Diabetes Muddy Waters: Is it Type 1 or Type 2?

Susan Cornell, PharmD, CDE, FAPhA, FAADE
Associate Professor of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, IL

Kam Capoccia, PharmD, BCPS, CDE
Clinical Professor of Community Care
Western New England University
College of Pharmacy and Health Sciences
Springfield, MA
Disclosures

• Dr. Cornell serves on an advisory board for Novo Nordisk and Becton Dickinson, as well as, speakers bureau for Novo Nordisk and Abbott Diabetes Care.

• Dr. Capoccia reports no disclosures.
CPE Information

• Target Audience:
• ACPE#:
• Activity Type:

(APhA will complete this information.)
Learning Objectives

• Describe the eleven pathways that lead to hyperglycemia and how this impacts the diagnosis and treatment of diabetes.

• Discuss the new recommendations for antihyperglycemic therapy from the updated guidelines for type 2 diabetes.

• Compare the various non-insulin pharmacologic agents for the management of type 1 diabetes.

• Formulate a patient-centered diabetes treatment plan considering the A1C target, cardiovascular impact, and “egregious eleven”.

Every 6 seconds a person dies from diabetes, or diabetes is a contributing cause of their death.
Why is Glucose Control Important?

• 60% of people with type 2 diabetes have at least 1 complication because of diabetes

( > 50% before or at diagnosis)

Complications at Diagnosis

Adults with complications at diagnosis of T2D (%)

- Ischemic heart disease: 40%
- Myocardial infarction: 10%
- PAD: 10%
- Microalbuminuria: 20%
- Retinopathy: 5%
- Impaired foot sensitivity: 50%

### JEOPARDY

<table>
<thead>
<tr>
<th>What’d You Mean It’s Broke?</th>
<th>Just my Type.</th>
<th>It’s the part of the new plan, Stan.</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

**Double Jeopardy**
Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet: Circa 2008

- Impaired Insulin Secretion (Islet b-cell)
- Increased Glucagon Secretion (Islet a-cell)
- Increased Hepatic Glucose Production
- GI tract/Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

Egregious Eleven – Circa 2016

1) Pancreatic β-cell
   - ↓ β-cell function
   - ↓ β-cell mass
   - ↓ amylin

2) ↓ incretin effect

3) α-cell defect
   - ↑ glucagon

4) Adipose
   - ↑ lipolysis

5) Muscle
   - ↓ uptake

6) Liver
   - ↑ glucose production

7) Brain
   - ↑ appetite
   - ↓ morning dopamine

8) Colon/biome
   - abnormal microbiota
   - ↓ GLP-1 production

9) Stomach and small intestine
   - ↑ glucose absorption

10) ↓ immune dysregulation / inflammation

11) Kidney
    - ↑ glucose reabsorption

GI tract

B-cell decline in Pre-diabetes and T2DM

DeFronzo RA. Diabetes. 2009:58(4)
Pathways that lead to B-cell Dysfunction

• The following contribute to b-cell dysfunction
  • Insulin resistant organs
    • Liver
      • Increased lipids exposure can lead to b-cell dysfunction
    • Muscle
    • Adipose tissue
      • Increased lipids exposure can lead to b-cell dysfunction
  
• Other organs
  • Brain
  • Colon
  • Immune system
B-Cell Loss is Responsible for Hyperglucagononemia in T2DM

-- Beta cells outnumber alpha cells in healthy subjects.
-- Alpha cell mass is not altered by T2DM
-- As T2DM progresses, the ratio of alpha to beta cells increases.

The Role of the Kidney in Diabetes

• Normal renal threshold is 180 mg/dl

• As blood glucose increases, the kidney reabsorbs the glucose, so it will not spill into the urine.
  • A1c of 6.5% -- renal threshold is ~ 205 mg/dl
  • A1c of 9% -- renal threshold is ~ 260 mg/dl

DeFronzo RA. Diabetes. 2009;58(4):773-795
Gut Microbiome

• Gut microbiome role in digestion
  • Strengthens immune system
    • Prevents infections

• Antibiotic use may increase risk of T2DM
  • Kill good bacteria – allowing bad bacteria to dominate GI tract
    • Alters nutrient absorption and metabolism

• Pre/Probiotics may address this mediator of hyperglycemia

Presented at ENDO 2016. Endocrine Society. Early childhood antibiotics may change gut microbes and lead to adolescent prediabetes.
Environmental Factors

• Endocrine disruptors
  • Food additives
  • Abnormal gut biome
  • Ingested advanced glycation end products

• Concern that some environmental factors may alter genotype in reproductive cells
  • Diabetes genetic inheritance

Presented at ENDO 2016. Endocrine Society.
Early childhood antibiotics may change gut microbes and lead to adolescent prediabetes.
Inflammation in Diabetes

• Systemic low grade inflammation in:
  • Type 1
  • Type 1.5
  • Type 2

• Endoplasmic stress due to increased metabolic demand for insulin.

• Early studies show incretin hormones exert anti-inflammatory affects.
  • E.g. DDP-4i may delay progression of type 1.5
Natural History of Type 2 Diabetes

Years from diagnosis

-10  -5  0  5  10  15

Onset  Diagnosis

Insulin resistance

Insulin secretion

Postprandial glucose

Fasting glucose

Macrovascular complications

Microvascular complications

Pre-diabetes

Type 2 diabetes

Insulin Resistance

• Major defect in individuals with pre-diabetes/T2DM
• Reduced biological response to insulin
• Closely associated with obesity
• Associated with cardiovascular risk
• Type 1 diabetes patients can be insulin resistant as well
• Type 1.5 has also been called
  • Latent Autoimmune Diabetes in Adults (LADA)
  • Latent onset type 1 diabetes

• Presentation:
  • Adult age
  • Presence of diabetes associated auto-immune antibodies (DAA’s)
    • ≥ 2 DAA’s often found in younger adults
  • Lack of insulin requirement at diagnosis

Pozzilli P and Dimario U. Diabetes Care 24:1460-1467, 2001
Type 1 Vs. Type 1.5

Multiple autoantibodies
Marked loss of insulin
On insulin therapy
HLA DR4-DQ8
High heritability

Single autoantibodies
Less marked loss of insulin
Not always on insulin therapy
HLA DR3-DQ2 / TCF7L2
Low heritability

## Comparisons of Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>LADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies</td>
<td>ICA, GADA, IA2, insulin antibodies</td>
<td>None</td>
<td>ICA, GADA</td>
</tr>
<tr>
<td>Require insulin?</td>
<td>Yes</td>
<td>No</td>
<td>Not initially</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Children and Adults</td>
<td>Children and Adults</td>
<td>Adults</td>
</tr>
<tr>
<td>Possess high risk genes?</td>
<td>Yes</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>No – (However, is possible)</td>
<td>Yes</td>
<td>Possible, not always</td>
</tr>
<tr>
<td>Therapy</td>
<td>Lifestyle, Insulin and potentially other non-insulin agents adjunctively</td>
<td>Lifestyle, Insulin and non-insulin agents</td>
<td>Lifestyle, non-insulin agents initially, then insulin</td>
</tr>
</tbody>
</table>
Type 3C Diabetes

- **T3cDM - pancreatogenic diabetes,**
  - diabetes caused by disease of the exocrine pancreas
  - destruction of islet cells by pancreatic inflammation
    - Pancreatitis
    - Exocrine pancreatic insufficiency (EPI)

- Any patient with chronic pancreatitis should be monitored for type 3c diabetes.
  - The prevalence with established dx of chronic pancreatitis is up to 70%
  - For chronic calcific pancreatitis up to 90%

*World J Gastroenterol*. 2013 Nov 14; 19(42): 7276–7281
Type 3C Diabetes

- Frequently misclassified or difficult to differentiate from T1DM or T2DM.
  - Often co-exists with T2DM.
    - Impaired b-cell function
    - Impaired GLP-1
    - Glucose intolerance
    - Insulin resistance
  - Progressive nutrient maldigestion
  - Malnutrition
  - Elevated pancreatic polypeptide levels

World J Gastroenterol. 2013 Nov 14; 19(42): 7276–7281
Classification and Treatment

• Leaders in Diabetes are calling for a change in how diabetes is classified
  • Focus should be β-cell centric
    • Opposed to Type 1, Type 1.5, Type 2, monogenic, etc.

• Abnormal or genetically pre-disposed B-cells lead to:
  • Insulin resistance
  • Susceptibility to environmental influences
  • Immune dysregulation
    • Inflammation

B-cell Centric Model

Type 1
Type 1.5
Type 2

Age
Not obese
HLA DQB1
Auto-antibodies
T-cells
Insulin treatment

Metabolic syndrome
TCF7L2
FTO
Systemic inflammation
C-peptide

First line: Metformin + comprehensive lifestyle (weight management & physical activity)

**Established ASCVD or CKD**
- If A1c above target:
  - GLP-1 RA with proven CVD benefit
  - SGLT-2i with proven CVD benefit if eGFR adequate
  - GLP-1 RA with proven CVD benefit if SGLT-2i contraindicated or eGFR not adequate

**Without established ASCVD or CKD**
- Need to minimize hypoglycemia:
  - DPP-4i
  - GLP-1 RA
  - SGLT-2i
  - TZD
- If A1c above target:
  - GLP-1 RA with good efficacy for weight loss

**Cost is a major issue**
- SU
- TZD

**Need to minimize weight gain or promote weight loss**
- GLP-1 RA
- SGLT-2i

**If A1c above target**
- GLP-1 RA
- DPP-4i
- GLP-1-RA
- TZD

**Adapted from:** Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2018. Diabetes Care. 2019;42(suppl 1).
SGLT-2 Inhibitors

1) ↓ renal glucose reabsorption in proximal tubule of kidney
2) Some ↓ in body fat (possibly due to SGLT-1 inhibition)

First line: Metformin + comprehensive lifestyle (weight management & physical activity)

### Established ASCVD or CKD
- **ASCVD**
  - GLP-1 RA with proven CVD benefit
  - SGLT-2i with proven CVD benefit if eGFR adequate
- **HF or CKD**
  - SGLT-2i with evidence of reducing HF and/or CKD, if eGFR adequate

### Without established ASCVD or CKD
- **GLP-1 RA with proven CVD benefit**
- **SGLT-2i with proven CVD benefit if eGFR adequate**

#### If A1c above target
- **DPP-4i**
- **GLP-1 RA**
- **SGLT-2i**
- **TZD**

#### Need to minimize hypoglycemia
- GLP-1 RA with good efficacy for weight loss
- SGLT-2i

#### Need to minimize weight gain or promote weight loss
- GLP-1 RA with good efficacy for weight loss
- SGLT-2i

#### Cost is a major issue
- **SU**
- **TZD**

#### If A1c above target
- SGLT-2i
- GLP-1 RA with good efficacy for weight loss

### If A1c above target
- Consider adding the other class (GLP-1-RA or SGLT-2i)
- **DPP-4i**
- **Basal insulin**
- **TZD**
- **SU**

### Avoid TZD
- Consider adding the other class (GLP-1-RA or SGLT-2i)
- **DPP-4i** (not saxagliptin)
- **Basal insulin**
- **SU**

Adapted from: Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2018. Diabetes Care. 2019;42(suppl 1).
## SGLT-2 Inhibitors: Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
<th>Ertugliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy (A1c lowering)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>↓ 0.77 - 1.03%</td>
<td>↓ 0.8 – 0.9%</td>
<td>↓ 0.7 – 0.8%</td>
<td>↓ 0.7 – 0.8%</td>
</tr>
<tr>
<td>Combination</td>
<td>↓ 0.79 - 0.94%</td>
<td>↓ 0.7 – 0.8%</td>
<td>↓ 0.7 – 0.8%</td>
<td>↓ 0.7 – 0.9%</td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100-300 mg</td>
<td>5-10 mg</td>
<td>10-25 mg</td>
<td>5-15 mg</td>
</tr>
<tr>
<td></td>
<td>once daily</td>
<td>once daily</td>
<td>once daily</td>
<td>once daily</td>
</tr>
<tr>
<td><strong>Renal dose adjustment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce dose if:</td>
<td>eGFR 45-59:</td>
<td>Not recommended if eGFR 30-60</td>
<td>No recommendation</td>
<td>Not recommended if eGFR 30-60</td>
</tr>
<tr>
<td></td>
<td>100 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraindicated if:</td>
<td>eGFR &lt;45ml/min</td>
<td>eGFR &lt;30ml/min</td>
<td>eGFR &lt;30ml/min</td>
<td>eGFR &lt;30ml/min</td>
</tr>
</tbody>
</table>

The Next Generation of SGLT2 Inhibitors
Sotagliflozin (LX4211) for type 1 and type 2 diabetes

SGLT-1 is a transporter responsible for glucose and galactose absorption in the GI tract and glucose reabsorption in the kidneys (though to a lesser extent than SGLT-2).

PCT = proximal convoluted tubule; PST = proximal straight tubule
Neurotransmitter Dysfunction

GLP-1 RA

1) Enhances appropriate pancreatic beta cell (insulin and amylin) secretion
2) Pancreatic alpha cell (glucagon) suppression
3) Decrease liver glucose production
4) Increase brain satiety
5) Slows gastric emptying time
6) Increase insulin uptake in peripheral tissue via weight loss

First line: Metformin + comprehensive lifestyle (weight management & physical activity)

- **Established ASCVD or CKD**
  - **ASCVD**
    - GLP-1 RA with proven CVD benefit
    - SGLT-2i with proven CVD benefit if eGFR adequate
    - If A1c above target
  - **HF or CKD**
    - GLP-1 RA with proven CVD benefit if SGLT-2i contraindicated or eGFR not adequate
    - If A1c above target
  - Consider adding the other class (GLP-1-RA or SGLT-2i)
  - DPP-4i
  - Basal insulin
  - TZD
  - SU
  - Avoid TZD
  - Consider adding the other class (GLP-1-RA or SGLT-2i)
  - DPP-4i (not saxagliptin)
  - Basal insulin
  - SU

- **Without established ASCVD or CKD**
  - **Need to minimize hypoglycemia**
    - DPP-4i
    - GLP-1 RA
    - SGLT-2i
    - TZD
    - If A1c above target
  - **Need to minimize weight gain or promote weight loss**
    - GLP-1 RA with proven CVD benefit
    - SGLT-2i
    - With evidence of reducing HF and/or CKD, if eGFR adequate
    - If A1c above target
    - GLP-1 RA with evidence of reducing HF and/or CKD, if eGFR adequate
    - SGLT-2i with evidence of reducing HF and/or CKD, if eGFR adequate
    - If A1c above target
    - GLP-1 RA with proven CVD benefit
    - If SGLT-2i contraindicated or eGFR not adequate
    - If A1c above target

- **Cost is a major issue**
  - SU
  - TZD
  - If A1c above target
  - SU
  - TZD
  - If A1c above target
  - SU
  - TZD
  - Basal insulin
  - With the lowest cost

Adapted from: Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2018. Diabetes Care. 2019;42(suppl 1).
### Differences in GLP-1 RA

<table>
<thead>
<tr>
<th></th>
<th>Exenatide BID</th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Exenatide QW</th>
<th>Dulaglutide</th>
<th>Semaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td>Short-acting</td>
<td>Short-acting</td>
<td>Long-acting</td>
<td>Long-acting</td>
<td>Long-acting</td>
<td>Long-acting</td>
</tr>
<tr>
<td><strong>Twice daily</strong></td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once weekly</td>
<td>Once weekly</td>
<td>Once weekly</td>
</tr>
<tr>
<td><strong>Once daily</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 &amp; 10 mcg</strong></td>
<td>5 &amp; 10 mcg</td>
<td>10 &amp; 20 mcg</td>
<td>0.6, 1.2 &amp; 1.8 mg</td>
<td>2 mg</td>
<td>0.75 &amp; 1.5 mg</td>
<td>0.25, 0.5 &amp; 1.0 mg</td>
</tr>
<tr>
<td><strong>within 30-60 min of am/pm meal</strong></td>
<td>within 30-60 min of am/pm meal</td>
<td>within 60 min of same meal</td>
<td>0.6mg initially then ↑ to 1.2 mg.</td>
<td></td>
<td>0.25 mg initially then ↑ to 0.5mg</td>
<td>Can ↑ to 1.0 mg if needed</td>
</tr>
<tr>
<td><strong>within 60 min of same meal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>0.6mg initially then ↑ to 1.2 mg.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Can ↑ to 1.8 mg if needed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Max dose</strong></td>
<td>10mcg BID</td>
<td>20mcg daily</td>
<td>1.8mg daily</td>
<td>2mg weekly</td>
<td>1.5mg weekly</td>
<td>1.0mg weekly</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>2-4 hours</td>
<td>2-4 hours</td>
<td>13 hours</td>
<td>5 days</td>
<td>5 days</td>
<td>7 days</td>
</tr>
<tr>
<td><strong>Homology to GLP-1</strong></td>
<td>53%</td>
<td>50%</td>
<td>97%</td>
<td>53%</td>
<td>90%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td>44%</td>
<td>69.8%</td>
<td>8.6%</td>
<td>44%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Renal dosing:</strong></td>
<td>&lt;30 not recommended</td>
<td>&lt;15 avoid</td>
<td>No adjustment</td>
<td>&lt;30 not recommended</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td><strong>(eGFR - mL/min/1.73 m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>&lt;30 not recommended</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>15–59 use caution and monitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>&lt;30 not recommended</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No adjustment</strong></td>
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<td></td>
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</tbody>
</table>

## CV Effects of Diabetes Medications

<table>
<thead>
<tr>
<th></th>
<th>ASCVD</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Potential benefit</td>
<td>Neutral</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Benefit (cana, empa)</td>
<td>Benefit (cana, empa)</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>lixisenatide, exenatide XR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benefit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>liraglutide</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Neutral</td>
<td>Potential risk (saxa, alo)</td>
</tr>
<tr>
<td>TZDs</td>
<td>Potential benefit (pioglitazone)</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

DPP4 Inhibitors (Gliptins)

1) Inhibits DPP-4 enzyme in the GI tract that breaks down GLP-1 resulting in ↑ endogenous GLP-1.

2) Enhances appropriate pancreatic beta cell (insulin and amylin) secretion

3) Pancreatic alpha cell (glucagon) suppression

4) ↓ liver glucose production

First line: Metformin + comprehensive lifestyle (weight management & physical activity)

### Established ASCVD or CKD

<table>
<thead>
<tr>
<th>ASCVD</th>
<th>HF or CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA with proven CVD benefit</td>
<td>SGLT-2i with proven CVD benefit if eGFR adequate</td>
</tr>
<tr>
<td>SGLT-2i with evidence of reducing HF and/or CKD, if eGFR adequate</td>
<td>------- or -------</td>
</tr>
<tr>
<td>GLP-1 RA with proven CVD benefit If SGLT-2i contraindicated or eGFR not adequate</td>
<td></td>
</tr>
</tbody>
</table>

- **If A1c above target**
  - Consider adding the other class (GLP-1-RA or SGLT-2i)
  - DPP-4i
  - Basal insulin
  - TZD
  - SU

### Without established ASCVD or CKD

#### Need to minimize hypoglycemia

**DPP-4i**

- GLP-1 RA
- SGLT-2i
- TZD

**If A1c above target**

- SGLT-2i Or TZD
- SGLT-2i Or TZD
- GLP-1-RA Or DPP-4i Or TZD
- SGLT-2i Or DPP-4i Or GLP-1-RA

#### Need to minimize weight gain or promote weight loss

**GLP-1 RA** with good efficacy for weight loss

**SGLT-2i**

- **If A1c above target**
  - SGLT-2i
  - GLP-1 RA with good efficacy for weight loss

**Cost is a major issue**

- **SU**
- **TZD**

**If A1c above target**

- **TZD**
- **SU**

**Basal insulin With the lowest cost**

Adapted from: Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2018. Diabetes Care. 2019;42(suppl 1).
## DPP-4 Inhibitors: Comparisons

<table>
<thead>
<tr>
<th></th>
<th>sitagliptin</th>
<th>saxagliptin</th>
<th>linagliptin</th>
<th>alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose/frequency</strong></td>
<td>100 mg</td>
<td>5 mg</td>
<td>5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>once daily</td>
<td>once daily</td>
<td>once daily</td>
<td>once daily</td>
</tr>
<tr>
<td><strong>Efficacy (A1C lowering): monotherapy</strong></td>
<td>↓ 0.6%</td>
<td>↓ 0.7%</td>
<td>↓ 0.4%</td>
<td>↓ 0.8%</td>
</tr>
<tr>
<td><strong>Efficacy (A1C lowering): combination therapy</strong></td>
<td>↓ 0.7%</td>
<td>↓ 1.2%</td>
<td>↓ 0.7%</td>
<td>↓ 0.9%</td>
</tr>
<tr>
<td><strong>Renal dosing</strong></td>
<td>50 mg daily</td>
<td>2.5 mg daily</td>
<td><strong>No dose adjustment necessary</strong></td>
<td>12.5 mg daily</td>
</tr>
<tr>
<td></td>
<td>(moderate)</td>
<td>(moderate-severe)</td>
<td></td>
<td>(moderate)</td>
</tr>
<tr>
<td></td>
<td>25 mg daily</td>
<td></td>
<td>6.25 mg daily</td>
<td>(severe)</td>
</tr>
<tr>
<td><strong>Approximate ex Vivo DPP-4 Inhibition, % (maximum)</strong></td>
<td>97</td>
<td>80</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

Januvia® (sitagliptin). Prescribing information.
Onglyza® (saxagliptin). Prescribing information.
Tradjenta® (linagliptin). Prescribing information.
Nesina™ (alogliptin). Prescribing information.
Sulfonylureas

- **Impaired Insulin Secretion**
- **Increased Glucagon Secretion**
- **Increased Hepatic Glucose Production**
- **Decreased Glucose Uptake**
- **Increased Lipolysis**
- **Increased Glucose Reabsorption**
- **Neurotransmitter Dysfunction**

1. Stimulates pancreatic beta cell (insulin) secretion

First line: Metformin + comprehensive lifestyle (weight management & physical activity)

Established ASCVD or CKD

<table>
<thead>
<tr>
<th>ASCVD</th>
<th>HF or CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA with proven CVD benefit</td>
<td>SGLT-2i with proven CVD benefit if eGFR adequate</td>
</tr>
<tr>
<td>SGLT-2i with evidence of reducing HF and/or CKD, if eGFR adequate</td>
<td>---------- or ----------</td>
</tr>
<tr>
<td>GLP-1 RA with proven CVD benefit if SGLT-2i contraindicated or eGFR not adequate</td>
<td></td>
</tr>
</tbody>
</table>

If A1c above target

Consider adding the other class (GLP-1-RA or SGLT-2i)
DPP-4i
Basal insulin
TZD
SU

Without established ASCVD or CKD

<table>
<thead>
<tr>
<th>Need to minimize hypoglycemia</th>
<th>Need to minimize weight gain or promote weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4i GLP-1 RA SGLT-2i TZD</td>
<td>GLP-1 RA with good efficacy for weight loss</td>
</tr>
</tbody>
</table>

Cost is a major issue

SU TZD
If A1c above target

If A1c above target

Avoid TZD
Consider adding the other class (GLP-1-RA or SGLT-2i)
DPP-4i (not saxagliptin)
Basal insulin
SU

SGLT-2i
If A1c above target

SGLT-2i GLP-1 RA
If A1c above target

SGLT-2i
If A1c above target

GLP-1 RA with good efficacy for weight loss

Basal insulin
With the lowest cost

Adapted from: Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2018. Diabetes Care. 2019;42(suppl 1).
TZD's

1) ↑ insulin uptake in peripheral tissue
2) ↑ free fatty acid utilization (conversion of bad fat to good fat)

First line: Metformin + comprehensive lifestyle (weight management & physical activity)

Established ASCVD or CKD

<table>
<thead>
<tr>
<th>ASCVD</th>
<th>HF or CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA with proven CVD benefit</td>
<td>SGLT-2i with evidence of reducing HF and/or CKD, if eGFR adequate</td>
</tr>
<tr>
<td>GLP-1 RA with proven CVD benefit if eGFR adequate</td>
<td>SGLT-2i</td>
</tr>
<tr>
<td>If A1c above target</td>
<td>If A1c above target</td>
</tr>
</tbody>
</table>

Consider adding the other class (GLP-1-RA or SGLT-2i)

DPP-4i

Basal insulin

TZD

SU

If A1c above target

Avoid TZD

Consider adding the other class (GLP-1-RA or SGLT-2i)

DPP-4i (not saxagliptin)

Basal insulin

SU

Without established ASCVD or CKD

Need to minimize hypoglycemia

DPP-4i

GLP-1 RA

SGLT-2i

TZD

If A1c above target

Need to minimize weight gain or promote weight loss

GLP-1 RA with good efficacy for weight loss

SGLT-2i

If A1c above target

Cost is a major issue

SU

TZD

If A1c above target

Basal insulin

With the lowest cost

Adapted from: Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2018. Diabetes Care. 2019;42(suppl 1).
Insulin

1) Mimics pancreatic beta cell (insulin) secretion
2) Pancreatic alpha cell (glucagon) suppression
3) ↓ liver glucose production
4) ↑ insulin uptake in peripheral tissue
5) ↑ free fatty acid utilization

First line: Metformin + comprehensive lifestyle (weight management & physical activity)

Established ASCVD or CKD

- **GLP-1 RA with proven CVD benefit**
- **SGLT-2i with proven CVD benefit if eGFR adequate**

Without established ASCVD or CKD

- **Need to minimize hypoglycemia**
  - DPP-4i
  - GLP-1 RA
  - SGLT-2i
  - TZD
  - If A1c above target

- **Need to minimize weight gain or promote weight loss**
  - GLP-1 RA with good efficacy for weight loss
  - SGLT-2i
  - If A1c above target

- **Cost is a major issue**
  - SU
  - TZD
  - If A1c above target

- **Basal insulin With the lowest cost**

- **Avoid TZD Consider adding the other class (GLP-1-RA or SGLT-2i) DPP-4i (not saxagliptin)**

Adapted from: Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes -2018. Diabetes Care. 2019;42(suppl 1).
<table>
<thead>
<tr>
<th>21st Century Type 1</th>
<th>Name that Trial</th>
<th>Patient-pourri</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>600</td>
<td>600</td>
<td>600</td>
</tr>
</tbody>
</table>

Final Jeopardy
Empagliflozin Clinical Data on Safety & Efficacy
(5 trials that vary)

• Design – open label vs placebo RCT
• Duration 4-8 weeks
• Δ A1C ~-0.3-0.5 %
• Δ Wt ~-1.5-2.6 kg
• Δ TDD insulin range 0-~9 units
• BP, eGFR, hypoglycemia
• DKA 0-2 episodes

Warnes et al. Diabetes Ther 2018;9:1831-1851
Canagliflozin Clinical Data on Safety & Efficacy
(4 trials that vary)

• Design – open label vs placebo RCT
• Duration up to 18 weeks
• A1C reduction ≥ 0.4 %*
• Δ Wt ~-2.6-4.2 kg*
• Δ TDD insulin range 0-~8 units*
• BP, eGFR, hypoglycemia
• DKA 0-12 episodes

SGLT-2 Inhibitors in Type 1 Diabetes

Dapagliflozin Clinical Data on Safety & Efficacy
(4 trials that vary)

• Design – proof of concept vs placebo RCT
• Duration up to 24 weeks
• Δ A1C ~-0.5 %*
• Δ Wt ~-2-3 kg*
• Δ TDD insulin range ~ -7-8 units*
• BP, eGFR, hypoglycemia, DKA no difference
• ↑genital infections

2010
2014
2016
2017
2019
2000’s
1998
1987
1985

10 T1D non-obese
Metformin x7days added to insulin improved insulin sensitivity.

UKPDS in T2D
Metformin led to less wt gain, less hypoglycemia, 33% ↓ risk of MI

Systematic Review
Metformin in T1D ↓ insulin dose, wt loss, A1C inconsistent

CIMT trial
Insulin + metformin, T2D no ↓ in cIMT

CAMERA trial
CVD but no diabetes, metformin x18mths no change in cIMT

REMOVAL trial
T1D + ≥3 CVD risk factors, met x 3yrs - ↓ wt, ↓ insulin dose, maximal cIMT ↓

8 T1D
Metformin x 3 weeks – no change in FPG, wt, insulin dosing

ADA Guideline
Adding metformin...may ↓ insulin and improve metabolic control in poorly controlled T1D

Multiple trials
RCTs with small numbers showing ↓ insulin doses, ↓ A1C and LDL

GLP-1 RA’s in Type 1 Diabetes

8 trials from 2014-2018

• Exenatide (2) Liraglutide (6)
• Duration 12-52 weeks
• Participants 11-1398
• A1C reduction 0-0.6%
• Weight reduction 2.2-6.8 kg*
• Mixed GI adverse events, hypoglycemia, hyperglycemia with ketosis (1.8mg liraglutide – 2 cases)

Liraglutide in Type 1 Diabetes

Abstract presented at ADA’s 78th Scientific Session in June 2018 – Dandona et al

• 52 week, double-blind, placebo, RCT
• T1DM, N=46 (avg age 47.6 yrs)
• Baseline A1C 7.82, BMI 28.9
• 1.8mg liraglutide daily vs placebo
• CGM x 4 wks before and 4 wks after treatment

Liraglutide in Type 1 Diabetes

- A1C reduction ~0.4-0.7%
- Weekly avg BG ↓ ~11-19 mg/dl
- Fasting weekly BG ↓ ~8-15 mg/dl
- Weight loss ~2.5-3 kg
- SBP ↓ ~6-12 mmHg
- DBP ↓ ~4-6
- Total insulin dose did not change
- No difference in hypoglycemia or % time <70mg/dl

Pramlintide (Symlin®)

• Only FDA approved adjunctive therapy for T1DM
• When added to insulin
  • Reduction in post prandial glucose excursions
  • Reduction in weight
  • Variable A1C reduction
• Black Box Warning – Severe Hypoglycemia
Other Agents in Type 1 Diabetes

• Bromocriptine (Cycloset)
• Colesevelam (Welchol)
• DPP-4 inhibitors
• Thiazolidinediones
Clinical Trials
REMOVAL Trial

• ≥40yrs T1DM with at least 3 CVD risk factors
• Double-blind, placebo controlled trial
• 23 diabetes clinics in 5 countries x 3 years
• Metformin 1000mg po BID or placebo

1° - Averaged mean far wall carotid artery intima-media thickness (cIMT)
  - Quantified annually for 3 years

2° - A1C, LDL-C, eGFR, body wt, insulin dose, incident microalbuminuria and retinopathy, endothelial function

REMOVAL Trial

1° No significant differences

2° Reduction in weight*

Discontinuation rate - 27% metformin vs 12% placebo*
DEPICT-1 Trial

• T1DM, A1C 7.5-10%, insulin ≥ 12 months
• Double-blind, placebo controlled Phase 3
• 52 weeks of dapagliflozin 5mg, 10mg, or placebo as add-on to adjustable insulin

• A1C, weight, total daily insulin dose

DEPICT-1 Trial

Sotagliflozin (Zynquista™)

• Investigational oral dual SGLT1/2 inhibitor

• North American inTandem1 trial

• European inTandem2 trial

• The target FDA action date under the Prescription Drug User Fee Act (PDUFA) is anticipated to be March 22, 2019

Role of SGLT-1/SGLT-2 Inhibitors in Type 1 Diabetes

Insulin-independent mechanism

SGLT-2 primarily in

SGLT-1 found in
inTandem1 Trial

• T1DM, A1C 7.0-11%
• Double-blind, placebo controlled Phase 3
• Sotagliflozin 200mg, 400mg, or placebo added after 6wks optimization of insulin

• Δ A1C from baseline at 24 weeks
• A1C, weight, safety at 52 weeks

**inTandem1 Trial**

- **24-Week Difference from PBO**
  - -0.36% (-0.45, -0.27); *P* < 0.001
  - -0.41% (-0.50, -0.32); *P* < 0.001
- **52-Week Difference from PBO**
  - -0.25% (-0.37, -0.14); *P* < 0.001
  - -0.31% (-0.43, -0.20); *P* < 0.001

Baseline = 7.5% - 7.6%

**Screening = 8.2% - 8.3%**

**DB CT—IDMC, No HbA1c**

**DB EXT—No IDMC, HbA1c**

inTandem1 Trial

inTandem1 Trial

24-Week Difference from PBO
-2.35 kg (-2.85, -1.85); P<0.001
-3.45 kg (-3.95, -2.94); P<0.001

52-Week Difference from PBO
-3.14 kg (-3.81, -2.46); P<0.001
-4.32 kg (-5.00, -3.64); P<0.001

Baseline = 87 kg

Week

inTandem1 Trial

Figure 3—Sotagliflozin inTandem1 interstitial glucose. 24-h CGM tracing consisting of interstitial glucose readings collected every 5 min. Solid lines represent mean values from each treatment group (light purple, placebo [n = 45]; light blue, sotagliflozin 200 mg [n = 44]; dark blue, sotagliflozin 400 mg [n = 47]); shaded areas represent ± 1 SEM. The figure shows data collected from midnight. Actual start time for 24-h readings may vary for each subject. Top of target CGM range = 10.0 mmol/L (180 mg/dL).

Henry

82 year old man, divorced, lives alone, drives, is in the PACE program and uses a Medacube

PMH: T2DM x 10 yrs, HTN, Stage 3 CKD, BPH, Afib, pacemaker, osteoporosis, cognitive deficit
2002 – MI, Stent, Valve replacement, CABG

Current prescribed diabetes regimen:
Glargine insulin 34 units subcut daily
Aspart insulin 5-10 units subcut with meals
(history of GI intolerance to metformin)

Current diabetes regimen at home:
Glargine insulin 25 units subcut daily

A1C 8.9%; eGFR 43ml/min; BP 140/60mmHg
BMI 26.4
LEADER Trial

• 9340 adults with T2DM, A1C ≥ 7.0%,
• CVD or CKD or HF and ≥50 years of age
• CV risk and ≥ 60 years of age
• Liraglutide 1.8mg once daily or placebo

1° MI, Stroke or CV death

Population: Mean age 64.3 yrs and diabetes duration 12 years, 81.3% with prior CVD, 76% metformin, 72% statin, mean baseline A1C 8.7%

Clinical Outcomes with Liraglutide

**LEADER**  
(N=9340)

Median follow-up: 3.5 years

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.85 (0.74-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66-0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.86 (0.73-1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.78 (0.67-0.92)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

SUSTAIN-6 Trial

- 3297 adults with T2DM, A1C ≥ 7.0%,
- CVD or CKD or HF and ≥50 years of age
- CV risk and ≥ 60 years of age
- Semaglutide 0.5mg and 1mg/week or placebo

1° MI, Stroke or CV death

Population: Mean age 64.6 yrs and diabetes duration 13.9 years, 60% with prior CVD, 73% metformin, 73% statin, mean baseline A1C 8.7%

Clinical Outcomes with Semaglutide

SUSTAIN 6 Results (N=3297)

Median follow-up: 2.1 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.74 (0.58-0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
<td>0.002</td>
</tr>
<tr>
<td>All-cause death, nonfatal MI, nonfatal stroke</td>
<td>0.77 (0.61-0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1.05 (0.74-1.50)</td>
<td>0.79</td>
</tr>
<tr>
<td>CV death</td>
<td>0.98 (0.65-1.48)</td>
<td>0.92</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.74 (0.51-1.08)</td>
<td>0.12</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.61 (0.38-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.65 (0.50-0.86)</td>
<td>0.003</td>
</tr>
<tr>
<td>Retinopathy complications</td>
<td>1.76 (1.11-2.78)</td>
<td>0.02</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>0.64 (0.46-0.88)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

EMPA-REG Trial

- 7020 adults T2DM A1C 7-10%, with CVD
- Empagliflozin 10mg, 25mg, or placebo

1° composite of CV death, nonfatal MI (excluding silent MI), or nonfatal stroke

Population: Mean age 63.1 yrs and diabetes duration 57% >10 years, 99% with prior CVD, 74% metformin, 77% statin, mean baseline A1C 8.1%

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard ratio (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.86 (0.74-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Secondary composite endpoint†</td>
<td>0.89 (0.78-1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.65 (0.50-0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for HF or CV death</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Renal Outcomes with Empagliflozin Over 3.2 Years

**EMPA-REG RENAL**
(N=7020)

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy or CV death</td>
<td>0.61 (0.55-0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>0.61 (0.53-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>0.62 (0.54-0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤45</td>
<td>0.56 (0.39-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
<td>0.45 (0.21-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death</td>
<td>0.54 (0.40-0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria*</td>
<td>0.95 (0.87-1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*In patients with normal albuminuria at baseline.

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; SCr, serum creatinine.

CANVAS & CANVAS-R Trial

• CANVAS 4330 + CANVAS-R 5812 = 10,142
• T2DM + CVD ≥ 30 yrs of age
• T2DM + >2 CVD risk factors ≥ 50 yrs of age
• Canagliflozin 100mg, up to 300mg, once daily or placebo

1° composite of CV death, nonfatal MI (excluding silent MI), or nonfatal stroke

Population: Mean age 63.3 yrs and diabetes duration 13.5 years, 65.6% with prior CVD, 77% metformin, 75% statin, mean baseline A1C 8.2%

Clinical Outcomes with Canagliflozin

CANVAS Program
(N=10,142)

Median follow-up: 2.4 years

<table>
<thead>
<tr>
<th>Event</th>
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<tr>
<td>Primary composite endpoint*</td>
<td>0.86 (0.75-0.97)</td>
<td>0.02†</td>
</tr>
<tr>
<td>CV death</td>
<td>0.87 (0.72-1.06)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.85 (0.69-1.05)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.71-1.15)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.89 (0.73-1.09)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>0.87 (0.69-1.09)</td>
<td></td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.67 (0.52-0.87)</td>
<td></td>
</tr>
<tr>
<td>CV death or HF hospitalization</td>
<td>0.78 (0.67-0.91)</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.87 (0.74-1.01)</td>
<td></td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>0.73 (0.67-0.79)</td>
<td></td>
</tr>
<tr>
<td>40% reduction in eGFR, renal replacement therapy, or renal death</td>
<td>0.60 (0.47-0.77)</td>
<td></td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI, or nonfatal stroke. †Superiority.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Ed

67 year old man, married, trying to retire
He has a very busy, stressful job that always has
snacks, treats, and food around the office

PMH: T2DM x 18 yrs, HTN, Afib, dyslipidemia,
chronic low back pain (inoperable), sleep apnea

Current diabetes regimen:
Glargine insulin 130 units subcut daily (split into 2 injections)
Lispro insulin 50 units subcut 3-4 times a day
Metformin 1000mg po BID
Exenatide extended-release 2mg subcut once a week

A1C 8.8%; eGFR >60ml/min
BMI 42; TC 168 HDL 32 LDL 81 Tg 283; Alb:Cr 11.8
Pioglitazone Data – 2 studies

• PROactive Study
  • 5238 adults T2DM, CVD, pioglitazone 15-45mg
  • lowered MACE (CV death, nonfatal myocardial infarction [MI], nonfatal stroke), which was the main secondary end point, by 16% (P = 0.027)

• ISIS Trial
  • 3876 adults recent ischemic stroke or TIA
  • Insulin resistance but NO diabetes
  • ↓ recurrent stroke and MI by 24%

Resurrection of Low-dose Pioglitazone

- Cardiovascular benefit
- Recurrent stroke
- All cause mortality
- Death, myocardial infarction, stroke

- Nonalcoholic Steatohepatitis (NASH) benefit
  - Resolution of NASH
  - Improved histology involving steatosis, lobular inflammation, hepatocellular ballooning and fibrosis
  - Decreased hepatic fat content measured by MRI

- Bladder Cancer harm
- Ever vs never use
- Low, moderate, high exposure
- Years of exposure (<1 year, 1-2 year, >2 years)

• The addition of 15mg daily of pioglitazone
  • A1C decreased from 8.8% to 6.3% over 9 month period
  • TDD insulin decreased by 75 units
  • Weight decreased 4.45kg
  • Sense of feeling full so eating less
  • Lipid panel pending
Sandy

62 year old woman, works at home, currently the legal guardian/parent for 18 month old grandson

PMH: T2D x 13 years, HTN, dyslipidemia, metabolic syndrome, h/o MI (2 years ago), chronic low back pain

Current diabetes regimen
Glargine insulin 60 units subcut BID
Glimepiride 4mg po daily
Metformin ER 1000mg po BID

A1C 8.2%; BP 134/82 mmHg; eGFR >60ml/min
TC 145 HDL 43 LDL 76 Tg 130; Alb:Cr 8.0
BMI 37.7; LFTs WNL
• Diabetes pathophysiology continues to evolve.
  • Accurate diagnosis of the type of diabetes is crucial to appropriate treatment.

• Optimal therapy should be individualized and include glucose lowering, CVD safety and related condition consideration.

• Pramlintide remains the only non-insulin pharmacologic agent approved for people with type 1 diabetes. Keep your eyes open for the SGLT-1 and 2 dual inhibitors.

• Utilize the evidence-based treatment algorithms when formulating a patient-centered diabetes treatment plan.