South Carolina Chapter
American College of Physicians
Scientific Meeting 2021:
Update on Clinical Diabetes
and Therapeutics

Kathie L. Hermayer, MD, MS, FACP, FACE
Professor of Medicine
Medical University of South Carolina
Charleston, South Carolina
October 24, 2021
Disclosure Verification for:
Name: Kathie L. Hermayer, MD, MS, FACP, FACE

The presenter listed above:
___ Does not have any significant financial relationships to disclose

___ Has disclosed the following relationship with:

Eli Lilly

___ Research Grants       ___ Speaker’s Bureau       ___ Ownership
___ Consultant for fee    ___ Stock/Bond Holding     ___ Employment
___ Partnership          Other:_________

Was this activity Supported by an educational grant or received in-kind support?

___ Yes  Name:  CME activity for SC Chapter ACP lecture
___ No
Learning Objectives

1. 2021 evidence based updates about diabetes treatment guidelines

2. The role of new GLP-1 agonists, SGLT-2 inhibitors, and continuous glucose monitors for treatment of diabetes

3. The link between diabetes and COVID-19
National Diabetes Statistics Report, 2020

Fast Facts on Diabetes

Diabetes

• **Total:** 34.2 million people have diabetes (10.5% of the US population)
• **Diagnosed:** 26.9 million people, including 26.8 million adults
• **Undiagnosed:** 7.3 million people (21.4% are undiagnosed)

Prediabetes

• **Total:** 88 million people aged 18 years or older have prediabetes (34.5% of the adult US population)
• **65 years or older:** 24.2 million people aged 65 years or older have prediabetes

Diabetes in South Carolina

• In 2019, South Carolina had the 6th highest percent of adult population with diabetes in the US
• More than 540,000 adults in South Carolina are estimated to have been diagnosed with diabetes
• The prevalence of diabetes is higher among non-Hispanic Black adults (16.2%) than among non-Hispanic Whites (12.9%), and non-Hispanic Blacks had 2.4x higher age-adjusted death rate compared to non-Hispanic Whites.
• The estimated cost of care for people in South Carolina with diabetes is $5.89 billion, including $4.25 billion in medical and $1.64 billion in indirect costs.

Standards of Medical Care In Diabetes - 2021

Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S1-S232
### Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

<table>
<thead>
<tr>
<th><strong>A1C</strong></th>
<th>&lt;7.0% (53 mmol/mol)*#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preprandial capillary plasma glucose</strong></td>
<td>80–130 mg/dL* (4.4–7.2 mmol/L)</td>
</tr>
<tr>
<td><strong>Peak postprandial capillary plasma glucose†</strong></td>
<td>&lt;180 mg/dL* (10.0 mmol/L)</td>
</tr>
</tbody>
</table>

*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and Fig. 6.1. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per Fig. 6.2). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.
Pharmacologic Therapy for Type 2 Diabetes

9.4 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

9.5 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. A

9.6 Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. A

9.7 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. E
Pharmacologic Therapy for Type 2 Diabetes (continued)

9.8 A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (Table 9.1 and Figure 9.1). E

9.9 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (Table 9.1, Table 10.3B, Table 10.3C) is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors (Fig. 9.1 and Section 10). A
Pharmacologic Therapy for Type 2 Diabetes (continued)

9.10 In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. A

9.11 Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed. A

9.12 The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (Fig. 4.1 and Table 9.1). E
9.13 Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 IU/ kg, high bedtime-morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. E
Treatment Goals

12.6 Older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as A1C <7.0–7.5% [53–58 mmol/mol]), while those with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less stringent glycemic goals (such as A1C <8.0–8.5% [64–69 mmol/mol]). C

12.7 Glycemic goals for some older adults might reasonably be relaxed as part of individualized care, but hyperglycemia leading to symptoms or risk of acute hyperglycemia complications should be avoided in all patients. C

Glycemic Targets:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S73-S84
Cardiovascular Risk and Diabetes

Type 2 Diabetes (T2D) is a significant risk factor for cardiovascular disease (CVD)

- Cardiovascular complications are main cause of mortality in T2D patients
- The Emerging Risk Factors Collaboration: Diabetes and CVD
  - N=698,782; 102 prospective studies; 52,765 events
    - Cardiovascular heart disease death HR = 2.31
    - Non-fatal myocardial infarction HR = 1.82
    - Ischemic cerebral vascular accident HR = 2.27
    - Hemorrhagic cerebral vascular accident HR = 1.84
- Duration of diabetes is associated with higher risk of cardiovascular disease
- Diabetes + CV disease (MI or CVA) reduces life expectancy

© AACE. All Rights Reserved.
Prior Landmark Clinical Trials: Intensive Glucose Control and Macrovascular Risk in T2D

Meta-analysis of Five Prospective RCTs Assessing Effect of Intensive Glucose Lowering on CV Outcomes (ACCORD, ADVANCE, PROactive, UKPDS, VADT)

<table>
<thead>
<tr>
<th>Event</th>
<th>Odds ratio</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>0.83 (0.75-0.93)</td>
<td>-17%</td>
</tr>
<tr>
<td>Any CHD event</td>
<td>0.85 (0.77-0.93)</td>
<td>-15%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.93 (0.81-1.06)</td>
<td>-7% (NS)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.02 (0.87-1.19)</td>
<td>+2% (NS)</td>
</tr>
</tbody>
</table>

Macrovascular Risk Reduction in Type 2 Diabetes

- Hypertension control
- Dyslipidemia control
- Smoking cessation
- Glycemic control

- Aspirin therapy
- Lifestyle modification
- Weight loss
Cardiovascular Risk and Diabetes

- Intensive vs. conventional glucose control in older studies did not reduce short term all-cause, CV or non-CV mortality
  - Lowering HbA1c below conventional targets did not confer CV benefit
  - Intensive control confirmed reduction in microvascular disease
- Newer diabetes drugs (SGLT-2 inhibitor and GLP-1 receptor analogs) have consistently shown cardiovascular and renal protection in large cardiovascular outcome trials
- Individualized diabetes management approach is important for:
  - HbA1c lowering
  - Microvascular risk reduction (nephropathy, retinopathy, neuropathy)
  - Macrovascular risk reduction (ASCVD, Heart failure, diabetic kidney disease)
Pharmacologic Treatment for T2D

Two classes of newer DM2 therapy with added cardiovascular benefits.

- Sodium-Glucose CoTransporter 2 (SGLT2) Inhibitors
- Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists

- Each will be reviewed for:
  - Mechanism
  - Summary of CV outcome trials (CVOT)
  - Benefits
  - Adverse effects
  - Dosing
Pharmacologic Treatment for T2D With Existent Cardiovascular Disease

**SGLT2 inhibitors:**
- Canagliflozin
- Empagliflozin
- Dapagliflozin
- Ertugliflozin

**Human analog GLP-1 RA:**
- Liraglutide
- Dulaglutide*
- Semaglutide
- Albiglutide (off the market)

*Only drug with primary prevention indication
## Medications for T2D with CV Benefit

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th>GLP-1 RAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative stress-induced endothelial cell dysfunction</td>
<td>Oxidative stress-induced endothelial cell dysfunction</td>
</tr>
<tr>
<td>Inflammation and atherogenesis</td>
<td>Inflammation and atherogenesis</td>
</tr>
<tr>
<td>Glucose lowering effect</td>
<td>Glucose lowering effect</td>
</tr>
<tr>
<td>Natriuretic / diuretic effect</td>
<td>Natriuretic / diuretic effect</td>
</tr>
<tr>
<td>RAAS effect</td>
<td>RAAS effect</td>
</tr>
<tr>
<td>Uriscosuric effect</td>
<td></td>
</tr>
<tr>
<td>Beta hydroxybutyrate increase</td>
<td></td>
</tr>
</tbody>
</table>
SGLT2 Inhibitors Benefits

- Improved Glycemia
  - Rare hypoglycemia
- Weight loss
  - Average weight loss of 1-3 kg
- ↓ Blood pressure
- ↓ Triglycerides
- Oral route
- Cardiac and renal protection
# Cardiovascular Safety Studies

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th>Previous CVD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>Empagliflozin 99</td>
</tr>
<tr>
<td>CANVAS</td>
<td>Canagliflozin 65</td>
</tr>
<tr>
<td>DECLARE TIMI 58</td>
<td>Dapagliflozin 40</td>
</tr>
<tr>
<td>CREDENCE (renal study)</td>
<td>Canagliflozin 50</td>
</tr>
<tr>
<td>VERTIS</td>
<td>Ertugliflozin 73</td>
</tr>
<tr>
<td>GLP-1RAs</td>
<td></td>
</tr>
<tr>
<td>ELIXA</td>
<td>Lixisenatide 100</td>
</tr>
<tr>
<td>LEADER</td>
<td>Liraglutide ~81</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>Semaglutide ~83</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide 73</td>
</tr>
<tr>
<td>Harmony Outcomes</td>
<td>Albiglутide 100</td>
</tr>
<tr>
<td>REWIND</td>
<td>Dulaglutide 31</td>
</tr>
<tr>
<td>PIONEER 6</td>
<td>Oral semaglutide 35</td>
</tr>
</tbody>
</table>

© AACE. All Rights Reserved.
SGLT2 Inhibitors

Mechanisms for Cardioprotection
- Reduce preload and afterload segment
- Improved profile of anti-inflammatory vs. pro-inflammatory cytokine
- Reduced cardiac fibrosis
- Increased hematocrit and erythropoietin production
- Increased cardiac metabolic efficiency

Mechanisms for Renoprotection
- Glycosuria
- Natriuresis
- Decreased glomerular pressure
- Reduced albuminuria
Physiological Effects of SGLT2 Inhibitors

Selectively blocks the transporter responsible for > 90% of glucose reabsorption in the nephron (SGLT2).

- This results in reduced absorption of glucose and sodium, leading to glycosuria and natriuresis.
- Greatest rate of glycosuria occurs during periods of hyperglycemia.
- Risk for hypoglycemia is not significant.

*Figure 1. The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule. Modified from Bakris et al.² with permission of the publisher. Copyright © 2009, Elsevier.*
## SGLT2 inhibitors: Summary of CV Outcome Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>MACE HR (95%CI)</th>
<th>CV Death HR (95%CI)</th>
<th>HHF HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG (empagliflozin)</td>
<td>0.86 (0.74-0.99)</td>
<td>0.62 (0.49-0.77)</td>
<td>0.65 (0.50-0.85)</td>
</tr>
<tr>
<td>CANVAS (canagliflozin)</td>
<td>0.86 (0.75-0.97)</td>
<td>0.87 (0.72-1.06)</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>DECLARE-TIMI (dapagliflozin)</td>
<td>0.93 (0.84-1.03)</td>
<td>0.98 (0.82-1.17)</td>
<td>0.73 (0.61-0.88)</td>
</tr>
<tr>
<td>VERTIS-CV (ertugliflozin)</td>
<td>0.97 (0.85-1.11)</td>
<td>0.92 (0.77-1.11)</td>
<td>0.70 (0.54-0.90)</td>
</tr>
</tbody>
</table>

MACE = composite of death from CV cause, nonfatal MI and nonfatal stroke; CV death = cardiovascular death; HHF = hospitalization for heart failure
## SGLT-2 inhibitors in Patients with Proteinuria

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (CREDEENCE)</th>
<th>Dapagliflozin (DAPA-CKD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion without diabetes</td>
<td>0%</td>
<td>32%</td>
</tr>
<tr>
<td>Duration</td>
<td>2.6 years</td>
<td>2.4 years</td>
</tr>
<tr>
<td>Primary Outcome Composite Components</td>
<td>Hemodialysis, GFR&lt;15, Doubling in Creatinine, Renal or CV death</td>
<td>50% GFR reduction ESKD, Renal or CV death</td>
</tr>
<tr>
<td>Primary Outcome [HR (95% CI)]</td>
<td>0.80 (0.67-0.95)</td>
<td>0.61 (0.51-0.72)</td>
</tr>
<tr>
<td>Renal Composite outcome (worsening GFR, ESKD, renal death)</td>
<td>0.66 (0.53–0.81)</td>
<td>0.56 (0.45–0.68)</td>
</tr>
<tr>
<td>ESKD (HD or GFR &lt;15)</td>
<td>0.68 (0.54–0.86)</td>
<td>0.64 (0.50–0.82)</td>
</tr>
<tr>
<td>CV Death or Hospitalization HF</td>
<td>0.69 (0.57–0.83)</td>
<td>0.71 (0.55–0.92)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.61-1.00)</td>
<td>0.81 (0.58–1.12)</td>
</tr>
<tr>
<td>Hospitalizations HF</td>
<td>0.61 (0.47–0.80)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.83 (0.68–1.02)</td>
<td>0.69 (0.53–0.88)</td>
</tr>
</tbody>
</table>


© AACE. All Rights Reserved.
SGLT-2 inhibitors in patients with heart failure and reduced ejection fraction (with and without diabetes)

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (DAPA-HF)</th>
<th>Empagliflozin (EMPEROR HF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion without diabetes</td>
<td>58%</td>
<td>50%</td>
</tr>
<tr>
<td>Duration</td>
<td>1.5 years</td>
<td>1.3 years</td>
</tr>
<tr>
<td>Primary Outcome Composite Components</td>
<td>CV death, urgent visit or Hospitalization for HF</td>
<td>CV death or Hospitalization for HF</td>
</tr>
<tr>
<td>Primary Outcome [HR (95% CI)]</td>
<td>0.74 (0.65 to 0.85)</td>
<td>0.75 (0.65 to 0.86)</td>
</tr>
<tr>
<td>CV Death or Hospitalization HF</td>
<td>0.75 (0.65 to 0.85)</td>
<td>0.75 (0.65 to 0.86)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.82 (0.69 to 0.98)</td>
<td>0.92 (0.75 to 1.12)</td>
</tr>
<tr>
<td>Hospitalizations HF</td>
<td>0.70 (0.59 to 0.83)</td>
<td>0.69 (0.59 to 0.81)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.83 (0.71 to 0.97)</td>
<td>0.92 (0.77 to 1.10)</td>
</tr>
</tbody>
</table>

© AACE. All Rights Reserved.
SGLT2 Inhibitors: Summary of CV Outcome Trials

For T2D patients with or without established CVD
• Reduced hospitalization for heart failure
• Renoprotection

For T2D patients with established CVD
• Reduced MACE (EMPA-REG, CANVAS, CREDENCE)
• Reduced hospitalization for heart failure
• Renoprotection
• Some cases of reduced mortality (EMPA-REG, CREDENCE)

Cardiorenal benefit also shown in patients without diabetes (DAPA-CKD, DAPA-HF, EMPEROR HF) ¹

© AACE. All Rights Reserved.
SGLT2 Inhibitors: Adverse Effects

- Genital mycotic infections (women > men)
- Urinary tract infections
- Polyuria
- Volume depletion/hypotension/dizziness
- ↑ LDL-C
- ↑ Creatinine (transient)
- DKA/ euglycemic DKA

• Increased rate of lower extremity amputations (seen in CANVAS, not CREDENCE)
  CANVAS: numerically low numbers but statistically significant; 6.3 vs. 3.4%, HR 1.97 (95%CI 1.41-2.75)
• Side effect of Fournier’s gangrene
• Increased risk of bone fractures
SGLT2 Inhibitors Dosing

• Canagliflozin (Invokana) – 100 or 300mg oral once daily
  • Dose adjust if eGFR< 60 mL/min/1.73m2
• Dapagliflozin (Farxiga) – 5 or 10mg oral once daily
  • Dose adjust if eGFR< 45 mL/min/1.73m2
• Empagliflozin (Jardiance) – 10 or 25mg oral once daily
  • Dose adjust if eGFR< 45 mL/min/1.73m2
• Ertugliflozin (Steglatro) – 5 or 15mg oral once daily
  • Dose adjust if eGFR< 60 mL/min/1.73m2
Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RA)

Currently available drugs:
• Exenatide (Byetta, Bydureon)
• Liraglutide (Victoza)
• Lixisenatide (Adlyxin, component of Soliqua) (Available in US as a fixed ratio combination drug)
• Semaglutide (Ozempic, Rybelsus)
• Dulaglutide (Trulicity)

Mechanisms for Cardioprotection:
• GLP-1 receptor is expressed in cardiomyocytes and coronary endothelial cells
• Improved left ventricular and endothelial function
GLP-1 RAs: Mechanism of Action

Kidney
↑ Natriuresis
↑ Diuresis

Heart
↑ Cardioprotection

Blood vessel
↓ Blood pressure

Brain
↓ Body weight

Fats and other tissues
↓ Inflammation

Intestines
↓ Postprandial lipids

Pancreas
↓ Glucose
↓ Hypoglycemia

α-Cell
↓ Glucagon secretion

β-Cell
↑ Insulin secretion
↑ Insulin biosynthesis
↓ Apoptosis

Platelets
↓ Coagulation

## GLP-1 RA: Summary of CV Outcome Trials

<table>
<thead>
<tr>
<th></th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Semaglutide</th>
<th>Exenatide</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE, HR (95% CI)</strong></td>
<td>1.02 (0.89-1.17)</td>
<td><strong>0.87 (0.78-0.97)</strong></td>
<td>0.74 (0.58-0.95)</td>
<td>0.91 (0.83-1.00)</td>
<td><strong>0.78 (0.68-0.90)</strong></td>
<td><strong>0.88 (0.79-0.99)</strong></td>
</tr>
<tr>
<td><strong>CV death, HR (95% CI)</strong></td>
<td>0.98 (0.78-1.22)</td>
<td><strong>0.78 (0.66-0.93)</strong></td>
<td>0.98 (0.65-1.48)</td>
<td>0.88 (0.76-1.02)</td>
<td>0.93 (0.73-1.19)</td>
<td>0.91 (0.78-1.06)</td>
</tr>
<tr>
<td><strong>Fatal or nonfatal MI, HR (95% CI)</strong></td>
<td>1.03 (0.87-1.22)</td>
<td>0.86 (0.73-1.00)</td>
<td>0.74 (0.51-1.08)</td>
<td>0.97 (0.85-1.10)</td>
<td><strong>0.75 (0.61-0.90)</strong></td>
<td>0.96 (0.79-1.15)</td>
</tr>
<tr>
<td><strong>Fatal or nonfatal stroke, HR (95% CI)</strong></td>
<td>1.12 (0.79-1.58)</td>
<td>0.86 (0.71-1.06)</td>
<td><strong>0.61 (0.38-0.99)</strong></td>
<td>0.85 (0.70-1.03)</td>
<td>0.86 (0.66-1.14)</td>
<td><strong>0.76 (0.62-0.94)</strong></td>
</tr>
<tr>
<td><strong>All-cause mortality, HR (95% CI)</strong></td>
<td>0.94 (0.78-1.13)</td>
<td><strong>0.85 (0.74-0.97)</strong></td>
<td>1.05 (0.74-1.50)</td>
<td><strong>0.86 (0.77-0.97)</strong></td>
<td>0.95 (0.79-1.16)</td>
<td>0.90 (0.80-1.01)</td>
</tr>
<tr>
<td><strong>HF hospitalization, HR (95% CI)</strong></td>
<td>0.96 (0.75-1.23)</td>
<td>0.87 (0.73-1.05)</td>
<td>1.11 (0.77-1.61)</td>
<td>0.94 (0.78-1.13)</td>
<td>0.93 (0.77-1.12)</td>
<td></td>
</tr>
</tbody>
</table>
GLP1 Receptor Agonists
Summary of CV Outcome Trials

• All trials met non-inferiority
• Superiority for MACE
  • Semaglutide, liraglutide, albiglutide, dulaglutide
• Reduced ischemic events (stroke or MI)
• Renoprotection in meta-analysis (mediated by reduction in albuminuria)
• Potential benefit for heart failure hospitalization (small effect in meta-analysis)
• Mortality benefit seen only in LEADER
GLP1 Receptor Agonists Benefits

• ↓ Postprandial glucose excursions

• Weight loss
  ▪ Average weight loss of 2-4 kg

• Increased satiety

• ↓ LDL-C and ↓ triglycerides

• Low rate of hypoglycemia

• Cardiac and renal protection
GLP-1 RA: Adverse Effects

• Gastrointestinal side effects
  • Nausea, vomiting most common
  • Diarrhea
  • Association with acute gallstone disease
• ↑ Heart rate
• Acute pancreatitis
  • Risk not confirmed in CVOT
GLP1 Receptor Agonists: Adverse Effects

• C-cell hyperplasia/medullary thyroid tumors in animals. Do not prescribe if personal or family history of multiple endocrine neoplasia syndrome type 2.

• Increased risk of worsening retinopathy with semaglutide
  • SUSTAIN-6 trial: semaglutide vs. placebo, 3.0 vs. 1.8%, HR 1.76, 95% CI 1.11-2.78.
GLP1 Receptor Agonists Dosing

• Exenatide
  • Byetta - 5 or 10 mcg SC twice daily. (Not recommended for CrCl <30 ml/min)
  • ER formulation (Bydureon) - 2mg SC once weekly. (Not recommended with eGFR<45 mL/min/1.73m2)

• Liraglutide
  • Victoza – 0.6, 1.2 or 1.8mg SC once daily. (Use with caution with severe renal impairment).
GLP1 Receptor Agonists Dosing

• Lixisenatide
  • 10-20mg SC once daily. Not recommended with eGFR<15 mL/min/1.73m2

• Semaglutide
  • Ozempic – 0.25, 0.5, or 1.0 mg SC once weekly
  • Rybelsus – 3, 7 or 14 mg oral once daily

• Dulaglutide
  • Trulicity - 0.75, 1.5, 3.0, or 4.5 mg SC once weekly
Drug selection: SGLT2-i vs. GLP1-RA

AACE/ADA/EASD/ACC

• Can begin with metformin monotherapy for T2D but consider adding GLP-1 RA or SGLT2-i independent of HbA1c target.
• Can consider beginning therapy with GLP-1 RA or SGLT2-i prior to metformin in patients with higher risk.

• If atherosclerotic CVD or stroke predominates: Choose GLP-1 RA with proven benefit
• If heart failure or CKD predominates: Choose SGLT2-I with proven benefit
Guideline Updates 2019-2020

ACC/AHA*, AACE/ACE, and ESC/EASD recommend GLP-1 RA monotherapy as first-line option for patients with T2DM and established or at high risk for ASCVD^[a-c]^.

**T2DM drug-naïve^[c]^†**
- ASCVD or high/very high CV risk (target organ damage or multiple risk factors)

- GLP-1 RA (1st choice for established ASCVD) or SGLT2 inhibitor monotherapy‡

- Metformin monotherapy

- Add metformin

- If HbA1c above target, consider adding GLP-1 RA or SGLT2 inhibitor* or other

- If HbA1c above target, add another class (e.g., DPP-4i, GLP-1 RA, SGLT2i if eGFR adequate, TZD)

- (Last-line option) If HbA1c above target, consider addition of SU or basal insulin

---

*For adults with T2DM and additional ASCVD risk factors (IIb, B-R).
†Please refer to original figure for more detail. ‡Use drugs with proven CVD benefit.

**Pharmacologic Approaches to Glycemic Management: Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S111-S124**

### Table 9.1 – Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight change</th>
<th>CV effects</th>
<th>Cost</th>
<th>Onset</th>
<th>Renal effects</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD</td>
<td>HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maritimide</td>
<td>High</td>
<td>No</td>
<td>Neutral/</td>
<td>Potential</td>
<td>Neutral</td>
<td>Low</td>
<td>Onset</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>Intermediate</td>
<td>No</td>
<td>Loss</td>
<td>NA</td>
<td>Neutral</td>
<td>High</td>
<td>Onset</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Neutral/</td>
<td>NA</td>
<td>Neutral</td>
<td>High</td>
<td>Onset</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Increased</td>
<td>Risk</td>
<td>Low</td>
<td>Onset</td>
</tr>
<tr>
<td>Sulfonylureas (3rd generation)</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Low</td>
<td>Onset</td>
</tr>
<tr>
<td>Insulin</td>
<td>Highest</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Low</td>
<td>Onset</td>
</tr>
<tr>
<td>Analogue</td>
<td>High</td>
<td>Yes</td>
<td>High</td>
<td>Onset</td>
<td>Onset</td>
<td>Onset</td>
<td>Onset</td>
</tr>
</tbody>
</table>

**ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium-glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to the manufacturers’ prescribing information. **FDA-approved for cardiovascular disease benefit. **FDA-approved for heart failure indication. **FDA-approved for chronic kidney disease indication.
PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Glucose-lowering Medication in Type 2 Diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. and Buse et al.

Pharmacologic Approaches to Glycemic Management: Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S111-S124
Medication Access/Medication Cost

• Despite promising data described above, many patients are unable to utilize these classes of medications due to high cost involved and economic hardship.

• Uninsured patients, and even some insured patients, with high copays or deductibles may be limited in their ability to obtain diabetes medications with the best profiles for organ protection.

• Often a particular insurance company will only cover one agent within a particular class so ability to select a specific drug may be limited.

• Be aware of limitations when prescribing and consider options for cost-reduction or alternative medications if cost remains prohibitive.
Intensifying to injectable therapies (1 of 2)

Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSEM to meet individualized treatment goals.

If injectable therapy is needed to reduce A1C:

Consider GLP-1 RA in most patients prior to insulin:
- **INITIATION:** Initiate appropriate starting dose for agent selected (varies within class)
- **TITRATION:** Titration to maintenance dose (varies within class)

If above A1C target:

Add basal insulin:
- Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.

Add basal analog or bedtime NPH insulin:
- **INITIATION:** Start 10 IU a day OR 0.1-0.2 IU/kg a day
- **TITRATION:**
  - Set FPG target (see Section 6: Glycemic Targets)
  - Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
  - For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred.
Intensifying to injectable therapies (2 of 2)

Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose >0.5 U/kg, elevated bedtime-morning and/or post-prandial differential, hypoglycemia [aware or unaware], high variability)

If above A1C target

Add prandial insulin
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:
- 4 IU a day or 10% of basal insulin dose
- If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 IU a day or 10% of basal dose

TITRATION:
- Increase dose by 1-2 IU or 10-15% twice weekly
- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10-20%

If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:

INITIATION:
- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:
- Titrates based on individualized needs

Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)

Proceed to full basal-bolus regimen
(i.e., basal insulin and prandial insulin with each meal)

Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately

INITIATION:
- Total NPH dose = 80% of current NPH dose
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 IU of short/rapid-acting insulin to each injection or 10% of reduced NPH dose

TITRATION:
- Titrates each component of the regimen based on individualized needs

Consider twice daily premix insulin regimen

INITIATION:
- Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs

TITRATION:
- Titrates based on individualized needs
Conclusions

Diabetes is a multifactorial disease

Many people with T2DM have ASCVD, kidney disease, and/or HF

Role for PCPs, cardiologists, nephrologists, and diabetologists in risk management for T2DM and CVD, or CKD, or risk factors

We can prevent progression of diabetes complications

Latest guidelines recommend SGLT2 inhibitors and GLP-1 RAs for organ protection in individualized diabetes care

Novel glucose-lowering drugs have a role beyond T2DM: in HF, ASCVD, and kidney disease
Three Apples That Changed The World

Newton's Apple (1687)  
Eve's Apple (At the world start)  
Steve Job's Apple (1976)
Overview

- During the past two decades, continuous glucose monitoring (CGM) has become a standard of care for many individuals with insulin-treated diabetes.
- CGM presents information about the direction, magnitude, duration, frequency and causes of fluctuations in glucose levels, and it provides insight into glucose levels throughout the day.
- This information can help identify and prevent unwanted periods of hypoglycemia and hyperglycemia.
Components of a CGM

**Sensor**
- Adhesive attaches sensor to the skin or needs to be surgically implanted
- Cannula implants into the interstitial fluid
- Sensors can last from 7-90 days depending on the device

**Transmitter**
- Attaches to the sensor
- Sends BG readings to the app/reader

**Cell phone app/reader**
- View current BG and track trends
- Some devices can alert patient to expected high or low BG (10-60 min prior)
CGM Options

Professional CGM

- Dexcom Pro (G6 Pro)
- Medtronic iPro
- Freestyle Libre Pro

Personal CGM

- Dexcom (G6)
- Medtronic (Guardian and Enlite)
- Freestyle Libre and Freestyle Libre 2
- Eversense
### Table 7.3—Continuous glucose monitoring (CGM) devices

<table>
<thead>
<tr>
<th>Type of CGM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-time CGM (rtCGM)</td>
<td>CGM systems that measure and display glucose levels continuously</td>
</tr>
<tr>
<td>Intermittently scanned CGM (isCGM)</td>
<td>CGM systems that measure glucose levels continuously but only display glucose values when swiped by a reader or a smartphone</td>
</tr>
<tr>
<td>Professional CGM</td>
<td>CGM devices that are placed on the patient in the provider’s office (or with remote instruction) and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. These devices are not fully owned by the patient—they are a clinic-based device, as opposed to the patient-owned rtCGM/isCGM devices.</td>
</tr>
</tbody>
</table>

Diabetes Technology:
*Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S85-S99*
Glycemic Targets:
*Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S73-S84*
Three Patients, Three Treatment Plans...Same A1C
CGM Users Have Lower HbA1c Regardless of Insulin Delivery Method

T1DM Exchange Clinic Registry

New Medicare Coverage Requirements Make CGMs More Accessible

• The diabetes community is celebrating a huge win! Beginning on July 18, 2021, Medicare will permanently eliminate the requirement of the four-time-daily fingerstick in order to qualify for coverage of a continuous glucose monitor (CGM).

• This requirement was an unnecessary barrier for Medicare beneficiaries, delaying access to this effective technology for individuals with diabetes.

• CGMs provide users with real-time, dynamic information about their blood glucose (blood sugar) levels around the clock and alerts to prevent dangerous high or low glucose levels, leading to better diabetes management and ultimately improved health outcomes. One out of five people on Medicare have diabetes, and the elimination of the fingerstick requirement means Medicare beneficiaries with diabetes will have easier access to this critical technology.

Summary of the Clinical Evidence Around CGM As Standard of Care

• It is NOT about how you deliver insulin, *it is about using CGM*
• CGM needs to be worn on a near daily basis for sustaining clinical benefit
• CGM has a broad value to all different types of patients
  • All patients (T1D and T2D) on intensive insulin therapy regimens
  • Hypoglycemia/hypoglycemia unawareness
  • Patients with high A1c are candidates for CGM
• CGM is an appropriate first technology to be added to a patient’s diabetes management regimen*
• Patients who do not carb count, do not do ‘diabetes math’ well, at all education levels and ages seem to benefit from CGM

*young children may be an exception*
Illustration of Parallels in Acute COVID-19 Pathology versus Chronic Diabetes Pathology

COVID-19
- Acute cytokine storm inflammatory response
- Acute tissue damage, ACI, AKI, ARDS, neurological
- Hyperglycemic surges
- Hypercoagulability
- Endothelial dysfunction
- Fibrosis

Diabetes
- Chronic, low grade inflammatory response & insulin resistance
- Slowly progressing tissue damage, CVD, CKD, neuropathy, brain changes
- Glucose variability
- Hypercoagulability
- Endothelial dysfunction
- Fibrosis

ACE2 and Its Role in the Renin Angiotensin System and SARS-CoV-2 Infection

The Potential Interplay of SARS-CoV-2 and Diabetes

<table>
<thead>
<tr>
<th>Medication</th>
<th>Suggested withholding in patients with COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Temporarily withhold while unwell due to risk of lactic acidosis ($62, 66, 83, 86)</td>
</tr>
<tr>
<td>SGLT2-I emapaglitozin, dapaglitozin, canagliflozin, ertugliflozin</td>
<td>Temporarily withhold while unwell due to risk of diabetic ketoacidosis ($62, 66, 80, 83, 86)</td>
</tr>
<tr>
<td>Sulphonylureas gliclazide, glipizide, glibenclamide, tolbutamide, chlorpropamide</td>
<td>Temporarily withhold while unwell due to risk of hypoglycaemic events ($86)</td>
</tr>
<tr>
<td>GLP-1 receptor agonists liraglutide, dulaglutide, exenatide</td>
<td>Continue with close monitoring ($62) OR temporarily withheld while unwell ($66, 90) due to risk of volume contraction</td>
</tr>
<tr>
<td>DPP4i sitagliptin, vildagliptin, saxagliptin, linagliptin</td>
<td>Consider withholding saxagliptin and alogliptin in critically unwell patients due to risk of exacerbated heart failure ($71). Continuation of DPP4i in mild disease may be considered ($62)</td>
</tr>
</tbody>
</table>
Endocrinology and COVID-19 – The Link

**PREDISPPOSING FACTORS**
- Uncontrolled diabetes
- Compromised Immunity states

**PROTECTIVE FACTORS**
- Childhood, due to thymic hormones involved in calcium regulation

**ENDOCRINE INVESTIGATIONS**
- Screen for diabetes
- Be aware of stress hyper glycaemia
- Check for serum level of thyroid hormones (clinically low in sick euthyroid syndrome)
- Screen for adrenal insufficiency

**ENDOCRINE MANAGEMENT**
- Strengthen immunity through glucose control
- Strengthen neuro muscular system through intake of vitamin D, calcium and testosterone.
- Discontinue drugs that may cause infection

**COVID-19 MANAGEMENT**
- Follow standard of care
- Be vigilant regarding potential endocrine and metabolic complication of therapy

Kashyap, S, et. Al. Environmental Science and Pollution Research. Published online: May 21, 2021.
Conclusions:

• Since T2DM is a progressive disease, maintenance of glycemic targets with monotherapy is often possible only for a few years

• Need combination therapy via stepwise addition of medications to metformin to maintain A1c at target

• For patients with established ASCVD or indicators of high ASCVD risk, an SGLT2 inhibitor or a GLP-1 RA with demonstrated CVD benefit is recommended

• For patients without ASCVD risk, heart failure, or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence comparing across multiple classes. Rather, drug choice is based on efficacy, avoidance of side effects (particularly hypoglycemia and weight gain), cost, and patient preferences.
Questions?