Treating Diabetes To Lower Cardiovascular Disease Risk

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Director, USC Clinical Diabetes Programs

**Consultantship**
Abbott Diabetes Care
BD
Janssen
Lilly
Medscape
Medtronic Minimed
NovoNordisk
Sanofi
Takeda

**Speakers Bureau**
BMS/AstraZeneca
NovoNordisk
Changes in Diabetes-Related Complications in the United States, 1990–2010

Edward W. Gregg, Ph.D., Yanfeng Li, M.D., Jing Wang, M.D., Nilka Rios Burrows, M.P.H., Mohammed K. Ali, M.B., Ch.B., Deborah Rolka, M.S., Desmond E. Williams, M.D., Ph.D., and Linda Geiss, M.A.
LDL Cholesterol Targets in Diabetes

Residual Risk of CVD

*Role of other lipid and non-lipid factors*
UKPDS: “Legacy Effect” of Insulin/Sulfonylurea Therapy

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>P:    0.029</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>P:    0.009</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>P:    0.052</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>P:    0.44</td>
<td>0.007</td>
</tr>
</tbody>
</table>

After median 8.8 years post-trial followup

RRR = Relative Risk Reduction     P = Log Rank

UKPDS: “Legacy Effect” of Insulin/Sulfonylurea vs Metformin Therapy

Meta-Analysis of Glycemic Control Trials and Coronary Heart Disease

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Events</td>
<td></td>
</tr>
<tr>
<td>UKPDS(^4,7)</td>
<td>3071/1549</td>
<td>426/259</td>
</tr>
<tr>
<td>PROactive(^18–20^*)</td>
<td>2605/2633</td>
<td>164/202</td>
</tr>
<tr>
<td>ADVANCE(^5)</td>
<td>5571/5569</td>
<td>310/337</td>
</tr>
<tr>
<td>VADT(^21,22)</td>
<td>892/899</td>
<td>77/90</td>
</tr>
<tr>
<td>ACCORD(^8)</td>
<td>5128/5123</td>
<td>205/248</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>1182/1136</td>
</tr>
</tbody>
</table>

Hyperglycemia and Coronary Heart Disease (CHD)

• Possible reasons that individual trials failed to show a beneficial effect on CHD
  – Event rates were lower than expected
  – Differences in glycemic control were not large enough
  – The intervention or observation period was too short
  – Need to start intervention earlier in natural history of the disease

• Conclusions
  – Do not discount the benefits of managing hyperglycemia
    • Reduced microvascular disease well established
    • Premature to conclude that glucose control plays no part in CHD residual risk
    • Benefits of glucose control will be less than BP and lipid control
  – Additional studies needed to evaluate the effects of controlling hyperglycemia on CHD risk

HTN and DM: Drug Classes in US Over Past Half Century

Number of Medication Classes

- Angiotensin II receptor blockers
- ACE inhibitors
- Ca+ channel blockers
- β1 blockers
- β2 agonists
- peripheral blockers
- central blockers
- adrenergic neuronal blockers
- diuretics
- Biguanides
- Sulfonylureas
- Vasodilators
- Renin inhibitors
- Bile acid sequestrants
- Dopamine agonists
- GLP-1 Receptor Agonists
- 'Glinides
- Thiazolidinediones
- DPP-4 inhibitors
- Amylinomimetics
- SGLT-2 inhibitors
- Dopamine agonists
- Renin inhibitors
- Bile acid sequestrants
- Dopamine agonists
- Renin inhibitors
- Bile acid sequestrants

Slide from: Inzucchi S.
The ADA/EASD Position Statement on Management of Hyperglycemia in Type 2 Diabetes

**ADA**

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Apostolos Tsapas MD, PhD  
Aristotle University, Thessaloniki, Greece

David R. Matthews MD, Dphil  
Oxford University, Oxford, UK
# Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td><img src="icon" alt="Down" /> <img src="icon" alt="Down" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Down" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Down" /></td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td><img src="icon" alt="Down" /> <img src="icon" alt="Down" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Down" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Equal" /></td>
</tr>
<tr>
<td>ACCORD</td>
<td><img src="icon" alt="Down" /> <img src="icon" alt="Equal" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Equal" /></td>
<td><img src="icon" alt="Up" /> <img src="icon" alt="Equal" /></td>
</tr>
<tr>
<td>ADVANCE</td>
<td><img src="icon" alt="Down" /> <img src="icon" alt="Equal" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Equal" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Equal" /></td>
</tr>
<tr>
<td>VADT</td>
<td><img src="icon" alt="Down" /> <img src="icon" alt="Equal" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Equal" /></td>
<td><img src="icon" alt="Equal" /> <img src="icon" alt="Equal" /></td>
</tr>
</tbody>
</table>

Kendall DM, Bergenstal RM. © International Diabetes Center 2009


Risk of CV Events and Death in Patients With Versus Without Severe Hypoglycemia (ADVANCE)

Study inclusion criteria: T2DM + major vascular disease or ≥ 1 CV risk factor

- **Macrovascular events**
  - Adjusted Hazard Ratio: 3.45 (2.34-5.08); *P* < .001

- **Death—any cause**
  - Adjusted Hazard Ratio: 3.30 (2.31-4.72); *P* < .001

- **Death—CV cause**
  - Adjusted Hazard Ratio: 3.78 (2.34-6.11); *P* < .001

- **Death—non-CV cause**
  - Adjusted Hazard Ratio: 2.86 (1.67-4.90); *P* < .001

Lessons from Accord
Severe Hypoglycemia and Mortality Risk

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hypo (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive (%)</td>
<td>3.1%</td>
<td>0.7%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Standard (%)</td>
<td>1.1%</td>
<td>0.4%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

Annual mortality

Bonds et al. BMJ 2010;340:b4909
Severe Hypoglycemia in ACCORD

• “Patients with type 2 diabetes who experience symptomatic, severe hypoglycaemia are at increased risk of death, regardless of the intensity of glucose control.”
• “The increased risk of death seen in the ACCORD trial among participants in the intensive glycaemia control arm cannot be attributed to the increased rate of severe hypoglycaemia in intensive arm participants.”

Bonds et al. BMJ 2010;340:b4909
Healthy eating, weight control, increased physical activity

**Initial drug monotherapy**
- Efficacy (HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

**Two drug combinations**
- Efficacy (HbA1c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Sulfonylurea†</td>
<td>high</td>
<td>moderate risk</td>
<td>gain</td>
<td>hypoglycemia‡ low</td>
</tr>
<tr>
<td>Metformin + Thiazolidinedione</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>edema, HF, fx’s‡ high</td>
</tr>
<tr>
<td>Metformin + DPP-4 Inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
<td>neutral</td>
<td>rare‡</td>
</tr>
<tr>
<td>Metformin + GLP-1 receptor agonist</td>
<td>high</td>
<td>low risk</td>
<td>loss</td>
<td>low</td>
</tr>
<tr>
<td>Metformin + Insulin (usually basal)</td>
<td>high</td>
<td>high risk</td>
<td>gain</td>
<td>hypoglycemia‡ variable</td>
</tr>
</tbody>
</table>
If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea†</strong></td>
<td><strong>Thiazolidinedione</strong></td>
<td><strong>DPP-4 Inhibitor</strong></td>
<td><strong>GLP-1 receptor agonist</strong></td>
<td><strong>Insulin (usually basal)</strong></td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>hypoglycemia†</td>
<td>edema, HF, fx’s†</td>
<td>edema, HF, fx’s†</td>
<td>high</td>
<td>hypoglycemia†</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>low</td>
<td>variable</td>
<td>variable</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea†</strong> +</td>
<td><strong>Thiazolidinedione</strong> +</td>
<td><strong>DPP-4 Inhibitor</strong></td>
<td><strong>GLP-1 receptor agonist</strong> +</td>
</tr>
<tr>
<td>TZD</td>
<td>SU†</td>
<td>SU†</td>
<td>TZD</td>
</tr>
<tr>
<td>or</td>
<td>DPP-4-i</td>
<td>DPP-4-i</td>
<td>or</td>
</tr>
<tr>
<td>or</td>
<td>GLP-1-RA</td>
<td>GLP-1-RA</td>
<td>or</td>
</tr>
<tr>
<td>or</td>
<td>Insulin§</td>
<td>Insulin§</td>
<td>or</td>
</tr>
</tbody>
</table>

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

<table>
<thead>
<tr>
<th>Insulin#</th>
</tr>
</thead>
<tbody>
<tr>
<td>(multiple daily doses)</td>
</tr>
</tbody>
</table>
ANTI-HYPERGLYCEMIC THERAPY

• Glycemic targets
  - HbA1c < 7.0% (mean PG 150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - **Individualization** is key:
    - Tighter targets (6.0 - 6.5%) - younger, healthier
    - Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

*Diabetes Care* 2012;35:1364–1379

*Diabetologia* 2012;55:1577–1596
Approach to management of hyperglycemia:

- **Patient attitude and expected treatment efforts**
  - more stringent: highly motivated, adherent, excellent self-care capacities
  - less stringent: less motivated, non-adherent, poor self-care capacities

- **Risks potentially associated with hypoglycemia, other adverse events**
  - low (newly diagnosed)
  - high (long-standing)

- **Disease duration**
  - newly diagnosed (long)
  - long-standing (short)

- **Life expectancy**
  - long
  - short

- **Important comorbidities**
  - absent
  - few / mild
  - severe

- **Established vascular complications**
  - absent
  - few / mild
  - severe

- **Resources, support system**
  - readily available
  - limited

*Figure 1*
1. Patient-Centered Approach

“...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions.”

• Gauge patient’s preferred level of involvement.

• **Shared** decision making – final decisions re: lifestyle choices ultimately lies with the patient.

• Explore, where possible, therapeutic choices.

• Utilize decision aids.

*Diabetes Care* 2012;35:1364–1379
Lifestyle: “Easy” Recommendations for Patients

• Eat breakfast
• Keep a regular eating schedule
  • Don’t skip meals
  • Identify and avoid stress triggers for eating
• Don’t take “seconds”
• Choose fruits for dessert
• Drink a lot of water (at least 8 glasses each day)
• No late-night eating
Metformin: The Only Choice in Type 2 DM?

• Most commonly used therapy for T2 DM (2/3rds of patients)

• Clinical effects
  • Lowers A1C 1-2% (especially at high baseline A1C), no weight gain
  • Maximal clinical effect at 1500-2000 mg/day

• Possible side effects and precautions
  • GI side effects common – less well tolerated by up to 10%
  • Not advised if significant renal or liver disease, heart failure (~20%)

• Other features
  • Lower CV risk in obese patients (UKPDS)
  • Extensive clinical experience and lower cost
  • ? Favorable impact on cancer risk and mortality
Sulfonylureas and the Secretagogues

How Do We Use Them Now?

• Most common (traditional) 2nd agent in T2 DM
  • Stimulate insulin release – during hyperglycemia and post-meal

• Clinical Use
  • Inexpensive and commonly used, rapid glucose lowering
  • Limited dose effect and limited “durability” of effect

• Side effects
  • Associated with weight gain and risk of hypoglycemia

• Precautions and contraindications
  • Associated with risk of severe hypoglycemia (elderly, renal disease)
  • Highest risk of hypoglycemia with GLYBURIDE
  • May not be good for those at CVD risk (longstanding discussion)
Thiazolidinediones (TZDs)

Do We Target Insulin Resistance?

• Clinical application
  • Targeted patients with clinical markers of insulin resistance
    • Dyslipidemia, HTN, established CVD, central obesity
  • May limit CVD risk and alter progression of diabetes

• Adverse effects and considerations
  • Significant weight gain and increase risk of edema and HF
  • Increased risk of long-bone fractures
  • Macular edema

• Patient selection
  • Higher CVD risk – particularly with dyslipidemia, est. CVD
  • Those at lower risk for fracture and with central obesity, NASH

Summary Of Pioglitazone Clinical Trials
Center for Drug Evaluation & Research, July 30, 2007

Hazard Ratio

- PIO Meta-analysis - without PROactive: 0.75
- PROactive: 0.84
- PIO Meta-Analysis plus PROactive: 0.83

#CV Events
- PIO: 375
- COMP: 450

# of Subjects
- PIO: 8554
- COMP: 7836
Physiological Actions of GLP-1

- Neuroprotection
- Appetite
- Cardioprotection
- Cardiac output
- Reduce BP
- Gastric emptying
- Glucagon secretion
- Insulin secretion
- Insulin biosynthesis
- \( \beta \) cell proliferation
- \( \beta \) cell apoptosis
- Glucose production
- Glucose disposal
- Sodium excretion
Cardiovascular Effects of GLP-1-Based Therapies

- Improved weight, SBP, lipids
- Improved endothelial function
- Increased vasorelaxation
- Increased peripheral and coronary flow
- Increased ventricular function
- Decreased microvascular permeability
- Reduced inflammation

Effects in isolated vessels/hearts and GLP-1R localization to CV tissues indicate some effects may be direct

Okerson T, Chilton R. Cardiovasc Ther 30:e146-55, 2012
GLP-1 Secretion and Inactivation

DPP-4 Inhibitors
- Sitagliptin
- Weight neutral
- No hypoglycemia
- A glucoses/pill

GLP-1 Agonists
- Exenatide
- Weight loss
- Albiglutide
- GI side effects

DPP-4
- AIC reduction
- Weight loss
- Linagliptin
- Alogliptin

DPP-4 Inhibitors: Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta) and Alogliptin (Nesina)

• Clinical Use
  • Moderate effectiveness (A1C reduction ~0.5-0.8%)
  • Use in both combo and mono therapy

• Unique Features
  • Limited side effect profile, very well tolerated, pancreatitis?
  • Weight neutral, no significant weight loss, no hypoglycemia
  • Variable clinical response (A1C reduction 0.2-1.1%)

• Reduced dosing in chronic kidney disease (except for linagliptin)

• Saxagliptin increased risk of CHF in high risk population
SAVOR-TIMI 53: No Impact of Saxagliptin on Primary Outcome (MACE)

Hazard ratio, 1.00 (95% CI, 0.89–1.12)
P<0.001 for noninferiority
P=0.99 for superiority

2-yr Kaplan–Meier rate:
Saxagliptin, 7.3%
Placebo, 7.2%

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Saxagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>8212</td>
<td>7983</td>
<td>7761</td>
</tr>
<tr>
<td>7761</td>
<td>7267</td>
<td>4855</td>
</tr>
<tr>
<td>7267</td>
<td>4920</td>
<td>847</td>
</tr>
</tbody>
</table>

EXAMINE: No Impact of Alogliptin on the Primary Outcome (MACE)

![Graph showing cumulative incidence of primary end-point events](chart.png)

- **No. at Risk**
  - Placebo: 2679, 2299, 1891, 1375, 805, 286
  - Alogliptin: 2701, 2316, 1899, 1394, 821, 296

- **Hazard ratio, 0.96** (upper boundary of the one-sided repeated CI, 1.16)

### Table 2. Prespecified Clinical End Points.\(^*\)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Saxagliptin (N=8280)</th>
<th>Placebo (N=8212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point</td>
<td>613 (7.3)</td>
<td>609 (7.2)</td>
<td>1.00 (0.89–1.12)</td>
<td>0.99</td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point</td>
<td>1059 (12.8)</td>
<td>1034 (12.4)</td>
<td>1.02 (0.94–1.11)</td>
<td>0.66</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>420 (4.9)</td>
<td>378 (4.2)</td>
<td>1.11 (0.96–1.27)</td>
<td>0.15</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>269 (3.2)</td>
<td>260 (2.9)</td>
<td>1.03 (0.87–1.22)</td>
<td>0.72</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>265 (3.2)</td>
<td>278 (3.4)</td>
<td>0.95 (0.80–1.12)</td>
<td>0.52</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>157 (1.9)</td>
<td>141 (1.7)</td>
<td>1.11 (0.88–1.39)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>97 (1.2)</td>
<td>81 (1.0)</td>
<td>1.19 (0.89–1.60)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>289 (3.5)</td>
<td>228 (2.8)</td>
<td>1.27 (1.07–1.51)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hospitalization for coronary revascularization</td>
<td>423 (5.2)</td>
<td>459 (5.6)</td>
<td>0.91 (0.80–1.04)</td>
<td>0.18</td>
</tr>
<tr>
<td>Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine &gt;6.0 mg/dl (530 μmol/liter)</td>
<td>194 (2.2)</td>
<td>178 (2.0)</td>
<td>1.08 (0.88–1.32)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hospitalization for hypoglycemia</td>
<td>53 (0.6)</td>
<td>43 (0.5)</td>
<td>1.22 (0.82–1.83)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

\(^*\) Event rates and percentages are 2-year Kaplan-Meier estimates.
# SAVOR-TIMI 53: Safety End Points

## Table 3. Safety End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Saxagliptin (N = 8280)</th>
<th>Placebo (N = 8212)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>55 (0.7)</td>
<td>65 (0.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>49 (0.6)</td>
<td>40 (0.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Severe infection</td>
<td>590 (7.1)</td>
<td>576 (7.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Opportunistic infection</td>
<td>21 (0.3)</td>
<td>35 (0.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>93 (1.1)</td>
<td>89 (1.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>241 (2.9)</td>
<td>240 (2.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>228 (2.8)</td>
<td>232 (2.8)</td>
<td>0.81</td>
</tr>
<tr>
<td>Renal abnormality</td>
<td>483 (5.8)</td>
<td>418 (5.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Any hypoglycemia†</td>
<td>1264 (15.3)</td>
<td>1104 (13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major</td>
<td>177 (2.1)</td>
<td>140 (1.7)</td>
<td>0.047</td>
</tr>
<tr>
<td>Minor</td>
<td>1172 (14.2)</td>
<td>1028 (12.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cancer</td>
<td>327 (3.9)</td>
<td>362 (4.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Any liver abnormality†</td>
<td>55 (0.7)</td>
<td>67 (0.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>AST &gt;3× ULN</td>
<td>60 (0.7)</td>
<td>61 (0.7)</td>
<td>0.93</td>
</tr>
<tr>
<td>AST &gt;10× ULN</td>
<td>12 (0.1)</td>
<td>15 (0.2)</td>
<td>0.57</td>
</tr>
<tr>
<td>ALT or AST &gt;3× ULN and total bilirubin &gt;2× ULN</td>
<td>13 (0.2)</td>
<td>23 (0.3)</td>
<td>0.097</td>
</tr>
<tr>
<td>Any pancreatitis‡</td>
<td>24 (0.3)</td>
<td>21 (0.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>Acute: definite or possible</td>
<td>22 (0.3)</td>
<td>16 (0.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Acute: definite</td>
<td>17 (0.2)</td>
<td>9 (0.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Acute: possible</td>
<td>6 (0.1)</td>
<td>7 (0.1)</td>
<td>0.79</td>
</tr>
<tr>
<td>Chronic</td>
<td>2 (&lt;0.1)</td>
<td>6 (0.1)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* P values were calculated with the use of Fisher’s exact test. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.  
† Patients may have had more than one type of event.

## Supplementary Table 2. Other Safety End Points

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=2679)</th>
<th>Alogliptin (n=2701)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious Adverse Event,</td>
<td>952 (35.5)</td>
<td>907 (33.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Serious hypoglycemia**</td>
<td>16 (0.6)</td>
<td>18 (0.7)</td>
<td>0.86</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>2111 (78.8)</td>
<td>2160 (80.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Any hypoglycemia **</td>
<td>173 (6.5)</td>
<td>181 (6.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>Pancreatitis†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>8 (0.3)</td>
<td>12 (0.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Chronic</td>
<td>4 (0.1)</td>
<td>5 (0.2)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
## Newest Drugs on the US Market

### GLP-1 RA

**Daily**
- Exenatide (BID) (Byetta)
- Liraglutide (Victoza)

**Weekly**
- Exenatide (Bydureon)
- Albiglutide (Tanzuem)
- Dulaglutide (Trulicity)

### SGLT-2 Inhibitors

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
Structure of US Approved GLP-1 RAs
Albiglutide

**GLP-1**

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG

(7-37) amide

**Site of proteolytic inactivation (DPP-4)**

7 10 15 20 25 30 35 37

**Albiglutide**

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

- 2 GLP-1 molecules in tandem
- Covalently bound to albumin
- DPP-4 resistant
- Half-life ~ 6-7 days

Dulaglutide

- Dulaglutide is a recombinant fusion protein linking a human GLP-1 peptide analog and a variant of a human IgG4 Fc fragment

- Dulaglutide was engineered for:
  - Duration of pharmacodynamic activity
  - DPP-IV inactivation
  - Solubility
  - Reduced immunogenic potential

GLP-1 peptide
Linker peptide
Modified IgG4 Fc domain
Exenatide Added to Basal Glargine


**A1C Change (%)**

- **OG + EXE BID (Baseline 8.3 ± 0.1%)**
  - 0%: 7.41 ± 0.09%
  - 18%: 6.70 ± 0.09%
  - 30%: 6.70 ± 0.09%

- **OG + PLB BID (Baseline 8.5 ± 0.1%)**
  - 0%: 7.41 ± 0.09%
  - 18%: 6.70 ± 0.09%
  - 30%: 6.70 ± 0.09%

LS mean ± SE
Exenatide Added to Basal Glargine

**LS mean ± SE** *P*<.001 between-treatment comparison

Effects of Liraglutide on Systolic BP With or Without Concomitant Antihypertensive Agents

Meta-analysis of 6 × 26-week clinical trials (N = 3967)\(^1\)

- **Overall**
  - PBO: -2.55 \(\pm 0.3\)
  - LIRA (1.8 mg): -3.55 \(\pm 0.3\)

- **With antihypertensive**
  - PBO: -0.76
  - LIRA (1.8 mg): -2.03 \(\pm 0.3\)

- **No antihypertensive**
  - PBO: -2.03 \(\pm 0.3\)
  - LIRA (1.8 mg): -3.07 \(\pm 0.3\)

\(\alpha < .05\) vs PBO.

---

Fonseca V, et al. 70th ADA Scientific Sessions. 2010:296-OR.
GLP-1 RAs Improve Lipid Profiles in Patients With T2DM


Significantly greater change vs EXN BID.
Anti-Inflammatory Effects of GLP-1 RAs in Patients With T2DM

EXN (10 mcg, 2 X daily) vs PBO
12 weeks (N = 24)\(^1\)

LIRA (1.9 mg, 1 X daily) vs PBO
14 weeks (N = 165)\(^2\)

EXN BID also significantly reduced mononuclear cell
• Production of reactive oxygen species (ROS)
• NFκB activation
• TNFα and IL-1β expression

BL, baseline; BNP, B-type natriuretic peptide; MCP-1, monocyte chemoattractant protein-1; PBO, placebo; SAA, serum amyloid A.
\(^a\) \(P < .05\) vs baseline and control; \(^b\) \(P < .05\) vs baseline.

**SGLT-2 Inhibitors—Canagliflozin, Dapagliflozin, Empagliflozin**

**Clinical Effects**
- Novel mechanism of action/oral agent
- Most will respond—action independent of beta-cell function
- A1C reduction ~1% with 2-3 kg weight loss

**Possible Side Effects and Precautions**
- Mycotic genital infections
- Findings due to volume depletion
- Don’t use if eGFR <45%

**Other Features**
- Lowers BP slightly
- Raises LDL cholesterol

The Prospect of SGLT2 Inhibition

RENAL HANDLING OF GLUCOSE

(180 L/day) (900 mg/L) = 162 g/day

Glucose

SGLT 2

90%

SGLT 1

10%

NO GLUCOSE
Healthy 180 mg/dL
RTG

T2DM 240 mg/dL
RTG

SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion ($RT_G$)

Adapted with permission from Abdul-Ghani MA, DeFronzo RA. T2DM = type 2 diabetes mellitus.
Effect of Canagliflozin on A1C as Mono or Combination Therapy

<table>
<thead>
<tr>
<th>Combination</th>
<th>N</th>
<th>Baseline A1C (%)</th>
<th>LS Mean Change From Baseline in A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono</td>
<td>584</td>
<td>8.06</td>
<td>-0.91%†</td>
</tr>
<tr>
<td>+Met</td>
<td>1284</td>
<td>7.94</td>
<td>-0.62%†</td>
</tr>
<tr>
<td>+SU</td>
<td>127</td>
<td>8.29</td>
<td>-0.77%†</td>
</tr>
<tr>
<td>+Met + SU</td>
<td>469</td>
<td>8.13</td>
<td>-0.74%†</td>
</tr>
<tr>
<td>+Met + Pio</td>
<td>342</td>
<td>7.99</td>
<td>-0.83%†</td>
</tr>
<tr>
<td>+Insulin ± AHAs*</td>
<td>1718</td>
<td>8.33</td>
<td>-0.71%†</td>
</tr>
<tr>
<td>Older subjects</td>
<td>714</td>
<td>7.7</td>
<td>-0.92%†</td>
</tr>
</tbody>
</table>

*Studies for combinations including SU or insulin were 18 weeks in duration; all others were 26 weeks in duration.

†P<0.001 for reduction vs control.

Percent Change in Body Weight

- PBO = placebo; CANA = canagliflozin; LS = least squares; SE = standard error
- mITT = modified intent-to-treat; LOCF = last observation carried forward

Canagliflozin and Dapagliflozin Warnings and Precautions

- Hypoglycemia: risk with secretagogues and/or insulin
- Genital mycotic infections
- Volume depletion/orthostatic changes
- Hypersensitivity
- Increased LDL
- Bladder cancer: don’t use if active; use with caution if prior history of bladder cancer (dapagliflozin only)
Dapa/Cana/Empa in Patients with Renal Impairment

Both dapagliflozin and canagliflozin are contraindicated in patients with severe renal impairment, ESRD, or on dialysis:

Canagliflozin
- Contraindicated in patients with eGFR <45 ml/min/1.73 m2 and should be discontinued in patients if eGFR falls to <45 ml/min/1.73 m2
- Dose is limited to 100 mg once daily in patients with eGFR 45-<60 ml/min/1.73 m2

Dapagliflozin
- Contraindicated in patients with eGFR <60 ml/min/1.73 m2 and should be discontinued in patients if eGFR falls to <60 ml/min/1.73 m2

Empagliflozin
- Contraindicated if eGFR <45 ml/min/1.73 m2
**Volume Reductions Observed with Canagliflozin and Dapagliflozin: Results from Clinical Trials**

- SGLT2 inhibitors cause osmotic diuresis that may result in intravascular volume reductions

<table>
<thead>
<tr>
<th></th>
<th>Pool of 12 placebo controlled studies*</th>
<th>Pool of 13 placebo controlled studies*</th>
<th>Pool of 8 clinical trials†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Dapa 5 mg</td>
<td>Dapa 10 mg</td>
</tr>
<tr>
<td>Overall population</td>
<td>0.4%</td>
<td>0.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Patients on loop diuretics</td>
<td>1.8%</td>
<td>0</td>
<td>9.7%</td>
</tr>
<tr>
<td>eGFR ≥30 and &lt;60 ml/min/1.73 m²</td>
<td>1.9%</td>
<td>0.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>≥65-years of age</td>
<td>0.4%</td>
<td>0.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>≥75-years of age</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
When Goal is to Avoid Hypoglycemia

Healthy eating, weight control, increased physical activity

- Initial drug monotherapy
  - Efficacy (↓ HbA1c)
  - Hypoglycemia
  - Weight
  - Side effects
  - Costs

- Two drug combinations
  - Efficacy (↓ HbA1c)
  - Hypoglycemia
  - Weight
  - Major side effect(s)
  - Costs

- Three drug combinations

- More complex insulin strategies

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

- Metformin + Thiazolidinedione
  - high
  - low risk
  - gain
  - edema, HF, fx s¹
  - high

- Metformin + DPP-4 Inhibitor
  - intermediate
  - low risk
  - neutral
  - rare
  - high

- Metformin + GLP-1 receptor agonist
  - high
  - low risk
  - loss
  - GI²
  - high

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

- Metformin + Thiazolidinedione + DPP-4-i
  - high

- Metformin + DPP-4 Inhibitor + GLP-1-RA
  - TZD

- Metformin + GLP-1 receptor agonist + TZD

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:
Reducing CVD Risk Treating T2DM

- Use statins, control BP, give aspirin
- Use diabetes drugs that don’t cause hypoglycemia
- Improve control early and maintain it
- Pioglitazone potentially beneficial based on clinical trial data
- GLP-1 RA’s and SGLT-2 I’s reduce BP
- GLP-1 RA reduce inflammatory markers
- TZD’s and DPP-IV increase CHF risk
Thank You