Hypertension

Prevalence of Hypertension
- 50 million people in the U.S.
- 1 billion worldwide
- European Americans: 15% of women, 25% of men over 45 years of age
- African Americans: 35% of women, almost 40% of men over 45 years of age

Morbidity and Mortality
- CHD/MI
- LVH and LV dysfunction
- Dysrrhythmias
- Stroke
- PVD
- Renal insufficiency and failure
- Retinopathy

Diabetes Mellitus and Hypertension: Diagnosis and Management

T. Villela, M.D.
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University of California, San Francisco-San Francisco General Hospital
Family and Community Medicine Residency Program
July 2008
Classification of Blood Pressure for Adults

(JNC 7, May 2003)

<table>
<thead>
<tr>
<th>BP classification</th>
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</tr>
</tbody>
</table>

Cardiovascular Risk

- Any 20 mmHg increment in SBP or
- Any 10 mmHg increment in DBP

Doubles risk for CVD among 40-70 year olds across entire BP range (115/75 – 185/115)

Pharmacologic Therapy

Consider:
- Severity of BP
- End organ damage, including LVH
- Presence of other conditions or risk factors: DM, CHD, smoking, LDL

Remember:
- 50% of patients controlled with one drug; another 30% will need two;
- The vast majority of patients with diabetes require two or more drugs

Pharmacologic Therapy

- Diuretics
- Beta Blockers
- ACE Inhibitors
- Calcium Channel Blockers

- Others
  - Central Sympatholytics
  - Direct Vasodilators
  - Peripheral Adrenergic Inhibitors
Diuretics

- Thiazides are the only agents shown to decrease morbidity and mortality related to CHD in major trials
- Decrease plasma volume and CO
- Reduce peripheral vascular resistance
- Most of anti-hypertensive effect at low doses
- Biochemical effects are dose related
- Thiazides; loop; potassium sparing

Adverse effects:
- Electrolyte imbalance: potassium, magnesium, sodium, calcium, uric acid, glucose
- Transient effect on cholesterol

Useful in:
- All populations
- Older patients
- Isolated systolic hypertension
- CHF
- Combination with second drug

In patients w/kidney disease (CrCl < 30-50), use a loop diuretics

Beta Adrenergic Blockers

- Decrease heart rate, cardiac output, renal blood flow
- Inhibit vasoconstriction and decrease peripheral resistance
- Agents with intrinsic sympathomimetic activity: less reduction in HR & CO
Beta Adrenergic Blockers

Useful in:
- Patients with LVH, angina, tachycardia, anxiety, migraine, glaucoma
- Patients with CHD -- provides significant protection against MI recurrence

Adverse effects:
- CHF exacerbation acutely
- AV block
- Bronchospasm (in reversible disease)
- CNS: depression, fatigue
  - Depends on lipid solubility
  - Propranolol, metoprolol >> atenolol
- Transient effects on carbohydrate metabolism
- Transient effects on lipid metabolism
  - Labetolol < ISA’s < others

Angiotensin Converting Enzyme Inhibitors

- Block formation of angiotensin II
- Promote vasodilation & decrease aldosterone
- Increase bradykinin & vasodilatory prostaglandins

Preferred in:
- Congestive heart failure
- Diabetes type 1 and 2
- Known coronary heart disease
- Patients at high risk for CHD
- Nephropathy
Angiotensin Converting Enzyme Inhibitors

**Adverse effects:**
- Cough (5-15% of patients)
- Skin rash, taste alterations (esp. Captopril)
- Hyperkalemia
- Hypotension, dizziness
- Renal dysfunction
  - Expect a rise in Scr of up to 35% even in normal function
- Rare: angioedema, neutropenia, proteinuria
- Teratogenic

Angiotensin Receptor Blockers

- Losartan, valsartan, candesartan, et.al.
- No cough, rare angioedema
- Less potent antihypertensive effect--improves if combined with diuretic
- Teratogenic

Calcium Channel Blockers

- Peripheral vasodilators
- Dihydropiridines
  - amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine
- Non-dihydropiridines
  - diltiazem, verapamil

Calcium Channel Blockers

- Short Acting Nifedipine
  - Not FDA approved for treatment of hypertension
  - Poorly absorbed from oral mucosa
  - Adverse effects: neurological symptoms, hypotension, myocardial ischemia, acute MI
  - Similar concerns with other short acting CCB like isradipine
Calcium Channel Blockers

Adverse effects:
- Dizziness, headache, peripheral edema
- DHP’s: worse edema, flushing, tachycardia, rash
- Non-DHP’s: CHF exacerbation, AV block, bradycardia, constipation

Useful in: angina; hypertension refractory to other agents
Diltiazem found to be most effective in African Americans in one trial of single drug therapy
In patients with DM, its use assoc. with greater risk of MI compared with ACEI

Alpha Adrenergic Blockers

Prazosin, terazosin, doxazosin
- Can cause postural hypotension and syncope
- Use with caution in elderly
- Useful in men with BPH
- Caution with concurrent use of sildenafil/Viagra, vardenafil/Levitra, tadalafil/Cialis

Central Sympatholytics

Clonidine, Methyldopa
- Adverse effects: sedation, drowsiness, dry mouth, bradycardia, heart block
- Clonidine withdrawal: hypertension, headache, palpitations, perspiration
- Methyldopa: hepatitis, lupus-like syndrome, thrombocytopenia, hemolytic anemia
Direct Vasodilators
- Hydralazine, Minoxidil
  - Adverse effects: Tachycardia (can aggravate angina), headache, dizziness, fluid retention
  - Hydralazine: lupus-like syndrome, hepatitis
  - Minoxidil: hirsutism, pericardial effusion

Peripheral Adrenergic Inhibitors
- Guanadrel and Reserpine
  - Adverse effects: Orthostatic hypotension, diarrhea, drowsiness, bradycardia
  - Reserpine: depression, sedation, nasal congestion

Goals of therapy
- Decrease morbidity and mortality
  - Stroke, CHD, CHF
- Maintain function/quality of life
- Minimize side effects
- Treat co-morbidities
- Maximize therapy of other CV risk factors

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</table>
Stage 1, No Compelling Indications

- Thiazide diuretic for most patients
- Consider ACEI, ARB, BB, CCB

Compelling Indications

- Ischemic Heart Disease: BB, L.A. CCB, ACEI; lipid management, aspirin
- Heart Failure: ACEI, BB, ARB, spironolactone, loop diuretics
- Diabetes: ThD, BB, ACEI, ARB, L.A. CCB
- Renal disease: ACEI, ARB, loop diuretics
- Stroke: ACEI, ThD

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Stage 2, No Compelling Indications

- 2-drug combination for most patients
  - Thiazide diuretic + ACEI, ARB, BB, or CCB
Diabetes Mellitus

- Prevalence and incidence
- Screening and diagnostic criteria
- Review of medical therapies for type 2 DM
- Diagnosis and treatment of complications

Etiologic Classification

- **Type 1**
  - Immune-mediated, Idiopathic
  - β-cell destruction, leading to absolute insulin deficiency

- **Type 2**
  - From predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance

- **Other Specific Types**
  - Genetic defects of β-cell function
  - Genetic defects in insulin action
  - Diseases of the exocrine pancreas
  - Endocrinopathies
  - Drug or chemical induced
  - Infections
  - Uncommon forms of immune-mediated
  - Other genetic syndromes

- **Gestational Diabetes**
Gestational Diabetes
- Any glucose intolerance first detected during pregnancy
- Affects ~ 5% of all pregnancies
- Increases risk of
  - Macrosomia
  - Cesarean section
  - Hypertension
  - Diabetes type 2

Prevalence of diabetes
- 6.2% of total population
- 20% of persons over 65
- Highest in certain ethnic groups
  - African American (up to 12%)
  - Asian American (up to 22%)
  - Latin American (up to 20%)
  - Native American (up to 60%)

Prevalence of diabetes
- 800,000 new cases every year
- 2,000 new cases every day

Incidence of diabetes type 2
- 1 million Type 1
- 11 million Type 2 diagnosed
- 6 million Type 2 undiagnosed
- 150,000 GDM
Screening and Diagnosis

- 45 years and older, every three years
- Younger age, more frequently if
  - BMI > 27 kg/m²
  - First degree relative with diabetes
  - Physical inactivity
  - African American, Latin American, Asian American, Pacific Islander, or Native American
  - History of GDM or baby weighing over 9 pounds
  - Hypertensive
  - HDL < 35 mg/dl or TG > 250 mg/dl
  - History of impaired glucose tolerance

Criteria for Diagnosis

- Fasting plasma glucose > 126 mg/dl, or
- Symptoms plus random plasma glucose > 200 mg/dl, or
- Two-hour plasma glucose > 200 mg/dl on OGTT of 75 gm glucose

Symptoms

- None
- Usual: polys, constipation, nocturia
- Change in vision
- Fatigue
- Numbness or tingling
- Infections: Yeast, UTI’s
- Periodontal disease
- Impotence

Criteria for Diagnosis

- Fasting plasma glucose > 126 mg/dl, or
- Symptoms plus random plasma glucose > 200 mg/dl, or
- Two-hour plasma glucose > 200 mg/dl on OGTT of 75 gm glucose
Criteria for Diagnosis

<table>
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<tr>
<th></th>
<th>Normal</th>
<th>Impaired</th>
<th>Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>&lt; 100</td>
<td>100 – 125</td>
<td>&gt; 126</td>
</tr>
<tr>
<td>OGTT</td>
<td>&lt; 140</td>
<td>140 – 199</td>
<td>&gt; 200</td>
</tr>
</tbody>
</table>

Diabetes Control and Complications Trial (DCCT)

- 1400 patients with Type 1 DM
- Randomized to intensive vs. conventional therapy
- Followed for an average of 6.5 years
- 36 person-hours/patient/month
- Glycated hemoglobin levels of 7% vs. 9%

DCCT

- Intensive therapy provided significant 1st and 2nd prevention of retinopathy (73% and 54%)
- Intensive therapy was associated with decreased incidence of microalbuminuria, albuminuria, and clinical neuropathy (40% to 70%)
- Benefits persisted four years after trial stopped
- Two to three times increased incidence of severe hypoglycemia, and increased costs with intensive treatment

Treatment of DM Type 1

- Insulin regimens
  - Multiple dosing
  - Continuous subcutaneous infusion
  - Aim for tight control except in younger children
- Individualized therapy
- Family education
Flexible Insulin Regimens

- Usual requirements 0.5 to 1.0 U/kg/d
- Absorption depends on site, conc., mixing
- Basal (background) therapy balanced with mealtime (bolus) insulin
- If pre-meal glucose above 250
  - urine ketones
  - ↑ basal and mealtime dose
  - hydration status

Physiologic Insulin Response

Basal insulin supplies about 50% of the body’s needs. Insulin secreted in response to meals supplies the other 50%.

UKPDS (1998)

- 5,000 patients monitored over ten years
- Intensive treatment: insulin, sulfonylurea, metformin, or combination
- Conventional treatment: diet
- Initial differences in glycated hemoglobin: 7.0% vs. 7.9%
- Final overall differences: 7.9% vs. 8.5%

UKPDS -- results

15-46% risk reduction in microvascular complications
< 18% increase for each 1% drop in HbA1c

14-46% risk reduction in microvascular complications
UKPDS

- Overall risk of microvascular complications decreased with intensive therapy by 25%
- 80% of patients in conventional group eventually needed drug therapy
- No increase or decrease in cardiovascular complications

UKPDS: Hypertension

- 1000 patients
- Tight (144/82) vs. less tight (154/87) control
- Decreased risk of all complications by 24% - 56%
- ACEI and β-blocker equally effective
- Additive benefit of glucose and hypertension control

Target A1C: how low?

- Microvascular disease
  - Each % drop = 25% reduction
- Macrovascular disease
  - ACCORD (NEJM June 08): 3.5 years
  - High risk patients = CVD
  - 6.4 vs. 7.5 (targets: normalization vs. 7 – 8)
  - No reduction of CV events
  - Increased overall mortality; NNH: 95

Oral Agents for DM Type 2

- Secretagogues
  - Sulfonylureas
  - Meglitinides – repaglinide
  - D-Phenylalanine derivative - nateglinide
- Insulin sensitizers
  - Metformin
  - Glitazones
- Others
  - α - Glucosidase inhibitors
### Sulfonylureas

- Stimulate receptor-mediated insulin secretion
- Improve hepatic and peripheral insulin sensitivity
- Secondary treatment failure 5% to 10% per year

### Sulfonylureas

- Increase dose every 7 -14 days by 50% - 100%
- Side effects: hypoglycemia, weight gain, skin reactions, rare cholestatic hepatitis
- Maximum effective dose is half maximum recommended dose

### Glipizide Dose Response

![Glipizide Dose Response Graph]

### Sulfonylureas

<table>
<thead>
<tr>
<th>Name</th>
<th>Metabolism/excretion</th>
<th>Duration (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetohexamide</td>
<td>Liver/kidney</td>
<td>10-16</td>
</tr>
<tr>
<td>chlorpropamide</td>
<td>Kidney</td>
<td>~ 60</td>
</tr>
<tr>
<td>tolazamide</td>
<td>Liver</td>
<td>12-20</td>
</tr>
<tr>
<td>tolbutamide</td>
<td>Liver</td>
<td>6-12</td>
</tr>
<tr>
<td>glimepiride</td>
<td>Liver/kidney</td>
<td>24</td>
</tr>
<tr>
<td>glyburide</td>
<td>Liver/kidney</td>
<td>up to 36</td>
</tr>
<tr>
<td>glipizide</td>
<td>Liver/kidney</td>
<td>12-24</td>
</tr>
<tr>
<td>glipizide XL</td>
<td>Liver/kidney</td>
<td>24</td>
</tr>
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</table>
Repaglinide and Nateglinide

- A meglitinide and a d-phenylalanine derivative
- Stimulate insulin secretion, different receptor than sulfonylureas; no effect on peripheral tissues
- Quickly absorbed; short half life (2 hours)
- OK to use in renal insufficiency
- Prescription guidelines
  - Take before meals
  - Skip dose if not able to eat within 30 minutes
  - Increase dose weekly
  - Side effects: hypoglycemia

Insulin Sensitizers

- Metformin and the glitazones
- Ongoing studies to determine if they prevent or delay onset of DM2

Metformin

- Suppresses hepatic glucose output
- Improves oxidative disposal of glucose and lactate
- Improves sensitivity of muscle to insulin
- Decreases total cholesterol and triglycerides
- Weight neutral or small weight loss

Metformin

- Absorbed in small intestine; maximal plasma concentration 1 to 2 hours after dose
- Plasma half life 1.5 to 5 hours; not metabolized: 90% eliminated within 12 hours
- Increases clearance of warfarin, decreases clearance of cimetidine, decreases B12 absorption
- Accounts for majority of survival effect in UKPDS – specifically decreased MI incidence
Effect of Metformin on CVD

Metformin Treatment Guidelines
- Initial monotherapy or in combination (Metformin/glyburide)
- Start with 500 mg q.d.
- Take with meals; can increase dose quickly if tolerated
- Maximum dose up to 2550 mg/day (850 mg t.i.d.). Maximum response at 2000 mg/day.
- Limited by side effects: abdominal cramps, diarrhea, nausea, anorexia

Metformin Dose Response

Metformin Precautions
- Contraindicated in
  - Renal insufficiency (SCreat >1.4 women, >1.5 men)
  - Liver disease or active alcohol abuse
  - Pregnancy and lactation
- Discontinue for
  - IV contrast agents
  - Surgical procedures
  - Cardiac or respiratory failure, hypoxemia
  - Severe infection, sepsis
Thiazolidinediones (Glitazones)

- Bind to receptors that regulate transcription of insulin-responsive genes
- Insulin-sensitizing in muscle, liver, and adipose tissue
- Decrease hypertriglyceridemia, hyperinsulinemia, and hyperglycemia
- Increase both HDL and LDL cholesterol

Troglitazone was first agent
- Associated with severe, idiosyncratic liver injury
- Off the market as of March, 2000
- Rosiglitazone and pioglitazone appear safe(r)

Troglitazone induces cytochrome p450 isoform 3A4; prone to multiple drug interactions
- In clinical trials, incidence of significant increases in ALT with rosiglitazone and pioglitazone was similar to placebo
- Few reports of liver injury with rosiglitazone and pioglitazone after millions of prescriptions
Thiazolidinediones (Glitazones)

- Begin with lowest daily dose, with or without food
- Maximal response to therapy takes up to 12 weeks
- Monitor liver enzymes: prior to therapy and every two months
- Side effects: transaminitis, weight gain, fluid retention, edema

Thiazolidinediones: CV Risk

- Nissen, NEJM 2007: “Our data suggest a cardiovascular risk associated with the use of rosiglitazone.”
- Home, NEJM 2007: “Our interim findings from this ongoing study were inconclusive... There was no evidence of any increase in death from either cardiovascular causes or all causes. Rosiglitazone was associated with an increased risk of heart failure. The data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction.”
- Erdmann, AJCC: “In high-risk patients with type 2 diabetes and previous MI, pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and ACS.”

Thiazolidinediones

- Contraindicated in CHF class III and IV.
- Use with caution in anyone with CHF
- Contraindicated in pregnancy
- OK to use in renal insufficiency
- For CV risk, pioglitazone safer

α-Glucosidase Inhibitors

- Act upon uptake at the intestinal brush border
- Slow absorption of carbohydrates and reduces rise in postprandial glucose levels
- Acarbose or miglitol, initial dose 25 mg t.i.d. with first bite of meal, increase slowooowoowly
- Side effects: flatulence, diarrhea, abdominal cramps, decreased metformin absorption
- Contraindicated in significant liver or renal disease (SCreat >2.0)
**Treatment Effectiveness**

Average Reduction of HbA1c

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reduction (%)</th>
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<tbody>
<tr>
<td>Sulfonylurea</td>
<td>1-2</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1-2</td>
</tr>
<tr>
<td>Metformin</td>
<td>1-2</td>
</tr>
<tr>
<td>Acarbose</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>0.5-1.5</td>
</tr>
</tbody>
</table>

**Goals for Glycemic Control**

<table>
<thead>
<tr>
<th>Whole Blood Values</th>
<th>Normal</th>
<th>Goal</th>
<th>Add'l Action Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average preprandial glucose</td>
<td>&lt;100</td>
<td>80-120</td>
<td>&lt;80/&gt;140</td>
</tr>
<tr>
<td>Average bedtime glucose</td>
<td>&lt;110</td>
<td>100-140</td>
<td>&lt;100/&gt;160</td>
</tr>
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<table>
<thead>
<tr>
<th>Plasma Values</th>
<th>Normal</th>
<th>Goal</th>
<th>Add'l Action Suggested</th>
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<tr>
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<td>&lt;110</td>
<td>90-130</td>
<td>&lt;90/&gt;150</td>
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<tr>
<td>Average bedtime glucose</td>
<td>&lt;120</td>
<td>110-150</td>
<td>&lt;110/&gt;180</td>
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HbA1c (%)

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<th>Goal</th>
<th>Suggested</th>
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<tbody>
<tr>
<td>&lt;6</td>
<td>&lt;7</td>
<td>&gt;8</td>
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**Approaching Glycemic Goals**

- Targets must be individualized
  - All measurements do not have to fall within the target range with self-monitoring
  - If over half of the measurements within a given time fall within the range, glucose control is considered acceptable
  - Risk of hypoglycemia should be factored into goals
- About 50 percent of people with type 2 diabetes require insulin to maintain a HbA1c level below 7%

**Progressive decline in beta-cell function/insulin secretion in DM2**

- About 50 percent of people with type 2 diabetes require insulin to maintain a HbA1c level below 7%
Ms. A is a 46 year old woman who was diagnosed with type 2 DM about 6 years ago. She has a history of GDM (her daughter is now 8 years old); both her sisters have DM2.

She works as a home health aide. She is on metformin 1000 mg bid, and on glipizide 10 mg every morning. Her A1C, which was 7% in 2002, has been climbing steadily and is now 9.6%.

**Patient, 2004, continued**

- Adherence?
- Adequate doses of medications, taken at correct times?
- Changes in activity, weight, or diet? OR
- Natural progression of disease?

**Options**

- Increase physical activity/Nutrition consult
- Glitazone
  - Expensive
  - MUST monitor ALT regularly
  - Weight gain/edema
- Increase Glipizide to 20 mg q AM
  - Not much extra benefit
- Add bedtime insulin (augmentation therapy, B.I.D.S.)

**Insulin resistance syndrome**
Patient, 2004, continued

- Her weight is 90 Kg
- She eats three meals/day
- She has the following record of her SMG

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Before dinner</th>
<th>Before bed</th>
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<tbody>
<tr>
<td>Thurs.</td>
<td>250</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>Fri.</td>
<td>240</td>
<td>160</td>
<td>175</td>
</tr>
<tr>
<td>Sat.</td>
<td>255</td>
<td>160</td>
<td>188</td>
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</table>

Insulin Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Onset</th>
<th>Peak (hrs)</th>
<th>Duration (hrs)</th>
</tr>
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<tbody>
<tr>
<td>Lispro (rapid-acting)</td>
<td>10 - 30 mins</td>
<td>0.5 - 1</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Regular (short-acting)</td>
<td>30 - 60 mins</td>
<td>1.5 - 2</td>
<td>5 - 12</td>
</tr>
<tr>
<td>Premixed (70% NPH/30% R)</td>
<td>30 - 60 mins</td>
<td>3 (2-12)</td>
<td>13 - 18</td>
</tr>
<tr>
<td>NPH/Lente (intermediate-acting)</td>
<td>1-2 hrs</td>
<td>4.8</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Ultralente (long-acting)</td>
<td>2 – 4 hrs</td>
<td>8 - 20</td>
<td>16 - 24</td>
</tr>
<tr>
<td>Glargine (long-acting)</td>
<td>1 – 2 hrs</td>
<td>No peak</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

Physiologic Insulin Response

Basal insulin supplies about 50% of the body’s needs. Insulin secreted in response to meals supplies the other 50%.

Bedtime insulin: augmentation

- Basal insulin
  - NPH
  - Glargine
Duration of Insulin

Bedtime insulin: augmentation

- Initial dose 10 – 20 U
- Approximate:
  - $0.15 - 0.2 \text{ U/Kg/d}$
  - $90 \text{ Kg} \times 0.15 = 13.5 \text{ U}$
  - FCG in mmol/L, (i.e.: if FCG = 250)
  - $250 \div 18 = 14 \text{ U}$
- Adjust to a FCG 90-130
  - Increase by 4U if FCG > 140 on three consecutive mornings

Glargine

- Long-acting insulin analogue - used once daily
- Structure is modified to a more acidic pH - delays its absorption over 24 hours, with no clear peak
- A clear insulin (most longer-acting insulins are cloudy)
- Cannot be mixed with other insulins

Glargine

- Mimics the action of basal or background insulin
- More consistent action because of lack of peak
- Risk of hypoglycemia is reduced because of its long duration of action
- Usually given once daily
- Most will require bolus coverage as well
Basal augmentation with NPH

![Intermediate-acting Insulin Administered at Bedtime Only](image)

Starting glargine therapy

<table>
<thead>
<tr>
<th>Fasting</th>
<th>Before dinner</th>
<th>Before bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thurs.</td>
<td>116</td>
<td>108</td>
</tr>
<tr>
<td>Fri.</td>
<td>104</td>
<td>126</td>
</tr>
<tr>
<td>Sat.</td>
<td>120</td>
<td>118</td>
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</tbody>
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Basal augmentation with glargine

Patient, 2004, continued

- Insulin, NPH 18 U SQ at bedtime
- Continue lifestyle changes
- SMG
Patient, 2008

Ms. A. developed nephropathy, despite being on benazepril for the last 3 years. Since her CrCl is approximately 52, she had to discontinue her metformin. Her BP is 120/80, her LDL is 95, and she is on daily aspirin.

You start her on NPH/Reg premixed 70/30 insulin at 20 U b.i.d.

At follow-up 2 months later, her A1C is now 10.2, and she tells you that she often feels sweaty and anxious mid morning and at bedtime, and that she has gained 4 Kg.

Goals for Glycemic Control (ADA)

<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>GOAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ave pre-prandial</td>
<td>100</td>
<td>80 – 120</td>
</tr>
<tr>
<td>Ave bedtime</td>
<td>110</td>
<td>100 - 140</td>
</tr>
<tr>
<td>Plasma values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ave pre-prandial</td>
<td>110</td>
<td>90 – 130</td>
</tr>
<tr>
<td>Ave bedtime</td>
<td>120</td>
<td>110 - 150</td>
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Patient, 2008, continued

- Her weight is now 98 Kg
- She eats three meals and two snacks/day
- She has the following record of her SMG

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Patient, 2008, what is going on?

- Not enough insulin?
- Too much insulin?
- Not at the right times?
- Increased caloric intake (carbohydrate snacks)?
- All of the above?
**Insulin and its analogues**

<table>
<thead>
<tr>
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<th>Onset</th>
<th>Peak (hrs)</th>
<th>Duration (hrs)</th>
</tr>
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<tbody>
<tr>
<td>Lispro (rapid-acting)</td>
<td>10 - 30 mins</td>
<td>0.5 - 1</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Regular (short-acting)</td>
<td>30 – 60 mins</td>
<td>1.5 – 2</td>
<td>5 - 12</td>
</tr>
<tr>
<td>Premixed (70% NPH/30% R)</td>
<td>30 – 60 mins</td>
<td>3 (2-12)</td>
<td>13 - 18</td>
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<tr>
<td>NPH/Lente (intermediate-acting)</td>
<td>1-2 hrs</td>
<td>4 -8</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Ultralente (long-acting)</td>
<td>2 – 4 hrs</td>
<td>8 - 20</td>
<td>16 - 24</td>
</tr>
<tr>
<td>Glargine (long-acting)</td>
<td>1 – 2 hrs</td>
<td>No peak</td>
<td>24 hours</td>
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**NPH dosed b.i.d.**

**Total insulin effect**

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Total insulin effects & stacking

Physiologic Insulin Response

Patient, 2004, continued

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</tr>
<tr>
<td>Sun.</td>
<td>234</td>
<td>211</td>
<td>80</td>
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Bolus therapy/prandial therapy

Basal insulin supplies about 50% of the body’s needs.
Insulin secreted in response to meals supplies the other 50%. 
Bolus therapy/prandial therapy

- Advantages:
  - Less weight gain
  - Fewer hypoglycemic episodes
  - Flexible meal times

- Regular insulin
  - Needs to be given 30 mins. before meals

- Lispro (Humalog®)
  - Can be given at mealtime

Basal-bolus therapy

Average insulin needs (patients w/DM2):
- 0.5 U/Kg/day – 2.0 U/Kg/day

About 50% should be given as prandial therapy

Replacement therapy

Supplement:
- About 1 U will change BG by 50 mg/dL (less in the face of increased resistance)

Correct (in this order):
1. Hypoglycemia
2. Fasting glucose (by increasing basal insulin)
3. Pre-prandial levels (by increasing bolus insulin or changing to rapid
Replacement therapy: NPH & lispro

Insulin: the advanced seminar

- Individualized; flexible; plans for sick days
- Accounting for and counting carbs
  - 1U for every 5 – 15 gms of CHO
- Accounting for activity level
  - Decrease dose by 30 – 50% depending on timing and length of exercise
- Team care
  - Weekly adjustments with acute changes
  - Chronic management

Replacement therapy: glargine and lispro

Hypoglycemia episodes (about one severe episode/year in the UKDPS)

Weight gain: from insulin effect and from over treatment/hunger response
  - About 2 Kg in UKDPS

Worsening of retinopathy
  - Reported with rapid correction of initial A1C>10
  - However, early worsening rarely progresses to neovascularization
Goals of Therapy

- Decrease morbidity and mortality
  - CHD, Stroke
- Maximize therapy of CV risk factors
- Identify and treat complications early
- Maintain function/quality of life
- Minimize side effects

Prevention of Complications

- Coronary heart disease
- Stroke
- Ischemic peripheral vascular disease
- Retinopathy
- Nephropathy
- Neuropathy

Coronary Heart Disease and Stroke

- Smoking cessation
- Daily aspirin therapy
- Hypertension control
  - ACE inhibitors, β-blockers, Diuretics
- Treatment of dyslipidemia

Treatment of Dyslipidemia

- West of Scotland Coronary Prevention Study
- Scandinavian Simvastatin Survival Study
- Cholesterol and Recurrent Events Study
- Long-term Intervention with Pravastatin in Ischaemic Disease Study
- Veterans’ Administration HDL Cholesterol Intervention Trial Study
Treatment of Dyslipidemia

- Treatment based on LDL cholesterol level
  - Highest risk is LDL > 130
- Statins are the best studied agents
- Gemfibrozil helpful in isolated low HDL
  - Veterans’ Administration HDL Cholesterol Intervention Trial Study
  - Benefit in treating isolated decreased HDL in patients at risk for CHD
- Medical treatment recommended
  - If CVD or DM, and LDL > 100

Prevention of Microvascular Complications

- Control of blood pressure
- Glucose control
- Early identification and treatment of neuropathy, nephropathy, and retinopathy

Nephropathy

- Occurs in ~6% of patients with Type 2 DM (30% - 40% of patients with Type 1 DM)
- 40% of new ESRD diagnoses are patients with Type 2 DM
- Persistent microalbuminuria predicts progression to nephropathy.
- Risk for microalbuminuria rises with HgbA1c values above 8.1% in Type 1 DM

Nephropathy

- ACEI’s slow progress to albuminuria and renal failure and reduce risk of death in Type 1 DM
- ACEI’s decrease rate of progress and slow rate of loss of renal function in Type 2 DM
  - 24% in the HOPE study
- ARB’s decrease progression to proteinuria in Type 2 DM
Nephropathy

- Non-dihydropyridine calcium channel blockers (i.e. diltiazem) have similar protective effects
- Control of systolic blood pressure to 130/80 mmHg offers similar protection
- Smoking cessation, glucose control, statin therapy,

The End

Good Luck on your exam!

Nephropathy

- Screen all patients at intake with urinalysis
- If proteinuria, quantify and begin treatment
- If normal, check for microalbuminuria
  - If abnormal, confirm and begin treatment
  - If normal, repeat every one to two years

Multifactorial Intervention of CVD (Snemo 2 study, Denmark 1/2003)

- Open, parallel trial of 160 patients half each in conventional vs. multifactorial intervention treatment
- Target driven, intensified intervention
- Stepwise implementation of behavioral mod, pharmacologic therapy, treatment of HTN, dyslipidemia, microalbuminuria, and secondary prevention with aspirin
- Average age 55 years, mean FU 7.8 years
Multifactorial Intervention of CVD

Interventions:
- Nutrition: <30% fats, <10% saturated fats
- Exercise: 30 min exercise 3-5x/week
- Protocol treatment
  - Stepwise treatment with metformin, a SU, and insulin
  - Followed guidelines for treating microalbuminuria, hypertension, and dyslipidemia

Decreased risk CVD (HR 0.47)
Decreased risk of nephropathy (HR 0.42)
Decreased risk of neuropathy (HR 0.37)

Major differences between intervention and control groups?
- Lifestyle Modification: Exercise
- Treatments: ACEI and or ARB’s, Statins, Aspirin, multivitamin

Program Research Group
- 3200 patients with glucose intolerance
- Randomized: placebo vs. metformin vs. lifestyle modification (goals 7% weight loss and 150 min exercise/week)
- Average age 51, BMI 34, 68% women, 35% ethnic minorities
- Mean FU 2.8 years
Diabetes Prevention Program Research Group

- Incidence of DM2
  - 11% in placebo
  - 7.8% metformin
    - most effective in <45 y.o. or BMI>35
  - 4.8% lifestyle mod
    - most effective in >60 y.o, regardless of BMI

- Metformin decreased incidence by 31% (NNT 14 for 3 years)
- Lifestyle mod decreased incidence by 58% (NNT 7 for 3 years)