Latest Treatment Strategies for Type 2 Diabetes and Cardiovascular Disease
Faculty
Amit Gupta, DNB, FACE, FICP, FRCP (Glasgow, Edinburgh), FACP
Director, Centre For Diabetes Care
Greater Noida, India

Javier Morales, MD, FACP, FACE
Clinical Associate Professor of Medicine
Donald and Barbara Zucker School of Medicine At Hofstra/Northwell University
Vice President, Advanced Internal Medicine Group, P.C

Rifka C. Schulman-Rosenbaum, MD, FACE, CNSC
Director of Inpatient Diabetes, Long Island Jewish Medical Center, Division of Endocrinology, Northwell Health
Associate Professor, Donald and Barbara Zucker School of medicine at Hofstra/Northwell

Vijay Shivaswamy, MD
Associate Professor, Division of Diabetes, Endocrinology and Metabolism, The University of Nebraska Medical Center, VA Nebraska-Western Iowa Health Care System
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
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

SGL T2 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></th>
<th>Previous CVD%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT2 Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>Empagliflozin</td>
</tr>
<tr>
<td></td>
<td>99</td>
</tr>
<tr>
<td>CANVAS</td>
<td>Canagliflozin</td>
</tr>
<tr>
<td></td>
<td>65</td>
</tr>
<tr>
<td>DECLARE TIMI 58</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td>CREDENCE (renal study)</td>
<td>Canagliflozin</td>
</tr>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td>VERTIS</td>
<td>Ertugliflozin</td>
</tr>
<tr>
<td></td>
<td>73</td>
</tr>
<tr>
<td><strong>GLP-1RAs</strong></td>
<td></td>
</tr>
<tr>
<td>ELIXA</td>
<td>Lixisenatide</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
<tr>
<td>LEADER</td>
<td>Liraglutide</td>
</tr>
<tr>
<td></td>
<td>~81</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>Semaglutide</td>
</tr>
<tr>
<td></td>
<td>~83</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide</td>
</tr>
<tr>
<td></td>
<td>73</td>
</tr>
<tr>
<td>Harmony Outcomes</td>
<td>Albiglutide</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
<tr>
<td>REWIND</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td></td>
<td>31</td>
</tr>
<tr>
<td>PIONEER 6</td>
<td>Oral semaglutide</td>
</tr>
<tr>
<td></td>
<td>35</td>
</tr>
</tbody>
</table>
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. with permission of the publisher. Copyright © 2009, Elsevier.*
# SGLT2 inhibitors: Summary of CV Outcome Trials

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

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>

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) \(^1\)
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 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>0.87 (0.78-0.97)</td>
<td>0.74 (0.58-0.95)</td>
<td>0.91 (0.83-1.00)</td>
<td>0.78 (0.68-0.90)</td>
<td>0.88 (0.79-0.99)</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

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‡

Add metformin

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

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

Metformin monotherapy

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

*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.
GLYCEMIC CONTROL ALGORITHM

INDIVIDUALIZE GOALS

**A1C ≤6.5%**
For patients without concurrent serious illness and at low hypoglycemic risk

**A1C >6.5%**
For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY AND ONGOING GLUCOSE MONITORING (CGM preferred)

INDEPENDENT OF GLYCEMIC CONTROL, IF ESTABLISHED OR HIGH ASCVD RISK AND/OR CKD, RECOMMEND SGLT2I AND/OR LA GLP-1 RA

**Entry A1C ≥7.5% - 9.0%**

**Entry A1C >9.0%**

MONOTHERAPY**

- Metformin
- GLP1-RA
- SGLT2
- DPP4i
- TZD
- Agi
- SU/GLN

**3 MONTHS**

- GLP1-RA
- SGLT2I
- DPP4i
- TZD
- SU/AGI
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGI

**DUAL THERAPY**

- GLP1-RA
- SGLT2I
- DPP4i

**3 MONTHS**

- GLP1-RA
- SGLT2I
- DPP4i

**TRIPLE THERAPY**

- GLP1-RA
- SGLT2I
- DPP4i
- TZD
- SU/AGI
- Basal Insulin
- Colesevelam
- Bromocriptine QR

**SYMPTOMS**

- NO
- YES

- DUAL Therapy
- INSULIN & Other Agents

- TRIPLE Therapy

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- Few adverse events and/or possible benefits
- Use with caution

PROGRESSION OF DISEASE

© AACE. All Rights Reserved.
# AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

## Profiles of Antihyperglycemic Medications

<table>
<thead>
<tr>
<th>MET</th>
<th>GLP1-RA</th>
<th>SGLT2i</th>
<th>DPP4i</th>
<th>AGI</th>
<th>TZD (moderate: 2008)</th>
<th>SU</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Severe</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
</tr>
<tr>
<td>RENAL / GU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Prevent HF</td>
<td>Manage HF</td>
<td>See #1</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>CHF Risk</td>
</tr>
<tr>
<td>CARDIAC ASCVD</td>
<td>Neutral</td>
<td>Neutral</td>
<td>See #2</td>
<td>See #3</td>
<td>See #4</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>KETOACIDOSIS</td>
<td>Neutral</td>
<td>Neutral</td>
<td>DKA Can Occur</td>
<td>in Various Stress Settings</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

1. Caragilimab indicated for eGFR <45 mL/min/1.73 m² in patients with CKD 3a or albuminuria.
2. Stepagil—potential primary prevention of HF hospitalization & demonstrated efficacy in HFpEF.
3. Empagliflozin—FDA approved to reduce CV mortality. Caragilimab—FDA approved to reduce MACE events.
4. Possible increased hospitalizations for heart failure with angion and paroxysmal.

[Link to website](https://pro.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines-treatment-algorithms/comprehensive)
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.
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
Practice Patient Scenario 1

A 52-year-old male presents for follow up of his diabetes shortly after a recent hospitalization with a STEMI, and status post 2 cardiac stents placed. He is currently feeling well. He has been taking metformin 1000mg twice daily and glipizide 5mg once daily for diabetes therapy. HbA1c is currently 6.7%. He denies hypoglycemia events at home and reports home glucose monitoring values are 78-120 mg/dl. BMI is 32.

**Question:** What would you recommend to patient regarding his diabetes therapy at this time?

**Answer Choices:**

A. No change to therapy as diabetes is well controlled  
B. Increase glipizide to 5mg twice daily to reduce HbA1c < 6.5%  
C. Add basal insulin for tighter glycemic control  
D. Add GLP1-RA and discontinue glipizide
Practice Patient Scenario 1

Correct Answer: Add GLP1-RA and discontinue glipizide

Rationale: Although HbA1c is in the target range, given the presence of active ASCVD the patient would benefit from cardioprotection via addition of a GLP1-RA, along with weight loss benefit. Since some glucose values are borderline low it would be prudent to discontinue the sulfonylurea when adding his GLP1-RA to prevent hypoglycemia. Higher sulfonylurea and adding basal insulin would not confer cardioprotection and could raise the risk of hypoglycemia.
Practice Patient Scenario 2

49-year-old male is seen in the emergency department for a skin infection. His lab work is notable for HbA1c 7.5%. He has not seen a doctor for several years but reports having a history of an MI in his early 40s. He was never told of diabetes or prediabetes in the past. He has no medical insurance and mentions having trouble paying his rent. He usually eats fast food and notes that it is the most affordable option for him.

**Question:** What would you recommend for diabetes therapy?

**Answer Choices:**

A. Lifestyle modification and metformin
B. Lifestyle modification and SGLT2-I
C. Lifestyle modification and GLP1-RA
D. Lifestyle modification, SGLT2-i and GLP1-RA
Practice Patient Scenario 2

Correct Answer: Lifestyle modification and metformin

Rationale: Although this patient’s history of CAD would indicate a benefit for adding GLP1-RA, given his lack of insurance and trouble affording basic expenses it would be unlikely that this patient could afford this therapy (or SGLT2-i). Metformin is available as a generic and relatively inexpensive medication option for patients without insurance. Cost factors should be considered for patients when prescribing medications.
References


References


References


References


References


References


References


References


References


References
