CURRENT ISSUES IN DIABETES MANAGEMENT

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Declaration of full disclosure: No conflict of interest
Screening for Diabetes 2013

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

- Age 45

ADA Diabetes Care, 2013
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

ADA Diabetes Care, 2013
Advantages of HbA1c as a Diagnostic Test

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

ADA Diabetes Care, 2013
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>Stroke</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
Case 1
Her glycemic goal should be:

A. HbA1c <6.0%
B. HbA1c <6.5%
C. HbA1c <7.0%
D. HbA1c <7.5%
E. 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, NEJM, 2008
## ACCORD trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive</th>
<th>Standard</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=5,128</td>
<td>n=5,123</td>
<td></td>
</tr>
<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>
ACCORD Trial

<table>
<thead>
<tr>
<th>Standard</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>203</td>
</tr>
<tr>
<td></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
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)

ACCORD, NEJM, 2011
Outcome of Intensive Glucose Lowering in Type 2 DM

Meta-analysis of 13 RCTs in DM 2; 34,533 pts

<table>
<thead>
<tr>
<th>Event</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>1.04 (0.91 – 1.19)</td>
</tr>
<tr>
<td>CV death</td>
<td>1.11 (0.86 – 1.43)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.85 (0.74 – 0.96)*</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>0.90 (0.85 – 0.96)*</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>2.33 (21.62 -3.36)*</td>
</tr>
</tbody>
</table>

* P <0.001

Boussageon, BMJ 2011
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

Boussageon, BMJ 2011
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
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

ADA Diabetes Care, 2013
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:

A. Exenatide (Byetta™) or Liraglutide (Victoza™)
B. Sitagliptin (Januvia™) or Saxagliptin (Onglyza™)
C. exenatide and sitagliptin
D. Pramlintide (Symlin™)
E. All three of the above
F. 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:

A. Continue current therapy
B. Begin a sulfonylurea
C. Begin pioglitizone
D. Begin NPH insulin or long-acting insulin analogue
E. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™) or saxagliptin (Onglyza™)

[Bar chart showing percentages of different treatment options]
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>Condition</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

<table>
<thead>
<tr>
<th>Obesity</th>
<th>IFG*</th>
<th>Diabetes</th>
<th>Uncontrolled hyperglycemia</th>
</tr>
</thead>
</table>

**Glucose (mg/dL)**

- Post-meal Glucose
- Fasting Glucose

**Relative Function (%)**

- Insulin Resistance
- Insulin Level
- Beta-cell failure

*IFG = impaired fasting glucose
Natural History of Type 2 Diabetes

- **Glucose (mg/dL)**
  - Post-meal Glucose
  - Fasting Glucose

- **Relative Function (%)**
  - Insulin Resistance
  - Insulin Level

- **Years of Diabetes**
  - Beta-cell failure
  - Biguanide
  - Lifestyle
  - SU
  - Insulin

**Key Points**
- Insulin resistance and failure are key factors in the progression of Type 2 Diabetes.
- Lifestyle modifications and medications (such as Biguanide and SU) are crucial in managing the disease.
- The graph illustrates the trend of glucose levels and relative function over time.
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>- Alogliptin</td>
</tr>
<tr>
<td>- Aliglutide</td>
<td>- Linagliptin</td>
</tr>
<tr>
<td>- Taspoglutide</td>
<td>- Dutogliptin</td>
</tr>
<tr>
<td>- Lixsenatide</td>
<td>- Metogliptin</td>
</tr>
</tbody>
</table>
## 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>-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 HbA$_{1C}$ With Initial Co-administration of Sitagliptin and Metformin

Mean Baseline HbA$_{1C}$ = 8.8%
N=1091

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

Aschner P, et al. Oral presentation at the EASD 42$^{nd}$ Annual Meeting; 14-17 September 2006; Copenhagen.
## Sitagliptin – adverse reactions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sitagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td>n = 443</td>
<td>n = 363</td>
</tr>
<tr>
<td><strong>Nasopharyngitis</strong></td>
<td>23 (5.2)</td>
<td>12 (3.3)</td>
</tr>
<tr>
<td>+ pioglitazone</td>
<td>n = 175</td>
<td>n = 178</td>
</tr>
<tr>
<td><strong>Upper resp. infection</strong></td>
<td>11 (6.3)</td>
<td>6 (3.4)</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

- **Lifestyle**
- **SU**
- **Insulin**

**Incretins/Others?**

**Thiazolidinedione ? - Biguanide**

**Glucose (mg/dL)**

- Post-meal Glucose
- Fasting Glucose

**Relative Function (%)**

- Insulin Resistance
- Insulin Level

- Beta-cell failure

Years of 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</td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>$4-14</td>
</tr>
<tr>
<td>Brand</td>
<td>$50</td>
</tr>
<tr>
<td>Rapaglinide 2 mg tid</td>
<td>$193</td>
</tr>
<tr>
<td>Acarbose 100 mg tid</td>
<td>$88</td>
</tr>
<tr>
<td>Metformin 1000 bid</td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>$4-32</td>
</tr>
<tr>
<td>Brand</td>
<td>$161</td>
</tr>
<tr>
<td>Rosiglitazone 8 mg qd</td>
<td>$266</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>$271/280</td>
</tr>
<tr>
<td>Glargine, 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>
Tier 1: Well-validated core therapies

At diagnosis:
- Lifestyle + Metformin

STEP 1
- Lifestyle + Metformin + Basal insulin

STEP 2
- Lifestyle + Metformin + Sulfonylurea

STEP 3
- Lifestyle + Metformin + Intensive insulin

Tier 2: Less well-validated therapies

- Lifestyle + Metformin + Pioglitazone
  - No hypoglycemia
  - Oedema/CHF
  - Bone loss

- Lifestyle + Metformin + GLP-1 agonist
  - No hypoglycemia
  - Weight loss
  - Nausea/vomiting

- Lifestyle + Metformin + Pioglitazone + Sulfonylurea

- Lifestyle + Metformin + Basal insulin
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™)
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