmetric decreased sensation to the ankle. What should you do next?

A. Change to losartan as it causes less hyperkalemia
B. Increase her furosemide to lower the K
C. Educate her about situations that would elevate her K further
D. Stop the lisinopril

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A New Era for the Treatment of Hyperkalemia?

Hyperkalemia is in the Eye of the Beholder

Mild hyperkalemia: 5.0-5.9
Moderate hyperkalemia: 6.0-7.0
Severe hyperkalemia: >7.0

New Agent to Treat Hyperkalemia in CKD (Patiromer) Wirr MB, NEJM 2015

- FDA approved
- Subjects: CKD and mild/moderate hyperkalemia (5.0-5.6)
  - eGFR: 38
  - K: 5.6
- Intervention: patiromer (4.2g or 8.4mg BID)
- Adverse effect: constipation – 11%

Baseline: 5.7
1 week: 4.9
Day 3: 5.2

Thank you!
Any Questions?
**Dermatologic Procedures**

Toby Maurer, MD
University of California, San Francisco

- Liquid nitrogen
- Intralesional steroids
- Unna Boots
- Biopsies-snip, shave, punch
- .....scabies prep and KOH preps

**The Gun vs. The Q-Tip**

- Cost:
- Gun delivers more constant pressure
- Gun is faster if you have the volume

**Liquid Nitrogen**

- Thaw time is key
- Thawing destroys the cells
- Freeze to get sustained ice ball & adequate thaw time
- Thaw time - From time the lesion is white until it goes back to normal color
- Always do 2 cycles of thawing
Liquid Nitrogen (cont’d)
- Thaw times differ by location
  - Face/genital 2 x 15 sec. thaws and dorsal arms
  - Palms/soles 2 x 30-45 sec. thaws
- Thaw times differ by diagnosis
  - Seborrheic keratoses - 15 sec. thaws
  - Actinic keratoses - 15 sec. thaws
  - Warts - need more & want to go 1mm around periphery

Know what you are freezing
- Check that pt has resolution of lesion - document that you told them or that you are bring them back

Side Effects
- So cold it feels like a burn
- Blister tonight then crust that will take 5 days to resolve (15 sec. thaws) vs. 10 days (30-45 sec. thaws)
- Can break the blister
- Warn re: hypo/hyperpigmentation in persons w/underlying pigment

Intralesional Steroids
- Used for keloids, hypertrophic scars, patches of alopecia areata
- Trick is not to go into fat but stay in dermis (don’t want atrophy)
- Warn patient and document potential side effects like pigment change and atrophy
- For alopecia areata -10 mg/cc; 1-3 cc per month
- For Keloids -20-40 mg/cc; 1 cc per month
Keloids

- Intralesional steroids-20–40 mg/cc
- Pts will absorb steroids systemically so limit is 40 mg per month
- Anaesthetize surface with lidocaine and epinephrine using 30 gauge needle
- Get into the right space and inject steroid with 22 gauge needle

How to do a KOH

- Scrape the area and GET LOTS of scale-use a 15 scalpel
- Place cover slip on top of scale
- Put a drop of KOH on the side of the cover slip and let it go under the slip by osmosis

- Heat the specimen not to point of boiling (Important to do when you have dry skin)
- Use your pen to put pressure on cover slip to separate the cells
- Bring your condensor all the way down
- Use 4x power and MAX of 10 x power to look for hyphae
Scabies Prep

- Why do it? Not everything that itches is scabies Tip: itchy nodules on penis=scabies
- Don’t rely on finding a burrow but if you do, scrape it-high yield
- Highest yield areas-between the fingers, wrists, scapula, lateral edge of the feet-look for papulovesicular lesions that are primary (not scratched)
Juice and scale go on slide, place cover slip on top
Mineral oil is great but water will do
Bring condenser all the way up
Look at every part of slide and especially around cover slip edges

Unna Boots
- For venous ulcers when there is edema
- Make sure there is no cellulitis before you cover an area
- You will need:
  Currette, +/- lidocaine (no epi), metrogel, duoderm, allevyn, unna boot
Unna Boots

- Never too tight
- Leave folds in place
- Anchor joints
- Start at mid foot and work up to the knee
- Coban layer on outside
- If pt notes pain, take dressing off
BIOPSIES

- Pathologists are only as good as the clinician
- REFER - If you have no idea what you are looking at, neither will the pathologist.
- Must include history, location and DIFFERENTIAL diagnosis-what are you ruling out AT LEAST

Biopsy Tips

- Give your pathologist an adequate and representative sample
- Choose a lesion that has not yet evolved
- Don’t crush the tissue
- If your results don’t make sense, call the pathologist or a dermatologist for review
- Billing: procedural code for biopsy (including closure)-neoplasm of uncertain behavior
• NUMBING IS STANDARD OF CARE
• 1% Lidocaine and epinephrine
• Epi-okay to use on fingers, toes, and penis unless using large doses
• Do not use Epi in Reynaunds or other vascular problems (lower leg vascular insufficiency)
• EMLA in Kids followed by IL numbing
• Lidocaine allergy
• IL Benadryl

Informed Consent
• Why are you doing this?
• What could be done instead?
• Risks involved
  – Scar
  – Infection
  – Bleeding

Snip Biopsies/Excision
• Scissor snip
• Skin tags
• AlCl for hemostasis
• Send to pathology
• Do NOT use silver nitrate or Monsels on visible skin

Shave Biopsies
• Leave half of lesion behind so you know to where to return for definitive treatment
• Puff up section with anesthetic and LIGHTLY pick up with forceps-scalpel cuts under skin
• Al CI for hemostasis
• Petroleum jelly/bandaid
Punch Biopsies

- Allows you to get to the top of the fat
- You will get the epidermis and dermis
- Use for diseases that go into the dermis from the epidermis or that originate in the dermis. (Hint: There is a palpable or papular/nodular component.)

Punch Biopsy

- Punch (sizes 2-6mm)
  - 2mm - Not enough info for pathologist
  - 3mm - Use in cosmetically sensitive areas
  - 4mm - Standard
  - 5-6mm - Use to get around lesion or if submitting part of a biopsy for tissue culture
Punch Biopsy - You Will Need

• Non-absorbable suture
  – 2mm & 3mm - one stitch
  – 4mm - two stitches
  – 5mm and 6mm - three stitches
  – GELFOAM

How to make a hole oval?

• All in skin tension lines

Suturing

• Interrupted adequate
• Double knot for first throw then 3 more single knot throws
• Remove sutures in 3 days face, 7 days back, chest and 10-14 days limbs
• Petroleum jelly/bandaid-keep wound dry

Excisional Biopsies

• You have control
• Go down to fat, through fat to fascia & beyond
• Lets you get around the lesion entirely
  – Malignant melanoma
  – r/o Dysplastic nevus vs. malignant melanoma
  – Vasculitis
  – Panniculitis
  – Epidermoid cysts
- Mark it with pen before putting in anesthetic
- 3:1 rule-measure lesion- If 1 cm, then will need total length to be 3 cm (1.5 cm on each side) for proper closure
- Don’t bevel blade—should be perpendicular

- Undermine edges for larger wounds—helps to close
Keeping up with the Literature

- Impossible task for busy clinicians
- Nearly impossible task for academician
- My sources:
  - Journal table of contents
  - Email newsletters (Journal Watch, specialty newsletters, AMA, etc.)
  - Popular press
  - If the topic is interesting, then I go to the manuscript

Manuscript Review:

Questions I Consider

- Does this study address an important question?
- Can the study design answer the question?
- What were the results?
  - Overall conclusion
  - Strength of the findings
  - Generalizability of population
  - Ethical or cost considerations
- Does this change my practice?

Today’s Outline

- 6 articles to discuss
  - 10 minutes per article
- Audience participation is essential
- Questions and comments can relate to:
  - Overall topic
  - Methods
  - Clinical implications
  - Practical experience
Questions Addressed

1. Is Celecoxib worse than Ibuprofen and Naproxen as a Cardiovascular Risk promoter?
2. How much lower are toxins and carcinogens in electronic cigarettes and nicotine supplements vs. tobacco?
3. Does CPAP Reduce Cardiovascular Risk in OSA?
4. Does the BMI need to be interpreted differently across different ethnic groups?
5. In patients with moderate COPD, does oxygen therapy prevent deaths and hospitalizations?
6. Must Benzodiazepines be kept away from Opiate users?

Clinical Question/Challenge

- **Situation:** Your arthritic patient requires NSAIDS, but gets dyspepsia with most of them. You recall that Vioxx was removed from the market because of CVD harms.

Is celecoxib (celebrex) any worse for CVD risk than ibuprofen or naproxen?
**PRECISION TRIAL:** Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen

- **Design:** RCT; 3 arms (celebrex, ibuprofen, naproxen)
- **Non-Inferiority Trial**
- **Co-intervention:** PPI (esomeprazole 20-40mg) for all
- **N=44,222** (936 centers, 13 countries)
- **Inclusion:** OA, RA; daily users of NSAIDS for pain
- **Outcomes:**
  - Primary: CVD events (MI, stroke, CVD death)
  - Secondary: a) primary + revascularization, unstable angina, TIA
  - Tertiary: renal events, anemia (GI origin), HF hospitalization, hypertension hospitalization
- **Funding:** Pfizer


---

What does “non-inferiority” mean?

- Goal to prove that Celebrex is not worse than naproxen (one-tail hypothesis); not that Celebrex is different (<,>) from naproxen (two-tails)
- This is like “proving” the null hypothesis of the treatments being equal.
- The funder is motivated to find no difference between medications
- This is the complete opposite of an efficacy trial, where you want to find differences between trial groups.
- Crossover and dropout kill an efficacy trial, but actually help a non-inferiority trial.
- Statistically, in this trial, non-inferiority defined as HR \( \leq 1.12 \) (comparing celecoxib with naproxen) with a CI \( \leq 1.33 \) at high end

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**Participants**

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
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</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td>90%</td>
</tr>
<tr>
<td>RA</td>
<td>10%</td>
</tr>
</tbody>
</table>


---

**Participants continued**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA use</td>
<td>46%</td>
</tr>
<tr>
<td>CVD</td>
<td>23%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>21%</td>
</tr>
<tr>
<td>Statins</td>
<td>54%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 ± 0.3</td>
</tr>
</tbody>
</table>

**Initial Max Mean Dose in RCT**

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Max</th>
<th>Mean Dose in RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>200mg BID</td>
<td>200mg BID</td>
<td>200mg</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>600mg TID</td>
<td>800mg TID</td>
<td>800mg</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500mg BID</td>
<td>500mg BID</td>
<td>500mg</td>
</tr>
</tbody>
</table>

**Compliance:**
- Mean time on treatment: 20 months
- Follow-up: 34 months
- 69% stopped study drug

**Results: Intention-to-Treat Analysis**

**Results: On-Treatment Analysis**

**Results: Celebrex Reduced GI Events**
Results: Celebrex Reduced Renal Events

Conclusions

- Celecoxib/Celebrex appears to be no worse than naproxen or ibuprofen for cardiovascular risk.
- Celecoxib appears to offer lower GI and renal risk, even among PPI users.
- Naproxen may have lower MI risk than ibuprofen.

How much lower are toxins and carcinogens in electronic cigarettes and nicotine supplements vs. tobacco?
Clinical Question/Challenge

• **Scenario:** Your patient is a long-term smoker, and has tried to quit many times. The patch and gum have not worked well, but he finds that e-cigarettes satisfy his cravings well enough.
  - Are e-cigarettes almost as bad as tobacco cigarettes?
  - Do nicotine levels differ between NRTs, e-cigarettes, and “combustible cigarettes”, aka tobacco?

Design

- **Setting:** London, UK
  - 2014 (January-June)
- **Design:** cross-sectional
  - Single session (30 minutes)
  - 1 hour without food, water, or nicotine
- **Participants:** N= 180
  - Recruited from newspapers, online ads
  - Ever smokers
  - 6 months continuous tobacco use/non-use
- **Funding:** Cancer Research UK

Results

- 5 groups (N= 36 per group)

<table>
<thead>
<tr>
<th></th>
<th>Current Age</th>
<th>Mean cigs/day</th>
<th>Age started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current tobacco</td>
<td>34</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Tobacco + NRT</td>
<td>36</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Tobacco + ecig</td>
<td>39</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>NRT only</td>
<td>40</td>
<td>0 (15 before)</td>
<td>20</td>
</tr>
<tr>
<td>Ecig only</td>
<td>39</td>
<td>0 (16 before)</td>
<td>17</td>
</tr>
</tbody>
</table>

NRT = nicotine replacement therapy: patch, gum, lozenge, etc.
Ecig = electronic cigarette

Toxins Assessed from Urine and Saliva

<table>
<thead>
<tr>
<th>Parent Compound</th>
<th>Biomarker/Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco-specific N-nitrosamines</td>
<td></td>
</tr>
<tr>
<td>4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol</td>
<td>4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol</td>
</tr>
<tr>
<td>Volatile organic compounds</td>
<td></td>
</tr>
<tr>
<td>Acrolein</td>
<td>N-acetyl-3-hydroxypropyl-L-cysteine</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>N-acetyl-S-(2-cyanoethyl)-L-cysteine</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>N-acetyl-S-(2-carbamoyl)-L-cysteine</td>
</tr>
<tr>
<td>1,3-butadiene</td>
<td>N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>N-acetyl-S-(2-hydroxyethyl)-L-cysteine</td>
</tr>
</tbody>
</table>

Nicotine Content Relative To Tobacco Only

Urinary Metabolite Levels for Selected Toxins and Carcinogens, by Group

Urinary Metabolite Levels for Selected Toxins and Carcinogens, by Group

Nicotine Content Relative To Tobacco Only

Urinary Metabolite Levels for Selected Toxins and Carcinogens, by Group
Urinary Metabolite Levels for Selected Toxins and Carcinogens, by Group

**Acrylamide**
- ref: 45% 43%

**Acrylonitrile**
- ref: 11% 3%

**1,3-butadiene**
- ref: 28% 11%

**Ethylene Oxide**
- ref: 54% 43%
Conclusions

• Former smokers get equivalent nicotine from NRT or e-cigs as do current smokers
• Alternative nicotine products have lower levels of tobacco toxins
• No difference between NRTs and e-cigs observed
• NRT and e-cigs both associated with quantifiable levels of carcinogens and toxins, so complete nicotine cessation remains the safest option.

Clinical Question/Challenge

• OSA is believed to be a risk factor for stroke and CVD, perhaps by its effects on blood pressure, sympathetic nervous system activation, and inflammation.
• RCTs show that CPAP lowers blood pressure, improves endothelial function, and increases insulin sensitivity.
• I have several patients with diagnosed CVD and OSA that I cannot get to use their CPAP.
• Would they have lower CVD risk if they used CPAP, and should I try harder to convince them?
Design: The SAVE Trial

- **Sleep Apnea Cardiovascular Endpoints Study (SAVE Trial)**
- **Design:** RCT, parallel group, open-label
  - 80 centers, 7 countries
  - CPAP: 1346; Usual Care: 1341
  - REM Star equipment
- **Inclusion:**
  - Prior CVD (excluding heart failure)
  - Moderate-severe OSA defined as 12 episodes/hour of \( \downarrow \) SPO\(_2\) \( \geq 4\%
- **Exclusion:**
  - Severe daytime sleepiness
  - Severe hypoxemia (<80% for >10% time)
  - Cheyne-Stokes
- **Run-in:** sham CPAP ≤ 3 hours/night during 1-week
- **Funding:** National Health and Medical Research Council of Australia


The SAVE Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPAP Group (N=1346)</th>
<th>Usual-Care Group (N=1341)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Male sex</td>
<td>81%</td>
<td>81%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>64%</td>
<td>63%</td>
</tr>
<tr>
<td>White</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>BMI</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>29</td>
<td>30</td>
</tr>
</tbody>
</table>


Results

- 3.5 hours/night average of CPAP use
- In CPAP group, 42% ≥ 4 hours/night
- API: 29 (pre) to 3 (CPAP)
- Only 4% of usual care chose to use CPAP

### End Point

<table>
<thead>
<tr>
<th>End Point</th>
<th>CPAP Group (N=1346)</th>
<th>Usual-Care Group (N=1341)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Primary outcome</td>
<td>229 (17.0)</td>
<td>207 (15.4)</td>
<td>1.10 (0.91-1.32)</td>
</tr>
<tr>
<td>CV death</td>
<td>25 (1.9)</td>
<td>20 (1.5)</td>
<td>1.22 (0.68-2.20)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>42 (3.1)</td>
<td>39 (2.9)</td>
<td>1.06 (0.68-1.64)</td>
</tr>
<tr>
<td>Stroke</td>
<td>67 (5.0)</td>
<td>68 (5.1)</td>
<td>0.97 (0.68-1.35)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>17 (1.3)</td>
<td>17 (1.3)</td>
<td>0.98 (0.56-1.70)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>99 (7.4)</td>
<td>90 (6.7)</td>
<td>1.09 (0.82-1.45)</td>
</tr>
<tr>
<td>Death</td>
<td>40 (3.0)</td>
<td>43 (3.2)</td>
<td>0.91 (0.56-1.40)</td>
</tr>
</tbody>
</table>


### Conclusions

- Among patients at high risk of CVD, effective CPAP did not alter CVD risk.
- CPAP improved quality of life, mental health, and work attendance.

---

### CPAP Improved Sleepiness, Anxiety, and Depression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPAP Group (N=1346)</th>
<th>Usual-Care group (N=1341)</th>
<th>% change during study</th>
<th>% change during study</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epworth sleepiness scale score</td>
<td>↓42%</td>
<td>↓9%</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Anxiety score</td>
<td>↓17%</td>
<td>↓9%</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Depression score</td>
<td>↓14%</td>
<td>↓2%</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Lost work days</td>
<td>↓18%</td>
<td>Ref.</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>


### Does the BMI need to be interpreted differently across different ethnic groups?
Clinical Question/Challenge

- **Situation**: We are well-calibrated to the BMI categories, but they may not apply to our Asian patients. Within the “normal weight” population, BMI < 30, studies have shown East Asians have elevated metabolic risk at lower BMI levels.

My South Asian patient has a BMI of 24, but is this low enough to be ideal?

**Design**

- **Design**: cross-sectional, community-based cohorts
  - Multi-Ethnic Study of Atherosclerosis (MESA)
  - Mediators of Atherosclerosis in South Asians Living in America (MASALA)

- **Participants**:
  - MESA: 2622 Whites, 803 Chinese American, 1801 African American, and 1496 Hispanics
  - MASALA: 803 South Asians

- **Outcomes**:
  - HDL < 40 (men); <50 (women) (or medication)
  - TG > 150
  - Glucose > 100 (or medication)
  - Blood pressure > 130/85 (or medication)

- **Metabolically Abnormal Normal Weight (MAN phenotype)** ≥ 2

- **Funding**: NIH

**Prevalence of Metabolically Abnormal Normal Weight (MAN phenotype)**

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>23%</td>
</tr>
<tr>
<td>Chinese</td>
<td>32%*</td>
</tr>
<tr>
<td>African American</td>
<td>31%*</td>
</tr>
<tr>
<td>Hispanic</td>
<td>35%*</td>
</tr>
<tr>
<td>South Asian</td>
<td>44% (men 53%; women 26%)</td>
</tr>
</tbody>
</table>

* Similar in men and women
Race/ethnic-specific BMI values associated with same prevalence of metabolic abnormalities as Whites with BMI 25

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>White 25</th>
<th>White 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Asian</td>
<td>18.9</td>
<td>23.3</td>
</tr>
<tr>
<td>Chinese</td>
<td>20.5</td>
<td>24.5</td>
</tr>
<tr>
<td>African American</td>
<td>22.3</td>
<td>29.9</td>
</tr>
</tbody>
</table>

Prevalence Ratios of the Metabolically Abnormal Phenotype Among Normal Weight Individuals

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Prevalence Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>South Asian</td>
<td>2.53 (1.99, 3.22)</td>
</tr>
<tr>
<td>Chinese</td>
<td>1.47 (1.30, 1.66)</td>
</tr>
<tr>
<td>African American</td>
<td>1.66 (1.33, 2.05)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.56 (1.26, 1.92)</td>
</tr>
</tbody>
</table>

* adjusted for age, sex, education, alcohol use, smoking status, physical activity, daily calorie intake, hepatic fat attenuation, and pericardial fat volume

Conclusions

- MAN phenotype (Metabolically Abnormal and Normal weight) is most common in Hispanics and South Asians.
- If diabetes screening is conducted by BMI category, then BMI thresholds should differ by race/ethnicity.
Clinical Question/Challenge

- **Situation**: My patient with advanced COPD presents with persistent dyspnea. At triage his oxygen saturation (SPO2) is 91%, but when I walk him around the office it drops to 87%. I feel pressure to get him home oxygen, because it will make him live longer, right? Won’t it at least keep him out of the hospital?

Design: Long Term Oxygen Treatment Trial

- **Background**:
  - In the 1970’s, oxygen therapy proven to decrease mortality in COPD with severe resting hypoxemia
  - Recommended for resting SPO2 < 89%
  - Unclear benefit for SPO2 89-93%
  - Medicare paid $2B for oxygen in 2011

Design: Long Term Oxygen Treatment Trial

- **Design**: RCT, “parallel group”, meaning no blinding
  - Supplemental oxygen, N=368
  - No supplemental oxygen, N=370
  - 14 centers

- **Inclusion**:
  - Stable COPD and either former smoker or willing to quit
  - Resting 89-93%, or
  - < 90% during walk test

- **Oxygen Group**:
  - Portable and 2L at night
  - Adjust to ≥ 90% while walking

- **Control Group**:
  - No oxygen unless develop severe hypoxemia ≤ 88%

- **Funding**: NIH, CMS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Supplemental Oxygen (N=370)</th>
<th>Supplemental Oxygen (N=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr.</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>White race</td>
<td>89%</td>
<td>85%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>SpO2 at rest on room air</td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td>Nadir SpO2 during 6-min walk</td>
<td>&lt;96%</td>
<td>29%</td>
</tr>
<tr>
<td>86-88%</td>
<td>36%</td>
<td>36%</td>
</tr>
<tr>
<td>&gt;88%</td>
<td>35%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Conclusions

- In stable COPD, long-term supplemental oxygen has no benefit in patients with only moderate desaturation
- No difference across multiple outcomes
- Potential caveats:
  - Participants less sick than general population?
  - Effects of altitude?

Other Outcomes without Difference Between Groups

- No Change in:
  - COPD exacerbations
  - Hospitalizations
  - QOL
  - Anxiety, depression
  - Functional status
  - 6 minute walk
- 51 adverse events from oxygen (23 trips on wires/hose; 6 fires)
**Clinical Question/Challenge**

- Opiate prescriptions: 3-fold rise over 15 years, and substantial rise in opioid related deaths
- 30% of fatal overdoses with opiates have concurrent BZDs.
- The FDA has black-box caution for dual use of opiate/BZD.
- Perhaps BZDs are a major contributor to the epidemic.

For my patients that I inherit on combined opiate/BZD, how urgent is it to stop one or the other?

**Design**

- **Private Claims data: Marketscan**
  - 2001-2013
  - Included patients with at least one opiate treatment, AND
  - Enrolled for entire 13 years, AND
  - 18-64, without cancer during time period
  - N= 315,428
- **Dual use**: overlap of treatment time period for opiate + BZD
- **Outcomes**: ER visit or admission for opioid overdose
  - Must be during the opiate treatment interval + 7 days
- **Research Questions:**
  - Is there a rise of BZD use among opiate users over 13 years?
  - What is BZD effect on overdose?
  - What is attributable risk of BZDs on all opiate overdoses?

**Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>BZD</th>
<th>No BZD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>Women</td>
<td>65%</td>
<td>57%</td>
</tr>
<tr>
<td>Depression</td>
<td>17%</td>
<td>4%</td>
</tr>
<tr>
<td>2001</td>
<td>9%</td>
<td>--</td>
</tr>
<tr>
<td>2013</td>
<td>17%</td>
<td>--</td>
</tr>
</tbody>
</table>

Sun HC et al. BMJ, 2017
Population Attributable Fraction

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>15%</td>
</tr>
<tr>
<td>Chronic users</td>
<td>27%</td>
</tr>
<tr>
<td>Intermittent users</td>
<td>4%</td>
</tr>
</tbody>
</table>

Discussion

- From 2001-2013, ↑80% in the prevalence of opiate users also on a BZD (9% → 17%)
- BZDs lead to two-fold incidence of overdose
- Eliminating co-treatment could potentially ↓ opiate overdose epidemic substantially

Thank you!
Any Questions?
Cardiometabolic Abnormalities Among Normal-Weight Persons From Five Racial/Ethnic Groups in the United States

A Cross-sectional Analysis of Two Cohort Studies

Unjali P. Gujral, PhD; Eric Vittinghoff, PhD; Morgana Mongraw-Chaffin, PhD; Dhananjay Vaidya, PhD; Namratha R. Kandula, MD, MPH; Matthew Allison, MD, MPH; Jeffrey Carr, MD; Kiang Liu, PhD; K.M. Venkat Narayan, MD; and Alka M. Kanaya, MD

Background: The relationship between body weight and cardiometabolic disease may vary substantially by race/ethnicity.

Objective: To determine the prevalence and correlates of the phenotype of metabolic abnormality but normal weight (MAN) for 5 racial/ethnic groups.

Design: Cross-sectional analysis.

Setting: 2 community-based cohorts.

Participants: 2622 white, 803 Chinese American, 1893 African American, and 1496 Hispanic persons from MESA (Multi-Ethnic Study of Atherosclerosis) and 803 South Asian participants in the MASALA (Mediators of Atherosclerosis in South Asians Living in America) study.

Measurements: Prevalence of 2 or more cardiometabolic abnormalities (high fasting glucose, low high-density lipoprotein cholesterol, and high triglyceride levels and hypertension) among normal-weight participants was estimated. Correlates of MAN were assessed by using log-binomial models.

Results: Among normal-weight participants (n = 846 whites, 323 Chinese Americans, 334 African Americans, 252 Hispanics, and 195 South Asians), the prevalence of MAN was 21.0% (95% CI, 18.4% to 23.9%) in whites, 32.2% (CI, 27.3% to 37.4%) in Chinese Americans, and 38.5% (CI, 32.6% to 44.6%) in Hispanics, and 43.6% (CI, 36.8% to 50.6%) in South Asians. Adjustment for demographic, behavioral, and ectopic body fat measures did not explain racial/ethnic differences. After adjustment for age, sex, and race/ethnicity–body mass index interaction, for the equivalent MAN prevalence at a BMI of 25.0 kg/m² in whites, the corresponding BMI values were 22.9 kg/m² (CI, 19.5 to 26.3 kg/m²) in African Americans, 21.5 kg/m² (CI, 18.5 to 24.5 kg/m²) in Hispanics, and 20.9 kg/m² (CI, 19.7 to 22.1 kg/m²) in Chinese Americans, and 19.6 kg/m² (CI, 17.2 to 22.0 kg/m²) in South Asians.

Limitation: Cross-sectional study design and lack of harmonized dietary data between studies.

Conclusion: Compared with whites, all racial/ethnic minority groups had a statistically significantly higher prevalence of MAN, which was not explained by demographic, behavioral, or ectopic fat measures. Using a BMI criterion for overweight to screen for cardiometabolic risk may result in a large proportion of racial/ethnic minority groups being overlooked.

Primary Funding Source: National Institutes of Health.


See also: Summary for Patients......................... I-20

Overweight and obesity are well-known cardiometabolic risk factors (1-3). However, some persons with normal weight have elevated cardiometabolic risk (4-7), and the relationship between excess adiposity and cardiometabolic abnormality may vary by race/ethnicity (4-7). Although some information is available regarding the prevalence and correlates of metabolic abnormality but normal weight (MAN) in non-Hispanic whites, non-Hispanic African Americans, and Mexican Americans (4, 5), no direct comparisons have been made among East or South Asians who are at high risk for cardiometabolic abnormalities, even at relatively low levels of body mass index (BMI) (8-13).

We therefore compared the prevalence of MAN among members of 5 racial/ethnic groups, including 2 Asian subgroups, by using data from 2 large, well-characterized community-based U.S. cohorts. We also examined the correlates associated with MAN in the 4 racial/ethnic minority groups compared with whites. Lastly, we determined the BMI values in the racial/ethnic minority participants that would yield a MAN prevalence equal to that in whites with a BMI of 25 kg/m².

METHODS

We conducted a cross-sectional analysis of pooled data from MESA (Multi-Ethnic Study of Atherosclerosis) and the MASALA (Mediators of Atherosclerosis in South Asians Living in America) study. To maintain consistency with the lower age limit of MESA participants, we excluded 94 MASALA participants younger than 44 years. Excluded participants differed from those who remained in the study only by age-related clinical outcomes. We compared 803 South Asian participants from MASALA with 2622 white, 803 Chinese American, 1893 African American, and 1496 Hispanic participants from MESA.

MESA Study

The design and conduct of the MESA study have been described elsewhere (14). In brief, study participants included members of 4 racial/ethnic groups...
Cardiometabolic Abnormalities Among Normal-Weight Persons

The protocols used in the MASALA study for seated blood pressure and anthropometry were the same as those used in MESA. After resting in a seated position for 5 minutes, each participant had his or her blood pressure assessed with an automated blood pressure machine (V100 Vital Signs Monitor, GE Healthcare). Seated blood pressure was measured 3 times, and the last 2 readings were averaged to determine systolic and diastolic blood pressure. Participant weight was measured with a standing balance beam or digital scale, height with a stadiometer. Body mass index was calculated as weight in kilograms divided by height in square meters. Waist circumference was determined by using a flexible tape measure at the site of maximum circumference, halfway between the lower ribs and the anterior superior iliac spine. The circumference was measured twice, and the average was used for analysis. Blood samples were collected after a 12-hour overnight fast. Total cholesterol, triglyceride, and HDL-C levels were analyzed by enzymatic methods, and low-density lipoprotein cholesterol concentrations were calculated. Fasting plasma glucose levels were analyzed by using the hexokinase method. Serum insulin was measured by the sandwich immunoassay method (Elecsys 2010, Roche Diagnostics) (19). As in MESA, Luminex adipokine panel A (EMD Millipore) was used to measure adiponectin and resistin levels. The interassay coefficient of variations was 2.34% to 4.12% for adiponectin and 3.25% to 5.03% for resistin (19). Computed tomography scans of the abdomen (Philips Medical Systems, Toshiba Medical Systems, and Siemens Medical Solutions) were used to assess visceral, subcutaneous, and intermuscular fat mass. Contrast cardiac CT images were obtained with a cardiac-gated CT scanner (Phillips 16D or Toshiba MDA Aquilion 64 at the University of California, San Francisco, and Siemens Sensation Cardiac 64 at Northwestern University) to assess pericardial fat volume and hepatic fat attenuation. Measurement methods and reading centers were similar to those used in MESA (20).

Classification of Cardiometabolic Abnormalities

We used National Cholesterol Education Program-Adult Treatment Panel III criteria to consider 4 cardiometabolic abnormalities (21). Decreased HDL-C was defined as a level lower than 1.03 mmol/L (<40 mg/dL) in men or 1.29 mmol/L (<50 mg/dL) in women, or any use of lipid-lowering medication (22). Elevated triglyceride was classified as a fasting triglyceride level of 1.7 mmol/L (150 mg/dL) or greater (22). Elevated glucose was classified as a fasting plasma glucose level of 5.6 mmol/L (100 mg/dL) or greater (23) or any use of glucose-lowering medication. High blood pressure was defined as 130/85 mm Hg or greater or any use of antihypertensive medication. The waist circumference criterion was not used because of collinearity with BMI (correlation coefficient, 0.85; P < 0.0001). On the basis of previous literature, cardiometabolic abnormality was defined as the presence of 2 or more of the aforementioned components (4, 24–28).
BMI Categories

For white, African American, and Hispanic participants, BMI was classified according to World Health Organization (WHO) standard cut points for normal weight (BMI, 18.5 to 24.9 kg/m²), overweight (BMI, 25.0 to 29.9 kg/m²), and obesity (BMI, ≥30 kg/m²) (27). For South Asian and Chinese American participants, BMI was classified according to WHO Asian cut points for normal weight (BMI, 18.5 to 22.9 kg/m²), overweight (BMI, 23.0 to 27.4 kg/m²), and obesity (BMI, ≥27.5 kg/m²) (28). We also conducted sensitivity analyses by using the standard WHO BMI cut points for all racial/ethnic groups.

Body size phenotypes were defined on the basis of a combination of BMI category (normal weight) and cardiometabolic health. Combinations of BMI and cardiometabolic status yielded 2 distinct phenotypes (normal weight without cardiometabolic abnormalities and normal weight with cardiometabolic abnormalities [MAN]). We focused our analysis on the discordant MAN phenotype.

Statistical Analysis

Analyses were conducted by using pooled data from the 2 cohorts. Participant characteristics were described as means, geometric means, and percentages by race/ethnicity. Differences in these characteristics across race/ethnicity were assessed by using chi-square tests or analysis of variance as appropriate. The prevalence of metabolic abnormality was calculated by BMI strata. Prevalence ratios of MAN in Chinese, African American, Hispanic, and South Asian participants compared with whites were estimated by using Poisson models with robust SEs (29). Multivariate models were adjusted for age, sex, education, physical activity, daily caloric intake, alcohol use, smoking status, hepatic fat

**Figure 1.** Prevalence of BMI categories and metabolic status, by race/ethnicity.

Top. Prevalence of BMI category, by race/ethnicity. Error bars are 95% CIs. Bottom. Prevalence of metabolic normality, by BMI category and race/ethnicity. Metabolically abnormal was defined as the presence of ≥2 of the following components: decreased high-density lipoprotein cholesterol levels (<1.036 mmol/L [<40 mg/dL] in men or <1.295 mmol/L [<50 mg/dL] in women or use of lipid-lowering medication), elevated triglyceride levels (fasting triglyceride levels ≥1.7 mmol/L [≥150 mg/dL]), elevated glucose levels (fasting plasma glucose level ≥5.6 mmol/L [≥100 mg/dL] or use of glucose-lowering medication), and high blood pressure (≥130/85 mm Hg or use of antihypertensive medication). Error bars are 95% CIs. BMI = body mass index.
### Original Research

**Table 1. Characteristics of Participants With MAN Phenotype, by Race/Ethnicity***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>South Asian (n = 85)</th>
<th>White (n = 178)</th>
<th>P Value</th>
<th>Chinese American (n = 104)</th>
<th>White (n = 178)</th>
<th>P Value</th>
<th>African American (n = 104)</th>
<th>P Value</th>
<th>Hispanic (n = 97)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence, %</td>
<td>43.6</td>
<td>21.0</td>
<td>&lt;0.001</td>
<td>32.2</td>
<td>0.008</td>
<td>31.1</td>
<td>0.004</td>
<td>38.5</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Men, %</td>
<td>72.9</td>
<td>39.3</td>
<td>&lt;0.001</td>
<td>47.1</td>
<td>&lt;0.001</td>
<td>53.4</td>
<td>0.007</td>
<td>50.5</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>59.6 (8.9)</td>
<td>68.0 (9.6)</td>
<td>&lt;0.001</td>
<td>66.8 (9.0)</td>
<td>&lt;0.001</td>
<td>67.0 (9.6)</td>
<td>&lt;0.001</td>
<td>64.6 (10.9)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Mean systolic blood pressure (SD), mm Hg</td>
<td>128.4 (15.9)</td>
<td>132.1 (21.7)</td>
<td>0.17</td>
<td>129.7 (24.3)</td>
<td>0.68</td>
<td>136.1 (19.6)</td>
<td>0.004</td>
<td>134.0 (20.9)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Mean diastolic blood pressure (SD), mm Hg</td>
<td>74.9 (8.8)</td>
<td>71.6 (10.0)</td>
<td>&lt;0.001</td>
<td>71.6 (11.7)</td>
<td>0.04</td>
<td>75.4 (9.9)</td>
<td>0.67</td>
<td>72.8 (10.1)</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>67.1</td>
<td>78.1</td>
<td>0.57</td>
<td>65.4</td>
<td>0.81</td>
<td>92.3</td>
<td>0.002</td>
<td>69.1</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Mean fasting glucose level (SD)</td>
<td>&lt;0.001</td>
<td>1128.4 (24.6)</td>
<td>0.64</td>
<td>1093.3 (37.6)</td>
<td>0.68</td>
<td>1080.0 (43.7)</td>
<td>0.004</td>
<td>1202.0 (65.4)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Mean total cholesterol level (SD) (mg/dL)</td>
<td>&lt;0.001</td>
<td>1175.5 (40.0)</td>
<td>0.64</td>
<td>1915.1 (31.7)</td>
<td>0.68</td>
<td>1859.5 (40.6)</td>
<td>0.004</td>
<td>2013.8 (38.3)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Mean LDL-C level (SD) (mg/dL)</td>
<td>&lt;0.001</td>
<td>101.2 (32.4)</td>
<td>0.05</td>
<td>111.6 (26.4)</td>
<td>0.02</td>
<td>113.7 (37.3)</td>
<td>&lt;0.001</td>
<td>120.8 (35.4)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Mean HDL-C level (SD) (mg/dL)</td>
<td>1.25 (0.34)</td>
<td>1.28 (0.40)</td>
<td>0.58</td>
<td>1.24 (0.32)</td>
<td>0.78</td>
<td>1.29 (0.41)</td>
<td>0.46</td>
<td>1.16 (0.36)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Geometric mean triglyceride level (SD)</td>
<td>0.03</td>
<td>48.3 (13.3)</td>
<td>0.07</td>
<td>47.8 (12.5)</td>
<td>0.16</td>
<td>49.9 (15.9)</td>
<td>&lt;0.001</td>
<td>44.7 (13.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean cholesterol level (SD) (mg/dL)</td>
<td>&lt;0.001</td>
<td>123.5 (2.4)</td>
<td>0.13</td>
<td>141.9 (2.7)</td>
<td>0.01</td>
<td>110.8 (2.6)</td>
<td>&lt;0.001</td>
<td>161.5 (2.5)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Mean HOMA-IR score (SD)</td>
<td>2.4 (0.5)</td>
<td>1.6 (0.2)</td>
<td>&lt;0.001</td>
<td>1.9 (0.3)</td>
<td>0.02</td>
<td>2.0 (0.5)</td>
<td>0.12</td>
<td>1.9 (0.4)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Mean HOMA-β score (SD)</td>
<td>70.5 (2.5)</td>
<td>99.7 (2.9)</td>
<td>&lt;0.001</td>
<td>69.9 (2.8)</td>
<td>0.94</td>
<td>82.8 (4.0)</td>
<td>0.17</td>
<td>66.2 (3.8)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Geometric mean C-reactive protein level (SD), (mg/dL)</td>
<td>8.6 (9.5)</td>
<td>15.2 (5.7)</td>
<td>&lt;0.001</td>
<td>8.6 (9.5)</td>
<td>0.88</td>
<td>18.1 (7.6)</td>
<td>&lt;0.001</td>
<td>15.2 (5.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean adiponectin level (SD), ng/mL†</td>
<td>9.3 (1.3)</td>
<td>20.4 (1.6)</td>
<td>&lt;0.001</td>
<td>14.3 (1.7)</td>
<td>0.008</td>
<td>19.8 (1.9)</td>
<td>&lt;0.001</td>
<td>18.8 (1.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean resistin level (SD), ng/mL†</td>
<td>22.2 (9.5)</td>
<td>15.8 (4.6)</td>
<td>&lt;0.001</td>
<td>13.0 (4.6)</td>
<td>&lt;0.001</td>
<td>21.6 (8.7)</td>
<td>0.99</td>
<td>16.7 (7.6)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Mean waist circumference (SD), cm</td>
<td>86.2 (6.0)</td>
<td>88.9 (7.1)</td>
<td>&lt;0.001</td>
<td>82.5 (5.7)</td>
<td>&lt;0.001</td>
<td>87.6 (7.2)</td>
<td>0.15</td>
<td>88.1 (6.3)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Mean subcutaneous fat area (SD), cm²</td>
<td>155.2 (45.0)</td>
<td>168.4 (55.6)</td>
<td>0.16</td>
<td>144.8 (48.8)</td>
<td>0.38</td>
<td>182.7 (62.7)</td>
<td>0.02</td>
<td>177.7 (68.8)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Mean visceral fat area (SD), cm²†</td>
<td>122.4 (44.4)</td>
<td>121.0 (48.7)</td>
<td>0.87</td>
<td>97.6 (33.6)</td>
<td>0.03</td>
<td>102.4 (47.4)</td>
<td>0.02</td>
<td>120.3 (47.4)</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Mean hepatic fat attenuation (SD), Hounsfield units</td>
<td>55.9 (9.5)</td>
<td>64.0 (10.2)</td>
<td>&lt;0.001</td>
<td>64.3 (10.7)</td>
<td>&lt;0.001</td>
<td>63.4 (9.5)</td>
<td>&lt;0.001</td>
<td>63.7 (12.1)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean pericardial fat volume (SD), cm³</td>
<td>51.0 (20.4)</td>
<td>66.4 (30.2)</td>
<td>&lt;0.001</td>
<td>64.9 (19.4)</td>
<td>&lt;0.001</td>
<td>53.3 (25.6)</td>
<td>0.49</td>
<td>64.3 (25.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean intramuscular fat area (SD), cm²</td>
<td>17.4 (6.4)</td>
<td>22.9 (8.2)</td>
<td>&lt;0.001</td>
<td>18.2 (4.7)</td>
<td>0.61</td>
<td>16.6 (6.9)</td>
<td>0.57</td>
<td>18.2 (6.0)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Mean physical activity (SD), metabolic equivalent min/wk</td>
<td>1057.7 (7.0)</td>
<td>1995.8 (8.0)</td>
<td>&lt;0.001</td>
<td>1093.7 (7.0)</td>
<td>0.82</td>
<td>1791.8 (7.7)</td>
<td>0.002</td>
<td>1059.8 (8.0)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Never smoker, %</td>
<td>81.2</td>
<td>46.6</td>
<td>&lt;0.001</td>
<td>73.1</td>
<td>0.19</td>
<td>39.4</td>
<td>&lt;0.001</td>
<td>66.0</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Alcohol use, %</td>
<td>41.1</td>
<td>61.0</td>
<td>0.003</td>
<td>19.4</td>
<td>0.001</td>
<td>63.5</td>
<td>0.002</td>
<td>41.2</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

**HDL-C = high-density lipoprotein cholesterol; HOMA-β = homeostasis model assessment of β-cell function; HOMA-IR = homeostasis model assessment of insulin resistance; LDL-C = low-density lipoprotein cholesterol; MAN = metabolic abnormality but normal weight.**

***P values compare characteristics with those of South Asians.
† Data are from a restricted sample that included only metabolically abnormal participants with measurements of adiponectin and resistin levels, subcutaneous and intramuscular fat area, and visceral fat area (396 South Asian, 281 white, 112 Chinese American, 145 African American, and 202 Hispanic participants).
‡ Defined as consumption of ≥1 drink weekly.

Cardiometabolic Abnormalities Among Normal-Weight Persons

Attenuation, and pericardial fat volume. Additional, restricted models including only the subset of participants who had measures of visceral fat, adiponectin, and resistin also were performed. To estimate the BMI values for South Asian, African American, Hispanic, and Chinese American participants that result in metabolic outcomes equal to those in whites with a BMI of 25 kg/m² or 30 kg/m², we first fit a proportional odds model.
The overall prevalence of normal weight and obesity varied by race/ethnicity, with white and Chinese American participants having the highest prevalence of normal weight (32.3% and 40.2%, respectively) and African American participants having the highest prevalence of obesity (45.4% and 38.6%, respectively) (Figure 1, top). Overall, 29.1% of the participants with normal weight had the MAN phenotype, whereas 35.8% of those with obesity were metabolically normal. The prevalence of MAN varied significantly by race/ethnicity: 21.0% (95% CI, 18.4% to 23.8%) among whites, 29.1% (95% CI, 25.7% to 32.5%) among African Americans, 29.2% (95% CI, 25.8% to 32.7%) among Hispanics, 34.1% (95% CI, 30.6% to 37.6%) among Chinese Americans, 35.8% (95% CI, 32.3% to 39.2%) among South Asians, and 45.4% (95% CI, 42.0% to 48.7%) among African Americans. The prevalence of MAN among normal-weight persons varied by age, sex, race/ethnicity, and other factors. The prevalence of MAN was higher among older adults (75–84 y) than among younger adults (44–54 y) (2.52 times higher). The prevalence of MAN was also higher among men than among women (1.00 vs. 0.79). The prevalence of MAN was highest among African American participants (1.83 times higher compared to whites).
The prevalence of MAN remained greater in South Asians and whites. In multivariable-adjusted models, the prevalence of MAN was 40.4% in Chinese Americans, 36.4% in African Americans, and 37.9% in South Asian participants. Among participants with 2 or more cardiometabolic abnormalities, the most common risk factor combination in whites was hypertension and a low HDL-C level (40.0%). In all other racial/ethnic groups, the risk factor combination of high glucose and low HDL-C levels was most common (48.7% in South Asians, 37.3% in Chinese Americans, 36.4% in African Americans, and 37.9% in Hispanics). Appendix Table 2 (available at Annals.org) details the prevalence of risk factor combinations among all racial/ethnic groups.

Among participants with MAN, South Asians were significantly younger than members of all other racial/ethnic groups (Table 1). A significantly greater proportion of South Asians than whites or Hispanics had diabetes. Mean daily caloric intake was significantly higher in South Asians than members of any other racial/ethnic group except Hispanics. Levels of circulating adiponectin were significantly lower in South Asians than members of all other racial/ethnic groups. South Asians also had less hepatic fat attenuation (more fat in the liver) than all other racial/ethnic groups and less pericardial fat volume than all other groups except African Americans. Appendix Table 3 (available at Annals.org) details the characteristics of participants who were normal weight regardless of metabolic phenotype.

**Correlates of the MAN Phenotype**

Compared with whites, the prevalence of MAN was approximately 100% greater in South Asians, 50% in Chinese and African Americans, and 80% in Hispanics (Table 2). It was also higher in older participants and those with greater pericardial fat volume and lower in those with higher educational status and greater hepatic fat attenuation (less fat in the liver). In a multivariable-adjusted model, South Asian, Chinese, African American, and Hispanic race/ethnicity remained independently associated with MAN, as did older age, pericardial fat volume, educational status, and hepatic fat attenuation. Adjustment for age, sex, education, smoking status, alcohol use, physical activity, daily caloric intake, hepatic fat attenuation, and pericardial fat volume did not explain the differences in MAN among the study groups.

In restricted models including only normal-weight persons with measured visceral fat mass, adiponectin, and resistin (Appendix Table 4, available at Annals.org), MAN was more prevalent in South Asians, Chinese Americans, African Americans, and Hispanics than whites. In multivariable-adjusted models, the prevalence of MAN remained greater in South Asians and Hispanics, but not in Chinese and African American participants, compared with whites.

**Ethnic-Specific BMI Values**

We estimated the BMI values at which the expected numbers of metabolic abnormalities among South Asians, Chinese Americans, African Americans, and Hispanics would equal those among whites with a BMI of 25 kg/m². For the equivalent number of cardiometabolic abnormalities at a BMI of 25.0 kg/m² in white participants, the corresponding BMI values were 22.3 kg/m² (CI, 19.7 to 24.9 kg/m²) in African Americans, 21.5 kg/m² (CI, 18.5 to 24.5 kg/m²) in Hispanics, 20.5 kg/m² (CI, 19.6 to 21.4 kg/m²) in Chinese Americans, and 18.9 kg/m² (CI, 16.7 to 21.1 kg/m²) in South Asians. For the equivalent number at a BMI of 30.0 kg/m² in whites, the corresponding BMI values were 29.9 kg/m² (CI, 25.6 to 34.2 kg/m²) in African Americans, 27.0 kg/m² (CI, 26.0 to 28.0 kg/m²) in Hispanics, 24.5 kg/m² (CI, 23.6 to 25.5 kg/m²) in Chinese Americans, and 23.3 kg/m² (CI, 22.3 to 24.3 kg/m²) in South Asians.

**Figure 2.** Race/ethnicity-specific BMI values associated with MAN compared with whites with a BMI of 25 kg/m².

MAN was defined as a BMI of 18.5 to 24.9 kg/m² for white, African American, and Hispanic participants or a BMI of 18.5 to 22.9 kg/m² for South Asian and Chinese American participants and ≥2 of the following components: decreased high-density lipoprotein cholesterol levels (<1.036 mmol/L [<40 mg/dL] in men or 1.295 mmol/L [<50 mg/dL] in women or use of lipid-lowering medication), elevated triglyceride levels (fasting triglyceride levels ≥1.7 mmol/L [≥150 mg/dL]), elevated glucose levels (fasting plasma glucose level ≥5.6 mmol/L [≥100 mg/dL] or use of glucose-lowering medication), and high blood pressure (≥130/85 mm Hg or use of antihypertensive medication). To obtain BMI values for South Asians, African Americans, Hispanics, and Chinese Americans that would result in an expected MAN prevalence approximately equal to that among whites with a BMI of 25 kg/m², based on a Poisson model for MAN, a proportional odds model was fit for the prevalence of MAN in white participants with a BMI of 25 kg/m², with group-specific 4-knot restricted cubic splines in BMI, adjusting for sex and a 4-knot restricted cubic spline in age. A search algorithm then was used to find the BMI values for each of the other 4 groups that resulted in approximately the same expected prevalence of MAN. BMI = body mass index; MAN = metabolic abnormality but normal weight.
in whites, the corresponding BMI values were 22.9 kg/m² (CI, 19.5 to 26.3 kg/m²) in African Americans, 21.5 kg/m² (CI, 18.5 to 24.5 kg/m²) in Hispanics, 20.9 kg/m² (CI, 19.7 to 22.1 kg/m²) in Chinese Americans, and 19.6 kg/m² (CI, 17.2 to 22.0 kg/m²) in South Asians.

**DISCUSSION**

In this cross-sectional study of 2 large community-based cohorts including participants from several racial/ethnic groups in the United States, we found that nearly a third of those who were normal weight had cardiometabolic abnormalities. Furthermore, MAN prevalence varied by race/ethnicity, with a significantly higher proportion of South Asians and Hispanics, followed by Chinese and African Americans, having this phenotype compared with whites. Adjustment for demographic, behavioral, and ectopic fat variables did not explain these differences. For a MAN prevalence equivalent to that in whites with a BMI of 25 kg/m², the corresponding BMI values were lower in all racial/ethnic minority groups, suggesting that BMI alone is a poor indicator of cardiometabolic risk in most of these populations. A recent, nationally representative study assessing the prevalence and correlates of MAN in whites, African Americans, and Mexican Americans reported that 23.5% of all normal-weight adults had metabolic abnormalities (4). This percentage is lower than our findings of 29%, which partly may be a result of the younger mean age of the prior study’s participants. Another difference is that our study included South Asian and Chinese American participants as well as measures of ectopic fat and adipokine levels; a previous study comparing the MESA and MASALA populations found significant differences in ectopic fat distribution and adipokine levels between South Asians and the 4 MESA racial/ethnic groups (30). Although these differences may partially account for the increased predisposition to insulin resistance and type 2 diabetes among South Asians, adjustment for ectopic fat measures and adipokine levels did not explain the difference in MAN among racial/ethnic groups in our study. Our findings also are consistent with those of a larger, longitudinal study, which found that a BMI cut point of 30 kg/m² in whites was equivalent to lower BMI cut points for South Asians, Chinese Americans, and African Americans in terms of diabetes incidence (13). Finally, our results build on those of a study that found elevated glucose and lipid levels at lower BMI values in non-European (South Asian, Chinese, and Aboriginal Canadian) versus European populations (12). Taken together, these findings suggest that established BMI cut points may be practical markers for detecting overweight but may not necessarily correlate with overall cardiometabolic health and that race/ethnicity alone may be a better predictor of cardiometabolic risk in racial/ethnic minority populations.

Our study has several strengths. We investigated cardiometabolic abnormalities in normal-weight persons from 5 U.S. racial/ethnic groups, including the relatively understudied South Asian and Chinese American populations, in whom previous studies showed cardiometabolic abnormalities developing at lower BMI levels than in other racial/ethnic groups (11–13). Furthermore, our study used harmonized data from 2 large cohorts that included several radiographic measures of body composition to assess ectopic fat and adipokine levels. However, our results also should be interpreted within the context of several limitations. The difference in timing of data collection between studies (2000 to 2002 for MESA and 2010 to 2013 for MASALA) may have resulted in some differences in the prevalence of overweight and obesity between the 2 cohorts. Because the initial enrollment of the MESA cohort began a decade and a half ago, secular changes may have occurred in the adoption of healthier behaviors, such as a decreased prevalence of smoking (31). However, the prevalence of obesity and diabetes has not decreased substantially during the past 2 decades (32–34). Thus, we do not believe that the prevalence of metabolic abnormalities observed in the MESA participants would be much different from that observed in a current sample of middle- to older-aged adults. Furthermore, MESA and MASALA used different food-frequency questionnaires, limiting our ability to assess whether dietary patterns contribute to MAN prevalence. Of note, adjustment for daily caloric intake did not explain differences in MAN prevalence among racial/ethnic groups. Although the MASALA and MESA cohorts are community-based samples, neither is nationally representative; therefore, the results may not be generalizable to younger persons or South Asians and Chinese Americans born in the United States.

In conclusion, our findings suggest a high prevalence of cardiometabolic abnormality among normal-weight persons, particularly those in racial/ethnic minority populations. This disparity cannot be explained by differences in demographic, behavioral, or ectopic fat measures. Therefore, clinicians using overweight and obesity as the main criteria for cardiometabolic screening, as currently recommended by the U.S. Preventive Services Task Force for diabetes testing (35), may fail to identify cardiometabolic abnormalities in many patients from racial/ethnic minority groups. Although the Task Force recommends earlier screening in racial/ethnic minority populations, testing for cardiometabolic abnormalities in normal-weight and underweight members of these groups also may be an important consideration. Future research is needed to identify the prospective associations between MAN and incident diabetes and cardiovascular disease in various racial/ethnic groups.

From Emory University, Atlanta, Georgia; University of California, San Francisco, San Francisco, and University of California, San Diego, San Diego, California; Wake Forest School of Medicine, Winston-Salem, North Carolina; Johns Hopkins University School of Medicine, Baltimore, Maryland; Northwestern University Feinberg School of Medicine, Chicago, and Northwestern University, Evanston, Illinois; and Vanderbilt University, Nashville, Tennessee.

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Cardiometabolic Abnormalities Among Normal-Weight Persons

Acknowledgment: The authors thank the other investigators, the staff, and the MASALA and MESA participants for their valuable contributions. A full list of participating MESA investigators and institutions may be found at www.mesa-nhlbi.org.

Grant Support: The MASALA study was supported by NIH grants R01HL093009 and K24HL112827. Data collection at the University of California, San Francisco, was supported by NIH/NCRR grant UL1 RR024131. The MESA study was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the NHLBI and by grants UL1-TR-00040 and UL1-TR-001079 from the NCRR.

Disclosures: Dr. Vittinghoff reports grants from the National Institute of Diabetes and Digestive and Kidney Diseases during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictofInterestForms.do?msNum=M16-1895.

Reproducible Research Statement: Study protocol: MASALA protocol available from Dr. Kanaya (e-mail, alka.kanaya@ucsf.edu); MESA protocol available at www.mesa-nhlbi.org. Statistical code: Available from Dr. Gujral (e-mail, ugujral@emory.edu). Data set: Available with steering committee approval from both MESA and MASALA.

Requests for Single Reprints: Unjali P. Gujral, PhD, Emory University, Hubert Department of Global Health, Rollins School of Public Health, 1518 Clifton Road, CNR 7040-K, Atlanta, GA 30322; e-mail, ugujral@emory.edu.

Current author addresses and author contributions are available at Annals.org.

References


VITAL STATISTICS

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**Current Author Addresses:**

Dr. Gujral: Emory University, Hubert Department of Global Health, Rollins School of Public Health, 1518 Clifton Road, CNR 7040-K, Atlanta, GA 30322.

Dr. Vittinghoff: Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, 550 16th Street, 2nd Floor, San Francisco, CA 94158.

Dr. Mongraw-Chaffin: Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157.

Dr. Vaidya: Department of Medicine, Johns Hopkins University School of Medicine, 1830 East Monument Street, Room 8025, Baltimore, MD 21287.

Dr. Kandula: Center for Community Health, 420 East Superior, 6th floor, Chicago, IL 60640.

Dr. Allison: Department of Family and Preventive Medicine, University of California, San Diego, 8950 Villa La Jolla Drive, Suite B122, Mailcode 0811, La Jolla, CA 92037.

Dr. Carr: Department of Radiology, Vanderbilt University, 1161 21st Avenue South, Nashville, TN 37232.

Dr. Liu: 680 North Lakeshore Drive, Suite 1200, Chicago, IL 60640.

Dr. Narayan: Rollins School of Public Health, Emory University, 1518 Clifton Road Northeast, Room 7047, Atlanta, GA 30322.

Dr. Kanaya: Division of General Internal Medicine, University of California, San Francisco, 1545 Divisadero Street, Suite 311, San Francisco, CA 94115.

**Author Contributions:**


Drafting of the article: U.P. Gujral.


Provision of study materials or patients: N.R. Kandula, A.M. Kanaya.


Obtaining of funding: N.R. Kandula, A.M. Kanaya.

Administrative, technical, or logistic support: J. Carr, A.M. Kanaya.

Appendix Table 1. Characteristics of Study Participants, by Race/Ethnicity*
Characteristic

South
Asian
(n ⴝ 803)

White
(n ⴝ 2622)

P
Value

Chinese
American
(n ⴝ 803)

P
Value

African
American
(n ⴝ 1893)

P
Value

Hispanic
(n ⴝ 1496)

P
Value

Missing,
n

Prevalence, %
Men, %
Mean age (SD), y
Mean systolic blood
pressure (SD), mm Hg
Mean diastolic blood
pressure (SD), mm Hg
Hypertension, %
Mean fasting glucose
level (SD), mg/dL
Diabetes, %
Mean total cholesterol
level (SD), mg/dL
Mean LDL-C level (SD),
mg/dL
Mean HDL-C level (SD),
mg/dL
Geometric mean
triglyceride level (SD),
mg/dL
Mean calories, kcal/d
Mean geometric mean
HOMA-IR score (SD)
Geometric mean HOMA-␤
score (SD)
Geometric mean
C-reactive protein level
(SD), μg/mL
Geometric mean
adiponectin level (SD),
ng/mL†
Mean resistin level (SD),
ng/mL†
Mean waist circumference
(SD), cm
Mean subcutaneous fat
area (SD), cm2
Mean visceral fat area
(SD), cm2†
Mean hepatic fat
attenuation (SD),
Hounsﬁeld units
Mean pericardial fat
volume (SD), cm3
Mean intermuscular fat
area (SD), cm2
Mean physical activity
(SD), metabolic
equivalent min/wk
Never smoker, %
Alcohol use, %‡

10.5
52.8
56.9 (8.6)
125.6 (15.9)

34.4
48.0
62.6 (10.2)
123.5 (20.4)

<0.001
0.02
<0.001
0.01

10.5
48.6
62.3 (10.3)
124.6 (21.6)

1.0
0.09
<0.001
<0.001

24.9
44.5
62.1 (10.5)
131.7 (21.6)

<0.001
<0.001
<0.001
<0.001

19.6
48.2
62.3 (10.3)
126.7 (21.9)

<0.001
0.04
0.001
0.02

0
3

73.3 (9.9)

70.2 (10.0)

<0.001

72.0 (10.3)

0.007

74.5 (10.2)

0.007

71.6 (10.1)

<0.001

3

52.8
104.2 (25.4)

47.4
91.4 (21.5)

0.007
<0.001

48.1
99.0 (28.2)

0.06
<0.001

68.3
100.0 (32.0)

<0.001
0.001

50.7
103.6 (39.1)

0.34
0.72

0
37

21.9
187.3 (36.7)

6.0
195.7 (35.1)

<0.001
<0.001

13.1
192.6 (31.8)

<0.001
0.002

17.5
189.6 (36.2)

0.008
0.12

17.7
197.9 (37.5)

0.01
<0.001

0
27

110.6 (32.0)

117.0 (30.1)

<0.001

115.1 (29.0)

0.004

116.5 (33.0)

<0.001

119.5 (32.9)

<0.001

112

50.3 (13.3)

52.2 (15.7)

<0.001

49.5 (12.7)

0.22

52.4 (15.3)

<0.001

47.6 (13.1)

<0.001

29

<0.001

26

0

119.1 (2.1)

114.4 (2.5)

0.05

124.5 (2.5)

0.07

92.3 (2.2)

<0.001

136.7 (2.5)

1675 (499)
2.6 (0.7)

1688 (761)
1.8 (0.3)

0.66
<0.001

1152 (612)
2.0 (0.4)

<0.001
<0.001

1683 (995)
2.2 (0.5)

0.85
<0.001

1696 (930)
2.4 (0.6)

0.56
0.008

293
92

100.6 (2.9)

118.0 (2.6)

<0.001

96.8 (2.9)

0.22

108.9 (3.2)

0.01

109.9 (3.4)

0.004

92

1.3 (0.3)

1.8 (0.7)

<0.001

0.9 (0.1)

<0.001

1.1 (0.8)

<0.001

2.4 (0.9)

<0.001

64

10.2 (1.5)

20.9 (1.7)

<0.001

14.1 (1.6)

<0.001

15.8 (1.6)

<0.001

17.3 (1.5)

<0.001

0

21.9 (12.1)

16.1 (5.3)

<0.001

15.3 (7.5)

<0.001

18.0 (13.7)

<0.001

16.1 (6.7)

<0.001

0

92.7 (10.0)

98.0 (14.4)

<0.001

87.1 (9.9)

<0.001

101.2 (14.7)

<0.001

100.6 (13.1)

<0.001

1

236.5 (95.2)

254.5 (115.4)

0.002

179.4 (70.9)

<0.001

298.5 (132.2)

<0.001

264.0 (108.5)

<0.001

0

136.1 (57.0)

151.9 (74.9)

<0.001

113.9 (47.8)

<0.001

119.1 (55.9)

<0.001

151.6 (60.7)

<0.001

0

55.1 (10.6)

61.4 (12.2)

<0.001

61.9 (12.0)

<0.001

63.0 (11.7)

<0.001

59.4 (14.2)

<0.001

80

59.5 (29.6)

85.2 (46.1)

<0.001

73.7 (31.4)

<0.001

67.5 (34.7)

0.49

88.3 (43.8)

<0.001

30

21.7 (8.8)

26.9 (12.0)

<0.001

18.7 (7.5)

<0.001

19.9 (12.3)

0.004

23.5 (9.9)

0.001

0

0.009

19

<0.001
<0.001

22
84

1048 (6.4)

1741 (7.7)

<0.001

1122 (7.6)

0.20

1574 (8.8)

<0.001

1205 (8.7)

82.9
32.3

44.1
64.5

<0.001
<0.001

75.2
21.4

<0.001
<0.001

44.9
51.7

<0.001
<0.001

53.9
46.8

HDL-C = high-density lipoprotein cholesterol; HOMA-␤ = homeostasis model assessment of ␤-cell function; HOMA-IR = homeostasis model
assessment of insulin resistance; LDL-C = low-density lipoprotein cholesterol.
* This sample includes all participants from the pooled MESA (Multi-Ethnic Study of Atherosclerosis) and MASALA (Mediators of Atherosclerosis in
South Asians Living in America) cohorts regardless of weight and metabolic status. P values compare characteristics with those of South Asians. To
convert glucose, cholesterol, or triglyceride values to mmol/L, multiply by 0.0555, 0.0259, or 0.0113, respectively.
† Data are from a restricted sample that included only participants with adiponectin, resistin, and visceral fat area measurements (708 South Asian,
645 white, 235 Chinese American, 337 African American, and 382 Hispanic participants).
‡ Deﬁned as consumption of ≥1 drink weekly.

Appendix Table 2. Prevalence of Risk Factor Combinations Among Persons With ≥2 Cardiometabolic Risk Factors, by
Race/Ethnicity*
Race/Ethnicity

Elevated
Triglycerides/High
Blood Pressure

Elevated
Triglycerides/Elevated
Glucose

Elevated
Triglycerides/Low
HDL-C

High Blood
Pressure/Elevated
Glucose

High Blood
Pressure/Low
HDL-C

Elevated
Glucose/Low
HDL-C

White
Chinese American
African American
Hispanic
South Asian

104 (9.25)
23 (5.68)
38 (4.00)
57 (6.58)
17 (3.79)

11 (0.98)
13 (3.21)
7 (0.74)
19 (2.19)
9 (2.01)

172 (15.3)
51 (12.59)
24 (2.53)
137 (15.82)
42 (9.38)

106 (9.43)
58 (11.85)
211 (22.23)
112 (12.93)
65 (14.51)

449 (39.95)
119 (29.38)
324 (34.14)
213 (24.60)
97 (21.65)

282 (25.09)
151 (37.28)
345 (36.35)
328 (37.88)
218 (48.66)

HDL-C = high-density lipoprotein cholesterol.
* Values are numbers (percentages).
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### Appendix Table 3. Characteristics of Normal-Weight Participants, by Race/Ethnicity*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>South Asian (n = 195)</th>
<th>White (n = 846)</th>
<th>P Value</th>
<th>Chinese American (n = 323)</th>
<th>P Value</th>
<th>African American (n = 334)</th>
<th>P Value</th>
<th>Hispanic (n = 252)</th>
<th>P Value</th>
<th>Missing, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence, %</td>
<td>24.3</td>
<td>32.3</td>
<td>&lt;0.001</td>
<td>40.2</td>
<td>&lt;0.001</td>
<td>17.6</td>
<td>&lt;0.001</td>
<td>16.8</td>
<td>&lt;0.001</td>
<td>0</td>
</tr>
<tr>
<td>Men, %</td>
<td>55.4</td>
<td>37.0</td>
<td>&lt;0.001</td>
<td>45.5</td>
<td>0.03</td>
<td>52.7</td>
<td>0.55</td>
<td>48.4</td>
<td>0.14</td>
<td>0</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>57.8 (8.8)</td>
<td>62.7 (10.7)</td>
<td>&lt;0.001</td>
<td>62.8 (10.1)</td>
<td>&lt;0.001</td>
<td>63.5 (10.7)</td>
<td>&lt;0.001</td>
<td>62.0</td>
<td>(11.2)</td>
<td>&lt;0.001 0</td>
</tr>
<tr>
<td>Mean systolic blood pressure (SD), mm Hg</td>
<td>122.9 (16.1)</td>
<td>118.9 (21.9)</td>
<td>0.02</td>
<td>121.0 (22.8)</td>
<td>0.31</td>
<td>127.6 (21.5)</td>
<td>0.009</td>
<td>123.1 (24.1)</td>
<td>0.94</td>
<td>0</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (SD), mm Hg</td>
<td>72.2 (9.4)</td>
<td>67.9 (10.1)</td>
<td>&lt;0.001</td>
<td>70.3 (10.3)</td>
<td>0.03</td>
<td>74.3 (10.1)</td>
<td>0.02</td>
<td>69.4 (10.1)</td>
<td>0.004</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>42.6</td>
<td>36.3</td>
<td>0.01</td>
<td>37.8</td>
<td>0.28</td>
<td>59.3</td>
<td>&lt;0.001</td>
<td>42.9</td>
<td>0.95</td>
<td>0</td>
</tr>
<tr>
<td>Mean fasting glucose level (SD), mg/dL</td>
<td>100.7 (20.3)</td>
<td>85.7 (18.2)</td>
<td>&lt;0.001</td>
<td>95.3 (25.9)</td>
<td>0.01</td>
<td>91.5 (27.3)</td>
<td>&lt;0.001</td>
<td>98.9 (44.4)</td>
<td>&lt;0.001</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>18.0</td>
<td>2.3</td>
<td>&lt;0.001</td>
<td>8.7</td>
<td>0.002</td>
<td>9.6</td>
<td>0.005</td>
<td>10.7</td>
<td>0.03</td>
<td>0</td>
</tr>
<tr>
<td>Mean total cholesterol level (SD), mg/dL</td>
<td>185.3 (35.2)</td>
<td>196.5 (34.9)</td>
<td>&lt;0.001</td>
<td>193.0 (31.3)</td>
<td>0.01</td>
<td>186.6 (36.5)</td>
<td>0.70</td>
<td>197.9 (36.3)</td>
<td>&lt;0.001</td>
<td>5</td>
</tr>
<tr>
<td>Mean LDL-C level (SD), mg/dL</td>
<td>108.4 (30.3)</td>
<td>115.3 (29.6)</td>
<td>0.004</td>
<td>114.6 (27.5)</td>
<td>0.02</td>
<td>108.7 (33.7)</td>
<td>0.91</td>
<td>118.8 (33.0)</td>
<td>&lt;0.001</td>
<td>20</td>
</tr>
<tr>
<td>Mean HDL-C level (SD), mg/dL</td>
<td>54.2 (14.8)</td>
<td>59.8 (17.7)</td>
<td>0.002</td>
<td>54.5 (13.3)</td>
<td>0.22</td>
<td>59.5 (18.9)</td>
<td>&lt;0.001</td>
<td>52.8 (16.2)</td>
<td>&lt;0.001</td>
<td>7</td>
</tr>
<tr>
<td>Geometric mean triglyceride level (SD), mg/dL</td>
<td>101.2 (2.1)</td>
<td>92.0 (2.2)</td>
<td>0.01</td>
<td>105.7 (2.3)</td>
<td>0.32</td>
<td>80.1 (2.2)</td>
<td>&lt;0.001</td>
<td>115.3 (2.4)</td>
<td>0.006</td>
<td>5</td>
</tr>
<tr>
<td>Mean calories (SD), kcal/d</td>
<td>1648 (494)</td>
<td>1553 (726)</td>
<td>0.08</td>
<td>1150 (613)</td>
<td>&lt;0.001</td>
<td>1617 (911)</td>
<td>0.66</td>
<td>1597 (995)</td>
<td>0.51</td>
<td>55</td>
</tr>
<tr>
<td>Geometric mean HOMA-IR score (SD)</td>
<td>1.7 (0.3)</td>
<td>1.2 (0.1)</td>
<td>&lt;0.001</td>
<td>1.5 (0.2)</td>
<td>&lt;0.001</td>
<td>1.3 (0.2)</td>
<td>&lt;0.001</td>
<td>1.5 (0.2)</td>
<td>0.002</td>
<td>29</td>
</tr>
<tr>
<td>Geometric mean HOMA-β score (SD)</td>
<td>75.0 (2.3)</td>
<td>102.5 (2.4)</td>
<td>&lt;0.001</td>
<td>83.1 (2.5)</td>
<td>0.05</td>
<td>94.3 (3.0)</td>
<td>&lt;0.001</td>
<td>84.5 (3.2)</td>
<td>0.06</td>
<td>29</td>
</tr>
<tr>
<td>Geometric mean C-reactive protein level (SD), μg/mL</td>
<td>0.8 (0.2)</td>
<td>1.1 (0.1)</td>
<td>&lt;0.001</td>
<td>0.7 (0.4)</td>
<td>0.12</td>
<td>1.4 (0.4)</td>
<td>&lt;0.001</td>
<td>1.5 (0.5)</td>
<td>&lt;0.001 15</td>
<td></td>
</tr>
<tr>
<td>Geometric mean adiponectin level (SD), ng/mL†</td>
<td>11.6 (1.5)</td>
<td>26.6 (1.8)</td>
<td>&lt;0.001</td>
<td>17.2 (1.5)</td>
<td>&lt;0.001</td>
<td>18.7 (1.9)</td>
<td>&lt;0.001</td>
<td>20.0 (1.4)</td>
<td>&lt;0.001 0</td>
<td></td>
</tr>
<tr>
<td>Mean resistin level (SD), ng/mL†</td>
<td>21.6 (9.0)</td>
<td>15.1 (4.3)</td>
<td>&lt;0.001</td>
<td>14.0 (7.5)</td>
<td>0.008</td>
<td>17.9 (10.4)</td>
<td>&lt;0.001</td>
<td>15.8 (6.9)</td>
<td>&lt;0.001 0</td>
<td></td>
</tr>
<tr>
<td>Mean waist circumference (SD), cm</td>
<td>84.0 (6.3)</td>
<td>84.6 (8.8)</td>
<td>0.36</td>
<td>79.3 (7.0)</td>
<td>&lt;0.001</td>
<td>84.5 (7.7)</td>
<td>0.43</td>
<td>86.2 (7.4)</td>
<td>&lt;0.001 0</td>
<td></td>
</tr>
<tr>
<td>Mean subcutaneous fat area (SD), cm²</td>
<td>162.5 (50.0)</td>
<td>183.4 (72.0)</td>
<td>0.001</td>
<td>137.2 (49.8)</td>
<td>&lt;0.001</td>
<td>188.4 (78.2)</td>
<td>0.002</td>
<td>179.7 (67.2)</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>Mean visceral fat area (SD), cm²†</td>
<td>99.2 (43.9)</td>
<td>97.3 (44.7)</td>
<td>0.67</td>
<td>82.2 (32.0)</td>
<td>0.003</td>
<td>81.0 (40.3)</td>
<td>0.003</td>
<td>107.9 (46.0)</td>
<td>0.14</td>
<td>0</td>
</tr>
<tr>
<td>Mean hepatic fat attenuation (SD), Hounsfield units</td>
<td>59.6 (9.1)</td>
<td>65.9 (8.7)</td>
<td>&lt;0.001</td>
<td>65.5 (9.2)</td>
<td>&lt;0.001</td>
<td>65.8 (9.0)</td>
<td>&lt;0.001</td>
<td>65.5 (9.8)</td>
<td>&lt;0.001 42</td>
<td></td>
</tr>
<tr>
<td>Mean pericardial fat volume (SD), cm³</td>
<td>41.6 (18.9)</td>
<td>54.0 (24.6)</td>
<td>&lt;0.001</td>
<td>57.1 (19.9)</td>
<td>&lt;0.001</td>
<td>43.4 (21.7)</td>
<td>0.03</td>
<td>56.7 (25.2)</td>
<td>&lt;0.001 8</td>
<td></td>
</tr>
<tr>
<td>Mean intermuscular fat area (SD), cm²</td>
<td>17.2 (6.1)</td>
<td>22.1 (8.1)</td>
<td>&lt;0.001</td>
<td>16.5 (5.3)</td>
<td>0.40</td>
<td>14.2 (6.0)</td>
<td>&lt;0.001</td>
<td>18.5 (6.8)</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>Mean physical activity (SD), metabolic equivalent min/wk</td>
<td>1099 (6.7)</td>
<td>2039 (7.7)</td>
<td>&lt;0.001</td>
<td>1072 (7.5)</td>
<td>0.80</td>
<td>1841 (8.8)</td>
<td>&lt;0.001</td>
<td>1408 (8.7)</td>
<td>&lt;0.001 5</td>
<td></td>
</tr>
<tr>
<td>Never smoker, %†‡</td>
<td>86.2</td>
<td>44.6</td>
<td>&lt;0.001</td>
<td>78.0</td>
<td>0.02</td>
<td>42.5</td>
<td>&lt;0.001</td>
<td>58.7</td>
<td>&lt;0.001 6</td>
<td></td>
</tr>
<tr>
<td>Alcohol use, %‡</td>
<td>35.4</td>
<td>66.3</td>
<td>&lt;0.001</td>
<td>19.7</td>
<td>&lt;0.001</td>
<td>57.7</td>
<td>&lt;0.001</td>
<td>42.9</td>
<td>0.10</td>
<td>18</td>
</tr>
</tbody>
</table>

HDL-C = high-density lipoprotein cholesterol; HOMA-β = homeostasis model assessment of β-cell function; HOMA-IR = homeostasis model assessment of insulin resistance; LDL-C = low-density lipoprotein cholesterol.

* This sample includes both metabolically normal and abnormal participants. P values compare characteristics with those of South Asians. To convert glucose, cholesterol, or triglyceride values to mmol/L, multiply by 0.0555, 0.0259, or 0.0113, respectively.

† Data are from a restricted sample that included only participants with adiponectin, resistin, and visceral fat mass measurements (708 South Asian, 645 white, 235 Chinese American, 337 African American, and 382 Hispanic participants).

‡ Defined as consumption of ≥1 drink weekly.
### Appendix Table 4. Unadjusted and Multivariable-Adjusted Prevalence Ratios of the Metabolically Abnormal Phenotype Among Normal-Weight Persons*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Prevalence Ratio (95% CI)</th>
<th>Unadjusted</th>
<th>Multivariable-Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>2.10 (1.55–2.84)</td>
<td>1.49</td>
<td>(1.10–2.04)</td>
</tr>
<tr>
<td>Chinese American</td>
<td>1.20 (0.75–1.91)</td>
<td>1.10</td>
<td>(0.79–1.53)</td>
</tr>
<tr>
<td>African American</td>
<td>1.57 (1.05–2.37)</td>
<td>1.37</td>
<td>(0.99–1.88)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.97 (1.38–2.82)</td>
<td>1.30</td>
<td>(1.00–1.69)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44–54 y</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>55–64 y</td>
<td>1.25 (0.90–1.72)</td>
<td>1.02</td>
<td>(0.82–1.27)</td>
</tr>
<tr>
<td>65–74 y</td>
<td>1.65 (1.21–2.25)</td>
<td>1.16</td>
<td>(0.93–1.44)</td>
</tr>
<tr>
<td>75–84 y</td>
<td>2.00 (1.40–2.86)</td>
<td>1.29</td>
<td>(0.93–1.78)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.61 (0.49–0.77)</td>
<td>1.07</td>
<td>(0.88–1.29)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than a bachelor’s degree</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree or higher</td>
<td>0.82 (0.67–1.03)</td>
<td>0.87</td>
<td>(0.74–1.03)</td>
</tr>
<tr>
<td><strong>Alcohol use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 drink daily</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;1 drink daily</td>
<td>1.05 (0.84–1.32)</td>
<td>0.97</td>
<td>(0.81–1.16)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>0.92 (0.71–1.19)</td>
<td>1.02</td>
<td>(0.84–1.24)</td>
</tr>
<tr>
<td>Current</td>
<td>0.82 (0.54–1.26)</td>
<td>1.08</td>
<td>(0.79–1.48)</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–750 metabolic equivalent min/wk</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>751–1575 metabolic equivalent min/wk</td>
<td>1.08 (0.84–1.56)</td>
<td>1.12</td>
<td>(0.90–1.39)</td>
</tr>
<tr>
<td>1576–3131 metabolic equivalent min/wk</td>
<td>0.94 (0.68–1.30)</td>
<td>1.14</td>
<td>(0.90–1.44)</td>
</tr>
<tr>
<td>&gt;3131 metabolic equivalent min/wk</td>
<td>0.91 (0.67–1.30)</td>
<td>1.14</td>
<td>(0.91–1.43)</td>
</tr>
<tr>
<td><strong>Calories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1033 kcal/d</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1033–1394 kcal/d</td>
<td>1.20 (0.87–1.65)</td>
<td>1.05</td>
<td>(0.82–1.33)</td>
</tr>
<tr>
<td>1394–1912 kcal/d</td>
<td>1.18 (0.89–1.63)</td>
<td>0.99</td>
<td>(0.76–1.25)</td>
</tr>
<tr>
<td>&gt;1912 kcal/d</td>
<td>1.13 (0.81–1.56)</td>
<td>0.91</td>
<td>(0.71–1.16)</td>
</tr>
<tr>
<td><strong>Pericardial fat volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.84 cm³</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>0.84–1.12 cm³</td>
<td>1.51 (1.04–2.24)</td>
<td>1.13</td>
<td>(0.87–1.47)</td>
</tr>
<tr>
<td>1.13–1.48 cm³</td>
<td>1.68 (1.16–2.47)</td>
<td>1.17</td>
<td>(0.88–1.55)</td>
</tr>
<tr>
<td>&gt;1.48 cm³</td>
<td>2.47 (1.73–3.52)</td>
<td>1.35</td>
<td>(0.99–1.82)</td>
</tr>
<tr>
<td><strong>Hepatic fat attenuation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4.48 Hounsfield units</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>4.48–5.19 Hounsfield units</td>
<td>0.52 (0.39–0.69)</td>
<td>0.90</td>
<td>(0.79–1.03)</td>
</tr>
<tr>
<td>5.19–6.50 Hounsfield units</td>
<td>0.53 (0.40–0.71)</td>
<td>0.91</td>
<td>(0.79–1.04)</td>
</tr>
<tr>
<td>&gt;6.50 Hounsfield units</td>
<td>0.38 (0.27–0.54)</td>
<td>0.88</td>
<td>(0.75–1.01)</td>
</tr>
<tr>
<td><strong>Adiponectin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10.03 ng/mL</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>10.03–15.19 ng/mL</td>
<td>1.06 (0.83–1.35)</td>
<td>0.86</td>
<td>(0.70–1.08)</td>
</tr>
<tr>
<td>15.20–22.9 ng/mL</td>
<td>0.91 (0.77–1.11)</td>
<td>1.00</td>
<td>(0.79–1.24)</td>
</tr>
<tr>
<td>&gt;22.93 ng/mL</td>
<td>0.33 (0.23–0.48)</td>
<td>0.80</td>
<td>(0.66–0.98)</td>
</tr>
</tbody>
</table>

* Metabolic abnormality was defined by the presence of ≥2 of the following components: decreased high-density lipoprotein cholesterol (<1.036 mmol/L [<40 mg/dL] in men or <1.295 mmol/L [<50 mg/dL] in women or use of lipid-lowering medication), elevated triglyceride levels (fasting triglyceride levels ≥1.7 mmol/L [≥150 mg/dL]), elevated glucose levels (fasting plasma glucose level ≥5.6 mmol/L [≥100 mg/dL] or use of glucose-lowering medication), and high blood pressure (≥130/85 mm Hg or use of antihypertensive medication). Data are from a restricted sample that included only metabolically abnormal participants with adiponectin, resistin, subcutaneous fat area, visceral fat area, and intermuscular fat area measurements (396 South Asian, 281 white, 112 Chinese American, 145 African American, and 202 Hispanic participants).

† Each factor was adjusted for every other factor in the table.

### Appendix Table 4—Continued

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Prevalence Ratio (95% CI)</th>
<th>Unadjusted</th>
<th>Multivariable-Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resistin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12.73 ng/mL</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>12.73–16.32 ng/mL</td>
<td>1.73 (1.19–2.52)</td>
<td>1.07</td>
<td>(0.98–1.17)</td>
</tr>
<tr>
<td>16.32–21.08 ng/mL</td>
<td>1.58 (1.08–2.33)</td>
<td>1.04</td>
<td>(0.95–1.14)</td>
</tr>
<tr>
<td>≥21.08 ng/mL</td>
<td>2.17 (1.52–3.11)</td>
<td>1.06</td>
<td>(0.98–1.17)</td>
</tr>
<tr>
<td><strong>Visceral fat area</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;97.38 cm²</td>
<td>1.00 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>97.38–134.78 cm²</td>
<td>1.44 (0.89–2.35)</td>
<td>1.06</td>
<td>(0.89–1.15)</td>
</tr>
<tr>
<td>134.79–184.68 cm²</td>
<td>2.90 (1.90–4.41)</td>
<td>1.29</td>
<td>(0.98–1.71)</td>
</tr>
<tr>
<td>&gt;184.68 cm²</td>
<td>3.67 (2.45–5.51)</td>
<td>1.35</td>
<td>(1.01–1.81)</td>
</tr>
</tbody>
</table>
Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Steven E. Nissen, M.D., Neville D. Yeomans, M.D., Daniel H. Solomon, M.D., M.P.H., Thomas F. Lüscher, M.D., Peter Libby, M.D., Elaine Husni, M.D., David Y. Graham, M.D., Jeffrey S. Borer, M.D., Lisa M. Wisniewski, R.N., Katherine E. Wolski, M.P.H., Qiuqing Wang, M.S., Venu Menon, M.D., Frank Ruschitzka, M.D., Michael Gaffney, Ph.D., Bruce Beckerman, M.D., Manuela F. Berger, M.D., Weihang Bao, Ph.D., and A. Michael Lincoff, M.D., for the PRECISION Trial Investigators*

ABSTRACT

BACKGROUND

The cardiovascular safety of celecoxib, as compared with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), remains uncertain.

METHODS

Patients who required NSAIDs for osteoarthritis or rheumatoid arthritis and were at increased cardiovascular risk were randomly assigned to receive celecoxib, ibuprofen, or naproxen. The goal of the trial was to assess the noninferiority of celecoxib with regard to the primary composite outcome of cardiovascular death (including hemorrhagic death), nonfatal myocardial infarction, or nonfatal stroke. Noninferiority required a hazard ratio of 1.12 or lower, as well as an upper 97.5% confidence limit of 1.33 or lower in the intention-to-treat population and of 1.40 or lower in the on-treatment population. Gastrointestinal and renal outcomes were also adjudicated.

RESULTS

A total of 24,081 patients were randomly assigned to the celecoxib group (mean [±SD] daily dose, 209±37 mg), the naproxen group (852±103 mg), or the ibuprofen group (2045±246 mg) for a mean treatment duration of 20.3±16.0 months and a mean follow-up period of 34.1±13.4 months. During the trial, 68.8% of the patients stopped taking the study drug, and 27.4% of the patients discontinued follow-up. In the intention-to-treat analyses, a primary outcome event occurred in 188 patients in the celecoxib group (2.3%), 201 patients in the naproxen group (2.5%), and 218 patients in the ibuprofen group (2.7%) (hazard ratio for celecoxib vs. naproxen, 0.93; 95% confidence interval [CI], 0.76 to 1.13; hazard ratio for celecoxib vs. ibuprofen, 0.85; 95% CI, 0.70 to 1.04; P<0.001 for noninferiority in both comparisons). In the on-treatment analysis, a primary outcome event occurred in 188 patients in the celecoxib group (2.3%), 201 patients in the naproxen group (2.5%), and 218 patients in the ibuprofen group (2.7%) (hazard ratio for celecoxib vs. naproxen, 0.93; 95% confidence interval [CI], 0.76 to 1.13; hazard ratio for celecoxib vs. ibuprofen, 0.85; 95% CI, 0.70 to 1.04; P<0.001 for noninferiority in both comparisons). In the on-treatment analysis, a primary outcome event occurred in 134 patients in the celecoxib group (1.7%), 144 patients in the naproxen group (1.8%), and 155 patients in the ibuprofen group (1.9%) (hazard ratio for celecoxib vs. naproxen, 0.90; 95% CI, 0.71 to 1.15; hazard ratio for celecoxib vs. ibuprofen, 0.81; 95% CI, 0.65 to 1.02; P<0.001 for noninferiority in both comparisons). The risk of gastrointestinal events was significantly lower with celecoxib than with naproxen (P=0.01) or ibuprofen (P=0.002); the risk of renal events was significantly lower with celecoxib than with ibuprofen (P=0.004) but was not significantly lower with celecoxib than with naproxen (P=0.19).

CONCLUSIONS

At moderate doses, celecoxib was found to be noninferior to ibuprofen or naproxen with regard to cardiovascular safety. (Funded by Pfizer; ClinicalTrials.gov number, NCT00346216.)
Nonsteroidal Antiinflammatory drugs (NSAIDs) were introduced in the 1960s and became the most widely prescribed class of drugs in the world, with more than 100 million prescriptions issued annually in the United States alone. NSAIDs inhibit cyclooxygenase (COX), which reduces pain and inflammation through the inhibition of prostaglandins. However, the COX enzyme is also present in gastric mucosa, where it stimulates gastrointestinal prostaglandins. The identification of two isoforms, COX-1 and COX-2, and the recognition that antiinflammatory and analgesic effects are mediated through COX-2 inhibition — whereas the gastrointestinal toxic effects are linked to COX-1 inhibition — resulted in the development of selective COX-2 inhibitors that offered the potential to retain efficacy while reducing gastrointestinal adverse effects.

Evidence of adverse cardiovascular outcomes in a placebo-controlled trial resulted in the withdrawal of the selective COX-2 inhibitor rofecoxib in 2004. On the basis of a small number of events, the results of another trial suggested that cardiovascular harm may result from the use of higher-than-approved doses of celecoxib. Subsequently, the Food and Drug Administration (FDA) allowed continued marketing of celecoxib, the sole remaining selective COX-2 inhibitor, but mandated a cardiovascular safety trial. In the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial, we sought to assess cardiovascular, gastrointestinal, renal, and other outcomes with celecoxib as compared with two nonselective NSAIDs.

**METHODS**

**TRIAL DESIGN AND OVERSIGHT**

PRECISION was a randomized, multicenter, double-blind, noninferiority trial involving patients who were at increased cardiovascular risk and had rheumatoid arthritis or osteoarthritis. Randomization was stratified according to the primary diagnosis (osteoarthritis or rheumatoid arthritis), aspirin use, and geographic region. Detailed methods for the trial have been published previously, and both the protocol and the statistical analysis plan are available with the full text of this article at NEJM.org. At each center, either a central institutional review board (Schulman IRB) or the local institutional review board approved the trial, and the patients provided written informed consent. A multidisciplinary executive committee supervised the trial, and an independent data and safety monitoring committee reviewed unblinded data to assess safety. The members of the committees are listed in Supplementary Appendix, available at NEJM.org. The members of the executive committee agreed not to accept any financial payments from any maker of NSAIDs for the duration of the trial. The trial sponsor (Pfizer) participated in the design of the trial and in the writing of the protocol in collaboration with the executive committee and in consultation with the FDA; the sponsor also assisted with data collection and maintained the trial database. The sponsor shared operational roles with the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and several contract research organizations. After the conclusion of the trial, the database was transferred to C5Research for statistical analyses. The academic authors wrote the manuscript. The sponsor was allowed to review and comment on the manuscript, but the decision to publish and the final contents were determined by the academic authors, with no contractual limits on the right to publish. All the authors had access to the final results, approved the manuscript, and assume responsibility for its accuracy and completeness and for the adherence of the trial and this report to the protocol.

**INCLUSION AND EXCLUSION CRITERIA**

We enrolled patients who were 18 years of age or older and who, as determined by the patient and physician, required daily treatment with NSAIDs for arthritis pain; patients whose arthritis pain was managed adequately with acetaminophen were not eligible. A key inclusion criterion was established cardiovascular disease or an increased risk of the development of cardiovascular disease (defined in the Supplementary Appendix). Other inclusion criteria and the exclusion criteria are provided in the protocol and in a previous publication.

**TREATMENT**

Patients were randomly assigned, in a 1:1:1 ratio, to receive celecoxib (100 mg twice a day), ibuprofen (600 mg three times a day), or naproxen (375 mg twice a day) with matching placebo. At subsequent visits, for patients with rheumatoid arthri-
tis, investigators could increase the dose of celecoxib to 200 mg twice a day, the dose of ibuprofen to 800 mg three times a day, or the dose of naproxen to 500 mg twice a day for the treatment of symptoms. For patients with osteoarthritis, increases in the doses of ibuprofen and naproxen were permitted; however, regulatory dosing restrictions precluded dose escalation for celecoxib in these patients. Esomeprazole (20 to 40 mg) was provided to all patients for gastric protection. Investigators were encouraged to provide cardiovascular preventive management in accordance with local standards and guidelines. Patients who were taking low-dose aspirin (≤325 mg daily) were permitted to continue this therapy.

**ADJUDICATED AND OTHER OUTCOMES**

The primary composite outcome, in a time-to-event analysis, was the first occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria (i.e., death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke).6 A secondary composite outcome, major adverse cardiovascular events, included the components of the primary outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack. Secondary outcomes also included clinically significant gastrointestinal events. Tertiary outcomes included clinically significant renal events, iron deficiency anemia of gastrointestinal origin, and hospitalization for heart failure or hypertension. (Definitions are provided in the Supplementary Appendix.) Although it is not described in the protocol, the composite outcome of clinically significant gastrointestinal events or iron deficiency anemia of gastrointestinal origin was designated as the key gastrointestinal safety outcome before the trial data were unblinded. An independent committee of multidisciplinary specialists at C5Research who were unaware of the treatment assignments reviewed and adjudicated events. An assessment of the intensity of arthritis pain with the use of the Visual Analogue Scale for Pain (VAS) (scores range from 0 to 100 mm, with higher scores indicating worse pain) was a nonadjudicated secondary outcome; differences greater than 13.7 mm are considered to be clinically meaningful.7 The incidence of death from any cause was a prespecified tertiary outcome. Other prespecified outcomes are listed in the protocol and statistical analysis plan.

**STATISTICAL ANALYSIS**

Naproxen was designated as the primary comparator for the assessment of the noninferiority of celecoxib. Noninferiority comparisons of celecoxib versus ibuprofen and of ibuprofen versus naproxen were also prespecified. Noninferiority required four criteria to be met; in the original design, a hazard ratio not exceeding 1.12 was required, with an upper limit of the one-sided 97.5% confidence interval of less than 1.33 in both the intention-to-treat population and the on-treatment population. The assessment of the on-treatment population included events that occurred while patients were taking the study drug and during the 30 days after discontinuation. The trial was event-driven, requiring 762 events to provide 90% power to determine noninferiority. Under the assumption of an annual event rate of 2% and a treatment discontinuation rate of 40%, the required sample size was estimated to be 20,000 patients. The observed event rate was lower, the discontinuation rate higher, and the enrollment rate slower than anticipated. At the recommendation of the data and safety monitoring committee and after consultation with the FDA, the protocol was amended to have the study provide 80% power, and the upper 97.5% confidence limit for noninferiority in the on-treatment population was modified to 1.40, which required 580 events in the intention-to-treat population and 420 events in the on-treatment population. The protocol prespecified a minimum follow-up time of 18 months, with censoring of data from event-free patients after 30 months in the intention-to-treat population and after 43 months in the on-treatment population.

A Cox proportional-hazards model with adjustment for stratification factors was used to calculate the hazard ratios and confidence intervals. A one-sided noninferiority P value of less than 0.025 was considered to indicate statistical significance for the primary end point, with no adjustment for multiple comparisons. P values for secondary analyses in the intention-to-treat population are reported for descriptive purposes; a twosided P value of less than 0.05 was considered to indicate statistical significance, with no adjustment for multiple comparisons. For the on-treatment analyses, P values for noninferiority are reported for the primary APTC outcome, but P values are not reported for superiority comparisons. Additional details regarding the statistical
analyses are provided in the Supplementary Appendix.

RESULTS

PATIENT POPULATION

We screened 31,857 patients; a total of 24,222 patients underwent randomization at 926 centers in 13 countries between October 23, 2006, and June 30, 2014, and 141 were excluded from the analysis (106 were determined to be fraudulently enrolled, and 35 enrolled more than once), leaving 24,081 participants who could be included in the analysis. There were 8072 patients assigned to the celecoxib group (mean ±SD daily dose, 209±37 mg), 7969 assigned to the naproxen group (852±103 mg), and 8040 assigned to the ibuprofen group (2045±246 mg). The characteristics of the patients at baseline were similar among the treatment groups (Table 1). The mean durations of treatment and follow-up, respectively, were 20.3±16.0 and 34.1±13.4 months for all patients: 20.8±16.0 and 34.2±13.4 months in the celecoxib group, 20.5±15.9 and 34.2±13.3 months in the naproxen group, and 19.6±16.0 and 33.8±13.6 months in the ibuprofen group. During this 10-year trial, 68.8% of patients stopped taking the study drug, and 27.4% of patients discontinued follow-up; 2.5% of patients died, 8.3% withdrew consent in writing, 7.4% verbally expressed unwillingness to continue participation, and 7.2% were lost to follow-up before a final follow-up visit. Details regarding patient disposition, time to study-drug discontinuation, and time to nonretention in the trial are provided in Figures S1, S2, and S3 in the Supplementary Appendix.

PRIMARY APTC OUTCOME

In the intention-to-treat population (Table 2 and Fig. 1), the primary APTC outcome occurred in 134 patients in the celecoxib group (1.7%), 144 in the naproxen group (1.8%), and 155 in the ibuprofen group (1.9%). The hazard ratio in the celecoxib group, as compared with the naproxen group, was 0.90 (95% CI, 0.71 to 1.15; P<0.001 for noninferiority); for celecoxib versus ibuprofen, the hazard ratio was 0.81 (95% CI, 0.65 to 1.02; P<0.001 for noninferiority), and for ibuprofen versus naproxen, the hazard ratio was 1.12 (95% CI, 0.89 to 1.40; P=0.025 for noninferiority) (Table S2 in the Supplementary Appendix).

Celecoxib, as compared with either naproxen or ibuprofen, met all four prespecified noninferiority requirements (P<0.001 for noninferiority in both comparisons). Ibuprofen, as compared with naproxen, just met the noninferiority criteria (P=0.025).

MAJOR ADVERSE CARDIOVASCULAR EVENTS AND MORTALITY OUTCOMES

The results of the intention-to-treat analyses for the composite outcome of major adverse cardiovascular events and for the components of the outcome are reported in Table 2 and Figure 1. The hazard ratio for celecoxib versus naproxen was 0.97 (95% CI, 0.83 to 1.12; P=0.64), and the hazard ratio for celecoxib versus ibuprofen was 0.87 (95% CI, 0.75 to 1.01; P=0.06). In pairwise comparisons for the components of the primary outcome, the differences between celecoxib and naproxen and between celecoxib and ibuprofen were not significant. The hazard ratio for death from any cause was 0.80 for celecoxib versus naproxen (95% CI, 0.63 to 1.00; P=0.052) (Table 2 and Fig. 1). The rate of nonfatal myocardial infarction was higher in the ibuprofen group than in the naproxen group (hazard ratio, 1.39; 95% CI, 1.01 to 1.91; P=0.04) (Table S1 in the Supplementary Appendix).

GASTROINTESTINAL AND RENAL OUTCOMES

The results of the intention-to-treat analyses of gastrointestinal and renal outcomes are provided in Table 2 and Figure 1. The event rate for the composite outcome of serious gastrointestinal events was lower in the celecoxib group than in the naproxen group (hazard ratio, 0.71; 95% CI, 0.54 to 0.93; P=0.01) and was lower in the celecoxib group than in the ibuprofen group (hazard ratio, 0.65; 95% CI, 0.50 to 0.85; P=0.002). The
hazard ratio for gastrointestinal events in the ibuprofen group versus the naproxen group was 1.08 (95% CI, 0.85 to 1.39; P = 0.53). Serious renal events occurred at a significantly lower rate in the celecoxib group than in the ibuprofen group (hazard ratio, 0.61; 95% CI, 0.44 to 0.85; P = 0.004), but the difference in the rate of this outcome in the celecoxib group versus the naproxen group was not significant (hazard ratio, 0.79; 95% CI, 0.56 to 1.12; P = 0.19).

**Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib Group (N = 8072)</th>
<th>Naproxen Group (N = 7969)</th>
<th>Ibuprofen Group (N = 8040)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>63.0±9.5</td>
<td>63.3±9.4</td>
<td>63.2±9.4</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>5175 (64.1)</td>
<td>5096 (63.9)</td>
<td>5174 (64.4)</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6058 (75.0)</td>
<td>5926 (74.4)</td>
<td>5991 (74.5)</td>
</tr>
<tr>
<td>Black</td>
<td>1090 (13.5)</td>
<td>1134 (14.2)</td>
<td>1108 (13.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>164 (2.0)</td>
<td>172 (2.2)</td>
<td>173 (2.2)</td>
</tr>
<tr>
<td>Unspecified or other</td>
<td>760 (9.4)</td>
<td>737 (9.2)</td>
<td>768 (9.6)</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td>32.7±7.3</td>
<td>32.6±7.3</td>
<td>32.5±7.4</td>
</tr>
<tr>
<td>Primary arthritis diagnosis — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>7259 (89.9)</td>
<td>7178 (90.1)</td>
<td>7208 (89.7)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>813 (10.1)</td>
<td>791 (9.9)</td>
<td>832 (10.3)</td>
</tr>
<tr>
<td>Current aspirin use — no. (%)</td>
<td>3701 (45.8)</td>
<td>3652 (45.8)</td>
<td>3712 (46.2)</td>
</tr>
<tr>
<td>Cardiovascular risk category — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>6209 (76.9)</td>
<td>6186 (77.6)</td>
<td>6206 (77.2)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>1863 (23.1)</td>
<td>1783 (22.4)</td>
<td>1834 (22.8)</td>
</tr>
<tr>
<td>History of diabetes — no. (%)</td>
<td>2843 (35.2)</td>
<td>2768 (34.7)</td>
<td>2885 (35.9)</td>
</tr>
<tr>
<td>History of hypertension — no. (%)</td>
<td>6296 (78.0)</td>
<td>6145 (77.1)</td>
<td>6301 (78.4)</td>
</tr>
<tr>
<td>History of dyslipidemia — no. (%)</td>
<td>5080 (62.9)</td>
<td>4966 (62.3)</td>
<td>5002 (62.2)</td>
</tr>
<tr>
<td>Current smoker — no. (%)</td>
<td>1689 (20.9)</td>
<td>1611 (20.5)</td>
<td>1680 (20.9)</td>
</tr>
<tr>
<td>Current statin use — no. (%)</td>
<td>4367 (54.1)</td>
<td>4304 (54.0)</td>
<td>4307 (53.6)</td>
</tr>
<tr>
<td>Current DMARD use — no. (%)</td>
<td>572 (7.1)</td>
<td>602 (7.6)</td>
<td>584 (7.3)</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg§</td>
<td>125.3±10.5</td>
<td>125.0±10.6</td>
<td>125.4±10.4</td>
</tr>
<tr>
<td>Diastolic blood pressure — mm Hg</td>
<td>75.5±8.0</td>
<td>75.4±8.0</td>
<td>75.5±7.9</td>
</tr>
<tr>
<td>Creatinine level — mg/dl</td>
<td>0.9±0.23</td>
<td>0.9±0.22</td>
<td>0.9±0.22</td>
</tr>
<tr>
<td>HAQ disability index¶</td>
<td>1.1±0.61</td>
<td>1.1±0.61</td>
<td>1.1±0.61</td>
</tr>
<tr>
<td>VAS score — mm‖</td>
<td>54.0±23.5</td>
<td>54.1±24.0</td>
<td>54.1±23.6</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Percentages may not total to 100 because of rounding. DMARD denotes disease-modifying antirheumatic drug.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ P = 0.044 for the comparison among the three treatment groups.
¶ The Health Assessment Questionnaire (HAQ) disability index is based on 20 questions in eight categories regarding daily functioning; overall scores range from 0 to 3, with 0 indicating no disability and 3 indicating complete disability.
‖ Visual Analogue Scale of Pain (VAS) scores range from 0 to 100 mm, with higher scores indicating worse pain; differences greater than 13.7 mm are considered to be clinically significant.

**OTHER OUTCOMES**

The rate of hospitalization for hypertension was significantly lower in the celecoxib group than in the ibuprofen group (hazard ratio, 0.60; 95% CI, 0.36 to 0.99; P = 0.04) but was not significantly lower in the celecoxib group than in the naproxen group (Table 2). The results of analyses of quality of life and efficacy for the relief of arthritis symptoms are reported in Table S3 in the Supplementary Appendix. In the assessment...
Table 2. Adjudicated Outcomes in the Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Celecoxib Group (N = 8072)</th>
<th>Naproxen Group (N = 7969)</th>
<th>Ibuprofen Group (N = 8040)</th>
<th>Celecoxib vs. Naproxen*</th>
<th>Celecoxib vs. Ibuprofen*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td></td>
<td></td>
<td>Adjusted Hazard Ratio</td>
<td>P Value</td>
</tr>
<tr>
<td>Primary APTC end point†</td>
<td>188 (2.3)</td>
<td>201 (2.5)</td>
<td>218 (2.7)</td>
<td>0.93 (0.76–1.13)</td>
<td>0.45</td>
</tr>
<tr>
<td>Major adverse cardiovascular events‡</td>
<td>337 (4.2)</td>
<td>346 (4.3)</td>
<td>384 (4.8)</td>
<td>0.97 (0.83–1.12)</td>
<td>0.64</td>
</tr>
<tr>
<td>Composite of serious gastrointestinal events‡</td>
<td>86 (1.1)</td>
<td>119 (1.5)</td>
<td>130 (1.6)</td>
<td>0.71 (0.54–0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinically significant gastrointestinal events§</td>
<td>55 (0.7)</td>
<td>56 (0.7)</td>
<td>72 (0.9)</td>
<td>0.97 (0.67–1.40)</td>
<td>0.86</td>
</tr>
<tr>
<td>Iron-deficiency anemia of gastrointestinal origin§</td>
<td>33 (0.4)</td>
<td>69 (0.9)</td>
<td>64 (0.8)</td>
<td>0.47 (0.31–0.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal events</td>
<td>57 (0.7)</td>
<td>71 (0.9)</td>
<td>92 (1.1)</td>
<td>0.79 (0.56–1.12)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hospitalization for congestive heart failure</td>
<td>45 (0.6)</td>
<td>48 (0.6)</td>
<td>46 (0.6)</td>
<td>0.92 (0.62–1.39)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hospitalization for hypertension</td>
<td>24 (0.3)</td>
<td>34 (0.4)</td>
<td>40 (0.5)</td>
<td>0.69 (0.41–1.17)</td>
<td>0.17</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>132 (1.6)</td>
<td>163 (2.0)</td>
<td>142 (1.8)</td>
<td>0.80 (0.63–1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>Components of composite end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>68 (0.8)</td>
<td>86 (1.1)</td>
<td>80 (1.0)</td>
<td>0.78 (0.57–1.07)</td>
<td>0.13</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>76 (0.9)</td>
<td>66 (0.8)</td>
<td>92 (1.1)</td>
<td>1.14 (0.82–1.59)</td>
<td>0.43</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>51 (0.6)</td>
<td>57 (0.7)</td>
<td>53 (0.7)</td>
<td>0.88 (0.61–1.30)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>55 (0.7)</td>
<td>64 (0.8)</td>
<td>65 (0.8)</td>
<td>0.86 (0.60–1.23)</td>
<td>0.40</td>
</tr>
<tr>
<td>Revascularization</td>
<td>174 (2.2)</td>
<td>161 (2.0)</td>
<td>198 (2.5)</td>
<td>1.07 (0.87–1.33)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization for TIA</td>
<td>18 (0.2)</td>
<td>18 (0.2)</td>
<td>27 (0.3)</td>
<td>0.99 (0.51–1.90)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with adjustment for stratification factors.
† The primary composite outcome in the time-to-event analysis was the first occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria (death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke). The P value for the noninferiority of celecoxib as compared with either naproxen or ibuprofen with regard to this outcome was <0.001.
‡ The composite outcome of major adverse cardiovascular events included the components of the primary APTC outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack (TIA).
§ Definitions are provided in the Supplementary Appendix.
of pain with the use of the VAS scale, a significant but small benefit was found for naproxen relative to celecoxib or ibuprofen; the change in VAS score from baseline was $-9.3\pm0.26$ mm for celecoxib, $-9.5\pm0.26$ for ibuprofen, and $-10.2\pm0.26$ for naproxen ($P<0.001$ for naproxen versus celecoxib, $P=0.01$ for naproxen versus ibuprofen). The analyses of the primary composite outcome among prespecified subgroups showed no significant interactions for any pairwise comparison, including among the subgroups that were defined by aspirin use at baseline (Fig. S5 in the Supplementary Appendix). Investigator-reported adverse effects that occurred in 3% or more of the patients in any treatment group are reported in Table S4 in the Supplementary Appendix.

**DISCUSSION**

The PRECISION trial was designed in the aftermath of the withdrawal of rofecoxib during a period of considerable scientific and public controversy about the cardiovascular safety of selective COX-2 inhibitors. Previous knowledge about the relative safety of selective or nonselective COX inhibitors was limited, because NSAIDs received initial approval on the basis of relatively small, short-term studies that typically had been designed to assess pain relief and general safety. The primary clinical concern was that celecoxib might be associated with adverse cardiovascular effects similar to those associated with rofecoxib. The PRECISION trial provides statistically strong evidence that the cardiovascular risk associated with moderate doses of celecoxib is not greater than that associated with nonselective NSAIDs. As compared with two widely used nonselective NSAIDs — naproxen and ibuprofen — celecoxib was associated with numerically fewer cardiovascular events, which resulted in noninferiority $P$ values of less than 0.001. The trial results do not support the widely advocated belief that naproxen treatment, as compared with treatment with other NSAIDs, results in better cardiovascular outcomes.

To establish noninferiority, the trial design required that prespecified criteria be met in both the intention-to-treat population and the on-treatment population. We selected this approach because these two alternative analyses provide complementary insights into drug safety. The intention-to-treat analysis is the only analysis that preserves the integrity of randomization, but it tends to dilute safety signals when patients do not adhere to the study treatment. The on-treatment analysis considers events that occur only while patients are actually taking the study drug, which can strengthen safety signals. Although both the intention-to-treat and the on-treatment analyses were used to assess noninferiority, superiority comparisons were performed with the intention-to-treat population. The on-treatment analyses are included to provide a complete accounting of outcomes, but the results in this population may have been influenced by between-group differences in rates of treatment discontinuation; therefore, these results are reported without $P$ values and should be considered exploratory (Table 3).

We also included a broader outcome — major adverse cardiovascular events — as a secondary composite outcome to provide greater power to detect differences among the three treatments. Fewer major adverse cardiovascular events occurred in the celecoxib group than in the ibuprofen group, but the difference did not reach significance in the intention-to-treat population ($P=0.06$). The rate of death from any cause was lower in the celecoxib group than in the naproxen group, although the difference did not reach significance ($P=0.052$). We urge caution in interpreting these findings, because major adverse cardiovascular events was a secondary outcome and death from any cause a tertiary outcome, and these outcomes were not adjusted for end-point multiplicity; in addition, major adverse cardiovascular events included more subjective components than did the APTC outcome.

Although the primary purpose of the trial was to assess cardiovascular outcomes, we also adjudicated gastrointestinal and renal outcomes to provide a comprehensive safety evaluation. To compare the three drugs, we constructed a two-component composite of two adjudicated outcomes — clinically significant gastrointestinal events and iron-deficiency anemia of gastrointestinal origin. For this outcome, significantly fewer events occurred in the celecoxib group than in either the naproxen group or the ibuprofen group. These findings were expected on the basis of the theoretical gastrointestinal advantages of selective COX-2 inhibition. The differences were found despite esomeprazole, a proton-pump inhibitor, being provided for all patients, although we do not have information on adherence to this ther-
Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen

apy. The rates of renal adverse events and hospitalization for hypertension were also significantly lower in the celecoxib group than in the ibuprofen group, although they did not differ significantly between the celecoxib group and the naproxen group. The pattern we found for investigator-reported adverse effects was similar to that for centrally adjudicated events, with a higher reported incidence of increased creatinine levels in the ibuprofen group than in the celecoxib group and a higher incidence of hypertension in both the naproxen group and the ibuprofen group, as compared with the celecoxib group (Table S4 in the Supplementary Appendix). Although naproxen-treated patients had a slightly greater reduction in pain, as assessed with the use of VAS scores,

### Table 3. Adjudicated Outcomes in the On-Treatment Population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Celecoxib (N = 8030)</th>
<th>Naproxen (N = 7933)</th>
<th>Ibuprofen (N = 7990)</th>
<th>Celecoxib vs. Naproxen Adjusted Hazard Ratio (95% CI)*</th>
<th>Celecoxib vs. Ibuprofen Adjusted Hazard Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>number of patients (percent)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary APTC outcome†</td>
<td>134 (1.7)</td>
<td>144 (1.8)</td>
<td>155 (1.9)</td>
<td>0.90 (0.71–1.15)</td>
<td>0.81 (0.65–1.02)</td>
</tr>
<tr>
<td>Major adverse cardiovascular events‡</td>
<td>247 (3.1)</td>
<td>253 (3.2)</td>
<td>284 (3.6)</td>
<td>0.95 (0.80–1.13)</td>
<td>0.82 (0.69–0.97)</td>
</tr>
<tr>
<td>Composite of serious gastrointestinal events</td>
<td>54 (0.7)</td>
<td>115 (1.4)</td>
<td>115 (1.4)</td>
<td>0.45 (0.33–0.63)</td>
<td>0.44 (0.32–0.61)</td>
</tr>
<tr>
<td>Clinically significant gastrointestinal events§</td>
<td>27 (0.3)</td>
<td>52 (0.7)</td>
<td>59 (0.7)</td>
<td>0.51 (0.32–0.81)</td>
<td>0.43 (0.27–0.68)</td>
</tr>
<tr>
<td>Iron-deficiency anemia of gastrointestinal origin§</td>
<td>27 (0.3)</td>
<td>66 (0.8)</td>
<td>58 (0.7)</td>
<td>0.40 (0.25–0.62)</td>
<td>0.43 (0.27–0.68)</td>
</tr>
<tr>
<td>Renal events</td>
<td>42 (0.5)</td>
<td>62 (0.8)</td>
<td>73 (0.9)</td>
<td>0.66 (0.44–0.97)</td>
<td>0.54 (0.37–0.80)</td>
</tr>
<tr>
<td>Hospitalization for congestive heart failure</td>
<td>28 (0.3)</td>
<td>35 (0.4)</td>
<td>38 (0.5)</td>
<td>0.78 (0.47–1.27)</td>
<td>0.70 (0.43–1.13)</td>
</tr>
<tr>
<td>Hospitalization for hypertension</td>
<td>25 (0.3)</td>
<td>32 (0.4)</td>
<td>37 (0.5)</td>
<td>0.76 (0.45–1.28)</td>
<td>0.64 (0.39–1.07)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>53 (0.7)</td>
<td>79 (1.0)</td>
<td>73 (0.9)</td>
<td>0.65 (0.46–0.92)</td>
<td>0.68 (0.48–0.97)</td>
</tr>
<tr>
<td>Components of composite outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>35 (0.4)</td>
<td>49 (0.6)</td>
<td>51 (0.6)</td>
<td>0.69 (0.45–1.07)</td>
<td>0.64 (0.42–0.99)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>58 (0.7)</td>
<td>53 (0.7)</td>
<td>76 (1.0)</td>
<td>1.06 (0.73–1.54)</td>
<td>0.72 (0.51–1.01)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>43 (0.5)</td>
<td>45 (0.6)</td>
<td>32 (0.4)</td>
<td>0.93 (0.61–1.42)</td>
<td>1.26 (0.80–1.99)</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>46 (0.6)</td>
<td>44 (0.6)</td>
<td>49 (0.6)</td>
<td>1.02 (0.68–1.54)</td>
<td>0.89 (0.59–1.33)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>132 (1.6)</td>
<td>122 (1.5)</td>
<td>158 (2.0)</td>
<td>1.06 (0.83–1.35)</td>
<td>0.79 (0.62–0.99)</td>
</tr>
<tr>
<td>Hospitalization for TIA</td>
<td>12 (0.1)</td>
<td>16 (0.2)</td>
<td>21 (0.3)</td>
<td>0.73 (0.35–1.55)</td>
<td>0.54 (0.27–1.10)</td>
</tr>
</tbody>
</table>

* Hazard ratios were estimated with the use of a Cox proportional-hazards model with adjustment for stratification factors.
† The primary composite outcome in the time-to-event analysis was the first occurrence of an adverse event that met APTC criteria (death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke). The P value for the noninferiority of celecoxib as compared with either naproxen or ibuprofen with regard to this outcome was <0.001.
‡ The composite outcome of major adverse cardiovascular events included the components of the primary APTC outcome plus coronary revascularization or hospitalization for unstable angina or TIA.
§ Definitions are provided in the Supplementary Appendix.

Figure 1 (facing page). Time-to-Event Analysis for Primary and Secondary Outcomes.

The primary composite outcome in the time-to-event analysis was the first occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria (death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke). The definitions for all outcomes are provided in the Supplementary Appendix. The cumulative incidences were estimated with the Kaplan–Meier method, and the hazard ratios were calculated with the Cox proportional-hazards regression model with adjustment for stratification factors. The intention-to-treat data analyses were truncated at 30 months, and the on-treatment analyses were truncated at 43 months. The insets show the same data on an enlarged y axis.
than did patients treated with celecoxib or ibuprofen, the differences were smaller than the 13.7-mm difference that is considered to be clinically meaningful.

The PRECISION trial had limitations. Adherence and retention were lower than in most trials that assess cardiovascular outcomes, which reflects the challenges of long-term treatment of a painful condition in patients who frequently experience frustration with unrelieved symptoms and switch therapies or leave the trial. Low levels of adherence and retention have also been found in previous pain studies.9 Although the similarity in the results for the intention-to-treat and on-treatment populations suggests that low adherence was unlikely to have influenced the principal conclusions, the high levels of nonretention make interpretation of the findings challenging. Although the rates of nonretention were similar for all three treatments, the possibility of informative censoring (i.e., the bias that is created when participants drop out of a study because of factors related to the study itself) cannot be ruled out. The large number of comparisons without adjustment for multiplicity increases the possibility of false positive findings.

The dose of celecoxib was limited by regulatory restrictions to 200 mg daily for most patients, which may have provided a potential safety advantage for celecoxib, although the mean doses for both nonselective NSAIDs were also submaximal. Three previous trials assessed higher doses of celecoxib (400 to 800 mg per day),10,11 one of which showed a significantly higher risk of cardiovascular events in association with the unapproved 800-mg dose than with placebo, although the trial included only a small number of events. Our results provide reassurance regarding the safety of moderate doses of celecoxib but not the safety of high doses of celecoxib. Although ibuprofen and naproxen have been reported to potentially interfere with the antiplatelet effects of aspirin,12 we found no statistical interaction for aspirin use (Fig. S4 in the Supplementary Appendix). However, the trial was not specifically designed to assess the effects of aspirin on the relative safety of NSAIDs. Although enrollment was stratified according to aspirin use to ensure equal distribution of aspirin use among the treatment groups, patients were not randomly assigned to receive or not receive aspirin.

The current results reflect the relative safety of only these three drugs and cannot provide insight into the effects of the more than two dozen other marketed NSAIDs, particularly because each of these drugs may have a unique safety profile. No inferences are possible regarding the effects of NSAIDs as compared with placebo or regarding the safety of intermittent treatment with low-dose over-the-counter preparations. For ethical reasons, a placebo comparison group was not feasible, since we required all patients and physicians to document that participants had required NSAID treatment for at least 6 months for adequate symptom relief. Acetaminophen was not selected as a comparator because previous studies had shown this drug to be ineffective for the treatment of patients with NSAID-dependent arthritis.13

In summary, the PRECISION trial showed the noninferiority of moderate doses of celecoxib, as compared with naproxen or ibuprofen, with regard to the primary APTC cardiovascular outcome. Celecoxib treatment also resulted in lower rates of gastrointestinal events than did either comparator drug and in lower rates of renal adverse events than did ibuprofen.

Supported by Pfizer.

Dr. Solomon and Dr. Lüscher report receiving grant support to their institutions from Pfizer; Dr. Libby, receiving consulting fees from MedIntelligence, lecture fees from MedIntelligence, Omniplex, and HealthScience Media, and travel support from the Academy for Continued Healthcare Learning (ACHL), Healthcare21 Communications, PSL Group Services, MEDCON International, Regeneron Pharmaceuticals, Esperion Therapeutics, Takeda, Bayer Yakuhin, and Amgen, serving on advisory boards (uncompensated) for Regeneron Pharmaceuticals, Merck, and Novartis, chairing a peer review of grant applications (uncompensated) for Healthmatters Communications, providing consulting (uncompensated) for GlaxoSmithKline, MedIntelligence, and Regeneron Pharmaceuticals, and giving talks (uncompensated) at meetings held by Rx Worldwide Meetings, Pri-Med, VHA-UHC Alliance NewCo (now Vizient), AstraZeneca, and Tarsus; Dr. Husni, receiving fees for serving on advisory boards from AbbVie, Bristol-Myers Squibb, Amgen, UC Berkeley Pharma, Regeneron, and Janssen, and grant support from Sanofi–Genzyme; Dr. Borer, receiving fees for serving on data and safety monitoring boards from Cardiorentis, Novartis, Celladon, GlaxoSmithKline, and Pfizer, fees for serving on executive committees from Servier and Biotronik, fees for serving on an advisory board from ARMO Pharma, consulting fees from Boehringer Ingelheim, Abbott Laboratories, Sarepta Therapeutics, Amgen, Servier, and Gilead Sciences, and holding stock in BioMarin Pharmaceutical; Dr. Ruschitzka, receiving personal fees from St. Jude Medical, Servier, ZOLL Medical, AstraZeneca, HeartWare, Sanofi, Cardiorentis, Novartis, Amgen, and Bristol-Myers Squibb, and grant support from St. Jude Medical; Dr. Gaffney, Dr. Beckerman, Dr. Berger, and Dr. Bao, being employ-
REFERENCES


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CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

R. Doug McEvoy, M.D., Nick A. Antic, M.D., Ph.D., Emma Heeley, Ph.D., Yuanming Luo, M.D., Qiong Ou, M.D., Xilong Zhang, M.D., Olga Mediano, M.D., Rui Chen, M.D., Luciano F. Drager, M.D., Ph.D., Zhihong Liu, M.D., Ph.D., Guofang Chen, M.D., Baoliang Du, M.D., Nigel McArdle, M.D., Sutapa Mukherjee, M.D., Ph.D., Manjari Tripathi, M.D., Laurent Billot, M.Sc., Qiang Li, M.Biostat., Geraldo Lorenzi-Filho, M.D., Ferran Barbe, M.D., Susan Redline, M.D., M.P.H., Jiguang Wang, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Bruce Neal, M.D., Ph.D., David P. White, M.D., Ron R. Grunstein, M.D., Ph.D., Nanshan Zhong, M.D., and Craig S. Anderson, M.D., Ph.D., for the SAVE Investigators and Coordinators*

ABSTRACT

BACKGROUND
Obstructive sleep apnea is associated with an increased risk of cardiovascular events; whether treatment with continuous positive airway pressure (CPAP) prevents major cardiovascular events is uncertain.

METHODS
After a 1-week run-in period during which the participants used sham CPAP, we randomly assigned 2717 eligible adults between 45 and 75 years of age who had moderate-to-severe obstructive sleep apnea and coronary or cerebrovascular disease to receive CPAP treatment plus usual care (CPAP group) or usual care alone (usual-care group). The primary composite end point was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. Secondary end points included other cardiovascular outcomes, health-related quality of life, snoring symptoms, daytime sleepiness, and mood.

RESULTS
Most of the participants were men who had moderate-to-severe obstructive sleep apnea and minimal sleepiness. In the CPAP group, the mean duration of adherence to CPAP therapy was 3.3 hours per night, and the mean apnea–hypopnea index (the number of apnea or hypopnea events per hour of recording) decreased from 29.0 events per hour at baseline to 3.7 events per hour during follow-up. After a mean follow-up of 3.7 years, a primary end-point event had occurred in 229 participants in the CPAP group (17.0%) and in 207 participants in the usual-care group (15.4%) (hazard ratio with CPAP, 1.10; 95% confidence interval, 0.91 to 1.32; P = 0.34). No significant effect on any individual or other composite cardiovascular end point was observed. CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood.

CONCLUSIONS
Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease. ( Funded by the National Health and Medical Research Council of Australia and others; SAVE ClinicalTrials.gov number, NCT00738179; Australian New Zealand Clinical Trials Registry number, ACTRN12608000409370.)

*The authors’ affiliations are listed in the Appendix. Address reprint requests to Dr. McEvoy at the Adelaide Institute for Sleep Health, Flinders University and Respiratory and Sleep Services, Southern Adelaide Local Health Network, Repatriation General Hospital, Daw Park, Adelaide SA 5041, Australia, or at doug.mcevoy@ flinders.edu.au; or to Dr. Luo at the First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, Guangzhou, China, or at yuanmingluo9431@yahoo.co.uk.

A complete list of sites and trial investigators and coordinators in the Sleep Apnea Cardiovascular Endpoints (SAVE) study is provided in the Supplementary Appendix, available at NEJM.org. This article was published on August 28, 2016, at NEJM.org.
Obstructive sleep apnea causes episodic hypoxemia and nocturnal sympathetic nervous system activation and elevates blood pressure and markers of oxidative stress, inflammation, and hypercoagulation. Large negative intrathoracic pressure swings also impose mechanical stress on the heart and great vessels. Population-based and sleep-clinic–based cohort studies have shown an association between obstructive sleep apnea and cardiovascular events, particularly stroke. Randomized, controlled trials have shown that treatment with continuous positive airway pressure (CPAP) lowers systolic blood pressure by 2 to 3 mm Hg in patients with normotensive obstructive sleep apnea and by 6 to 7 mm Hg in patients with resistant hypertension, improves endothelial function, and increases insulin sensitivity.

Observational clinical studies have shown that the use of CPAP is associated with lower rates of cardiovascular complications and of death from cardiovascular causes, especially among patients who are adherent to treatment.

Obstructive sleep apnea is a common condition among patients with cardiovascular disease, affecting 40 to 60% of such patients. Because the risks of recurrent cardiovascular events among these patients remain high despite contemporary therapies, CPAP could be a useful additional treatment for the prevention of these events. We describe the main results of the Sleep Apnea Cardiovascular Endpoints (SAVE) study, a secondary prevention trial that was designed to evaluate the effectiveness of CPAP in reducing the rate of cardiovascular events among patients with obstructive sleep apnea.

METHODS

STUDY DESIGN AND OVERSIGHT

The SAVE study was an international, multicenter, randomized, parallel-group, open-label trial, with blinded end-point assessment. Details of the design and analysis plan of the trial have been published previously. An executive committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study and supervised the conduct of the trial and the collection of the data. The Adelaide Institute for Sleep Health of Flinders University of South Australia was responsible for the overall management of the trial and provided the core sleep laboratory analysis and monitoring of the CPAP data and treatment at the sites. Investigators at the George Institute for Global Health coordinated the trial, managed the database, and performed the statistical analyses. All the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol, available at NEJM.org. An independent data and safety monitoring board monitored unblinded trial results and safety events. The trial protocol was approved by all appropriate regulatory authorities and ethics committees at the participating centers. All participants provided written informed consent.

The National Health and Medical Research Council of Australia and Philips Respironics provided the main funding for the trial. In-kind donations were provided by Respironics for the CPAP equipment and by ResMed for the sleep apnea diagnostic devices. None of the funding agencies contributed to the design of the trial, the collection or analysis of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.

PATIENTS AND PROCEDURES

Patients were recruited at 89 clinical centers in 7 countries; eligibility criteria included an age between 45 and 75 years, a diagnosis of coronary artery disease or cerebrovascular disease, and a diagnosis of moderate-to-severe obstructive sleep apnea. The diagnosis of moderate-to-severe obstructive sleep apnea, which was defined as an oxygen desaturation index (the number of times per hour during the oximetry recording that the blood oxygen saturation level drops by ≥4 percentage points from baseline) of at least 12, was established with the use of a home sleep-study screening device (ApneaLink, ResMed) and was confirmed by review of the data at a central core sleep laboratory. Patients were excluded from the study if they reported severe daytime sleepiness (Epworth Sleepiness Scale score >15; scores range from 0 to 24, with higher scores indicating greater severity) or were considered to have an increased risk of an accident from falling asleep, if they had very severe hypoxemia (oxygen saturation <80% for >10% of recording time), or if they had a pattern of Cheyne–Stokes respiration on the ApneaLink nasal pressure recording.

Potential participants were required to have a minimum level of adherence to CPAP therapy,
which was defined as an average of 3 hours per night, during a 1-week run-in period in which sham CPAP was used (i.e., CPAP at subtherapeutic pressure). Further details of the inclusion and exclusion criteria and of the procedures performed at the core sleep laboratory are provided in the Supplementary Appendix.

RANDOMIZATION AND INTERVENTIONS
After eligibility was confirmed, the patients were randomly assigned, at a central location, to receive either CPAP therapy plus usual care (CPAP group) or usual care alone (usual-care group). Randomization was performed with the use of a minimization procedure to balance the group assignments according to site, type of cardiovascular disease (cardiac, cerebrovascular, or both), and severity of daytime sleepiness (Epworth Sleepiness Scale score <11 vs. ≥11).

The patients who were assigned to receive mask-delivered CPAP treatment were provided with an automated positive airway pressure machine (REMstar Auto, M or PR series, Philips Respironics) that was initially set in automatic mode for 1 week and thereafter fixed to the 90th percentile of pressure that was calculated by the automated positive airway pressure device from the recorded data. The core sleep laboratory monitored trends in adherence to CPAP therapy and provided corrective advice to investigators (further details are provided in the Supplementary Appendix). Concomitant management of cardiovascular risk factors was performed in accordance with national guidelines. All participants were given advice on healthful sleep habits and lifestyle changes to minimize obstructive sleep apnea. Clinic visits were scheduled for all participants at 1, 3, 6, and 12 months and annually thereafter; the participants were contacted by telephone at 6 months between annual clinic visits.

STUDY MEASUREMENTS
At randomization and at each follow-up visit, participants had resting blood pressure and heart rate measured at the clinic, and details of current medication use and health behaviors were documented through a structured interview. Among the participants in the CPAP group, data on adherence to the use of the CPAP device were recorded. At randomization, at 6 months, and at 2 and 4 years, anthropometric measurements were obtained in all participants, and all participants completed several questionnaires: questionnaires that assessed symptoms of obstructive sleep apnea (snoring, witnessed episodes of apnea, and degree of sleepiness according to the Epworth Sleepiness Scale score), the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; scores range from 0 to 100, with higher scores indicating better quality of life) for assessment of health-related quality of life, and the Hospital Anxiety and Depression Scale (on which anxiety and depression scores range from 0 to 21, with higher scores indicating more symptoms) for assessment of mood. Electrocardiography was performed in all participants at the time of randomization and at 2 years. The European Quality of Life–5 Dimensions questionnaire (EQ-5D; scores range from 1 to 3, with higher scores indicating more problems across five categories of quality of life) was administered only at the end-of-study visit.

The end-of-study visits were conducted from September 2015 through January 2016 (except in India, where they were conducted from July through October 2013). In addition to performing a regular central review of data quality, research staff visited the participating sites to monitor and verify the completeness and authenticity of source documents and adverse-event reporting. Additional details on study measurements and monitoring procedures are provided in the Supplementary Appendix.

STUDY END POINTS
A committee whose members were unaware of the study-group assignments adjudicated the major cardiovascular outcomes specified in the protocol. The primary end point was a composite of death from any cardiovascular cause, myocardial infarction (including silent myocardial infarction), stroke, or hospitalization for heart failure, acute coronary syndrome (including unstable angina), or transient ischemic attack. Prespecified secondary cardiovascular end points included the individual components of the primary composite end point, other composites of cardiovascular events, revascularization procedures, new-onset atrial fibrillation, new-onset diabetes mellitus, and death from any cause. Other secondary end points included symptoms of obstructive sleep apnea, health-related quality of life, and mood.

Prespecified safety end points were assessed each time the participant was contacted; these
end points included all serious adverse events, self-reported accidents causing personal injury that occurred while the participant was driving or while at work, and any accidents or near-miss accidents that occurred as a result of the participant falling asleep. Two safety end points that were not prespecified — the number of self-reported road-traffic accidents from any cause and the number of days off from work because of poor health — were also assessed. Descriptions of the study end points and of the procedures used by the data and safety monitoring board and end-point adjudicators are provided in the Supplementary Appendix.

**STATISTICAL ANALYSIS**

Our original plan was to recruit 5000 patients. In 2012, challenges in achieving recruitment targets prompted us to review the accumulated blinded study data and an updated meta-regression of studies of cardiovascular events and severity of obstructive sleep apnea. The meta-regression showed that cardiovascular risk increased by 25 to 32% for every increase of 10 events per hour in the apnea–hypopnea index (the number of occurrences of apnea or hypopnea per hour of sleep), which was a stronger relationship than we had originally assumed. In consideration of this information, together with interim blinded trial data showing an annual event rate of 6.86% and better-than-expected adherence to CPAP therapy, we revised our sample size to 2500 patients; we estimated that with this sample size, the study would have 90% statistical power (at an alpha level of 0.05) to detect a 25% lower incidence with CPAP plus usual care than with usual care alone. In consideration of this information, together with interim blinded trial data and an updated meta-regression, we anticipated an overall event rate of 6% among adherent patients and worse-than-expected adherence to CPAP therapy, which was defined as an average of 4 hours or more of treatment per night over the first 2 years, we used prespecified propensity-score matching to match adherent patients one-to-one with participants selected from the usual-care (control) group who never used CPAP. The change in clinical variables from baseline to 48 months or to the end-of-study visit (whichever came first) was assessed with the use of analysis of covariance with adjustment for baseline values. All P values are two-sided and were not adjusted for multiple testing. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute). (Additional details regarding the sample-size calculations and other aspects of the statistical analysis are provided in the Supplementary Appendix.)

**RESULTS**

**STUDY PARTICIPANTS**

A total of 15,325 patients were assessed for eligibility; 5844 met the initial eligibility criteria and underwent ApneaLink testing, and 3246 entered the 1-week run-in phase (Fig. 1). The 2717 patients who were eligible for participation after the run-in phase were enrolled in the study from December 2008 through November 2013 and were randomly assigned to receive CPAP plus usual care (1359 patients) or usual care alone (1358 patients).

All 21 participants from one site were excluded from the study because it was determined during site monitoring that the required standard for conducting clinical trials was not met; in addition, 9 other participants withdrew consent at the time of randomization or did not adhere to the trial protocol from the time of randomization. Thus, 2687 participants were included in the primary analysis (Fig. 1 and Table 1). The mean age of the participants was 61 years, and 81% were men. The mean body-mass index (the weight in kilograms divided by the square of the height in meters) of the participants was 29; the mean oxygen desaturation index, 28 events per hour; and the mean Epworth Sleepiness Scale score, 7.4. Participants were evenly divided between those with coronary artery disease and those with cerebrovascular disease.

Final follow-up visits were completed by January 2016; a total of 147 patients discontinued their participation in the study before the intended...
CPAP in Obstructive Sleep Apnea

15,325 Patients were assessed for eligibility
9,481 Were ineligible or declined to participate
3,373 Did not meet inclusion criteria
2,716 Did not give consent
326 Lived too far from the clinical center
306 Had other reasons

5,844 Had validated sleep tests for OSA
2,598 Were excluded
1,796 Had either no or mild OSA
607 Did not meet other inclusion criteria
6 Had Cheyne–Stokes respiration
189 Had other reasons

3,246 Entered the 1-wk run-in period
2,598 Were excluded
1,796 Had either no or mild OSA
607 Did not meet other inclusion criteria
6 Had Cheyne–Stokes respiration
189 Had other reasons

2,717 Underwent randomization
529 Were excluded because of poor adherence or other reasons
324 Used device <3 hr per night
39 Had problems attending clinic
62 Had Cheyne–Stokes respiration
104 Had other reasons

1,359 Were assigned to receive CPAP plus usual care
13 Were excluded
2 Withdrew their consent
1 Was nonadherent to protocol
10 Were excluded owing to irregularities identified during monitoring at one site

1,358 Were assigned to receive usual care
57 Tried CPAP and continued treatment
33 Tried CPAP but did not continue treatment

1,346 Were included in the primary analysis
1,341 Were included in the primary analysis
62 Discontinued the study
12 Were lost to follow-up
25 Withdrew their consent
19 Were nonadherent
6 Had other reasons

1,284 Were followed through the final follow-up visit

1,256 Were followed through the final follow-up visit
85 Discontinued the study
18 Were lost to follow-up
44 Withdrew their consent
16 Were nonadherent
7 Had other reasons

Figure 1. Screening, Randomization, and Follow-up Analyses.
Testing for obstructive sleep apnea (OSA) involved the use a home sleep-study screening device (ApneaLink [ResMed]). During the 1-week run-in period, the participants received sham continuous positive airway pressure (CPAP) and were educated on the use of the equipment. In the case of participants who discontinued the study, only data that were acquired before discontinuation were included in the analysis.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPAP Group (N = 1346)</th>
<th>Usual-Care Group (N = 1341)</th>
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<tr>
<td>Age — yr</td>
<td>61.3±7.7</td>
<td>61.2±7.91</td>
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<tr>
<td>Male sex — no./total no. (%)</td>
<td>1092/1346 (81.1)</td>
<td>1082/1341 (80.7)</td>
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<td>Race — no./total no. (%)†</td>
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<tr>
<td>Asian</td>
<td>857/1346 (63.7)</td>
<td>843/1340 (62.9)</td>
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<tr>
<td>White</td>
<td>336/1346 (25.0)</td>
<td>341/1340 (25.4)</td>
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<tr>
<td>Other</td>
<td>153/1346 (11.4)</td>
<td>156/1340 (11.6)</td>
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<td>Type of cardiovascular disease — no./total no. (%)</td>
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<tr>
<td>Coronary artery disease</td>
<td>682/1346 (50.7)</td>
<td>681/1341 (50.8)</td>
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<td>Cerebrovascular disease</td>
<td>664/1346 (49.3)</td>
<td>660/1341 (49.2)</td>
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<tr>
<td>Both</td>
<td>50/1346 (3.7)</td>
<td>58/1341 (4.3)</td>
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<td>Medical history — no./total no. (%)‡</td>
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<td>Hypertension</td>
<td>1057/1343 (78.7)</td>
<td>1046/1338 (78.2)</td>
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<td>589/1343 (43.9)</td>
<td>594/1338 (44.4)</td>
</tr>
<tr>
<td>Any transient ischemic attack</td>
<td>135/1343 (10.1)</td>
<td>130/1338 (9.7)</td>
</tr>
<tr>
<td>Any heart disease</td>
<td>556/1343 (41.4)</td>
<td>534/1338 (39.9)</td>
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<td>Myocardial infarction</td>
<td>434/1343 (32.3)</td>
<td>465/1338 (34.8)</td>
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<tr>
<td>Coronary stent insertion</td>
<td>451/1343 (33.6)</td>
<td>462/1338 (34.5)</td>
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<tr>
<td>Coronary-artery bypass surgery</td>
<td>160/1341 (11.9)</td>
<td>159/1338 (11.9)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>405/1343 (30.2)</td>
<td>393/1338 (29.4)</td>
</tr>
<tr>
<td>Tobacco use§</td>
<td>213/1343 (15.9)</td>
<td>194/1338 (14.5)</td>
</tr>
<tr>
<td>Medications — no./total no. (%)</td>
<td></td>
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<td>Antihypertensive agent</td>
<td>1049/1346 (77.9)</td>
<td>1040/1341 (77.6)</td>
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<td>Statin or other lipid-lowering agent</td>
<td>762/1346 (56.6)</td>
<td>800/1341 (59.7)</td>
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<td>Antidiabetic oral medication</td>
<td>291/1346 (21.6)</td>
<td>291/1341 (21.7)</td>
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<td>80/1346 (5.9)</td>
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<td>1009/1346 (75.0)</td>
<td>1009/1341 (75.2)</td>
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<td>Body-mass index¶</td>
<td>28.8±4.6</td>
<td>28.5±4.4</td>
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<td>Waist-to-hip ratio</td>
<td>0.96±0.08</td>
<td>0.95±0.08</td>
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<td>Neck circumference — cm</td>
<td>40.8±4.0</td>
<td>40.6±4.2</td>
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<td>Obstructive sleep apnea characteristics</td>
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<tr>
<td>Oxygen desaturation index</td>
<td>28.1±14.1</td>
<td>28.4±14.5</td>
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<tr>
<td>Apnea–hypopnea index**</td>
<td>29.0±15.9</td>
<td>29.6±16.4</td>
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<td>Epworth Sleepiness Scale score††</td>
<td>7.3±3.6</td>
<td>7.5±3.6</td>
</tr>
<tr>
<td>Reported snoring almost every day — no./total no. (%)‡‡</td>
<td>1091/1305 (83.6)</td>
<td>1049/1288 (81.4)</td>
</tr>
<tr>
<td>Adherence to sham CPAP device use during the run-in phase — hr per night</td>
<td>5.2±1.4</td>
<td>5.2±1.4</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There was no significant differences in baseline values between the participants assigned to receive continuous positive airway pressure plus usual care (CPAP group) and the participants assigned to received usual care alone (usual-care group).
† Race was self-reported.
‡ Medical history was self-reported or determined though a review of medical records.
§ Values reflect current use of tobacco.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ The oxygen desaturation index is the number of times per hour during the oximetry recording that the blood oxygen saturation level drops by at least 4 percentage points from baseline.
** The apnea–hypopnea index is the number of apnea and hypopnea events per hour of recording.
†† The Epworth Sleepiness Scale ranges from 0 to 24, with higher scores indicating greater sleepiness; a score higher than 10 indicates pathologic sleepiness.
‡‡ Snoring was reported by the patient on a questionnaire.
final visit, but their data up to the time of withdrawal were included in the primary analysis performed in the intention-to-treat population (Fig. 1). The mean duration of follow-up was 3.7 years. (Further details on the study participants are provided in Tables S1, S2, and S3 in the Supplementary Appendix.)

INTERVENTION ADHERENCE, MEDICATIONS, AND LIFESTYLE FACTORS
The mean duration of use of the sham CPAP device during the 1-week run-in phase was 5.2 hours per night (Table 1). Among the participants in the CPAP group, the mean (±SD) duration of adherence to CPAP therapy in the first month of treatment was 4.4±2.2 hours per night, which decreased to 3.5±2.4 hours per night by 12 months and remained relatively stable thereafter (mean adherence during follow-up, 3.3±2.3 hours). The residual apnea–hypopnea index during CPAP use, as measured by the CPAP machine, averaged 3.7 events per hour, which indicated good control of obstructive sleep apnea with CPAP. Of the 1346 patients in the CPAP group, 566 (42%) had good adherence to treatment (≥4 hours per night) during follow-up. Of the 1341 patients who were followed in the usual-care group, 90 (6.7%) tried CPAP but only 57 (4.3%) continued the treatment. No significant differences were observed between the CPAP group and the usual-care group in the use of medications for diabetes mellitus and cardiovascular conditions, in lifestyle factors including diet and smoking, and in body-mass index from baseline to the end of the study. (Further details are provided in Fig. S1 and Tables S4 through S6 in the Supplementary Appendix.)

PRIMARY END POINT
A primary end-point event was confirmed in 436 participants — 229 (17.0%) in the CPAP group and 207 (15.4%) in the usual-care group (hazard ratio with CPAP, 1.10; 95% confidence interval [CI], 0.91 to 1.32; P=0.34) (Table 2 and Fig. 2). No significant effect of CPAP was found in the adjusted analysis or in the analyses that were based on total event rates and on primary endpoint events reported by the investigators. No significant heterogeneity was observed for the primary end point across subgroups defined according to region (China vs. outside China), age group (>60 years vs. ≤60 years), sex, severity of obstructive sleep apnea, body-mass index (<30 vs. ≥30), daytime sleepiness, type of cardiovascular disease, and presence or absence of diabetes mellitus.

Anthropometric and disease characteristics of patients with good adherence to CPAP therapy (24 hours per night) differed from those of patients with lower adherence and from the patients in the usual-care group as a whole. One-to-one propensity-score matching was performed to compare 561 patients who were adherent to CPAP therapy with 561 patients in the usual-care group. Among these propensity-score–matched patients, 184 primary end-point events occurred — 86 (15.3%) in the CPAP group and 98 (17.5%) in the usual-care group (hazard ratio, 0.80; 95% CI, 0.60 to 1.07; P=0.13). The adjusted Cox regression model (adjusted for the baseline factors used in the propensity-score–matching comparison) that compared patients with good adherence and those with poor adherence in the CPAP group with the patients in the usual-care group showed a similar result. (Further details on the results for the primary end point are provided in Tables S7 through S12 and Figs. S2 and S3 in the Supplementary Appendix.)

SECONDARY AND OTHER END POINTS
No significant between-group differences were observed in any of the cause-specific or composite secondary cardiovascular end points in the primary analysis (Table 2) or in the subsidiary analyses, except for a higher rate of total hospital admissions for transient ischemic attack among the patients in the CPAP group (relative risk, 2.29; 95% CI, 1.05 to 4.99; P=0.04). The propensity score–matched analyses showed that the patients who were adherent to CPAP therapy had a lower risk of stroke than those in the usual-care group (hazard ratio, 0.56; 95% CI, 0.32 to 1.00; P=0.05), as well as a lower risk of the nonprespecified composite end point of cerebral events (hazard ratio, 0.52; 95% CI, 0.30 to 0.90; P=0.02), but these results were not adjusted for multiple testing. A post hoc CPAP dose–response analysis of the primary and secondary cardiovascular end points showed no significant association.

The reductions from baseline in sleepiness and other symptoms of obstructive sleep apnea
were greater in the CPAP group than in the usual-care group (estimated mean between-group difference in the change from baseline in Epworth Sleepiness Scale score, −2.5; 95% CI, −2.8 to −2.2; P<0.001) (Table 3). Greater reductions from baseline in the anxiety and depression subscale scores of the Hospital Anxiety and Depression Scale were also observed in the CPAP group than in the usual-care group (Table 3), and the percentage of patients with clinically relevant depression scores was 25 to 30% lower in the CPAP group than in the usual-care group at the end of follow-up. The CPAP group had greater improvement in scores on the physical and mental subscales of the SF-36 than the usual-care group (Table 3), as well as fewer days off from work because of poor health (a nonprespecified end point) than the usual-care group (Table 4). The number of serious adverse events and the rate of road-traffic accidents and accidents causing injury did not differ significantly between the two groups (Table 4). (Further de-
tails on the results for the secondary and other end points are provided in Figs. S4 and S5 and Tables S8 and S12 through S16 in the Supplementary Appendix.)

DISCUSSION

This secondary prevention trial in adults with cardiovascular disease and obstructive sleep apnea showed that the risk of serious cardiovascular events was not lower among patients who received treatment with CPAP in addition to usual care than among those who received usual care alone. Treatment with CPAP was associated with a greater reduction in symptoms of daytime sleepiness and with improved health-related quality of life, mood, and attendance at work. This study was not powered to provide definitive answers regarding the effects of CPAP on secondary cardiovascular end points, but there was no indication of a significant benefit with respect to any cause-specific cardiovascular outcome.

Three other randomized trials have investigated the effect of CPAP on cardiovascular end points in patients with obstructive sleep apnea. Two studies — a multicenter study conducted in Spain that compared CPAP with usual care in 725 patients with obstructive sleep apnea who did not have prior cardiovascular disease and a single-center study involving 224 patients with obstructive sleep apnea and coronary artery disease who had just undergone revascularization — showed no difference in composite cardiovascular end points over several years of follow-up, although in adjusted analyses, both studies reported better outcomes among patients who were adherent to CPAP therapy (≥4 hours per night) than among patients who did not receive CPAP or who used CPAP less than 4 hours per night. The third study involving 140 patients with recent ischemic stroke showed no effect of CPAP on event-free survival over 2 years.

One important potential limitation of our trial is that, for several of the participating countries, the diagnosis and treatment of sleep apnea were not well established in clinical practice when the trial began. However, before trial recruitment, we expended substantial time and effort in conducting training workshops for investigators and study coordinators. In addition, extensive site monitoring was conducted throughout the trial to ensure a high standard of study conduct.

Participants in the SAVE study who were assigned to CPAP adhered to the treatment for a mean of 3.3 hours per night over several years, which is similar to the mean adherence in other reports of CPAP use in patients who had no or minimal daytime sleepiness and which is consistent with CPAP use in clinical practice. However, although this overall level of adherence to CPAP therapy exceeded the estimates in our power calculations, it may still have been insufficient to provide the level of effect on cardiovascular outcomes that had been hypothesized. For practical reasons and to ensure efficient recruitment and consistency of data across multiple sites, we used a simple screening device (ApneaLink) that was based on oximetry and nasal pressure recordings and used automated algorithms to analyze signals, rather than the conventional standard test for obstructive sleep apnea in which polysomnographic data from an overnight stay in a hospital or clinic are scored manually. The ApneaLink screening device has been shown to be a reliable method for diagnosing moderate- to-severe obstructive sleep apnea. To mitigate...
Table 3. Other Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPAP Group (N = 1346)</th>
<th>Usual-Care Group (N = 1341)</th>
<th>Adjusted Difference in Change from Baseline (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of Study</td>
<td>Change from Baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no. of patients with data</td>
<td>value</td>
<td>no. of patients with data</td>
<td>value</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1346</td>
<td>7.3±3.6</td>
<td>1221</td>
<td>7.5±3.6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>1346</td>
<td>4.2±3.5</td>
<td>1221</td>
<td>4.3±3.6</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
<td>1346</td>
<td>1166</td>
<td>1166</td>
<td>132±16</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety score</td>
<td>1341</td>
<td>4.6±3.7</td>
<td>1220</td>
<td>4.3±3.6</td>
</tr>
<tr>
<td>Depression score</td>
<td>1341</td>
<td>5.1±3.9</td>
<td>1220</td>
<td>5.2±3.9</td>
</tr>
<tr>
<td>SF-36§</td>
<td>1335</td>
<td>45.4±7.7</td>
<td>1218</td>
<td>46.9±8.0</td>
</tr>
<tr>
<td>Physical-component summary score</td>
<td>1332</td>
<td>52.6±8.6</td>
<td>1218</td>
<td>53.6±8.0</td>
</tr>
<tr>
<td>Mental-component summary score</td>
<td>—</td>
<td>1252</td>
<td>0.8±0.3</td>
<td>1229</td>
</tr>
<tr>
<td>EQ-SD utility score¶</td>
<td>—</td>
<td>—</td>
<td>1252</td>
<td>0.8±0.3</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ±SD.
† Analysis of covariance was used to compare the change from baseline in the CPAP group with that of the usual-care group; the analysis was adjusted for the baseline value.
‡ The change in systolic blood pressure from baseline to the end of the study is not apparent because mean blood pressure values were rounded to the nearest integer value.
§ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better quality of life with respect to either the physical or mental component.
¶ Utility scores on the European Quality of Life–5 Dimensions questionnaire (EQ-SD) are described in the Supplementary Appendix. The EQ-SD was administered only at the end of the study.
Table 4. Serious Adverse Events and Other Conditions of Interest.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPAP Group (N = 1346)</th>
<th>Usual-Care Group (N = 1341)</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants</td>
<td>Events</td>
<td>Annual Rate</td>
<td>Participants</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>498 (37)</td>
<td>1031</td>
<td>—</td>
<td>469 (35)</td>
</tr>
<tr>
<td>Road-traffic accidents‡</td>
<td>41 (3.0)</td>
<td>56</td>
<td>1.1</td>
<td>47 (3.5)</td>
</tr>
<tr>
<td>Accident causing injury</td>
<td>99 (7.4)</td>
<td>219</td>
<td>4.4</td>
<td>118 (8.8)</td>
</tr>
<tr>
<td>Accidents and near-miss accidents from falling asleep§</td>
<td>16 (1.2)</td>
<td>—</td>
<td>—</td>
<td>25 (1.9)</td>
</tr>
<tr>
<td>Days off from work because of poor health‡</td>
<td>306 (22.7)</td>
<td>6543</td>
<td>130¶</td>
<td>317 (23.6)</td>
</tr>
</tbody>
</table>

* Poisson regression was used to calculate the rate ratio between the CPAP group and the usual-care group.
‡ The end points of road-traffic accidents and days off from work because of poor health were not prespecified.
§ The participants were asked whether they had had an episode of falling asleep while driving or working that resulted in an accident or near-miss accident since their last review. The number of such events was not recorded.
¶ The annual rate is given as the number of days off from work because of poor health per 100 participants in 1 year.

In conclusion, in a large group of adults with both cardiovascular disease and moderate-to-severe obstructive sleep apnea, the use of CPAP therapy had no significant effect on the prevention of recurrent serious cardiovascular events, despite significantly reduced sleepiness and other symptoms of obstructive sleep apnea and improved quality-of-life measures.

Presented at the European Society of Cardiology Conference, Rome, August 28, 2016.

Supported by project grants (1006501 [2011–2015] and 1060078 [2014–2016]) from the National Health and Medical Research Council (NHMRC) of Australia and by Respironics Sleep and Respiratory Research Foundation and Philips Respironics. Supplementary trial funding was provided by Fisher & Paykel Healthcare, the Australasian Sleep Trials Network (grant 340202 from the NHMRC), the Spanish Respiratory Society (grant 105-2011 to Drs. Barbe and Mediano), and Fondo de Investigaciones Sanitarias (grant 13/02053 to Drs. Barbe and Mediano). In-kind donations were provided by Respironics for CPAP equipment and by ResMed for sleep apnea diagnostic devices.

Dr. McEvoy reports receiving research study equipment from Air Liquide; Dr. Antic, receiving lecture fees and payment for the development of educational presentations from ResMed, AstraZeneca, and GlaxoSmithKline and research study equipment from Air Liquide; Dr. Drager, receiving research study equipment from Philips Respironics; Dr. McArdle, receiving honoraria and grant support from ResMed; Dr. Barbe, receiving grant support from ResMed; Dr. Redline, being involved in a clinical trial supported with funds from Jazz Pharma to her institution; Dr. Wang, receiving consulting and lecture fees from Pfizer, Merck Sharp & Dohme, Sanofi, Novartis, and Daiichi-Sankyo; Dr. Neal, receiving fees for serving on an advisory board from Janssen, honoraria from Janssen, Roche, Abbott, Novartis, Pfizer, and Servier, lecture fees from Roche, Abbott, Novartis, Pfizer, and Servier, travel support from Janssen, Roche, and Servier, and grant support from AbbVie, Dr. Reddy’s Laboratories, Merck Schering Plough, and Roche and serving as chair of the steering committee for two ongoing large-scale trials of an SGLT2 inhibitor funded by Janssen and as a member of the steering committee for a third trial funded by Janssen — all honoraria, grants, and travel reimbursements are paid to his institution; Dr. White, receiving fees for serving on an advisory board from Night Balance and consulting fees from Philips Respironics and serving as chief medical officer of Apnicure; Dr. Grunstein, receiving honoraria and travel support from Merck; and Dr. Anderson, receiving fees for serving on advisory boards from AstraZeneca and Medtronic, lecture fees from Boehringer Ingelheim and Takeda, and travel support from Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who participated in this trial and their relatives; the clinical and research teams of the various sleep, cardiology and neurology departments; and the teams at George Clinical in Australia and China and the core laboratory staff at the Adelaide Institute for Sleep Health for their work on the study.
The authors’ affiliations are as follows: the Adelaide Institute for Sleep Health (R.D.M., N.A.A.) and the School of Medicine, Faculty of Medicine, Nursing, and Health Sciences (R.D.M., N.A.A., E.H., B.N., C.S.A.), Flinders University, and Sleep Health Service, Respiratory and Sleep Services, Southern Adelaide Local Health Network (R.D.M., N.A.A., S.M.), Adelaide, SA; George Institute for Global Health (E.H., L.B., Q.L., H.A., B.N., C.S.A.), Sydney Medical School (E.H., L.B., Q.L., H.A., B.N., C.S.A.), and Woolcock Institute of Medical Research (R.R.G.), University of Sydney, and the Departments of Respiratory and Sleep Medicine (R.R.G.) and Neurology (C.S.A.), Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, and the Western Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital, Perth, WA (N.M., S.M.) — all in Australia; the First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease (Y.L., N.Z.), and Guangdong General Hospital and Guangdong Academy of Medical Sciences (Q.O.), Guangzhou, the First Affiliated Hospital of Nanjing Medical University, the Second Affiliated Hospital of Soochow University, Suzhou (R.C.), the Department of Cardiology, Fuwai Hospital (Z.L.), and George Institute for Global Health China (C.S.A.), Peking University Health Sciences Center, Beijing, the Department of Neurology, Xuzhou Central Hospital, Xuzhou (G.C.), Hejian Municipal People’s Hospital, Hejian (B.D.), and Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University, Shanghai (J.W.) — all in China; University Hospital of Guadalajara, Guadalajara (O.M.), the Respiratory Department, Institut de Recerca Biomèdica de Lleida, Lleida (F.B.), and Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid (F.B.) — all in Spain; Instituto do Coracao (Incor) and Hospital Universitario (L.F.D., G.L.-F.) and the Hypertension Unit, Renal Division, University of São Paulo Medical School (L.F.D.), São Paulo; the Department of Neurology, All India Institute of Medical Sciences, Delhi (M.T.I.); and the Division of Sleep and Circadian Disorders, Brigham and Women’s Hospital and Harvard Medical School, Boston (S.R., D.P.W.).

REFERENCES
A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation

The Long-Term Oxygen Treatment Trial Research Group

ABSTRACT

BACKGROUND
Long-term treatment with supplemental oxygen has unknown efficacy in patients with stable chronic obstructive pulmonary disease (COPD) and resting or exercise-induced moderate desaturation.

METHODS
We originally designed the trial to test whether long-term treatment with supplemental oxygen would result in a longer time to death than no use of supplemental oxygen among patients who had stable COPD with moderate resting desaturation (oxyhemoglobin saturation as measured by pulse oximetry [SpO₂], 89 to 93%). After 7 months and the randomization of 34 patients, the trial was redesigned to also include patients who had stable COPD with moderate exercise-induced desaturation (during the 6-minute walk test, SpO₂ ≥80% for ≥5 minutes and <90% for ≥10 seconds) and to incorporate the time to the first hospitalization for any cause into the new composite primary outcome. Patients were randomly assigned, in a 1:1 ratio, to receive long-term supplemental oxygen (supplemental-oxygen group) or no long-term supplemental oxygen (no-supplemental-oxygen group). In the supplemental-oxygen group, patients with resting desaturation were prescribed 24-hour oxygen, and those with desaturation only during exercise were prescribed oxygen during exercise and sleep. The trial-group assignment was not masked.

RESULTS
A total of 738 patients at 42 centers were followed for 1 to 6 years. In a time-to-event analysis, we found no significant difference between the supplemental-oxygen group and the no-supplemental-oxygen group in the time to death or first hospitalization (hazard ratio, 0.94; 95% confidence interval [CI], 0.79 to 1.12; P=0.52), nor in the rates of all hospitalizations (rate ratio, 1.01; 95% CI, 0.91 to 1.13), COPD exacerbations (rate ratio, 1.08; 95% CI, 0.98 to 1.19), and COPD-related hospitalizations (rate ratio, 0.99; 95% CI, 0.83 to 1.17). We found no consistent between-group differences in measures of quality of life, lung function, and the distance walked in 6 minutes.

CONCLUSIONS
In patients with stable COPD and resting or exercise-induced moderate desaturation, the prescription of long-term supplemental oxygen did not result in a longer time to death or first hospitalization than no long-term supplemental oxygen, nor did it provide sustained benefit with regard to any of the other measured outcomes. (Funded by the National Heart, Lung, and Blood Institute and the Centers for Medicare and Medicaid Services; LOTT ClinicalTrials.gov number, NCT00692198.)
Two trials that were conducted in the 1970s showed that long-term treatment with supplemental oxygen reduced mortality among patients with chronic obstructive pulmonary disease (COPD) and severe resting hypoxemia.\(^1\) These results led to the recommendation that supplemental oxygen be administered to patients with an oxyhemoglobin saturation, as measured by pulse oximetry (\(\text{Spo}_2\)), of less than 89%.\(^3\) In the 1990s, two trials evaluated long-term treatment with supplemental oxygen in patients with COPD who had mild-to-moderate daytime hypoxemia; neither trial showed a mortality benefit, but both were underpowered to assess mortality.\(^5,6\) The effects of oxygen treatment on hospitalization,\(^7,9\) exercise performance, and quality of life are unclear.\(^10\)

Medicare reimbursements for oxygen-related costs for patients with COPD exceeded $2 billion in 2011.\(^11\) If long-term treatment with supplemental oxygen reduces the incidence of COPD-related hospitalizations, increased use could be cost-effective. Reliable estimates of the number of prescriptions for supplemental oxygen that are written for the indication of exercise-induced desaturation are unavailable. Data suggest that many patients with advanced emphysema who are prescribed oxygen may not have severe resting hypoxemia.\(^12\)

The Long-Term Oxygen Treatment Trial (LOTT) was originally designed to test whether the use of supplemental oxygen would result in a longer time to death than no use of supplemental oxygen among patients with COPD and moderate resting desaturation (\(\text{Spo}_2\) 89 to 93%). After 7 months and the randomization of 34 patients, the trial design was judged to be infeasible owing to lower-than-projected mortality and the phenotypic overlap between patients with moderate resting desaturation and those with exercise-induced desaturation. Accordingly, the investigators redesigned the trial to include patients with exercise-induced desaturation and to incorporate the secondary outcome of hospitalization for any cause into the new composite primary outcome. Patients who underwent randomization under the original design continued in the redesigned trial.

The amended trial tested whether the use of supplemental oxygen resulted in a longer time to death or first hospitalization for any cause (composite primary outcome) than no use of supplemental oxygen among patients with moderate resting desaturation or moderate exercise-induced desaturation. The original and amended trial protocols are available with the full text of this article at NEJM.org. Herein we report the primary and secondary outcomes and 11 of the 14 other outcomes listed in the trial protocol (see the Supplementary Appendix, available at NEJM.org, for the reasons that 3 outcomes are not reported).

**METHODS**

**DESIGN**

We conducted this parallel-group, randomized clinical trial of long-term supplemental oxygen versus no long-term supplemental oxygen in patients with COPD and moderate resting or exercise-induced desaturation. Randomization was performed in a 1:1 ratio, and the trial-group assignment was not masked. The primary outcome in the time-to-event analysis, measured from randomization, was the composite of death or first hospitalization. The protocol specified that the consistency of treatment effects would be tested in subgroups of patients that were defined according to prespecified baseline characteristics. The protocol and amendments were approved by the data and safety monitoring board for the trial and by the institutional review board at each center. No materials were donated to this trial.

**PATIENTS**

A total of 14 regional clinical centers and their associated sites (a total of 47 centers) screened patients who had stable COPD and moderate resting desaturation (\(\text{Spo}_2\) 89 to 93%) or moderate exercise-induced desaturation (during the 6-minute walk test, \(\text{Spo}_2\) ≥80% for ≥5 minutes and <90% for ≥10 seconds). All the patients signed a contract in which they agreed not to smoke while using oxygen, and they provided written informed consent. Table S1 in the Supplementary Appendix lists all the selection criteria.

**INTERVENTIONS**

Patients in the supplemental-oxygen group were prescribed 24-hour oxygen if their resting \(\text{Spo}_2\) was 89 to 93% and oxygen only during sleep and exercise if they had desaturation only during exercise. All the patients in the supplemental-oxygen
group were prescribed stationary and portable oxygen systems and 2 liters of oxygen per minute during sleep. Patients in the supplemental-oxygen group who had been prescribed 24-hour oxygen were prescribed 2 liters of oxygen per minute at rest. The ambulatory dose of oxygen was individually prescribed and reassessed annually: 2 liters of oxygen per minute or adjusted higher to maintain an \( \text{SpO}_2 \) of 90% or more for at least 2 minutes while the patient was walking. The protocol specified that patients in the supplemental-oxygen group continue the use of supplemental oxygen regardless of increase in the \( \text{SpO}_2 \) level and that patients in the no-supplemental-oxygen group avoid the use of supplemental oxygen unless severe resting desaturation (\( \text{SpO}_2 \leq 88\% \)) or severe exercise-induced desaturation (\( \text{SpO}_2 < 80\% \) for \( \geq 1 \) minute) developed. If either of these conditions developed, oxygen was prescribed and the oxygen requirement was reassessed after 30 days.

Each patient in the supplemental-oxygen group spoke with an adherence educator regularly to discuss barriers to adherence to the assigned regimen and to report average daily use. Each patient in the group that received no long-term supplemental oxygen (no-supplemental-oxygen group) spoke with an adherence educator 1 week after randomization to discuss living without supplemental oxygen. Every 4 months, all the patients were asked about supplemental-oxygen use; those who reported some oxygen use were asked to estimate the average daily use. Patients in the supplemental-oxygen group who used stationary oxygen concentrators also kept logs of meter readings.

OUTCOMES

In addition to the composite primary outcome and its components, outcomes included the incidence of COPD exacerbation, adherence to the supplemental-oxygen regimen, development of severe resting desaturation (as assessed by means of pulse oximetry), development of severe exercise-induced desaturation (as assessed by means of pulse oximetry), the distance walked in 6 minutes, and scores on the Quality of Well-Being Scale (mean daily scores range from 0 to 1, with higher scores indicating better quality of life; minimum clinically important difference, 0.03)\(^{13,14} \) and the St. George’s Respiratory Questionnaire (total scores range from 0 to 100, with higher scores indicating worse health-related quality of life; minimum clinically important difference, 4).\(^{15,16} \) A total of 33 centers elected to obtain spirometric measurements after randomization and to administer the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; the summary scores for the physical and mental components each range from 0 to 100, with higher scores indicating better function; minimum clinically important difference, 5).\(^{17} \) The Hospital Anxiety and Depression Scale (scores on each measure [anxiety or depression] range from 0 to 21, with higher scores indicating greater anxiety or depression; minimum clinically important difference, 1.5)\(^{18,19} \) and the Pittsburgh Sleep Quality Index (total scores range from 0 to 21, with higher scores indicating worse sleep quality).\(^{20} \)

The protocol lists three additional outcomes (nutritional status, risk of cardiovascular disease, and neurocognitive function) that are not reported here.

Patients attended visits yearly after randomization, were interviewed by telephone twice yearly, and completed mailed questionnaires at 4 months and 16 months (Table S2 in the Supplementary Appendix). Details regarding the ascertainment of the primary composite outcome and procedures for measuring resting and exercise-induced desaturation are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Calculation of the final required sample was based on a time–to–composite event survival model with the use of the log-rank test statistic. Assuming 90% power to detect a hazard ratio for death or first hospitalization of 0.60 in the supplemental-oxygen group versus the no-supplemental-oxygen group, a two-sided type I error rate of 0.05, an 11.7% overall crossover rate from the no-supplemental-oxygen group to the supplemental-oxygen group, a two-sided type I error rate of 0.05, an 11.7% overall crossover rate from the supplemental-oxygen group to the no-supplemental-oxygen group, and a 3.1% overall crossover rate from the supplemental-oxygen group, we calculated a sample size of 737 patients. The hazard ratio of 0.60 corresponds to the smallest difference in mortality that the investigators judged to be clinically worthwhile (a 40% lower rate in the supplemental-oxygen group than in the no-supplemental-oxygen group), on the basis of the number of patients needed to treat.
tial oxygen is expensive and its use is burdensome, the hazard ratio of 0.60 was also judged to be appropriate for the composite primary outcome of death or first hospitalization in the time-to-event analysis.

Under the original trial design, we assumed that the crossover rate from the no-supplemental-oxygen group to the supplemental-oxygen group would be 21% and the crossover rate from the supplemental-oxygen group to the no-supplemental-oxygen group would be 50%, on the basis of investigator consensus. In March 2012, the data and safety monitoring board approved the use of the observed crossover rates of 11.7% (from the no-supplemental-oxygen group to the supplemental-oxygen group) and 3.1% (from the supplemental-oxygen group to the no-supplemental-oxygen group) to refine the sample-size calculation. Additional details about the sample-size calculation are provided in the Supplementary Appendix.

Data were analyzed according to the treatment group to which the patients were randomly assigned (intention-to-treat approach) except as otherwise noted. A Cox proportional-hazards model with one binary covariate for treatment group was used to estimate the between-group hazard ratio for the primary composite outcome in the time-to-event analysis; the log-rank test was used for the P value. This method was also used for each of the secondary outcomes in the time-to-event analysis.

The consistency of the hazard ratio for the primary outcome across prespecified subgroups was assessed by a series of Cox proportional-hazard models with covariates that included the treatment-group indicator, indicators for the levels of the subgroup factor, and treatment-by-subgroup interaction terms. The P values for consistency of hazard ratios across subgroups were determined by Wald chi-square tests. Per the trial protocol, all reported P values are nominal and two-sided and were not corrected for multiple, prespecified comparisons. A P value of less than 0.05 was considered to indicate statistical significance for the composite primary outcome, and a P value of less than 0.01 was considered to indicate statistical significance for a treatment-by-subgroup interaction effect on the primary outcome. Bonferroni corrections were used to determine the P values that were required for statistical significance of the trial-group differences on the secondary and other outcomes and for statistical significance of the multiple treatment-by-subgroup interaction effects on the primary outcome that were assessed. Additional details about the statistical analysis are provided in the protocol and the Supplementary Appendix.

RESULTS

TRIAL POPULATION

From January 2009 through August 2014, a total of 738 patients at 42 centers underwent randomization in the trial: 368 patients were randomly assigned to the supplemental-oxygen group and 370 to the no-supplemental-oxygen group (Fig. S1 and Table S3 in the Supplementary Appendix). In the supplemental-oxygen group, 220 patients were prescribed 24-hour oxygen and 148 were prescribed oxygen during exercise and sleep only. Of the 738 patients who underwent randomization, 133 (18%) had resting desaturation only, 319 (43%) had exercise-induced desaturation only, and 286 (39%) had both types of desaturation. The trial groups were similar at baseline except that the patients in the supplemental-oxygen group had a lower BODE index (a scoring system incorporating information on the body-mass index, airflow obstruction, dyspnea, and 6-minute walk distance; higher scores indicate a greater risk of death) than those in the no-supplemental-oxygen group (Table 1, and Table S4 in the Supplementary Appendix).

Patients were followed for 1 to 6 years; the last visits occurred during the period from May through August 2015 (median follow-up, 18.4 months). Vital status as of August 31, 2015, was ascertained in all patients. A total of 97% of the patients had at least 1 year of follow-up for hospitalization. Most patients in the supplemental-oxygen group used 2 liters of oxygen per minute during exercise throughout follow-up (Table S5 in the Supplementary Appendix).

PRIMARY OUTCOME

In a time-to-event analysis, we found no significant difference between the trial groups in the composite outcome of death or first hospitalization for any cause or in either component (Fig. 1 and Table 2). No significant difference was noted in the subgroups defined according to oxygen...
Table 1. Characteristics of the Patients at Enrollment.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Supplemental Oxygen (N = 370)</th>
<th>Supplemental Oxygen (N = 368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>69.3±7.4</td>
<td>68.3±7.5</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>276 (75)</td>
<td>266 (72)</td>
</tr>
<tr>
<td>Race — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>34 (9)</td>
<td>46 (12)</td>
</tr>
<tr>
<td>White</td>
<td>328 (89)</td>
<td>311 (85)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (3)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Medicare coverage — no. (%)</td>
<td>273 (74)</td>
<td>268 (73)</td>
</tr>
<tr>
<td>Current tobacco-cigarette smoker — no. (%)</td>
<td>92 (25)</td>
<td>110 (30)</td>
</tr>
<tr>
<td>Quality of Well-Being Scale mean daily score‡</td>
<td>0.56±0.13</td>
<td>0.56±0.13</td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire total score§</td>
<td>50.2±17.1</td>
<td>49.8±18.7</td>
</tr>
<tr>
<td>Oxygen-desaturation type qualifying the patient for enrollment — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting only</td>
<td>60 (16)</td>
<td>73 (20)</td>
</tr>
<tr>
<td>Exercise only</td>
<td>171 (46)</td>
<td>148 (40)</td>
</tr>
<tr>
<td>Resting and exercise</td>
<td>139 (38)</td>
<td>147 (40)</td>
</tr>
<tr>
<td>(\text{Sp}_2) at rest while breathing ambient air — %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>93.5±1.9</td>
<td>93.3±2.1</td>
</tr>
<tr>
<td>Resting only</td>
<td>92.3±0.8</td>
<td>92.4±0.9</td>
</tr>
<tr>
<td>Exercise only</td>
<td>95.2±1.2</td>
<td>95.4±1.4</td>
</tr>
<tr>
<td>Resting and exercise</td>
<td>91.9±1.2</td>
<td>91.7±1.1</td>
</tr>
<tr>
<td>(\text{Nadir Sp}_2) during 6-min walk while breathing ambient air — no./total no. (%)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;86%</td>
<td>85/290 (29)</td>
<td>86/292 (29)</td>
</tr>
<tr>
<td>86–88%</td>
<td>103/290 (36)</td>
<td>105/292 (36)</td>
</tr>
<tr>
<td>&gt;88%</td>
<td>102/290 (35)</td>
<td>101/292 (35)</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ±SD. There were no significant differences at baseline between the group of patients assigned to receive long-term supplemental oxygen (supplemental-oxygen group) and the group of those assigned to receive no long-term supplemental oxygen (no-supplemental-oxygen group), except that the patients in the supplemental-oxygen group had a lower BODE index (a scoring system incorporating information on body-mass index, airflow obstruction, dyspnea, and 6-minute walk distance; higher scores indicate a greater risk of death)‡ than those in the no-supplemental-oxygen group (P = 0.007); details of the BODE index values and other characteristics at baseline are provided in Table S4 in the Supplementary Appendix. \(\text{Sp}_2\) denotes oxyhemoglobin saturation as measured by means of pulse oximetry.

† Race was self-reported. Patients were permitted to select more than one race group.
‡ The Quality of Well-Being Scale is a 77-item quality-of-life questionnaire completed by the patient. A score of 0 indicates death. The mean daily score ranges from 0 to 1, with higher scores indicating better quality of life. The minimum clinically important difference is 0.03.13,14
§ The St. George’s Respiratory Questionnaire is a 51-item questionnaire on the health-related quality of life with regard to respiratory symptoms that is completed by the patient. The total score ranges from 0 to 100, with lower scores indicating better health-related quality of life. The minimum clinically important difference is 4.15,16
¶ The nadir \(\text{Sp}_2\) is the 10th lowest \(\text{Sp}_2\) observed during the 6-minute walk. A total of 10 patients (6 patients in the supplemental-oxygen group and 4 in the no-supplemental-oxygen group) either did not attempt or began but did not complete the 6-minute walk. Reasons included being in a wheelchair, amputation of foot or leg, sciatic pain, starting the walk and stopping because of back pain, or other reason; these 10 participants met the resting hypoxemia criterion. The nadir \(\text{Sp}_2\) could not be calculated for 146 patients (70 patients in the supplemental-oxygen group and 76 in the no-supplemental-oxygen group) owing to loss of their oximetry data file or a technical issue with their oximetry data file obtained at enrollment.
Figure 1. Kaplan–Meier Analyses of the Primary Outcome of Death or First Hospitalization for Any Cause and for the Component Events in the Intention-to-Treat Population.

Panel A shows the results of a time-to-event analysis of the primary outcome, which was a composite of death or first hospitalization for any cause; the median follow-up was 18.4 months. Data for 120 patients who were assigned to receive long-term supplemental oxygen (supplemental-oxygen group) and 120 assigned to receive no long-term supplemental oxygen (no-supplemental-oxygen group) who neither died nor had a hospitalization were censored at the date of the last interview. Error bars indicate 95% confidence intervals (assessed every 12 months). For the time-to-event analysis of the first hospitalization for any cause, the median follow-up was 18.4 months. Data for 139 patients in the supplemental-oxygen group and 133 in the no-supplemental-oxygen group were censored as of their date of death (if there was no hospitalization before death) or as of the date of their last interview (if they were alive and had no hospitalization). Panel B shows the results of a time-to-event analysis of death; the median follow-up was 41.5 months. Data for 302 patients in the supplemental-oxygen group and 297 in the no-supplemental-oxygen group who were alive on August 31, 2015, were censored as of that date. The hazard ratios and 95% confidence limits were derived from Cox regression models, with supplemental oxygen versus no supplemental oxygen as the single model variable. P values were derived from log-rank tests. For the components of the composite primary outcome (death and first hospitalization), a P value of less than 0.025 (0.05 divided by 2) was considered to indicate statistical significance, with the use of a Bonferroni adjustment for multiple comparisons.22
Table 2. Primary Composite Outcome of Death or First Hospitalization for Any Cause and Composite Events in the Intention-to-Treat Population.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Supplemental Oxygen (N = 370)</th>
<th>Supplemental Oxygen (N = 368)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or first hospitalization for any cause</td>
<td>250</td>
<td>248</td>
<td>0.94 (0.79–1.12)</td>
<td>0.52</td>
</tr>
<tr>
<td>No. of events</td>
<td>36.4</td>
<td>34.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite rate per 100 person-yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary-outcome component events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>73</td>
<td>66</td>
<td>0.90 (0.64–1.25)</td>
<td>0.53</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>5.7</td>
<td>5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per 100 person-yr</td>
<td>237</td>
<td>229</td>
<td>0.92 (0.77–1.10)</td>
<td>0.37</td>
</tr>
<tr>
<td>First hospitalization for any cause</td>
<td>34.5</td>
<td>31.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of first hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate per 100 person-yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The primary outcome was death or first hospitalization for any cause, whichever came first, in patients randomly assigned to receive supplemental oxygen as compared with those assigned to receive no supplemental oxygen. For the composite-event analysis, data from 120 patients in the supplemental-oxygen group and 120 in the no-supplemental-oxygen group who neither died nor had a hospitalization were censored as of their last interview. For the analysis of death, data for 302 patients in the supplemental-oxygen group and 297 in the no-supplemental-oxygen group who were alive on August 31, 2015, were censored as of that date. For the analysis of the first hospitalization, data for 139 patients in the supplemental-oxygen group and 133 in the no-supplemental-oxygen group were censored as of their date of death (if there was no hospitalization before death) or as of the date of their last interview (if they were alive and had no hospitalization). For the components of the composite primary outcome (death and first hospitalization), a P value of less than 0.025 (0.05 divided by 2) was considered to indicate statistical significance, with the use of a Bonferroni adjustment for multiplicity of comparisons.22 P values were calculated by the log-rank test. CI denotes confidence interval.

prescription, desaturation profile, race, sex, smoking status, nadir $\text{SpO}_2$ during exercise (the 10th lowest $\text{SpO}_2$ observed during the 6-minute walk), forced expiratory volume in 1 second, BODE index, SF-36 physical-component score, body-mass index, or history of anemia (Table S6 in the Supplementary Appendix).

Patients in the supplemental-oxygen group who reported having had a COPD exacerbation 1 to 3 months before enrollment had a longer time to death or first hospitalization than similar patients in the no-supplemental-oxygen group (hazard ratio, 0.58; 95% confidence interval [CI], 0.39 to 0.88; P=0.007 for interaction), as did patients who were 71 years of age or older at enrollment (hazard ratio, 0.75; 95% CI, 0.57 to 0.99; P=0.03 for interaction) and those who had a lower quality of life (Quality of Well-Being Scale score, <0.55) at enrollment (hazard ratio, 0.77; 95% CI, 0.60 to 0.99; P=0.03 for interaction). However, none of these subgroup-by-treatment interaction effects were significant when the analysis was adjusted for multiple comparisons. In the as-treated analysis, no difference was found between patients who used oxygen for at least 16 hours per day and all others. (Details are provided in Tables S6 and S7 in the Supplementary Appendix.)

**ADHERENCE TO REGIMEN**

Histograms of self-reported use of supplemental oxygen as averaged over follow-up indicate much longer daily mean (±SD) use in the supplemental-oxygen group than in the no-supplemental-oxygen group (13.6±6.1 vs. 1.8±3.9 hours per day) (Fig. 2). There was a separation of patients in the supplemental-oxygen group according to prescription (15.1±6.2 hours per day in the 24-hour group vs. 11.3±5.0 hours per day in the sleep–exercise group), but there was considerable overlap. A comparison of self-reported stationary concentrator use with use that was calculated from meter readings in 100 patients in the supplemental-oxygen group who had available data showed a significant linear trend in bias (P<0.001), in which patients with less-than-average hours of
daily use tended to overestimate their use and those with greater-than-average hours of daily use tended to underestimate their use (Fig. S2 in the Supplementary Appendix).

### Comparison with Design Assumptions

Fewer enrollees than expected were hospitalized in the year before screening. However, more patients than expected were hospitalized during follow-up. Observed mortality rates compared well with the design assumptions (Table S8 in the Supplementary Appendix).

### Other Outcomes

The two trial groups did not differ significantly with regard to the rates of all hospitalizations (rate ratio, 1.01; 95% CI, 0.91 to 1.13), COPD exacerbations (rate ratio, 1.08; 95% CI, 0.98 to 1.19), COPD-related hospitalizations (rate ratio, 0.99; 95% CI, 0.83 to 1.17), or non–COPD-related hospitalizations (rate ratio, 1.03; 95% CI, 0.90 to 1.18). (Fig. S3 and Table S9 in the Supplementary Appendix). We found no consistent differences between groups in the change from baseline in measures of quality of life, anxiety,
depression, or in lung function, distance walked in 6 minutes, or other measures of functional status (Fig. S4 and Table S10 in the Supplementary Appendix).

ADVERSE EVENTS
A total of 51 adverse events were attributed to the use of supplemental oxygen (Table S11 in the Supplementary Appendix). There were 23 reports of tripping over equipment, with two patients requiring hospitalization. Five patients reported a total of six instances of fires or burns, with one patient requiring hospitalization.

Discussion
We found that the prescription of supplemental oxygen for patients with stable COPD and resting or exercise-induced moderate desaturation did not affect the time to death or first hospitalization, time to death, time to first hospitalization, time to first COPD exacerbation, time to first hospitalization for a COPD exacerbation, the rate of all hospitalizations, the rate of all COPD exacerbations, or changes in measures of quality of life, depression, anxiety, or functional status. We found no effect on the primary outcome in subgroups of patients defined according to desaturation type, prescription type, or adherence to the regimen. The consistency of the null findings strengthens the overall conclusion that long-term supplemental oxygen in patients with stable COPD and resting or exercise-induced moderate desaturation has no benefit with regard to the multiple outcomes measured.

Our data support the conclusions of earlier studies that among patients with COPD who have a resting $SpO_2$ of more than 88%, long-term treatment with supplemental oxygen does not result in longer survival than no long-term supplemental oxygen therapy, regardless of whether the patients have exercise-induced desaturation.\textsuperscript{5,24} Our findings contrast with the prolonged survival that was observed among patients with COPD and severe desaturation who were treated with supplemental oxygen.\textsuperscript{1,2} Possible reasons for this discrepancy are the nonlinear threshold effects of oxygen saturation on pulmonary vasoconstriction, mediator release, and ventilatory drive,\textsuperscript{25,26} which occur with an $SpO_2$ of 88% or less and which may be more important in patients with chronic hypoxemia.

A systematic review and meta-analysis suggested that oxygen therapy may reduce dyspnea in patients with COPD and mild or no hypoxemia.\textsuperscript{27} We found no consistent benefit of long-term supplemental oxygen with regard to measures of quality of life, depression, anxiety, or functional status.

This trial has some limitations. First, some patients may not have enrolled in the trial because they or their providers believed that they were too ill or that they benefited from oxygen. Highly symptomatic patients who declined enrollment might have had a different response to oxygen than what we observed in the enrolled patients. Second, the lack of masking may have influenced some of the patient-reported outcomes; however, it is unlikely to have influenced the primary outcome. Third, we did not use uniform devices for oxygen delivery; it is possible that there was variability in the amount of oxygen delivered. Fourth, the immediate effects of oxygen on symptoms or exercise performance were not assessed. We did not measure nocturnal oxygen saturation; some patients with COPD and severe nocturnal desaturation might benefit from nocturnal oxygen supplementation.\textsuperscript{28,29} Fifth, patients’ self-reported adherence may have been an overestimate of their actual oxygen use. However, we found good agreement with the use as measured by means of serial meter readings on the concentrator. The estimated mean hours per day of use in the supplemental-oxygen group (15.1±6.2 hours per day in the 24-hour group and 11.3±5.0 hours per day in the sleep–exercise group) (Fig. 2) was similar to the use observed in the Nocturnal Oxygen Therapy Trial (17.7 hours per day in the continuous-oxygen group and 12.0 hours per day in the nocturnal-oxygen group).\textsuperscript{1} However, we cannot exclude the possibility that longer exposures to oxygen in the supplemental-oxygen group might have given different results. Finally, because hospitalization was recorded from self-report every 4 months, it is possible that we underestimated the number of hospitalizations; however, there did not appear to be systematic bias in follow-up between groups.

In conclusion, among patients with stable COPD and resting or exercise-induced moderate desaturation, we found that long-term supplemental oxygen did not provide any benefit with respect to the time to death or first hospitaliza-
tion or any sustained benefit with respect to any other measured outcome.


Dr. Au reports serving on a data monitoring committee for Novartis; Dr. Casaburi, serving on advisory boards for Boehringer Ingelheim, AstraZeneca, and Novartis and receiving consulting fees from GlaxoSmithKline and Astellas Pharma, lecture fees from Boehringer Ingelheim and AstraZeneca, and grant support to his institution from Boehringer Ingelheim and Novartis; Dr. Cooper, receiving grant support from AstraZeneca; Dr. Fuhlbrigge, serving on an adjudication committee for ICON Medical Imaging, serving as an unpaid consultant for AstraZeneca, and receiving consulting fees from GlaxoSmithKline and travel support from AstraZeneca; Dr. MacIntyre, receiving consulting fees from Breathe Technologies and Ventec Life Systems; Dr. Martinez, serving on steering committees for Bayer, Boehringer Ingelheim, Centocor, Gilead Sciences, Takeda Pharmaceuticals (formerly Nycomed), Affrent Pharmaceuticals, Forest Laboratories, Janssen, GlaxoSmithKline, AstraZeneca, and Pearl Therapeutics, serving on advisory boards for Boehringer Ingelheim, Genentech, Ikaria, Kadmon, Takeda Pharmaceuticals (formerly Nycomed), Pfizer, Veracyte, Forest Laboratories, Janssen, GlaxoSmithKline, AstraZeneca, Bellerophon Therapeutics (formerly Ikaria), Novartis, Pearl Therapeutics, Roche, Sunovion Pharmaceuticals, Theravance Biopharma, and Concert Pharmaceuticals, serving on a data and safety monitoring board for Biogen (formerly Storredex) and GlaxoSmithKline, and receiving fees for participating in continuing medical education activities from AcademicCME, MedEd Consulting, Continuing Education, Potomac Center for Medical Education, CME Incite, Annenberg Center for Health Sciences at Eisenhower, Integrata Communications, inThought Research, Miller Medical Communications, Paradigm Medical Communications, PeerVoice, HayMarket Communications, Prime Healthcare, WebMD, and PeerView Academic Network, consulting fees from Axon Communications, Johnson & Johnson, Clarion Communications, Adept Field Solutions, Amgen, Proterixbio (formerly Bioscale), Unity Biotechnology, and Lucid Communiqué Medical Education, and lecture fees from AstraZeneca; Dr. Stoller, receiving consulting fees from Baraxa, CSL Behring, Grifols, and Arrowhead Pharmaceuticals; and Dr. Wise, receiving consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, ContraFect, GlaxoSmithKline, Janssen, Mylan, Novartis, Pfizer, Pulmonx, Roche, Spririon, Sunovion Pharmaceuticals, Teva Pharmaceutical Industries, Theravance, Verona Pharma, and Vertex Pharmaceuticals and grant support from Boehringer Ingelheim, GlaxoSmithKline, Teva Pharmaceutical Industries, and Pearl Therapeutics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The affiliations of the members of the writing group are as follows: University of Colorado, Denver (R.K.A.); Veterans Affairs (VA) Puget Sound Health Care System and University of Washington, Seattle (D.H.A.); Johns Hopkins University School of Medicine (A.L.B., R.W.); and Johns Hopkins University Bloomberg School of Public Health (D.S., J.T., A.L.S.), Baltimore; Los Angeles Biomedical Research Institute at Harbor—UCLA Medical Center (R.C.) and Cedars—Sinai Medical Center (S.P.) — both in Los Angeles; Birmingham VA Medical Center (J.A.C.) and the University of Alabama (J.A.C., W.B.), Birmingham; Lewis Katz School of Medicine at Temple University, Philadelphia (G.J.C.), and University of Pittsburgh, Pittsburgh (F.S.) — both in Pennsylvania; Ohio State University, Columbus (P.D.), Cincinnati VA Medical Center and University of Cincinnati College of Medicine, Cincinnati (R.J.P.), and Cleveland Clinic, Cleveland (J.K.S.) — all in Ohio; Brigham and Women’s Hospital and Harvard Medical School, Boston (A.L.F.); University of Michigan, Ann Arbor (S.E.G.); University of Utah Health Sciences Center, Salt Lake City (R.E.K.); Duke University Medical Center, Durham, NC (N.M.); Weill Cornell Medical Center, New York (F.J.M.); Kaiser Permanente Center for Health Research, Portland, OR (T.S.); and Washington University School of Medicine, St. Louis (R.D.Y.).

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Long-Term Oxygen for COPD with Moderate Desaturation

information Products and Data Analytics, August 2013.
Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users
A Cross-sectional Study

Lion Shahab, PhD; Maciej L. Goniewicz, PhD; Benjamin C. Blount, PhD; Jamie Brown, PhD; Ann McNeill, PhD; K. Udeni Alwis, PhD; June Feng, PhD; Lanqing Wang, PhD; and Robert West, PhD

Background: Given the rapid increase in the popularity of e-cigarettes and the paucity of associated longitudinal health-related data, the need to assess the potential risks of long-term use is essential.

Objective: To compare exposure to nicotine, tobacco-related carcinogens, and toxins among smokers of combustible cigarettes only, former smokers with long-term e-cigarette use only, former smokers with long-term nicotine replacement therapy (NRT) use only, long-term dual users of both combustible cigarettes and e-cigarettes, and long-term users of both combustible cigarettes and NRT.

Design: Cross-sectional study.

Setting: United Kingdom.

Participants: The following 5 groups were purposively recruited: combustible cigarette–only users, former smokers with long-term e-cigarette use only, former smokers with long-term nicotine replacement therapy (NRT) use only, long-term dual users of both combustible cigarettes and e-cigarettes, and combustible cigarette–NRT users (n = 36 to 37 per group; total n = 181).

Measurements: Sociodemographic and smoking characteristics were assessed. Participants provided urine and saliva samples and were analyzed for biomarkers of nicotine, tobacco-specific N-nitrosamines (TSNAs), and volatile organic compounds (VOCs).

Results: After confounders were controlled for, no clear between-group differences in salivary or urinary biomarkers of nicotine intake were found. The e-cigarette–only and NRT-only users had significantly lower metabolite levels for TSNAs (including the carcinogenic metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol [NNAL]) and VOCs (including metabolites of the toxins acrolein; acrylamide; acrylonitrile; 1,3-butadiene; and ethylene oxide) than combustible cigarette–only, dual combustible cigarette–e-cigarette, or dual combustible cigarette–NRT users. The e-cigarette–only users had significantly lower NNAL levels than all other groups. Combustible cigarette–only, dual combustible cigarette–NRT, and dual combustible cigarette–e-cigarette users had largely similar levels of TSNA and VOC metabolites.

Limitation: Cross-sectional design with self-selected sample.

Conclusion: Former smokers with long-term e-cigarette–only or NRT–only use may obtain roughly similar levels of nicotine compared with smokers of combustible cigarettes only, but results varied. Long-term NRT-only and e-cigarette–only use, but not dual use of NRTs or e-cigarettes with combustible cigarettes, is associated with substantially reduced levels of measured carcinogens and toxins relative to smoking only combustible cigarettes.

Primary Funding Source: Cancer Research UK.
profile is well-established (19) and NRT effectiveness for smoking cessation through initial partial (20) or complete substitution (21) has been shown. Therefore, NRT is recommended as a harm reduction strategy in several countries (22).

Although longitudinal cohort studies and randomized, controlled trials will provide the best data to answer questions about the safety and efficacy of e-cigarettes for smoking cessation, these designs are time- and resource-intensive. In the absence of long-term data, a more pragmatic approach is to compare smokers and former smokers with or without concurrent e-cigarette use in real-life settings. This study aimed to address the gap in the literature by measuring biomarker levels in long-term e-cigarette users compared with an appropriate control—NRT users. Specifically, this study assessed whether long-term e-cigarette-only, NRT-only, dual combustible cigarette-e-cigarette, or dual combustible cigarette-NRT use is associated with differences in metabolites of nicotine, TSNAs, and volatile organic compounds (VOCs) compared with combustible cigarette-only use.

**METHODS**

**Study Design and Procedure**

This cross-sectional study was done in London, United Kingdom, from January 2014 to June 2014. It evaluated the range of toxin levels measured in smokers and former smokers with or without concurrent long-term use of e-cigarettes or NRT. The study methodology has been described elsewhere (23). Briefly, participants visited the laboratory for a single session, lasting 30 minutes, after abstaining from eating, drinking, or using combustible cigarettes or other nicotine products for an hour before their visit to standardize assessment. At the laboratory, after providing written consent, participants completed a short questionnaire assessing sociodemographic, smoking, and product use characteristics and provided breath, saliva, and urine samples. Exhaled air was assessed for carbon monoxide with a breathalyzer (Micro IV Smokerlyzer, Bedfont Scientific). In addition, 2 saliva samples were collected with sterile dental rolls (Salivette, Sarstedt) that participants were asked to gently chew for about 2 minutes or until saturated. Urine was collected in a sealable, sterilized cup by participants on site and transferred by staff into cryovials. Urine and saliva samples were then kept frozen at 20 °C until they were shipped in dry ice to laboratories at Roswell Park Cancer Institute (Buffalo, New York) and the Centers for Disease Control and Prevention (Atlanta, Georgia) for analysis. All participants were reimbursed for time and travel (£25). The study was approved by the University College London Ethics Committee (project ID 0483/002).

**Participants**

Participants were purposively recruited in the greater London area using various methods to increase sample diversity, including newspapers and online advertisements, posters in pharmacies, and the use of marketing companies. They had to be ever smokers and to meet the following eligibility criteria: Current smokers had to smoke an average of 5 or more combustible cigarettes per day for at least 6 months, and former smokers had to have stopped using tobacco products (including combustible cigarettes, water pipes, cigars, and such smokeless products as snus or chewing tobacco) for at least 6 months. Because we sought to evaluate the effect of long-term use of noncombustible nicotine delivery devices (NRT and e-cigarettes), smokers (that is, dual combustible cigarette–e-cigarette or combustible cigarette–NRT users) and former smokers (that is, e-cigarette–only or NRT-only users) had to have been using these products at least weekly for 6 months or more (users of nicotine-free products, such as e-liquid without nicotine, were excluded). In practice, however, participants used products daily as indicated by latency to last product use across groups (combustible cigarettes–only users, 1.4 hours; combustible dual cigarette-NRT users, 4.3 hours; combustible dual cigarette-e-cigarette users, 1.3 hours; NRT-only users, 24 hours; and e-cigarette-only users, 5.4 hours). Product use was verified by asking participants to bring in the NRT or e-cigarette that they were currently using, and smoking status was verified with carbon monoxide readings (10-ppm cutoff) (24). We excluded persons who used both NRT and e-cigarettes as well as those who were younger than 18 years; were pregnant; had a history of heart or lung disease; or had bleeding gums, illness, or an active infection within 24 hours of their scheduled appointment.

**Measures**

**Biomarkers of Exposure**

Level of nicotine exposure was measured to assess effectiveness of nicotine delivery products by using 2 methods. Saliva samples were analyzed for nicotine, and its major metabolite, cotinine, using an established gas chromatography method (25, 26). Urine samples were analyzed for main nicotine metabolites to derive total nicotine equivalents and for minor tobacco alkaloids using validated tandem mass spectrometry (27, 28).

Levels of urinary TSNA and VOC metabolites were measured using either liquid chromatography/atmospheric pressure ionization/tandem mass spectrometry (29) or ultra-high performance liquid chromatography coupled with electrospray ionization and tandem mass spectrometry (30) to assess the potential risks of nicotine delivery products. Although we assessed a comprehensive battery of metabolites (Appendix Table 1, available at Annals.org), we focus here on well-established metabolites of compounds that are known to contribute significantly to smoking-related toxicologic and carcinogenic risks (31–39) (Table 1). All urinary and salivary biomarkers were analyzed by the Centers for Disease Control and Prevention and Roswell Park Cancer Institute, respectively.

**Table 1**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Description</th>
<th>Assay Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNK</td>
<td>Nicotine(4-(methylethylidene)dihydropiperdine)</td>
<td>Liquid chromatography/atmospheric pressure ionization/tandem mass spectrometry</td>
</tr>
<tr>
<td>NNA</td>
<td>Nicotine(4-(methylethylidene)hydropiperdine)</td>
<td>Liquid chromatography/atmospheric pressure ionization/tandem mass spectrometry</td>
</tr>
<tr>
<td>NNN</td>
<td>Nicotin...</td>
<td>Liquid chromatography/atmospheric pressure ionization/tandem mass spectrometry</td>
</tr>
</tbody>
</table>

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E-Cigarettes and Toxin Exposure
Table 1. Major Toxicants and Carcinogens Related to Tobacco Use

<table>
<thead>
<tr>
<th>Parent Compound</th>
<th>Biomarker/Metabolite</th>
<th>Rationale for Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco-specific N-nitrosamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-(methylnitrosamo)-1-(3-pyridyl)-1-butanone</td>
<td>4-(methylnitrosamo)-1-(3-pyridyl)-1-butanol</td>
<td>A potent lung carcinogen (40) and major contributor to cancer risk (34); IARC group 1 carcinogen (39)*; and 1 of 9 toxins recommended for mandated reduction in tobacco smoke on the WHO TobReg list (36)</td>
</tr>
<tr>
<td>Volatile organic compounds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acrolein</td>
<td>N-acetyl-S-(3-hydroxypropyl)-L-cysteine</td>
<td>A major contributor to respiratory effects (34, 35); IARC group 3 carcinogen (41); and 1 of 9 toxins recommended for mandated reduction in tobacco smoke on the WHO TobReg list (36)</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>N-acetyl-S-(2-carbamoyethyl)-L-cysteine</td>
<td>IARC group 2A carcinogen (37); a neurotoxin</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>N-acetyl-S-(2-cyanoethyl)-L-cysteine</td>
<td>A major contributor to cancer risk (34) and highly specific volatile organic compound biomarker for tobacco use (33); IARC group 2B carcinogen (37); and 1 of 9 toxins considered high priority for disclosure and monitoring on the WHO TobReg list (36)</td>
</tr>
<tr>
<td>1,3-butadiene</td>
<td>N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine</td>
<td>A major contributor to cancer risk (34, 35); IARC group 1 carcinogen (42)*; and 1 of 9 toxins recommended for mandated reduction in tobacco smoke on the WHO TobReg list (36)</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>N-acetyl-S-(2-hydroxyethyl)-L-cysteine</td>
<td>IARC group 1 carcinogen (37)*</td>
</tr>
</tbody>
</table>

IARC = International Agency for Research on Cancer; WHO TobReg = World Health Organization Study Group on Tobacco Product Regulation.

* Carcinogenic to humans.
† Not classifiable with regard to carcinogenicity to humans.
‡ Probably carcinogenic to humans.
§ Possibly carcinogenic to humans.
| More selective metabolite of parent compound than N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (33). |
¶ A major urinary metabolite of ethylene oxide exposure and a minor metabolite of acrylonitrile and vinyl chloride exposure (toxic tobacco smoke constituents).

Covariates

Sociodemographic characteristics (age, sex, ethnicity, education, and marital status) were assessed in addition to self-reported recently resolved physical illness (chest infection, cold or flu, sore throat, or fever) and subjective well-being (happiness and satisfaction, both assessed with established single-item measures (40). Salivary C-reactive protein level was used as a marker of inflammation (and thus potential health problems) and analyzed with an enzyme-linked immunosorbent assay (Galimetrics Europe) (41). Smoking characteristics, including current and past daily combustible cigarette consumption as a measure of dependence for smokers and former smokers, respectively; age at which participants had started smoking; and the proportion of family members or friends who smoke were assessed to gauge environmental tobacco smoke exposure.

Statistical Analysis

Because this was a cross-sectional study, exposure biomarkers, including metabolites of known tobacco-related carcinogens and toxins, were used as proxies for future disease risk. Previous research on the association of the carcinogenic metabolite 4-(methylnitrosamo)-1-(3-pyridyl)-1-butanol (NNAL) with lung cancer suggests that medium to large reductions in NNAL levels (Cohen $\gamma = 0.25$ to 0.40) would result in an appreciable reduction in risk (42) and could thus be considered clinically meaningful in magnitude and warrant further investigation (43). A priori power calculation showed that 180 participants (36 per group) would provide 90% power to detect between-group differences of a medium effect size (Cohen $\gamma = 0.3$) in NNAL levels when comparing 5 groups by using analysis of variance (44). However, this calculation did not account for multiple outcomes being tested, and based on 35 biomarker outcomes reported here, power to detect such an effect size across all biomarkers would have been reduced to 54%. The sample size therefore only provided sufficient power ($\geq 80\%$) to detect effects at the upper range of the estimate (Cohen $\gamma \geq 0.36$) when multiple comparisons were accounted for.

Analyses were conducted with SPSS, version 22.0 (IBM). In initial analysis of between-group differences on covariates, 1-way analysis of variance was used for continuous covariates and chi-square analysis was used for categorical covariates. Before the main analysis, urinary metabolites were standardized algebraically to account for individual differences in urine concentration by dividing metabolite data by the ratio of observed urinary metabolites to age-, sex-, and ethnicity-adjusted creatinine levels. Creatinine (measured by standard colorimetric method at Roswell Park Cancer Institute) was also included as a covariate in the analysis (45). Due to nonnormal distribution of data, generalized linear models with a log link and $\gamma$ distribution were used to assess between-group differences in outcome measures, which were adjusted for all covariates and latency to product use. B coefficients were exponentiated to calculate the percentage of change in biomarker levels in all groups compared with combustible cigarette–only smokers. For prespecified tests of the main effects of a group, type I errors were controlled for by using the false discovery rate (46) separately for sociodemographic-related endpoints.
graphic comparisons (n = 13) and biomarker comparisons (n = 35). Where overall omnibus effects were considered significant, the Sidak correction was used in post hoc analysis to determine which (if any) between-group differences persisted. Biomarker values below the limit of detection (LOD) were imputed using standard methods (LOD divided by the square root of 2) (47), and biomarkers with 50% or more values below the LOD were not analyzed.

Role of the Funding Source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Dr. Shahab had full access to all study data and had final responsibility for the decision to submit the manuscript for publication.

RESULTS

Overall, participants were relatively young, were mainly men, were white, and had at least a high school education; about half of them were single (Table 2). On average, participants had started smoking nearly 1 pack of cigarettes per day in their late teens, and a substantial proportion (16% to 51%) of their family members or friends also smoked. Salivary C-reactive protein levels were within the range observed for healthy adults (0.05 to 64.3 μg/L) (48), and the reported level of well-being was similar to that of representative population samples (40). Between-group differences included that the proportion of women varied from 19.4% in e-cigarette–only users to 61.1% in dual combustible cigarette–NRT users, fewer e-cigarette–only users were women, NRT-only users started smoking the latest, and e-cigarette–only users had the lowest proportion of family members or friends who smoked. Considerable variation in ethnicity, marital status, combustible cigarette consumption, recent illness, and reported happiness levels were also found (Table 2).

As previously reported, length of product use was broadly similar across groups at around 17 months, and mean daily NRT and e-cigarette use, measured by self-reported nicotine dose, was higher for NRT-only and e-cigarette–only users than for dual combustible cigarette–NRT and combustible cigarette–e-cigarette users (23). For the product type used, first-generation “cig-a-likes,” with replaceable or disposable cartridges, were most popular among dual combustible cigarette–e-cigarette users (60.0%). Third- or fourth-generation advanced personal vaporizers were most popular among e-cigarette–only users (47.2%). Refillable pen-style, second-generation e-cigarettes were equally popular among dual combustible cigarette–e-cigarette (31.4%) and e-cigarette–only (36.1%) users. For both dual combustible cigarette–NRT and NRT-only users, gum (44.4% and 33.3%, respectively) and patches (both 33.3%) were the most popular NRTs, and a similar proportion (27.8%) used more than 1 NRT.

Nicotine Levels

Nicotine intake among the products was roughly similar (Figure 1), with some variation across groups (Appendix Table 1). For urinary biomarkers, users of all

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Participants (n = 181)</th>
<th>Cigarette-Only Users (n = 37)</th>
<th>Dual Cigarette-NRT Users (n = 36)</th>
<th>Dual Cigarette-EC Users (n = 36)</th>
<th>Former Smokers (n = 36)</th>
<th>EC-Only Users (n = 36)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>37.8 (11.8)</td>
<td>34.4 (14.0)</td>
<td>36.4 (8.5)</td>
<td>39.3 (13.1)</td>
<td>40.3 (11.1)</td>
<td>38.5 (11.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>71 (39.2)</td>
<td>16 (43.2)</td>
<td>22 (61.1)</td>
<td>11 (30.6)</td>
<td>15 (41.7)</td>
<td>7 (19.4)</td>
<td>0.024</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>131 (72.4)</td>
<td>30 (81.1)</td>
<td>21 (58.3)</td>
<td>27 (75.0)</td>
<td>23 (63.9)</td>
<td>30 (83.3)</td>
<td>0.111</td>
</tr>
<tr>
<td>High school, n (%)</td>
<td>140 (77.3)</td>
<td>25 (67.6)</td>
<td>30 (83.3)</td>
<td>29 (80.6)</td>
<td>28 (77.8)</td>
<td>28 (77.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>Single, n (%)</td>
<td>97 (53.6)</td>
<td>26 (70.3)</td>
<td>21 (58.3)</td>
<td>16 (50.0)</td>
<td>13 (36.1)</td>
<td>19 (52.8)</td>
<td>0.104</td>
</tr>
<tr>
<td>Mean age started smoking (SD), y</td>
<td>17.8 (4.3)</td>
<td>16.6 (3.2)</td>
<td>18.2 (3.4)</td>
<td>17.3 (3.1)</td>
<td>20.3 (6.4)</td>
<td>16.6 (3.2)</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean cigarettes per day (SD), n</td>
<td>13.3 (8.7)</td>
<td>13.9 (9.0)</td>
<td>10.8 (4.6)</td>
<td>11.9 (9.6)</td>
<td>14.7 (10.3)</td>
<td>15.9 (8.3)</td>
<td>0.104</td>
</tr>
<tr>
<td>Mean proportion of friends/family who smoke (SD)</td>
<td>35.6 (27.5)</td>
<td>50.9 (23.6)</td>
<td>39.8 (24.1)</td>
<td>38.0 (32.4)</td>
<td>33.2 (27.7)</td>
<td>15.6 (15.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent illness, n (%)</td>
<td>42 (23.2)</td>
<td>14 (37.8)</td>
<td>3 (8.3)</td>
<td>7 (19.4)</td>
<td>10 (27.8)</td>
<td>8 (22.2)</td>
<td>0.104</td>
</tr>
<tr>
<td>Geometric mean salivary C-reactive protein level (SD), mmol/L</td>
<td>0.017 (3.32)</td>
<td>0.020 (2.99)</td>
<td>0.013 (3.48)</td>
<td>0.016 (3.15)</td>
<td>0.018 (3.20)§</td>
<td>0.021 (3.78)</td>
<td>0.47</td>
</tr>
<tr>
<td>Mean global life satisfaction (SD)</td>
<td>3.9 (1.0)</td>
<td>4.1 (0.9)</td>
<td>3.8 (1.1)</td>
<td>3.7 (1.1)</td>
<td>3.9 (0.9)</td>
<td>3.9 (1.1)</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean happiness levels (SD)</td>
<td>5.0 (1.5)</td>
<td>4.6 (1.7)</td>
<td>5.6 (1.1)</td>
<td>4.7 (1.7)</td>
<td>5.3 (1.3)</td>
<td>5.0 (1.6)</td>
<td>0.104</td>
</tr>
</tbody>
</table>

Cigarette = combustible cigarette; EC = e-cigarette; NRT = nicotine replacement therapy.

* Omnibus test result, adjusted for the reported comparisons in this table using the false discovery rate (46).
† Former smokers were asked about their typical past consumption levels.
‡ Statistical comparison conducted on log-transformed values (not shown).
§ Data are missing for 1 participant.
|| Assessed by asking, “All things considered, how satisfied are you with your life as a whole?” Response options ranged from “very dissatisfied” (1) to “very satisfied” (5).
‡ Assessed by asking, “Some people are very generally very happy. They enjoy life regardless of what is going on, getting the most out of everything. To what extent does this characterization describe you?” Response options ranged from “not at all” (1) to “a great deal” (7).
products had levels of total nicotine equivalents at least as high as combustible cigarette–only users in adjusted analysis (Table 3). Findings related to salivary biomarkers varied. Dual combustible cigarette–NRT users had relatively low nicotine and cotinine levels, and e-cigarette–only users had relatively low nicotine levels—at around half that of combustible cigarette–only users—with other groups obtaining levels slightly less or more than those from combustible cigarette–only users (Table 3). The minor tobacco alkaloids anabasine and anatabine, which are specific to tobacco as opposed to nicotine exposure, were clearly distinguished between smokers and former smokers, with significantly lower levels than combustible cigarette–only, dual combustible cigarette–NRT, or dual combustible cigarette–e-cigarette users (Appendix Table 1).

**TSNA Levels**

There were clear between-group differences in NNAL levels (Figure 2). The NRT-only and e-cigarette–only users had markedly lower NNAL levels than combustible cigarette–only, dual combustible cigarette–NRT, and dual combustible cigarette–e-cigarette users ($P < 0.001$); e-cigarette–only users had significantly lower NNAL levels than all other groups—equivalent to a 97% reduction compared with the levels of combustible cigarette–only users (Table 3). Compared with combustible cigarette–only users, there were no large differences in NNAL levels for dual combustible cigarette–e-cigarette users but dual combustible cigarette–NRT users had somewhat lower NNAL levels. Results followed a similar, albeit less pronounced, pattern for the other TSNAAs measured (Appendix Table 1).

**VOC Levels**

Of the major urinary VOC metabolites, e-cigarette–only users had the lowest levels overall, with acrylonitrile levels as low as 2.9% for combustible cigarette–only users; further, NRT-only users had the second lowest levels overall, with acrylonitrile levels as low as 10.5% for combustible cigarette–only users (Table 3). By contrast, dual combustible cigarette–NRT, dual combustible cigarette–e-cigarette, and combustible cigarette–only users all had very similar urinary VOC metabolite levels (Figure 2). Compared with all other groups, NRT-only and e-cigarette–only users had at least half of the reference values of combustible cigarette–only users (Table 3) and had significantly lower levels of all major metabolites of selected toxic and carcinogenic VOCs (all $P < 0.001$) (Appendix Table 1).

Results were largely confirmed by reviewing other VOC metabolites that were assessed. E-cigarette–only users generally had the lowest levels, followed by NRT-only users, with no detectable differences among dual combustible cigarette–NRT, dual combustible cigarette–e-cigarette, and combustible cigarette–only users (Appendix Table 1). The only exceptions were metabolites of benzene (N-acetyl-S-(1- and 2-phenyl)-L-cysteine [PMA] and muconic acid [MU]), carbon disulfide (2-thioxothiazolidine-4-carboxylic acid [TTCA]), and styrene (N-acetyl-S-(1- and 2-phenyl-2-hydroxyethyl)-L-
cysteine [PHEMA] and phenylglyoxylic acid [PGA]). Dual convertible cigarette–e-cigarette users had somewhat higher detection rates (PMA and PHEMA) (Appendix Table 1). There were no appreciable between-group differences in TTCA levels. However, these metabolites were either nonspecific to the parent VOC measured (MU and TTCA have dietary contributions, and PGA is a metabolite of ethylbenzene and styrene exposure) or had low detection rates (PMA and PHEMA) (Appendix Table 2, available at Annals.org).

**DISCUSSION**

To our knowledge, this is the first direct comparison of the metabolite levels of nicotine and important carcinogens and toxins in long-term e-cigarette or NRT users. We found that former smokers who had switched to e-cigarette–only or NRT–only use obtained roughly similar levels of nicotine compared with convertible cigarette–only smokers, but results varied. Long-term NRT–only use and especially e-cigarette–only use, but not dual use of NRTs or e-cigarettes with convertible cigarettes, were associated with lower levels of known tobacco-related carcinogens and toxins measured in this study compared with convertible cigarette–only use.

The finding that NRT–only or e-cigarette–only use is associated with roughly similar nicotine intake compared with that of convertible cigarette–only use supports the view that users seek a particular level of nicotine intake, regardless of the delivery system (49), and adjust product use accordingly (50). This finding is consistent with more recent (51) but not older (8) studies on nicotine delivery from e-cigarettes, which may reflect the improved design of newer generations of e-cigarettes (52), and highlights the importance of focusing on experienced, long-term users rather than naive, short-term users. Similarly, efficient nicotine intake from NRT–only use has been observed in long-term (53) but not short- or intermediate-term NRT users (54). Nicotine intake was largely similar for both groups, which suggests that greater craving reductions observed in e-cigarette–only users than in NRT–only users (23, 55) may be due to factors other than nicotine delivery, such as the greater behavioral similarity of e-cigarette use (unlike NRT use) with smoking. This is consistent with research on nonnicotine sensory factors that have been shown to influence tobacco withdrawal (56). However, this study was not powered to detect anything other than relatively large effects, so results about smaller differences in nicotine intake between e-cigarettes and NRTs are indeterminate.

The lower levels of carcinogens and toxins associated with NRT–only and e-cigarette–only use in this study confirm the known low risk for complications from long-term NRT use (57). This finding also underscores the translation of greatly reduced concentrations of some carcinogens and toxins from e-liquids and aerosols (4, 6, 58) to body-level exposure, contrary to worries that long-term e-cigarette use would result in substantial harmful exposure (59). Given the involvement of these TSNA and VOCs with cancer, cardiovas-
**Figure 2.** Urinary metabolite levels for selected toxins and carcinogens, by group.

Data are raw values divided by ratio of observed urinary metabolites to covariate-adjusted creatinine levels. The levels below the limit of detection were imputed by the limit of detection divided by square root of 2. Boxplots show the median with interquartile range (25th percentile, 75th percentile). Error bars show Tukey’s whiskers, and cross indicate arithmetic means (geometric means are provided in Appendix Table 1). Circles indicate outliers. Significant pairwise comparisons are presented in Appendix Table 1. Cigarette = combustible cigarette; EC = e-cigarette; NRT = nicotine replacement therapy.

A. Tobacco-specific N-nitrosamine. NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

B. Acrolein. 3HPMA = N-acetyl-S-(3-hydroxypropyl)-L-cysteine.

C. Acrylamide. AAMA = N-acetyl-S-(2-carbamoylethyl)-L-cysteine.

D. Acrylonitrile. CYMA = N-acetyl-S-(2-cyanoethyl)-L-cysteine.

E. 1,3-butadiene. MHBMA3 = N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine.

F. Ethylene oxide. HEMA = N-acetyl-S-(2-hydroxyethyl)-L-cysteine.
cicular diseases, and pulmonary diseases (42, 60), our results suggest that complete substitution of combustible cigarettes with e-cigarettes may reduce disease risk and support the assertion that e-cigarette use may be less harmful than smoking (2, 61–63). We found no evidence that long-term e-cigarette–only use was associated with greater levels of carcinogens or toxins than NRT-only use; on some measures, e-cigarette–only use was associated with lower levels. Although this could be due to occasional combustible cigarette smoking lapses by long-term NRT-only users, it is unlikely to have made a substantial contribution, given very low levels of tobacco-specific (as opposed to nicotine-specific) biomarkers for acrylonitrile, anabasine, and anatabine (64, 65) in this group. Alternatively, these differences may reflect typical low-level contamination in these products (for example, with TSNA from tobacco-derived nicotine) (66), nonspecificity of the metabolite for the toxin (for example, muconic acid for benzene) (67), or non-smoking-related environmental sources of toxin exposure (for example, for styrene) (68). Contrary to findings from a recent short-term switching study (12), dual combustible cigarette–NRT or combustible cigarette–e-cigarette use was not associated with appreciable reductions in carcinogen and toxin levels. This may be because participants in our study may have been even heavier smokers before starting concurrent e-cigarette or NRT use, thus masking the benefit of potential partial substitution in our cross-sectional study, or because dual users used noncombustible products to bridge times of nonsmoking and thus did not actually reduce combustible cigarette consumption. Alternatively, lack of notable reductions in carcinogens and toxins after dual use may reflect either differences in study design (for example, different use pattern in long-term vs. short-term users) or our study’s relatively low power to detect smaller, yet meaningful, effects. Further longitudinal research is needed to differentiate among these explanations.

Our findings have several implications. Although complete, long-term switching to e-cigarettes may produce a net benefit for the health outcomes of the smoking population because e-cigarette–only use significantly reduced exposure to known tobacco-related carcinogens and toxins, we found that dual use of e-cigarettes with combustible cigarettes did not reduce exposure appreciably. Therefore, e-cigarettes are likely to be beneficial only if complete cessation of combustible cigarette smoking is achieved. Thus, dual users should be encouraged to cease using combustible products to reduce long-term health risks. Our results also indicate that machine-derived and actual body-level exposure to toxins can be very different, as shown, for example, by greatly reduced aldehyde levels in e-cigarette users in this study compared with reportedly high levels in e-cigarette aerosols under certain laboratory conditions (5, 69). Of note, although e-cigarette–only and NRT-only use was associated with marked reductions in carcinogens and toxins compared with combustible cigarette–only use, use of these products did not eliminate exposure (and thus possible health risks) completely. Full cessation of all nicotine products remains the best option to avoid harm.

The study had several limitations. Although participants were recruited through diverse methods, resulting in a sample broadly similar to the population of NRT and e-cigarette users (16, 70), and we controlled for important confounders, between-group differences may not generalize and reflect self-selection. The sample was too small to allow more sophisticated analyses to evaluate the association of different types of e-cigarettes or NRTs (and other characteristics, such as e-cigarette flavors) with intake, and we may not have picked up on small but important differences in exposure levels. In particular, the lack of between-group differences in nicotine intake has to be interpreted cautiously given the low power to detect smaller effects and the variability across different urinary and salivary measures. Lastly, we did not assess indirect exposure and the analysis was limited by the number of biomarkers available and spot sampling, which can only provide a snapshot of exposure. However, given the lack of long-term data, we chose this pragmatic design to quickly evaluate potentially important associations of e-cigarette use with intake of carcinogens and toxins to inform further longitudinal work. Moreover, the relatively slow pharmacokinetics of the assessed metabolites provides stable estimates of recent exposure and should mitigate against variations associated with different patterns of use for different products. Future work should sample a larger range of biomarkers over a longer period, including those of actual harm, such as lung function measures, and evaluate the effect of potential interactions of users with device characteristics on the delivery of toxins to users and bystanders.

In conclusion, long-term NRT-only or e-cigarette–only use among former smokers is associated with substantially reduced levels of selected carcinogens and toxins compared with combustible cigarette smoking; however, concurrent use of NRTs or e-cigarettes with combustible cigarettes does not seem to offer this benefit. We found no evidence that e-cigarette–only use compared with NRT-only use is associated with greater levels of carcinogens and toxins. Nicotine delivery of e-cigarettes and NRTs, although variable, is roughly similar to combustible cigarettes, but smaller meaningful differences may exist.

From University College London and King’s College, London, United Kingdom; Roswell Park Cancer Institute, Buffalo, New York; and Centers for Disease Control and Prevention, Atlanta, Georgia.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health and the U.S. Food and Drug Administration.

Acknowledgment: The authors thank Kate Sheals and Victoria Nelson for their help with data collection and the Centers for Disease Control and Prevention reviewers for providing a thorough review of the manuscript.
E-Cigarettes and Toxin Exposure

Financial Support: This work was supported by Cancer Research UK (grant C27061/A16929, with additional funding from grants C1417/A14135 and C36048/A11654). Dr. Brown’s post is funded by a fellowship from the Society for the Study of Addiction, and Cancer Research UK also provides support (grants C1417/A7972 and C44576/A19501). Drs. McNeill and West are part of the UK Centre for Tobacco and Alcohol Studies, which is a UK Clinical Research Collaboration Public Health Research Centre of Excellence. Funding from the Medical Research Council, British Heart Foundation, Cancer Research UK, Economic and Social Research Council, and the National Institute for Health Research under the auspices of the UK Clinical Research Collaboration is gratefully acknowledged (grant MR/K023195/1). Dr. Goniewicz was supported by the National Institute on Drug Abuse and the National Cancer Institute of the National Institutes of Health (awards R01DA037446 and P30 CA016056, respectively) and by an award from Roswell Park Alliance Foundation.

Disclosures: Dr. Shahab reports grants from Cancer Research UK during the conduct of the study and grants from Pfizer (unrestricted research funding to study smoking cessation) and personal fees from Atlantis Health Care outside of the submitted work. Dr. Goniewicz reports grants from Pfizer (2011 GRAND [Global Research Awards for Nicotine Dependence] recipient) and personal fees from Johnson & Johnson (as a member of the advisory board) outside the submitted work. Dr. Brown reports grants (unrestricted research funding to study smoking cessation) from Pfizer outside the submitted work. Dr. West reports grants, personal fees, and nonfinancial support (that is, research grants, consultancy, travel, and hospitality) from Pfizer, Johnson & Johnson, and GlaxoSmithKline outside the submitted work; in addition, Dr. West’s salary is funded by Cancer Research UK and he is an advisor to the UK National Centre for Smoking Cessation and Training. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-1107.

Reproducible Research Statement: Study protocol: Not available. Statistical code and data set: Available from Dr. Shahab (e-mail, lion.shahab@ucl.ac.uk).

Requests for Single Reprints: Lion Shahab, PhD, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Street, London WC1E 7HB, United Kingdom; e-mail, lion.shahab@ucl.ac.uk.

Current author addresses and author contributions are available at Annals.org.

References


Current Author Addresses: Drs. Shahab and West: Department of Epidemiology and Public Health, University College London, 1-19 Torrington Street, London WC1E 7HB, United Kingdom.
Dr. Goniewicz: Department of Health Behavior, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263.
Drs. Blount, Alwis, Feng, and Wang: Tobacco and Volatiles Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Highway, Atlanta, GA 30341.
Dr. Brown: Department of Clinical, Educational and Health Psychology, University College London, 1-19 Torrington Street, London WC1E 7HB, United Kingdom.
Dr. McNeill: Addictions Department, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, 4 Windsor Walk, London SE5 8AF, United Kingdom.

Author Contributions: Conception and design: L. Shahab, M.L. Goniewicz, J. Brown, A. McNeill, R. West.
Drafting of the article: L. Shahab, B.C. Blount, A. McNeill, K.U. Alwis, R. West.
Critical revision of the article for important intellectual content: L. Shahab, M.L. Goniewicz, B.C. Blount, J. Brown, A. McNeill, R. West.
Final approval of the article: L. Shahab, M.L. Goniewicz, B.C. Blount, J. Brown, A. McNeill, R. West.
Statistical expertise: L. Shahab.
Administrative, technical, or logistic support: L. Shahab, M.L. Goniewicz.
### Appendix Table 1. Urinary and Saliva Biomarker Levels, by Group*

<table>
<thead>
<tr>
<th>Parent Compound</th>
<th>Biomarker/Metabolite</th>
<th>Smokers Cigarette-Only Users (n = 37)</th>
<th>Dual Cigarette-NRT Users (n = 36)</th>
<th>Dual Cigarette-EC Users (n = 36)</th>
<th>Former Smokers NRT-Only Users (n = 36)</th>
<th>EC-Only Users (n = 36)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco alkaloids (saliva), ng/mL</td>
<td>Nicotine†</td>
<td>260.3 (189.1–358.4)</td>
<td>147.2 (102.1–212.0)</td>
<td>299.4 (193.2–464.0)</td>
<td>158.5 (97.1–258.6)</td>
<td>184.4 (125.2–271.6)</td>
<td>0.0035</td>
</tr>
<tr>
<td></td>
<td>Cotinine‡</td>
<td>174.8 (105.1–290.8)</td>
<td>67.1 (39.1–115.1)</td>
<td>149.2 (95.8–232.3)</td>
<td>83.9 (45.8–153.7)</td>
<td>179.6 (118.1–273.0)</td>
<td>0.134</td>
</tr>
<tr>
<td>Tobacco alkaloids (urine)</td>
<td>Nicotine, nmol/mg of creatinine</td>
<td>21.1 (14.0–31.8)</td>
<td>8.5 (3.9–18.4)</td>
<td>28.8 (16.6–49.8)</td>
<td>6.3 (2.9–14.1)</td>
<td>25.0 (14.8–42.0)</td>
<td>0.204</td>
</tr>
<tr>
<td></td>
<td>Cotinine</td>
<td>8.5 (5.1–143.3)</td>
<td>3.2 (1.4–7.4)</td>
<td>10.9 (6.9–19.8)</td>
<td>2.8 (1.2–6.3)</td>
<td>11.4 (6.5–19.9)</td>
<td>0.442</td>
</tr>
<tr>
<td></td>
<td>Total nicotine equivalents‡</td>
<td>5.9 (3.8–9.3)</td>
<td>1.8 (0.7–4.4)</td>
<td>8.2 (4.6–14.8)</td>
<td>1.4 (0.6–3.5)</td>
<td>7.5 (4.5–12.4)</td>
<td>0.188</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>1.9 (1.2–3.3)</td>
<td>1.2 (0.5–2.5)</td>
<td>4.2 (2.3–7.1)</td>
<td>0.8 (0.3–1.7)</td>
<td>2.5 (1.5–4.2)</td>
<td>0.088</td>
</tr>
<tr>
<td></td>
<td>Cotinine N-oxide</td>
<td>0.6 (0.4–1.0)</td>
<td>0.2 (0.1–0.5)</td>
<td>0.8 (0.5–1.4)</td>
<td>0.2 (0.1–0.4)</td>
<td>0.8 (0.5–1.3)</td>
<td>0.254</td>
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<tr>
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<td>Nicotine 1-oxide</td>
<td>0.7 (0.4–1.1)</td>
<td>0.4 (0.2–0.8)</td>
<td>1.3 (0.7–2.2)</td>
<td>0.2 (0.1–0.6)</td>
<td>0.9 (0.5–1.6)</td>
<td>0.166</td>
</tr>
<tr>
<td></td>
<td>Norcotinine</td>
<td>0.2 (0.1–0.3)</td>
<td>0.1 (0.1–0.2)</td>
<td>0.3 (0.2–0.5)</td>
<td>0.1 (0.1–0.2)</td>
<td>0.2 (0.1–0.3)</td>
<td>0.161</td>
</tr>
<tr>
<td></td>
<td>Nonnicotine</td>
<td>0.2 (0.1–0.3)</td>
<td>0.1 (0.1–0.2)</td>
<td>0.2 (0.1–0.4)</td>
<td>0.1 (0.1–0.2)</td>
<td>0.1 (0.1–0.2)</td>
<td>0.0225</td>
</tr>
<tr>
<td></td>
<td>Tobacco-specific N-nitrosamines, pg/mg of creatinine</td>
<td>Anabasine</td>
<td>17.0 (11.2–25.8)</td>
<td>11.1 (6.3–19.4)</td>
<td>25.5 (16.3–40.1)</td>
<td>5.5 (3.5–7.1)</td>
<td>6.2 (4.1–9.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anatabine per mg of creatinine</td>
<td>26.0 (16.3–41.4)</td>
<td>14.9 (7.6–29.2)</td>
<td>36.0 (22.0–59.1)</td>
<td>3.8 (2.4–6.2)</td>
<td>4.6 (2.8–7.6)</td>
</tr>
<tr>
<td></td>
<td>4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)</td>
<td>Anatabine &amp; Anabasine</td>
<td>33.4 (23.2–52.1)</td>
<td>21.6 (12.1–39.9)</td>
<td>53.4 (36.6–77.8)</td>
<td>24.4 (13.2–45.1)</td>
<td>44.5 (28.5–69.4)</td>
</tr>
<tr>
<td></td>
<td>N′-nitrosoanabasine</td>
<td>6.17 (4.31–8.82)</td>
<td>3.64 (2.20–6.02)</td>
<td>6.02 (4.15–8.73)</td>
<td>1.52 (1.09–2.12)</td>
<td>1.07 (0.79–1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>N′-nitrosoanatabine</td>
<td>32.8 (20.5–52.5)</td>
<td>11.8 (5.77–24.0)</td>
<td>30.8 (18.5–51.1)</td>
<td>2.95 (1.81–4.81)</td>
<td>1.79 (1.21–2.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Volatile organic compounds, ng/mg of creatinine</td>
<td>Benzene</td>
<td>78.6 (58.2–106.2)</td>
<td>268.6 (180.1–377.3)</td>
<td>488.4 (345.1–691.2)</td>
<td>499.7 (350–713.5)</td>
<td>574.5 (429.1–769.2)</td>
</tr>
<tr>
<td></td>
<td>Acrolein</td>
<td>119.8 (88.2–162.9)</td>
<td>136.1 (100.7–184.1)</td>
<td>141.8 (105.9–188.4)</td>
<td>141.9 (106.7–188.4)</td>
<td>67.8 (49.3–93.2)</td>
<td>54.6 (41.7–71.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrylamide</td>
<td>65.5 (50.6–85.1)</td>
<td>52.5 (40.4–68.8)</td>
<td>82.4 (66.1–102.8)</td>
<td>33.6 (25.8–43.7)</td>
<td>29.3 (22.3–38.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrylamide</td>
<td>18.5 (14.7–23.3)</td>
<td>16.8 (13.1–21.5)</td>
<td>24.3 (19.6–30.2)</td>
<td>12.1 (9.5–15.5)</td>
<td>10.0 (7.6–13.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acrylonitrile</td>
<td>49.2 (32.9–73.6)</td>
<td>28.4 (15.6–51.9)</td>
<td>51.6 (33.6–79.2)</td>
<td>3.7 (2.1–6.5)</td>
<td>1.4 (1.1–4.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzene</td>
<td>78.6 (58.2–106.2)</td>
<td>268.6 (180.1–377.3)</td>
<td>488.4 (345.1–691.2)</td>
<td>499.7 (350–713.5)</td>
<td>574.5 (429.1–769.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,3-butadiene</td>
<td>202.7 (162.8–252.3)</td>
<td>204.3 (162.3–257.3)</td>
<td>294.9 (242.9–358.0)</td>
<td>204.2 (156.9–265.9)</td>
<td>156.3 (126.0–193.8)</td>
</tr>
</tbody>
</table>

*Continued on following page*
<table>
<thead>
<tr>
<th>Parent Compound</th>
<th>Biomarker/Metabolite</th>
<th>Cigarette-Only Users (n = 37)</th>
<th>Dual Cigarette-NRT Users (n = 36)</th>
<th>Dual Cigarette-EC Users (n = 36)</th>
<th>NRT-Only Users (n = 36)</th>
<th>EC-Only Users (n = 36)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon disulfide</td>
<td>2-thioxothiazolidine-4-carboxylic acid (TTCA)</td>
<td>6.03 (4.40–8.27)</td>
<td>13.8 (8.79–21.7)</td>
<td>9.95 (6.85–14.5)</td>
<td>13.4 (9.07–19.7)</td>
<td>6.84 (4.33–10.8)</td>
<td>0.015§</td>
</tr>
<tr>
<td>Crotonicdehyde</td>
<td>N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine (HPMMA)</td>
<td>804.2 (563.8–1147.1)†‡¶</td>
<td>735.3 (495.2–1091.7)†‡¶</td>
<td>1199.5 (881.9–1631.6)†‡¶</td>
<td>366.3 (266.0–504.5)†‡†‡‡</td>
<td>235.9 (179.1–310.7)†‡†‡‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cyanide</td>
<td>2-aminothiazoline-4-carboxylic acid (ATCA)</td>
<td>162.2 (120.6–218.1)¶</td>
<td>138.5 (95.4–201.2)</td>
<td>176.3 (129.1–240.5)</td>
<td>100.2 (72.4–138.7)</td>
<td>60.8 (44.4–83.3)†‡†‡‡</td>
<td>0.013</td>
</tr>
<tr>
<td>N,N-dimethylformamide</td>
<td>N-acetyl-S-(N-methylcarbamoyl)-L-cysteine (AMCC)</td>
<td>0.81 (0.61–1.07)¶</td>
<td>0.81 (0.55–1.18)</td>
<td>1.15 (0.84–1.57)</td>
<td>0.64 (0.48–0.84)†‡¶</td>
<td>0.42 (0.32–0.55)§‡‡§‡‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethylene oxide, acrylonitrile, vinyl chloride</td>
<td>N-acetyl-S-(2-hydroxyethyl)-L-cysteine (HEMA)‡</td>
<td>41.1 (30.4–55.6)¶</td>
<td>47.3 (35.6–63.0)¶</td>
<td>68.9 (52.6–90.4)¶</td>
<td>37.4 (28.7–48.9)†‡‡¶</td>
<td>29.3 (21.9–39.3)∗†‡‡¶</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Propylene oxide</td>
<td>N-acetyl-S-(2-hydroxypropyl)-L-cysteine (2HPMA)</td>
<td>188.6 (147.4–241.2)¶</td>
<td>198.7 (153.8–256.7)¶</td>
<td>227.2 (181.1–284.9)¶</td>
<td>173.0 (127.3–235.3)</td>
<td>100.8 (78.2–129.9)†‡‡¶</td>
<td>0.001</td>
</tr>
<tr>
<td>Styrene</td>
<td>Mandelic acid (MA)</td>
<td>0.75 (0.57–0.98)¶</td>
<td>0.82 (0.56–1.18)</td>
<td>1.09 (0.8–1.48)‡</td>
<td>0.75 (0.55–1.00)</td>
<td>0.48 (0.36–0.63)†‡‡§‡²</td>
<td>0.01</td>
</tr>
<tr>
<td>Styrene, ethylbenzene</td>
<td>Phenylglyoxylic acid (PGA)</td>
<td>88.0 (62.6–123.8)¶</td>
<td>129.9 (92.1–183.3)¶</td>
<td>124.5 (91.1–170.0)¶</td>
<td>88.1 (60.6–128.2)</td>
<td>71.1 (53.7–94.1)†‡‡†‡</td>
<td>0.007</td>
</tr>
<tr>
<td>Xylene</td>
<td>2-methylthiopuric acid (2MHA)</td>
<td>41.9 (30.1–58.4)¶</td>
<td>36.3 (23.9–55.2)§</td>
<td>56.9 (41.8–77.4)§</td>
<td>19.6 (13.3–29.7)**§‡‡§‡</td>
<td>10.5 (7.8–14.2)†‡‡§‡²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3- and 4-methylthiopuric acids (34MHA)</td>
<td>266.5 (182.1–390.1)¶</td>
<td>181.1 (119.7–274.0)¶</td>
<td>273.2 (201.1–371.0)¶</td>
<td>76.3 (48.8–119.4)†‡‡§‡‡¶</td>
<td>51.4 (38.5–68.6)†‡‡§‡²</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cigarette = combustible cigarette; EC = e-cigarette; NRT = nicotine replacement therapy.
* Data presented are log-transformed raw values (for urinary metabolites also standardized for creatinine). Statistical comparisons were carried out on nontransformed data and adjusted for all variables in Table 2, latency to product use, and creatinine levels. Values are geometric means (95% CIs).
† Omnibus test result, adjusted for the number of reported comparisons in this table using the false discovery rate (46).
‡ Non–log-transformed data shown in Figures 1 and 2.
§ Overall differences but no significant (Sidak-corrected) difference in post hoc test.
¶ Indicates statistically significant (Sidak-corrected) difference (P < 0.05) for NRT-only users.
|| Indicates statistically significant (Sidak-corrected) difference (P < 0.05) for EC-only users.
** Indicates statistically significant (Sidak-corrected) difference (P < 0.05) for cigarette-only smokers.
†† Indicates statistically significant (Sidak-corrected) difference (P < 0.05) for dual cigarette-EC users.
‡‡ Indicates statistically significant (Sidak-corrected) difference (P < 0.05) for dual cigarette-NRT users.
Appendix Table 2. Proportion of Samples Below Limit of Detection, by Group and Across All Samples*

<table>
<thead>
<tr>
<th>Biomarker/Metabolite†</th>
<th>Limit of Detection</th>
<th>All Samples</th>
<th>Cigarette-Only Users (n = 37)</th>
<th>Dual Cigarette-NRT Users (n = 36)</th>
<th>Dual Cigarette-EC Users (n = 36)</th>
<th>NRT-Only Users (n = 36)</th>
<th>EC-Only Users (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine‡</td>
<td>10 ng/mL</td>
<td>1.1</td>
<td>0.0</td>
<td>0.0</td>
<td>2.8</td>
<td>2.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Cotinine‡</td>
<td>10 ng/mL</td>
<td>14.4</td>
<td>13.5</td>
<td>16.7</td>
<td>5.6</td>
<td>27.8</td>
<td>8.3</td>
</tr>
<tr>
<td>trans-3'-hydroxycotinine</td>
<td>0.03 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Cotinine</td>
<td>0.03 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nicotine</td>
<td>10.5 ng/mL</td>
<td>11.0</td>
<td>2.7</td>
<td>13.9</td>
<td>5.6</td>
<td>30.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Cotinine N-oxide</td>
<td>2 ng/mL</td>
<td>7.7</td>
<td>0.0</td>
<td>13.9</td>
<td>2.8</td>
<td>19.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Nicotine 1'-oxide</td>
<td>2.5 ng/mL</td>
<td>8.8</td>
<td>0.0</td>
<td>13.9</td>
<td>2.8</td>
<td>25.0</td>
<td>2.8</td>
</tr>
<tr>
<td>Norcocotinine</td>
<td>2.5 ng/mL</td>
<td>11.6</td>
<td>0.0</td>
<td>22.2</td>
<td>5.6</td>
<td>27.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Nornicotine</td>
<td>1.1 ng/mL</td>
<td>17.7</td>
<td>5.4</td>
<td>30.6</td>
<td>11.1</td>
<td>33.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Anatabine</td>
<td>0.5 ng/mL</td>
<td>29.3</td>
<td>5.4</td>
<td>27.8</td>
<td>11.1</td>
<td>61.1</td>
<td>41.7</td>
</tr>
<tr>
<td>Anabasine</td>
<td>0.0 ng/mL</td>
<td>29.3</td>
<td>5.4</td>
<td>27.8</td>
<td>11.1</td>
<td>61.1</td>
<td>41.7</td>
</tr>
<tr>
<td>N-acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA)</td>
<td>8 ng/mL</td>
<td>2.8</td>
<td>0.0</td>
<td>2.8</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>N-acetyl-S-(3-hydroxypropyl)-L-cysteine (3HPMA)</td>
<td>13 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>N-acetyl-S-(2-carbamoyethyl)-L-cysteine (AAMA)</td>
<td>2.2 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (GAMA)</td>
<td>9.4 ng/mL</td>
<td>30.9</td>
<td>16.2</td>
<td>25.0</td>
<td>19.4</td>
<td>41.7</td>
<td>52.8</td>
</tr>
<tr>
<td>N-acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA)</td>
<td>0.5 ng/mL</td>
<td>2.2</td>
<td>0.0</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>trans,trans-muconic acid (MU)</td>
<td>20 ng/mL</td>
<td>6.6</td>
<td>2.7</td>
<td>28.8</td>
<td>30.6</td>
<td>86.1</td>
<td>36.1</td>
</tr>
<tr>
<td>N-acetyl-S-(phenyl)-L-cysteine (PMA)</td>
<td>0.6 ng/mL</td>
<td>46.9</td>
<td>37.8</td>
<td>94.4</td>
<td>30.6</td>
<td>8.3</td>
<td>19.4</td>
</tr>
<tr>
<td>N-acetyl-S-(3,4-di-hydroxybutyl)-L-cysteine (DHBMA)</td>
<td>5 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>N-acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine (MHBMA3)</td>
<td>0.6 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2-thioxothiazolidine-4-carboxylic acid (TTCA)</td>
<td>3.5 ng/mL</td>
<td>28.2</td>
<td>29.7</td>
<td>22.2</td>
<td>41.7</td>
<td>13.9</td>
<td>33.3</td>
</tr>
<tr>
<td>N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine (HPMMA)</td>
<td>2 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>2-aminothiazoline-4-carboxylic acid (ATCA)</td>
<td>15 ng/mL</td>
<td>7.2</td>
<td>0.0</td>
<td>8.3</td>
<td>5.6</td>
<td>5.6</td>
<td>16.7</td>
</tr>
<tr>
<td>N-acetyl-S-(N-methylcarbamoyl)-L-cysteine (AMCC)</td>
<td>5.5 ng/mL</td>
<td>9.6</td>
<td>0.0</td>
<td>2.8</td>
<td>0.0</td>
<td>2.8</td>
<td>0.0</td>
</tr>
<tr>
<td>N-acetyl-S-(2-hydroxyethyl)-L-cysteine (HEMA)</td>
<td>0.6 ng/mL</td>
<td>48.6</td>
<td>32.4</td>
<td>41.7</td>
<td>27.8</td>
<td>61.1</td>
<td>80.6</td>
</tr>
<tr>
<td>N-acetyl-S-(2-hydroxypropyl)-L-cysteine (2HPMA)</td>
<td>1.3 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Mandelic acid (MA)</td>
<td>12 ng/mL</td>
<td>1.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>N-acetyl-S-(1 and 2-phenyl-2-hydroxyethyl)-L-cysteine (PHEMA)</td>
<td>0.7 ng/mL</td>
<td>61.3</td>
<td>48.6</td>
<td>58.3</td>
<td>55.6</td>
<td>63.9</td>
<td>80.6</td>
</tr>
<tr>
<td>Phenylglyoxylic acid (PGA)</td>
<td>12 ng/mL</td>
<td>9.9</td>
<td>18.8</td>
<td>11.1</td>
<td>8.3</td>
<td>11.1</td>
<td>8.3</td>
</tr>
<tr>
<td>2-methylhippuric acid (2MHMA)</td>
<td>5 ng/mL</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>3-4-methylhippuric acids (34MHA)</td>
<td>8 ng/mL</td>
<td>1.7</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>2.8</td>
<td>5.6</td>
</tr>
<tr>
<td>4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)</td>
<td>0.6 pg/mL</td>
<td>6.6</td>
<td>0.0</td>
<td>2.8</td>
<td>0.0</td>
<td>8.3</td>
<td>22.2</td>
</tr>
<tr>
<td>N'-nitrosoanabasine (NAB)</td>
<td>4.0 pg/mL</td>
<td>47.0</td>
<td>8.1</td>
<td>38.9</td>
<td>25.0</td>
<td>80.6</td>
<td>83.3</td>
</tr>
<tr>
<td>N'-nitrosoanatabine (NAT)</td>
<td>1.6 pg/mL</td>
<td>43.1</td>
<td>5.4</td>
<td>41.7</td>
<td>13.9</td>
<td>75.0</td>
<td>80.6</td>
</tr>
</tbody>
</table>

Cigarette = combustible cigarette; EC = e-cigarette; NRT = nicotine replacement therapy.

* Values are percentages.
† Urinary biomarkers unless otherwise indicated.
‡ Measured in saliva.

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Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis

Eric C Sun,1 Anjali Dixit,2 Keith Humphreys,3 Beth D Darnall,1 Laurence C Baker,4 Sean Mackey1

ABSTRACT
OBJECTIVES
To identify trends in concurrent use of a benzodiazepine and an opioid and to identify the impact of these trends on admissions to hospital and emergency room visits for opioid overdose.

DESIGN

SETTING
Administrative health claims database.

PARTICIPANTS
315 428 privately insured people aged 18-64 who were continuously enrolled in a health plan with medical and pharmacy benefits during the study period and who also filled at least one prescription for an opioid.

INTERVENTIONS
Concurrent benzodiazepine/opioid use, defined as an overlap of at least one day in the time periods covered by prescriptions for each drug.

MAIN OUTCOME MEASURES
Annual percentage of opioid users with concurrent benzodiazepine use; annual incidence of visits to emergency room and inpatient admissions for opioid overdose.

RESULTS
9% of opioid users also used a benzodiazepine in 2001, increasing to 17% in 2013 (80% relative increase). This increase was driven mainly by increases among intermittent, as opposed to chronic, opioid users. Compared with opioid users who did not use benzodiazepines, concurrent use of both drugs was associated with an increased risk of an emergency room visit or inpatient admission for opioid overdose (adjusted odds ratio 2.14, 95% confidence interval 2.05 to 2.24; P<0.001) among all opioid users. The adjusted odds ratio for an emergency room visit or inpatient admission for opioid overdose was 1.42 (1.33 to 1.51; P<0.001) for intermittent opioid users and 1.81 (1.67 to 1.96; P<0.001) chronic opioid users. If this association is causal, elimination of concurrent benzodiazepine/opioid use could reduce the risk of emergency room visits related to opioid use and inpatient admissions for opioid overdose by an estimated 15% (95% confidence interval 14 to 16).

CONCLUSIONS
From 2001 to 2013, concurrent benzodiazepine/opioid use sharply increased in a large sample of privately insured patients in the US and significantly contributed to the overall population risk of opioid overdose.

Introduction
In the US, the increased use of prescription opioids and the resulting potential for addiction and overdose impose substantial public burden of morbidity, mortality, and economic costs. Opioid prescriptions have increased sharply—nearly threefold—over the past fifteen years, with a concurrent increase in opioid related overdoses and deaths. As a result, policymakers and researchers have expended considerable effort towards finding ways to reduce the misuse of, and overdose from, opioids.

Nearly 30% of fatal “opioid” overdoses also involve benzodiazepines, which are often used concurrently with opioids, raising the possibility that some of the increase in opioid related deaths could be caused by increases in concurrent benzodiazepine/opioid use over time. Although benzodiazepines have received less public safety attention than opioids, the combination of the two drugs is dangerous because benzodiazepines potentiate the respiratory depressant effects of opioids. Indeed, the US Food and Drug Administration (FDA) recently released a “black box” caution, warning patients and providers about the potential risks of combined use. Understanding the degree to which concurrent benzodiazepine/opioid use has increased over time, as well as the magnitude of its potential adverse effects, could have important implications for policy and clinical practice. These concerns are particularly salient in the US, but there is also some evidence of high rates of concurrent use internationally. For example, one study found that 47% of patients in methadone treatment programs in Spain also used benzodiazepines, while another study reported that nearly 52% of Swiss patients in methadone treatment programs were “regular” benzodiazepine users. Studies have also found high rates of benzodiazepine use among heroin users in Australia.
A recent study examined the incidence of opioid and benzodiazepine use among the subset of the veteran population who receives care from the Veterans Health Administration (VHA). Nearly 30% of VHA patients who were prescribed opioids also received a concurrent prescription for benzodiazepines, defined as having at least one day’s overlap between a benzodiazepine and opioid prescription in a given calendar year. Moreover, this study found that co-prescribing was associated with a significantly higher risk of death than with the use of opioids alone. Similar results were found in studies examining opioid prescriptions in North Carolina and in Ontario, Canada.

As prescribing behaviors are likely to vary nationally and across clinical settings, however, the applicability of these findings to the broader population (including to veterans, most of whom do not access VHA care) is unclear. For example, compared with the general population, veterans in the US have a higher prevalence of substance misuse and mental health disorders. We focused on concurrent benzodiazepine/opioid use in a privately insured population broadly representative of the entire US, in whom concurrent use was defined as one day of overlap in the time periods covered by each prescription. We have built on previous work by focusing on trends in concurrent benzodiazepine/opioid use over time and their effects on population health, which has not been fully characterized. Using a large dataset of administrative health claims data, we explored trends in concurrent use in 2001-13. In addition, we examined the degree to which patients using these two prescribed drugs have an increased risk of an emergency room visit or inpatient admission for opioid overdose. Finally, we examined the degree to which reducing concurrent use could reduce the risk of emergency room visits and inpatient admissions for opioid overdose at the population level.

Methods

Data

We obtained a sample of administrative health claims provided by Marketscan (Truven Health Analytics, Ann Arbor, MI). Marketscan provides patient level data on use and expenditures for the care of patients enrolled in private insurance plans through a participating employer, health plan, or government organization. The database has grown from six million beneficiaries to comprise over 35 million beneficiaries today. Compared with the general US population, the Marketscan population includes more women, is more likely to come from the southern areas of the US, and is less likely to be drawn from the western areas of the US. The data are frequently used in analyses of healthcare use and spending. Our data include all claims from 1 January 2001 to 31 December 2013, inclusive. As we used de-identified patient data, institutional review board approval was not required.

The information on inpatient and outpatient data claims provided details from specific encounters, including diagnosis codes (ICD-9 (international classification of diseases, ninth edition)), procedure codes (current procedural terminology, CPT), and date of service provision. For the pharmacy claims data, the information provided includes fill date, quantity supplied, and number of days supplied. The data also provide the National Drug Code, which can be linked to Red Book data (Truven Health Analytics, Ann Arbor, MI) to obtain the generic name and dose of the prescribed drug.

Sample

Our initial sample consisted of the 599 410 patients who were continuously enrolled in a plan with medical and pharmaceutical benefits from 1 January 2001 to 31 December 2013. We restricted our analysis to patients who were continuously enrolled during the study period because, as noted above, the set of employers and health plans contributing data to Marketscan has markedly increased over time, leading to a large increase in the number of people in the database. Our approach thus reduces the risk of confounding that might occur because of changes over time in the underlying population reporting data to Marketscan.

From this sample, we identified and excluded patients with a history of cancer or those who received a diagnosis of cancer during the study period (n=28 780) as well as those aged under 18 or over 64 when they first entered the study (n=42 789), giving a sample of 428 419 patients. Our final sample was the subset of patients (315 428) who filled at least one prescription for an opioid during the study period. A flow diagram (fig A) describing the construction of our sample is in the appendix.

Outcomes

Our primary outcome was an emergency room visit or inpatient admission for opioid overdose within a given calendar year. Using methods described elsewhere, we defined opioid overdose to be an admission or visit with ICD-9 codes indicating either opioid related poisoning or a potential opioid related adverse event (such as respiratory depression) and an ICD-9 code corresponding to opioid overdose. For each opioid prescription, we defined a time interval starting the day the prescription was filled and lasting the number of days supplied in the prescription. We counted visits only if they occurred during this time interval or within seven days after the end of this interval. For example, if a patient received an opioid prescription on 1 January 2007 with 10 days’ supply, we counted only visits that occurred between 1 January 2007 and 17 January 2007. In our sensitivity analyses we considered alternative definitions, such as visits occurring within 30 days of the time interval previously described.

Variables

Our key independent variable of interest was whether an opioid user also used a benzodiazepine concurrently within a given calendar year. First, we identified opioid use by isolating all prescriptions for outpatient opioids (table A in appendix), excluding prescriptions containing hydrocodone in a cough/cold formulation. We then isolated all prescriptions for a benzodiazepine (table B in appendix) and directly examined the degree of temporal overlap between prescriptions among individuals who were prescribed benzodiazepines.
who filled a prescription for both classes of drugs. Specifically, for each opioid prescription, we defined an interval in which the prescription took effect as the interval starting on the day the prescription was filled and lasting up to the number of day’s supply provided in the prescription. We defined a similar interval for a benzodiazepine prescription and quantified the total number of opioid prescription days that overlapped with a benzodiazepine prescription days. For example, suppose a given patient filled an opioid prescription and received a 30 day supply on 1 January 2001. If the same individual filled a benzodiazepine prescription on 20 January 2001 with 30 days’ supply, then 11 out of the 30 days of the opioid prescription overlapped with a benzodiazepine prescription. For our baseline analyses, we defined concurrent use as having at least one day of overlap in a given calendar year,26,39 in line with previous studies. We also considered alternative definitions of concurrent opioid/baseline in our sensitivity analyses.

Our analysis included several controls for patients’ demographics and health. Age and sex were directly obtained from the claims data. ICD-9 diagnosis codes were used to control for comorbidities including diabetes mellitus and congestive heart failure (table 1 provides a full list of comorbidities).40 For each comorbidity, we identified the earliest year with at least two claims containing the associated ICD-9 codes (table B in appendix) and defined the patient as having a history of the given comorbidity from that year onwards. Finally, we also controlled for total healthcare spending in the time period before the first opioid prescription in a given year. To do so, we isolated all pharmacy, inpatient, and outpatient claims submitted before the earliest opioid prescription in a given year. We then summed the spending across all these claims and divided by the number of calendar days in the interval between 1 January of the given year and the date of the earliest opioid prescription.

Analyses

We first calculated the annual percentage of opioid users with concurrent benzodiazepine use. We stratified our analysis by intermittent and chronic opioid users. Following previous work,30 chronic users were defined as patients who filled more than 10 prescriptions or had more than 120 days’ supply in a given year, with the remaining opioid users being defined as intermittent users. Because our study sample consisted of patients who were continuously enrolled during the study period, the average age of our population increased by one year annually. Therefore, we calculated age adjusted estimates using methods described in the appendix.

We then used multivariate logistic regression to estimate the association between concurrent benzodiazepine/opioid use and opioid overdose among opioid users. The dependent variable in this regression was an indicator variable that equaled 1 if the patient had at least one emergency room visit or admission for opioid overdose (using the methods described above) in the given calendar year and 0 otherwise. Our independent variable of interest was an indicator variable that equaled 1 if the opioid user met the criteria for concurrent benzodiazepine use in the given year and 0 otherwise. We also included controls for age, year, and the set of additional variables in table 1.

Finally, we calculated the population attributable fraction (PAF) of concurrent benzodiazepine/opioid use to the risk of opioid overdose. This fraction represents the relative risk reduction for a given event at the population level under a counterfactual scenario for a specific risk factor. For example, the population attributable fraction has been used to describe the degree to which low birth weight would be reduced if maternal smoking could be eliminated entirely.41 In our case, we calculated the population level risk reduction that would occur if concurrent benzodiazepine/opioid use could be

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Table 1 | Characteristics of study population with any opioid use at start of study period (2001) according to concurrent filled prescription for benzodiazepine. Figures are numbers (percentage; 95% CI) of patients meeting criteria (unless stated otherwise)

<table>
<thead>
<tr>
<th></th>
<th>No benzodiazepine (n=53 389)</th>
<th>With benzodiazepine (n=5425)</th>
<th>P value for difference between groups</th>
<th>Hedge's g for standardized difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>23 194 (43; 43 to 44)</td>
<td>1888 (35; 34 to 36)</td>
<td>&lt;0.001</td>
<td>−0.30</td>
</tr>
<tr>
<td>Mean age (years)*</td>
<td>42.4 (42.4 to 42.5)</td>
<td>44.5 (44.4 to 44.7)</td>
<td>&lt;0.001</td>
<td>0.18</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>79 (0.15; 0.12 to 0.18)</td>
<td>42 (0.77; 0.54 to 1.01)</td>
<td>&lt;0.001</td>
<td>−0.14</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>81 (0.15; 0.12 to 0.18)</td>
<td>22 (0.41; 0.24 to 0.58)</td>
<td>&lt;0.001</td>
<td>−0.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3686 (6.9; 6.7 to 7.1)</td>
<td>516 (9.5; 8.7 to 10)</td>
<td>&lt;0.001</td>
<td>−0.10</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1041 (2.0; 1.8 to 2.1)</td>
<td>252 (4.7; 4.1 to 5.2)</td>
<td>&lt;0.001</td>
<td>−0.19</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1813 (3.4; 3.2 to 3.6)</td>
<td>259 (4.8; 4.2 to 5.3)</td>
<td>&lt;0.001</td>
<td>−0.07</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>77 (0.14; 0.11 to 0.16)</td>
<td>12 (0.22; 0.096 to 0.35)</td>
<td>0.16</td>
<td>−0.02</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1010 (19; 0.15 to 0.23)</td>
<td>35 (0.65; 0.43 to 0.86)</td>
<td>&lt;0.001</td>
<td>−0.10</td>
</tr>
<tr>
<td>Dementia</td>
<td>66 (0.12; 0.09 to 0.15)</td>
<td>15 (0.28; 0.14 to 0.42)</td>
<td>&lt;0.001</td>
<td>−0.04</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>69 (0.13; 0.10 to 0.16)</td>
<td>22 (0.41; 0.24 to 0.58)</td>
<td>&lt;0.001</td>
<td>−0.07</td>
</tr>
<tr>
<td>Liver disease</td>
<td>251 (0.47; 0.41 to 0.53)</td>
<td>76 (1.6; 1.1 to 1.7)</td>
<td>&lt;0.001</td>
<td>−0.12</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>162 (0.30; 0.26 to 0.35)</td>
<td>61 (1.1; 0.86 to 1.4)</td>
<td>&lt;0.001</td>
<td>−0.13</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>318 (0.22; 0.18 to 0.26)</td>
<td>63 (1.2; 0.88 to 1.5)</td>
<td>&lt;0.001</td>
<td>−0.17</td>
</tr>
<tr>
<td>Psychosis</td>
<td>67 (0.13; 0.10 to 0.16)</td>
<td>30 (0.55; 0.36 to 0.75)</td>
<td>&lt;0.001</td>
<td>−0.11</td>
</tr>
<tr>
<td>Depression</td>
<td>2362 (6.4; 6.3 to 6.6)</td>
<td>915 (17.16 to 18)</td>
<td>&lt;0.001</td>
<td>−0.55</td>
</tr>
<tr>
<td>Mean daily health spending ($)*</td>
<td>$21.83 (20.91 to 22.74)</td>
<td>$33.62 (29.22 to 38.02)</td>
<td>&lt;0.001</td>
<td>−0.10</td>
</tr>
</tbody>
</table>

*Mean and 95% CI only.
eliminated entirely. These estimates were calculated by using the results from the logistic analyses described above, following methods described elsewhere.42–43

Because the unit of observation in our data is a person-year, patients will contribute multiple observations if they used opioids in more than one calendar year. We therefore adjusted our standard errors for clustering at the patient level.44 All analyses were performed with Stata 14.0 (College Station, TX).

Sensitivity analyses
We conducted several sets of sensitivity analyses. First, in our baseline analyses we defined concurrent benzodiazepine/opioid overdose as requiring at least one day of overlap; we considered an alternative (stricter) definition that required 25% of the days’ supply of opioids to overlap with a benzodiazepine prescription. Similarly, our baseline analyses defined an opioid overdose as an emergency room visit or admission occurring during the time interval covered by an opioid prescription or within seven days after the end of the prescription; we considered alternative definitions that both loosened (allowing a visit to occur within 30 days after the time interval covered by an opioid prescription) and tightened (requiring the visit to occur exactly during the interval covered by an opioid prescription) this criterion.

Second, a potential issue arises because our sample was constructed as a set of individuals who were continuously enrolled between 2001 and 2013. The advantage of this approach is that allows us to follow a uniform set of people over time. By contrast, other approaches—such as including all patients regardless of enrollment duration—would have the drawback of having to deal with a changing population over time as people enter and exit the sample. Restriction to people who did not leave the sample (because of death or loss of employment), however, could lead to bias because people who die (or lose employment) secondary to opioid use would probably have experienced a series of emergency room visits or inpatient admissions for opioid overdose before the actual event. To the degree that the concurrent benzodiazepine/opioid use increases the risk of these events (and of attrition), our approach will therefore underestimate the true effect of concurrent use (as our sample is limited to people who did experience these events, but not enough to result in death or loss of employment). To deal with this, we conducted a secondary analysis using a broader sample consisting of all people who were continuously enrolled for at least two years (n=3 810 747). Each individual remained in the sample until the study end date or until they exited the sample. Thus, this broader sample includes our original sample as well as patients who subsequently entered and exited the sample.

Finally, one potential source of bias is that opioid users who concurrently used benzodiazepines could differ from those who did not. We performed a residual confounding analysis45–46 to investigate the extent to which our results could be explained by other unobservable factors, such as differences in health status between the two groups. Specifically, we assumed the presence of an unmeasured binary confounder that was patient specific and independent of our measured confounders. We assumed that this confounder had a prevalence of 75% among our surgical sample and 0% among the non-surgical patients. The assumed difference in prevalence between surgical and non-surgical patients of this unmeasured confounder is much larger than the difference in prevalence for all the medical comorbidities we examined. Using methods described elsewhere, we then estimated the degree of confounding that would be necessary for this confounder to eliminate the estimated association between opioid overdose and concurrent benzodiazepine/opioid use.46

Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results
Table 1 shows descriptive statistics for patients who filled at least one prescription for an opioid during the year, stratified by whether those patients also filled at least one prescription for a benzodiazepine. Among opioid users, patients who also filled a prescription for a benzodiazepine were older (44.5 v 42.4, P<0.001) and less likely to be men (35% v 43%, P<0.001) compared with those who did not. In addition, the prevalence of every comorbidity examined was significantly higher (P<0.001) among opioid users who also filled prescriptions for a benzodiazepine. Given our large sample size, we are likely to find many differences between the two groups that are small in magnitude but nonetheless significant. We therefore calculated the standardized difference between the two groups using Hedge’s g (table 1).

Overall, the differences between the two groups for most of the characteristics were of modest magnitude (<0.2 SD), with the exception of depression (roughly 0.5 SD).

The proportion of opioid users who were co-prescribed benzodiazepines nearly doubled from 9% (5425/53 389) in 2001 to 17% (14 415/85 617) in 2013 (fig 1). Most of this growth occurred among intermittent opioid users, in whom the percentage of patients who also used a benzodiazepine increased from 7% (4122/55 960) to 13% (9292/65 114) during the study period. By contrast, although a higher percentage (46%; 1596/34 57) of chronic opioid users also used benzodiazepines in 2001, this percentage remained fairly constant during the study period.

Among all opioid users who did not use benzodiazepines, the age adjusted incidence of emergency room visits or inpatient admissions for opioid overdose increased from 1.08% (95% confidence interval 0.99% to 1.16%) in 2001 to 1.35% (1.26% to 1.43%) from 2001 to 2013 (fig 2). For intermittent opioid users who did use benzodiazepines, the age adjusted incidence of opioid overdose increased from 1.05% (0.96% to 1.14%) to 1.15% (1.06% to 1.23%) during this time period, and
Figure 1: Annual age-adjusted prevalence of concurrent benzodiazepine/opioid use, 2001-13. Concurrent use was defined as having at least one day of overlap between time covered by prescriptions.

Figure 2: Unadjusted incidence of opioid overdose for patients using opioids with or without benzodiazepines in 2001-13 stratified by intermittent v chronic benzodiazepine/opioid use and concurrent benzodiazepine/opioid use.

Figure 3: Adjusted incidence of opioid overdose for patients taking opioids with and without benzodiazepines. Adjusted incidence incorporates controls for year, sex, age, and characteristics listed in table 1 (95% confidence intervals calculated with SE clustered at patient level).

Among chronic opioid users who did not use benzodiazepines, the incidence increased from 2.00% (1.30% to 2.70%) to 3.51% (3.05% to 3.98%). As shown in figure 2, the age-adjusted incidence of opioid overdose was higher among concurrent benzodiazepine/opioid users. For example, among all opioid users who also used benzodiazepines, the age-adjusted incidence of opioid overdose was 2.01% (1.64% to 2.39%) in 2001 and 3.99% (3.58% to 4.21%) in 2013.

Among all opioid users, the annual adjusted incidence of an emergency room visit or inpatient admission for opioid overdose was 1.16% (95% confidence interval 1.13% to 1.18%; fig 3) for those who did not use a benzodiazepine compared with 2.42% (2.32% to 2.51%) among concurrent benzodiazepine/opioid users, a significant difference (odds ratio 2.14, 95% confidence interval 2.05 to 2.24; P<0.001). Intermittent opioid users who used a benzodiazepine concurrently also experience a higher incidence of emergency room visits or inpatient admissions for opioid overdose (1.45%, 1.36% to 1.51%) compared with intermittent opioid users who did not use a benzodiazepine concurrently (1.02%, 0.996% to 1.04%), with an odds ratio of 1.42 (1.33 to 1.51; P<0.001). Chronic opioid users with concurrent benzodiazepine use also experienced a higher adjusted incidence of emergency room visits or inpatient admissions for opioid overdose (5.36%, 5.12% to 5.61%) compared with those who did not use benzodiazepines (3.13%, 2.94% to 3.31%), with an odds ratio of 1.81 (1.67 to 1.96; P<0.001).

Using the logistic regression model results, we estimated the population attributable fraction for benzodiazepine co-prescribing to be 0.15 (95% confidence interval 0.14 to 0.16) among all opioid users, suggesting that eliminating concurrent benzodiazepine/opioid use could reduce the population risk for an opioid-related emergency room visit or inpatient admission by 15%. Among intermittent opioid users, the population attributable fraction was 0.043 (0.034 to 0.051), whereas the population attributable fraction was 0.27 (0.23 to 0.30) for chronic users.

We conducted three sets of sensitivity analyses. First, we considered alternative measures of concurrent benzodiazepine/opioid use (requiring 25% of the days of opioid to overlap with a benzodiazepine prescription) as well as alternative measures of opioid overdose. The results were qualitatively similar to our main results (appendix).

A second set of analyses examined whether imposing the requirement that our study population be continuously enrolled from 2001 to 2013 could have resulted in bias. This set of analyses used a broader sample, consisting of the patients in our original sample as well as patients who were continuously enrolled for at least two years but who might have subsequently left the sample. Among this larger sample, the adjusted relative risk was 1.66 for intermittent users (95% confidence interval 1.64 to 1.69; P<0.001) and 1.61 (1.58 to 1.63; P<0.001) for chronic users.

Finally, we performed a residual confounding analysis to estimate the degree of confounding that would need to be present to explain our results. Assuming the presence of an unmeasured binary confounder with a prevalence of 75% among concurrent benzodiazepine/opioid users or a prevalence of 0% among persons with no concurrent use, our analysis suggested that residual confounding would negate our results only if the odds ratio associated with the unmeasured confounder was at least 2.40. The odds ratio associated with this confounder would need to be at least 1.45 among intermittent users and at least 1.89 among chronic users.

Discussion

Principal findings

In a sample of privately insured patients, we found that the incidence of concurrent benzodiazepine/opioid use increased by roughly 80% from 2001 to 2013. Moreover, we found that opioid users who concurrently used benzodiazepines were at an increased risk of opioid overdose and that eliminating concurrent benzodiazepine/opioid use could reduce the risk of opioid overdose by 15%. Opioid use was defined as having at least one day of overlap between time covered by prescriptions.
prescribing, use, and overdose are receiving increased attention given the sharp increase in the number of opioid related adverse events over the past decade. Understanding the underlying causes for these secular increases in opioid related events is an important step towards developing policies aimed at reducing their incidence.

Comparison with other studies
A previous study of patients receiving care from the Veteran’s Administration found that 27% of opioid users also received benzodiazepines and that concurrent opioid/benzodiazepine use was associated with an increased risk of death from opioid overdose.26 Another study found that nearly 80% of patients taking an opioid also used a benzodiazepine and that those who used both drugs concurrently were at a tenfold increased risk of death from overdose,26 although in that study concurrent use was defined as having used an opioid and benzodiazepine at least once in a given year, without an attempt to identify the extent of overlap between the periods of opioid and benzodiazepine use. Using toxicology analysis, another study found that benzodiazepines were involved in 60% of deaths from opioid overdose in patients in Ontario, Canada.27

We also found that concurrent opioid/benzodiazepine use was fairly common; differences in the magnitude of concurrent use between our studies and previous work is possibly because of differences in the definition of concurrent use as well as differences in the underlying patient population. Our study builds on these results by examining growth in concurrent use over time and estimating the effect of this growth on population health. Moreover, we examined concurrent use in a national sample that is broadly representative of the privately insured population in the US.

Strengths and limitations of this study
Our results should be viewed in the light of the study’s limitations. First, we cannot exclude the possibility of confounding because of unobservable differences between opioid users who did and did not use benzodiazepines. While we dealt with this issue by adjusting for an extensive set of covariates and comorbidities, we cannot exclude the possibility of further confounding. We did, however, perform a residual confounding analysis to judge the extent of confounding that would be needed to explain our results. Our analysis suggested that any unobserved confounder would need to exert effects larger than the estimated effect for concurrent benzodiazepine/opioid use and be unequally distributed across concurrent and non-concurrent users to a far larger extent than any of the potential measured confounders we considered, a scenario we consider to be unlikely.

Second, the construction of our sample—which required people to be continuously enrolled for the entire 13 year period—could also result in confounding as it excluded those who might have left the sample secondary to opioid related death or job loss. To deal with this issue, we performed sensitivity analyses in which we added to our original sample individuals who were continuously enrolled for at least two years but who might have subsequently left the sample secondary to death or job loss. The point estimates for this set of sensitivity analyses were qualitatively similar to our baseline estimates.

Third, we note that our analysis examined only cases of opioid overdose/poisoning when a patient received emergency room/hospital care and ultimately survived, which could mean that our analysis underestimated the true risk of opioid overdose.

Fourth, our analysis does not take into account changes in prescribing/patient behaviors that could evolve in response to reduced concurrent benzodiazepine/opioid prescribing. For example, if patients increase their dose of opioids in response to a reduction in concurrent benzodiazepine/opioid prescribing, this would mitigate some of the benefits we observed in the study.

Finally, we note that a prescription database would not capture heroin use or the use of prescription drugs bought illegally.

Conclusions and policy implications
These findings have several implications. From a clinical perspective, providers should exercise caution in prescribing opioids for patients who are already using benzodiazepines (or vice versa), even in a non-chronic setting. Indeed, we note that the association between concurrent benzodiazepine/opioid use and the risk of opioid overdose was broadly similar for both intermittent and chronic opioid users. Therefore, opioids should be prescribed cautiously—even if only for a short term course—among patients who are also using benzodiazepines. From a policy perspective, in addition to the current focus on opioid prescribing, policymakers and healthcare systems should also focus on benzodiazepine prescribing behaviors, as these behaviors can play an important role in mitigating the risks of opioid prescriptions. Healthcare systems might also want to implement education programs that warn prescribers and patients about the risks of taking benzodiazepines and opioids concurrently, with the Veterans Health Administration’s system-wide opioid safety initiative being a potential model to emulate.

Contributors: All authors contributed to the design and conduct of the study, data collection and management, analysis interpretation of the data, and preparation, review, or approval of the manuscript. ECS is guarantor.

Funding: ECS was supported by a mentored research training grant from the Foundation for Anesthesia Education and Research and the Anesthesia Quality Institute. KNH was supported by funding from the Veterans Affairs health services research and development service. The research conducted was independent of any involvement from the sponsors of the study. Study sponsors were not involved in study design, data interpretation, writing, or the decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support provided by grants from the Foundation for Anesthesia Education and Research; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required as patient data were de-identified.

Data sharing: No additional data available.

Transparency statement: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being...
reported; that no important aspects of the study have been omitted; and that any discrepancies are disclosed.

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New Developments in Osteoporosis: Screening, Prevention and Treatment

Judith Walsh, MD, MPH
Departments of Medicine and Epidemiology and Biostatistics
UCSF

Osteoporosis: Overview

• Definitions
• Risk factors
• Screening and Monitoring
• Treatment

Background

• Hip and vertebral fractures are associated with premature mortality
• Any fracture is associated with an increased risk of 5-10 year mortality
• A subsequent fracture is associated with an increased mortality risk for 5 more years
  » Dubbo Osteoporosis Epidemiology Study

Osteoporosis: Definitions

• Normal: BMD no lower than 1 SD below mean for young adult women
• Osteopenia (Low bone mass): BMD 1.0-2.5 SD below the mean for young adults
  – (T=-1 to -2.5)
• Osteoporosis: BMD more than 2.5 SD below young adult mean
  – (T<-2.5)
Osteoporosis: Definitions

- T scores vs. Z scores
- T scores compare the patient with the average young adult female
  - Useful for treatment decisions
- Z scores compare the patient with an age matched female
  - Useful for ruling out secondary causes of bone loss

Risk Factors

- Age
  - Risk of hip fracture increases with age
  - Older women have a much higher fracture rate than younger women with the same bone density
- Vertebral fractures: very high risk
  - Even if asymptomatic
  - 20% risk of new fracture in the year following a fracture

10-Year Fracture Probability Age vs. Femoral Neck T-score

**Risk Factors in the WHO Risk Factor Assessment Tool**

- Age
- Gender
- Personal history of fracture
- Low body mass index
- Oral glucocorticoids
- Secondary osteoporosis
- Parental history of hip fracture
- Current smoking
- Alcohol intake of 3 or more drinks per day
- Femoral neck BMD

**Drugs Associated with an Increased Risk of Osteoporosis**

- Thyroid hormone (over replacement)
- Aromatase inhibitors
- SSRIs
- PPIs
- Androgen deprivation agents
- Thiazolidinediones
- Anticonvulsants

**Screening and Monitoring**

**Question**

- Which of the following women would you screen for Osteoporosis?
  a) 66 year old healthy woman
  b) 57 year old healthy woman who does not exercise
  c) 55 year old woman whose mother had a hip fracture
  d) a and c
  e) a, b and c
Screening for Osteoporosis

- Bone density is the single best predictor of future fracture
  - Hip BMD is best predictor of hip fracture
- Central dual x-ray absorptiometry (DXA) of spine, hip and body most commonly used and preferred when available

NOF : BMD Screening

- Women age 65 and older, men >70 regardless of risk factors
- Adults who have a low trauma fracture after age 50
- In postmenopausal women age 50 to 64
  - Adults with a condition (e.g., RA) or taking a medication associated with low BMD or bone loss
    - ≥ 5 mg prednisone QD or equivalent for ≥ 3 months
  - Historical height loss of 1.5 inches or more (4 cm)
  - Prospective height loss of 0.8 inches or more (2 cm)

Case

- Bonnie Bony is a 68 year old woman who wants to know when she should have her next bone mineral density test. Her last BMD was 2 years ago and showed Osteopenia with a t score of -1.8. What do you tell her?

Choices

1) Let's schedule it now
2) We should do it in 2 years
3) We should do it in 3 years
4) We should do it in 5 years
5) I have no idea...when do you want to do it?
USPSTF Recommendations

- Screen all women age 65 and older
  - Evidence for screening is indirect
- Screen younger women whose fracture risk is equal to or greater than a 65 year old white woman who has no additional risk factors
- “Evidence is lacking about optimal intervals for repeated screening”
  - A minimum of 2 years may be needed to reliably measure a change in BMD
  - Longer intervals may be needed to improve fracture risk prediction

BMD Testing

- Medicare pays for BMD every two years regardless of baseline BMD
- Is repeat BMD useful?
- Does change in BMD provide additional information about fracture risk?

The News

- Bone-density testing interval and transition to osteoporosis in older women.
  - Gourlay et al. NEJM 2012
- Aim: To determine how the BMD testing interval relates to the timing of the transition from normal BMD or osteopenia to the development of osteoporosis before a hip or vertebral fracture occurs

Methods

- 4,597 women from the Study of Osteoporotic Fractures (SOF)
  - Aged 65 and older, population based
  - Study examinations at year 2, 6, 8, 10 and 16
- Outcome: Estimated interval for 10% of individuals to make transition from normal BMD or osteopenia to osteoporosis before a hip or clinical vertebral fracture or treatment for Osteoporosis
Results

- Within each t score range, a percentage of women developed osteoporosis over 15 years
  - Normal 0.8%
    - (-1.00 or higher)
  - Mild Osteopenia 4.6%
    - (-1.01 to -1.49)
  - Moderate Osteopenia 20.9%
    - (-1.50 to -1.99)
  - Advanced Osteopenia 62.3%
    - (-2.00 to -2.49)

Results/Competing Risk Analyses

- Adjusted interval between baseline testing and the development of osteoporosis in 10% of study participants
  - Normal BMD 16.8 (11.5-24.6) yrs
  - Mild Osteopenia 17.3 (13.9-21.5) yrs
  - Moderate Osteopenia 4.7 (4.2-5.2) yrs
  - Advanced Osteopenia 1.1 (1.0-1.3) yrs

Conclusions

- Osteoporosis would develop in <10% of individuals during rescreening intervals of 15 years for women with normal BMD or mild osteopenia, 5 years for women with moderate osteopenia and 1 year for women with advanced osteopenia

- Future screening recommendations will probably be based on likelihood of osteoporosis progression based on initial BMD

Take Home Message

- Decisions about when to rescreen should be based on the results of initial screening
- Few women with normal BMD will develop osteoporosis at 15 year follow-up
- Back to Bonnie: Would probably wait at least 5 years from her prior BMD
Repeat BMD Screening: The News

- Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture.
- Aim: To determine whether BMD changes after 4 years provide additional information on fracture risk and to quantify the change in fracture risk classification after a second BMD measure

Methods

- Framingham Osteoporosis Study population based cohort of 310 men and 492 women
  - Two BMD measures from 1987 to 1999
- Outcome: risk of hip or major osteoporotic fracture through 2009 or 12 years after second BMD measure
- Net Reclassification Index (NRI):
  - Quantifies change in risk classification after a second BMD measure
  - High risk: Risk of hip fracture 3% or greater or major osteoporotic fracture 20% or greater (vs low risk)

Results

- Mean age 74.8 years
- Mean BMD change -0.6% per year
- Median follow up 9.6 years
- NRI increased proportion classified as high risk by 3.9% and decreased the proportion defined as low risk by 2.2%
- Adding BMD change to a model that included baseline BMD did not improve performance of the ROC curve
  - AUC baseline 0.71 (0.65-0.67) vs 0.72 (0.66-0.79)

ROC Curves for Hip and Major Osteoporotic Fractures

Figure Legend:
Receiver Operating Characteristic Curves for Models Investigating Fracture in Older Adults From the Framingham Osteoporosis Study. BMD indicates bone mineral density. All models are adjusted for age, sex, body mass index, weight loss (per pound), and history of fracture measured at the time of the second BMD test. Models are defined in the Methods section.
Conclusion and Take Home Message

• In untreated men and women with a mean age of 75, a repeat BMD after 4 years did not meaningfully improve the prediction of major hip or Osteoporotic fracture.
• Repeating a BMD after 4 years to improve fracture risk prediction may not be necessary in adults of this age untreated for osteoporosis.

Monitoring Guidelines

• Monitoring for those on osteoporosis treatment:
  – What is “treatment failure”?
• ISCD: DEXA spine and hip when expected change in BMD exceeds LSC expected on bone densitometer
  – Every 1-2 years and less often when stable
• NAMS: DEXA hip every 2 years
• Question: What are you going to do?

Monitoring Guidelines

• Prior guidelines recommend follow-up monitoring but no consensus on site or frequency
• New ACP Guidelines for women on osteoporosis treatment
  – No bone density monitoring during the 5 year treatment period

OSTEOPOROSIS

Absolute Risk Assessment
WHO Fracture Risk Algorithm

- FRAX
- Calculate the 10 year probability of a hip fracture and the 10 year probability of any osteoporotic fracture
- Includes femoral neck BMD and risk factors
- Can be used only in previously untreated patients
- Can be used with or without BMD
- Algorithm adapted for the U.S.
- Available as an iPhone app

WHO Fracture Risk Algorithm

- Most useful in identifying individuals in the osteopenia range who are most likely to benefit from treatment
- Treat when there is a 10 year risk of hip fracture ≥3% or a 10 year risk of a major Osteoporosis-related fracture that is ≥20% based on the U.S. adapted WHO algorithm
- In the future some BMD machines may be able to provide a report with absolute fracture risk
Question

Mrs. P is a 66 year old woman who has no previous fracture or other risk factors. Her hip BMD t score is -2.3. She is on no medications. What are your next steps?

a) Discuss Calcium and Vitamin D intake
b) Start Raloxifene 60 mg per day
c) Start Alendronate 70 mg per week
d) a and c

NOF Treatment Guidelines

- Prior hip or vertebral fracture
- Other prior bone fracture, or
- Secondary medical condition, or
- Elevated 10 year fracture risk

T-Score

-0 -1.0 -1.5 -2.0 -2.5 -3.0

No Risk Factors

NOF: Vertebral Imaging

- Vertebral fractures indicate very high risk
- Consider in women age 70 and over and men aged 80 and over with BMD T score ≤-1.0
- Consider in women aged 65-69 and men aged 70-79 with BMD T score ≤-1.5
- Consider
  - Low trauma fracture during adulthood
  - Long term glucocorticoid use
  - Height loss
  - Historical ≥ 1.5 inch
  - Prospective ≥ 0.8 inch
- No evidence for treatment initiation based on these criteria
**NOF: Osteoporosis Prevention**

- Preventive measures for everyone:
  - Calcium: diet alone or with supplements
    - 1,000 to 1,200 mg a day
  - Vitamin D intake of 800-1,000 IU a day
  - Weight bearing and muscle strengthening exercise to improve agility, strength, posture and balance, increase bone density and avoid falls and fractures
  - Assess fall risk and appropriate modifications
  - Avoid tobacco and excessive alcohol
  - Hip protectors for some at risk?

**Calcium/Vitamin D**

- Women should ideally get RDA for calcium and Vitamin D from diet
- Previous studies have suggested that calcium/Vitamin D are necessary but not sufficient
  - Even if a woman is receiving adequate calcium and Vitamin D, she may still be at risk for fracture
  - Additional therapies (e.g. anti-resorptive therapies) may also be necessary

**What do you most commonly use for treatment of Osteoporosis?**

- Weekly bisphosphonate
- Monthly bisphosphonate
- Yearly bisphosphonate
-Raloxifene
-PTH
-Denosumab

**Pharmacologic Therapies**

- Estrogen
- Bisphosphonates
- Calcitonin
-SERMs
-Parathyroid hormone
-Denosumab
Estrogen

- 50% reduction in hip and other non-spine fractures in observational studies
- Estrogen reduced the risk of new vertebral fractures by half in two RCTs
- Reduced hip fracture risk by 34% in WHI
  - No overall benefit even in women at high risk for osteoporosis
- USPSTF does not recommend the use of estrogen for the treatment of any chronic disease
  - Some women may be taking estrogen for other reasons

Bisphosphonates

- Four approved: Alendronate, Risedronate, Ibandronate, Zolendronate
- Increase BMD by 3% per year
- Reduce fracture risk
  - All reduce vertebral fracture
  - All but Ibandronate reduced non-vertebral fracture (including hip fracture)
- Therapeutic effects with 10 year use of alendronate
- Gradual loss of effect with discontinuation of medication

Bisphosphonates: Adverse Effects

- Osteonecrosis of the jaw
- Femoral shaft fractures

Potential Long-term Side Effect of Bisphosphonates?
Osteonecrosis of the Jaw

- Associated with potent bisphosphonate use:
  - 94% treated with IV bisphosphonates
  - 4% of cases have OP, most have cancer
  - 60% caused by tooth extraction.
- Extremely rare
  - Estimated risk in those treated for osteoporosis
    - 1/10,000 to 1/100,000 person years
- Dental exam recommended before Rx, but no need to stop for dental procedures

Ann Intern Med, 2006
ADA Guidelines, 2011

Osteonecrosis of the Jaw

- 7332 patients receiving oral alendronate in Taiwan
  - 40 cases of ONJ
  - 22 had preceding invasive dental procedures
- Risk increased with longer duration of therapy
  - 0.23% to 0.92% as duration went from 2-10 years
- Risk factors: advanced age, diabetes, rheumatoid arthritis and duration of use
  » Chiu, J Clin Endocrinol Metab 2014

Atypical Femoral Fractures (AFF)

- Long-term BP users (and others)
- Transverse not spiral, cortical thickening, minimal trauma
- Often bilateral, prodromal pain, abn. imaging (x-ray, bone scan/MR)
- ASBMR Task Force (2013)
  Stress fractures. Micro damage?
  Clinical studies: RR for BPs = 2-50
  Risk goes up with longer use and down 1 year after stopping

Re-analysis of Data in 3 RCTs

- 284 hip or femur fractures in 14,195 women
  - 12 were atypical
- Relative hazards
  - RH 1.03 (95% C.I. 0.06, 16.46) for Alendronate in FIT
  - RH 1.50 (95% C.I. 0.25, 9.00) for Zolendronic acid in HORIZON-PFT
  - RH 1.33 (95% C.I. 0.12, 14.67) for continued Alendronate in FLEX
- Conclusions
  - Fracture of subtrochanteric or diaphyseal femur was rare even in women on bisphosphonates for up to 10 years
  - No significant increase in risk but wide confidence intervals

Black et al NEJM 2010
The News

• Risk of hip, subtrochanteric and femoral shaft fractures among mid and long term users of alendronate: nationwide cohort and nested case control study
  – Abrahamsen et al BMJ 2016
• Objective: To determine overall safety and efficacy of long term use of alendronate in patients with osteoporosis

Methods

• Nationwide population based study in Denmark
• 61,990 men and women aged 50-94 at the start of treatment who had not previously taken alendronate
• Outcomes
  – Fracture of hip, subtrochanteric femur or femoral shaft
• Non-fracture controls matched by sex, year of birth and year of alendronate initiation

Results

• Incidence of subtrochanteric/femoral neck fracture
  – 3.4/1000 person years (95% CI: 3.2-3.6)
• Incidence of hip fracture
  – 16.2/1000 person years (95% CI: 15.8 to 16.6)
• Risk no higher in long term users than in current or past users
• Higher medication adherence and longer duration of use were associated with a reduced risk of hip fracture
  – 0.73 (95% CI: 0.68 to 0.78) for MPR >80%
  – 0.74 (95% CI: 0.56 to 0.97) for use ≥10 years

Conclusion

• The benefit/risk ratio supports a benefit of alendronate even with use for more than 10 years
Take Home

- The overall benefit to risk ratio is favorable for alendronate, even with long term use.
- Long term alendronate use will avert many more hip fractures than will it cause atypical femoral fractures.

Case

- Francis Fragile is a 76 year old woman who has been on alendronate for 5 years after having a hip T-score of -2.8. She also has diabetes and hypertension. Her best friend, Veronica Vertebrae, just stopped her bisphosphonate because she had been on it “long enough.” Bonnie wants to know if she should continue taking the alendronate or whether she should stop. What do you tell her?

What do you tell her?

1) Yes, everyone should stop after 5 years of treatment
2) No, you should continue the medication
3) We can stop it if you are having a dental procedure
4) Let’s repeat your bone density and decide
5) I’m not sure. What do you want to do?

FDA View of Long-term Bisphosphonate Use (Sept. 2011)

- Independent review of epidemiologic studies to date and all bisphosphonate trial data...
- FDA conclusions about atypical fractures
  - “conflicting results...causality uncertain”
  - “no agreement on effects of duration or cumulative dose”
- FDA conclusions about ONJ
  - “some evidence that risk increases after 4 yr.”
  - “causality not established”

www.fda.gov, 2011
Bisphosphonates: Duration of Use

- “Bisphosphonates may be safely discontinued in some patients without compromising therapeutic gains but no adequate clinical trials have yet delineated how long the drugs’ benefits are maintained after cessation.”
- "Important Limitation of Use Statement"
  - Optimal duration of use has not been determined
  - Periodic re-evaluation of continued need

The News

- Objective:
  - To provide guidance on bisphosphonate therapy duration with a risk-benefit perspective

Background

- Fracture risk increases with age
- Does continued bisphosphonate therapy continue to confer benefit?
  - Long half life
- Rare but real side effects
  - Jaw osteonecrosis
  - Atypical femoral fractures
- How long should women remain on therapy?
  - Drug holidays?
- FDA “Limitation of Use Statement”
  - Optimal duration of use has not been determined
  - “All patients on bisphosphonates should have the need for continued therapy reevaluated on a periodic basis”

Methods

- Systematic literature reviews
  - Two RCTS (FLEX and HORIZON) provide evidence on long term use
- Evaluation of benefits and risks of bisphosphonates and alternatives
Recommendations

- After 5 years of oral bisphosphonates or 3 years of IV bisphosphonates, reassessment of risk should be considered
  - In women at high fracture risk, consider continuation of oral BP for 10 years or IV BP for 8 years
    - High risk based on age (>70 or 75), medication use, new dx of disorder associated with secondary osteoporosis
    - Clinician deemed high risk based on femoral neck T score, age or other risk factors
  - For women not at high fracture risk after 3-5 years of treatment, consider a drug holiday of 2-3 years
- For high risk women, risks of atypical femoral fracture and ONJ are outweighed by reduction in vertebral fracture

What is “high risk?”

- Older women (>70 or 75)
- Low hip T score or high fracture risk score (FRAX criteria)
- Previous osteoporotic major fracture
- Fracture on therapy
- Limitations
  - Limited evidence
  - White postmenopausal women
  - Vertebral fracture reduction only

Impact for practice

- Patients at “low risk” may safely have bisphosphonates discontinued
  - Younger, no fracture history, medication was started for osteopenia, BMD approaching normal?
- Patients at “increased risk” may benefit from continued therapy
  - Older, history of fracture, BMD remaining in osteoporotic range?
- Decisions about when to restart?
  - Role of BMD
  - Currently, no evidence to support use of bone turnover markers

Back to Francis

- Francis is “high risk” based on her age
- Reasonable to continue for 10 years
- Consider BMD?
Bea Brittle

• Bea Brittle is a 68 year old woman whom you started on Alendronate two years ago for a hip BMD t score of -2.8. She keeps hearing bad things about the bisphosphonates and wonders if she should switch to a different drug. What do you tell her?

What do you tell her?

1) We should change to PTH
2) We should change to Denosumab
3) We should change to Raloxifene
4) We should change to Zolendronic Acid
5) We should continue the Alendronate

Raloxifene

• Selective Estrogen Receptor Modulators
• Ideally maximize bone and cardiovascular protective effects of estrogen, while minimizing negative effects (endometrial and breast cancers)

• Raloxifene reduces vertebral fractures, but not hip fracture
• Increased risk of thromboembolic events
• Breast cancer prevention
  – Similar to Tamoxifen
• No effect on vaginal bleeding/endometrial cancer
Calcitonin

- Intranasal spray
- Increased BMD 10-15% in two years
- Fracture evidence limited and inconclusive
- Analgesic effect in acute osteoporotic fracture
- Oral calcitonin in studies
- Possible increased cancer risk
  - Basal cell and other cancers

Parathyroid Hormone

- Anabolic therapy
  - Vs. anti-resportive
  - Reduces vertebral fractures by 65% and non-vertebral fractures by 53% after 18 months
- FDA approved for postmenopausal women at high risk for fracture
- Safety and efficacy has been shown for 2 years
  - Most BMD gains occur in first few months
- Daily subcutaneous injection

PTH vs. Bisphosphonates

- They have not been compared head to head in a trial that evaluated fracture outcomes
- PTH increased BMD more than alendronate
- PTH is much more expensive
- Long term safety of PTH?

PTH: Adverse Effects

- Hypercalcemia and Hypercalcuria
- Concern for Osteosarcoma
  - Higher doses for longer duration increased risk in rats
  - Case reports of co-existing Osteosarcoma in patients with primary Hyperparathyroidism
  - Only one reported case in post-menopausal woman on PTH
- FDA currently recommends limiting PTH therapy to two years
  - Post-marketing surveillance is ongoing
After PTH…

• PTH is recommended for two years
• Some BMD decline after discontinuing PTH
• Some anti-resorptive therapy should be added after PTH discontinuation
  – Bisphosphonate
  – Raloxifene is an alternative

PTH Alternatives to Daily Injection

• Intermittent PTH
  – 3 months on and 3 months off
• Weekly PTH injection?
• Transdermal patch with 1300 microneedles
  – Phase 2 trial
  – Results in PTH surge and pulsatile effect
  – Increase BMD

PTH: Summary

• Big impact on BMD
• Reduces spine and non-spine fractures compared with placebo
  – Hip fracture?
• Long term safety issues
• Daily injection of an expensive drug
• Consider use in severe osteoporosis when other agents have failed

Denosumab: FREEDOM Trial

• Human monoclonal antibody against RANKL
  – RANKL is a cytokine essential to osteoclast function
  – Inhibits osteoclast mediated bone resorption
• 7,868 women with osteoporosis received Denosumab 60 mg or placebo SQ every 6 months for 36 months
  – Reduced fracture risk
    – Vertebral fractures (2.3% vs 7.2%)
    – Hip fracture (0.7% vs 1.2%)
    – Non-vertebral fracture (6.5% vs 8.0%)

Cummings SR et al. NEJM 2009: 361: 756-65
Denosumab

- FDA approved for the following groups
  - High risk for fracture including androgen deprivation therapy for prostate cancer and aromatase inhibitor therapy for breast cancer
  - Treatment for osteoporosis in postmenopausal women at high risk for fracture

Quick Take: Abaloparatide

- Abaloparatide-Comparator Trial in Vertebral Endpoints (ACTIVE) Phase 3 double blind RCT with 2463 woman
- Over 18 months, abaloparatide reduced the risk of new vertebral and nonvertebral fractures
- More information about the benefits and risks needed
  - FDA approved for postmenopausal women with recent osteoporotic fracture (Tymlos®)
- How does it compare with other osteoporosis treatments?

Quick Take: Romosozumab

- Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) double blind placebo control study randomized 7180 women to receive romosozumab or placebo
- Monthly subcutaneous injection for 12 months followed by denosumab (every 6 months) for 12 months
- Lower risk of vertebral fracture at 12 months and at 24 months after transition to denosumab
- One cases of ONJ and two atypical femoral fractures in romosozumab group
- How does it compare to other osteoporosis therapies?

Back to Bea......

- There is currently no compelling reason for her to switch from a bisphosphonate to any other osteoporosis therapy
ACP Guidelines

• Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians
• Issued in May 2017 and updates the 2008 Guidelines

ACP Guidelines

• Offer treatment with alendronate, risedronate, zoledronic acid or denosumab to reduce risk of hip and vertebral fractures in women with known osteoporosis
  – Strong recommendation, High quality evidence
• Treat osteoporotic women with pharmacologic therapy for 5 years
  – Weak recommendation, low-quality evidence
  – “High risk patients may benefit from more than 5 years of treatment”

ACP Guidelines

• Offer pharmacologic treatment with bisphosphonates to reduce risk of vertebral fracture to men with clinically recognized osteoporosis
  – Weak recommendation, low quality evidence
• No bone density monitoring in women during the 5 year treatment period
  – Weak recommendation, low quality evidence

ACP Guidelines

• Recommends against using estrogen, estrogen/progestin or raloxifene for osteoporosis treatment in women
  – Strong recommendation, moderate quality evidence
• Decisions about treating osteopenic women age 65 and older who are at high fracture risk should include patient preferences, fracture risk profile and benefits, harms and costs of medications
  – Weak recommendation, low quality evidence
**Summary: Osteoporosis Prevention**

- Avoid or quit smoking and avoid excess alcohol use
- Regular weight bearing and muscle strengthening exercise
- Calcium and vitamin D
- Fall prevention

**Summary**

- Measure bone mineral density in women aged 65 and older
- Consider risk factors in measuring BMD in younger postmenopausal women
- WHO FRAX tool is useful for absolute risk assessment especially in women with low bone mass
- BMD monitoring frequency should be based on initial BMD and impact on management

**Choice of Pharmacologic Therapies**

- The Bisphosphonates have been studied most extensively and should remain first line agents
  - Consider stopping after 5 years in “low risk” patients
  - Guidelines about when or whether to stop Bisphosphonates remain in evolution

- Raloxifene, Calcitonin PTH and denosumab should remain second line agents
  - Raloxifene not recommended by ACP
  - Raloxifene reduces breast cancer risk

- Calcitonin may be an option for women who decline or cannot tolerate other options or who desire analgesic effect
- PTH may be an option for women who have failed other treatments
  - Treatment for 2 years should be followed by an anti-resorptive therapy
- Denosumab for women with breast cancer on AIs and for high risk postmenopausal women with osteoporosis
- Abaloparatide is a new FDA approved option
Let's ask the dog.....

Questions?

Thank you!
Updates in Preoperative Evaluation and Perioperative Care

Henry Crevensten, MD
Associate Professor of Medicine
Division of General Internal Medicine
San Francisco Veterans Affairs Medical Center

August 2017

Learning Objectives

You will be able to...

1. Perform an appropriate preoperative evaluation for elective surgical procedures using updated guidelines
2. Manage anticoagulation in the perioperative period using updated guidelines

Outline and Scope

• Scope:
  • Non-cardiac, elective procedures
• We will review:
  • Guidelines for testing
  • Updates over the last few years
  • Issues for selected populations (women, geriatrics) in perioperative care
  • Anticoagulants and Antiplatelet agents
• Methodology:
  • Case based learning

Disclosures

• Shareholder in Seattle Genetics
• No discussion of investigational or 'off label' use of medications or products

*All images from UCSF brand photography, in the public domain from governmental sites, or personal collection
Consider these Patients…

1. A 68 year old woman with atrial fibrillation (on anticoagulation) and heart failure about to undergo cataract surgery.

2. A 68 year old man with heart failure, diabetes, COPD, hypertension and CAD with left knee pain who is scheduled for left total knee replacement. His orthopaedist is wondering what workup and management needs to be done prior to surgery.

3. A 68 year old woman with atrial fibrillation (on anticoagulation) who would like to have a total knee arthroplasty. Her orthopaedist asks you to manage her anticoagulation in the perioperative period.

Goals of Perioperative Management

- Evaluate risk of procedure to allow patient, primary care physician, surgeon, and anesthesiologist to make informed decisions regarding surgical management.
- Optimize medical conditions.
- Minimize unnecessary testing.
- Minimize complications.

Sources of Recommendations

- American College of Physicians
- American College of Surgeons
- American Society of Anesthesiologists
- NEJM Review Article 2015
- ACOG Guidelines
- AHA/ACC 2014
- ACC Periprocedural Anticoagulation Consensus Pathway 2017
- US Preventative Services Task Force
- University of Washington Medicine Consult Service

Prevalence, Cost, and Risk of Preoperative Testing

- ~30 million people undergo surgery per year in the United States, most are ambulatory.
- ~18% of patients undergoing cataract surgery had a preoperative consultation.
- ~50% of perioperative consultants recommended an unnecessary test.
- Preoperative testing is estimated to cost $18 Billion annually in the U.S.

- **Risks**: unnecessary delay in procedure, unnecessary testing and harm from investigating results, unnecessary cost to patient.

- You can make a difference!
General Framework

1. Perform / Update H&P
   - Note cardiac or pulmonary issues
2. Address / Optimize Medical Issues
   - (incl. nutrition, smoking, sleep apnea)
3. Review Medications
   - Anticoagulants
   - Diabetes
   - Steroids
4. Assess Functional Status
5. Evaluate Surgical Risk (patient + procedure)
6. Consider Additional Testing (Risk is Elevated)

Case 1: Mrs. Haniger

Mrs. Haniger is seeing you in clinic prior to left eye cataract surgery. Her ophthalmologist has contacted you and has asked you to determine what testing and management is needed prior to her procedure.

Mrs. Haniger is a 68 year old woman with a history of:
- heart failure with reduced ejection fraction (EF 45%) (Rx: furosemide, metoprolol, lisinopril)
- diabetes (HgbA1c 7.5%) (Rx: metformin)
- mild COPD (FEV1/FVC 0.65, FEV1 85% pred, current non smoker) (Rx: albuterol)
- and atrial fibrillation (Rx: metoprolol, warfarin)


Case 1: Mrs. Haniger, continued:

Mrs. Haniger is a complicated patient, right?

BUT:
- For cataract surgery preoperative testing has NOT been shown to affect outcomes. Rates of adverse events in patients were similar (~3%) whether or not they underwent testing (American Academy of Ophthalmology Guideline 2014).

Case 1: Mrs. Haniger, continued

- What pre-operative evaluation should you perform?
  - History & Physical exam:
    - No recent chest pain
    - No murmurs or wheezes on exam
    - No evidence for volume overload
    - Normal creatinine 3 months ago
  - Functional Status
    - She can walk up 3 flights of stairs without difficulty
**Case 1: Mrs. Haniger, continued**

- Medication Management:
  - Continue warfarin: for procedures with low risk of bleeding (i.e., cataract, pacemaker, dental extraction), interruption of anticoagulation is usually NOT necessary. However, consulting with surgeon and anticoagulation clinic and adhering to your local practice is always advisable.
  - Continue lisinopril, furosemide, metoprolol
  - Hold metformin (NPO)

**Case 1: Mrs. Haniger, Take Home Points**

- Routine preoperative testing is not indicated in cataract surgery
- Perform your usual history, physical, and review of systems and address any abnormalities
- May continue anticoagulation (warfarin) for procedures with very low risk of bleeding

**Case 2: Mr. Cano**

Mr. Cano is seeing you in clinic prior to left knee arthroplasty surgery. His orthopaedic surgeon has contacted you and has asked you to determine what testing and management is needed prior to his procedure.

Mr. Cano is a 68 year old man with a history of:
- Heart failure with reduced ejection fraction (EF 45%) (Rx: furosemide, metoprolol, lisinopril)
- Diabetes (HgbA1c 7.5%) (Rx: insulin glargine PM)
- Mild COPD (FEV1/FVC 0.65, FEV1 85% pred, current non smoker) (Rx: albuterol, one 5 day steroid burst in last year)
- CAD (DES to RCA 5 years ago) (Rx: ASA, atorvastatin, metoprolol)
- Hypertension (Rx: metoprolol)

**Determining Surgical Risk**

Goal is to divide patients into two categories:

- **LOW RISK:**
  - Combined patient and surgical procedure characteristics result in a predicted risk of ≤ 1% of a Major Adverse Cardiac Event (MACE = death or myocardial infarction)

- **ELEVATED RISK:**
  - MACE ≥ 1%
Why Determine Surgical Risk?

- **LOW RISK** patients (MACE < 1%) do NOT need preoperative testing except as indicated by H&P (as you would normally practice)

- **ELEVATED RISK** patients (MACE ≥ 1%) MAY need preoperative testing depending on functional status. Surgical procedure may need to be modified.

Tools for Determining Surgical Risk

- Revised Cardiac Risk Index (RCRI)
- American College of Surgeons NSQIP Surgical Risk Calculator

Revised Cardiac Risk Index (RCRI)

- **Clinical Predictors (1 point each)**
  - 'High Risk' surgery (intrathoracic, intraperitoneal, suprainguinal vascular)
  - Ischemic Heart Disease
  - Heart Failure
  - Diabetes Requiring Insulin
  - Creatinine > 2.0
  - CVA or TIA

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Complications</th>
<th>MACE</th>
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<tbody>
<tr>
<td>0</td>
<td>0.2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>1</td>
<td>1.3%</td>
<td>1%</td>
</tr>
<tr>
<td>2</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>9%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

Pros:
- Simple
- Validated outside original cohort

Cons:
- Older
- Smaller sample
- Other tools with greater predictive ability

ACC / AHA Flowchart (2014)

Evaluate Risk

Low Risk

MACE < 1%, RCRI 0 or 1

Proceed to Surgery

Elevated Risk

MACE ≥ 1%, RCRI ≥ 2 +

Evaluate Functional Capacity

≥ 4 METs

Yes

No

≥ 4 METs

Normal

Optimizing Medical Management Consider Noninvasive Approach to Surgery

Abnormal

Revascularization

Pharmacologic Stress Test

Optimize Medical Management Consider Noninvasive Approach to Surgery

Revascularization

Abnormal

Revascularization

Pharmacologic Stress Test

Optimize Medical Management Consider Noninvasive Approach to Surgery

Revascularization

Abnormal
American College of Surgeons NSQIP Surgical Risk Calculator

- **Pros:**
  - Provides other outcomes
  - Probably best predictor
- **Cons:**
  - Only validated within cohort
  - Need specific surgery
  - Need ASA class
  - MI defined as STEMI

---

**Functional Status, defined**

- **MET** = Metabolic Equivalent of Task
- 1 MET = basal oxygen consumption of a 40 year old, 70 kg male

<table>
<thead>
<tr>
<th>METs</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>Simple activities of daily living, walk &lt; 2 blocks</td>
</tr>
<tr>
<td>4 - 6</td>
<td>Moderate, walk 2 flights of stairs, heavy housework/yardwork</td>
</tr>
<tr>
<td>7 - 10</td>
<td>Good, jogging, bicycling (light effort)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>Excellent, 10-minute mile</td>
</tr>
</tbody>
</table>

Note: capability of less than 4 METs of activity associated with higher cardiac risk

---

Cardiac Testing and Intervention

- Even in patients with known, stable coronary disease revascularization does NOT improve long-term survival
- CARP trial: 510 patients with 1+ coronary artery with 70% occlusion. Randomized to revascularization vs. not prior to major vascular surgery.
  - No difference in death or MI
  - Excluded: unstable angina, left main stenosis > 50%, severe aortic stenosis, and LVEF < 20%

---

Case 2: Mr. Cano, continued

- **What pre-operative evaluation should you perform?**
  - History & Physical exam:
    - No recent chest pain
    - No murmurs or wheezes on exam
    - No evidence for volume overload
    - Normal creatinine 3 months ago
    - BMI 24
  - Functional Status
    - He can walk up 3 flights of stairs without dyspnea or chest pain. Has some pain in his left knee

---

Case 2: Take Home

• Cardiac Testing?
  • RCRI: 3 (ischemia, insulin, HF);
    NSQIP MACE: 0.2%
  • Higher risk by RCRI, but good functional status, so NO cardiac testing

Bottom line: If a patient has low risk of MACE, or higher risk but good functional status, then proceed with surgery. If higher risk of MACE and functional status cannot be assessed then may consider further cardiac testing.

Case 2: Mr. Cano, continued

• NSQIP:
  • RCRI: 3 (ischemia, insulin, HF);
    NSQIP MACE: 0.2%
  • Higher risk by RCRI, but good functional status, so NO cardiac testing

Pause Procedure

• Questions?
  • Think about 1 or 2 things you have learned so far about pre-operative cardiac testing
Other Testing and Evaluation: updates

- Sleep Apnea
- Biomarkers

Obstructive Sleep Apnea (OSA)

- OSA is associated with increased post-operative cardiac and pulmonary complications (1.5 to 3x risk)
- Undiagnosed OSA patients have a higher risk of cardiovascular complications compared to diagnosed OSA patients treated with CPAP and controls. This risk increases with OSA severity.
- Risk of pulmonary complications appears to be high whether or not the OSA is diagnosed
- It is not clear if CPAP treatment actually decreases pulmonary risk in surgical patients. However, it is reasonable to continue CPAP treatment while hospitalized. Also patients with OSA may benefit from closer cardiopulmonary monitoring.


Biomarkers

- Troponin:
  - Retrospective cohort study examined relationship between pre-operative troponin and mortality. Patients with more recent, elevated levels had elevated post-operative mortality (OR 4.5).^1^
  - Prospective cohort study examined utility of adding troponin (hsTnT) to RCRI in patients undergoing intermediate + surgery and some cardiac risk factors. An elevated troponin did increase sensitivity. proBNP did not.\[^2^\]
- BNP
  - An elevated BNP (>92) and pro-BNP (>300) pre- and post-operatively were associated with increased death/MI (OR ~2).\[^3^\]

Take home: if a patient has had an elevated pre-operative troponin it would be prudent to investigate further. Only order troponin or BNP if it would change management.

^1^ Maile M, Jewell, E, Engoren M, et al; Anesthesia & Analgesia 2016; 123(1) 135-140


Case 2: Mr. Cano, continued

- How should we manage his Aspirin?
Antiplatelet Medications

- Aspirin for primary / secondary prevention (excluding recent stents):
  - Aspirin in the perioperative period did not decrease death or non-fatal MI and increased hemorrhage. (NOTE: low rate of PCI, low rate of vascular surgery)
  - recommend: stop aspirin 5-10 days prior to procedure. Restart 8-10 days afterward


Antiplatelet Medications, continued

- Aspirin in patients with stents:
  - Highest thrombosis risk is within 4-6 weeks after stent placement.
  - Optimally, delay elective procedure at least 14 days after balloon angioplasty, 30 days after bare metal stent and 1 year after drug-eluting stent.
  - Continue dual antiplatelet medications perioperatively if possible.
  - If surgery needs to be performed and risk of hemorrhage deems dual antiplatelet therapy unacceptable: Continue aspirin, discontinue P2Y12 inhibitor (i.e. clopidogrel – 5 days) and resume as soon as possible.


Case 3: What about anticoagulation? Mrs. Segura

Mrs. Segura is seeing you in clinic prior to left knee arthroplasty surgery. Her orthopaedic surgeon has contacted you and has asked you to determine what testing and management is needed prior to her procedure as well as how to manage her anticoagulation.

Mrs. Segura is a 68 year old woman with a history of:

- heart failure with reduced ejection fraction (EF 45%) (Rx: furosemide, metoprolol, lisinopril),
- diabetes (HbgA1c 7.5%) (Rx: insulin glargine PM)
- CAD (DES to RCA 5 years ago) (Rx: atorvastatin, metoprolol, no ASA – on warfarin**)
- hypertension (Rx: metoprolol)
- And atrial fibrillation [CHA2DS2-VASc = 5 (CHF, HTN, age, DM, female)]] (Rx: warfarin, metoprolol)

Anticoagulants

- Recent Updates:
  - It is becoming more common to perform procedures while continuing anticoagulation
  - There are fewer indications for bridging anticoagulation

- General Framework and Key Points:
  - Evaluate procedural bleeding risk
  - Evaluate perioperative thromboembolic risk
  - For warfarin, can do very low - low risk patients/procedures un-interrupted. Generally interrupt 3-5 days prior to procedure
  - For Direct Oral Anticoagulants (DOAC), check renal function, do not bridge. Generally interrupt from one dose to 120 hrs depending on creatinine clearance.

Managing Anticoagulation: a Pathway

Major Clinical Decisions:

- Should anticoagulation be interrupted?
- If so, when should anticoagulation be interrupted?
- Does this patient need bridging anticoagulation and if so, how should this be done?
- When should anticoagulation be restarted?

NOTE: ACC 2017 Guideline applies only to anticoagulation for non-valvular atrial fibrillation and elective procedures

Managing Anticoagulation: Interruption

What is the Patient’s Bleeding Risk?

- HAS-BLED Score
  - Hypertension: > 160mmHg systolic
  - Abnormal Renal / Hepatic Function: dialysis, Transplant, Cr > 2.3mg/dL, cirrhosis, Bili > 2x
  - Stroke history
  - Bleeding history
  - Labile INR (VKA): < 60% time within INR range
  - Elderly: > 65 years old
  - Drugs: Use of Anti-platelet or NSAID; Alcohol Use: > 8 drinks weekly

- Bleed event within 3 months (esp. intracranial hemorrhage)
- Platelet Dysfunction
- INR out of therapeutic range at time of procedure
- Bleed history with prior bridging
- Bleed history with prior procedure

LOW or HIGH

Managing Anticoagulation: Procedural Hemorrhage Risk

<table>
<thead>
<tr>
<th>Very Low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>Ablation for AF</td>
<td>PCI, transcaterval</td>
<td>Total Hip/ Knee Arthroplasty</td>
<td>Retroperitoneal dissection for renal, adrenal cancer</td>
</tr>
<tr>
<td>ICD / pacemaker</td>
<td>Carotid artery stenosis</td>
<td>Hysterectomy (not radical)</td>
<td>Spine Surgery</td>
<td>Pericardiocentesis</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>Therapandectomy</td>
<td>Lumbar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopy without biopsy</td>
<td>D&amp;C</td>
<td>Prostate biopsy</td>
<td>Aortic Valve replacement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticoagulation</td>
<td>Endoscopy with biopsy</td>
<td>Kidney biopsy</td>
<td></td>
</tr>
</tbody>
</table>

Managing Anticoagulation: Interruption

Assessing the Patient’s Bleeding Risk

What type of anticoagulant?
VKA or DOAC?

What is the Procedural Hemorrhage Risk?

Managing Anticoagulation: Interruption

Online Appendix to 2017 ACC expert consensus decision pathway. Accessed June 2017
Managing Anticoagulation: Decision to Interrupt, **Warfarin**

- **Patient Bleeding Risk**
  - LOW or LOW
  - INTERMEDIATE or HIGH
  - UNCERTAIN

- **Procedure Hemorrhage Risk**
  - LOW or LOW
  - INTERMEDIATE or HIGH
  - UNCERTAIN

- **Low enough INR, long interval**
  - Use clinical judgment
  - Consult with proceduralist

- **Interrupt**

Case 3: Mrs. Segura, update

- On Warfarin for atrial fibrillation
- LOW patient bleeding risk
- HIGH procedural hemorrhage risk

Managing Anticoagulation: When to Interrupt, **Warfarin**

- **Subtherapeutic**
  - 5 – 7 days prior to procedure
  - Discontinue 1 – 4 days prior to procedure
  - Proceed to BRIDGING

- **Therapeutic**
  - 2.0 – 2.5 or 2.0 – 3.0
  - 5 days prior to procedure
  - Proceed to BRIDGING

- **Supratherapeutic**
  - 5 days prior to procedure
  - Discontinue 3 – 4 days prior to procedure
  - Recheck INR 24 hours prior to procedure

Managing Anticoagulation: Bridging, **Warfarin**

- **KEY POINTS**
  - Evaluate patient bleeding risk
  - Evaluate Thrombotic risk (low, intermediate, high)
  - There are fewer indications for bridging anticoagulation (BRIDGE Trial)
BRIDGE Trial, 2015

- Double-blinded, placebo-controlled noninferiority study
- 1,884 atrial fibrillation patients (valvular and nonvalvular) on warfarin with plan to interrupt for a procedure
- Randomized to bridging with dalteparin or placebo
- Most were low bleeding risk and avg CHADS2 score: 2.3
- The primary endpoints were arterial thromboembolism and major bleeding.

RESULTS: The rate of arterial thromboembolism in the placebo group was noninferior to the bridging group (0.4% vs. 0.3%) and major and minor bleeding in the placebo group was significantly less than in the bridging group (1.3% vs. 3.2%). No difference in other endpoints.

CONCLUSION: for patients with low bleeding risk and intermediate risk of TE bridging anticoagulation does not reduce risk of TE and increases risk of hemorrhage.


Managing Anticoagulation: Bridging, Warfarin

CHA2DS2-Vasc Score:
- CHF
- Hypertension
- Age (65-74 1 pt, ≥75 2 pts)
- Diabetes
- Stroke or TIA (2 pts)
- Vascular disease (MI, PAD, aortic plaque)
- Sex Category (female = 1 pt)

Managing Anticoagulation: Bridging, risk stratification for other anticoagulation indications

<table>
<thead>
<tr>
<th>Risk</th>
<th>Mechanical Heart Valve</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Bileaflet aortic valve, no other risk factors</td>
<td>More than 12 months ago, no other risk factors</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Bileaflet aortic valve w/ ab, CVA/TIA, HF, age, DM</td>
<td>3-12 months ago, or recurrent, malignancy, factor V Leiden</td>
</tr>
<tr>
<td>High</td>
<td>Mitral valve, cage-ball or tilting disc aortic valve, recent (&lt; 6 mo) CVA/TIA</td>
<td>&lt; 3 months, protein C &amp; S deficiency, antiphospholipid AB</td>
</tr>
</tbody>
</table>

NOTE: ACC 2017 Guideline applies only to anticoagulation for non-valvular atrial fibrillation and elective procedures. DOAC not indicated for use in mechanical valve anticoagulation.
Managing Anticoagulation: How to Bridge, **Warfarin**

- **High Stroke Risk AND High Patient Bleed Risk**
- **Consult with proceduralist, pharmacy**
- **Consider use of prophylactic dose anticoagulation or only pre-procedure bridging**

- **Renal Function Impaired? (CrCl < 30)**
  - **Unfractionated Heparin (UFH)**
    - **Start UFH when INR < 2**
    - **Stop UFH >4 hours prior to procedure if aPTT wnl**
  - **Low-Molecular Weight Heparin (LMWH)**
    - **Start LMWH when INR < 2 (~36hrs after last dose)**
    - **Stop LMWH 12-24 hours prior to procedure**

**Case 3: Mrs. Segura, update**

- On Warfarin for atrial fibrillation
- LOW patient bleeding risk
- HIGH procedural hemorrhage risk

**Managing Anticoagulation: When to Restart, **Warfarin**

**KEY POINTS**

- Ensure complete hemostasis achieved
- Consider the type of surgery and the possible consequences of hemorrhage (i.e. spine surgery, open cardiac surgery, intracranial procedures)
- Consider patient’s history with respect to bleeding risk: prior hemorrhage, platelet dysfunction
- When appropriate (usually 24 hours), can restart patient’s home dose without loading
- If bridging or using prophylactic anticoagulation, if bleeding risk is HIGH start this 48-72 hrs post-procedure. Otherwise 24 hrs. Continue until INR 2-3.

**Case 3: Mrs. Segura, update**

A 68 year old woman with CAD, diabetes, heart failure, hypertension, atrial fibrillation on warfarin. Scheduled to undergo a LEFT total knee arthroplasty.

- LOW patient bleeding risk, HIGH procedural hemorrhage risk
- **CHA2DS2-Vasc Score: 5, INTERMEDIATE thromboembolic risk**
- **NO prior stroke, TIA, recent hemorrhage, or thrombotic event**
- **INR 2.5**

We INTERRUPTED warfarin 5 days prior to surgery and did NOT BRIDGE. She underwent a successful left total knee arthroplasty. Hemostasis achieved and warfarin RESTARTED at her home dose 24 hours after her procedure, along with prophylactic dose LMWH. This was continued until her INR was >2. There were no post-procedural complications.
Case 3a: Mrs. Segura, what if she were on a DOAC?

A 68-year-old woman with CAD, diabetes, heart failure, hypertension, atrial fibrillation on apixaban. Scheduled to undergo a LEFT total knee arthroplasty.

- LOW patient bleeding risk, HIGH procedural hemorrhage risk
- CHA2DS2-Vasc Score: 5, INTERMEDIATE thromboembolic risk
- NO prior stroke, TIA, recent hemorrhage

**KEY POINTS vs. Warfarin**
- Usually will interrupt, at least one dose
- Measure renal function to determine timing of interruption
- Bridging NOT indicated

### Managing Anticoagulation: Decision to Interrupt, DOAC

**Patient Bleeding Risk**

- LOW
- HIGH
- VERY LOW
- INTERMEDIATE
- UNCERTAIN

**Procedure Hemorrhage Risk**

- LOW
- INTERMEDIATE
- HIGH

**CrCl**

- DTI Xa Inhibitor
  - No data
  - Consider anti-Xa

- 15 – 29
  - ≥ 72 hrs
  - ≥ 36 hrs

- 30 – 79
  - ≥ 24 hrs
  - ≥ 24 hrs

- > 80
  - ≥ 24 hrs

**Managing Anticoagulation: When to Interrupt, DOAC**

**LOW procedural hemorrhage risk**

- CCI
- DTI
- Xa inhibitor

- No data
- at least 96 hrs
- DTIConsider anti-Xa

- 15 – 29
- ≥ 72 hrs
- ≥ 36 hrs

- 30 – 49
- ≥ 24 hrs
- ≥ 24 hrs

- > 80
- ≥ 24 hrs

**INTERMEDIATE, HIGH, or UNCERTAIN procedural hemorrhage risk**

- CCI
- DTI
- Xa inhibitor

- No data
- at least 72 hrs
- Consider anti-Xa

- 15 – 29
- ≥ 120 hrs
- ≥ 96 hrs

- 30 – 49
- ≥ 96 hrs
- ≥ 48 hrs

- > 80
- ≥ 48 hrs

**Managing Anticoagulation: When to Restart, DOAC**

**KEY POINTS**

- Ensure complete hemostasis achieved
- Consider the type of surgery and the possible consequences of hemorrhage (i.e., spine surgery, open cardiac surgery, intracranial procedures)
- Consider patient’s history with respect to bleeding risk: prior hemorrhage, platelet dysfunction
- Measure post-procedure renal function to guide dosing
- If post-procedural bleeding risk is LOW, can start 24 hours post-procedure/hemostasis. Otherwise, 48 – 72 hours.
Case 3a: Mrs. Segura, update

A 68 year old woman with CAD, diabetes, heart failure, hypertension, atrial fibrillation on apixaban. Scheduled to undergo a LEFT total knee arthroplasty.

- LOW patient bleeding risk, HIGH procedural hemorrhage risk
- CHA2DS2-Vasc Score: 5, INTERMEDIATE thromboembolic risk
- NO prior stroke, TIA, recent hemorrhage or thromboembolic event
- CrCl ~ 64 pre-procedure (Cr 0.9); CrCl ~ 53 post-procedure (Cr 1.1)

We INTERRUPTED apixaban 48 hours prior to surgery and did NOT BRIDGE. She underwent a successful left total knee arthroplasty. Hemostasis achieved. We started prophylactic dose LMWH the following day and then apixaban RESTARTED at her home dose 72 hours after her procedure. LMWH stopped. There were no post-procedural complications.

Bridging Anticoagulation, There's an App for that

- http://tools.acc.org/bridgeanticoag
  or for iPhone or Android
- Takes you through the decision
tree, presents a summary, and you
can email it to yourself

Pause Procedure

- Questions?
  - Think about 1 or 2 things you have learned so
  far about perioperative anticoagulation
  management

Select Populations…
Female Patients

- Oral Contraceptives / Hormone Therapy – increased risk of thromboembolic events
  - Low-risk procedures / early ambulation: CONTINUE
  - Moderate- to High-Risk procedures / relative immobility: DISCONTINUE 4-6 weeks prior to procedure after DISCUSSION with patient:
    - Risk of unintended pregnancy (use backup method)
    - Post-operative prophylaxis: defer to surgeon

Older Patients

- Risk of mortality in elective surgery increases slightly with age but probably due to co-morbidities rather than age alone

- ‘No Care Without Goals of Care’
  - Discuss risks and benefits of procedure given life expectancy, expected outcome
  - Advance Directive / Code Status
  - Surrogate Decision-Maker

Older Patients, Pre-Operative Evaluation

- Evaluate Cognitive Status and decision-making capacity. Cognitive impairment increases risk of perioperative delirium and mortality. Advise patient to bring assistive devices (hearing aids, glasses) to hospital
- Evaluate Functional Status – older patients are at risk for loss of functional status simply due to hospitalization. Decreased functional status is a risk for increased morbidity.
- Evaluate Nutrition – poor nutrition may be risk for mortality (studies variable)
- Consider pre-operative rehabilitation program to improve functional status and nutrition and ensure post-operative rehabilitation plan is in place.

Summary of Recent Updates

- NO testing is required prior to cataract surgery
- Determining need for cardiac testing has been simplified:
  - Determine risk of MACE: if < 1%, proceed with surgery, if ≥ 1% and good functional status, proceed with surgery
  - If not, consider cardiac testing if management would change.
- Screening and treating for OSA can decrease cardiovascular events
- HOLD Aspirin in the perioperative period unless patient has recent coronary stent
- DO NOT use bridging anticoagulation in patients on warfarin and low-moderate thromboembolic risk
References – Good Places to Start

- ACC/AHA Guideline 2014

- University of Washington Medicine Consult Service

- American College of Obstetrics and Gynecology

- Cataract Surgery Guidelines

References – Additional Reading

Appendix A: Anticoagulation Methodology in Table Form

- See next two slides

- Anticoagulants: warfarin

- **Procedural Bleeding Risk**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Postoperative Thromboembolic Risk (%)</th>
<th>Probable dose and concurrent anticoagulation</th>
</tr>
</thead>
</table>

# Anticoagulants: DOACs

## Procedural Bleeding Risk

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Cataract, ICD/pacemaker, skin biopsy, and endoscopic procedures)</td>
<td>(Vascular, CABG, knee/hip replacement, kidney biopsy, and neurosurgical procedures)</td>
<td>(Neurosurgical, cardiothoracic, spine)</td>
</tr>
</tbody>
</table>

### Low

- **Do not need to interrupt anticoagulation.**

### Moderate

- **Interrupt anticoagulation depending on pharmacokinetics of agent and renal function.**
  - Generally 24–48 hours prior to procedure.
  - Resume at 5-7 days post-procedure.

### High

- **Interrupt anticoagulation depending on pharmacokinetics of agent and renal function.**
  - Generally 72–120 hours prior to procedure.
  - Resume at 5-7 days post-procedure.

---

Adapted from UCSF, SFVA, and ZSFGH Guidelines for the Peri-Procedural Management of Adults Taking Target-Specific Anticoagulants. Approved 2015.
Shoulder and Hip for the Primary Care Clinician

Carlin Senter, MD
Associate Professor
Primary Care Sports Medicine
UCSF Medicine and Orthopaedics

UCSF Essentials of Primary Care
August 10, 2017

Objectives

Upon completion of this session, participants should be able to:
1. Name 2 causes of shoulder pain when both active and passive range of motion are limited.
2. Identify a full thickness rotator cuff tear on physical exam.
3. Explain treatment for rotator cuff disease.
4. Identify intraarticular hip pathology by history and exam.
5. Provide a differential diagnosis for intraarticular hip pathology based on patient age.

Disclosures

I have nothing to disclose.

Shoulder Problems
Case #1

50 y/o RHD woman with type 2 diabetes presents with 3 months of severe R shoulder pain. No injury. Waking up at night due to pain. Shoulder feels very stiff. She is having trouble reaching behind and raising arm above head.

On exam she has no muscle atrophy and no point tenderness. There is decreased active and passive range of motion of the right shoulder. Her rotator cuff strength is 5/5 though difficult to perform due to limited range of motion and pain. A R shoulder xray is normal.

How would you treat this patient?

A. Provide R shoulder sling to use for comfort.
B. Provide shoulder steroid injection to reduce pain.
C. Obtain shoulder MRI.
D. Obtain PET CT.
E. Refer to surgeon for arthroscopy.

Adhesive capsulitis

Shoulder: diagnosis driven exam

Shoulder active range of motion

Limited ER key finding

Shoulder passive range of motion
Adhesive capsulitis is associated with:

- Diabetes ➔ screen for this if hasn’t been done recently
- Hyper and hypothyroidism
- Hypoadrenalism
- Parkinson’s disease
- Cardiac disease
- Pulmonary disease
- Stroke
- Surgery (cardiac, cardiac cath, neurosurgery, radical neck dissection)

Adhesive capsulitis is a clinical diagnosis:

- No need for MRI
- X-rays helpful to rule out glenohumeral joint arthritis

3 stages of adhesive capsulitis:

- **Freezing** (3-9 months):
  - ↑ pain
  - ↓ ROM
  - Pain at rest, sleep

- **Frozen** (4-12 months):
  - ↓ pain
  - Stable, decreased ROM

- **Thawing** (12-42 months):
  - Gradual ↑ ROM

- **Resolution**
  - Average time to resolution: 1-3 years

Treatment for adhesive capsulitis:

- Pain control: NSAIDs, oral or injected corticosteroids
  - Does not change disease course
  - Does help significantly with pain control
- +/- physical therapy to help restore ROM
- Capsular distention injections
- Surgery
  - Manipulation under anesthesia
  - Arthroscopic release and repair

Case #2

57 y/o RHD man presents with R shoulder pain that started after he slipped and fell 3 months ago. Pain at R deltoid. He tried physical therapy without benefit. Waking at night from sleep due to pain.

Exam: Point tenderness just below the acromion. AROM intact with pain on abduction between 60 and 120 degrees. Difficulty fully abducting the R arm. Moderate pain with resisted internal and external rotation of the shoulder. (+) External rotation lag test, (+) internal rotation lag test.

What is the most likely cause of his shoulder pain?

A. Frozen shoulder
B. Glenohumeral joint arthritis
C. Rotator cuff tendinitis (tendinopathy)
D. Partial thickness rotator cuff tear
E. Full thickness rotator cuff tear

Rotator cuff disease in primary care

- The 3rd most frequent musculoskeletal reason patients present to the office
- The most common cause of shoulder pain in patients in the US primary care settings

What is rotator cuff disease?

- Impingement
- Tendinitis/tendinopathy
- Partial thickness tear
- Full thickness tear

Rotator cuff disease treatment

Most do well with conservative treatment

- Impingement
- Tendinitis, tendinopathy
- Partial thickness tear
- Full thickness tear → Consider ortho referral.


Physical exam maneuvers that increase likelihood of rotator cuff disease

1. Painful arc
2. Drop arm test

Pain test: Painful arc

If painful, positive LR 3.7 for rotator cuff disease.
If not painful, negative LR 0.36 for rotator cuff disease.
Pain/strength test: Drop arm test

Positive LR 3.3, negative LR 0.82 for rotator cuff disease. JAMA. Rational clinical exam: Does this patient have rotator cuff disease? Aug 2013.

Physical exam maneuvers that increase likelihood of full thickness rotator cuff tear

1. External rotation lag test
2. Internal rotation lag test

https://www.healthbase.com/hb/images/cm/procedures/orthopedics/rotator_cuff_tear.jpg

Strength test: External rotation lag test

Positive LR 7.2, Negative LR 0.57 for full thickness rotator cuff tear. JAMA. Rational clinical exam: Does this patient have rotator cuff disease? Aug 2013.

Strength test: Subscapularis = internal rotation lag test

Positive LR 5.6, negative LR 0.04 for full thickness rotator cuff tear. JAMA. Rational clinical exam: Does this patient have rotator cuff disease? Aug 2013.
Case #2

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D. Partial thickness rotator cuff tear
E. Full thickness rotator cuff tear

Treatment

A. Refer for surgical consult
B. Repeat trial of physical therapy, f/u 3 months.
C. Give NSAIDs and activity modification, f/u 3 months
D. Give subacromial injection, f/u 3 months

Case #3

• 30 y/o RHD man fell off bike 9 months ago, injured R shoulder
• Went to PT but continues to have pain
• Anterior shoulder
• Only feels pain if moves shoulder in certain directions quickly
• Does not wake him from sleep at night
Physical examination

- No atrophy
- Tender biceps tendon, nontender AC joint
- AROM R shoulder
  - FF 0-170 with pain at top
  - Abd 0-170 with pain at top
  - ER 45, IR L1 (Same as L shoulder)
- Strength 5/5 rotator cuff
- (-) Neers and Hawkins
- (+) O’Brien’s test

Case #3 differential diagnosis

- Labral tear
- AC joint separation
- Rotator cuff tear
- Shoulder dislocation
- Fracture
  - Humerus or clavicle

Glenoid labrum

O’Brien’s Test for Labral Tear

- Arm forward flexed to 90°
- Elbow fully extended
- Arm adducted 10° to 15° with thumb down
- Downward pressure
- Repeat with thumb up
- Suggestive of labral tear if more pain with thumb down
- Sens = 59-94%, Spec = 28-92%
SLAP tears

- Superior Labrum Anterior to Posterior
  - Many different types, classifications
- Diagnosis: MR arthrogram
- Treatment:
  - Trial of physical therapy
  - Surgery: debridement vs repair
- NOT a disease of older people (do not consider as etiology for shoulder pain in most >50 y/o as labrum degenerates naturally)

Locate the hip pain

- Anterior groin = hip joint, hip flexor
- Buttock = SI joint, lumbar spine
- Lateral hip = greater trochanteric bursitis, gluteus tendinopathy
- Radiating to thigh = could be hip joint
- Radiating to the foot = lumbar spine


Hip Problems

Hip palpation

- Abdomen
- Pelvis
  - Iliac crest
  - ASIS
- Inguinal canal
  - Lymph nodes
- Pubic tubercles
- Hip
  - Greater trochanter
- Back: Sacroiliac joints, lumbar spine

http://www.rush.edu/rumc/page-109897346941.html
Hip palpation

Hip passive range of motion

Hip passive range of motion: internal and external rotation

Hip passive range of motion

http://www.youtube.com/watch?v=5LNYdJf0WYo
Hip neurovascular exam

- Strength
  - Hip flexion (T12-L3)
  - Knee extension (L2-4)
  - Plantar flexion (S1)
  - Foot dorsiflexion (L4)
  - Great toe extension (L5)
- Sensation to light touch
- Reflexes: patellar (L4) and Achilles (S1)

Signs of intra-articular hip pathology

- Pain with passive ROM
- Most pain with IR of affected hip
  - Narrows joint space
  - Decreased IR of affected compared to unaffected side

If pain with passive ROM be concerned about hip emergencies

- Septic arthritis
- Femoral neck fracture or stress fracture
- X-rays
- Make non weight bearing (crutches or wheelchair)

Non-emergent intraarticular hip pathology

- Osteoarthritis (>50 y/o)
- Femoroacetabular impingement (< 50 y/o)
- Labral tear (< 50 y/o)
Case #4

- 29 y/o woman with R hip pain
- Localizes to R groin
- Started when running on sand
- Was running 10 miles/week
- Pain 2/10 sitting, 5/10 standing
- Aleve helps
- Groin pain can be sharp with certain movements
- Did PT but didn’t help
- No h/o amenorrhea, no eating disorder, no h/o stress fracture

Case #4 exam

- No ecchymosis
- Tender R inguinal canal
- ROM: bilateral flexion 130, IR 40 and ER 60 but R groin pain with flexion and IR.
- FADIR and FABER R hip cause R groin pain
- No pain with FADIR and FABER L hip


What’s the diagnosis?

A. Greater trochanteric bursitis
B. Sacroiliac joint dysfunction
C. Femoroacetabular impingement
D. Femoral neck stress fracture
E. Hip osteoarthritis

FADIR

- Flexion
- Adduction
- Internal
- Rotation

FABER

- Flexion
- Abduction
- External
- Rotation

http://kurumiyama.web.fc2.com/PT/orthopedic_test.htm

Femoroacetabular Impingement (FAI)

- Abnormal bony anatomy that forms during development
- Age group 15 to 45 years old
- More commonly chronic injury (can be acute)
- Can lead to intra-articular injury to labrum and cartilage
- Can lead to early arthritis

FAI

- Cam-Type - femoral head neck asphericity
- Pincer Type - acetabulum overcoverage
- Mixed Type - both Cam and Pincer

Hip Labral Tear - can be acute event

Slide courtesy of Alan Zhang, MD
FAI X-rays

- AP pelvis
- Dunn view lateral
- Hip flexed 90 and abducted 20 degrees
- Lateral can miss impingement


Hip labral tear imaging

- X-rays: normal or impingement, r/o OA
- MR arthrogram
  - Contrast injected into hip joint
  - 92% sensitivity (DeLee and Drez’s Orthopaedic Sports Medicine, 3rd ed)

http://www.currentprotocols.com/WileyCDA/CPUnit/refId-mia2602.html

Treatment FAI/labral tear

- Physical therapy
  - Core strengthening
  - Hip muscle strengthening
- Activity modification
- Corticosteroid injection
  - Short term pain relief
  - Confirm that provides pain relief (right diagnosis)

Hip Arthroscopy

Slide courtesy of Alan Zhang, MD
Surgery for FAI/labral tear

- Indications
  - Pain with flexion and IR
  - Labral tear on MRI or MR arthrogram
  - Relief of pain after injection
  - Failed physical therapy
  - Arthroscopy
    - Labral debridement or repair
    - Osteoplasty of femoral neck and/or acetabulum to restore normal bony alignment
    - Higher pt satisfaction if no co-existing hip cartilage damage (chondropathy)


Objectives

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5. Provide a differential diagnosis for intraarticular hip pathology based on patient age.

Name 2 causes of shoulder pain when both active and passive range of motion are limited.

Identify a full thickness rotator cuff tear on physical exam.
Explain treatment for rotator cuff disease

Identify intraarticular hip pathology

- History
  - Groin pain
  - "C" sign
  - Worse with hip flexion
  - Worse when putting on shoe (or can't put on shoe)
- Physical exam
  - Groin pain with
  - PROM
    - Flexion
    - Internal rotation
  - Limited PROM on affected side
  - (+) FADIR → groin pain
  - (+) FABER → groin pain

Differential dx intraarticular hip pain by age

- Age < 50 yrs
  - Femoroacetabular impingement
  - Labral tear
  - FAI + labral tear
  - Femoral neck stress fracture
    - Physical activity
    - Bone health
- Age > 50 yrs
  - Osteoarthritis
  - Fracture (trauma)
  - Femoral neck or acetabular stress fracture
    - Physical activity
    - Bone health

Thank you!
Carlin.Senter@ucsf.edu
Clinical Pearls in Caring for Older Adults

Anna Chodos, MD
Assistant Professor
Division of Geriatrics, UCSF

Doing Geriatrics in a Busy Practice

1. Assessing Function & Cognition in Primary Care
2. Prognosis and Advance Care Planning
3. De-prescribing tips

Function & Cognition

Prognosis & Advance Care Planning
De-prescribing Tips

Plan for Workshop

• Break into groups of 3-6 people

• Do the cases: 20 min each

• After each case, bell will ring and there will be time for group questions.
Update in Women’s Health

Judith Walsh MD, MPH
University of California, San Francisco
Women’s Health Center of Excellence
Division of General Internal Medicine

Plan for today...

- Review some of the most significant published advances in the Women’s Health medical literature over the past two years
  - Top articles
  - Key articles
  - Guidelines
- Assess the strength and scope of the evidence presented in the selected literature
- Apply this new information to our clinical practice
  - Take-home points
- SGIM Annual Meetings 2016 and 2017
  - Erin Contratto MD, Bimla Schwarz, MD and Lydia Pace MD

Process

Criteria

- How new/innovative is this information?
- Strength of the evidence?
- How will it change my practice?
• OCPs and Cancer
• Binge Eating
• Cranberry and UTIs
• Tomosynthesis

• Lymphedema & blood draws
• Hormone therapy and CVD
• Osteoporosis Treatment
• Atypical fractures

ISSUES AFFECTING REPRODUCTIVE AGE WOMEN

Case
• 39 year old woman who has been on OCPs since she was 19, when she started them for irregular and painful menses. She does not desire children and is happy with her light and relatively painless menses. She would like to continue but is worried that they may not be safe for women after 40. What do you tell her?

The News
• Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners’ Oral Contraception Study – Iversen et al. AJOG 2017
UK Royal College of General Practitioners' Oral Contraception Study

- 46,022 women recruited 1968-1969
- Followed for up to 44 years
  - 4661 ever COC users with at least one cancer during 884,895 woman-years of observation
  - 2341 never COC users with at least one cancer during 388,505 woman-years of observation.

Iversen et al. AJOG 2017

Results

- Previous concerns of any increased risk of breast and cervical cancer lost within five years of stopping COC
  - No evidence of increased risk of either cancer recurring with time.
  - Suggests earlier diagnosis rather than true harm
- Increased risk of lung cancer was seen only among ever users who smoked

Important cancer reductions persist many years after stopping COC use

- Poisson regression to estimate incidence rate ratios (IRR) between ever and never COC users — adjusted for age, parity, smoking, and social class

Ever use of COC associated with reduced cancer:
- Endometrial (IRR 0.66, 99% CI 0.48-0.89)
- Ovarian (IRR 0.67, 99% CI 0.50-0.89)
- Colorectal (IRR 0.81, 99% CI 0.66-0.99)
- Lymphatic/Hematopoietic (IRR 0.74, 99% CI 0.58-0.94)

Iversen et al. AJOG 2017

Implications for practice

- Hormonal “contraception” may be important for cancer prevention
  - Especially if BMI>30
  - Even if she were not seeking contraception
  - Even if she were 50 years of age
- Levonorgestrel Intrauterine Device as an Endometrial Cancer Prevention Strategy in Obese Women: A Cost-Effectiveness Analysis
Case: HPV

- 25 year old woman received 2 doses of HPV vaccine several years ago and wants to know if she should restart the HPV series? You tell her...

A. Since last dose > 12 months ago, she should restart the full 3 dose series.
B. If she received 2 doses before age 15, no further doses are needed.
C. HPV vaccine is only 2 doses now, regardless of age.

Background: HPV vaccination

- 9v HPV vaccine
  - Gardasil 9 (Merck®)
  - FDA approved Dec 2014
  - 2016: only vaccine distributed in US
  - 6,11 (genital warts)
  - 16, 18 + 31,33,45,52,58 (oncogenic)

The News

- Immunogenicity of 9-valent HPV vaccine Using 2-Dose Regimen in Girls and Boys vs a 3-Dose Regimen in Women – Iversen et al. JAMA 2016
  - 1377 boys & girls ages 9-14
  - 97.9% seroconversion 4 weeks after 2nd dose
- ACIP Dec 2016
  (Advisory Committee on Immunization Practices)
  - Routine vaccine 11-12 yo
  - 2 dose series ages 9-14 (0, 6-12mo)
  - 15-26: 3 dose series (0, 1-2, 6 mo)
Conclusion

- How many doses of HPV vaccine should patients receive?
  - If 2 doses initiated before age 15 years, no further doses.
  - If series started after age 15, 3 doses given.
  - If vaccination schedule is interrupted, do not restart series.

SCREENING PELVIC EXAMINATION

Henrietta

- Henrietta is a 36-year-old woman who comes to see you for a well-woman preventive examination. You perform a Pap with HPV co-testing. She recalls that in the past you have done a bimanual examination in order to "check her ovaries." She wants to know why you did not do that today.

Screening Pelvic Examination?

- A part of preventive health care for women for many years
- Not needed for contraception or STD screening
- What is the goal of a screening pelvic examination?
Pelvic Exam at the Well-Woman Visit
ACOG Committee Opinion 534; August 2012

- Women younger than 21 years
  - Pelvic exam only when indicated by medical history
  - Screen for GC, chlamydia with vaginal swab or urine
- Women aged 21 years or older
  - “ACOG recommends an annual pelvic examination”
  - No evidence supports or refutes routine exam if low risk
  - If asymptomatic, pelvic exam should be a “shared decision”
    - Individual risk factors, patient expectations, and medico-legal concerns may influence these decisions.
  - If TAH-BSO, decision “left to the patient” if asymptomatic

Screening Pelvic Examination:
ACP Evidence Report

- Review of 52 studies
- No evidence supporting the use of pelvic examination in asymptomatic average risk women
  - May cause pain, discomfort, fear, anxiety and embarrassment in about 30% of young women

Routine Pelvic Examination?

- Diagnostic accuracy for detecting ovarian cancer or BV is low
- Rarely detects non-cervical cancer or other treatable conditions
- ACP recommends against performing screening pelvic examination in asymptomatic, non-pregnant adult women

USPSTF Recommendations

- No studies assessing effectiveness of pelvic examination in reducing all cause mortality, cancer and disease specific morbidity and mortality or improving QOL
- Evaluated diagnostic accuracy and potential harms for ovarian cancer, bacterial vaginosis, trichomoniasis and genital herpes
- Current evidence is insufficient to assess the balance of benefits and harms for performing screening pelvic examinations in asymptomatic women for the early detection and treatment of a range of gynecologic conditions

- USPSTF Final Recommendation 2017
Does YOUR Patient need a pelvic exam?

- Clinicians who choose to perform pelvic examinations in asymptomatic women should be aware that there is uncertain benefit and there is the potential to cause harm through a positive test result and subsequent testing.

Case

38 yo woman presents to discuss weight loss options. She has difficulty with portion control and describes weekly episodes of eating large quantities of food in a short period of time. She feels that she cannot control herself during these binges. Recently she consumed an entire bag of Oreos in 30 minutes. She does not induce vomiting or exercise excessively after binges. BMI is 29.

What therapy will prevent binge eating & reduce weight?

A. sibutramine
B. self-directed - cognitive behavior therapy
C. lisdexamfetamine
D. sertraline

Binge Eating Disorder

- Most common eating disorder in the US
- Lifetime prevalence
  - women 3.5% (vs men 2%)
  - obese 5-30%
- DSM V Criteria
  - recurrent (>1x/wk) over 3 mo
  - brief (<2 hrs)
  - psychologically distressed binge-eating; consume larger amounts of food than most people would under similar circumstances & lack control over eating
- Current treatment guidelines are conflicting
  [American Psychiatric Association, National Institute for Health & Care Excellence]
News: Lisdexamfetamine for Binge Eating disorders

*Binge-Eating Disorders in Adults: A systematic Review and Meta-analysis


**Objective:** summarize evidence about benefits & harms of psychological & pharmacologic therapies for adults with binge-eating disorder.

**Methods:** Systematic review

**Funding:** AHRQ

---

### Results

- 34 trials with low/medium risk of bias
- Female: 77%
- Mean age: 36-47 years
- Mean BMI: 28.8-41
- Treatments: 6 weeks – 6 months

---

### Binge Eating Disorder Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Abstinence from binge eating</th>
<th>Depression symptoms</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation antidepressants*</td>
<td>Improved (RR 1.67)</td>
<td>Improved (MD -1.97)</td>
<td>No change</td>
</tr>
<tr>
<td>Therapist led-CBT</td>
<td>Improved (RR 4.95)</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>Improved (RR 2.61)</td>
<td>-</td>
<td>Decreased (5.2-6.3%)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Moderate benefit (58-64% vs 20-30%) 2 trials</td>
<td>-</td>
<td>Decreased (47%)</td>
</tr>
</tbody>
</table>

* citalopram, escitalopram, duloxetine, bupropion, fluvoxamine, paroxetine, sertraline

---

### Harms of Treatment

- Not reported in
  - Psychological studies
  - 20/25 pharmacologic studies

- 3 Trials = lisdexamfetamine
  - Sympathetic nervous system arousal: RR 4.28
  - Insomnia: RR 2.8 (CI 1.74-4.51)
  - GI upset: RR 2.71
  - General sleep disturbances: RR 2.19
  - Headache: RR 1.63
Conclusions

- In adults with binge eating disorder:
  - Increase abstinence from binge eating
    - therapist led-CBT
    - topiramate
    - lisdexamfetamine
    - 2nd generation antidepressants (i.e. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
  - Reduce weight
    - topiramate
    - lisdexamfetamine

Brownley et al. Annals 2016

Case

Nellie Natural is here for her annual visit. She mentions mild UTI symptoms for 4 days. UA is + for LE and nitrites. She's not a fan of medications, tends to prefer “natural supplements”, and asks you if antibiotics are truly necessary. You tell her:

A. Antibiotics may lower her risk of pyelonephritis
B. She can try ibuprofen 400 tid instead of an antibiotic
C. More than 2/3 of typical UTIs resolve on their own
D. All of the above
The News

• Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial.

• Objective: Can uncomplicated UTI be treated with ibuprofen to reduce antibiotic prescriptions without a significant increase in symptoms, recurrences, or complications?

Methods

• Double blind randomized multicenter trial of 42 GPs in Germany
• Intervention:
  – 779 women, up to age 65, with suspected UTI randomized
  • Fosfomycin 3 g sachet x 1 day or
  • Ibuprofen 400 tid x 3 days
  – Women scored their daily symptoms and activity impairment
  – Safety data collected q 6mo, between 2012-2014
• Inclusion criteria:
  – Dysuria, frequency, urgency, +/- lower abdominal pain
• Exclusion criteria:
  – Fever, “loin” tenderness
  – Pregnancy, renal disease
  – UTI within 2 wks
  – Urinary catheterization
  – Contraindication to NSAIDs

Results

<table>
<thead>
<tr>
<th>Selected outcome</th>
<th>Ibuprofen n=241</th>
<th>Fosfomycin n=243</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courses of antibiotic within 28d</td>
<td>81</td>
<td>277</td>
</tr>
<tr>
<td>Mean duration of symptoms</td>
<td>5.6 days</td>
<td>4.6 days</td>
</tr>
<tr>
<td>% Patients symptoms-free at day 7</td>
<td>70%</td>
<td>82%</td>
</tr>
<tr>
<td>% Patients with recurrence of UTI (d 15-28)</td>
<td>6%</td>
<td>11%</td>
</tr>
<tr>
<td>Number of patients with pyelonephritis</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Number of patients with GI symptoms</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>

Conclusions

• Women with mild to moderate symptoms may benefit
  – Nonparticipants had higher symptom scores

Reminder:

Treatment of asymptomatic bacteruria not recommended. 2015 Cochrane review showed no benefit of antibiotics to prevent:
• Symptomatic UTI
• Complications
• Death

Cranberry juice

• Nellie has just one more question: “My mother told me cranberry juice treats UTI’s, is this true?” You tell her...

A) There is no evidence on cranberry juice and UTIs  
B) Cranberry juice/capsules have not been proved effective at preventing UTI  
C) Cranberry juice/capsules prevent UTIs for nursing home patients  
D) Wrong juice - try orange juice

Background

• Cranberry proanthocyanidins  
  – inhibit adherence of *E. coli* to uroepithelial cells

• Prior studies UTI prophylaxis  
  – women 78.5 yrs  
  – 300ml (~10 oz) = 36mg  
  – daily x 6 months  
  – decreased bacteria & pyuria

The News

• **Effect of Cranberry Capsules on Bacteriuria Plus Pyuria Among Older Women in Nursing Homes.**  

• **Objectives**  
  – effect of 2 cranberry capsules/day (72mg proanthocyanidin)  
  • bacteriuria + pyuria  
  • women nursing home residents

Methods

**Study Design**  
– Double-blind placebo-controlled, efficacy RCT  

**Outcomes**  
– Bacteriuria (>100K CFU) + pyuria (WBC)  
  • assessed q 2 months, followed 12 months

**Exclusion criteria**  
– chronic suppressive antibiotics  
– ESRD  
– Unable to provide baseline clean catch urine specimen  
– warfarin  
– hx of nephrolithiasis  
– indwelling bladder catheter  
– nursing home residence < 4 weeks
Results
No Differences

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cranberry tablets (n=92)</th>
<th>Placebo (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriuria + pyuria</td>
<td>29.1%</td>
<td>29.0%</td>
</tr>
<tr>
<td>Symptomatic UTI</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>All cause hospitalization</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>MDR GNB Bacteriuria</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Antibiotics for suspected UTI</td>
<td>692</td>
<td>909</td>
</tr>
<tr>
<td>Total antimicrobials</td>
<td>1415</td>
<td>1883</td>
</tr>
</tbody>
</table>

Conclusions

- Cranberry capsules unlikely to prevent UTI for women >65 years, residing in nursing homes
- Supported by Cochrane Review 2012
  - Cranberry unlikely to prevent UTI over 12 months

Take-Home

- Nellie can try ibuprofen for her UTI. She should be counseled to call if her symptoms persist, and to watch for possible pyelonephritis.
  - Two-thirds of UTIs resolved on their own
- Women who take ibuprofen are more likely to need additional antibiotic therapy, but still less likely to receive antibiotics overall.
- If she likes cranberry juice, she should drink it, but there is no evidence that it will prevent or treat UTIs

Mammography Screening

The Ongoing Saga
Case

Ms. Smith is a 50 year old woman who just had her first screening mammogram which shows heterogeneously dense breasts but no other abnormalities.

- Menarche at 12, first child at 32
- No history of a breast biopsy
- No fhx of breast cancer

She asks if she should have “one of those 3D mammograms”?

You say:

- No, Digital (2D) mammograms, every 2 years are fine for you
- Yes, Digital 3D mammograms (tomosynthesis), every 3 years
- 2D or 3D mammograms every 1 year are fine
- Let’s review your risk for developing breast cancer and your preferences

Digital Breast Tomosynthesis

- Digital Breast Tomosynthesis (DBT) as a primary screening strategy

http://www.nydailynews.com/

Yaffe Breast Cancer Research 2008 10:209
Background

• 50% of breasts are dense
• Tomosynthesis (3D mammography)
• Now available ~22% of U.S. facilities
  • Varibly covered by insurance

Chronic Heart Failure:
Update on Effective Monitoring and Treatment

Michael G. Shlipak, MD, MPH
Professor of Medicine, UCSF
Chief, Division of General Internal Medicine, SFVA Medical Center
Scientific Director, Kidney Health Research Collaborative, UCSF

Outline

• Diagnosis and Staging
• Diastolic Heart Failure
• Systolic Heart Failure Medications
• Devices and End-Stage Heart Failure

Heart Failure Epidemiology

• Only cardiovascular outcome that continues to increase
• Lifetime risk ~20%
• Complicated to manage with multiple other comorbidities
• Treatments improve survival and reduce morbidity substantially.
  • 5 classes of medications improve survival
  • 3 classes of medications improve symptoms

2013 ACCF/AHA Guideline for the Management of Heart Failure
A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines
CIRCULATION, 2013

2016 ACC/AHA/HFS
A Focused Update on New Pharmacological Therapy for Heart Failure
CIRCULATION, 2016
Why is Heart Failure Challenging to Manage?

- Patients are very complicated and often frail
- CHF travels with many other comorbidities:
  - CAD, hypertension, diabetes, CKD
- Polypharmacy
- Diastolic heart failure becoming more common

Question 1: Which of the following establishes a HF diagnosis?

a) EF < 35% on echo
b) BNP > 300 on blood test
c) S3 on exam
d) All of the above
e) None of the above

Heart Failure is a Clinical Diagnosis

- **Essential Symptoms**: dyspnea, fatigue, orthopnea
- **Signs**: rales, edema, JVD, S3
- **Physical exam**: does not distinguish systolic vs. diastolic
- Helpful features include:
  - Chest X-Ray: pulmonary congestion
  - Elevated BNP or Nt-proBNP
  - Echo showing diastolic or systolic dysfunction

Diastolic vs. Systolic Heart Failure

- **Diastolic HF**:
  - Official term is “Heart Failure with Preserved Ejection Fraction”
  - Abbreviated as HFpEF
  - Pronounced “huff-puff”
- **Systolic HF**:
  - Official term is “Heart Failure with Reduced Ejection Fraction”
  - Abbreviated as HFrEF
  - Pronounced “huff-ruff”
NYHA Functional Classes

Classes assume a prior diagnosis of heart failure
I. No limitation on ordinary physical activity
II. Slight limitation – ordinary physical activity
III. Marked limitation < ordinary physical activity
IV. Symptoms or discomfort at rest

Problems with these classes:
• Patients vary across stages, going up and down
• All class 4 at time of hospitalization

AHA (2009) Classification of Heart Failure
A. Risk factors for heart failure – no clear signs/symptoms
B. Asymptomatic LV disease – LVH, diastolic dysfunction, valve disease, low EF
C. Symptomatic heart failure – dyspnea at rest or exertion, fluid retention
D. Advanced heart failure – inotrope requirement, consideration for assist device or transplant

• Can only progress down the classes
• Emphasizes prevention over staging

Strategies that apply to all CHF Patients
• Initial ECHO
• Repeat only if major changes
• Salt restriction
• Daily weight monitoring
• Exercise
• Diuretics for symptoms
• Avoid NSAIDS
• Monitor:
  • Volume status
  • Electrolytes, renal function

Outline
• Diagnosis and Staging
• Diastolic Heart Failure
• Systolic Heart Failure Medications
• Devices and End-Stage Heart Failure
Question 2: Which of the following improve survival in diastolic heart failure?

a) ACE-I  
b) ARB’s  
c) Beta blockers  
d) Ca-channel blockers  
e) All of the above  
f) None of the above

What is Diastolic Heart Failure?

• “Stiff heart syndrome”- heart cannot relax in diastole to allow the left ventricle to fill  
• Causes increased pressure in the left atrium, and pulmonary edema  
• Defined by EF, yet actual stroke volume may be same as SHF  
• Same signs and symptoms as systolic HF  
• Especially common in women and elderly

Diastolic HF: Good and Bad News

Good news:  
• More favorable prognosis than SHF  
• Simpler regimen, as diuretics cornerstone of therapy  

Bad news:  
• Often progresses to SHF  
• No therapies improve DHF survival

ACC/AHA Guidelines for DHF Treatment

• BP control (SBP < 130)  
• Rate/rhythm control in AF  
• Diuretics for pulmonary congestion  
• Revascularization and other treatment for coronary ischemia  
• European guideline recommends cardiac rehabilitation, though limited evidence  
Outline

- Diagnosis and Staging
- Diastolic Heart Failure
- Systolic Heart Failure Medications
- Devices and End-Stage Heart Failure

ACE Inhibitors

- Improve symptoms and reduce hospitalizations
- Decrease mortality risk for all heart failure stages
- Class effect- all ACE inhibitors
- Aim for target dose (ATLAS finding)

Meta-Analysis of ACE Trials

- 30 RCTs- ACE-I vs. placebo
- Mortality
  - 0.77 (0.67-0.88)
- Death or hospitalization for heart failure
  - 0.65 (0.57-0.74)
- Specific ACE-I’s with benefits in RCT’s:
  - Benzaapril  -Enalapril  -Ramipril
  - Captopril  -Lisinopril

Kidney Function and ACE Inhibitors in Heart Failure

- Clinical trials show benefit if estimated GFR > 30
- No evidence for lower GFR levels
- Expect the creatinine to rise at least 30%
- Even creatinine doubling is OK- typically returns near baseline
- Worry about K increase (keep < 5.5); balance the K with diuretic dose.
- Continue ACE-Is as eGFR declines unless cannot control K.

Shlipak MG, Ann Intern Med 2003
ARBS in Systolic Heart Failure

- Generally equivalent to ACE inhibitors
- Use for patients with cough on ACE inhibitors
- Combination of ACE and ARB?
  - Decreases hospitalization risk; increases adverse effect risk (increased K)
  - No survival difference
  - Generally, not recommended, as safety probably lower in actual practice

Yunus S. et al. Lancet 2003

Question 3: What is an “ARNI”?

- A. Novel heart failure agent that slows down the SA node to allow greater ventricular filling
- B. New class of heart failure drugs that prevents arrhythmias so patients will not require an ICD
- C. A combination of an Angiotensin Receptor Blocker with a medication that blocks neprilysin
- D. A novel beta-blocker that has the ability to increase ejection fraction
- E. All of the above

PARADIGM-HF Trial: Angiotensin-Receptor blocker/Neprilysin Inhibitor (ARNI) vs. Enalapril

The NEW ENGLAND JOURNAL OF MEDICINE

Angiotensin–Neprilysin Inhibition versus Enalapril
In Heart Failure


PARADIGM-HF Trial

- N=8,442
- Class 2-4 HF symptoms
- EF< 40%
- The new drug:
  - LCZ696
  - Valsartan/Sacubitril
  - Entresto
  - 2015 FDA approval
- Sacubitril- blocks Neprilysin
  - ↓ vasoconstriction, ↓ Na retention, ↓ remodeling
- Prior ARNI- Omapatrilat (caused ↓ BP, angioedema, and cognitive dysfunction)
PARADIGM-HF Trial

**Inclusion Criteria:**
- EF < 40%
- BNP > 150
- Prior ACE/ARBs

**Exclusion Criteria:**
- SBP < 95
- eGFR < 30
- K > 5.2
- ACE/ARB angioedema

PARADIGM-HF Trial

**Baseline Characteristics of Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>64</td>
</tr>
<tr>
<td>% Female</td>
<td>22%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>66%</td>
</tr>
<tr>
<td>Black</td>
<td>5%</td>
</tr>
<tr>
<td>Asian</td>
<td>18%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
</tr>
<tr>
<td>Mean BP</td>
<td>125/72</td>
</tr>
<tr>
<td>Mean Creatinine</td>
<td>1.12</td>
</tr>
<tr>
<td>% eGFR&lt;60</td>
<td>36%</td>
</tr>
<tr>
<td>Class 2</td>
<td>70%</td>
</tr>
<tr>
<td>Class 3</td>
<td>24%</td>
</tr>
</tbody>
</table>

PARADIGM-HF Trial

*Baseline Characteristics of Patients (continued)*

<table>
<thead>
<tr>
<th>Medications</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE/ARB</td>
<td>100%</td>
</tr>
<tr>
<td>BB</td>
<td>93%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>80%</td>
</tr>
<tr>
<td>Aldo-Antagonist</td>
<td>55%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>30%</td>
</tr>
<tr>
<td>Devices</td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>15%</td>
</tr>
<tr>
<td>CRT</td>
<td>7%</td>
</tr>
</tbody>
</table>

PARADIGM-HF Trial

**Enrollment in 3 Phases**

1.) Enalopril 10mg 2x/day: 2 weeks (N= 10,513)
- 10% drop out (5.6% adverse effects)

2.) LCZ696: 4 weeks (N=9,419)
- 100 mg and 200 mg
- 10% drop out (5.8% adverse effect)

3.) RCT: Enalopril (10 mg 2x/day) vs. ARNI (200 mg 2x/day) (N=8,442)
- Trial stopped early
- Median follow-up 27 months
**PARADIGM Trial**  
*Primary and Secondary Outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death or HF Hospitalization</td>
<td>21.8%</td>
<td>26.9%</td>
<td>0.80 (0.73-0.87)</td>
</tr>
<tr>
<td>Death</td>
<td>13.3%</td>
<td>16.5%</td>
<td>0.80 (0.71-0.89)</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>12.8%</td>
<td>15.6%</td>
<td>0.79 (0.71-0.89)</td>
</tr>
<tr>
<td>Secondary outcomes (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>17.0%</td>
<td>19.8%</td>
<td>0.84 (0.76-0.93)</td>
</tr>
</tbody>
</table>

**PARADIGM Trial**  
*Adverse Events during Randomized Treatment*

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension Symptomatic</td>
<td>14.0%</td>
<td>9.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine &gt;2.5 mg/dl</td>
<td>3.3%</td>
<td>4.5%</td>
<td>0.007</td>
</tr>
<tr>
<td>Elevated serum potassium &gt;6.0 mmol/liter</td>
<td>4.3%</td>
<td>5.6%</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>11.3%</td>
<td>14.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema</td>
<td>0.5%</td>
<td>0.2%</td>
<td>0.19</td>
</tr>
</tbody>
</table>

**Controversies around Entresto**

- Cost - $4,560/year
  - Pay for performance models?
- Single trial
  - Only 5% Blacks
  - Low % with devices
  - Run in period required tolerance to the drug
- Potential “off target” effects?
  - Hypotension
  - Cognitive decline a concern (with Omapatrilat)

**Recommendations around Entresto**

**Recommendations**

1.) Class 1 agent for systolic HF
2.) For use in patients who are stable on maximum ACE or ARB
3.) Never use in combination with ACE or ARB
Beta Blockers in Systolic Heart Failure

- Beta blockers improve symptoms and increase ejection fraction by 5-10%
- Beta blockers decrease mortality in systolic heart failure, from both pump failure and arrhythmic causes
- Unlike ACE inhibitors, not a class effect
- Metoprolol or Carvedilol (U.S.)
- Bisoprolol in Europe

Heart Failure Survival

![Heart Failure Survival Chart]

Challenge of Titrating Beta Blockers in Heart Failure Patients

- Both metoprolol and carvedilol require subtle dose increases at 2 week intervals
- Can take up to 6 visits to reach target
- Hypo-tension is not a contra-indication unless symptomatic (even if SBP<90)
- Carvedilol may be more difficult to titrate dose up.
- Benefit greatest at maximum dose
- Unfortunately, many patients left at the low starting dose

Other Therapies in Systolic Heart Failure

- Diuretics
- Aldosterone Antagonists- spironolactone, eplerenone
- Hydralazine/Nitrates
- Invabradine
Diuretics

- Rapid relief of dyspnea and fluid retention
- Aim for lowest dose that reaches “dry weight”
- Therapeutic goals:
  - Improved dyspnea and orthopnea
  - Minimal pre-tibial edema
- Patients can manage the dose and schedule

Diuretic Refractory Patients

- Periodic thiazide (metolazone)
  - e.g. 3x/week doses
  - watch for hypo-Na+, hypo-K+
- Change the loop diuretic- furosemide (Lasix), bumetanide (Bumex), Torsemide (Demadex)
- Long-acting nitrates also useful for symptoms
- Occasional IV diuretics may be required- intestinal edema can block po absorption

Aldosterone Antagonists
(spironolactone, eplerenone)

- Improve survival and reduce hospitalization-RALES trial
- Only studied in NYHA class 3-4 heart failure patients on ACE inhibitors
- K allowed up to 5.6; very few hyper-K complications
- 1/3 on beta blockers

Rales Trial

HR = 0.70

Pitt B. et al., NEJM 1999

Enormous Rise in Spironolactone Use

Juurlink DN et al., NEJM 2004
Epidemic of Hyper-K Followed

![Graph showing rates of hospitalization for hyperkalemia from 2000 to 2004.]

Juurlink DN et al., NEJM 2004

What Happened?

- It’s in the fine print…
- RALES methods- inclusion if patients Cr < 2.5
- 2005 AHA Guidelines- spironolactone recommended in NYHA III heart failure if Cr < 2.5
- RALES table 1- actual Cr levels 1.2 ± 0.3
  - ~80% had Cr ≤ 1.5
  - ~ all had Cr < 2.0
  - average furosemide dose of 80mg

Shlipak MG et al., Ann Intern Med 2003

Case Details of Hyper-K on Spironolactone

- Case reviews of critical or fatal hyper-K (≥ 6.5) Schepters et al., Am J Med 2001
- Mean Cr of 2.1; all on ACE-I also
- Often in setting of other illness- decreased oral intake
- Lessons learned:
  - Caution in using spironolactone if eGFR < 45, or Cr ≥1.5
  - Stop spironolactone in acute illness

Guideline Recommendations on Aldosterone Antagonists

- AHA HF guidelines (2005, 2009, 2013) have vascillated on aldosterone antagonists

AHA Class I:
- Recommended for HF patients EF< 35%
- eGFR> 30; K < 5.0

AHA Class III (harmful):
- eGFR< 30, K > 5.0

My recommendation: Use extreme caution if eGFR 30-45
  - QOD dosing; cutting dose by ½
  - Advise patients to stop using when PO intake is reduced or acutely ill
**Hydralazine and Nitrates**


- 1,040 African American patients
- Hydralazine vs. Placebo
- Trial halted early
- HR= 0.57, p= 0.01

**Hydralazine/Nitrates**

- Recommended (Class I) for “self-described” African Americans
  - Reduced EF
  - Class III/IV symptoms
  - Already treated with ACE, BB
- Consider (Class 2A) in patients who cannot tolerate ACE/ARB

**Ivabradine (Corlanor)**

*SHIFT Trial*

- New class of HF drug
- Slows HR at SA node (I, current)
- Patients EF<35%, HR>70, on BB
- Results:
  - ↓ HF Hospitalization: 16% vs 21% (0.74; 0.66-0.8)
  - No difference in mortality risk
- AHA recommendation: class 2A for patients with HF and EF<35%
- Opinion: no clear role for this drug in most patients

**Outline**

- Diagnosis and Staging
- Diastolic Heart Failure
- Systolic Heart Failure Medications
- Devices and End-Stage Heart Failure
**Rationale for Implantable Cardiac Defibrillators (ICDs) in CHF**

- Ventricular arrhythmia - common cause of heart failure death
- ICDs can reverse VT/VF and save the patient
- VT/VF risk is highest in end-stage CHF patients; but those patients unlikely to survive to gain benefit
- Challenge for selecting ambulatory patients for ICDs:
  - VT/VF risk high enough to benefit
  - CHF moderate, so patient might live a few years

**ICD’s in Secondary Prevention**

- Studied in Systolic HF patients
- Patients who survived prior sudden death or unstable VT event
- ICD’s clearly improve survival
- Must be consistent with goals of care for patient/family – critical role for the PCP

**ICDs in Primary Prevention**

- Risk/benefit tradeoff
- Recommended for patients with EF < 35% AND:
  - moderate HF symptoms on appropriate treatment
  - expectation of survival > 1 year
  - Not for class 4 HF - prognosis too poor to benefit, unless as a bridge to transplant
- Prior MI patients appear to have higher SCD risk, among those with Systolic HF

**Rationale for CRT (Cardiac Resynchronization Therapy)**

- Cardiac dys-synchrony:
  - Concern in patients with EF< 35%
  - RV and LV may not be in harmony
  - Suspect dysynchrony in patients with persistent symptoms despite ideal treatment
- Causes: decrease ventricle filling, decrease EF, increase MR
- CRT: activates LV/RV together with bi-ventricular pacer
- Meta-analysis:
  - decrease in mortality by 25%
  - detectable after 3 months

McAlister FA, JACC 2004
Ideal Candidates for CRT

- EF < 35% and persistent symptoms
- 3 additional ECG criteria:
  - Sinus rhythm
  - LBBB
  - QRS > 150ms
- **Class I:** all 3 ECG criteria
- **Class 2A:** 2 of 3 ECG criteria
- **Class 2B:** 1 of 3 ECG criteria

End-Stage Heart Failure

**European Definition of Class D/Advanced HF**
- Severe symptoms at rest or with minimal exertion
- Hospitalized in last 6 months
- Treatment already optimized
- Poor functional status

**Clinical correlates of Advanced HF**
- Weight loss
- Worsening kidney function
- SBP<90
- Intolerance to ACE and/or BB
- Na<133
- Increasing diuretic requirement
- Frequent ICD shocks

Additional Support for End-Stage Heart Failure Patients

Consider:

- Specialized strategies (HF specialist):
  - Mechanical circulatory support
  - Inotrope infusions
  - Transplant or surgery referral

- Hospice/End-of-Life Care (Palliative care)
  - Comfort care
  - Turn off the ICD

Thank you! Any Questions?
Common Infections of the Skin

Toby Maurer, MD
University of California, San Francisco

Candida of Nails

- Occurs in persons who have hands in water
- Green nails represent the co-pathogen which is pseudomonas

TREATMENT:
- Fluconazole 150 mg qd x1 month PLUS Ciprofloxacin 500 bid x 2 weeks
  OR
- Thymol 2-4% soak 20 mins bid x 3 months and tobramycin or gentamycin ophthalmologic drops

How to diagnose

- Not all dystrophic nails = onychomycosis
- KOH-difficult to do and operator dependent
- CULTURE is gold standard but takes 3 weeks to grow out.
- Now PCR-used in Europe with high sensitivity and specificity
- Cost effective and results in 24-72 hours

Onychomycosis

- Topical treatment –use for the right type of lesions
- Naftin gel for small superficial lesions
- Penlac (Ciclopirox 8%) reported to work 35-52% of the time
  – cost: expensive
Right type of lesions for topicals

- Lunula not affected
- Less than 5 nails affected
- No thickening of nails
- No separation of nail plate on sides

- Griseofulvin-least hepatotoxic but lower efficacy- 250 mg bid x 12-18 months
- Fluconazole- 150 mg qweek for more than 6 months –July 2012 Dermat Tx Gupta AK et al
- Itraconazole- can pulse it- 400 mg qd x 7 days q month x 4 months

Terbinafine (Lamisil)

- Still the leader of the pack-most effective in terms of INITIAL and LONG-TERM cure rate.
- DOSE: 250 mg qd Continuously x 3 months for fingernails and x4 months for toenails (July 2012) i.e. no pulsing

<table>
<thead>
<tr>
<th></th>
<th>BASELINE</th>
<th>1 YR</th>
<th>5 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine</td>
<td>77%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>70%</td>
<td>50%</td>
<td>13%</td>
</tr>
<tr>
<td>Grispeg</td>
<td>41%</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Liver toxicity

- Transaminase elevation 0.4% to 1% with terbinafine and intraconazole
- Transaminase elevation does not predict liver failure
- Liver failure 1/100,000
- Terbinafine has gone generic

What about laser?

- Photo-inactivation laser and destructive laser
- 4 studies-2 – no results; 2 show results but with recurrence. Gp treated with laser and topical had fewer recurrences.

Dissecting Cellulitis of Scalp

- Occurs in persons of color
- Culture for tinea but usually bacterial
- Culture and ask lab to provide identification of organism regardless of colony count
- Can take 1-2 years to treat with long-term antibiotics

Tinea Capitis

- Scaling and alopecia
- Examine all children in the family
- “Brush” culture and begin empiric therapy
- Treatment
  - Gris-PEG: 15-25mg/day x 6 weeks
  - Terbinafine 2-4 weeks
  - 62.5mg/kg(10-20kg)
  - 125 mg/day(20-40 kg)
  - 250 mg/day(>40 kg)
Cutaneous Tinea

- KOH is helpful in distinguishing tinea from eczema
- Topical antifungals x 4-6 weeks
- Just say NO to Lotrisone PLEASE!

Pitted Keratolysis

- May be confused with tinea on foot
- See pits
- Bad odor
- From bacteria (corynibacteria)-topical erythromycin bid

Intertrigo

- Under pannus and breasts
- Always a component of candida
- Blow dry area
- Topical antifungals
- Tucks pads (wet to dry dressing)

Erosio interdigitalis blastomycetica

- Candida and bacteria between toes or fingers
- Spreads to DORSUM of foot and has impetiginous look
- Treatment:
  - Drying agents: Burow’s soaks (aluminum acetate)20 mins bid
  - Antibiotics for staph aureus
  - Topical or po antifungals
  - Mild topical steroid for itch
**Tinea Versicolor**

Treatment:
- for localized areas, topical antifungal
- otherwise:
  - Ketoconazole (Nizoral) 200 mg po daily x 4 days - NOT USING THIS ANYMORE
  - Fluconazole 400 mg x 1; tebinafine 250 qd x 7 days

**Recurrent Staph Infection**

- Tx for methcillin resistant staph (MRSA) right off the bat: Doxycycline, septra, clinda and cipro
- Eradicate staph for 3 months by adding rifampin 600 qd x 5 days (watch drug-drug interactions) or
- Mupiricin intranasally qd for first 5 days of every month

**Recurrent skin infection**

- UNDERLYING disease that could be portal of entry
- Dry skin-lubricate with grease
- Eczema/Contact Dermatitis-TAC and lubrication
- Psoriasis-staph exacerbates psoriasis and psoriasis portal of entry
- Tinea- portal of entry-tx with antifungals

**If not improving**

- Was patient treated long enough?
  Once hair structures are involved or deep tissues, treatment time may be longer
Don’t forget strep

- Strep: Doxycycline and septra may not cover strep
- Cipro/levo do not cover strep
- Add antibiotic that covers strep- Cephalosporins or Dicloxicillin

Jacobs et al Diagn Microb Inf Dis 2007, March

Cellulitis

- Goal in study was to have dermatologists diagnose cellulitis vs other diseases
- 635 pts seen-67% had cellulitis N=425
- 33% had OTHER-eczema, lymphedema, lipodermatosclerosis

Levell et al Br J of Dermatol (BJD) 2011 Feb

Take Home Points:

- Of the 425 with cellulitis, 30% had predisposing dermatologic disease like tinea, eczema, psoriasis (treat underlying derm disease!!!)
- Hospitalization was averted for 96% of those with cellulitis (p.o. antibiotics with close follow-up)

- Does the patient really have cellulitis?
- Is there an underlying dermatologic cause that contributes to condition-if treated could prevent repeated episodes?
- Does this patient require hospitalization?
Venous Insufficiency Ulcer

- **Control Edema**
  - Elevation of leg above heart 2 hours twice daily
  - Walk, don’t sit
  - Compression
- Diuretics overused and not of benefit unless fluid retention due to central problem is present (CHF, CRF)
- Create healing wound environment
  *lymphedema/venous ulcers biggest risk factor for recurrent cellulitis (Tay JAAD 2015)

---

Venous Insufficiency Ulcer

- **Metrogel** on ulcer-decreases anaerobes
- **Semipermeable Dressing** (Hydrosorb, Duoderm, etc)
- **Compression**
  - Unna boot covered by Coban –
  This both provides graded compression AND creates the correct wound environment
  - Change dressing weekly
  - Refer to dermatology if not healing

---

When is a Leg Ulcer Infected?

- All leg ulcers are colonized with bacteria. Surface culture of little value
  - Suspect infection if:
    - Increasing pain
    - Surrounding erythema, cellulitis
    - Focal area not healing and undermining present
  - Treat superficial contaminant with vinegar/Burow’s soaks

---

Was it an inflammatory condition and not an infection?

- Erythema nodosum
- Pyoderma gangrenosum
- Hidradenitis suppurativa
Erythema Nodosum

- Not an infection
- Reaction pattern to strep, cocci, oral contraceptives, estrogen replacement, inflammatory bowel disease, TB and INFLAMMATORY BREAST DISEASE
- Painful, red nodules lower legs
- Pt's feel bad
- Biopsy diagnosis - inflammation of fat
- Treatment with bedrest, NSAIDS, prednisone

Pyoderma Gangrenosum

- Not an infectious disease
- A "reactive" inflammatory disease
- Biopsy diagnosis
- Surgical I&D/excision make it worse

Treatment

- Do Not I&D
- Prednisone/cyclosporine
- Thalidomide
- Tacrolimus (protopic)
- Tx underlying disease

Hidradenitis Supparativa

- Not an infectious disease
- Disease of apocrine glands
- Treatment
  - IL Kenalog
  - Minocycline
  - NEW: clindamycin and rifampin for 12 weeks or acitretin

NOW Isotretinoin being used again - best in younger and thinner pts.
- Surgery
- NOT Antibiotics for bacteria i.e. 10 day course
- Biologics: infliximab (remicade), adalimumab (humira)
Inflammatory Diseases

- Trying to find specific cytokines in tissues and target them with biologics

Orolabial Herpes Simplex

- No prophylaxis
- Treat when symptomatic
- Sun exposure can activate HSV-ACV 800 mg 1 hour before sun exposure

Warts

- HSV can give an erythema multiforme reaction
- Usually painful targetoid lesions on elbows and knees

60 different wart types
We have been exposed by the age of 2 to cutaneous warts
60 ways to treat-only 50% efficacy
Tx every 3 wks
LN2 most common
Sal acid effective but use nightly for 3 months at least
Molluscum

- In normal host-self-limited
- LN2 works
- Picking center works
- Retinoids /imiquimod do not work
Best Practices in Palliative Care: What Works, What Doesn’t

ANNA CHODOS, MD, MPH
ASSISTANT PROFESSOR OF MEDICINE
DIVISION OF GERIATRICS
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Disclosures

I have no financial disclosures to report.

First, the bad news---What Doesn’t Work...

1. Docusate
2. Chemotherapy Near End of Life
3. IV Hydration Near End of Life
4. Oxygen in Non-Hypoxic Patients with Dyspnea

Docusate for Constipation

- Study: Double-blind RCT
  - 74 patients, 3 inpatient Canadian hospices
  - Randomized to 10 days of:
    - Senna 1-3 tabs/day + docusate 100 mg BID
    - Senna 1-3 tabs/day + placebo BID

Study Results

- Docusate group had marginally larger volume of stool $p=0.06$; stool consistency was slightly different between groups
- No differences in:
  - Average # of bowel movements/day
  - Patients’ perceptions of the difficulty or completeness of defecation
  - Pain
  - Percent of patients requiring additional bowel intervention (74% placebo; 69% docusate)
- Additional issues: tastes horrible, pill burden

Take-Homes

No appreciable benefit of adding Docusate to Senna in hospice patients

- What works for constipation:
  - Always rx laxative with opioid
  - Start with Senna, then add Miralax, Lactulose, etc
  - Suppository or enema (avoid Fleet's) if > 3-4 days
  - Hydration and activity
  - Consider Methylnatrexone for opioid-induced constipation if above not working

Chemotherapy Near End of Life

- Goals of chemotherapy for patients with metastatic cancer:
  1. Live longer
  2. Live better
- Study: Association of chemo in last 6 months of life with caregiver-reported quality of life in last week of life and survival

Chemotherapy Near End of Life

- 661 patients with advanced met cancer who had progressed on prior therapy
- MD estimate of < 6 months to live
- ½ of patients were on chemo at enrollment
- Median survival 4 months
- Patients with good functional status were more likely to receive chemo
Study Results

- No improvement in QOL for patients with moderate or poor baseline functional status
- Chemo associated with worse QoL for patients with better functional status at baseline
- No difference in survival (though study not designed for this)

Think twice about whether to support palliative chemotherapy for patients with metastatic cancer who are near the end of life.

IV Hydration Near End of Life

- Significant controversy
- Stopping to eat and drink at end of life is normal
- Associated with edema, effusions and ascites
- Does not reduce thirst
- Requires some sort of access/line

RCT of 129 hospice patients with cancer and mild-moderate dehydration

Intervention:
- 1L NS/day over 4 hours x 4 days
- 100mL NS/day over 4 hours x 4 days

Study Results

- No stat sig difference in:
  - Survival (21 vs 15 d, p value 0.83)
  - Symptoms (fatigue, myoclonus, sedation, hallucinations)
  - Quality of Life
- Both groups noted subjective improvement in dehydration symptoms

Typically best to minimize IVF at end of life.
Supplemental Oxygen for Dyspnea In Non-Hypoxic Patients

- Palliative oxygen therapy widely used for dyspnea
- Potential benefits: placebo effect, family feels like “doing something”
- Potential burdens: ties patient down, social stigma, uncomfortable, nosebleeds, fire risk

Supplemental Oxygen Trial

- Study:
  - Double-blind RCT
  - 239 outpatients in US, Australia and UK with life-limiting illness, refractory dyspnea, and PaO2 > 55 mmHg
  - Randomized to RA or O2 at 2 LPM x 7 days
    - Instructed to use O2 at least 15 hours/day

Abernathy A. Lancet 2010;376(9743):784-93

Study Results

- No difference between supp O2 vs RA by NC in:
  - Mean AM Breathlessness scores
  - Mean PM Breathlessness scores
  - Quality of Life

Compared with RA NC, oxygen by NC provides no benefit for dyspnea in patients who are not hypoxemic.

What Works for Dyspnea

- Treat the underlying cause
  - Pleural effusion, PE, pna, ascites
- Opioids
  - Low dose, Safe even in COPD
- Position
- Breathing training
- Fan and/or fresh air
- Cold cloth to face
- Acupuncture in COPD

Bausewein C. Cochrane Database Syst Rev. 2008(1):CD005163
**And now, the good news--- (Other things) that work!**

- Palliative Care
- Skillful and Sensitive Communication
- Advance Care Planning

**Palliative Care**

- Specialized medical care for patients with serious illness and their families
- Focuses on providing relief from the symptoms and stress of a serious illness
- Team-based approach
- No prognostic or treatment limitations
- Hospice is a type of palliative care
  - A Medicare Benefit (Part A)
  - For patients with prognosis less than six months who have chosen to forgo life-prolonging interventions
  - Can be offered at home, SNF, or other residential facility

**Old Paradigms of Palliative Care Engagement**

**Current Paradigm of Palliative Care Engagement**

Condition appropriate for palliative care may or may NOT progress to death
### Palliative Care Benefits

**Quality Improves**
- Reduction in symptom burden
- Improved quality of life
- Longer length of life
- Increased family satisfaction
- Better family bereavement outcomes
- Care matched to patient centered goals

**Costs Decrease**
- Hospital costs decrease
- Need for hospitalization/ICU decreases

### Early Palliative Care Intervention

- **Study:**
  - Non-blinded, RCT (single site)
  - Ambulatory patients with newly diagnosed metastatic NSCLC
  - Immediate PC + onc vs onc
  - Primary outcome: change in QOL at 12 weeks

**Study Results**
- Baseline characteristics did not differ between groups
- Intervention group:
  - Better QOL scores
  - Less depression
  - More documentation of resuscitation preferences
  - Less aggressive care at the end of life
  - Lived two months longer

Palliative Care appears beneficial for patients with newly diagnosed metastatic NSCLC.

### Access to Palliative Care

[www.getpalliativecare.org](http://www.getpalliativecare.org)
Skillful and Sensitive Communication

- Patients and families want their providers to:
  - Bring up end of life issues
  - Be available and willing to talk AND listen
  - Provide timely and clear information
  - Encourage questions

- Patients tend to want:
  - Prognostic information
  - For bad news to be delivered sensitively
  - Control over the timing of conversation
  - Active participation in decision-making, but desire recommendations

Yet, patients and families report...

- Not enough:
  - Contact with physician 78%
  - Emotional support (pt): 51%
  - Info re: dying process: 50%
  - Emotional support (family): 38%
  - Help with pain/dyspnea: 19%

- And a lack of:
  - Coordination
  - Access
  - Anticipatory Guidance
  - Assurance

In general...

- We spend a lot of time talking
- But sometimes, not enough
- We interrupt a lot
- We miss emotional cues
- We lack education and confidence

Audience Poll

The biggest barrier for me in having conversations about serious illness/end-of-life with my patients is:

1. Knowledge (of how to have the conversation)
2. Time
3. Money (I can’t or don’t know how to bill)
4. Personal Discomfort - Fear of Taking Away Hope or Damaging the Relationship
5. None, this stuff is easy
Unique Opportunity in Primary Care

- Systematic review of 126 articles: 77 directly addressed primary care, 26 addressed specific populations

**Strengths**
- Continuity
- Duration
- Trust
- Ability to coordinate across settings
- Unique ability to have these in an iterative manner

**Weaknesses**
- Deficits in knowledge, skills, and attitudes
- Discomfort with prognostication
- Lack of clarity about the appropriate timing and initiation of conversations

Lakin J. JAMA Intern Med 2016; 176(9):1380-1387

Key Communication Tools

- Asking for Permission

Key Communication Tools

- Respond to Emotion

<table>
<thead>
<tr>
<th>Name</th>
<th>“It sounds like you’re frustrated.”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand</td>
<td>“It must be hard going through this alone.”</td>
</tr>
<tr>
<td>Respect</td>
<td>“I am so impressed by your commitment to your mother.”</td>
</tr>
<tr>
<td>Support</td>
<td>“I’ll be with you through all this.”</td>
</tr>
<tr>
<td>Explore</td>
<td>“Tell me more.”</td>
</tr>
</tbody>
</table>

○ Practice: “I feel like my life is spiraling out of control”

Key Communication Tools

- Silence as a Tool
  ○ “Say something empathic and then just shut up.”
Improving Communication

- VitalTalk (www.vitaltalk.org)

Improving Communication (cont.)

- Readings
  - Eprognosis (ucsf.eprognosis.edu)
Advance Care Planning

- An *ongoing process* of discussing care preferences and making care plans between patients (*and their caregivers*) and providers
- Should include discussion of person’s priorities, beliefs, and values AND prognostic information
- May or may not lead to completion of advance directive
- Both physicians and patients think it’s important

Benefits of ACP

- Patients who have advance care planning or EOL conversations with their provider are:
  - More likely to received outpatient hospice and be referred to hospice earlier (Zhang et al. 2009, Wright et al. 2008)
  - More likely to have their interventions known and followed (Detering et al. 2010; Houbin 2014)
  - Family members are more likely to be satisfied with the quality of death (Detering et al. 2010)

Audience Poll

In my practice, I aim to have advance care planning conversations with:

1. None of my patients
2. All my patients over 65 years old
3. My patients who are terminally ill
4. Both 2 and 3
5. All my patients regardless of age

ACP Practices in Primary Care

- Systematic review of 10 studies (5 US) among PCPs providing care for patients living in the community or an assisted living
- ACP most frequently done with patients with cancer, Alzheimer’s dementia, or other terminal illness
- Of patients who died of non-sudden deaths, one-third had ACP
- Provider-reported ACP rates higher than patient-reported ones
- Lack of systematic approach; hard to judge when to initiate
- Patients want to discuss, even if healthy; feel it is responsibility of provider to bring up

Glaudermans et al. (2015) Fam Practice
ACP Documentation

- Include on problem list; be specific
- Many health systems working on streamlined EMR ACP documentation processes
- When patient preferences clear, complete advance directive and medical order (for patients with less than 1 year prognosis; in states where available)

ACP Billing

- ACP CPT codes NEW in 2016
  - "ACP includes the explanation and discussion of advance directives such as standard forms (with completion of such forms, when performed), by the physician or other qualified health professional"
  - 99497: first 30 min F2F (wRVU 2.40; $85.99)
  - 99498: each additional 30 min F2F (wRVU 2.09; $74.99)
  - Include pertinent diagnoses; can bill more than once/yr

ACP Tools

- www.prepareforyourcare.org
- www.theconversationproject.org
Miscellaneous PC Pearls

- “Easier to stay ahead of [insert symptom], than catch up”
- Symptom management and ACP are PROCESSES
- “Patients (and families) aren’t always looking to be “fixed,” often they just want someone to listen to them, validate them, and bear witness to their story.”

Summary

- What doesn’t work...
  - Docusate
  - Chemotherapy Near End of Life
  - IV Hydration Near End of life
  - Oxygen for Non-Hypoxic Patients
- What works!
  - Palliative Care
  - Skillful and sensitive communication
  - Advance Care Planning
- Great Resource: https://www.capc.org/fast-facts/

THANK YOU

- Brook Calton, MD
- www.geripal.org
Sports Concussion 2017
What the Clinician Needs to Know

Carlin Senter, MD
Associate Professor
Co-Director UCSF Sports Concussion Program
Primary Care Sports Medicine
University of California San Francisco

UCSF Essentials of Primary Care     August 11, 2017

Sports Concussion 2010

- Concussion is serious public health issue
- Need clinical care for sports concussion patients
- Need community education
- Need to advance diagnostic tools
- Need prevention measures

I have no disclosures.
UCSF PlaySafe

• Athletic trainer at high school
• M.D. on sideline and in clinic
• Preparticipation exams
• Baseline testing
• Education

Sports Concussion 2017

Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016


Outline

1. Epidemiology
2. Evaluation
3. Treatment
   • How much rest?
   • Return to learn
   • Return to play
4. Legislation
5. How many concussions is too many?

Concussions are common
Concussions are common

Concussion numbers increasing

Put these high school sports in order of highest to lowest incidence of concussion.

A. Soccer (boys)
B. Soccer (girls)
C. Basketball (girls)
D. Wrestling (boys)
E. Football (boys)

Rates of sports concussion in high school sports U.S. 2011-2012

<table>
<thead>
<tr>
<th>Sport</th>
<th>Rate per 1000 athletic exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Football (boys)</td>
<td>0.94</td>
</tr>
<tr>
<td>Soccer (girls)</td>
<td>0.73</td>
</tr>
<tr>
<td>Wrestling (boys)</td>
<td>0.57</td>
</tr>
<tr>
<td>Soccer (boys)</td>
<td>0.41</td>
</tr>
<tr>
<td>Basketball (girls)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Concussion definition

- Blow to head, neck, body → force to head
- Rapid onset of neurologic impairment
  - In some cases signs and symptoms can evolve over minutes-hours
- Acute functional injury (rather than structural injury)
  - CT and MRI normal
- Symptoms usually resolve in weeks, spontaneously, but in some cases can be prolonged.
- May or may not include loss of consciousness.
- Cannot be explained by drug, alcohol, medication use, or other injuries or comorbidities


TABLE 1
High School Reporting Information Online (HS RIO):
Total Concussion Rates for 2005-2006 and 2011-2012

<table>
<thead>
<tr>
<th></th>
<th>2005-2006</th>
<th>2011-2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys football</td>
<td>0.47 (0.41, 0.53)</td>
<td>0.94 (0.86, 1.00)</td>
</tr>
<tr>
<td>Soccer</td>
<td>0.22 (0.16, 0.31)</td>
<td>0.41 (0.32, 0.52)</td>
</tr>
<tr>
<td>Girls</td>
<td>0.05 (0.07, 0.47)</td>
<td>0.73 (0.60, 0.89)</td>
</tr>
<tr>
<td>Girls volleyball</td>
<td>0.05 (0.02, 0.10)</td>
<td>0.17 (0.12, 0.24)</td>
</tr>
<tr>
<td>Basketball</td>
<td>0.07 (0.04, 0.11)</td>
<td>0.24 (0.18, 0.33)</td>
</tr>
<tr>
<td>Girls</td>
<td>0.22 (0.16, 0.30)</td>
<td>0.37 (0.28, 0.47)</td>
</tr>
<tr>
<td>Boys wrestling</td>
<td>0.17 (0.12, 0.25)</td>
<td>0.57 (0.46, 0.70)</td>
</tr>
<tr>
<td>Boys baseball</td>
<td>0.04 (0.02, 0.08)</td>
<td>0.14 (0.09, 0.20)</td>
</tr>
<tr>
<td>Girls softball</td>
<td>0.07 (0.03, 0.12)</td>
<td>0.39 (0.21, 0.43)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.23 (0.21, 0.25)</td>
<td>0.51 (0.45, 0.55)</td>
</tr>
</tbody>
</table>

*CI, confidence interval.

Window of vulnerability

- The period between the concussion and the recovery.
- Return to play during this time could cause worse, even catastrophic, brain injury.
- May be unsafe to return to competition until brain activity has returned to normal.
- In rats, that time period averages ~10 days.

How severe is my concussion?

History of concussion grading

<table>
<thead>
<tr>
<th>Author</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantu</td>
<td>No LOC</td>
<td>LOC &lt; 5 min or PTA &gt; 30 min but &lt; 24 hours</td>
<td>LOC &gt; 5 min or PTA &gt; 24 hours</td>
</tr>
<tr>
<td>Colorado Medical Society</td>
<td>No LOC</td>
<td>No LOC Confusion without amnesias</td>
<td>LOC</td>
</tr>
<tr>
<td>American Academy of Neurology</td>
<td>No LOC Confusion without amnesias</td>
<td>No LOC Confusion without amnesias</td>
<td>LOC</td>
</tr>
<tr>
<td></td>
<td>Transient confusion</td>
<td>Transient confusion</td>
<td>LOC</td>
</tr>
<tr>
<td></td>
<td>3a LOC &lt; 15 min</td>
<td>3a LOC &gt; 15 min</td>
<td></td>
</tr>
</tbody>
</table>

History of concussion grading and RTP

<table>
<thead>
<tr>
<th>Author</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantu</td>
<td>RTP if asymptomatic</td>
<td>RTP in 1 wk if asympt or RTP within 2 weeks if asympt x 7 days</td>
<td>RTP in 1 m if asymptomatic for final 1 week</td>
</tr>
<tr>
<td>Colorado Medical Society</td>
<td>RTP if asympt at rest and exertion after 20 min</td>
<td>RTP in 1 wk if asympt at rest and exertion</td>
<td>RTP in 1 m if asympt at rest and exertion x 2 weeks</td>
</tr>
<tr>
<td>American Academy of Neurology</td>
<td>RTP if asympt within 15 min</td>
<td>RTP after 1 week w/o symptoms at rest and exertion</td>
<td>If brief LOC (sec), RTP after 2 weeks asympt if prolonged (min) RTP &gt; 1mio</td>
</tr>
</tbody>
</table>

2. CMS, 1991
3. AAN, Neurology 1997

Slide courtesy of Cindy Chang, MD
Symptom resolution in athletes

- Does not correlate with LOC nor amnesia
- Grading scales no longer used
- Concussion severity is determined retrospectively
- Typical time to resolve
  - Adults: 10-14 days
  - Kids: Up to 4 weeks

Factors associated with slower recovery

- Higher severity of symptoms in first days post injury
- Development of subacute
  - Depression
  - Migraine
- Children, adolescents, young adults with pre-injury
  - Mental health problems
  - Migraine

Case #1

- 16 y/o high school soccer goalie
- Presents to you in urgent care with wrist pain
- Also, she hit heads with teammate in practice earlier today and had 15 minutes of headaches and dizziness. She took a nap after practice as she felt unusually tired.
- Now she has no headache: "I feel fine."
- What do you do next?
3-pronged evaluation recommended

1. Self-reported symptom assessment
2. Motor control: Neurologic exam including balance. Balance Error Scoring System (BESS or modified BESS)
3. Mental status: Standardized Assessment of Concussion (SAC)

---

**1. Self-reported symptom assessment**

Please Check:  
- Baseline  
- Post-Injury

Please hand the form to the athlete

<table>
<thead>
<tr>
<th>Symptom</th>
<th>9th grade</th>
<th>10th grade</th>
<th>11th grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>17 +/- 5</td>
<td>16 +/- 5</td>
<td>17 +/- 6</td>
</tr>
<tr>
<td>“Pressure in head”</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neck pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Flickers</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Balance problems</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Valovich McLeod TC et al. Representative baseline values on the sport concussion assessment tool 2 (SCAT2) in adolescent athletes vary by gender, grade and concussion history. AJSM 2012.
2. Neurological exam with balance
Balance Error Scoring System: BESS


BESS scoring

- Each error is counted as one point
- Score = the sum of the error points for all six trials
- Errors
  - Eyes opening
  - Hands coming off the hips
  - Hip flexion or abduction of greater than 30°
  - Changing foot placement from the stance
  - Remaining out of the test position for > 5 seconds
- Max score 10 errors
- Also if cannot maintain for minimum 5 seconds then score = 10

BESS norms: ages 10-17


BESS norms: adults

3. Mental status


Case #2

- 25 y/o woman presents to your office for ER follow-up two days after bike accident.
- Slid out while crossing streetcar tracks on wet city streets.
- No loss of consciousness.
- Taken by ambulance to ER.
- Had trauma work-up including head CT (-).
- Has headache, fatigue, dizziness, light sensitivity. Trouble staying focused at work, sleeping more than usual.
- Normal neck and neurologic exam.

How would you treat this patient?

1. Order urgent head CT to rule out subtle post traumatic bleed, return to clinic after CT.
2. Gradually return to work now, rest from biking, f/u 1 week.
3. Rest from work and from biking, f/u 1 week.
4. Return to work and biking now.

Concussion treatment

- Cognitive rest
- Physical rest
- Medication
  - Tylenol
  - Ibuprofen after first 72 hours
- No driving
- No Etoh
How much rest after a concussion?


- 88 patients (11-22 y/o) seen at pediatric ED randomized
- Strict rest x 5 days vs. “usual care” of 1-2 days rest, then stepwise return to activity
- Neurocognitive and balance outcomes same at 3 and 10d post injury
- Strict rest group had more daily post concussive symptoms and slower symptom resolution over the 10d study period

Berlin Consensus 2017 on Rest

- “There is currently insufficient evidence that prescribing complete rest achieves these objectives.” (those of mitigating symptoms and/or promoting recovery by minimizing brain energy demands post concussion)
- “After a brief period of rest … 24-48 hours after injury, patients can be encouraged to become gradually and progressively more active while staying below their cognitive and physical symptom-exacerbation thresholds…”
- “The exact amount and duration of rest is not yet well defined in the literature and requires further study.”

Return to learn / work progression

- No school. OK to do light reading, light TV, drawing, cooking as long as doesn’t worsen symptoms.
- 15 min cognitive activity at a time.
- 30 min schoolwork at a time until can do 1-2 hours.
- Return to 1/2 day of school.
- Return to full day of school.
- Return to learn BEFORE
- Return to Play

http://www.chop.edu/service/concussion-care-for-kids/returning-to-school.html
Case #3

- 15 y/o high school girls soccer player
- Concussion f/u in clinic
- Injured 1 week ago
- Rested at home x 2 days then gradually returned to school with RTL protocol
- Tolerating school 100%
- Has not done any physical activity
- No concussion symptoms
- Soccer championship game in 2 days. She requests your clearance to play.
- What do you recommend?

California concussion legislation

- **AB 25 — Concussion Law 2012**
  - 3 parts (education, remove from play, written medical note to return)
- **AB 1451 — Coaches Concussion Training Law 2013**
  - Mandatory education every 2 years
- **AB 2127 — Concussion Safety Law 2015**
  - Limit FB full-contact practices
  - Mandatory RTP protocol of no less than 7 days from the diagnosed date of concussion
  - RTP under the supervision of LHCP
- **AB 2007 Concussion Mgmt in Youth Sports Act 2016**
  - Requires youth sports participants to undergo the same safety protocols as high school athletes

Slide courtesy of Cindy Chang, MD
Return to play progression

- After 24-48 hours: Daily activities that don't provoke symptoms
- Light aerobic activity
- Sport specific activity
- Non-contact training
- Full contact practice
- Game play

Per AB 2176 RTP protocol must last at least 7 days.

http://bjsm.bmj.com/content/early/2017/04/26/bjsports-2017-097699.

Return to play activity examples

<table>
<thead>
<tr>
<th>Step</th>
<th>Objective</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptom-limited activity</td>
<td>Gradually reintroduce work/school</td>
</tr>
<tr>
<td>2</td>
<td>Light aerobic activity</td>
<td>Increase heart rate; Walking, swimming, or stationary bike, &lt; 70% max heart rate; No weights.</td>
</tr>
<tr>
<td>3</td>
<td>Sport Specific: Add movement</td>
<td>Skating drills in hockey; running drills in soccer. No head impact activities.</td>
</tr>
<tr>
<td>4</td>
<td>Non-contact training: Add coordination and cognitive load</td>
<td>More complex drills (passing). Can start weights.</td>
</tr>
<tr>
<td>5</td>
<td>Restore confidence and assess functional skills by coaching staff</td>
<td>Full-contact practice</td>
</tr>
<tr>
<td>6</td>
<td>Normal game play</td>
<td></td>
</tr>
</tbody>
</table>

http://bjsm.bmj.com/content/early/2017/04/26/bjsports-2017-097699.

CIF: Return to play handout

- Concussion Information Sheet
- Acute Concussion Notification Form
- Graded Concussion Symptom Checklist
- Physician Letter to School After Concussion Visit
- Concussion Return to Learn (RTL) Protocol
- Physician Recommended School Accommodations Following Concussion
- Concussion Return to Play (RTP) Protocol

www.cifstate.org/sports-medicine/concussions/index
Case #4

A 23 y/o semi pro rugby player presents to you 3 months after her 5th concussion sustained when she was elbowed in the head during a game. She has had a headache with light sensitivity since the injury. She would like to know if and when she can return to rugby.

What is her diagnosis?
What do you worry about?

Post Concussion Syndrome

Frequency unclear (0-15%).
Concussion symptoms persist x months, usually <1 year.
Patients benefit from multidisciplinary approach to treatment.

Repeat concussion: short term risks

- Increased risk of
  - Repeat injury
  - More severe symptoms
  - Longer duration of symptoms
  - Interruption of school / work / physical activity


Repeat concussion: long term concerns

Chronic Traumatic Encephalopathy

- Athletes and military personnel
- Chronic, progressive
- Depression, cognitive impairment, aggression
- Diagnosed at autopsy: tau protein deposition
- Difficult to draw causality – no prospective data yet
- Concerning association between pro sports participation and long term neuropsych problems

Think about post concussion syndrome when…

• Symptoms not improving
  • Adults: expected recovery 10-14 days
  • Kids: expected recovery around 4 weeks
• Unable to return to school or work after 1-2 weeks of treatment.
• History of migraine, anxiety, depression, sleep disorder.
• History of concussion.

How Many Concussions is Too Many?

• Individualized to athlete.
• Concussion hx.
  • Number.
  • Less force.
  • More frequent.
• Increased severity of sx
• Increased duration of sx.
• Age: possibly more consequences if younger at time of concussion.

Corrigan JD, Concussion webcast 10/18/2011.
Lower concussion risk by decreasing exposure

Incidence of concussion
Reported as events per 1000 athlete exposures (AEs)

<table>
<thead>
<tr>
<th>Sport</th>
<th>Male</th>
<th>Female</th>
<th>Pooled incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rugby</td>
<td>0.48</td>
<td>NR</td>
<td>0.48</td>
</tr>
<tr>
<td>Hockey</td>
<td>NR</td>
<td>NR</td>
<td>1.20</td>
</tr>
<tr>
<td>American football</td>
<td>0.53</td>
<td>NR</td>
<td>0.53</td>
</tr>
<tr>
<td>Lacrosse</td>
<td>0.29</td>
<td>0.17</td>
<td>0.24</td>
</tr>
<tr>
<td>Soccer</td>
<td>0.19</td>
<td>0.27</td>
<td>0.23</td>
</tr>
<tr>
<td>Wrestling</td>
<td>0.17</td>
<td>NR</td>
<td>0.17</td>
</tr>
<tr>
<td>Basketball</td>
<td>0.10</td>
<td>0.17</td>
<td>0.13</td>
</tr>
<tr>
<td>Softball</td>
<td>NR</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Field hockey</td>
<td>NR</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Cheerleading</td>
<td>NR</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseball</td>
<td>0.06</td>
<td>NR</td>
<td>0.06</td>
</tr>
<tr>
<td>Volleyball</td>
<td>NR</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>


Highest risk positions by sport

- **Football – 1. quarterback, 2. running back, 3. linebacker** (Powell JW. Traumatic brain injury in high school athletes. JAMA. 1999 Sep 8;282(10):958-63.)
- **Soccer – goalkeepers and defensive midfield players due to collision with other player** (Helmich I. Game-specific characteristics of sport-related concussions. J Sports Med Phys Fitness. 2016 Sep 14.)
- **Volleyball – “libero” position due to hits from the ball** (Helmich I. Game-specific characteristics of sport-related concussions. J Sports Med Phys Fitness. 2016 Sep 14.)

Concussion resources

- UCSF Sports Concussion Program
  - concussion@ucsf.edu
- California Interscholastic Federation
  - http://www.cifstate.org/sports-medicine/concussions/index
  - http://bjsm.bmj.com/content/47/5/250.full
- CDC concussion toolkit for physicians
Outline: Sports Concussion 2017

1. Epidemiology
2. Evaluation
3. Treatment
   • How much rest?
   • Return to learn
   • Return to play
4. Legislation
5. How many concussions is too many?

Keys to managing sports concussion in 2017

• Recovery time on average:
  • Adults 10-14 days
  • Kids 4 weeks
• 3-pronged evaluation: Symptoms, Neuro/balance exam, Cognitive
• Gradual return to learn or work 24-48 hours post injury
• Low-level non-contact aerobic activity early on post injury as long as does not worsen symptoms
• Return to play protocol at least 7 days since day of diagnosis (in state of California)
• Consider referral for post concussion syndrome
• Repeat injuries: individual approach

Thank You!

Carlin Senter, M.D.
Carlin.Senter@ucsf.edu
UCSF Sports Medicine
**WHAT IS THE SCAT5?**

The SCAT5 is a standardized tool for evaluating concussions designed for use by physicians and licensed healthcare professionals. The SCAT5 cannot be performed correctly in less than 10 minutes.

If you are not a physician or licensed healthcare professional, please use the Concussion Recognition Tool 5 (CRT5). The SCAT5 is to be used for evaluating athletes aged 13 years and older. For children aged 12 years or younger, please use the Child SCAT5.

Preseason SCAT5 baseline testing can be useful for interpreting post-injury test scores, but is not required for that purpose. Detailed instructions for use of the SCAT5 are provided on page 7. Please read through these instructions carefully before testing the athlete. Brief verbal instructions for each test are given in italics. The only equipment required for the tester is a watch or timer.

This tool may be freely copied in its current form for distribution to individuals, teams, groups, and organizations. It should not be altered in any way, re-branded or sold for commercial gain. Any revision, translation or reproduction in a digital form requires specific approval by the Concussion in Sport Group.

**Recognise and Remove**

A head impact by either a direct blow or indirect transmission of force can be associated with a serious and potentially fatal brain injury. If there are significant concerns, including any of the red flags listed in Box 1, then activation of emergency procedures and urgent transport to the nearest hospital should be arranged.

**Key points**

- Any athlete with suspected concussion should be REMOVED FROM PLAY, medically assessed and monitored for deterioration. No athlete diagnosed with concussion should be returned to play on the day of injury.
- If an athlete is suspected of having a concussion and medical personnel are not immediately available, the athlete should be referred to a medical facility for urgent assessment.
- Athletes with suspected concussion should not drink alcohol, use recreational drugs and should not drive a motor vehicle until cleared to do so by a medical professional.
- Concussion signs and symptoms evolve over time and it is important to consider repeat evaluation in the assessment of concussion.
- The diagnosis of a concussion is a clinical judgment, made by a medical professional. The SCAT5 should NOT be used by itself to make, or exclude, the diagnosis of concussion. An athlete may have a concussion even if their SCAT5 is “normal”.

**Remember:**

- The basic principles of first aid (danger, response, airway, breathing, circulation) should be followed.
- Do not attempt to move the athlete (other than that required for airway management) unless trained to do so.
- Assessment for a spinal cord injury is a critical part of the initial on-field assessment.
- Do not remove a helmet or any other equipment unless trained to do so safely.
IMMEDIATE OR ON-FIELD ASSESSMENT

The following elements should be assessed for all athletes who are suspected of having a concussion prior to proceeding to the neurocognitive assessment and ideally should be done on-field after the first first aid / emergency care priorities are completed.

If any of the "Red Flags" or observable signs are noted after a direct or indirect blow to the head, the athlete should be immediately and safely removed from participation and evaluated by a physician or licensed healthcare professional.

Consideration of transportation to a medical facility should be at the discretion of the physician or licensed healthcare professional.

The GCS is important as a standard measure for all patients and can be done serially if necessary in the event of deterioration in conscious state. The Maddocks questions and cervical spine exam are critical steps of the immediate assessment; however, these do not need to be done serially.

STEP 1: RED FLAGS

RED FLAGS:
- Neck pain or tenderness
- Double vision
- Weakness or tingling/burning in arms or legs
- Severe or increasing headache
- Seizure or convulsion
- Loss of consciousness
- Deteriorating conscious state
- Vomiting
- Increasingly restless, agitated or combative

STEP 2: OBSERVABLE SIGNS

Witnessed □ Observed on Video □

Lying motionless on the playing surface Y N
Balance / gait difficulties / motor incoordination: stumbling, slow / laboured movements Y N
Disorientation or confusion, or an inability to respond appropriately to questions Y N
Blank or vacant look Y N
Facial injury after head trauma Y N

STEP 3: MEMORY ASSESSMENT

"I am going to ask you a few questions, please listen carefully and give your best effort. First, tell me what happened?"

Mark Y for correct answer / N for incorrect

What venue are we at today? Y N
Which half is it now? Y N
Who scored last in this match? Y N
What team did you play last week / game? Y N
Did your team win the last game? Y N

STEP 4: EXAMINATION

GLASGOW COMA SCALE (GCS)

Time of assessment
Date of assessment
Best eye response (E)
No eye opening 1 1 1
Eye opening in response to pain 2 2 2
Eye opening to speech 3 3 3
Eyes opening spontaneously 4 4 4
Best verbal response (V)
No verbal response 1 1 1
Incomprehensible sounds 2 2 2
Inappropriate words 3 3 3
Confused 4 4 4
Oriented 5 5 5
Best motor response (M)
No motor response 1 1 1
Extension to pain 2 2 2
Abnormal flexion to pain 3 3 3
Flexion / Withdrawal to pain 4 4 4
Localizes to pain 5 5 5
Obeys commands 6 6 6
Glasgow Coma score (E + V + M)

CERVICAL SPINE ASSESSMENT

Does the athlete report that their neck is pain free at rest? Y N
If there is NO neck pain at rest, does the athlete have a full range of ACTIVE pain free movement? Y N
Is the limb strength and sensation normal? Y N

In a patient who is not lucid or fully conscious, a cervical spine injury should be assumed until proven otherwise.
OFFICE OR OFF-FIELD ASSESSMENT

Please note that the neurocognitive assessment should be done in a distraction-free environment with the athlete in a resting state.

STEP 1: ATHLETE BACKGROUND

Sport / team / school: ____________________________
Date / time of injury: ____________________________
Years of education completed: ___________________
Age: __________________
Gender: M / F / Other
Dominant hand: left / neither / right
How many diagnosed concussions has the athlete had in the past?: ____________________________
When was the most recent concussion?: ____________________________
How long was the recovery (time to being cleared to play) from the most recent concussion?: ________ (days)

Has the athlete ever been:
Hospitalized for a head injury? Yes No
Diagnosed / treated for headache disorder or migraines? Yes No
Diagnosed with a learning disability / dyslexia? Yes No
Diagnosed with ADD / ADHD? Yes No
Diagnosed with depression, anxiety or other psychiatric disorder? Yes No

Current medications? If yes, please list:
________________________________________________
________________________________________________
________________________________________________
________________________________________________

STEP 2: SYMPTOM EVALUATION

The athlete should be given the symptom form and asked to read this instruction paragraph out loud then complete the symptom scale. For the baseline assessment, the athlete should rate his/her symptoms based on how he/she typically feels and for the post injury assessment the athlete should rate their symptoms at this point in time.

Please Check: □ Baseline □ Post-Injury

Please hand the form to the athlete

<table>
<thead>
<tr>
<th>Headache</th>
<th>none</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&quot;Pressure in head&quot;</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Balance problems</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sensitivity to light</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sensitivity to noise</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling slowed down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling like &quot;in a fog&quot;</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>&quot;Don't feel right&quot;</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty remembering</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue or low energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Confusion</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>More emotional</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Irritability</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sadness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nervous or Anxious</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble falling asleep (if applicable)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total number of symptoms: of 22
Symptom severity score: of 132

Do your symptoms get worse with physical activity? Y N
Do your symptoms get worse with mental activity? Y N

If 100% is feeling perfectly normal, what percent of normal do you feel?

If not 100%, why?

Please hand form back to examiner
STEP 3: COGNITIVE SCREENING

Standardised Assessment of Concussion (SAC)4

**ORIENTATION**

What month is it? 0 1
What is the date today? 0 1
What is the day of the week? 0 1
What year is it? 0 1
What time is it right now? (within 1 hour) 0 1

Orientation score of 5

**IMMEDIATE MEMORY**

The Immediate Memory component can be completed using the traditional 5-word per trial list or optionally using 10-words per trial to minimise any ceiling effect. All 3 trials must be administered irrespective of the number correct on the first trial. Administer at the rate of one word per second.

Please choose EITHER the 5 or 10 word list groups and circle the specific word list chosen for this test.

_I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order. For Trials 2 & 3: I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before._

<table>
<thead>
<tr>
<th>List</th>
<th>Alternate 5 word lists</th>
<th>Score (of 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Finger Penny Blanket Lemon Insect</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Candle Paper Sugar Sandwich Insect</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Baby Monkey Perfume Sunset Wagon</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Elbow Apple Carpet Saddle Bubble</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Jacket Arrow Pepper Cotton Movie</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Dollar Honey Mirror Saddle Anchor</td>
<td></td>
</tr>
</tbody>
</table>

Immediate Memory Score of 15

Time that last trial was completed

<table>
<thead>
<tr>
<th>List</th>
<th>Alternate 10 word lists</th>
<th>Score (of 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Finger Penny Blanket Lemon Insect</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Candle Paper Sugar Sandwich Insect</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Baby Monkey Perfume Sunset Wagon</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Elbow Apple Carpet Saddle Bubble</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Jacket Arrow Pepper Cotton Movie</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Dollar Honey Mirror Saddle Anchor</td>
<td></td>
</tr>
</tbody>
</table>

Immediate Memory Score of 30

Time that last trial was completed

**CONCENTRATION**

**DIGITS BACKWARDS**

Please circle the Digit list chosen (A, B, C, D, E, F). Administer at the rate of one digit per second reading DOWN the selected column.

_I am going to read a string of numbers and when I am done, you repeat them back to me in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7._

<table>
<thead>
<tr>
<th>List A</th>
<th>List B</th>
<th>List C</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-2-6</td>
<td>1-4-2</td>
<td>Y</td>
<td>0 1</td>
</tr>
<tr>
<td>6-2-9</td>
<td>4-1-5</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>3-8-1-4</td>
<td>1-7-9-5</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>3-2-7-9</td>
<td>4-9-6-8</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>6-2-9-7-1</td>
<td>4-8-5-2-7</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>1-5-2-8-6</td>
<td>6-1-8-4-3</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>7-1-8-4-6-2</td>
<td>8-3-1-9-6-4</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>5-3-9-1-4-8</td>
<td>7-2-4-8-5-6</td>
<td>Y</td>
<td></td>
</tr>
</tbody>
</table>

Immediate Memory Score of 4

<table>
<thead>
<tr>
<th>List D</th>
<th>List E</th>
<th>List F</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-9-3</td>
<td>5-2-6</td>
<td>1-4-2</td>
<td>Y</td>
</tr>
<tr>
<td>6-2-9</td>
<td>4-1-5</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>3-8-1-4</td>
<td>1-7-9-5</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>3-2-7-9</td>
<td>4-9-6-8</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>6-2-9-7-1</td>
<td>4-8-5-2-7</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>1-5-2-8-6</td>
<td>6-1-8-4-3</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>7-1-8-4-6-2</td>
<td>8-3-1-9-6-4</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>5-3-9-1-4-8</td>
<td>7-2-4-8-5-6</td>
<td>Y</td>
<td></td>
</tr>
</tbody>
</table>

Concentration Number Lists (circle one)

**MONTHS IN REVERSE ORDER**

Now tell me the months of the year in reverse order. Start with the last month and go backward. So you’ll say December, November. Go ahead.


Immediate Memory Score of 1

Times that last trial was completed

**Concentration Total Score (Digits + Months)**

Immediate Memory Score of 5

**Name:**

**DOB:**

**Address:**

**ID number:**

**Examiner:**

**Date:**
**STEP 4: NEUROLOGICAL SCREEN**

See the instruction sheet (page 7) for details of test administration and scoring of the tests.

Can the patient read aloud (e.g. symptom checklist) and follow instructions without difficulty? [ ] Y [ ] N

Does the patient have a full range of pain-free PASSIVE cervical spine movement? [ ] Y [ ] N

Without moving their head or neck, can the patient look side-to-side and up-and-down without double vision? [ ] Y [ ] N

Can the patient perform the finger nose coordination test normally? [ ] Y [ ] N

Can the patient perform tandem gait normally? [ ] Y [ ] N

**BALANCE EXAMINATION**

Modified Balance Error Scoring System (mBESS) testing

Which foot was tested

- [ ] Left
- [ ] Right

Testing surface (hard floor, field, etc.)

Footwear (shoes, barefoot, braces, tape, etc.)

Condition | Errors
---|---
Double leg stance | of 10
Single leg stance (non-dominant foot) | of 10
Tandem stance (non-dominant foot at the back) | of 10
Total Errors | of 30

**STEP 5: DELAYED RECALL**

The delayed recall should be performed after 5 minutes have elapsed since the end of the Immediate Recall section. Score 1 pt. for each correct response.

Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order.

Time Started

Please record each word correctly recalled. Total score equals number of words recalled.

Total number of words recalled accurately: of 5 or of 10

**STEP 6: DECISION**

Date and time of assessment:

<table>
<thead>
<tr>
<th>Domain</th>
<th>Date &amp; time of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom number (of 22)</td>
<td></td>
</tr>
<tr>
<td>Symptom severity score (of 132)</td>
<td></td>
</tr>
<tr>
<td>Orientation (of 5)</td>
<td></td>
</tr>
<tr>
<td>Immediate memory</td>
<td>of 15 of 30</td>
</tr>
<tr>
<td>Concentration (of 5)</td>
<td></td>
</tr>
<tr>
<td>Neuro exam</td>
<td>Normal Abnormal Normal Abnormal Normal Abnormal</td>
</tr>
<tr>
<td>Balance errors (of 30)</td>
<td></td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>of 5 of 10 of 5 of 10</td>
</tr>
</tbody>
</table>

If the athlete is known to you prior to their injury, are they different from their usual self?

- [ ] Yes
- [ ] No
- [ ] Unsure
- [ ] Not Applicable

(If different, describe why in the clinical notes section)

Concussion Diagnosed?

- [ ] Yes
- [ ] No
- [ ] Unsure
- [ ] Not Applicable

If re-testing, has the athlete improved?

- [ ] Yes
- [ ] No
- [ ] Unsure
- [ ] Not Applicable

I am a physician or licensed healthcare professional and I have personally administered or supervised the administration of this SCAT5.

Signature:

Date and time of injury:

If you need more information about the SCAT5, please visit the Concussion in Sport Group website at www.concussioninsport.com.
CLINICAL NOTES:

Name:__________________________________________
DOB:__________________________________________
Address:________________________________________
ID number:_____________________________________
Examiner:_______________________________________
Date:___________________________________________

CONCUSSION INJURY ADVICE
(To be given to the person monitoring the concussed athlete)

This patient has received an injury to the head. A careful medical examination has been carried out and no sign of any serious complications has been found. Recovery time is variable across individuals and the patient will need monitoring for a further period by a responsible adult. Your treating physician will provide guidance as to this timeframe.

If you notice any change in behaviour, vomiting, worsening headache, double vision or excessive drowsiness, please telephone your doctor or the nearest hospital emergency department immediately.

Other important points:

Initial rest: Limit physical activity to routine daily activities (avoid exercise, training, sports) and limit activities such as school, work, and screen time to a level that does not worsen symptoms.

1) Avoid alcohol
2) Avoid prescription or non-prescription drugs without medical supervision. Specifically:
   a) Avoid sleeping tablets
   b) Do not use aspirin, anti-inflammatory medication or stronger pain medications such as narcotics
3) Do not drive until cleared by a healthcare professional.
4) Return to play/sport requires clearance by a healthcare professional.

Clinic phone number:_____________________________________
Patient’s name:_________________________________________
Date / time of injury:_____________________________________
Date / time of medical review:_____________________________
Healthcare Provider:_____________________________________

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Contact details or stamp
**INSTRUCTIONS**

Words in Italic are throughout the SCAT5 are the instructions given to the athlete by the clinician

### Symptom Scale

The time frame for symptoms should be based on the type of test being administered. At baseline it is advantageous to assess how an athlete "typically" feels whereas during the acute/post-acute stage it is best to ask how the athlete feels at the time of testing.

The symptom scale should be completed by the athlete, not by the examiner. In situations where the symptom scale is being completed after exercise, it should be done in a resting state, generally by approximating his/her resting heart rate.

For total number of symptoms, maximum possible is 22 except immediately post injury, if sleep item is omitted, which then creates a maximum of 21.

For Symptom severity score, add all scores in table, maximum possible is 22 x 6 = 132, except immediately post injury if sleep item is omitted, which then creates a maximum of 21 x 6 = 126.

### Immediate Memory

The Immediate Memory component can be completed using the traditional 5-word per trial list or, optionally, using 10-words per trial. The literature suggests that the Immediate Memory has a notable ceiling effect when a 5-word list is used. In settings where this ceiling is prominent, the examiner may wish to make the task more difficult by incorporating two 5-word groups for a total of 10 words per trial. In this case, the maximum score per trial is 10 with a total trial maximum of 30.

Choose one of the word lists (either 5 or 10). Then perform 3 trials of immediate memory using this list.

Complete all 3 trials regardless of score on previous trials.

"I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order." "The words must be read at a rate of one word per second.

Trials 2 & 3 MUST be completed regardless of score on trial 1 & 2.

Trials 2 & 3:

"I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before."

Score 1 pt. for each correct response. Total score equals sum across all 3 trials. Do NOT inform the athlete that delayed recall will be tested.

### Concentration

#### Digits backward

Choose one column of digits from lists A, B, C, D, E or F and administer those digits as follows:

Say: "I am going to read a string of numbers and when I am done, you repeat them back to me in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7."

Begin with first 3 digit string.

If correct, circle "Y" for correct and go to next string length. If incorrect, circle "N" for the first string length and read trial 2 in the same string length. One point possible for each string length. Stop after incorrect on both trials (2 Ns) in a string length. The digits should be read at the rate of one per second.

#### Months in reverse order

"Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November... Go ahead"

1 pt. for entire sequence correct

### Delayed Recall

The delayed recall should be performed after 5 minutes have elapsed since the end of the Immediate Recall section.

"Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order."

Score 1 pt. for each correct response

### Modified Balance Error Scoring System (mBESS) testing

This balance testing is based on a modified version of the Balance Error Scoring System (BESS). A timing device is required for this testing.

Each of 20-second trial/stance is scored by counting the number of errors. The examiner will begin counting errors only after the athlete has assumed the proper start position. The modified BESS is calculated by adding one error point for each error during the three 20-second tests. The maximum number of errors for any single condition is 10. If the athlete commits multiple errors simultaneously, only one error is recorded but the athlete should quickly return to the testing position, and counting should resume once the athlete is set. Athletes that are unable to maintain the testing procedure for a minimum of five seconds at the start are assigned the highest possible score, ten, for that testing condition.

OPTION: For further assessment, the same 3 stances can be performed on a surface of medium density foam (e.g., approximately 50cm x 40cm x 6cm).

### Balance testing – types of errors

1. Hands lifted off iliac crest
2. Opening eyes
3. Step, stumble, or fall
4. Moving hip into > 30 degrees abduction
5. Lifting forefoot or heel
6. Remaining out of test position > 5 sec

"I am now going to test your balance. Please take your shoes off (if applicable), roll up your pant legs above ankle (if applicable), and remove any ankle taping (if applicable). This test will consist of three twenty second tests with different stances."

(a) Double leg stance:

"The first stance is standing with your feet together with your hands on your hips and with your eyes closed. You should try to maintain stability in that position for 20 seconds. I will be counting the number of times you move out of this position. I will start timing when you are set and have closed your eyes."

(b) Single leg stance:

"If you were to kick a ball, which foot would you use? [This will be the dominant foot] Now stand on your non-dominant foot. The dominant leg should be held in approximately 30 degrees of hip flexion and 45 degrees of knee flexion. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

(c) Tandem stance:

"Now stand heel-to-toe with your non-dominant foot in back. Your weight should be evenly distributed across both feet. Again, you should try to maintain stability for 20 seconds with your hands on your hips and your eyes closed. I will be counting the number of times you move out of this position. If you stumble out of this position, open your eyes and return to the start position and continue balancing. I will start timing when you are set and have closed your eyes."

### Tandem Gait

Participants are instructed to stand with their feet together behind a starting line (the test is best done with footwear removed). Then, they walk in a forward direction as quickly and as accurately as possible along a 38mm wide (sports tape), 3 metre line with an alternate foot heel-to-toe gait ensuring that they approximate their heel and toe on each step. Once they cross the end of the 3m line, they turn 180 degrees and return to the starting point using the same gait. Athletes fail the test if they step off the line, have a separation between their heel and toe, or if they touch or grab the examiner or an object.

### Finger to Nose

"I am going to test your coordination now. Please sit comfortably on the chair with your eyes open and your arm (either right or left) outstretched (shoulder flexed to 90 degrees and elbow and fingers extended), pointing in front of you. When I give a start signal, I would like you to perform five successive finger to nose repetitions using your index finger to touch the tip of the nose, then return to the starting position, as quickly and as accurately as possible."

### References

CONCUSSION INFORMATION

Any athlete suspected of having a concussion should be removed from play and seek medical evaluation.

Signs to watch for

Problems could arise over the first 24-48 hours. The athlete should not be left alone and must go to a hospital at once if they experience:

- Worsening headache
- Drowsiness or inability to be awakened
- Inability to recognize people or places
- Repeated vomiting
- Unusual behaviour or confusion or irritable
- Seizures (arms and legs jerk uncontrollably)
- Weakness or numbness in arms or legs
- Unsteadiness on their feet.

Consult your physician or licensed healthcare professional after a suspected concussion. Remember, it is better to be safe.

Rest & Rehabilitation

After a concussion, the athlete should have physical rest and relative cognitive rest for a few days to allow their symptoms to improve. In most cases, after no more than a few days of rest, the athlete should gradually increase their daily activity level as long as their symptoms do not worsen. Once the athlete is able to complete their usual daily activities without concussion-related symptoms, the second step of the return to play/sport progression can be started. The athlete should not return to play/sport until their concussion-related symptoms have resolved and the athlete has successfully returned to full school/learning activities.

When returning to play/sport, the athlete should follow a stepwise, medically managed exercise progression, with increasing amounts of exercise. For example:

Graduated Return to Sport Strategy

<table>
<thead>
<tr>
<th>Exercise step</th>
<th>Functional exercise at each step</th>
<th>Goal of each step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptom-limited activity</td>
<td>Daily activities that do not provoke symptoms</td>
<td>Gradual reintroduction of work/school activities</td>
</tr>
<tr>
<td>2. Light aerobic exercise</td>
<td>Walking or stationary cycling at slow to medium pace</td>
<td>Increase heart rate</td>
</tr>
<tr>
<td>3. Sport-specific exercise</td>
<td>Running or skating drills. No head impact activities</td>
<td>Add movement</td>
</tr>
<tr>
<td>4. Non-contact training drills</td>
<td>Harder training drills, e.g., passing drills. May start progressive resistance training</td>
<td>Exercise, coordination, and increased thinking</td>
</tr>
<tr>
<td>5. Full contact practice</td>
<td>Following medical clearance, participate in normal training activities</td>
<td>Restore confidence and assess functional skills by coaching staff</td>
</tr>
<tr>
<td>6. Return to play/sport</td>
<td>Normal game play</td>
<td></td>
</tr>
</tbody>
</table>

If the athlete continues to have symptoms with mental activity, some other accommodations that can help with return to school may include:

- Starting school later, only going for half days, or only to certain classes
- More time to finish assignments/tests
- Quiet room to finish assignments/tests
- Not going to noisy areas like the cafeteria, assembly halls, sporting events, music class, shop class, etc.
- Taking lots of breaks during class, homework, tests
- No more than one exam/day
- Shorter assignments
- Repetition/memory cues
- Use of a student helper/tutor
- Reassurance from teachers that the child will be supported while getting better

The athlete should not go back to sports until they are back to school/learning, without symptoms getting significantly worse and no longer needing any changes to their schedule.

Written clearance should be provided by a healthcare professional before return to play/sport as directed by local laws and regulations.