CURRENT CONTROVERSIES IN DIABETES CARE

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Professor and Associate Dean
UCSF School of Medicine

Declaration of full disclosure: No conflict of interest

Diabetes Mellitus: U.S. Impact

<table>
<thead>
<tr>
<th>DIABETES</th>
<th>IFG</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.7 Million (8.3%)</td>
<td>12.3 Million (6.3%)</td>
</tr>
</tbody>
</table>

- Type 1: ~1 Million
- Type 2: ~16 Million

2/3 Diagnosed
1/3 Undiagnosed (4.9 Million)

TOTAL: 29 Million (14.4%)

Screening for Diabetes 2010

- 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
  - HTN
  - A1C ≥5.7, IGT, IFG
- Age 45
CURRENT CONTROVERSIES IN DIABETES CARE

Diagnosis of Diabetes 2010

- A1C ≥ 6.5% (New, 2010)
- FPG ≥ 126
- 2-h plasma glucose ≥ 200 during OGTT
- Symptoms and random plasma glucose ≥ 200

2010 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

2010 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
CURRENT CONTROVERSIES IN DIABETES CARE

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>.02</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

Ms. EH is a 68 y.o. woman with type 2 diabetes, hypertension, and coronary heart disease (s/p MI in 2002).

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

Exam: BP 135/85, HR 72, BMI 29 kg/m²
   Normal heart, lungs, extremities

Her glycemic goal should be:
1. HbA1c <6.0%
2. HbA1c <6.5%
3. HbA1c <7.0%
4. HbA1c <7.5%
CURRENT CONTROVERSIES IN DIABETES CARE

Glycemic Control Update

- 3 newer trials
  - ADVANCE
  - ACCORD
  - VA Diabetes Trial

ADVANCE TRIAL

RCT in DM 2; 11,140 patients; 20 countries; 5 yr

- Intensive vs. standard BS control

- Intensive HbA1C goal 6.5% or less
  - Intensive: 6.5%
  - Standard: 7.3%

- Outcome: composite macrovascular and/or microvascular events

ADVANCE, NEJM 2008

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Intensive</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Events</td>
<td>20.0%</td>
<td>18.1%</td>
<td>0.01</td>
</tr>
<tr>
<td>Microvasc events</td>
<td>10.9%</td>
<td>9.4%</td>
<td>0.01</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>5.2%</td>
<td>4.1%</td>
<td>0.006</td>
</tr>
</tbody>
</table>

No differences in:
- Macrovascular events
- CV death
- Death from all causes

ADVANCE, NEJM, 2008
CURRENT CONTROVERSIES IN DIABETES CARE

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 (fibrates 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>

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

Deaths
- Standard: 203
- Intensive: 257 (14/1000/y)

Number Needed to Harm: 333
CURRENT CONTROVERSIES IN DIABETES CARE

**VA Diabetes Trial**
20 VA centers; n=1,791; started in 2000

**Intervention:**
- Intensive glycemic Rx (goal A1c<6.0%) vs. improved treatment (goal A1c 8-9.0%)
- A1c separation goal of ≥1.5%
- Protocol-based intervention (metformin, rosiglitazone, glimepiride, then insulin)
- BP and lipid treatment goals equal

**Outcomes:** CV events (CV deaths, MI, CVA, CHF, cardiac revascularization, ischemic amputation)

Abraira, Obes Met, 2008

**VADT: Results**
No significant reduction in CVD with intensive glycemic control (HR 0.87, 0.73-1.04, p=0.12)

**Subgroups:**
- Advanced subclinical disease:
  - Coronary calcium ≥100: no benefit
  - Coronary calcium <100: benefit from intensive control

- Duration of diabetes:
  - Shortest time period had the most benefit
  - 12-15 years had neutral effect
  - >16 years had increased risk of CV events

ADA meeting, 2008
CURRENT CONTROVERSIES IN DIABETES CARE

### Glycemic Control Summary

- No consistent evidence that tight glycemic control reduces risk of CVD
- Possible subgroups with benefit:
  - shorter diabetes duration
  - less CAC (no prior CVD)
- Strong evidence to support decrease in microvascular disease outcomes with more intensive glucose control
- More hypoglycemia and weight gain with most intensive regimens

### 2010 Practice Guidelines: Glucose Control

- Goal A1C ≤7 for most
- Goal A1C <7 for some: short duration, long life expectancy, and no CVD
- Goal less stringent for history of hypoglycemia, limited life expectancy, micro or macrovascular complications, comorbid conditions, and those in whom the goal is difficult to obtain

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

<table>
<thead>
<tr>
<th>Mortality Rates</th>
<th>Tight</th>
<th>Usual</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>21.6%</td>
<td>23.3%</td>
<td>0.93 (0.85-1.03)</td>
</tr>
<tr>
<td>Very tight, ≤110 mg/dl</td>
<td>23.0%</td>
<td>25.2%</td>
<td>0.90 (0.77-1.04)</td>
</tr>
<tr>
<td>Moderate, &lt;150 mg/dl</td>
<td>17.3%</td>
<td>18.0%</td>
<td>0.99 (0.83-1.18)</td>
</tr>
<tr>
<td>Medical ICU</td>
<td>26.9%</td>
<td>29.7%</td>
<td>0.92 (0.82-1.04)</td>
</tr>
<tr>
<td>Surgical ICU</td>
<td>8.8%</td>
<td>10.8%</td>
<td>0.88 (0.63-1.22)</td>
</tr>
<tr>
<td>Med-Surg ICU</td>
<td>26.1%</td>
<td>27.0%</td>
<td>0.95 (0.80-1.13)</td>
</tr>
</tbody>
</table>

Wiener, Jama, 2008
CURRENT CONTROVERSIES IN DIABETES CARE

Glycemic Control Summary

- No consistent evidence that tight glucose control improves mortality in hospitalized patients.

2010 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%
CURRENT CONTROVERSIES IN DIABETES CARE

In my practice, I have initiated:

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

Your next best step is:

1. Begin metformin
2. Begin a sulfonylurea
3. Begin a thiazolidinedione
4. Begin insulin
5. Begin exenatide (Byetta™) or sitagliptin (Januvia™)
CURRENT CONTROVERSIES IN DIABETES CARE

48 yo woman with DM, BMI 33, on diet and exercise and metformin. HbA1C is now 8.0. Your next best step is:

1. Continue current therapy
2. Begin a sulfonylurea
3. Begin a thiazolidinedione
4. Begin insulin
5. Begin exenatide (Byetta™) or sitagliptin (Januvia™)

Generic Oral Hypoglycemic Slide

ARE THIAZOLIDINEDIONES SUPERIOR?

Thiazolidinedione use slows progression to combination therapy

Thiazolidinediones reduce microalbuminuria and hyperfiltration

Reduced intimal proliferation
CURRENT CONTROVERSIES IN DIABETES CARE

ARE THIAZOLIDINEDIONES INFERIOR?

Meta-analysis of 42 trials of rosiglitazone:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>1.43</td>
<td>(1.03-1.98)</td>
</tr>
<tr>
<td>Death</td>
<td>1.64</td>
<td>(0.98-2.74)</td>
</tr>
</tbody>
</table>

Nissen, NEJM 2007

RECORD TRIAL: Rosiglitazone

RCT, 4447 patients, type 2 DM, A1C 7.9%, rosiglitazone plus metformin or sulfonylurea vs. the two together. Funded by GSK.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac hosp or death*</td>
<td>0.99</td>
<td>NS</td>
</tr>
<tr>
<td>All death</td>
<td>0.86</td>
<td>NS</td>
</tr>
<tr>
<td>CV death</td>
<td>0.84</td>
<td>NS</td>
</tr>
<tr>
<td>MI</td>
<td>1.14</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.72</td>
<td>NS</td>
</tr>
<tr>
<td>CHF</td>
<td>2.10</td>
<td>0.0010</td>
</tr>
<tr>
<td>Fractures</td>
<td>1.36</td>
<td>NS</td>
</tr>
</tbody>
</table>

Home, Lancet 2009

Comparison of CV risk observed in meta-analyses of RSG and PIO

Graham, FDA 2007

David Graham, MD MPH
CURRENT CONTROVERSIES IN DIABETES CARE

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
- 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
CURRENT CONTROVERSIES IN DIABETES CARE

**Natural History of Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Relative Function (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>400</td>
<td>300</td>
</tr>
</tbody>
</table>

**Insulin Plus Oral Agents**

Introduction of insulin
- Bedtime
- Intermediate/Long-acting insulins
  - NPH, glargine, levetirin
  - 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)
CURRENT CONTROVERSIES IN DIABETES CARE

Function of Insulin in Regimens

Meal coverage (carbohydrates)

Basal insulin

Correction of high blood sugar

More Options

Incretin mimetics

Exenatide (Byetta ™) 4/05
Sitagliptin (Januvia ™) 6/06

Amylinomimetics (amylin analog)

Pramlintide (Symlin ™) 3/05

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>– Vildagliptin</td>
</tr>
<tr>
<td>– Liraglutide</td>
<td>– Sitagliptin</td>
</tr>
<tr>
<td>– CJC-1131</td>
<td>– Saxagliptin</td>
</tr>
<tr>
<td>– AVE-0010</td>
<td>– PSN=931</td>
</tr>
<tr>
<td>– Albugon</td>
<td>– Takeda-Syrrx</td>
</tr>
<tr>
<td>– Gip-1-transferin</td>
<td></td>
</tr>
<tr>
<td>– Exenatide Lar</td>
<td></td>
</tr>
</tbody>
</table>
### CURRENT CONTROVERSIES IN DIABETES CARE

#### 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)
CURRENT CONTROVERSIES IN DIABETES CARE

Improvements in HbA1c With Initial Co-administration of Sitagliptin and Metformin

Mean Baseline HbA1c = 8.8%
N=1091

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Placebo</th>
<th>Sit 150 mg QD</th>
<th>Met 500 mg BID</th>
<th>Met 1000 mg BID</th>
<th>Sit 50 mg BID + Met 500 mg BID</th>
<th>Sit 50 mg BID + Met 1000 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2.1</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>62.8</th>
<th>62.0</th>
<th>61.5</th>
<th>61.0</th>
<th>60.5</th>
</tr>
</thead>
</table>

Mean Baseline HbA1c = 8.8%
N=1091

Aschner P, et al. Oral presentation at the EASD 42nd Annual Meeting; 14-17 September 2006; Copenhagen.

Sitagliptin – adverse reactions

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Sitagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>n = 443</td>
<td>n = 363</td>
</tr>
<tr>
<td>Nasopharyngitis + pioglitazone</td>
<td>n = 175</td>
<td>n = 178</td>
</tr>
<tr>
<td>Upper resp. infection</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

Drug Cost Comparison

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>$4-14</td>
</tr>
<tr>
<td>Brand</td>
<td>$34</td>
</tr>
<tr>
<td>Rapaglinide 2 mg tid</td>
<td>$111</td>
</tr>
<tr>
<td>Acarbose 100 mg tid</td>
<td>$75</td>
</tr>
<tr>
<td>Metformin 1000 tid</td>
<td>$4-60</td>
</tr>
<tr>
<td>Generic</td>
<td>$104</td>
</tr>
<tr>
<td>Rosiglitazone 8 mg qd</td>
<td>$175</td>
</tr>
<tr>
<td>Pioglitazone 40 mg/d</td>
<td>$180</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>$146</td>
</tr>
<tr>
<td>Exenatide 5mcg</td>
<td>$185</td>
</tr>
<tr>
<td>10mcg</td>
<td>$209</td>
</tr>
<tr>
<td>Glargine, 45 U/d</td>
<td>$118</td>
</tr>
<tr>
<td>24 hour fitness Center</td>
<td>$40</td>
</tr>
<tr>
<td>YMCA</td>
<td>$60</td>
</tr>
</tbody>
</table>
Case 2: 48 yo woman with DM, BMI 33, on diet and exercise. HbA1C is 9.2. Your next best step is:
1. Begin metformin
2. Begin a sulfonylurea
3. Begin a thiazolidinedione
4. Begin insulin
5. Begin exenatide (Byetta™) or sitagliptin (Januvia™)

48 yo woman with DM, BMI 33, on diet and exercise and metformin. HbA1C is now 8.0. Your next best step is:
1. Continue current therapy
2. Begin a sulfonylurea (my choice)
3. Begin a thiazolidinedione
4. Begin insulin
5. Begin exenatide (Byetta™) or sitagliptin (Januvia™)
Conclusions

- Tight glycemic control not effective in lowering CHD or CVD outcomes
- Many newer diabetes agents available, all with some side effects...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