Screening for Diabetes 2013

- BMI ≥25 plus other risk factors
  - Inactivity
  - Low HDL or high TG
  - First degree relative
  - PCOS
  - High-risk ethnicity
  - Acanthosis nigricans
  - Gestational DM
  - Hx CVD
- Age 45

Advantages of HbA1c as a Diagnostic Test

- Non fasting
- Lower intra-individual variation
  - HbA1c: 2%
  - FPG: 6.5%
  - 2 hour plasma glucose: 16-17%

MANAGEMENT OF DIABETES: A PRIMARY CARE PERSPECTIVE

Robert B. Baron MD MS
Professor and Associate Dean
UCSF School of Medicine

Declaration of full disclosure: No conflict of interest

Diagnosis of Diabetes 2013

- A1C ≥ 6.5% (New, 2010)
- 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
MANAGEMENT OF DIABETES: A PRIMARY CARE PERSPECTIVE

**Diagnosis of Pre-Diabetes 2013**
- A1C 5.7 – 6.4% *(New, 2010)*
- 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)

**Risk of Pre-Diabetes 2013**
- Increased risk of progression to diabetes
- 44,203 individuals; 16 studies, 5.6 years
  - A1C 5.5 – 6.0: risk of DM 9 - 25%
  - A1C 6.0 – 6.5: risk of DM 25 – 50%

**Treatment of Pre-Diabetes 2013**
- Weight loss 7%; physical activity 150 min/week
- Metformin (but only metformin) may be considered, especially for those with BMI >35, age <60, and women with history of gestational DM

**2013 Practice Guidelines: ASA**
- ASA: only in those at increased CV risk (10 year risk >10%. Typically men over 50, women over 60 with other risk factors)

2009:
- ASA: over age 40 and for those with other CHD risk factors
2013 Practice Guidelines: HTN and Lipids and Tobacco

- BP: Goal less than 130 and less than 80
- LDL: Goal less than 70 (with CVD); less than 100 (without CVD)
- Don’t forget tobacco

Intensive BP Control in Type 2 DM: ACCORD

- RCT of 4733 patients with type 2 DM
- Compare BP less than 120 mm Hg vs 140

<table>
<thead>
<tr>
<th></th>
<th>120</th>
<th>140</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>119</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>CV events plus death</td>
<td>1.87%</td>
<td>2.09%</td>
<td>.20</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.28%</td>
<td>1.19%</td>
<td>.55</td>
</tr>
<tr>
<td>Strokes</td>
<td>0.32%</td>
<td>0.53%</td>
<td>.01</td>
</tr>
<tr>
<td>Adverse events</td>
<td>3.3%</td>
<td>1.3%</td>
<td>.001</td>
</tr>
</tbody>
</table>

In type 2 DM: treating to 120 mm Hg did not reduce the rate of composite fatal and non-fatal CV events

Case 1

70 yo woman with type 2 diabetes, hypertension, and coronary heart disease (s/p MI in 2003).

Meds: Metformin, glipizide, aspirin, lisinopril, metoprolol, and simvastatin

Exam: BP 130/80, BMI 29 kg/m²
  Normal exam

Her glycemic goal should be:
1. HbA1c <6.0%
2. HbA1c <6.5%
3. HbA1c <7.0%
4. HbA1c <7.5%
5. HbA1c <8.0%
Glycemic Control Update

- 3 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</th>
<th>Standard</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>1st 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>

Deaths

- Standard: 203
- Intensive: 257

11/1000/y
14/1000/y

Number Needed to Harm: 333

February 2008 (after 3.5 years): NIH stops this arm of study
MANAGEMENT OF DIABETES: A PRIMARY CARE PERSPECTIVE

**ACCORD Trial 5-Year Outcomes**
- Additional follow-up of 1.5 years
- All subjects treated to HbA1c of 7-7.9% during this period
- Results:
  - Mortality still higher in intensive group (7.6% vs 6.4%; HR 1.19)

**Outcome of Intensive Glucose Lowering in Type 2 DM**
- Meta-analysis of 13 RCTs in DM 2; 34,533 pts
- RR
  - All cause mortality: 1.04 (0.91 – 1.19)
  - CV death: 1.11 (0.86 – 1.43)
  - Non-fatal MI: 0.85 (0.74 – 0.96)*
  - Microalbuminuria: 0.90 (0.85 – 0.96)*
  - Severe hypoglycemia: 2.33 (21.62 -3.36)*
- * P <0.001

**ORIGEN Trial**
- RCT, 12,537 subjects; impaired FBS, IGT, or new diabetes, and high CV risk
- Mean FBS 131 mg/dl
- Glargine to FBS <95 mg/dl; 6.2 years
- Results: No difference in CV outcomes

**Outcome of Intensive Glucose Lowering in Type 2 DM**
- Over five year period:
  - NNT to prevent one MI: 117-150
  - NNT to prevent one microalbuminuria: 32- 142
  - NNT to cause one episode of severe hypoglycemia: 15-52
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 to support decrease in microvascular disease outcomes with more intensive glucose control
- More hypoglycemia and weight gain with more intensive regimens

2013 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, micro or macrovascular complications, comorbid conditions, and those in whom the goal is difficult to attain

Critically Ill patients?
Meta-analysis of 29 RCTs (n=8,432 patients)

<table>
<thead>
<tr>
<th></th>
<th>Mortality Rates</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tight</td>
<td>Usual</td>
</tr>
<tr>
<td>Overall</td>
<td>21.6%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Very tight, ≤110 mg/dl</td>
<td>23.0%</td>
<td>25.2%</td>
</tr>
<tr>
<td>Moderate, &lt;150 mg/dl</td>
<td>17.3%</td>
<td>18.0%</td>
</tr>
<tr>
<td>Medical ICU</td>
<td>26.9%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Surgical ICU</td>
<td>8.8%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Med-Surg ICU</td>
<td>26.1%</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

Glycemic Control Summary

- No consistent evidence that tight glucose control improves mortality in hospitalized patients.
2013 Practice Guidelines:
Glucose Control in Hospital

- Critically ill: Goal 140 - 180.
  - IV protocol
- Non-critically ill: premeal <140 if can be done safely; random < 180. Less stringent if severe comorbidities
  - Scheduled subcu insulin with basal, nutritional, and correction components

Case 1

Her glycemic goal should be:

1. HbA1c <6.0%
2. HbA1c <6.5%
3. HbA1c <7.0%
4. HbA1c <7.5%
5. HbA1c <8.0%

In my practice, I have initiated:

1. Exenatide (Byetta™) or Liraglutide (Victoza™)
2. Sitagliptin (Januvia™) or Saxagliptin (Onglyza™)
3. Both exenatide and sitagliptin
4. Pramlintide (Symlin™)
5. All three of the above
6. None of the above
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™) or saxagliptin (Onglyza™)

Metformin: The Safest Hypoglycaemic Agent in Chronic Kidney Disease?

“There is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other oral hypoglycaemic treatments.”


Rosiglitazone vs Pioglitazone

Observational study, FDA, 227,571 Medicare patients, over 3 years.

<table>
<thead>
<tr>
<th>Event</th>
<th>Rosi/Pio HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>1.06</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.27</td>
</tr>
<tr>
<td>CHF</td>
<td>1.25</td>
</tr>
<tr>
<td>Death</td>
<td>1.14</td>
</tr>
<tr>
<td>Composite</td>
<td>1.18</td>
</tr>
</tbody>
</table>

Number Needed to Harm with Rosiglitazone = 60 per year

Graham et al, JAMA 2010
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

Relative Contributions of Fasting and Postprandial Plasma Glucose to Total Glycemic Excursions as a Function of A1C


Natural History of Type 2 Diabetes

*IFG = impaired fasting glucose
**Insulin Plus Oral Agents**

- Introduction of insulin
  - Bedtime
  - Intermediate/Long-acting insulins
    - NPH, glargine, levemir
    - 10 units
  - Self-monitoring of blood glucose (hypoglycemia education)

- Insulin plus other oral agent combinations (maintain effect on insulin sensitivity)

**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**

- Meal coverage (carbohydrates)
- Basal insulin
- 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

**Incretin Drugs**

<table>
<thead>
<tr>
<th>GLP Agonists</th>
<th>DPP IV Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxagliptin</td>
</tr>
<tr>
<td>Exenatide Lar</td>
<td>Vildagliptin</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Albiglutin</td>
</tr>
<tr>
<td>Alliglutide</td>
<td>Linagliptin</td>
</tr>
<tr>
<td>Taspoglutide</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Metformin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A1C (%) Effect (change from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo BID</td>
</tr>
<tr>
<td>MET</td>
</tr>
<tr>
<td>SFU</td>
</tr>
<tr>
<td>MET+SFU</td>
</tr>
</tbody>
</table>

Changes in A1C from baseline vs placebo statistically significant
Management of Diabetes: A Primary Care Perspective

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>-1.4</td>
<td>-3.1</td>
<td>-4.2</td>
</tr>
<tr>
<td>Hypoglycemia (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>5.3</td>
<td>4.5</td>
<td>5.3</td>
</tr>
<tr>
<td>SFU</td>
<td>3.3</td>
<td>14.4</td>
<td>35.7</td>
</tr>
<tr>
<td>MET + SFU</td>
<td>1.26</td>
<td>19.2</td>
<td>27.8</td>
</tr>
</tbody>
</table>

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

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>Placebo</th>
<th>Sitagliptin 100 mg QD</th>
<th>Sitagliptin 50 mg BID</th>
<th>Sitagliptin 1000 mg BID</th>
<th>Sitagliptin 50 mg BID + Met 1000 mg BID</th>
<th>Sitagliptin 50 mg BID + Met 500 mg BID + Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>-2.5</td>
<td>-2.0</td>
<td>-1.5</td>
<td>-1.0</td>
<td>-0.5</td>
<td>-1.3</td>
</tr>
</tbody>
</table>

Mean Baseline HbA1C = 8.8%
N=1091

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 (6.2)</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 WBC – neutrophil count higher by 200 on Sitagliptin
No nausea or vomiting
No weight loss
Increased Incidence of Pancreatitis and Cancer Among Patients Given Glucagon Like Peptide-1 Based Therapy

- Sitagliptin or exenatide increased the odds ratio for pancreatitis 6-fold (\( P < 2 \times 10^{-16} \)).
- Pancreatic cancer was more commonly reported among patients that took sitagliptin or exenatide, (\( P < 0.033, P < 2 \times 10^{-4} \)).
- All other cancers occurred more frequently among patients that took sitagliptin, (\( P < 1 \times 10^{-4} \)).

*SGLT2 Inhibitors*

**Sodium-glucose cotransporter 2 Inhibitors**

- Inhibit glucose reabsorption in renal proximal tubule
- **Potential advantages**
  - Weight loss, low risk of hypoglycemia, reduced BP
- **Potential disadvantages**
  - Polyuria, electrolyte disorders, UTI, fungal genital infections, ?

**Natural History of Type 2 Diabetes**

**Drug Cost Comparison**

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose strips (2 per day)</td>
<td>$66</td>
</tr>
<tr>
<td>Sulfonylurea Generic</td>
<td>$4-14</td>
</tr>
<tr>
<td>Brand</td>
<td>$50</td>
</tr>
<tr>
<td>Rapaglinide 2 mg tid</td>
<td>$198</td>
</tr>
<tr>
<td>Acarbose 100 mg tid</td>
<td>$88</td>
</tr>
<tr>
<td>Metformin 1000 bid Generic</td>
<td>$4-32</td>
</tr>
<tr>
<td>Brand</td>
<td>$161</td>
</tr>
<tr>
<td>Rosiglitazone 8 mg qid</td>
<td>$366</td>
</tr>
<tr>
<td>Pioglitazone 45 mg/d</td>
<td>$245</td>
</tr>
<tr>
<td>Sitagliptin/Saxagliptin</td>
<td>$207-190</td>
</tr>
<tr>
<td>Exenatide 10 mcg/Liraglutide 1.2mg</td>
<td>$275-280</td>
</tr>
<tr>
<td>Gliargine, 45 U/d</td>
<td>$150</td>
</tr>
<tr>
<td>24 hour fitness Center</td>
<td>$35</td>
</tr>
<tr>
<td>YMCA</td>
<td>$65</td>
</tr>
</tbody>
</table>
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
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3. Begin pioglitzone
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5. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™) or saxagliptin (Onglyza™)

Conclusions

- Tight glycemic control not effective in lowering total mortality or CV mortality.
- Many newer diabetes agents available, all with some side effects and higher costs...few with hard outcome data.
- Glucose control may be more important early in diabetes
- Good BP and lipid control is important throughout the diabetes life course