Individualizing Management of T2DM in the Hospital Setting to Reduce Macro and Microvascular Complications
Faculty

Richard E. Pratley, MD,
Medical Director, Florida Hospital Diabetes Institute
Senior Scientist and Diabetes Program Head,
Florida Hospital Translational Research Institute for Metabolism and Diabetes
Orlando, Florida
Faculty Disclosures

- Advisory Board / Consultant: AstraZeneca, Janssen, Lilly, Merck, Novo Nordisk, Sanofi
- Research Support: Janssen, Lexicon, Lilly, Merck, Novo Nordisk, Sanofi

Honoraria and fees directed toward a non-profit which supports education and research
Learning Objectives

- Summarize correlations between macro and microvascular complications of uncontrolled T2DM and hospitalization
- Evaluate the risk/benefit profiles of novel T2DM therapies in achieving glycemic control and reducing vascular complications
- Employ evidence-based strategies to individualize treatment for diverse patients with T2DM to achieve glycemic control and reduce hospitalizations from vascular complications
Diabetes and Its Complications

Introduction
Burden of Diabetes in the US

- Estimated incidence in 2015
  - 30.3 million with diagnosed diabetes*
  - 7.2 million undiagnosed
  - 84.1 million with prediabetes

- Increasing prevalence with rising overweight and obesity rates

- Significant risk for complications, including CHD, stroke, HT, depression, pain, polypharmacy, and functional disability

- Leading cause of new cases of blindness (among adults) and end-stage renal failure

*Approximately 1.25 million children and adults have type 1 diabetes.
CHD, congenital heart disease; HT, hypertension.

Available at: https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2017-508.pdf; Available at: http://www.diabetes.org/diabetes-basics/statistics/;
Vascular Complications of Diabetes

**Macrovascular**
- Peripheral vascular disease
- Ischemic heart disease
- Stroke

**Microvascular**
- Nephropathy
- Neuropathy
- Retinopathy
## Abnormalities of Vascular Function in Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Artery</th>
<th>Glomerular Capillary</th>
<th>Retinal Capillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow</td>
<td><img src="image1" alt="Artery Blood Flow" /></td>
<td><img src="image2" alt="Glomerular Capillary Blood Flow" /></td>
<td><img src="image3" alt="Retinal Capillary Blood Flow" /></td>
</tr>
<tr>
<td>Leukocyte adhesion</td>
<td><img src="image4" alt="Artery Leukocyte Adhesion" /></td>
<td><img src="image5" alt="Glomerular Capillary Leukocyte Adhesion" /></td>
<td><img src="image6" alt="Retinal Capillary Leukocyte Adhesion" /></td>
</tr>
<tr>
<td>Vascular permeability</td>
<td><img src="image7" alt="Artery Vascular Permeability" /></td>
<td><img src="image8" alt="Glomerular Capillary Vascular Permeability" /></td>
<td><img src="image9" alt="Retinal Capillary Vascular Permeability" /></td>
</tr>
<tr>
<td>Hemostasis</td>
<td><img src="image10" alt="Artery Hemostasis" /></td>
<td><img src="image11" alt="Glomerular Capillary Hemostasis" /></td>
<td><img src="image12" alt="Retinal Capillary Hemostasis" /></td>
</tr>
<tr>
<td>Proliferation</td>
<td><img src="image13" alt="Artery Proliferation" /></td>
<td><img src="image14" alt="Glomerular Capillary Proliferation" /></td>
<td><img src="image15" alt="Retinal Capillary Proliferation" /></td>
</tr>
<tr>
<td>Apoptosis</td>
<td><img src="image16" alt="Artery Apoptosis" /></td>
<td><img src="image17" alt="Glomerular Capillary Apoptosis" /></td>
<td><img src="image18" alt="Retinal Capillary Apoptosis" /></td>
</tr>
</tbody>
</table>

Prevalence of Vascular Complications in Diabetes

DM increases by 2-4 fold the risk of CAD (leading cause of morbidity and mortality in developed countries), stroke, PAD, and HF.

Patients with diabetes are up to 4 times more likely to have a stroke or die of heart disease.

Cardiovascular disease accounts for 50%-70% of all deaths in diabetes.

Heart disease is the leading cause of diabetes-related death in the US.

Diabetes in the Hospital Setting
Cause-specific Hospitalizations Among Patients with Diabetes

30-day Readmissions Among Patients with Diabetes

Inpatient Management
## Goals of Inpatient Diabetes Management

- **Prevent hypoglycemia and hyperglycemia**
- **Restore glycemic stability**
- **Initiate long-term antidiabetic treatment/optimize existing treatment**
- **Minimize the hospital stay**
- **Provide effective transitional care to prevent complications and readmission**

### ADA/AACE Recommended Glycemic Targets for ICU and Non-ICU Settings

<table>
<thead>
<tr>
<th>ICU</th>
<th>Non-ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initiate insulin therapy for persistent hyperglycemia (glucose &gt; 180 mg/dl)</td>
<td>• No specific guidelines for insulin initiation</td>
</tr>
<tr>
<td>• Treatment goal: For most patients, target a glucose level 140-180 mg/dl</td>
<td>• If treated with insulin:</td>
</tr>
<tr>
<td>• More stringent goals (110-140 mg/dl) may be appropriate for selected patients, if achievable without significant risk for hypoglycemia</td>
<td>• Pre-meal glucose &lt; 140 mg/dl</td>
</tr>
<tr>
<td></td>
<td>• Random glucose &lt; 180 mg/dl</td>
</tr>
<tr>
<td></td>
<td>• More stringent targets may be appropriate for patients with previously tight glycemic control</td>
</tr>
<tr>
<td></td>
<td>• Less stringent targets may be appropriate in patients with severe comorbidities</td>
</tr>
</tbody>
</table>

### ADA/AACE Recommended Glycemic Targets for ICU and Non-ICU Settings

<table>
<thead>
<tr>
<th>ICU</th>
<th>Non-ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initiate insulin therapy for persistent hyperglycemia (glucose &gt; 180 mg/dl)</td>
<td>• No specific guidelines for insulin initiation</td>
</tr>
<tr>
<td>• Treatment goal: For most patients, target a glucose level 140-180 mg/dl</td>
<td>• More stringent goals (110-140 mg/dl) may be appropriate for selected patients, if achievable without significant risk for hypoglycemia</td>
</tr>
<tr>
<td>• More stringent targets may be appropriate for patients with previously tight glycemic control</td>
<td>• Less stringent targets may be appropriate in patients with severe comorbidities</td>
</tr>
</tbody>
</table>

Many hospitals have adopted individual targets for hypoglycemia and hyperglycemia. Check with your medical staff.

ADA Recommendations for In-hospital Diabetes Management

- A1C for all patients with diabetes or hyperglycemia*
- Insulin infusions using validated written/computerized protocols that allow for predefined adjustments based on glycemic fluctuations and insulin dose
- Basal or basal plus bolus insulin correction for noncritically ill patients with poor oral intake or NPO
- Insulin with basal, nutritional, and correction components for noncritically ill patients and good nutritional intake

*If not obtained within last 3 months.
NPO, nothing by mouth.
ADA. Diabetes Care 2017; 40(S1):S120-S127.
ADA Recommendations for In-hospital Diabetes Management (Cont’d)

- Sole use of sliding scale insulin is strongly discouraged
- Established hypoglycemia management protocol
- An individualized plan for hypoglycemia prevention and treatment
- Medical record of hypoglycemic episodes
- Review of treatment regimen (change as needed to prevent further hypoglycemia)
- A structured, individualized discharge plan

ADA. Diabetes Care 2017;40(S1):S120-S127.
Factors Complicating Glucose Management in Hospitalized Patients

- Severity of illness
- Medications (eg, glucocorticoids)
- Inconsistent dietary intake
- Patient nutritional status
- Prevailing blood glucose concentration
- History and type of diabetes
- Pre-hospital diabetes treatment regimen

Pharmacologic Treatment of Hyperglycemia
## Non-insulin Antihyperglycemic Agents (AHA)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Average A1C Reduction</th>
<th>Potential Adverse Effects and Impact on Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>0.5% – 0.8%</td>
<td>Flatulence, diarrhea, abdominal bloating</td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>1.0% – 1.3%</td>
<td>Nausea, diarrhea, abdominal bloating; extended-release preparations have fewer GI adverse effects</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>0.5% – 0.9%</td>
<td>Headache, pancreatitis (rare)</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>0.8% – 2.0%</td>
<td>Nausea, vomiting, sense of fullness; weight loss of 2.2 – 8.8 lbs likely; pancreatitis (rare)</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>0.5% – 1.0%</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>0.5% – 0.9%</td>
<td>Increased urinary tract and genital infections, increased LDL; weight loss of 1.5 - 7.7 lbs is typical</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>0.4% – 1.2%</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5% – 1.4%</td>
<td>Weight gain, edema</td>
</tr>
</tbody>
</table>

DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter 2.
Mechanisms of Action of Non-insulin AHAs

**Pancreas**
- **Impaired Insulin Secretion**
  - Sulfonylureas
  - Glinides
  - DPP4-1
  - GLP-1 agonists
- **Increased Glucagon Secretion**
  - DPP4-1
  - GLP-1 agonists
  - Glucagon receptor antagonists

**Liver**
- **Increased Glucose Production**
  - Metformin
  - GK agonists
  - Glucagon receptor antagonists
- **Decreased Glucose Uptake**
  - TZDs
  - Metformin
  - Dual/Pan PPARs

**Muscle**
- **Increased Lipolysis**
  - TZDs
  - Metformin
  - Dual/Pan PPARs
  - 11βHSD-I
- **Decreased Incretin Effect**
  - DPP4-I
  - GLP-1 agonists
  - Glucagon receptor antagonist

**Adipose Tissue**
- **Increased Incretin Effect**
  - DPP4-I
  - GLP-1 agonists
  - Bile acid sequestrants
- **Increased Glucose Reabsorption**
  - SGLT2-I
- **Neurotransmitter Dysfunction**
  - Bromocriptine

**Gut**
- **Increased Glucose Reabsorption**
  - SGLT2-I

**Kidney**

**Brain**

Approach to AHA Selection for Patients with T2DM

- **Metformin** remains recommended first-line therapy
  - Use is often limited by development of diabetic nephropathy and GFR decline

- **Dual or triple therapy** is typically required to achieve glycemic goals as disease progression occurs
  - Combining complementary MOAs can help achieve additional reduction in A1c
  - Consider drug-specific and patient factors, including efficacy, hypoglycemia, weight change, CV effects, cost, administration, and renal effects

GFR, glomerular filtration rate; MOAs, mechanism of actions.

Antihyperglycemic Therapy in Adults with T2DM

ASCVD benefits = canagliflozin, empagliflozin, liraglutide, and possible metformin, pioglitazone.
CHF benefits = canagliflozin, empagliflozin; CHF risks – thiazolidinediones and possibly saxagliptin and alogliptin.

**Diabetes Care.** 2018 Jan; 41(supplement):S1-S2.

**Monotherapy**

Initiate metformin therapy if no contraindications* (See Table 8.1)

- A1C at target
  - Yes: Monitor A1C every 3-6 months
  - No: Assess medication-taking behavior
  - Consider Dual Therapy

- After 3 months of monotherapy?

**Dual Therapy**

Lifestyle Management + Metformin + Additional Agent

ASCVD?
- Yes: Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and Table 8.1)
- No: Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)
Targeting Vascular Outcomes in T2DM
Long-term Glycemic Control Improves Vascular Outcomes: UKPDS

Decrease per 1% Reduction in HbA1c

- Lower-extremity amputation or fatal PVD: -43%
- Microvascular disease: -37%
- Cataract extraction: -19%
- HF: -16%
- MI: -14%
- Stroke: -12%

Addition of EMPA to Standard Care Improves CV Outcomes and Mortality

**EMPA-REG Study**

### Primary Outcome

- **Placebo**
- **Empagliflozin**

**Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)**

*P*=.04 for superiority

### Death from Cardiovascular Causes

- **Placebo**
- **Empagliflozin**

**Hazard ratio, 0.62 (95% CI, 0.49–0.77)**

*P*<.001

EMPA, empagliflozin.

Addition of EMPA to Standard Care Improves CV Outcomes and Mortality

EMPA-REG Study

Death from Any Cause

Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P < .001

Placebo
Empagliflozin

Hospitalization for Heart Failure

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P = .002

Placebo
Empagliflozin

SGLT2 Inhibition Lowers the Risk of HF and Death

CVD-REAL Study

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Hazard Ratio (95% CI)</th>
<th>N</th>
<th># of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Truven Market Scan</td>
<td>0.55 (0.44, 0.69)</td>
<td>233,798</td>
<td>298</td>
</tr>
<tr>
<td>Norway National Registers</td>
<td>0.62 (0.49, 0.79)</td>
<td>25,050</td>
<td>278</td>
</tr>
<tr>
<td>Denmark National Registers</td>
<td>0.77 (0.59, 1.01)</td>
<td>18,468</td>
<td>167</td>
</tr>
<tr>
<td>Sweden National Registers</td>
<td>0.61 (0.45, 0.82)</td>
<td>18,378</td>
<td>191</td>
</tr>
<tr>
<td>UK CPRD/THIN</td>
<td>0.36 (0.12, 1.13)</td>
<td>10,462</td>
<td>16</td>
</tr>
<tr>
<td>Germany DPV</td>
<td>0.14 (0.03, 0.68)</td>
<td>2,900</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>0.61 (0.51, 0.73)</td>
<td>233,798</td>
<td>298</td>
</tr>
</tbody>
</table>

P-value for SGLT-2i vs. oGLD comparison: <.001
P-value for Heterogeneity: .169

All-cause death

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Hazard Ratio (95% CI)</th>
<th>N</th>
<th># of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Truven Market Scan</td>
<td>0.38 (0.29, 0.50)</td>
<td>143,264</td>
<td>250</td>
</tr>
<tr>
<td>Norway National Registers</td>
<td>0.55 (0.44, 0.68)</td>
<td>25,050</td>
<td>364</td>
</tr>
<tr>
<td>Denmark National Registers</td>
<td>0.46 (0.37, 0.57)</td>
<td>18,468</td>
<td>323</td>
</tr>
<tr>
<td>Sweden National Registers</td>
<td>0.47 (0.37, 0.60)</td>
<td>18,378</td>
<td>317</td>
</tr>
<tr>
<td>UK CPRD/THIN</td>
<td>0.73 (0.47, 1.15)</td>
<td>10,462</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>0.49 (0.41, 0.57)</td>
<td>143,264</td>
<td>250</td>
</tr>
</tbody>
</table>

P-value for SGLT-2i vs. oGLD comparison: <.001
P-value for Heterogeneity: .089

Hospitalization for HF

CVD, cardiovascular disease.
Treatment with CANA Improves CV, Renal, and Mortality Outcomes

CANVAS Program

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>myocardial infarction, or nonfatal stroke</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Death from cardiovascular stroke</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>0.60 (0.47–0.77)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td></td>
</tr>
</tbody>
</table>

CANA, canagliflozin.

Potential Pathways Associated with CV Effects of SGLT-2 Inhibitors

## Impact of Incretin-based Therapies on CV Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>GLP1RA</th>
<th>DPP-4I</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>• Reduced</td>
<td>• Reduced</td>
</tr>
<tr>
<td>Body weight</td>
<td>• Reduced</td>
<td>• Potential minor reduction (&lt;1 kg)</td>
</tr>
<tr>
<td>BP</td>
<td>• SBP lower (2-3 mmHg) in patients with HT • DBP less consistently affected</td>
<td>• No uniform lowering effect</td>
</tr>
<tr>
<td>HR</td>
<td>• 2–3 bpm rise</td>
<td>• No major effects reported</td>
</tr>
<tr>
<td>Lipids</td>
<td>• Lower triglycerides • Increased HDL cholesterol • Small reduction in LDL cholesterol</td>
<td>• No major effects on fasting lipoprotein patterns</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, spontaneous bacterial peritonitis; DBP, diastolic blood pressure; bpm, beats per minute.

# DPP-4 Inhibitors and CV Risk

<table>
<thead>
<tr>
<th>Clinical Trial Findings</th>
<th>AHA Investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral for CV risk factors</td>
<td>• Saxagliptin&lt;br&gt; • Alogliptin&lt;br&gt; • Sitagliptin&lt;br&gt; • Linagliptin</td>
</tr>
<tr>
<td>Increased risk for HF-related hospitalization</td>
<td>• Saxagliptin (significant)&lt;br&gt; • Alogliptin (nonsignificant trend)</td>
</tr>
</tbody>
</table>

In the absence of clear benefits regarding overall CV risk, further mechanistic clarification and caution is recommended for individuals at risk for CHF.

EXAMINE

- Hospitalization for Heart Failure (%)
  - Saxagliptin: 0, 1.1%, 1.9%, 3.5%
  - Placebo: 0, 0.6%, 1.3%, 2.8%

- HR 1.80 (1.29–2.55) \( P = .001 \)
- HR 1.46 (1.15–1.88) \( P = .002 \)

SAVOR-TIMI 53

- Cumulative Incidence of Events (%)
  - Placebo 120 events (15.7%)
  - Alogliptin 107 events (13.9%)

- HR 0.90 (95% CI 0.70–1.17)
CARMELINA Trial: Impact of Linagliptin on CV Safety and Kidney Outcomes

Patients (%) with CV Events, Decline in Kidney Function, or Hospitalization for HF - Linagliptin Compared to Placebo Added to Standard of Care. N=6980 patients randomized 1:1.

- CV Death, Non-fatal MI, Non-fatal Stroke: 12.4% (Linagliptin) vs 12.1% (Placebo)
- Decline in Kidney Function: 9.4% (Linagliptin) vs 8.8% (Placebo)
- Hospitalization for Heart Failure: 6.0% (Linagliptin) vs 6.5% (Placebo)

Data demonstrate no impact on cardiovascular (CV), heart failure, or renal events, even in those who already have kidney disease, when linagliptin is added to standard of care therapy.

CARMELINA Trial Results Summary. Available at: https://www.boehringer-ingelheim.com/CARMELINA.
Sitagliptin added on to usual care was NOT associated with increased risk for:

- MACE
- HF-related hospitalization
- Other AEs

MACE, major adverse cardiac events; AEs, adverse events.

Overview of the Impact of GLP-1R Agonists on CV Outcomes

## Risk Reduction in Four Completed Trials Showing CV Benefit

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Leader (10)</th>
<th>SUSTAIN-6 (11)</th>
<th>EMPA-REG Outcome (13,60)</th>
<th>CANVAS Program (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>9,340</td>
<td>3,297</td>
<td>7,020</td>
<td>10,142</td>
</tr>
<tr>
<td>Diabetes duration (years)*</td>
<td>64.3</td>
<td>64.6</td>
<td>63.1</td>
<td>63.3</td>
</tr>
<tr>
<td>Mean baseline A1C (%)</td>
<td>8.7</td>
<td>8.7</td>
<td>8.1</td>
<td>8.2</td>
</tr>
<tr>
<td>Mean placebo-corrected A1C difference (%)*</td>
<td>-0.4</td>
<td>-0.7 (0.5 mg dose)</td>
<td>-0.24 (10 mg dose)</td>
<td>-0.58</td>
</tr>
<tr>
<td>Median follow-up duration (years)</td>
<td>3.8</td>
<td>2.1</td>
<td>3.1</td>
<td>2.4</td>
</tr>
<tr>
<td>3-point MACE RRR (%)</td>
<td>13</td>
<td>26</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>3-point MACE ARR (%)</td>
<td>1.9</td>
<td>2.3</td>
<td>1.6</td>
<td>—†</td>
</tr>
<tr>
<td>CV death RRR (%)</td>
<td>22</td>
<td>2</td>
<td>38</td>
<td>4§; 13¶</td>
</tr>
<tr>
<td>Nonfatal MI RRR (%)</td>
<td>12</td>
<td>26</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Nonfatal stroke RRR (%)</td>
<td>11</td>
<td>39</td>
<td>+24</td>
<td>10</td>
</tr>
<tr>
<td>All-cause mortality RRR (%)</td>
<td>15</td>
<td>+5</td>
<td>32</td>
<td>13§; 10¶</td>
</tr>
<tr>
<td>HF hospitalization RRR (%)</td>
<td>13</td>
<td>+11</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Worsening nephropathy RRR (%)¶</td>
<td>22</td>
<td>36</td>
<td>39</td>
<td>40</td>
</tr>
</tbody>
</table>

RRR, relative risk reduction.

Recently Approved Incretin-based Therapies and SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent</td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>December 2017</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>December 2017</td>
</tr>
<tr>
<td>Fixed-dose combination</td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin and sitagliptin</td>
<td>December 2017</td>
</tr>
<tr>
<td>Dapagliflozin and saxagliptin</td>
<td>February 2017</td>
</tr>
<tr>
<td>Empagliflozin and linagliptin</td>
<td>January 2015</td>
</tr>
</tbody>
</table>
# Injectable Non-Insulin Agents Used to Treat Diabetes

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Agonists (incretin mimetics)</td>
<td>Liraglutide, exenatide, exenatide ER, dulaglutide, albiglutide</td>
</tr>
<tr>
<td>Amylin Analogs</td>
<td>Pramlintide</td>
</tr>
</tbody>
</table>
# Insulin Therapy Used to Treat Diabetes

### Drug Class Examples

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Insulin</td>
<td>Glargine (Lantus®️, Basaglar®️), degludec (Tresiba®️), detemir (Levemir®️), glargine U-300 (Toujeo®️)</td>
</tr>
<tr>
<td>Rapid-Acting Insulin Analogs</td>
<td>Aspart (NovoLog®️), degludec + aspart (Ryzodeg®️), lispro (Humalog®️), glulisine (Apidra®️), lispro U-200 (Humalog®️ U-200)</td>
</tr>
<tr>
<td>Premixed Insulin</td>
<td>70:30, 75:25, 50:50 (Humulin®️, Novolin®️)</td>
</tr>
<tr>
<td>Regular Insulin</td>
<td>U-500 (Humulin®️ R)</td>
</tr>
<tr>
<td>Inhaled Insulin</td>
<td>Afrezza®️</td>
</tr>
</tbody>
</table>

## Insulin Delivery Devices Used to Treat Diabetes

<table>
<thead>
<tr>
<th>Company</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic¹-⁴</td>
<td>MiniMed® 530G, 630G, 670G; Paradigm® Real-Time Revel™</td>
</tr>
<tr>
<td>Tandem⁵,⁶</td>
<td>t:slim X2™, t:flex®</td>
</tr>
<tr>
<td>Insulet⁷</td>
<td>Omnipod®</td>
</tr>
<tr>
<td>Accu-chek®⁸</td>
<td>Combo, Spirit</td>
</tr>
</tbody>
</table>

Potential Advantages of Fixed-dose SGLT2 and DPP-4 Inhibitor Combination Therapies

- Simplify treatment
- Reduce tablet burden
- Increase medication adherence
- May be particularly beneficial for patients for whom reduction of body weight, BP, and CV risk are important
Transitional Care
Discharge Planning

- Ensure stable blood glucose levels
- Measure A1C before discharge (if not measured during the previous months)
- Simplify treatment regimen for hyperglycemia (if possible)
- Schedule follow-up care within several weeks
- Communicate with outpatient providers regarding follow-up care
Patient Education, Instruction, and Referral

- Educate patients/caregivers
  - Self-monitoring of blood glucose and follow-up to address post-discharge changes (diet, exercise, and physiological stress)
  - Diabetes and self-care
  - Blood glucose targets
  - Signs and symptoms that require HCP consultation

- Provide specific instruction
  - Proper medication use
  - Self-monitoring of blood glucose
  - Hypoglycemia and hyperglycemia prevention

- Refer to a diabetes educator

Case Evaluation: Patient Description

A 50-year-old woman is admitted to the intensive care unit with significant chest pain, dizziness, nausea, and vomiting. Based upon an electrocardiogram and cardiac enzyme test results, she is diagnosed as having a myocardial infarction.
At what point do you recommend testing the patient’s blood glucose levels?

A. On admission
B. Once the patient has been stabilized
C. Throughout hospitalization every 24 to 48 hours
Case Evaluation: Discussion Question

The patient’s glucose level is 205 mg/dl. Which of the following would you recommend?

A. Treat her hyperglycemia only if she has a history of diabetes
B. Manage the MI first, then treat her hyperglycemia
C. Treat her hyperglycemia along with the MI
A 68-year-old man is admitted to the hospital following an acute ischemic stroke. He is obese and has a 10-year history of CVD and T2DM. His current treatment regimen consists of dual combination therapy with a DPP-4 inhibitor and metformin. At the time of admission, his blood glucose level is 270 mg/dl.
Case Evaluation: Discussion Question

Which of the following would you recommend to address the patient’s hyperglycemia during his hospital stay?

A. Sliding-scale insulin therapy after discontinuation of the outpatient diabetes regimen
B. Subcutaneous insulin treatment with a basal-bolus regimen
C. Continuous intravenous insulin infusion
T2DM is a chronic, progressive disease closely associated with a range of macro and microvascular complications, which frequently lead to hospitalization.

Hospital-based clinicians play a crucial role in ensuring optimal glycemic management during the hospital stay as well as providing guidance on antihyperglycemic therapy following discharge.

Optimal glycemic management requires treatment that takes into account a wide range of patient characteristics, including a high risk for vascular complications and the presence of comorbidities.

Many antihyperglycemic therapies with good efficacy and safety profiles have been developed, including incretin-based therapies and SGLT2 inhibitors, which have shown beneficial effects on both cv risk factors and vascular outcomes.

Summary
Patients with diabetes are at increased risk of vascular complications and hospitalizations for CV related events compared to patients without diabetes.

Diabetes and hypertension are among the 9 modifiable risk factors that account for >90% of the risk of initial acute MI.

For most hospitalized patients with diabetes, target a glucose level of 140-180 mg/dl.

Newer treatments for diabetes, including SGLT2 and GLP-1 indicators, have been shown to reduce micro and macrovascular events.

More intensive glucose control has been associated with a 20% reduction in kidney disease.

Prior to discharge of a patient with diabetes, ADA guidelines recommend measurement of hbA1c level.
Thank You!