Controversies in Diabetes Guidelines

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Professor of Medicine

Disclosures (2014 – 2015):
Member of the AACE BOD, Guideline committee
Advisory boards or consulting: Abbvie, Abbott, AstraZeneca, BI-Lilly, GSK, Janssen, Mannkind, Merck, NovoNordisk, Sanofi
Speaker’s bureau: Janssen
Grants for clinical trials: Novartis, NovoNordisk, Sanofi, Dexcom, Lexicon, Pfizer, Andromeda
Controversies in Diabetes Guidelines

- Diabetes is a complex disease with many ramifications for a person’s health.
- Easy to diagnose, difficult to manage, and with numerable associated conditions.
- This talk will focus on the management of hyperglycemia.

Glucose – centric or glucose eccentric?

Natural History of Type 2 Diabetes

### Two Major Sets of Diabetes “Guidelines”

<table>
<thead>
<tr>
<th>ADA</th>
<th>AACE/ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA: Standards of Care, published, updated annually</td>
<td>Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan, 2015</td>
</tr>
</tbody>
</table>

### Other Guidelines, Consensus Statements, Position Statements

- **Geriatrics** - Diabetes Mellitus in Older People: A Position Statement... IAGG, EDWPOP, 2012
- **ACC/AHA Cholesterol Guideline**, 2013 - 2014
- **JNC 8** - Blood Pressure Guidelines, 2014
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>
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<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↓</td>
<td>← →</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>← →</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>← →</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>← →</td>
<td>← →</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>← →</td>
<td>← →</td>
</tr>
</tbody>
</table>

Clinical Conundrums in Diabetes: Glucose Control

- What is the relationship between A1c and hypoglycemia?
  - Older studies: lower A1c levels were associated with higher rates of hypoglycemia
  - Newer studies: hypoglycemia risk depends on the therapy employed, and is problematic across the A1c spectrum
- What is the relationship between hypoglycemia and mortality?
  - Is the risk the same for all age groups?
- Do diabetes therapies contribute to, or prevent mortality?
  - And is this related to hypoglycemia or off target effects?

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

- **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
AACE/ACE Glycemic Targets

- **Pre-diabetes**: Aim for normalization of glucose

- **Confirmed diabetes**
  - A1c target is <6.5% for otherwise healthy adults
  - Individualization is needed for those with advanced age, co-morbidities, or those at high risk of hypoglycemia
ADA-EASD and AACE: Management of Hyperglycemia in T2DM

ANTI-HYPERGLYCEMIC THERAPY

• Implementation strategies:
  - Initial therapy
  - Advancing to dual combination therapy
  - Advancing to triple combination therapy
  - Transitions to & titrations of insulin

Diabetes Care, Diabetologia. January, 2015; Endocrine Practice 2015

Metabolic and Vascular Effects of Metformin

• Anti-hyperglycaemic action
  - Suppresses hepatic glucose output
  - Increases insulin-mediated glucose utilisation
  - Decreases fatty acid oxidation
  - Increases splanchnic glucose turnover
• Weight stabilisation or reduction
• Improves lipid profile
  - Reduces hypertriglyceridaemia
  - Lowers plasma fatty acids and LDL-cholesterol; raises HDL-cholesterol in some patients
• No risk of serious hypoglycaemia
• Counters insulin resistance
  - Decreases endogenous or exogenous insulin requirements
  - Reduces basal plasma insulin concentrations
• Vascular effects
  - Increased fibrinolysis
  - Decreases PAI-1 levels
  - Improved endothelial function

HDL=high-density lipoprotein; LDL=low-density lipoprotein; PAI-1=plasminogen activator inhibitor-1.
Krentz AJ, Bailey CJ. Oral Antidiabetic Agents. Drugs, 2005

Major Limitations: Tolerance Kidney Function
### Oral Class

<table>
<thead>
<tr>
<th>Oral Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>• Activates AMP-kinase (other) • ↓ Hepatic glucose production</td>
<td>• Extensive experience • No hypoglycemia • Weight neutral • ♦ ↓ CVD</td>
<td>• Gastrointestinal • Lactic acidosis (rare) • B-12 deficiency • Contraindications</td>
<td>Low</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>• Closes K(_{ATP}) channels • ↑ Insulin secretion</td>
<td>• Extensive experience • ↓ Microvascular risk</td>
<td>• Hypoglycemia • ↑ Weight • Low durability • ? Blunts ischemic preconditioning</td>
<td>Low</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>• Closes K(_{ATP}) channels • ↑ Insulin secretion</td>
<td>• ↓ Postprandial glucose • Dosing flexibility</td>
<td>• Hypoglycemia • ↑ Weight • ? Blunts ischemic preconditioning • Dosing frequency</td>
<td>Mod.</td>
</tr>
<tr>
<td>TZDs</td>
<td>• PPAR-( \gamma ) activator • ↑ Insulin sensitivity</td>
<td>• No hypoglycemia • Durability • ↓ TGs (pio) • ↑ HDL-C • ♦ ↓ CVD events (pio)</td>
<td>• ↑ Weight • Edema/heart failure • Bone fractures • ↑ LDL-C (rosi) • ? ↑ MI (rosi)</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Table 1. Properties of anti-hyperglycemic agents**

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
### Oral Class

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucosidase inhibitors</td>
<td>* Inhibits α-glucosidase&lt;br&gt;• Inhibits carbohydrate digestion/absorption&lt;br&gt;• No hypoglycemia&lt;br&gt;• Nonsystemic&lt;br&gt;• ↓ Postprandial glucose&lt;br&gt;• ? ↓ CVD events</td>
<td>* Gastrointestinal&lt;br&gt;• Dosing frequency&lt;br&gt;• Modest ↓ A1c</td>
<td>Mod.</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>* Inhibits DPP-4&lt;br&gt;• Increases incretin (GLP-1, GIP) levels</td>
<td>* No hypoglycemia&lt;br&gt;• Well tolerated</td>
<td>High</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>* Bind bile acids&lt;br&gt;• ↓ Hepatic glucose production</td>
<td>* No hypoglycemia&lt;br&gt;• ↓ LDL-C</td>
<td>High</td>
</tr>
<tr>
<td>Dopamine-2 agonists</td>
<td>* Activates DA receptor&lt;br&gt;• Alters hypothalamic control of metabolism&lt;br&gt;• ↑ insulin sensitivity</td>
<td>* No hypoglycemia&lt;br&gt;• ? ↓ CVD events</td>
<td>High</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>* Inhibits sodium-glucose cotransporter 2 (SGLT2) in proximal tubule&lt;br&gt;• Increases glucosuria</td>
<td>* ↓ Weight&lt;br&gt;• No hypoglycemia&lt;br&gt;• ↓ BP&lt;br&gt;• Effective at all stages</td>
<td>* GU infections&lt;br&gt;• Polyuria&lt;br&gt;• Volume depletion&lt;br&gt;• ↑ LDL-C&lt;br&gt;• ↑ Cr (transient)</td>
</tr>
</tbody>
</table>

Table 1. Properties of anti-hyperglycemic agents

### Injectable Class

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylin mimetics</td>
<td>* Activates amylase receptor&lt;br&gt;• ↓ glucagon&lt;br&gt;• ↓ gastric emptying&lt;br&gt;• ↑ satiety</td>
<td>* ↓ Weight&lt;br&gt;• ↓ Postprandial glucose</td>
<td>* Gastrointestinal&lt;br&gt;• Modest ↓ A1c&lt;br&gt;• Injectable&lt;br&gt;• Hypo if insulin dose not reduced&lt;br&gt;• Dosing frequency&lt;br&gt;• Training requirements</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>* Activates GLP-1 receptor&lt;br&gt;• ↑ Insulin, ↓ glucagon&lt;br&gt;• ↓ gastric emptying&lt;br&gt;• ↑ satiety</td>
<td>* ↓ Weight&lt;br&gt;• No hypoglycemia&lt;br&gt;• ↓ BP&lt;br&gt;• Some CV risk factors</td>
<td>* Gastrointestinal&lt;br&gt;• ↑ Heart rate&lt;br&gt;• Medullary ca (rodents)&lt;br&gt;• Injectable&lt;br&gt;• Training requirements</td>
</tr>
<tr>
<td>Insulin</td>
<td>* Activates insulin receptor&lt;br&gt;• Myriad</td>
<td>* Universally effective&lt;br&gt;• Unlimited efficacy&lt;br&gt;• ↓ Microvascular risk</td>
<td>* Hypoglycemia&lt;br&gt;• Weight gain&lt;br&gt;• ? Mitogenicity&lt;br&gt;• Injectable&lt;br&gt;• Patient reluctance&lt;br&gt;• Training requirements</td>
</tr>
</tbody>
</table>

Table 1. Properties of anti-hyperglycemic agents
Earlier and More Aggressive Intervention May Improve Patients’ Chances of Reaching Goal


Conceptual Approach

Insulin Secretion: SFU and Incretins

SUR1

K<sub>ATP</sub>

Gs receptor

Incretin

cAMP

PKA

Rap1

Ca<sup>2+</sup>

VDCC

ΔΨ

RRP

Insulin secretion

Durability of Glycemic Control: ADOPT

Hazard ratio (95% CI)
Rosiglitazone vs. metformin, 0.68 (0.55-0.85); P<0.001
Rosiglitazone vs. glyburide, 0.37 (0.30-0.45); P<0.001

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>1393</td>
<td>1397</td>
<td>1337</td>
</tr>
<tr>
<td>1 Year</td>
<td>1207</td>
<td>1205</td>
<td>1114</td>
</tr>
<tr>
<td>2 Years</td>
<td>1078</td>
<td>1076</td>
<td>958</td>
</tr>
<tr>
<td>3 Years</td>
<td>957</td>
<td>950</td>
<td>781</td>
</tr>
<tr>
<td>4 Years</td>
<td>844</td>
<td>818</td>
<td>617</td>
</tr>
<tr>
<td>5 Years</td>
<td>324</td>
<td>311</td>
<td>218</td>
</tr>
</tbody>
</table>

Kahn et al. NEJM 2006;355:2427-43

Adverse Effect of Metformin-SU Combination, Intensification From Oral Monotherapy, Mortality Risk vs. A1c, n=27,965

HR (95% CI)
†

Hypoglycemia vs. Mortality: Meta-regression Analysis


Differences between severe hypoglycemic rates (interventional vs. conventional group, %)

PPAR Activation: Reduces insulin resistance

http://en.wikipedia.org/wiki/Peroxisome_proliferator-activated_receptor
Problems With PPARS

- PPARs present complex toxicologic issues
- On-target effects such as stimulation of adipogenesis may cause weight gain and fat accumulation in the bone marrow/ balanced with reduction of fat in liver and other tissues.
- Off target effects: fluid accumulation that can lead to heart failure, effects on bone causing increased risk of fractures in women
- Cancer: increased risk of bladder cancer?

What Is DPP-4?

- Naturally occurring enzyme that degrades GLP-1 and GIP
- Inactivates GLP-1 >50% in ~1 to 2 minutes
- Inhibition of DPP-4 by DPP-4 inhibitors increases half-life and level of GLP-1
Postprandial GLP-1 Levels Are Decreased In Patients With IGT and Type 2 Diabetes


Initiation of pharmacotherapy with sitagliptin+/-metformin HCl: HbA\textsubscript{1C} results at 24 weeks

**Initiation of pharmacotherapy with sitagliptin +/- metformin HCl: A1C results at 24 weeks**

- **24-Week Placebo-Adjusted Results**
  - Mean A1C = 8.8%
  - LSM A1C Change From Baseline, %
    - -3.5
    - -3.0
    - -2.5
    - -2.0
    - -1.5
    - -1.0
    - -0.5
    - 0.0
    - 0.5
  - n=178 n=177 n=183 n=178 n=175
  - -0.8
  - -1.0
  - -1.3
  - -1.6
  - -2.1

- **Open label**
  - Mean A1C = 11.2%
  - LSM A1C Change From Baseline, %
    - -2.9a
  - n=117

*LSM change from baseline without adjustment for placebo.

**Available DPPIV Inhibitors**

- **Sitagliptin**
  - 100 mg for normal kidney function
  - 50 mg for eGFR <50 ml/min/1.73m²
  - 25 mg for eGFR <30 ml/min/1.73m²
- **Saxagliptin**
  - 5 mg for normal kidney function
  - 2.5 mg for eGFR <30 ml/min/1.73m²
- **Linagliptin**
  - 5 mg regardless of kidney function
  - OK to use in dialysis patients
  - Excreted unchanged via Gl tract
- **Alogliptin**
  - 25 mg for normal kidney function
  - 12.5 mg for eGFR <50 ml/min/1.73m²
Characteristics of Currently Marketed GLP-1 Receptor Agonists

Exenatide BID
- Exendin-4 based
- Resistant to DPP-4
- 2x daily dosing/2.4 hr half-life

Exenatide ER
- Exendin-4 based
- Microspheres with biodegradable polymer
- 1x weekly dosing/>1 week half-life

Liraglutide
- GLP-1 analog
- Self-association
- Plasma albumin binding
- Resistant to DPP-4
- 1x daily anytime/>1 week half-life

Potential Clinical Effects of GLP-1 Receptor Agonists

Physiologic Effects
- Increased GLP-1 activity
  - Decreased glucagon production
  - Increased insulin synthesis and secretion
- Glycemic control
  - Decreased A1C
  - Decreased FPG
  - Decreased PPG
- Weight effects
  - Decreased gastric emptying
  - Decreased caloric intake
  - Weight loss

Potential Clinical Advantages
- Low to no hypoglycemia
- Weight reduction
- Potential for improved β-cell mass/function?
- Potential cardiovascular protective actions?

Potential Clinical Disadvantages
- Gastrointestinal side effects
- Injectable
- Training requirements
- High cost

DURATION-6: Head to Head Comparison of Exenatide ER and Liraglutide

- A1C Change (%)
  - Baseline A1C: 8.4-8.5%
  - EXN ER: -1.48, P=0.002
  - LIRA: -1.28

- FPG Change
  - ΔFPG (mg/dL)
  - EXN ER: -38, P=.021
  - LIRA: -32

Treatment difference in HbA1C (-0.21) did not meet the non-inferiority criteria.

53% EXN ER and 60% LIRA patients reached HbA1C < 7%


DURATION-6: Impact of Exenatide ER and Liraglutide on Weight

- Weight Loss (kg)
  - LIRA: -3.57, P<0.001
  - EXN ER: -2.68

LIRA showed significant weight loss compared to EXN ER.

DURATION-6: Impact of Exenatide ER and Liraglutide on CV Risk Factors

Changes in blood pressure and lipid levels were similar for EXN ER and LIRA.


DURATON-6: Hypoglycemia

- Rates of minor hypoglycemia were similar
- There were no episodes of major hypoglycemia in either group

Two families of glucose transporters

**GLUT/SLC2A family**
- Facilitated glucose transporters
- Passive, downhill transport
- GLUT1 (widespread including the kidneys, found in S3 segment of proximal tubule)
- GLUT2 (S1 segment of proximal tubule of kidneys and pancreas)

**SGLT/SLC5A family**
- Sodium coupled glucose cotransporter
- Active transport of glucose (couples uphill transport of glucose with downhill transport of sodium)
- SGLT1 (brush border of small intestine, S3 segment of proximal tubule)
- SGLT2 (apical domains of S1 and S2 segments of proximal tubule)

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**SGLTs in the kidney**

<table>
<thead>
<tr>
<th></th>
<th>SGLT1</th>
<th>SGLT2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site</strong></td>
<td>Intestine, kidney</td>
<td>Kidney</td>
</tr>
<tr>
<td><strong>Sugar specificity</strong></td>
<td>Glucose or galactose</td>
<td>Glucose</td>
</tr>
<tr>
<td><strong>Glucose affinity</strong></td>
<td>High, Km=0.4 mM</td>
<td>Low, Km=2 mM</td>
</tr>
<tr>
<td><strong>Glucose transport capacity</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Sodium transport</strong></td>
<td>Na⁺: glucose = 1:2</td>
<td>Na⁺: glucose = 1:1</td>
</tr>
<tr>
<td><strong>Role</strong></td>
<td>Dietary absorption of glucose and galactose</td>
<td>Renal glucose reabsorption</td>
</tr>
<tr>
<td></td>
<td>Renal glucose reabsorption</td>
<td></td>
</tr>
</tbody>
</table>

Renal handling of glucose

180g glucose filtered each day

SGLT2: 90% of glucose reabsorption in S1/S2*

SGLT1: 10% of glucose reabsorption in S3*

Excretion: no glucose

Transmembrane transport of glucose and sodium: SGLT2

- 1 molecule of glucose is transported for every 1 molecule of sodium
- Hyperglycemia contributes to increased sodium reabsorption, possibly increasing BP, tissue edema

Selective SGLT2 inhibitors

- **Potential advantages**
  - Minimize gastrointestinal side effects associated with SGLT1 inhibition with nonselective agents
  - Unique potential to cause negative energy balance
  - No effect on insulin secretion

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Efficacy of SGLT2 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin</th>
<th>Canagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet (monotherapy)</td>
<td>-0.4 to 0.8%</td>
<td>-0.65 - 1.1%</td>
<td>-0.5 to 0.6%</td>
</tr>
<tr>
<td>Add to metformin</td>
<td>-0.4 to 0.8%</td>
<td>-0.53 - 0.8%</td>
<td>-0.6 - 0.95%</td>
</tr>
<tr>
<td>Add to SFU</td>
<td>-0.5 to 0.7%</td>
<td>-0.7 – 0.85%</td>
<td></td>
</tr>
<tr>
<td>Add to pioglitazone</td>
<td>-0.4 to 0.5%</td>
<td>-0.75 – 0.85%</td>
<td>-0.45 – 0.61%</td>
</tr>
<tr>
<td>Add to sitagliptin</td>
<td>-0.6 – 0.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add to insulin</td>
<td>-0.5 to 0.6%</td>
<td></td>
<td>-0.45 – 0.5%</td>
</tr>
<tr>
<td>Mean A1c reduction</td>
<td>-0.52%</td>
<td>-1.08% mono -0.73% add on</td>
<td>-0.64%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>-2.1 kg</td>
<td>-2.81 kg</td>
<td>-1.84 kg</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>-3.78 mmHg</td>
<td>-4.38 mmHg</td>
<td>-4.19 mmHg</td>
</tr>
</tbody>
</table>

Sheen AJ, Drugs, 2015
Time course of weight loss with dapagliflozin

![Graph showing weight loss over time with dapagliflozin dosage levels compared to placebo and metformin.](image)


### Cautions when using SGLT2 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin</th>
<th>Canagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in CKD</td>
<td>Not recommended if eGFR is &lt;60 ml/min/1.73m²</td>
<td>Contraindicated with eGFR &lt;45; use 100 mg dose when eGFR is 45 – 60 ml/min/1.73m²</td>
<td>Contraindicated with eGFR &lt;45 ml/min/1.73m²; either dose if eGFR is &gt;45 ml/min/1.73m²</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>↑Dig level by 36%</td>
<td>↑4.5 – 8%</td>
<td>?</td>
</tr>
<tr>
<td>LDL change</td>
<td>↑3.9%</td>
<td>↑4.5 – 8%</td>
<td>?</td>
</tr>
<tr>
<td>CV Events</td>
<td>Not observed</td>
<td>Possible ↑ stroke</td>
<td>Not observed</td>
</tr>
<tr>
<td>Cancer</td>
<td>Possible increase in bladder CA</td>
<td>Not observed</td>
<td>Not observed</td>
</tr>
</tbody>
</table>

Mikhail N, World J DM 2014
Adverse Effects of SGLT2 Inhibition

- Genital mycotic infections
  - 10-20% in women, 5% in uncircumcised men
- Orthostasis
  - Described, need to counsel patients to increase fluid intake
- Osteoporosis
  - Limited data sets, possible increase in fractures
  - No change in calcium, vitamin D, PTH
  - Modest increase in markers of bone resorption
- CV Disease
  - Increase in LDL
  - Insufficient data to recommend or limit use
- Euglycemic DKA
  - Ketosis or acidosis with blood glucose <200 mg/dl

Blood pressure

- Decrease in blood pressure and increase in hematocrit consistent with mild osmotic diuresis
- Potentially beneficial in diabetes with hypertension
- Possible risk in patients who are volume sensitive e.g. autonomic neuropathy, elderly, concomitant ACE inhibitor or ARB use
- Further evaluation of mechanism and risk/benefit warranted

Changes in Kidney Function with Canagliflozin and Dapagliflozin

Schernthaner G, Diab Vasc Dis Res 2014

Options for treatment of diabetes in patients with CKD

Schernthaner G, Diab Vasc Dis Res 2014
Relationship between A1c and Mortality

Currie C, Lancet 2010; 375: 481-489

Summary

- Treatment of the patient with T2DM should be individualized
  - Goals of treatment may include weight loss
  - In some patients avoidance of hypoglycemia is critical
  - Treatment may be predicated on concomitant conditions, such as renal impairment

- Non-insulin therapies include SFU, TZD, AGI, DPP-4 inhibitors, GLP-1 agonists and SGLT2 inhibitors
  - All are well studied, and approved for use with metformin and with most classes of anti-diabetic agents
  - None are free of adverse effects
  - Options are available for every patient type, limited by availability (cost) and expertise of the prescribing physician
Thank you for your attention!

Questions?

CV Outcomes Trials in Diabetes

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Drug</th>
<th>Primary end point</th>
<th>No. of subjects (length of study in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>MACE</td>
<td>5,400 (5)</td>
</tr>
<tr>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>MACE</td>
<td>4,500 (4)</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Linagliptin</td>
<td>MACE + unstable angina</td>
<td>6,000 (7)</td>
</tr>
<tr>
<td>AECARDIO</td>
<td>Aleglitazar</td>
<td>MACE</td>
<td>6,000 ACS (4.5)</td>
</tr>
<tr>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>MACE + unstable angina</td>
<td>14,000 (5)</td>
</tr>
<tr>
<td>SAVOR</td>
<td>Saxagliptin</td>
<td>MACE</td>
<td>16,500 (3)</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide LAR</td>
<td>MACE</td>
<td>12,000 (5.5)</td>
</tr>
<tr>
<td>LEADER</td>
<td>Liraglutide</td>
<td>MACE</td>
<td>9,000</td>
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</table>

ACS, acute coronary syndrome; CANVAS, CANagliflozin cardioVascular Assessment Study; EXAMINE, Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome; EXSCEL, EXenatide Study of Cardiovascular Event Lowering; LAR, long-acting release; TECOS, A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control. *Accessed through http://www.clinicaltrials.gov/.

Hirshberg, Diabetes Care, 2013
Major CV Outcome Trials in Diabetes

<table>
<thead>
<tr>
<th>Pre 2000 (5)</th>
<th>2010 to date (15)</th>
</tr>
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<tbody>
<tr>
<td>UGDP</td>
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<tr>
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<td>Kumamoto</td>
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<td>TECOS</td>
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<td>TIDE</td>
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</table>

2000 – 2009 (9)
• ACCORD
• Advance
• BARI 2D
• Heart 2D
• Navigator
• ProACTIVE
• RECORD
• VADT
• ORIGIN

GRADE Study

• Recruiting patients with T2DM duration <10 years
  • Currently taking and tolerating metformin
  • A1c 6.8% - 8.5%

• Will be randomized to one of the following
  • Glimepiride
  • Sitagliptin
  • Liraglutide
  • Insulin glargine

• Follow-up is 5 years, all meds free, rescue with insulin glargine