Type 2 Diabetes – 2010

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[Diagram showing the relationship between insulin, glucagon, hyperglycemia, hepatic glucose output, glucose uptake, and glucose utilization.]

[Diagram showing the relationship between postprandial glucagon secretion, hyperglycemia, and the α and β cells.]
Hyperglycemia

↑ FFA
Lipotoxicity

Incretins

β α

Hyperglycemia

Altered glucose reabsorption

Hyperglycemia
What is the only safe way to treat DM long-term?

Don’t develop it in the first place.
Is there a medication that can significantly delay progression of disease (meaning need for more medication)?

No

Is there a specific medication that can significantly delay progression of disease (meaning microvascular disease)?

No

Is there a specific medication that can significantly delay progression of disease (meaning macrovascular disease)?

Maybe
Today

- What are the goals?
- What differentiates the medications?
- Does it really matter what medication is used?
- Put it all together – ADA way, AACE way and of course, MY WAY

MacroDiabetes

MicroDiabetes

Frequency of Hypoglycemic Symptoms Among Patients With Type 2 Diabetes

<table>
<thead>
<tr>
<th>Frequency of Hypoglycemic Symptoms During the Preceding Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Self Reporting Hypoglycemic Events, %</td>
</tr>
<tr>
<td>Any insulin (n=133)</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Asymptomatic Episodes of Hypoglycemia May Go Unreported

- Hypoglycemia: glucose <60 mg/dl
- In a cohort of patients with diabetes, more than 50% had asymptomatic (unrecognized) hypoglycemia, as identified by 3 day continuous glucose monitoring
- HgA1c 8 (T1) 7.4 (T2)

Patients Are Worried About the Risk of Hypoglycemia: The Diabcare–Asia 2003 Study

- Survey of 15,549 patients with diabetes
- 96% had type 2 diabetes and 4% of patients had type 1 diabetes
- 54% of respondents were anxious about the risk of hypoglycemia all or most of the time

ADVANCE: Action in Diabetes and Vascular Disease

Goal: To examine effects of reducing HgA1c to < 6.5% and routine use of fixed dose ACE-thiazide combination in >55 y/o Type 2 DM

- 11,140 Enrollees
- 50% macrovascular dx
- 60% male 40% female
- 10% microvascular
- Mean age 66

Baseline HgA1c: 7.51%
"standard" : 7.30%    Intensive: 6.53%
ADVANCE: Relative Effects of Glucose-Control Strategy on All Prespecified Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Control (n=1531)</th>
<th>Standard Control (n=1484)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major macrovascular events</td>
<td>137 (2.9)</td>
<td>135 (2.9)</td>
<td>0.90</td>
<td>90 (2.8 - 2.9)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>119 (2.4)</td>
<td>116 (2.4)</td>
<td>0.90</td>
<td>90 (2.8 - 2.9)</td>
</tr>
<tr>
<td>Diabetic kidney disease</td>
<td>116 (2.6)</td>
<td>114 (2.5)</td>
<td>0.90</td>
<td>90 (2.8 - 2.9)</td>
</tr>
<tr>
<td>Major microvascular events</td>
<td>56 (1.1)</td>
<td>56 (1.1)</td>
<td>1.00</td>
<td>100 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Neuropathic vs neuropathic normosymp</td>
<td>50 (1.0)</td>
<td>50 (1.0)</td>
<td>1.00</td>
<td>100 (1.0 - 1.0)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>30 (0.6)</td>
<td>30 (0.6)</td>
<td>1.00</td>
<td>100 (1.0 - 1.0)</td>
</tr>
</tbody>
</table>

ACCORD: Action to Control Cardiovascular Risk in Diabetes

- 10,251 Enrollees
- 60% male 40% female
- Mean age 62.2
- Baseline HbgA1c 8.1%
- BMI - 32
- 30% macrovascular dx
- Duration DM: 10 years
- Majority of intensive group on 3-5 oral agents plus insulin
- Hypoglycemia 3 times greater in intensive group

Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (n=1531)</th>
<th>Standard Therapy (n=1484)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any outcome</td>
<td>153 (15.7)</td>
<td>146 (15.4)</td>
<td>1.00</td>
<td>0.56</td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td>139 (14.7)</td>
<td>135 (14.4)</td>
<td>1.00</td>
<td>0.82</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>106 (10.6)</td>
<td>103 (10.2)</td>
<td>1.00</td>
<td>0.73</td>
</tr>
<tr>
<td>Total stroke</td>
<td>87 (8.7)</td>
<td>85 (8.5)</td>
<td>1.00</td>
<td>0.74</td>
</tr>
<tr>
<td>Total or end-of-life congestive heart failure</td>
<td>121 (12.5)</td>
<td>116 (11.9)</td>
<td>1.00</td>
<td>0.73</td>
</tr>
</tbody>
</table>
ACCORD: Hazard Ratios for the Primary Outcome and Death from Any Cause in Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No of Patients</th>
<th>No of Events</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous cardiovascular disease</td>
<td>100</td>
<td>30</td>
<td>0.89</td>
<td>0.62</td>
</tr>
<tr>
<td>Yes</td>
<td>3,000</td>
<td>300</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Family history</td>
<td>3,252</td>
<td>211</td>
<td>0.84</td>
<td>0.12</td>
</tr>
<tr>
<td>Yes</td>
<td>2,598</td>
<td>111</td>
<td>0.83</td>
<td>0.13</td>
</tr>
<tr>
<td>Age of baseline</td>
<td>3,072</td>
<td>240</td>
<td>0.79</td>
<td>0.11</td>
</tr>
<tr>
<td>&lt; 65</td>
<td>2,181</td>
<td>140</td>
<td>0.76</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetic nephropathy at baseline</td>
<td>4,066</td>
<td>204</td>
<td>0.80</td>
<td>0.15</td>
</tr>
<tr>
<td>Yes</td>
<td>3,560</td>
<td>211</td>
<td>0.77</td>
<td>0.18</td>
</tr>
<tr>
<td>Race</td>
<td>3,267</td>
<td>211</td>
<td>0.82</td>
<td>0.14</td>
</tr>
<tr>
<td>White</td>
<td>6,666</td>
<td>301</td>
<td>0.81</td>
<td>0.16</td>
</tr>
</tbody>
</table>

VADT - Veterans Administration Diabetes Trial

- 1,742 Enrollees
- 97% male
- Mean age 60.4
- BMI 31.3
- Majority had multiple CV risk factors
- 72% HTN
- 40% macrovascular dx
- 62% retinopathy
- 43% neuropathy

Table 1. Cardiovascular Risk Factor Profile during VADT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Baseline</th>
<th>Intensive</th>
<th>Standard</th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>9.4</td>
<td>9.4</td>
<td>6.9</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>130/76</td>
<td>130/76</td>
<td>126/69</td>
<td>126/69</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>130</td>
<td>154</td>
<td>73</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>34</td>
<td>34</td>
<td>39</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>160</td>
<td>162</td>
<td>124</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Anti-platelet agent use (%)</td>
<td>76</td>
<td>76</td>
<td>91</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>57</td>
<td>59</td>
<td>60</td>
<td>66</td>
<td></td>
</tr>
</tbody>
</table>

VADT - Veterans Administration Diabetes Trial

- Primary Endpoint: NO DIFFERENCE IN CARDIOVASCULAR DISEASE OUTCOMES
  - Standard: 29.3% (predicted – 40%)
  - Intensive: 27.4% (predicted – 31.6%)
Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

Mean Systolic Blood-Pressure Levels at Each Study Visit

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

Lipid Values
Effects of Intensive Blood-Pressure Control and Combination Lipid Therapy in Type 2 Diabetes Mellitus

Kaplan-Meier Analysis of Primary Outcome in the ACCORD Study

a. Lipid Arm of Study

b. Blood Pressure Arm of Study

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

“The interpretation of the ACCORD BP results is complicated by the fact that the event rate observed in the standard-therapy group was almost 50% lower than the expected rate.”

Hazard Ratios for the Primary Outcome in Prespecified Subgroups

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus
Explaining Decline in Early Mortality with Type 2 DM

Trends in Drug Utilization

Diabetes Care. 2008; 31:1761-1766

UKPDS: 10 year follow-up

- Glucose Control
  - Between-group differences in HgA1c gone after 1 year
  - In the sulfonylurea–insulin group, relative reductions in risk persisted at 10 years for:
    - any diabetes-related end point (9%, P=0.04)
    - microvascular disease (24%, P=0.001)
    - risk reductions for myocardial infarction (15%, P=0.01)
    - death from any cause (13%, P=0.007)
  - In the metformin group:
    - any diabetes-related end point (21%, P=0.01)
    - myocardial infarction (33%, P=0.005)
    - and death from any cause (27%, P=0.002).

Published at www.nejm.org September 10, 2008

Effect of Metformin-Containing Antidiabetic Regimens on All-cause Mortality in Veterans With Type 2 Diabetes Mellitus

- Decreased Hazard Ratio for all cause mortality for patients on metformin
  - vs no metformin – 0.77 (p<0.01)

- Increased Hazard Ratio for all cause mortality for patients on insulin:
  - 1.62 (p<0.001)

- Decreased Hazard Ratio for all cause mortality for patients on metformin and insulin vs insulin
  - 0.62 (p<0.04)

Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study

Hazard ratios for progression to first large-vessel disease event by HbA1c

ADA Targets for Glycemic Control

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial plasma glucose</td>
<td>80–130 mg/dl (5.7–7.2 mmol/l)</td>
</tr>
<tr>
<td>Peak postprandial plasma glucose</td>
<td>&lt;180 mg/dl (&lt;10 mmol/l)</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>&lt;7 (%)</td>
</tr>
</tbody>
</table>

Key concepts in setting glycemic goals: A1C is the primary target for glycemic control. Goals should be individualized based on:
- duration of diabetes
- age/life expectancy
- comorbid conditions
- known CVD or advanced microvascular complications
- hypoglycemia unawareness
- individual patient considerations

More or less stringent glycemic goals may be appropriate for individual patients.
Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals.
Goals for Type 2 Diabetes

• For Decreasing Cardiovascular Disease:
  – Focus on blood pressure
  – Lipids
  – anti-platelet therapy
  – Smoking cessation.
  – Early aggressive glucose control

• Be cautious in your glucose lowering strategies in older, high-risk patients with long standing diabetes. Maintaining HbA1c close to 7% (but not necessarily <7%) may be the optimal target for these individuals.

• Avoid hypoglycemia.

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name (Brand Name)</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Relative Effectiveness</th>
<th>Major Side Effects / Interactions</th>
<th>Weight Effects (Average)</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide (Micronase)</td>
<td>Stimulate insulin release from beta cells of the pancreas</td>
<td>2.5-10 mg bid</td>
<td>1</td>
<td>Hypoglycemia</td>
<td>Gain 2 lbs</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>Glipizide (Glucotrol)</td>
<td></td>
<td>5-20 mg bid</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>glimepiride (Amaryl)</td>
<td></td>
<td>0.5-4 mg qd</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database

Glibenclamide-related excess in total and cardiovascular mortality risks: Data from large Ukrainian observational cohort study

All-cause mortality among:
1. glimepiride-treated
2. gliclazide-treated
3. glibenclamide-treated (glyburide)

Retrospective observational cohort studies of primary care-based diabetes register in Ukraine. (n = 50 341).

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Mechanism of Action</th>
<th>Design</th>
<th>Relative Effectiveness</th>
<th>Major Side Effects / Interactions</th>
<th>Weight Effects (average)</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td>Stimulate insulin release from beta cells of the pancreas</td>
<td>0.5-2 mg tid (before meals)</td>
<td>1</td>
<td>Hypoglycemia</td>
<td>2 lbs</td>
<td>$6</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>repaglinide (Prandin)</td>
<td>Stimulate insulin release from beta cells of the pancreas</td>
<td>0.5-2 mg tid (before meals)</td>
<td>0.8</td>
<td>Hypoglycemia</td>
<td>1 lb</td>
<td>$5</td>
</tr>
<tr>
<td></td>
<td>nateglinide (Starlix)</td>
<td></td>
<td>60-360 mg tid (before meals)</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diabetes Research and Clinical Practice 2009. 86:247-253
Metformin and Lactic Acidosis

- “Metformin may provoke lactic Acidosis which is most likely to occur in patients with renal impairment. It should not be used with even mild renal impairment” ¹
- Metformin probably not as unsafe as previously thought.
  - 25% users have relative contraindication ²
  - Patient’s with lactic acidosis usually have acute renal failure ³


Metformin and eGFR

- 186 x (Creat / 88.4)⁻¹.¹⁵⁴ x (Age)⁻².²⁰³ x (0.742 if female) x (1.210 if black)
- Current Guidelines call for discontinuation of Metformin serum creatinine >150 umol/l (1.7 mg/dl).
- Estimated GFR (eGFR) being introduced as possible better measure of renal function than serum creatinine alone
- eGFR of 36 ml/min per 1.73m² would be somewhat neutral to current use

Metformin and B12

- Decrease in vitamin B12 levels. (decreased in 4.2-47%)
- Metformin is thought to induce malabsorption of vitamin B12 and intrinsic factor in the ileum, an effect that can be reversed by increased calcium intake.
### Metformin and B12

- Anemia may be minimal to severe
- may present only as a peripheral neuropathy, possibly being misdiagnosed as diabetic neuropathy.

### Table: Hypoglycemic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Relative Effective ness</th>
<th>Major Side Effects / Interactions / Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glipizide</td>
<td>Stimulate insulin release</td>
<td>1</td>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gain 2 lbs</td>
</tr>
<tr>
<td></td>
<td>Glimepride</td>
<td>Stimulate insulin release</td>
<td>0.4</td>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gain 1 lb</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Nateglinide</td>
<td>Stimulate insulin, short-acting</td>
<td>0.4</td>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Loss 2-3 lbs</td>
</tr>
</tbody>
</table>
| Biguanide      | Metformin    | Primarily inhibits hepatic gluconeogenesis. | 500-2000 mg daily with meals | 1 | Diarrhea, nausea, vomiting
|                | (Glucophage) |                                             |        |                        | Increased risk of lactic acidosis if impaired renal or hepatic function or heavy EtOH use B12 deficiency |
|                |              |                                             |        |                        | Loss 2-3 lbs                                                                                           |
| Alpha-         | Acarbose     | Inhibits enzymes needed to break down complex CHO in the small intestine | 50 mg with 1st bit of each meal (start at 12.5 mg and titrate up over weeks) | 0.7 | Gas/ GI upset
| glucosidase    | (Precose)    |                                             |        |                        | Loss 1-2 lbs                                                                                           |
|                |              |                                             |        |                        | $5 $                                                                                                   |
Bile Acid Sequestrants

- Bile acid sequestrants lower LDL cholesterol
- Colesevelam (Welchol) a bile acid sequestrant, lowers glucose levels and AIC levels in T2D patients

![Graph showing effect of bile acid sequestrants on glucose levels](image)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Weight Effect</th>
<th>Relative Effectiveness</th>
<th>Major Side Effects</th>
<th>Uses</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Stimulate insulin release</td>
<td>1</td>
<td>1</td>
<td>Hypoglycemia</td>
<td>Gain 2 lbs</td>
<td>$</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Stimulate insulin release</td>
<td>1</td>
<td>1</td>
<td>Hypoglycemia, short-acting</td>
<td>Gain 1 lb</td>
<td>$$$</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Inhibits hepatic gluconeogenesis</td>
<td>1</td>
<td>1</td>
<td>Diarrhea, lactic acidosis</td>
<td>Loss 2-3 lbs</td>
<td>$</td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitors</td>
<td>Decreased CHO absorption</td>
<td>0.7</td>
<td>0.7</td>
<td>Gas/ GI upset</td>
<td>Loss 1-2 lbs</td>
<td>$$$</td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>unknown</td>
<td>3.75 g/d (3-625 mg tabs bid)</td>
<td>0.7</td>
<td>Esophageal obstruction, bowel obstruction, fecal impaction, dysphagia pancreatitis, nausea, constipation</td>
<td>neutral</td>
<td>$</td>
</tr>
<tr>
<td>Colesevelam (Welchol)</td>
<td>unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bromocriptine

- Ergot derivative. Sympatholytic dopamine D2 receptor agonist, inhibits serotonin turnover in CNS.
- Improved glucose control associated with improved glucose tolerance (enhanced stimulated insulin-mediated glucose disposal).

![Graph showing effect of bromocriptine on glucose levels](image)

Diabetes Care 2000. 23: 1154-1161
**Table:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Relative Effectiveness</th>
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<th>Weight Effects (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Stimulate insulin release</td>
<td>1 hypoglycemia</td>
<td>1</td>
<td>Gain 2 lbs</td>
<td>$</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Stimulate insulin release short-acting</td>
<td>1 hypoglycemia</td>
<td>2</td>
<td>Gain 1 lb</td>
<td>$</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Inhibit hepatic gluconeogenesis</td>
<td>1 diarrhea</td>
<td>1</td>
<td>Loss 2-3 lbs</td>
<td>$</td>
</tr>
<tr>
<td>Alpha-glucosidase</td>
<td>Decreased CHO absorption</td>
<td>0.7 gas</td>
<td>0.7</td>
<td>Loss 1-2 lbs</td>
<td>#$</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Inhibit hepatic gluconeogenesis</td>
<td>1 diarrhea</td>
<td>1</td>
<td>Loss 2-3 lbs</td>
<td>$</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Improved glucose tolerance (enhanced stimulated insulin-mediated glucose disposal)</td>
<td>0.25–0.5 mg/d</td>
<td>0.7</td>
<td>Nasal Stiffness, Nausea, headache, constrictive pericarditis, neuroleptic malignant syndrome, hypotension</td>
<td>$55</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Improved glucose tolerance (enhanced stimulated insulin-mediated glucose disposal)</td>
<td>0.25–0.5 mg/d</td>
<td>0.7</td>
<td>Nasal Stiffness, Nausea, headache, constrictive pericarditis, neuroleptic malignant syndrome, hypotension</td>
<td>$55</td>
</tr>
</tbody>
</table>

**Salsalate**

- Sodium salicylate does not irreversibly inhibit cyclooxygenase-1 and -2 (COX-1 and COX-2) and is thus not antithrombotic; salsalate, a prodrug of salicylate is well tolerated and considered safe after years of use for arthritis.
- Baseline HgA1c 7.8%

**Current TZD Side Effects**

- Weight Gain: 5-12 lbs in 1 year
  - Blunted with metformin
  - Worse with insulin
- Edema: 4-30%
  - Unresponsive to diuretics
- BUT:
  - Increased Cardiac Index
  - Increased Stroke volume
  - Decreased systemic resistance
  - Decreased Blood Pressure
Positive Side to TZDs

- Reduction in glucose
- Reduces BP
- Reduces albuminuria
- Reduces CRP
- Possible DM prevention
- Reduces NASH
- Reduces LFT
- Reduces stent failure
- Reduces death after CHF
- Increases adiponectin
- Increases HDL

**Effect of Rosiglitazone on the Risk of Myocardial Infarction And Death from Cardiovascular Causes**

**CONCLUSIONS**

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death...that had borderline significance.

**Meta-analysis of MI and Death risk with rosiglitazone**

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone group</th>
<th>Control group</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,280 (0.43)</td>
<td>22/6105 (0.36)</td>
<td>1.45 (0.88-2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2635 (0.57)</td>
<td>9/2634 (0.34)</td>
<td>1.65 (0.74-3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1456 (1.85)</td>
<td>41/2895 (1.44)</td>
<td>1.33 (0.80-2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td>86/14371 (0.60%)</td>
<td>72/11634 (0.62%)</td>
<td>1.45 (1.03-1.98)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Relative Risk = 86/72 = 1.19
Absolute Risk = .02%
PANIC

RECORD: Kaplan-Meier Plots of time to the Primary Endpoint (Cardiovascular Death or Cardiovascular Hospitalization)

Lancet. 2009 Jun 5. [Epub ahead of print]

Senate report links diabetes drug Avandia to heart attacks

February 28, 2010, 4:38 pm ET

(CNN) -- The diabetes drug Avandia is linked with tens of thousands of heart attacks, and drugmaker GlaxoSmithKline knew of the risks years ago but worked to keep them from the public, according to a Senate committee report released Saturday.

The 374-page report by the Senate Finance Committee also criticized the Food and Drug Administration, saying that the federal agency that regulates food, tobacco and medications overlooked or overrode safety concerns found.
Diabetes Care Publish Ahead of Print, published online on February 5, 2008

Changes in BMD during pioglitazone or placebo treatment in patients with PCOS

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Relative Effectiveness</th>
<th>Major Side Effects / Interactions</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td>Stimulate insulin release</td>
<td>1</td>
<td></td>
<td>Hypoglycemia</td>
<td>$</td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td>Stimulate insulin release</td>
<td>1</td>
<td></td>
<td>Hypoglycemia, short-acting</td>
<td>$$$</td>
</tr>
<tr>
<td>Biguanides</td>
<td></td>
<td>Inhibits hepatic gluconeogenesis</td>
<td>1</td>
<td></td>
<td>Diarrhea, lactic acidosis, Weight loss</td>
<td>$</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td></td>
<td>Decreased CHO absorption</td>
<td>0.7</td>
<td>1</td>
<td>Gas/GI upset, Weight loss</td>
<td>$$</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone (Avandia)</td>
<td>Insulin sensitizers — Activate receptor molecules inside cell nuclei to decrease insulin resistance</td>
<td>4-8 mg daily</td>
<td>1</td>
<td>Weight gain, edema which is resistant to diuretic therapy, CHF, Associated with bone loss and fractures</td>
<td>$5/12 lbs</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone (Actos)</td>
<td></td>
<td>15-45 mg daily</td>
<td>1</td>
<td></td>
<td>$</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

Plasma Insulin Responses to Oral and Intravenous Glucose

Glucose-Dependent Effects of GLP-1 on Insulin and Glucagon Levels in Patients With Type 2 Diabetes

- When glucose levels approach normal values, glucagon levels rebound.
- When glucose levels approach normal values, insulin levels decrease.

*P < 0.05

Patients with type 2 diabetes (N=10)

![Glucose vs. Time Graph]


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

- Meal
- Intestinal GIP and GLP-1 release
- DPP-4 (Dipeptidyl Peptidase IV) Enzyme
- GLP-1 (9-36) Metabolites
- GIP (1-42)
- GLP-1 (7-36) Intact
- Rapid Inactivation
- Half-life
- GLP-1 ~ 2 minutes
- GIP ~ 5 minutes


Incretin Drugs

- GLP Agonists
  - Exenatide
  - Liraglutide
  - Semaglutide
  - Albiglutide
  - Taspoglutide
  - Exenatide Lar
  - Lixisenatide

- DPP 4 Inhibitors
  - Vildagliptin
  - Sitagliptin
  - Saxagliptin
  - Alogliptin
  - Linagliptin
  - Taspoglutide
  - Exenatide Lar
  - Metaglipidin
Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)

Lancet. 2009 374: 39-47
Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)

- Administer once daily at any time of day, independently of meals
- The injection site and timing can be changed without dose adjustment
- Week one: Initiate at 0.6 mg per day. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control.
- Week two: Increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg.

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rodents. It is unknown whether Viiuss causes thyroid C-cell tumors, including medullary thyroid carcinomas (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1).
- Viiuss is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).
DPP-4 Study Summary

Vildagliptin plus insulin
- Patients on >30 U/d, added 100 mg/d
- Baseline HgA1c 8.5
- Drop in HgA1c 0.5% vildagliptin, 0.2% placebo
- >65 y/o: Drop in HgA1c 0.7% vildagliptin, 0.0% placebo
- Hypoglycemia: Placebo: 45 patients; 185 events; 6 severe
  Vildagliptin: 33 patients; 113 events; 0 severe

- Sitagliptin vs glipizide added to metformin
  - 52 weeks, 100 mg/d vs 20 mg/d
  - Baseline HgA1c 7.5
  - Both 0.67% reduction in HgA1c
  - Both about 60% reached HgA1c <7
  - Hypoglycemia – glipizide: 32% sitagliptin: 4.9%

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name (Brand Name)</th>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Relative Effectiveness vs Insulin</th>
<th>Weight Effects</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Exenatide (Byetta)</td>
<td>Mimics GLP-1 (gut hormone that affects insulin, glucagon, gastric emptying and satiety)</td>
<td>5-10 mcg bid SQ</td>
<td>0.6-1.8 mg bid SQ</td>
<td>1 Nausea, Vomiting, constipation, pancreatitis (?)</td>
<td>$5</td>
</tr>
<tr>
<td></td>
<td>Liraglutide (Victoza)</td>
<td>DPP-4 inhibitor (enzyme that breaks down GLP-1)</td>
<td>100, 50, or 25 mg/d (dose by Cr Cl)</td>
<td>0.7-1 Side effects are rare. Occ GI side effects.</td>
<td>Neutral</td>
<td>$5</td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incretins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Amylin

37-amino acid β-cell hormone that is co-secreted with insulin in response to meals
Acts as a neuroendocrine hormone that binds to specific receptors in the hindbrain, including area postrema
Has both glucoregulatory and anorexigenic actions
• decreases the rate of gastric emptying
• suppresses hepatic glucose output by inhibiting glucagon secretion
Anti-obesity effects in diet-induced obese (DIO) rodents:
• Reductions in food intake
• Reductions in body fat, with preservation of lean mass

Pramlintide: Soluble Analog of Human Amylin


Human amylin

Pramlintide or Mealtime Insulin Added to Basal Insulin Treatment for Patients With Type 2 Diabetes

Diabetes Care 2009 32:1577-1582

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name (Brand Name)</th>
<th>Mechanism of Action</th>
<th>Vagame</th>
<th>Relative Effectiveness</th>
<th>Major Side Effects / Interactions</th>
<th>Weight Effects (average)</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glimepiride (Avandia)</td>
<td>Stimulate insulin release</td>
<td>1</td>
<td>Hyperglycemia</td>
<td>Gain 3 lbs</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Nateglinide (Replens)</td>
<td></td>
<td>0.4</td>
<td>Hypoglycemia, meal setting</td>
<td>Gain 1 lb</td>
<td>$$$</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide (Prandin)</td>
<td>Stimulate insulin release, glucagon suppression</td>
<td>2</td>
<td>Diabetic acidosis</td>
<td>Gain 0.3 lbs</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone (Avandia)</td>
<td>Decrease CHF, increase weight</td>
<td>0.4</td>
<td>Insomnia, edema fractures</td>
<td>Gain 2 lbs</td>
<td>$$$</td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitor</td>
<td>Acarbose (Precose)</td>
<td>Decrease CHO absorption</td>
<td>0.7</td>
<td>Flatulence, GI upset</td>
<td>Loss 1-2 lbs</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Methadone</td>
<td>Analgesia</td>
<td>1</td>
<td>Weight gain, nausea, constipation</td>
<td>Gain 3 lbs</td>
<td>$$$</td>
<td></td>
</tr>
<tr>
<td>Synthetic exenatide</td>
<td>Liraglutide</td>
<td>Increase insulin, decrease glucagon</td>
<td>2</td>
<td>Nausea, weight loss</td>
<td>Loss 8 lbs</td>
<td>Neutral</td>
<td></td>
</tr>
</tbody>
</table>

**Insulin**

Titrated to need | 1+ | Hypoglycemia | Gain | 8 lbs | $$
Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed Type 2 diabetes

- 114 drug naïve patients
- Initial HgA1c
- Duration DM about 3 years
- Initial HgA1c 10%
- Body mass index 25

Time course of reduction in glycated haemoglobin (HbA1c) in patients receiving pioglitazone (O), metformin (●), or glimepiride (□). Data are mean ±sd. *P < 0.05; **P < 0.01; ***P < 0.005 vs. baseline.

Fasting Plasma glucose: Mean Change From Baseline

Diabetes Medicine 2005; 22:980-985
Effects of Colesevelam, Rosiglitazone, or Sitagliptin on Glycemic Control and Lipid Profile in Patients With Type 2 Diabetes Mellitus Inadequately Controlled by Metformin Monotherapy

Endocr Pract. 2010;16:53-63

Generic Oral Hypoglycemic Slide

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 S4-14</td>
<td></td>
</tr>
<tr>
<td>Brand $50</td>
<td></td>
</tr>
<tr>
<td>Ramaglinide 2 mg tid/nateglinide 120 tid</td>
<td>$203/164</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 5-4-32</td>
<td></td>
</tr>
<tr>
<td>Brand $161</td>
<td></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>Saxagliptin/Saxagliptin</td>
<td>$207/190</td>
</tr>
<tr>
<td>Exenatide 10 mcg /Liraglutide 1.2 mg</td>
<td>$271/280</td>
</tr>
<tr>
<td>Colesevelam 3750 mg/d</td>
<td>$224</td>
</tr>
<tr>
<td>Bromocriptine 2.5-5mg</td>
<td>$62-130</td>
</tr>
<tr>
<td>Glargine, 45 U/d (pen)</td>
<td>$150/182</td>
</tr>
<tr>
<td>Salicylate 4g/d</td>
<td>$50</td>
</tr>
<tr>
<td>24 hour fitness center</td>
<td>$35</td>
</tr>
<tr>
<td>YMCA</td>
<td>$65</td>
</tr>
</tbody>
</table>
An American Diabetes Association consensus statement represents the authors' collective analysis, evaluation, and opinion at the time of publication and does not represent official association opinion.

Diabetes Care. Published online Oct 22, 2008
TYPE 2 DIABETES

SYMPTOMATIC And very high

Start Metformin

Referral for:
- Diet
- HGM
- Exercise (+/- EST)
- Foot Care

Goal Met

NO

Add Medication

CONTINUE CURRENT TREATMENT

YES

Start on sulfonylurea or insulin

Referral for:
- Diet
- HGM
- Exercise
- Foot Care

Goal Met

NO

Consider transition to metformin

YES

Start on sulfonylurea or insulin

Referral for:
- Diet
- HGM
- Exercise
- Foot Care

Goal Met

NO

Continue Current Treatment

YES

Start Metformin

Referral for:
- Diet
- HGM
- Exercise
- Foot Care

Goal Met

NO

Add Medication

Goal Met

YES

Referral for:
- Diet
- HGM
- Exercise
- Foot Care

Goal Met