Effects of SGLT2-i and GLP1-RA on CV and Limb Events, Primarily in Patients with PAD

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Disclosures

- Consulting and speaking for Jenssen, A.Z., and Lexicon
- No financial conflict related to this talk
- Information: evidence-based

Learning Objectives

- PAD: a major under-represented health problem with worse outcome than CAD and CVD!
- Effects of SGLT2-i and GLP1-RA in patients with CV risk or disease
- Effects of SGLT2-i and GLP1-RA in patients with PAD
- Current guidelines and evidence-based recommendations
- Summary
PAD a Major Atherosclerotic Disease

- Globally, over 236 million people with PAD, up from 200 million in 2010.
- PAD: 3rd. most common ASO after CAD and CVD.
  ➢ More significant cause of morbidity, mortality, and disability.
- Compared with CAD and CVD, evidence for optimal CV risk reduction therapy in patients with PAD is lacking.


Major CV Event Rates Despite Majority on Standard Therapy

![Cumulative Incidence](chart)

MACE and Hospitalization in PAD, CAD and CVD at 3 Years
Limb Events in PAD at 2 and 4 Years
Despite Standard Therapy

- MACE+Hospitalization (%) at 3 Yrs
- Limb Events (%) at 2-4 Years


DM and Cardiovascular Including PAD

- CVD: leading cause of morbidity and mortality in patients with T2D.
- 8.5 M Americans with PAD, 1/3rd have concurrent DM.
- PAD: underestimated in pts with DM due to neuropathy.
- Prediabetes: 20% with abnormal ABI.

- DM increases incidence of limb ischemia and amputation in pts with PAD:
  ➢Mechanisms: increased inflammation, endothelial dysfunction, augmented vasoconstriction, and thrombosis.

DM and Cardiovascular Disease

- Multiple SGLT2-i and GLP1-RA drugs: have shown significant reduction in MACE in patients with T2D and established or at risk for CVD.

- Some SGLT2-i have also shown substantial reduction in HHF and progression of CKD.

- PAD population was underrepresented in these CVOT.

- Will provide a general review of CVOT with SGLT2-i and GLP1-RA.

- Focus on PAD population when available.
SGLT-i Mechanism of Action

- Blocks the Na-gluc cotransporter at proximal tubule leading to glucosuria and natriuria.
- Lowers BP, weight, lipids and uric acid.
- Reduces arterial stiffness, pre and afterload, epicardial fat, and cardiac thrombosis
- Hyperketonemia.
- Exact mechanism for CV benefit is not well known!

- Available agents globally:
  - Canagliflozin, dapagliflozin, empagliflozin, sotagliflozin, ertugliflozin, luseogliflozin, ipragliflozin, and tofogliflozin


SGLT2-i Mechanism of Action

Exact Mechanism for CV Benefit is Unknown!


SGLT-i

Reduction in MACE
Empagliflozin (EMPA-REG) Trial

- 7020 patients with T2D and established CVD.
- 10 or 25 mg of empagliflozin or placebo as add on to the standard of care therapies.
- Study Duration: up to 3.1 years.
- Outcome: MACE.
- Results: significant reduction in MACE with empagliflozin, (mainly CV death reduction).
  - HR, 0.86; 95.02% CI, 0.74 to 0.99; P=0.04 for superiority.

Reduction in MACE
Empagliflozin (EMPA-REG) Trial


1461 patients (20.8%) had PAD at baseline (982 treated with empagliflozin, 479 with placebo).

Results were consistent between patients with and without PAD

- **MACE**: HR, 0.84; 95% CI, 0.62-1.14.
- **CV Death**: HR, 0.57; 95% CI, 0.37-0.88.
- **All-cause mortality**: HR, 0.62; 95% CI, 0.44-0.88.
- **HHF**: HR, 0.56; 95% CI, 0.35-0.92.
- **Incidence or worsening nephropathy**: HR, 0.54; 95% CI, 0.41-0.71.

- **Limb amputation**: not different, 5.5% vs 6.3% with placebo (HR, 0.84; 95% CI, 0.54-1.32).

Reduction in MACE
Empagliflozin (EMPA-REG) Trial-Sub-analysis - PAD

Heart Failure and Renal Outcome
Empagliflozin (EMPEROR Reduced)

- 7020 patients with HF and EF ≤ 40%.

- Empagliflozin 10 mg/daily or placebo as add on to the standard of care therapies.

- Outcome: CV death and HHF.

- **Primary outcome**, significant reduction: 19.4 vs 24.7% (HR, 0.75; 95% CI, 0.65 to 0.86; P<0.001), (mainly HHF).

- **MACE**, significant reduction: HR, 0.86; 95.02% CI, 0.74 to 0.99; P=0.04 for superiority.

- **The annual rate of decline in the eGFR**: slower with empagliflozin.
  - ~0.55 vs. ~2.28 ml/min per year, P<0.001.

Heart Failure and Renal Outcome
Empagliflozin (EMPEROR-Reduced)

- 5988 patients with HF and EF > 40%.

- Empagliflozin 10 mg/daily or placebo as add on to the standard of care therapies.

- Outcome: CV death and HHF.

- Results, primary outcome, significant reduction: 13.8% vs 17.1% (HR, 0.79; 95% CI, 0.69 to 0.90; P<0.001).

- The annual rate of decline in the eGFR: was slower with empagliflozin.
  - ~0.55 vs. ~2.28 ml/min per year, P<0.001.


Heart Failure and Renal Outcome
Empagliflozin (EMPEROR-Preserved)
Heart Failure and Renal Outcome
Empagliflozin (EMPEROR-Preserved)

Table 2. Primary and Secondary Composite Outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin (N=2097)</th>
<th>Placebo (N=2031)</th>
<th>Hazard Ratio with 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome—no. (%)</td>
<td>343 (16.4)</td>
<td>367 (17.9)</td>
<td>0.90 (0.80-1.01)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>409 (19.5)</td>
<td>412 (20.3)</td>
<td>0.97 (0.80-1.18)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>391 (18.8)</td>
<td>393 (19.4)</td>
<td>0.96 (0.76-1.21)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Secondary outcomes specified in the factorial testing procedure:

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin (N=2097)</th>
<th>Placebo (N=2031)</th>
<th>Hazard Ratio with 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of hospitalizations for heart failure</td>
<td>407</td>
<td>412</td>
<td>0.97 (0.80-1.05)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ΔeGFR (2021-2013) mean change (mg/dl)</td>
<td>-1.25 ± 4.11</td>
<td>-1.80 ± 4.11</td>
<td>0.36 (0.16-0.56)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| Other prespecified analyses:

- Change in KCCQ clinical summary score at 12 wks: 4.13 ± 5.68
- Total no. of hospitalizations for any cause: 2984
- Composite renal outcome—no. (%): 308 (14.6)
- Onset of new diabetes in patients with prediabetes—no. (%): 32 (16.0)
- Death from any cause—no. (%): 417 (20.6)

PAD Subgroup Analysis
Empagliflozin (EMPEROR-Pooled)

- 821/9718 (8.4%) patients had PAD (261 in Reduced and 560 in Preserved).
- PAD pts were more likely to be men (70.5% vs 62.6%), white (83.9% vs 72.9%), and older (72.2±8.3 vs 69.7±10.5 years).
- Patients with PAD were:
  - More symptomatic: median KCCQ scores [PAD, 68.8 versus no PAD, 75.0].
  - NYHA class III [PAD, 27.4% versus no PAD, 20.3%].
  - More likely to have ischemic HF (60.5% versus 39.9%).
  - More likely to be previous/current smokers (65.0% versus 48.8%).
  - More likely to have DM (65.2% versus 47.9%).
  - More likely to have HTN (90.6% versus 82.9%).
  - More likely to have and HL (84.8% versus 62.9%).

PAD Subgroup Analysis
Empagliflozin (EMPEROR- Pooled)

- PAD vs placebo group had an elevated risk of HF outcomes and mortality compared with no PAD.
- HHF, CV death, all-cause mortality, and composite of CV death/HHF were higher in pts with PAD.
  - HHF: $P = 0.007$; CV death: $P = 0.02$; all-cause mortality: $P = 0.002$; HHF/CV death: $P = 0.08$.
- The efficacy of empagliflozin on cardiorenal outcomes was consistent regardless of PAD history.
  - PAD: HR for total HHF, 0.64 [95% CI, 0.42–0.98] vs no PAD: HR for total HHF, 0.73 [95% CI, 0.63–0.84]; $P_{interaction} = 0.56$.
- Absolute risk reductions for total HHF events was higher (6.0% in PAD and 3.2% in no PAD groups).

Heart Failure and Renal Outcome
Empagliflozin (EMPA-Kidney)

- 6609 pts with CKD: (eGFR of at least 20) with a urinary albumin-to-creatinine ratio of at least 200.
- Empagliflozin 10 mg/daily or placebo.

- Outcome: composite of progression of kidney disease (ESRD, sustained decrease in eGFR to <10 ml/min, a sustained decrease in eGFR of ≥40% from baseline, or renal death) or CV death.

- Results, primary outcome, significant reduction: 13.1 vs 16.9% (HR: 0.72; 95% CI: 0.64 to 0.82; P<0.001).

- Annual rate of decline in the eGFR: was slower with empagliflozin.
  - −0.55 vs. −2.28 ml per minute per 1.73 m2 of body-surface area per year, P<0.001.

Reduction in MACE
Canagliflozin (CANVAS-CANVAS-Renal) Trials

- 10,142 participants with T2D and high CV risk.
- Canagliflozin 300 mg, 100 mg, or a matching placebo.
- Study Duration: up to 3.6 years.
- Combined analysis primary outcome: MACE.
- Results, MACE: significant reduction
  - HR: 0.86, 95% CI, 0.75 to 0.97; P<0.001 for noninferiority and P=0.02 for superiority.
  - CV Death: no significant difference.

Amputation Risk
Canagliflozin (CANVAS-CANVAS-Renal) Trials

- The risk of LE amputation was almost doubled with canagliflozin.
  - 6.3 vs. 3.4 participants per 1000 pts-years: HR, CI, 1.41-2.75.

- 187 participants had amputation, with 290 amputation events.
  - 123 single amputation event.
  - 71% minor amputation at the level of the toe or metatarsal.

- The highest absolute risk of amputation occurred among patients with PAD.


Amputation Risk
Canagliflozin (CANVAS-CANVAS-Renal) Sub-analysis

- An increased risk of amputation (major and minor) with canagliflozin compared to placebo.

- Anticipated risk factors for amputation:
  - Prior history of amputation
  - PAD
  - Neuropathy

- No specific etiological mechanism or at-risk subgroup for canagliflozin was identified.

Amputation Risk
Canagliflozin (CANVAS-CANVAS-Renal) Sub-analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All amputation</td>
<td>6.30</td>
<td>3.27</td>
<td>1.97 (1.41, 2.79)</td>
</tr>
<tr>
<td>Minor amputation</td>
<td>4.44</td>
<td>2.44</td>
<td>1.84 (1.21, 2.89)</td>
</tr>
<tr>
<td>Toe</td>
<td>3.44</td>
<td>2.16</td>
<td>1.58 (1.03, 2.43)</td>
</tr>
<tr>
<td>Transmetatarsal</td>
<td>1.04</td>
<td>0.29</td>
<td>4.17 (1.43, 12.16)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>1.82</td>
<td>0.93</td>
<td>2.03 (1.06, 3.80)</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.04</td>
<td>0.07</td>
<td>0.69 (0.64, 1.15)</td>
</tr>
<tr>
<td>Below knee</td>
<td>1.16</td>
<td>0.54</td>
<td>2.28 (0.97, 5.42)</td>
</tr>
<tr>
<td>Above knee</td>
<td>0.62</td>
<td>0.21</td>
<td>2.91 (0.83, 10.22)</td>
</tr>
<tr>
<td>Canagliflozin 100 mg vs placebo</td>
<td>0.17</td>
<td>0.27</td>
<td>0.24 (0.13, 0.46)</td>
</tr>
<tr>
<td>Canagliflozin 300 mg vs placebo</td>
<td>0.54</td>
<td>2.76</td>
<td>0.21 (0.12, 0.37)</td>
</tr>
</tbody>
</table>

Primary Results: significant reduction with canagliflozin:

- **43.2 and 61.2 per 1000 patient-years**, (HR, 0.70; 95% [CI], 0.59 to 0.82; P=0.00001).
- **MACE**, lower: (HR, 0.80; 95% CI, 0.67 to 0.95; P=0.01).
- **HHF**, lower: (HR, 0.81; 95% CI, 0.47 to 0.80; P=0.001).
- **Amputation rate, not significant**: 12.3 and 11.2 per 1000 patient-years (HR, 1.11; 95% CI, 0.79 to 1.56).


Renal Outcome
Canagliflozin (CREDENCE) Trial

- 4401 patients with T2D and albuminuric CKD.
- Canagliflozin 100 mg daily or placebo in addition to ACE-i
- Study Duration: up to 2.62 years.
- Combined analysis primary outcome: ESRD, a doubling of the serum CR level, or death from renal or CV causes.

Primary Results: significant reduction with canagliflozin:

- 43.2 and 61.2 per 1000 patient-years, (HR, 0.70; 95% [CI], 0.59 to 0.82; P=0.00001).
- **MACE**, lower: (HR, 0.80; 95% CI, 0.67 to 0.95; P=0.01).
- **HHF**, lower: (HR, 0.81; 95% CI, 0.47 to 0.80; P=0.001).
- **Amputation rate, not significant**: 12.3 and 11.2 per 1000 patient-years (HR, 1.11; 95% CI, 0.79 to 1.56).
Renal Outcome
Canagliflozin (CRENDECE) Trial


PAD Outcome
Canagliflozin (CANVAS and CREDENCE) Pooled-Analysis

- 3159 out of 14543 total pts (21.7%) had PAD at baseline.

- *Consistent* CV and renal benefits with or without PAD.
  - All P interaction > .268.
  - *Absolute* benefits of canagliflozin were *greater* in those with PAD.

- *MALE*: Not increased with canagliflozin regardless of PAD status.
  - P interaction > .864.

- The FDA removed the black box warning of lower limb amputations with the use of canagliflozin.

Barraclough JY et al. Diabetes Obes Metab. 2022 Jun;24(6):1072-1083
**PAD Outcomes**

**Canagliflozin (CANVAS and CREDENCE) Pooled Analysis**


- **Reduction in MACE**

**Dapagliflozin (DECLARE-TIMI 58) Trial**

- 17,160 patients with T2D including 10,186 without ASCVD.
- Dapagliflozin (10 mg) or placebo.
- Combined analysis primary outcome: MACE

Results: No significant reduction in MACE: HR, 0.93; 95% CI, 0.84 to 1.03; P=0.17.

- CV death or HHF, lower: 4.9% versus 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; P=0.005.
  - Mostly driven by reduction in HHF: HR, 0.73; 95% CI, 0.61 to 0.88.

- 1025 out of 17,160 patients (6%) had PAD
  - Amputation: no evidence of high risk.

**Amputation**

Reduction in MACE
Dapagliflozin (DECLARE-TIMI 58) Trial

PAD Outcomes
Dapagliflozin (DECLARE-TIMI 58) Sub-analysis

- Of the 17,160 patients, 1,025 (6%) had PAD.
- Patients with PAD had higher risk of MACE, CV death, HHF and renal events regardless of study drug.
- RRR with dapagliflozin in patients with PAD versus without was consistent:
  - CV death and HHF (P-interaction=0.79) and renal events (P-interaction=0.84).
- The ARR with dapagliflozin was greater among patients with PAD compared to those without:
  - 1.4% versus 0.9% for CV death or HHF, and 2.1% versus 1.3% for renal events.
- Limb events: No significant difference between dapagliflozin and placebo:
  - 3.37% versus 3.16% for limb ischemia (P=0.45) and 1.43% versus 1.32% for amputation (HR, P=0.53).

PAD Outcomes

Dapagliflozin (DECLARE-TIMI 58) Sub-analysis


Heart Failure

Dapagliflozin (DAPA-HF) Trial

- 4744 patients with NYHA class II, III, or IV HF and an EF of 40% or less.
- Dapagliflozin (10 mg once daily) or placebo.
- Primary outcome: composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death

- Results, primary outcome, reduced with dapa:16.3% vs 21.2%, (HR, 0.74; 95% [CI], 0.65 to 0.85; P<0.001).
  - HHF: HR, 0.70; 95% CI, 0.59 to 0.83.
  - CV death: HR, 0.82; 95% CI, 0.69 to 0.98.
  - Death from any cause: HR, 0.83; 95% CI, 0.71 to 0.97.

- Amputation risk: No significant difference.

Heart Failure
Dapagliflozin (DAPA-HF) Trial

• Dapagliflozin (10 mg once daily) or placebo.

Primary outcome: composite of a sustained decline in the eGFR of at least 50%, ESRD, or death from renal or CV causes.

- Results, primary outcome: Significantly lower with dapagliflozin than placebo:
  - 9.2% vs 14.5% (HR, 0.61; 95% CI, 0.51 to 0.72; P<0.001).
  - Death from renal causes was also significantly reduced.
  - HR, 0.56; 95% CI, 0.45 to 0.68; P<0.001.

Renal Outcomes
Dapagliflozin (DAPA-CKD) Trial

• 4304 pts with an eGFR of 25-75 and a urinary alb-to-Cr ratio of 200 to 5000.

- Dapagliflozin risk:
  - No significant difference.
Renal Outcomes
Dapagliflozin (DAPA-CKD) Trial


PAD Outcomes
Dapagliflozin Pool-analysis of 2b-3a Trials

- LE amputation, not different: 8 (0.1%) with dapagliflozin and 7 (0.2%) with placebo.

- Risk factors for amputation in both groups were:
  - Neuropathy
  - CVD
  - Dyslipidemia

10,584 patients with T2D, CKD (eGFR 25–60 mL/min/1.73 m2) and risks for CVD.
- Sotagliflozin or placebo.
- Primary outcome: CV death, HHF, and urgent visits for HF.
- Ended early due to loss of fund.

Results, primary outcome: reduced with sotagliflozin.
- 5.6 vs. 7.5%; HR 0.74; 95% CI, 0.63 to 0.88; P<0.001.

MACE, reduced: HR 0.84; 95% CI, 0.72 to 0.99.

• 1222 patients with T2D and a recent hospitalization for acute decompensated HF (either reduced or preserved EF%).
• Sotagliflozin or placebo.
• Primary outcome: CV death and hospitalizations and urgent visits for HF.
• Ended early due to loss of fund.

• Results, primary outcome: reduced with sotagliflozin.
  ➢ 51.0 versus. 76.3%; HR, 0.67; 95% CI, 0.52 to 0.85; P<0.001.
• Death from CV or any cause: no significant difference.


### Table 1. Primary End Point and Secondary End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Sotagliflozin (N=614)</th>
<th>Placebo (N=614)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure — total no. of events (Rate)</td>
<td>245 (40.4)</td>
<td>355 (58.3)</td>
<td>0.67 (0.52 to 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary end points (in order of hierarchical testing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations and urgent visits for heart failure — total no. of events (Rate)</td>
<td>194 (31.6)</td>
<td>297 (48.3)</td>
<td>0.64 (0.49 to 0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deaths from cardiovascular causes — total no. of events (Rate)</td>
<td>51 (8.4)</td>
<td>58 (9.5)</td>
<td>0.84 (0.58 to 1.22)</td>
<td>0.346</td>
</tr>
</tbody>
</table>

Ertugliflozin (VERTIS-CV) Trial

- 8246 patients with T2D and ASCVD.
- Ertugliflozin 5 or 15 mg or placebo.
- Primary outcome: MACE.

- Results, MACE: not significant
  - HR, 0.97; 95.6% CI, 0.85 to 1.11; P=0.001 for non-inferiority.
- CV death or HF: were not significant
  - HR, 0.88; 95.8% CI, 0.75 to 1.03; P=0.11 for superiority.

- Amputations: in 54 pts (2.0%) with 5-mg of ertugliflozin and in 57 pts (2.1%) with 15-mg, as compared with 45 pts (1.6%) with placebo.

## SGLT-i Drugs Dosing and Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>10 mg daily</td>
<td>1- Improve glycemic control in T2D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Reduce the risk of CV death in adults with T2D and established CV disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Reduce CV death and HHF in adults with HF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4- Reduce renal disease progression, CV death or hospitalization in patients with CKD</td>
</tr>
<tr>
<td></td>
<td>100 mg daily</td>
<td>1- Improve glycemic control in T2D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Reduce MACE in adults with T2D and established CVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Reduce risk of ESRD, doubling of Cr, CV death, and HHF in T2D with albuminuria (&gt;300 mg/day)</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>10 mg daily</td>
<td>1- Improve glycemic control in T2D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Reduce risk of HHF in adults with T2D and known CVD or multiple CV risks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Reduce risk of CV death and HHF in adults with HF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4- Reduce risk of worsening renal disease, ESRD, CV death and HHF in pts with CKD</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>10 mg daily</td>
<td>1- Improve glycemic control in T2D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Reduce risk of HHF in adults with T2D and known CVD or multiple CV risks</td>
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<td></td>
<td>3- Reduce risk of CV death and HHF in adults with HF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4- Reduce risk of worsening renal disease, ESRD, CV death and HHF in pts with CKD</td>
</tr>
<tr>
<td>Sotagliflozin</td>
<td>200-400 mg daily</td>
<td>1- Reduce risk of CV death/HHF in adults with HF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Reduce risk of CV death/HHF in adults with T2D, CKD, and other CV risks</td>
</tr>
</tbody>
</table>


### SGLT-i: Summary

- **Empagliflozin**: Reduction in MACE (EMPA-REG), HHF and CV death (EPERORs), and renal and CV outcomes (EMPA-Kidney). *No difference in amputation risk (EMPA-REG sub-analysis).*

- **Canagliflozin**: Reduction in MACE (CANVAS). *Increased amputation risk.* Reduction in CV and renal outcomes (CREDENCE). *No difference in amputation risk.*

- **Dapagliflozin**: Reduction in HHF/CV death (DAPA-HF), renal/CV outcome (DAPA-CKD), no difference in MACE (DECLARE-TIMI 58). *No difference in amputation risk.*

- **Sotagliflozin**: Reduction in HHF/CV death and MACE (SCORED/SOLOIST-WHF).

- **Ertugliflozin**: No difference HHF/CV death (VERTIS-CV). *No difference in amputation risk.*

Glucagon Like Peptide Receptor Agonist (GLP1-RA)

**Mechanism of Action**

- **Food**—GLP1 secretion from L-cells—inactivated after 2-3 mins by the DPP-4, (GLP-1 is reduced in T2D).
- **GLP1-RA**—increases GLP-1—increases insulin/reduces glucagon and delaying gastric emptying—reduces gluc.
- **CV benefits**: weight, BP and Tg reductions, natriuresis, anti-inflammatory properties.
  - Anti-atherosclerotic and thrombotic effects.
- **Six GLP1-RA SC agents**:
  - Short-acting: exenatide, lixisenatide
  - Intermediate-acting: liraglutide
  - Long-acting: exenatide, dulaglutide, albiglutide, and semaglutide (comes in oral too)

- **GIP** (glucose dependent insulinotropic polypeptide) and GLP1-RA: Tirzepatide (*Mounjaro*)

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**GLP1-RA Mechanism of Action**

*Exact Mechanism Behind CV Benefit Not Well Known!*

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GLP1-RA Reduction in MACE
Dulaglutide (REWIND) Trial

- 9,901 patients with T2D and previous CV events or risk.
- Weekly SC dulaglutide (1.5mg) or placebo.
- Outcome: MACE.

Results, MACE: significant reduction with dulaglutide.
➢ HR: 0.88; 95% CI: 0.79 to 0.99, P=0.026.
➢ Driven by reduction of stroke: HR: 0.76; 95% CI: 0.62 to 0.94.

PAD Outcome

Dulaglutide (Effects of Dulaglutide on Endothelial Progenitor Cells and Arterial Elasticity in Patients with T2D) Study

- Sixty patients with T2D.
- Metformin monotherapy group (n = 30), and metformin combined with dulaglutide group (MET-DUL group, n = 30).

- Outcome: number of CD34+CD133+ endothelial progenitor cells (EPCs) and the brachial–ankle pulse wave velocity (baPWV).

- Results: NO levels and EPCs increased with dulaglutide (P < 0.05).
- EPC proliferation, adhesion, migration, and tubule formation abilities were significantly enhanced (P < 0.05).

Reduction in MACE
Liraglutide (LEADER) Trial

- 9,340 patients with T2D and high CV risk (81% had established CV disease).
- Weekly SC liraglutide or placebo.
- Outcome: MACE.
- Results, MACE, significant reduction: 13.0% vs 14.9% (P<0.001 for non-inferiority; P=0.01 for superiority).
  - Driven by reduction of CV death: 4.7 vs 6.0% (HR, 0.78; 95% CI, 0.66 to 0.93; P=0.007).
- Post-hoc analysis:
  - In pts with DFU, significant reduction in amputations (HR 0.65, 95% CI 0.45, 0.95; P = 0.03).
  - No difference in foot infection or revascularization.

Reduction in MACE
Semaglutide (SUSTAIN-6 and PIONEER-6) Trials

SUSTAIN-6 Trial
- 3,297 patients with T2D and high CV risk.
- Once weekly 0.5 - 1 mg SC semaglutide or placebo, follow up 2.1 years.
- Outcome: MACE.
- Results, MACE: significant reduction: HR, 0.74; 95% CI, 0.58 to 0.95; P<0.001 for non-inferiority.
  - Driven by reduction of non-fatal stroke: HR, 0.61; 95% CI, 0.38 to 0.99; P=0.04.

PIONEER-6 Trial
- 3183 patients with established CV or CKD
- Oral semaglutide or placebo
- Outcome: MACE
  - No significant difference 3.8% with semaglutide vs 4.8% in placebo: HR 0.79, 95% CI 0.57–1.11; P < 0.001 for non-inferiority.

PAD Outcome
Liraglutide/Semaglutide (LEADER and SUSTAIN-6) Post-hoc Analysis

- In LEADER and SUSTAIN 6 trials, 1184/9340 (12.7%) and 460/3297 (14%) of pts had PAD.
- Patients with PAD had ~35% greater risk of MACE irrespective of treatment, compared to those without.
  - LEADER: hazard HR 1.36, 95% CI 1.17-1.58; SUSTAIN 6: HR 1.33, 95% CI 0.94-1.83.
- The benefit of MACE risk reduction was consistent in PAD.
  - (Liraglutide: HR 0.77, 95% CI 0.58-1.01; semaglutide: 0.61, 0.33-1.13) vs without (liraglutide: HR 0.89, 95% CI 0.79-1.00; semaglutide: HR 0.77, 95% CI 0.58-1.01; P interaction = .34 for liraglutide and .49 for semaglutide).
- Absolute risk reductions of MACE with both medications were greater in patients with PAD.
  - (Liraglutide: 4.13%-point, 95% CI -0.15-8.42; semaglutide: 4.63%-point, 95% CI -0.58-9.84) versus without (liraglutide: 1.42%-point, 95% CI -0.03-2.87; semaglutide: 1.90%-point, 95% CI 0.00-3.80).

9463 patients with T2D and CVD.
Weekly SC albiglutide (30-50 mg based on glycemic control) or placebo.
Outcome: MACE at 1.5 year.
Results, MACE, significant reduction: HR: 0.78, 95% CI 0.68–0.90, p=0.0006.
Driven by risk reduction of MI.
The drug was withdrawn from the market due to economic reasons.

Reduction in MACE
Exenatide (EXCEL) Trial

- 14,752 patients with T2D with or without CVD.
- Weekly SC exenatide (2 mg) or placebo.
- Outcome: MACE.
- Median follow up of 3.2 years.
- MACE, non-inferior: HR, 0.91; 95% [CI], 0.83 to 1.00, P<0.001 for non-inferiority and P=0.06 for superiority.

2800 (19%) of the EXSCEL pts had PAD.

- Higher MACE: 13.6% versus 11.4%: adjusted HR, 1.13 [95% CI, 1.00-1.27]; P=0.047.
- Higher all-cause mortality: adjusted HR 1.38 [95% CI, 1.20-1.60]; P<0.001.
- More frequent lower extremity amputation: adjusted HR 5.48 [95% CI, 4.16-7.22]; P<0.001.

MACE and amputation: Similar with exenatide and placebo, regardless of PAD.
- All-cause mortality: Lower with exenatide in patients with T2D and PAD (consistent with main trial).
Reduction in MACE
Lixisenatide (ELIXA) Trial

- 6068 patients with T2D and a history of acute coronary syndrome.
- SC Lixisenatide or placebo.
- Outcome: 4-point MACE (CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina).
- Median follow up of 2.1 years.
- 4-Point MACE, non-inferior: HR 1.02, 95% CI 0.89–1.17, p = 0.81.
- HHF, not different: HR 0.96; 95% CI, 0.75 to 1.23.
- Rate of death, not different: HR, 0.94; 95% CI, 0.78 to 1.13.

Current and Future Research

- **STARDUST Trial:**
  - Open-label, randomized controlled trial, to evaluate the effects of liraglutide on peripheral perfusion, as compared to aggressive treatment of cardio-metabolic risk factors in people with T2D and PAD.
  - Pending results.

- **STRIDE Trial:**
  - Evaluates the effects of semaglutide vs placebo on walking ability in patients with T2D and PAD.
  - Closed with pending results.

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses</th>
<th>Indications</th>
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</table>
| Dulaglutide   | Initiate 0.75 mg SC/wk titrate to max | 1- Improve glycemic control in adults with T2D.  
2- Reduce MACE in adults with T2D with established or at risk for CVD. |
| Trulicity®    |                                |                                                                             |
| Liraglutide   | Initiate 0.6 mg SC/day titrate to max | 1- Improve glycemic control in adults with T2D.  
2- Reduce MACE in adults with T2D and established CVD.  
3- Weight reduction as adjunct to diet/exercise in obese or overweight+comorbidity. |
| Victosa®      |                                |                                                                             |
| Saxenda®      |                                |                                                                             |
| Semaglutide   | Initiate 0.25 mg SC/wk titrate to max | 1- Improve glycemic control in adults with T2D.  
2- Reduce MACE in adults with T2D and established CVD.  
3- Weight reduction as adjunct to diet/exercise in obese or overweight+comorbidity. |
| Ozempic®      |                                |                                                                             |
| Wegovy®       |                                |                                                                             |

**GLP1-RA: Summary**

- Dulaglutide: Reduction in MACE (REWIND) driven by reduction in stroke.
- Liraglutide: Reduction in MACE (LEADER) driven by reduction in CV death. *Significant reduction in amputation risk (Post-hoc).*
- Albiglutide: Reduction MACE (HARMONY), driven by reduction of MI risk.
- Exenatide: non-inferior MACE (EXCEL). *No significant difference in amputation risk*
- Lixisenatide: non-inferior 4-point MACE (VELIXA).


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**SGLT2-i**

**Risk of Amputation**

- Amputation risk: increased in CANVAS but not in a pooled analysis of CANVAS and CREDENCE trials.
- Not reported with other SGLT2-i agents.
- CANVAS and CREDENCE trials’ populations are different but no confirmed explanation for difference in amputation.
- Proposed mechanisms: glycosuria-induced hypovolemia and hypo-perfusion.
  - **SURDIAGENE study:** worsened amputation with diuresis.
- A meta-analysis of CRTs of SGLT2-i drugs in pts with T2D:
  - A positive association between SGLT2i-induced BP/weight reduction and limb events including amputation and PAD.
  - SGLT2-i drugs in 51,847 pts, with or without signs of hypovolemia, was not associated with an increased amputation!

SGLT2-i
Risk of Amputation, Cont.

• Six observational studies using the Truven Market Scan health claims database from the USA. The results vary:
  ➢ No difference in amputation risk with canagliflozin compared with non-SGLT2-i agents in 3 studies.
  ➢ Lower amputation risk with SGLT2-i drugs (canagliflozin comprised 70% of SGLT2-i use) compared with sulfonylurea, but not compared to DPP-4 inhibitors in 2 studies.
  ➢ Only one study showed a higher amputation risk with SGLT2-i drugs compared with DPP-4 inhibitors, but not compared with sulfonylurea or non-metformin, non-SGLT2-i agents.

• Observational study using the U.S. Department of Defense Health System:
  ➢ SGLT2-i associated with twofold risk of amputation vs non-SGLT2-i agents (HR 1.99; 95% CI 1.12–3.51 mostly with canagliflozin).

• Observational study using the Swedish/Danish National Register:
  ➢ Increased amputation incidence with SGLT2-i drugs compared with GLP1-RA (HR 2.48; 95% CI 1.14–5.40).

• Large multicenter observational study from seven Canadian provinces and the U.K.:
  ➢ No association with SGLT2-i drugs, including canagliflozin, compared with DPP-4 inhibitors.

• A retrospective analysis from Taiwan National Health Insurance Database:
  ➢ No difference in amputation between SGLT2-i drugs compared to DDP-4, GLP1-RA, and other medications.

• Heterogeneity of results: differences in studies population, methods, comparator drugs, the extent of amputation recorded, follow-up duration, and inclusion or exclusion of patients with a history of amputations.

• Until stronger data is available, SGLT2-i (mainly canagliflozin) may need to be avoided in patients with high risk for amputation (previous amputation, ischemic ulcers, or neuropathy).

GLP1-RAs Risk of Amputation

- Trials have *not exclusively* addressed PAD or lower limb complication as a primary or secondary endpoint.

- Although a post-hoc analysis of the LEADER trial demonstrated a *reduction in amputations* with liraglutide versus placebo, there is *no strong evidence* regarding the effect of GLP1-RAs on MALE.

- A real-world study has evaluated the role of GLP1-RA in 9772 patients in clinical practice:
  > GLP1-RAs were associated with *lower rates* of death, cerebrovascular disease and ischemic stroke, PVD, and lower limb complications compared with other therapies.

- Scandinavian population-based study:
  > *Lower risk* of limb outcome with liraglutide compared to DDP-4.

---

GLP1-RAs Risk of Amputation Cont.

- A retrospective analysis conducted using the Taiwan National Health Insurance database:
  > GLP1-RAs were associated with significantly *lower risks* of MALE when compared with DPP4i drugs.
  
  > This was mainly driven by the *reduction* of the amputation rate.
  
  > GLP1-RAs were associated with *lower risks* of MACE and death from any cause.
<table>
<thead>
<tr>
<th>Trials with SGLT-i</th>
<th>Study Design</th>
<th>Patients (n)</th>
<th>Primary End Point</th>
<th>Treatment Arms</th>
<th>Incidence</th>
<th>RR or HR</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMPAFLIFLOZIN</strong></td>
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<tr>
<td>EMPA-REG 2015</td>
<td>RCT</td>
<td>7,020</td>
<td>MACE</td>
<td>Empagliflozin – 10 or 25 mg Placebo</td>
<td>10.5%</td>
<td>HR 0.86 [0.74 – 0.99] Non-inferiority: &lt;0.001 Superiority: 0.04</td>
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</tr>
<tr>
<td>EMPEROR REDUCED 2020</td>
<td>RCT</td>
<td>4744</td>
<td>CV death or HHF</td>
<td>Empagliflozin – 10 mg Placebo</td>
<td>19.4%</td>
<td>HR 0.75 [0.65 – 0.86] Superiority &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>EMPEROR PRESERVED 2021</td>
<td>RCT</td>
<td>5988</td>
<td>CV death or HHF</td>
<td>Empagliflozin – 10 mg Placebo</td>
<td>13.8%</td>
<td>HR 0.79 [0.69 – 0.90] Superiority &lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>CANVAS &amp; CANVAS-Renal 2017</strong></td>
<td>RCT</td>
<td>10,142</td>
<td>MACE</td>
<td>Canagliflozin – 100 or 300 mg Placebo</td>
<td>26.9 patients/1000 patient-year 31.5 patients/1000 patient-year</td>
<td>HR 0.86 [0.75 – 0.97] Non-inferiority: &lt;0.001 Superiority: 0.02</td>
<td></td>
</tr>
<tr>
<td>CREDENCE 2019</td>
<td>RCT</td>
<td>4,401</td>
<td>ESRD, a doubling of the serum or level, or death from renal or CV causes</td>
<td>Canagliflozin – 100 mg Placebo</td>
<td>43.2 events per 1000 patient-years</td>
<td>HR 0.70 [0.59 – 0.82] P=0.00001</td>
<td></td>
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</tbody>
</table>


| **DAPAGLIFLOZIN** |              |              |                   |                |           |              |         |
| DECLARE-TIMI 2019 | RCT          | 17,160       | CV death or HHF   | Dapagliflozin – 10 mg Placebo | 4.0%     | HR 0.83 [0.73 – 0.95] 0.006 |
| DAPA-HF 2019      | RCT          | 4,744        | Composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death | Dapagliflozin – 10 mg Placebo | 16.3%     | HR 0.74 [0.65 – 0.85] <0.001 |
| DAPA-CKD 2020     | RCT          | 4,304        | Composite of a sustained decline in the eGFR of at least 50%, ESRD, or death from renal or CV causes | Dapagliflozin – 10 mg Placebo | 9.2%     | HR 0.61 [0.51 – 0.72] <0.001 |
| **SOTAGLIFLOZIN** |              |              |                   |                |           |              |         |
| SCORED 2021       | RCT          | 10,584       | CV death or HHF or urgent visit for HF | Solagliflozin Placebo | 5.6%     | HR 0.74 [0.63 – 0.88] Superiority: <0.001 |
| SOLOIST WHF 2021  | RCT          | 1222         | CV death and HHF and urgent visit for HF | Solagliflozin Placebo | 51.0%     | HR 0.67 [0.52 – 0.85] Superiority: <0.001 |
| **ERTUGLIFLOZIN** |              |              |                   |                |           |              |         |
| VERTIS-CV 2020    | RCT          | 8,246        | MACE              | Erugliflozin – 5 or 15 mg Placebo | 11.9%     | HR 0.97 [0.85 – 1.11] Non-inferiority <0.001 |

### GLP1-RA Related Clinical Trial Data

<table>
<thead>
<tr>
<th>Trial with GLP1-RA</th>
<th>Study Design</th>
<th>Patients (n)</th>
<th>Primary End Point</th>
<th>Treatment Arms</th>
<th>Incidence</th>
<th>RR or HR [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DULAGlutide</strong></td>
<td>RCT</td>
<td>9,901</td>
<td>MACE</td>
<td>Dulaglutide – 1.5 mg Placebo</td>
<td>12%</td>
<td>HR 0.88 [0.79 - 0.99]</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>LIRAglutide</strong></td>
<td>RCT</td>
<td>9,340</td>
<td>MACE</td>
<td>Liraglutide – 1.8 mg Placebo</td>
<td>13%</td>
<td>HR 0.87 [0.78 – 0.97]</td>
<td>Non-inferiority: &lt;0.001 Superiority: 0.01</td>
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<tr>
<td><strong>SEMAglutide</strong></td>
<td>RCT</td>
<td>3,297</td>
<td>MACE</td>
<td>Semaglutide – 0.5 or 1.0 mg Placebo</td>
<td>6.6%</td>
<td>HR 0.74 [0.58 – 0.95]</td>
<td>Non-inferiority: &lt;0.001 Superiority: 0.02</td>
</tr>
<tr>
<td><strong>ALBIGlutide</strong></td>
<td>RCT</td>
<td>9,463</td>
<td>MACE</td>
<td>Albiglutide – 30 or 50 mg Placebo</td>
<td>7%</td>
<td>HR 0.78 [0.68 – 0.90]</td>
<td>Non-inferiority: &lt;0.001 Superiority: 0.0006</td>
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<tr>
<td><strong>EXENAglutide</strong></td>
<td>RCT</td>
<td>14,752</td>
<td>MACE</td>
<td>Exenatide – 2mg Placebo</td>
<td>11.4%</td>
<td>HR 0.91 [0.83 – 1.00]</td>
<td>Non-inferiority: &lt;0.001 Superiority: 0.06</td>
</tr>
<tr>
<td><strong>LIXISENatide</strong></td>
<td>RCT</td>
<td>6,068</td>
<td>MACE</td>
<td>Lixisenatide – 10 or 20 μg Placebo</td>
<td>13.4%</td>
<td>HR 1.02 [0.89 – 1.17]</td>
<td>Non-inferiority: &lt;0.001 Superiority: 0.81</td>
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</tbody>
</table>

### SGLT-i and GLP1-RA with PAD Outcome

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Patients (n)</th>
<th>Primary End Point</th>
<th>Treatment Arms</th>
<th>Incidence</th>
<th>RR or HR [95% CI]</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>SGLT-i Drugs</strong></td>
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<tr>
<td>EMPA-REG 2015</td>
<td>RCT</td>
<td>1,461 (PAD Subgroup)</td>
<td>MACE</td>
<td>Empagliflozin 10 or 25 mg Placebo</td>
<td>12.2%</td>
<td>HR 0.84 [0.62 – 1.14]</td>
<td>P-interaction 0.9052 NR</td>
</tr>
<tr>
<td>CANVAS &amp; CANVAS-Renal 2017</td>
<td>RCT</td>
<td>2,113 (history of PAD)</td>
<td>MACE</td>
<td>Canagliflozin – 100 or 300 mg Placebo</td>
<td>33.9</td>
<td>HR 0.75 [0.58 – 0.97]</td>
<td>P-interaction &gt; 0.05 NR</td>
</tr>
<tr>
<td>DECLARE-TIMI 2019</td>
<td>RCT</td>
<td>6,994 (pts with any ASCVD)</td>
<td>CV death or HHF</td>
<td>Dapagliflozin – 10 mg Placebo</td>
<td>272/3474 = 7.8% 325/3500 = 9.3%</td>
<td>HR 0.83 [0.71 – 0.98] P-interaction 0.79 NR</td>
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<tr>
<td><strong>GLP1-RA Drugs</strong></td>
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<tr>
<td>LEADER 2018</td>
<td>Post Hoc</td>
<td>9,340</td>
<td>Diabetic foot ulcers</td>
<td>Liraglutide – 1.8 mg Placebo</td>
<td>3.8%</td>
<td>HR 0.92 [0.75 – 1.13]</td>
<td>0.41</td>
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<tr>
<td><strong>EXENAtide</strong></td>
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<tr>
<td>EXSCEL 2017</td>
<td>Post Hoc</td>
<td>13,951 (without -PAD) 2,800 (with -PAD)</td>
<td>MACE</td>
<td>Exenatide – 2 mg Placebo</td>
<td>11.4%</td>
<td>HR 1.13 [1 – 1.27] P-interaction 0.06</td>
<td>0.047</td>
</tr>
</tbody>
</table>
## Summary of Societal Guideline Recommendations

<table>
<thead>
<tr>
<th>Societal Guidelines</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **2023-ADA**        | • T2D and high risk for or eASCVD, DKD, or HF: Recommend SGLT2-i or GLP1-RA with demonstrated CV benefit.  
                      • T2D and high risk for or eASCVD and DKD: Recommend SGLT2-i.  
                      • T2D and high risk for or eASCVD: Recommend GLP1-RA or a combination with SGLT2-i (in CKD).  
                      • HFrEF/HFpEF: Recommend SGLT2i with proven benefit (eGFR>20ml/min).  
                      • CKD and albuminuria: Recommend a SGLT2-i with evidence of reducing CKD progression. |
| **2019-ACC/AHA: Primary Prevention of CVD** | • Glycemic Control: Recommend metformin as first line pharmacological agent.  
                      • T2D and additional ASCVD risk factors: reasonable to initiate a SGLT2-i or a GLP1-RA as add on to metformin. |
| **2020-ACC Expert Consensus Decision Pathway on Novel Therapies for CV Risk Reduction in Patients with T2D** | • T2D and ASCVD: Recommend starting SGLT2-i or GLP1-RA with CV benefit.  
                      • DKD and/or HF: Consider a SGLT2-i.  
                      • eGFR <30 ml/min/1.73 m²: Consider a GLP1-RA as an alternative.  
                      • At discharge after ASCVD admission: Consider a SGLT2-i or GLP1-RA.  
                      • Consider SGLT2-i in case of HFrEF. |
| **2022-AHA/ACC/HFSA Heart Failure** | • HFrEF: Recommend SGLT2i regardless of T2D.  
                      • SGLT2-i can also be beneficial in HFmrEF and HFpEF. |
| **2019-ESC on DM and CVD-2019** | • T2D and CVD or high CV risk: Recommend empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, or dulaglutide to reduce CV events.  
                      • Recommend empagliflozin or liraglutide to reduce risk of CV death. |

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**ASCVD:** atherosclerotic cardiovascular disease; **DM:** diabetes mellitus, **DKD:** diabetic kidney disease, **eGFR:** estimated glomerular filtration rate; **GLP1-RA:** glucagon like peptide 1 receptor agonist; **HF:** heart failure; **PAD:** peripheral arterial disease; **SGLT2i:** sodium glucose cotransporter-2 inhibitor.

* Defined as history of acute coronary syndrome, myocardial infarction, stable or unstable angina, coronary heart disease, PAD, arterial revascularization, stroke, atherosclerosis

** Age, hypertension, smoking, dyslipidemia, obesity, or patients with end organ damage (e.g. ventricular hypertrophy, retinopathy).

*** Defined as reduced eGFR, albuminuria, or both.
PAD and T2D are two prevalent and often concurrent major health problems with increased morbidity and mortality.

SGLT-i and GLP1-RA have shown a significant reduction of MACE in patients with T2D and CVD.

Some SGLT-i have shown a significant reduction in CV mortality, HHF, and renal outcome. Few GLP1-RA drugs have weight and stroke risk reductions.

PAD had worse CV outcomes in most trials. RRR of CV outcome was generally consistent and ARR was more in patients with and without PAD.

Amputation risk: Inconsistent data with SGLT-i (mainly with canagliflozin). Signal of reduced MALE with GLP1-RAs (mainly with liraglutide).

Summary


Thank You!
Nedaa Skeik

Sunset, Gaza City (Prayers for Peace!)