CURRENT ISSUES IN DIABETES MANAGEMENT: A Primary Care Perspective

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Declaration of full disclosure: No conflict of interest

Screening for Diabetes 2011

- 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
- Age 45

Diagnosis of Diabetes 2011

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

Advantages of HbA1c as a Diagnostic Test

- Non fasting
- Lower intra-individual variation
  - HbA1c: 2%
  - FPG: 6.5%
  - 2 hour plasma glucose: 16-17%
CURRENT ISSUES IN DIABETES MANAGEMENT

2011 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

2011 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

- BP
  - 119
  - 133
- CV events plus death
  - 1.97%
  - 2.09%
- Mortality
  - 1.28%
  - 1.19%
- Stroke
  - 0.32%
  - 0.53%
- Adverse events
  - 3.3%
  - 1.3%

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).

- Metoprolol, and simvastatin
- Exam: BP 130/80, BMI 29 kg/m
  - Normal exam

Normal exam
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%

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 TRIAL

<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
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

<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>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

ACCORD Trial

- 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, 2008

ACCORD, NEJM, 2011
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% (8.4% vs 6.9%)

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

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

Outcome of Intensive Glucose Lowering in Type 2 DM
Meta-analysis of 13 RCTs in DM 2; 34,533 pts

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>1.04 (0.91 – 1.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>1.11 (0.86 – 1.43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.85 (0.74 – 0.96)*</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>0.90 (0.85 – 0.96)*</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>2.33 (2.162 -3.36)*</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* P <0.001

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
CURRENT ISSUES IN DIABETES MANAGEMENT

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

2011 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

Mortality Rates

<table>
<thead>
<tr>
<th></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, &lt;150 mg/dl</td>
<td>23.0%</td>
<td>25.2%</td>
<td>0.90 (0.77-1.04)</td>
</tr>
<tr>
<td>Medical ICU</td>
<td>17.3%</td>
<td>18.0%</td>
<td>0.99 (0.83-1.18)</td>
</tr>
<tr>
<td>Surgical ICU</td>
<td>26.9%</td>
<td>29.7%</td>
<td>0.92 (0.82-1.04)</td>
</tr>
<tr>
<td>Med-Surg ICU</td>
<td>8.8%</td>
<td>10.8%</td>
<td>0.88 (0.63-1.22)</td>
</tr>
</tbody>
</table>

Glycemic Control Summary

- No consistent evidence that tight glucose control improves mortality in hospitalized patients.
2011 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 subcutaneous 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% (maybe...)

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
CURRENT ISSUES IN DIABETES MANAGEMENT

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™)

Case 3: 57 yo woman with DM, BMI 33, on diet and exercise, max doses metformin and glyburide. HbA1C is 8.5. Your next best step is:

1. Continue current therapy
2. Begin pioglitizone
3. Begin NPH insulin or long-acting insulin analogue
4. Begin sitagliptin (Januvia™) or saxagliptin (Onglyza™)
5. Begin exenatide (Byetta™) or liraglutide (Victoza™)

Generic Oral Hypoglycemic Slide

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.”

## Current Issues in Diabetes Management

### What about Thiazolidinediones?

Meta-analysis of 42 trials of rosiglitazone:

<table>
<thead>
<tr>
<th></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>Event</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

### 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


Composite primary endpoint: all cause mortality, non-fatal MI (including silent MI), stroke, leg amputation, ACS, cardiac intervention, leg revascularization.

PROactive Primary Endpoint: No Statistically Significant Difference vs Placebo in CV outcome
Rosiglitzone (Avandia) to Pulled From Retail Pharmacy Shelves

Rosiglizone (Avandia) will be pulled from retail pharmacy shelves November 18, 2011.

Only certified MDs will be allowed to prescribe the drug. Prescriptions filled by mail order only through specific pharmacies.

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
CURRENT ISSUES IN DIABETES MANAGEMENT

Natural History of Type 2 Diabetes

Insulin Plus Oral Agents

Introduction of insulin
- Bedtime
- Intermediate/Long-acting insulins
  - NPH, glargine, levetir
  - 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
**CURRENT ISSUES IN DIABETES MANAGEMENT**

**More Options**

<table>
<thead>
<tr>
<th>Incretin mimetics</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta ™)</td>
<td>4/05</td>
</tr>
<tr>
<td>Sitagliptin (Januvia ™)</td>
<td>6/06</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza ™)</td>
<td>8/09</td>
</tr>
<tr>
<td>Liraglutide (Victoza ™)</td>
<td>1/10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amylinomimetics (amylin analog)</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramlintide (Symlin ™)</td>
<td>3/05</td>
</tr>
</tbody>
</table>

**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></td>
<td>Vildagliptin</td>
</tr>
<tr>
<td></td>
<td>Alogliptin</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
</tr>
<tr>
<td></td>
<td>Dutogliptin</td>
</tr>
<tr>
<td></td>
<td>Metogliptin</td>
</tr>
</tbody>
</table>
CURRENT ISSUES IN DIABETES MANAGEMENT

GLP-1 and GIP Are Degraded by the DPP-4 Enzyme

GLP-1 and GIP are degraded by the DPP-4 enzyme. GLP-1 and GIP are released after a meal. DPP-4 (Dipeptidyl Peptidase IV) enzyme rapidly inactivates GLP-1 and GIP. The half-lives of GLP-1 and GIP are 2 minutes and 5 minutes, respectively.

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.
CURRENT ISSUES IN DIABETES MANAGEMENT

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>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</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>Upper resp. infection</td>
<td>11 (6.3)</td>
<td>6 (3.4)</td>
</tr>
</tbody>
</table>

Sitagliptin – adverse reactions

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 x 10\(^{-16}\)).
- Pancreatic cancer was more commonly reported among patients that took sitagliptin or exenatide, (P <0.033, P <2x10\(^{-4}\))
- All other cancers occurred more frequently among patients that took sitagliptin, (P <1x10\(^{-2}\))

Rationale for SGLT2 Inhibitors

- Inhibit glucose reabsorption in the renal proximal tubule
- Resultant glucosuria leads to a decline in plasma glucose and reversal of glucotoxicity
- Therapy is simple and nonspecific
- Even patients with refractory type 2 diabetes are likely to respond

SGLT2 Inhibitors

Potential Advantages
- Weight loss
- Low risk of hypoglycemia
- Possible BP lowering effect
- Effect independent of insulin

Concerns
- Polyuria
- Electrolyte disturbances
- Bacterial UTIs
- 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</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>$183</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 od</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></td>
</tr>
<tr>
<td></td>
<td>$150</td>
</tr>
<tr>
<td>24 hour fitness Center</td>
<td>$35</td>
</tr>
<tr>
<td>YMCA</td>
<td>$65</td>
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</tbody>
</table>
**Drug Cost Comparison**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine (45 units/d), metformin, glimepiride 1-2 checks</td>
<td>$226</td>
</tr>
<tr>
<td>Novolog 70/30 (80 Units/d), metformin 2 checks</td>
<td>$423</td>
</tr>
<tr>
<td>Glargine (45 units/d), metformin, glimepiride Exenatide (10 bl) 1-2 checks</td>
<td>$497</td>
</tr>
<tr>
<td>Glargine (45 units/d), Lispro 50 units/d, Metformin 4 checks</td>
<td>$507</td>
</tr>
<tr>
<td>Metformin, glimepiride, pioglitazone Symlin 1-2 checks</td>
<td>$526</td>
</tr>
<tr>
<td>Glargine (45 units/d), metformin, glimepiride</td>
<td>$537</td>
</tr>
</tbody>
</table>

**ADA Type 2 Consensus Statement**

**Diabetes Treatment Algorithm**

**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 pioglitazone
4. Begin NPH insulin or long-acting insulin analogue
5. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™) or saxagliptin (Onglyza™)

**Case 3:** 57 yo woman with DM, BMI 33, on diet and exercise, max doses metformin and glyburide. HbA1C is 8.5. Your next best step is:

1. **Continue current therapy**
2. Begin pioglitazone
3. Begin NPH insulin or long-acting insulin analogue
4. Begin sitagliptin (Januvia™) or saxagliptin (Onglyza™)
5. Begin exenatide (Byetta™) or liraglutide (Victoza™)
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