CARDIO-DIABETES CROSSFIRE
AT HF UPDATE
Faculty

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Conflict of Interest

Shelley Zieroth, MD, FRCPC, FCCS
- **Consulting Fees/Honoraria:** Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Servier, Akcea, Cardiol Therapeutics
- **Clinical Trials:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis

Eileen O’Meara, MD
- **Consulting Fees/Honoraria:** Amgen, AstraZeneca, Bayer, BMS/Pfizer Alliance, Novartis, Servier
- **Clinical Trials:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck

Lori Berard, RN, CDE
- **Consulting Fees/Honoraria:** AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Johnson & Johnson, Merck, Sanofi, Novo Nordisk
- **Clinical Trials:** N/A

Navdeep Tangri, MD, PhD, FRCPC
- **Consulting Fees/Honoraria:** AstraZeneca, Boehringer Ingelheim, Eli Lilly, Triceda Inc.
- **Clinical Trials:** AstraZeneca, Johnson & Johnson
Disclosure of Commercial Support

Specific details of relationship:
• This program has received financial support from BI-Lilly Pharmaceuticals Canada in the form of an educational grant

Potential for conflict(s) of interest:
• Speakers have received honoraria from BI-Lilly Pharmaceuticals Canada
• BI-Lilly is the manufacturer and benefits from the sale of empagliflozin
Mitigating Potential Bias

Potential biases are acknowledged and are mitigated by presenting data supported by national and international guidelines, and as follows:

• Information presented is evidence-based
• Material has been developed and reviewed by a Planning Committee

Off-label uses of drugs will be discussed and identified as such by the speaker
Learning Objectives

After attending the symposium, participants will be able to:

• Identify individualized treatment options for CV and renal protection in patients with T2DM
• Explain the role of SGLT2 inhibitors in the prevention and treatment of heart failure
• Describe practical recommendations and tips when starting SGLT2 inhibitors
Accreditation

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Canadian Cardiovascular Society. You may claim a maximum of 1 hour.
## Agenda

<table>
<thead>
<tr>
<th>TIME</th>
<th>TOPIC</th>
<th>SPEAKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:35 p.m.</td>
<td><strong>Welcome and Introductions</strong></td>
<td>Shelley Zieroth, MD</td>
</tr>
<tr>
<td>12:45 p.m.</td>
<td>Diabetes Management: What Every Cardiologist Needs to Know</td>
<td>Lori Berard, RN</td>
</tr>
<tr>
<td>1:05 p.m.</td>
<td>Heart Failure Management</td>
<td>Eileen O'Meara, MD</td>
</tr>
<tr>
<td>1:25 p.m.</td>
<td>Chronic Kidney Disease Management</td>
<td>Navdeep Tangri, MD</td>
</tr>
<tr>
<td>1:45 p.m.</td>
<td>Closing Remarks</td>
<td>Shelley Zieroth, MD</td>
</tr>
</tbody>
</table>
#Cardiotwitter Question

Shelley Zieroth @Shelle... · 14 Apr.

My 1st #CardioTwitter poll! Prep for #CardioDiabetes at #HFUpdate2019 + #CREDENCE LBCT at #ISNWCN today. @DocSavageTJU @DrMarthaGulati @HeartOTXHeartMD @mmamas1973 @hvanspall @AnastasiaSMihai @ErinMichos @mirvatalasnag Are you more likely to Rx SGLT2i’s for eligible pts with:
ARS Question

• Are you more likely to Rx SGLT2i’s for eligible patients with:
  • T2DM + CVD = 62%
  • T2DM + history of HF = 33%
  • I let endocrinologist start = 5%
  • I only prescribe GLP1-RA’s = 0%
#Cardiotwitter Answer

My 1st #CardioTwitter poll! Prep for #CardioDiabetes at #HFUpdate2019 + #CREDENCE LBCT at #ISNWCN today. @DocSavageTJU @DrMarthaGulati @HeartOTXHeartMD @mmamas1973 @hvanspall @AnastasiaSMihai @ErinMichos @mirvatalasnaq Are you more likely to Rx SGLT2is for eligible pts with:

- DM2 + CVD 51%
- DM2 + history of HF 32%
- I let endo start 15%
- I only prescribe GLP1-RA 2%

164 votes • Final results
LEADER: Summary

Liraglutide in addition to standard of care reduced CV risk and improved overall survival in adults with T2D and age ≥50 yrs with established CVD or CKD or age ≥60 yrs with an additional risk factor

13% 22% 15% 14% 22%

↓ CV death, non-fatal MI, non-fatal stroke (NNT 3y = 104)
↓ CV death (NNT 3y = 98)
↓ All-cause mortality (NNT 3y = 127)
↓ Fatal and non-fatal MI (NNT 3y = 127)
↓ New or worsening nephropathy (NNT 3y = 85)

The overall safety profile of liraglutide was consistent with previous clinical trials and current label information

LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation; CVD: cardiovascular disease; CKD: chronic kidney disease; T2D: type 2 diabetes; MI: myocardial infarction; NNT: number needed to treat

Liraglutide is not currently indicated for renal protection in Canada.

SUSTAIN-6: Summary

Semaglutide once weekly in addition to standard of care reduced CV risk in adults with T2D and age ≥50 yrs with established CVD or CKD or age ≥60 yrs with an additional risk factor

26% 39% 35% 76% 36%

↓ CV death, non-fatal MI, nonfatal stroke (NNT 2y = 91)
↓ Nonfatal stroke (NNT 2y = 91)
↓ Revascularization (NNT 2y = 46)
↓ Retinopathy complications (NNH 2y = 46)
↓ New or worsening nephropathy (NNT 2y = 44)

The overall safety profile of semaglutide was consistent with previous clinical trials and the GLP-1RA class, except for the retinopathy results

SUSTAIN: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; CVD: cardiovascular disease; CKD: chronic kidney disease; T2D: type 2 diabetes; MI: myocardial infarction; NNT: number needed to treat; NNH: number needed to harm

Semaglutide is not currently indicated for cardiovascular or renal protection in Canada and should not be used in patients with end stage renal impairment due to very limited clinical experience in this population.
The primary prevention cohort accounted for fewer primary MACE events and while subgroup analysis did not show heterogeneity, no conclusion can be made regarding the CV benefit in this group (HR 0.98; 95% CI 0.74-1.30)

Canagliflozin in addition to standard of care reduced CV risk in adults with T2D and age ≥30 years with established CVD (66%) or age ≥50 yrs with ≥2 CV risk factors (34%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Reduction (%)</th>
<th>NNT 5y</th>
<th>NNH 5y</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, non-fatal MI, non-fatal stroke</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, dialysis, renal death</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower extremity amputations</td>
<td>97%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures</td>
<td>26%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No increased risk of amputations was observed in EMPA-REG OUTCOME or DECLARE

The primary prevention cohort accounted for fewer primary MACE events and while subgroup analysis did not show heterogeneity, no conclusion can be made regarding the CV benefit in this group (HR 0.98; 95% CI 0.74-1.30)

Canagliflozin is not indicated for slowing the progression of renal disease in patients with type 2 diabetes in Canada and contraindicated for use in patients with an eGFR of <45 mL/min/1.73m²

CVD: cardiovascular disease; HF: heart failure; MI: myocardial infarction; NNT: number needed to treat; NNH: number needed to harm; T2D: type 2 diabetes

Empagliflozin in addition to standard of care reduced CV risk and improved overall survival in adults with T2D with established CVD

- CV death, non-fatal MI, non-fatal stroke (NNT 3y = 63)
- All-cause mortality (NNT 3y = 39)
- HF hospitalizations (NNT 3y = 72)
- New or worsening nephropathy (NNT 3y = 17)

The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information

Empagliflozin is not currently indicated for renal protection in Canada and is contraindicated in patients with eGFR less than 30 mL/min/1.73m².

CVD: cardiovascular disease; MI: myocardial infarction; NNT: number needed to treat; T2D: type 2 diabetes; HF: heart failure

DECLARE–TIMI 58: Summary

Dapagliflozin in addition to standard of care in patients with type 2 diabetes aged ≥40 years with established ischemic cerebrovascular disease, Ischemic heart disease or PAD, or aged ≥55 years (men) ≥66 (women) with ≥1 cardiovascular risk factor.

The overall safety profile of dapagliflozin was consistent with previous clinical trials and current label information.

Dapagliflozin is not currently indicated for renal protection in Canada and is contraindicated in patients with eGFR less than 30 mL/min/1.73m2.

CVD: cardiovascular disease; MI: myocardial infarction; NNT: number needed to treat; T2D: type 2 diabetes; HF: heart failure

Note: Dapagliflozin is an SGLT2 inhibitor administered orally; it is not currently indicated for cardiovascular protection in Canada

Mrs. P

- 73 year old woman with NYHA 2, CCS 1 HFpEF

Patients’ Medical History:
- Paroxysmal AF on DOAC
- T2DM
- Hypertension
- Ex-smoker
- MI 10 years ago
- 1 hospitalization for HF in 2018

MIBI 2017: LVEF 45%, fixed defect of inferior wall

- Medications:
  - Metformin 1000 mg po BID
  - Lasix 40 mg po OD
  - Ramipril 2.5 mg po OD
  - Metoprolol 25 mg po OD
  - Rivaroxaban 20 mg po OD
  - Atorvastatin 80 mg po OD

- Labs:
  - K 4.2, eGFR 72, hgb 130, hgbAlc 8.2, UACr neg

- Exam: BP 132/70, HR 80 irreg, JVP 3, S4, trace edema, chest clear
Diabetes Management: What Every Cardiologist Needs to Know

Lori Berard
RN
@ldb13
The Impact of Diabetes

Diabetes can reduce lifespan by up to 15 years\(^1\)

**CV disease** is the leading cause of morbidity and mortality in patients with T2DM\(^2\)

80% of Canadians with diabetes will die of CVD\(^2\)

By **2020**, diabetes is expected to cost the Canadian healthcare system **$16.9 billion** annually\(^3\)

---

Patients with Diabetes are More Likely to be Hospitalized for Many Conditions

Prevalence rate ratios† of complications among hospitalized individuals‡ aged >20 years, by diabetes status, Canada, 2008/09

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>Rate ratios (with diabetes: without diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular disease (stroke)</td>
<td>4</td>
</tr>
<tr>
<td>Acute myocardial infarction (heart attack)</td>
<td>6</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>10</td>
</tr>
<tr>
<td>Heart failure</td>
<td>12</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>16</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>20</td>
</tr>
<tr>
<td>Lower limb amputations</td>
<td>22</td>
</tr>
</tbody>
</table>

† Rate ratios based on rates age-standardized to the 1991 Canadian population.
‡ A person with diabetes hospitalized with more than one complication was counted once in each category, except for cases of acute myocardial infarction, where regardless of multiple counts in the acute myocardial infarction category, the individual was counted only once under the broader ischemic heart disease category.

Source: Public Health Agency of Canada (August 2011); using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada).
ABCDES$^3$ of Diabetes Care

✓ A • A1C – optimal glycemic control (usually ≤7%)
✓ B • BP – optimal blood pressure control (<130/80)
✓ C • Cholesterol – LDL <2.0 mmol/L or >50% reduction
✓ D • Drugs to protect the heart
  A – ACEi or ARB │ S – Statin │ A – ASA if indicated │ SGLT2i/GLP-1 RA with demonstrated CV benefit if T2DM with CVD and A1C not at target
✓ E • Exercise / Healthy eating
✓ S • Screening for complications
✓ S • Smoking cessation
✓ S • Self-management, stress and other barriers
Beyond Metformin in the DC Algorithm

Add another agent best suited to the individual by prioritizing patient characteristics:

- Clinical CVD?
  - YES
    - Start antihyperglycemic agent with demonstrated CV benefit:
      - empagliflozin (Grade A, Level 1A)
      - liraglutide (Grade A, Level 1A)
      - canagliflozin (Grade C, Level 2)
  - NO

If not at glycemic target:

Add additional antihyperglycemic agent best suited to the individual based on the following:

<table>
<thead>
<tr>
<th>Clinical Considerations</th>
<th>Choice of Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance of hypoglycemia and/or weight gain with adequate glycemial efficacy</td>
<td>DPP-4 inhibitor, GLP-1 receptor agonist or SGLT2 inhibitor</td>
</tr>
<tr>
<td>Other considerations:</td>
<td></td>
</tr>
<tr>
<td>- Reduced eGFR and/or albuminuria</td>
<td>See Appendix 7</td>
</tr>
<tr>
<td>- Clinical CVD or CV risk factors</td>
<td></td>
</tr>
<tr>
<td>- Degree of hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>- Other comorbidities</td>
<td></td>
</tr>
<tr>
<td>(CHF, hepatic disease)</td>
<td></td>
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<tr>
<td>- Planning pregnancy</td>
<td></td>
</tr>
<tr>
<td>- Cost/coverage</td>
<td></td>
</tr>
<tr>
<td>- Patient preference</td>
<td></td>
</tr>
</tbody>
</table>

See Table below.

Choosing Between SGLT2i and GLP-1 RA
Drugs that Protect the Heart And Lower Glucose

<table>
<thead>
<tr>
<th></th>
<th>SGLT2i</th>
<th>GLP-1RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative A1C lowering</td>
<td>↓↓ to ↓↓↓</td>
<td>↓↓ to ↓↓↓</td>
</tr>
<tr>
<td>Weight loss</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Side effects</td>
<td>Genital infections, UTI, hypotension, dose-related changes in LDL-C, increased risk of fractures with canagliflozin; increased risk of lower extremity amputation with canagliflozin (avoid if prior amputation); caution with renal dysfunction, loop diuretics and the elderly; treatment should be withheld prior to major surgery or with serious illness or infection.</td>
<td>Gastrointestinal side effects, rare cases of acute gallstone disease; contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Injectable</td>
</tr>
<tr>
<td>Dosing</td>
<td>Empagliflozin: Start at 10 mg OD; increase to 25 mg OD if needed for glycemic control Canagliflozin: Start at 100 mg OD; increase to 300 mg OD if needed for glycemic control</td>
<td>Liraglutide: Start at 0.6 mg OD and then titrate up to 1.8 mg OD; increase to 0.5 mg QW; increase to 1.0 mg in 4 weeks if needed for glycemic control</td>
</tr>
<tr>
<td>Cost</td>
<td>$$$</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>

A1C: glycated hemoglobin; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; GLP-1RA: glucagon like peptide-1 receptor agonist; UTI: urinary tract infection; LDL-C: low-density lipoprotein cholesterol; NNT: number needed to treat; OD: once daily; SGLT2i: sodium glucose co-transporter-2 inhibitor; OD: once daily; QW: Once-daily

*Superiority met; **SUSTAIN-6 was not designed with pre-specified testing for superiority. However, the treatment effect of semaglutide and the accrual of more events than estimated resulted in a significantly lower risk of the primary outcome among patients in the semaglutide group. #p<0.001; **exploratory

# Antihyperglycemic Agents and Renal Function


## Table: Recommended Doses of Antihyperglycemic Agents by CKD Stage

<table>
<thead>
<tr>
<th>CKD Stage: eGFR (mL/min/1.73 m²)</th>
<th>5 (&lt;15)</th>
<th>4 (15–29)</th>
<th>3 (30–59)</th>
<th>2 (60–89)</th>
<th>1 (≥90)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-glucosidase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td></td>
<td></td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanide</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Metformin</td>
<td></td>
<td></td>
<td>30</td>
<td>500-1000 mg</td>
<td>45</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td>15</td>
<td>15</td>
<td>30</td>
<td>25 mg</td>
<td>15</td>
</tr>
<tr>
<td>Alogliptin</td>
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<tr>
<td>Linagliptin</td>
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<tr>
<td>Saxagliptin</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sitagliptin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonists</strong></td>
<td>15</td>
<td></td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide (BID/QW)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td></td>
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</tr>
<tr>
<td>Semiaglutide</td>
<td></td>
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<tr>
<td><strong>Insulin secretagogues</strong></td>
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<td></td>
</tr>
<tr>
<td>Gliclazide/Glimepiride</td>
<td>30</td>
<td>45</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td></td>
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<tr>
<td>Repaglinide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SGLT-2 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td></td>
<td></td>
<td>45</td>
<td>100 mg</td>
<td>60*</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*May be considered when indicated for CV and renal protection with eGFR < 60 but >30 mL/min/1.73m²*

Legend:
- **Contraindicated**
- **Use alternate agent**
- **Caution and/or dose reduction**
- **More intensive monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction**
- **Should not be initiated**
- **Safe**
What will be the most important self monitoring advice you can provide Mrs P when starting her on an SGLT2i to reduce her risk of CV events?

- sick day protocol = 15%
- management of yeast infections = 12%
- monitor daily weights = 5%
- all of the above = 68%
Sick Day Medication List (SADMANS)

If people with diabetes become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g., due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function:
- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Direct renin inhibitors
- Nonsteroidal anti-inflammatory drugs
- Diuretics
- SGLT2 inhibitors

B) Have reduced clearance and increase risk for adverse effects:
- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S  sulfonylureas
A  ACE inhibitors
D  diuretics, direct renin inhibitors
M  metformin
A  angiotensin receptor blockers
N  nonsteroidal anti-inflammatory
S  SGLT2 inhibitors, sacubitril/valsartan

Heart Failure Management
Eileen O’Meara
MD
SGLT2 inhibitors and CV disease

Cardiorenal efficacy of SGLT2i

- Renal protection
- Hospitalisation for heart failure
- Major adverse cardiovascular events

Secondary prevention population
SGLT2i prevent heart failure and renal disease, and reduce atherosclerotic events (major adverse cardiovascular events)

Primary prevention population
SGLT2i prevent heart failure and renal disease, but may not reduce major adverse cardiovascular events

Diabetes and established cardiovascular disease

Diabetes and multiple risk factors

Figure: Cardiorenal benefits of SGLT2i in different patient populations

SGLT2i = sodium-glucose cotransporter-2 inhibitors
### Potential Mechanisms of SGLT2 Inhibitors Associated with CV Benefits

<table>
<thead>
<tr>
<th>Hemodynamic actions (via ‘Natriuresis’)</th>
<th>Metabolic actions (via ‘Glycosuria’)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac/Vascular</td>
<td>Renal</td>
</tr>
<tr>
<td>Plasma volume ↓</td>
<td>TGF ↑</td>
</tr>
<tr>
<td>Blood pressure ↓</td>
<td>Hyperfiltration ↑</td>
</tr>
<tr>
<td>Pulse pressure ↓</td>
<td>Intraglomerular pressure ↑</td>
</tr>
<tr>
<td>Double product ↓</td>
<td></td>
</tr>
<tr>
<td>Arterial stiffness ↓</td>
<td></td>
</tr>
<tr>
<td>Sympathetic tone ↓</td>
<td></td>
</tr>
<tr>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>eGFR ↓</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Proteinuria ↓</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td>Nephropathy ↓</td>
</tr>
<tr>
<td>Sympathetic tone</td>
<td>Renal event ↓</td>
</tr>
</tbody>
</table>

#### Glycemic
- HbA1c ↓
- Insulin ↓
- Glucotoxicity ↓

#### Non-glycemic
- Body weight ↓
- TG ↓
- Fat mass ↓
- Uric acid ↓

#### Energy
- Fuel-shift ↑
- Ketone bodies ↑

#### Derived mechanisms:
- Insulin resistance ↓
- Inflammation ↓
- Oxidative stress ↓

#### Derived parameters:
- Endothelial function ↑(?)
- Atherosclerosis ↓(?)
- Mitochondrial function ↑(?)
- Cardio/renal work ↑(?)

---

Empa-Heart: Mechanistic clues to SGLT2i’s benefit

**Primary Outcome**
Empagliflozin Reduces LVMI<sup>a</sup>

<table>
<thead>
<tr>
<th>Baseline LVMI&lt;sup&gt;a&lt;/sup&gt; (g/m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>62.2</th>
<th>59.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in LVMI&lt;sup&gt;a&lt;/sup&gt; from baseline (g/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>0.0</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>-0.01</td>
<td>-2.6</td>
</tr>
</tbody>
</table>

**LVM regression (g)**

- Placebo: -0.39 (10.83)
- Empagliflozin: -4.71 (15.43)

Data are presented as mean (95% CI) for the intention-to-treat population.

<sup>a</sup> LV mass with papillary muscle mass indexed to body surface area.
SGLT2i’s reduce HF Hospitalizations

<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Events per 1000 Patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (nN) Placebo (nN)</td>
<td>Treatment Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME 4687/7020 2333/7020 463</td>
<td>19.7</td>
<td>30.1</td>
<td>30.9</td>
<td>0.66 (0.55-0.79)</td>
</tr>
<tr>
<td>CANVAS Program 3756/6656 2900/6656 524</td>
<td>21.0</td>
<td>27.4</td>
<td>32.8</td>
<td>0.77 (0.65-0.92)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58 3474/6974 3500/6974 597</td>
<td>19.9</td>
<td>23.9</td>
<td>36.4</td>
<td>0.83 (0.71-0.98)</td>
</tr>
</tbody>
</table>

Fixed effects model for atherosclerotic cardiovascular disease (p<0.0001)

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Events per 1000 Patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (nN) Placebo (nN)</td>
<td>Treatment Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program 2039/3486 1447/3486 128</td>
<td>8.9</td>
<td>9.8</td>
<td>30.2</td>
<td>0.83 (0.58-1.19)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58 5108/10186 5078/10186 316</td>
<td>7.0</td>
<td>8.4</td>
<td>69.8</td>
<td>0.84 (0.67-1.04)</td>
</tr>
</tbody>
</table>

Fixed effects model for multiple risk factors (p=0.0634)

Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease
Atherosclerotic cardiovascular disease: Q statistic=3.49, p=0.17, I²=42.7%; multiple risk factors: Q statistic=0.0, p=0.96, I²=0%. The p value for subgroup differences was 0.41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.
EMPRISE Real World Data: Empagliflozin was associated with a reduced risk of HHF† in routine clinical practice compared with DPP-4i

HR 0.56
(95% CI 0.43, 0.73)
p<0.0001
CENTRAL ILLUSTRATION: Lower Cardiovascular Risk Associated With SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Event</th>
<th>Events</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Death (ACD)</td>
<td>5,216</td>
<td>0.51 [0.37, 0.70]</td>
</tr>
<tr>
<td>Hospitalization for Heart Failure (HHF)</td>
<td>5,997</td>
<td>0.64 [0.50, 0.82]</td>
</tr>
<tr>
<td>HHF + ACD</td>
<td>9,788</td>
<td>0.60 [0.47, 0.76]</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2,249</td>
<td>0.81 [0.74, 0.88]</td>
</tr>
<tr>
<td>Stroke</td>
<td>6,439</td>
<td>0.68 [0.55, 0.84]</td>
</tr>
</tbody>
</table>

CCS 2017 HF Guidelines: HF Prevention in Type 2 DM

Recommendations

• We recommend that diabetes should be treated according to the Canadian Diabetes Association’s national guidelines to achieve optimal control of blood glucose levels
  *(Strong Recommendation, Moderate Quality Evidence)*

• We suggest that the use of empagliflozin, a SGLT-2 inhibitor, be considered for patients with type 2 diabetes and established cardiovascular disease for the prevention of HF-related outcomes
  *(Weak Recommendation, Low Quality Evidence)*
Diabetes in Heart Failure Checklist

✓ Treat heart failure in people with diabetes the SAME as you would a person without diabetes

✓ METFORMIN recommended if eGFR >30 mL/min/1.73 m²

✓ If eGFR <60 mL/min, use Renin Angiotensin Aldosterone system or sacubitril/valsartan blockade carefully

✓ Do NOT use thiazolidinediones

✓ Avoid saxagliptin in patients with heart failure and diabetes
Proposed Management of Concomitant Diuretics When Initiating SGLT2 Inhibitors in Patients T2DM

1) What is the volume status?

- **Hypervolemia**
  - Continue diuretic and monitor BP/lytes/Cr/weight, assuming not hypotensive
  - Caution with multiple diuretics

- **Volume Contraction**
  - Stop diuretic and monitor
  - Initiate SGLT2i when euvoledmic

Euvolemia

2) What is the blood pressure?

- **Hypertensive**
  - Continue diuretic therapy and monitor BP/lytes/Cr/weight

- **Normotensive**
  - Thiazides
    - Continue therapy and monitor BP
  - Loop diuretics
    - Consider reducing dose by 50% and monitor BP/weight
      - If stable, continue therapy
      - If increasing, reinstitute diuresis
      - If decreasing, stop diuretic

- **Hypotensive**
  - Caution, hold or reduce diuretic and re-institute if required
Mrs. P

- 6 months ago following a routine Echo it was noted her LVEF had declined to 35%. You initiated her on triple therapy and she stable has NYHA 2 symptoms. She has not been hospitalized.

- Her Cr is 90 with an eGFR of 55

- She is asking if SGLT2i is a good option for her ("she read in her favourite magazine about a new drug that can lower her sugars and help her lose weight")
ARS

• Would you prescribe a SGLT2i for patients:
  • Prevention of HF in T2DM patients with CVD = 12%
  • T2DM with HFpEF = 2%
  • T2DM with HFrEF = 2%
  • All of the above = 82%
  • I don’t know = 2%
What’s coming up with SGLT2s and heart failure?

DAPA-HF: Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic HF

**Population:**
- ≥18 years of age
- Established documented diagnosis of symptomatic HFrEF (NYHA functional class II-IV) for ≥ 2 months
- LVEF ≤40%
- NTproBNP ≥ 600 pg/ml
- eGFR ≥30 ml/min/1.73m²
- Stable SoC HFrEF treatment

**Randomization:**
1:1

**N = ~4500**

**Primary endpoint:**
Time to first occurrence of any of the components of the composite:
- CV death or hospitalization for HF or an urgent HF visit

**Secondary endpoints:**
- Time to first occurrence of CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline in KCCQ at 8 months
- Time to first occurrence of renal composite (≥50% sustained decline in eGFR, ESRD or renal death)

**Study Start:** Feb 2017
**Estimated Study Completion:** BEFORE Fall 2019! ➔ AHA 2019?

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; N, number of patients; NTproBNP, N-terminal pro b-type natriuretic peptide; SCV, study closure visit; SED, study end date; SoC, standard of care
https://clinicaltrials.gov/show/NCT03036124
What’s coming up with SGLT2s and heart failure? DAPA-HF and DELIVER

**Aim:** To investigate the safety and efficacy of dapagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with *reduced* or *preserved ejection fraction*

**Population:** T2D and non-T2D, age ≥18 years, chronic HF (NYHA II–IV)

DAPA-HF
- LVEF ≤40%
- Dapagliflozin 10 mg qd + SoC†
- Placebo qd + SoC†

DELIVER
- LVEF >40%
- Dapagliflozin 10 mg qd + SoC
- Placebo qd + SoC
What’s coming up with SGLT2s and heart failure?
EMPEROR-Reduced and EMPEROR-Preserved
Phase III randomised double-blind placebo-controlled studies

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with reduced or preserved ejection fraction

Population: T2D and non-T2D, age ≥18 years, chronic HF (NYHA II–IV)

**EMPEROR-Reduced**
- LVEF ≤40%
- Planned recruitment: 2850 patients
- Empagliflozin 10 mg qd + SoC†
- Placebo qd + SoC†
- Estimated follow-up ~38 months (event-driven)

**EMPEROR-Preserved**
- LVEF >40%
- Planned recruitment: 6000
- Empagliflozin 10 mg qd + SoC†
- Placebo qd + SoC†
- Estimated follow-up ~38 months (event-driven)

*Based on blinded assessment of event rate; †Guideline-directed medical therapy
LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SoC, standard of care
Update on Mrs. P

Started on SGLT2 inhibitor

- Creatinine went from 120 to 144 mmol/L:
  - Creatinine back to 130 mmol/L 2 weeks later
- Last seen 08/4/2019, stable NYHA 2, NT-proBNP 2293
- Creatinine 130 mmol/L - eGFR 35 ml/min, Urine ACR 70 mg/mmol
- Kidney Failure Risk – 12 % over 5 years

Current meds: EF 35%, no ICD, NYHA 2

- Metformin 500 mg po BID
- Empa 10 mg po OD
- Lasix 80 mg po OD
- Sac/valsartan 50 mg po BID
- Metoprolol 25 mg po BID
- Atorvastatin 80 mg po OD
- Rivaroxaban dose 15 mg po OD
Chronic Kidney Disease Management
Navdeep Tangri
MD, PhD, FRCPC
@NavTangri
CKD is associated with adverse outcomes
Importance of Albuminuria - Risk

THE PROJECTED RISK OF KIDNEY FAILURE

KDIGO Heatmap

Composite Ranking for Relative Risks by GFR and Albuminuria:
KDIGO 2009

<table>
<thead>
<tr>
<th>Albuminuria Stages, Description and Range (mg/g)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>optimal and high-normal</td>
<td>&lt;10</td>
<td>10-29</td>
<td>30-299</td>
</tr>
<tr>
<td>high</td>
<td>300-199</td>
<td>&gt;2000</td>
<td></td>
</tr>
</tbody>
</table>

GFR Stages, Description and Range (mL/min/1.73m²)

- G1: high and optimal
  - >105
  - 90-104

- G2: mild
  - 75-89
  - 60-74

- G3a: mild-moderate
  - 45-59

- G3b: moderate-severe
  - 30-44

- G4: severe
  - 15-29

- G5: kidney failure
  - <15


Published CVOTs demonstrating superiority Secondary Renal Outcomes

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>New or worsening nephropathy</th>
<th>Doubling of SrCr</th>
<th>Progression to MAU / of albuminuria</th>
<th>Initiation of RRT</th>
<th>Composite: 40% eGFR, RRT, renal death</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG</td>
<td>0.61 (0.53, 0.70)</td>
<td>0.56 (0.39, 0.79)</td>
<td>0.62* (0.54, 0.72)</td>
<td>0.45 (0.40, 0.75)</td>
<td>0.54 (0.40, 0.75)</td>
</tr>
<tr>
<td>CANVAS</td>
<td>NR</td>
<td>NR</td>
<td>0.73** (0.67, 0.79)</td>
<td>NR</td>
<td>0.53 (0.33, 0.84)</td>
</tr>
<tr>
<td>DECLARE</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.53</td>
</tr>
</tbody>
</table>

NR, not reported; NS, not significant; * Progression to microalbuminuria; ** Progression of albuminuria. This was defined as more than a 30% increase in albuminuria and a change from either normoalbuminuria to microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria. § End-stage kidney disease, defined as dialysis, transplantation, or a sustained estimated GFR of <15 ml/min/1.73 m²; ‡ End-stage kidney disease, doubling of serum creatinine level, or renal death.

Many Renal Effects of SGLT2 Inhibition Have Been Proposed

- Intraglomerular pressure
- Glucose
- BP/arterial stiffness
- Volume
- Inflammation/fibrosis
- Albuminuria
- Oxidant stress
- Intrarenal angiotensinogen upregulation
- And many others…
ARS

- At what eGFR should we not prescribe SGLT2 inhibitors?
  - < 60 = 0%
  - < 45 = 4%
  - < 30 = 82%
  - It’s a moving target after Credence = 14%
### CREDENCE

<table>
<thead>
<tr>
<th>Albuminuria categories (mg/g)</th>
<th>Mean eGFR (mL/min/1.73 m²)</th>
<th>Median UACR (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1: &lt;30</td>
<td>85</td>
<td>13</td>
</tr>
<tr>
<td>A2: 30-300</td>
<td>76</td>
<td>12</td>
</tr>
<tr>
<td>A3: &gt;300</td>
<td>74</td>
<td>18</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
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<tr>
<td>E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DECLARE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDENCE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sustained RRT Events**

- DECLARE: Not reported
- CANVAS Program: 18
- EMPA-REG OUTCOME: 11
- CREDENCE: 176
CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

**Study design and participants**

- 4401 patients with T2DM & UACR >300 mg/g
- 62 years
- eGFR 57
- UACR 927 mg/g

**Intervention**

- Stable on maximum dose tolerated ACEi or ARB for 4 weeks

**Outcomes**

**Primary outcome**

- (Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)
- **HR 0.70** (95% CI 0.59-0.82)
- **NNT 21**

**End-stage kidney disease**

- **HR 0.68** (95% CI 0.54-0.86)
- **NNT 42**

**Conclusion**

In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

**No increased risk of:**

- Amputations
  - **HR 1.10** (95% CI 0.79-1.56)
- Fractures
  - **HR 0.98** (95% CI 0.70-1.37)
## Credence Summary

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. ESKD, doubling of serum creatinine, or renal or CV death</td>
<td>0.70 (0.59–0.82)</td>
<td>0.00001</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. CV death or hospitalization for heart failure</td>
<td>0.69 (0.57–0.83)</td>
<td>&lt;0.001</td>
<td>✔</td>
</tr>
<tr>
<td>3. CV death, MI, or stroke</td>
<td>0.80 (0.67–0.95)</td>
<td>0.01</td>
<td>✔</td>
</tr>
<tr>
<td>4. Hospitalization for heart failure</td>
<td>0.61 (0.47–0.80)</td>
<td>&lt;0.001</td>
<td>✔</td>
</tr>
<tr>
<td>5. ESKD, doubling of serum creatinine, or renal death</td>
<td>0.66 (0.53–0.81)</td>
<td>&lt;0.001</td>
<td>✔</td>
</tr>
<tr>
<td>6. CV death</td>
<td>0.78 (0.61–1.00)</td>
<td>0.0502</td>
<td></td>
</tr>
<tr>
<td>7. All-cause mortality</td>
<td>0.83 (0.68–1.02)</td>
<td>–</td>
<td>Not formally tested</td>
</tr>
<tr>
<td>8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina</td>
<td>0.74 (0.63–0.86)</td>
<td>–</td>
<td>Not formally tested</td>
</tr>
</tbody>
</table>
Published CVOTs demonstrating superiority
Secondary Renal Outcomes

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</tr>
</thead>
<tbody>
<tr>
<td>LEADER HR (95% CI)</td>
<td>0.78 (0.67, 0.92)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>SUSTAIN-6 HR (95% CI)</td>
<td>0.64 (0.46, 0.88)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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What’s Coming Up with SGLT2i’s and CKD?

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Trial ID</th>
<th>Primary completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Credence</td>
<td>T2DM and CKD</td>
<td>NCT02065791</td>
<td>Reported</td>
</tr>
<tr>
<td>Dapa-CKD</td>
<td>Chronic kidney disease</td>
<td>NCT03036150</td>
<td>Nov 2020</td>
</tr>
<tr>
<td>Scored</td>
<td>T2DM and CKD</td>
<td>NCT03315143</td>
<td>Mar 2022</td>
</tr>
<tr>
<td>Empa-Kidney</td>
<td>Chronic kidney disease</td>
<td>NCT03594110</td>
<td>Jun 2022</td>
</tr>
</tbody>
</table>
And a followup poll: @S_brimble @ChristosArgyrop @Msood99M @NavTangri @GBJohnMancini1 interested in your perspective: If you do prescribe SGLT2i's is your recommendation for or against use more influenced by:
ARS Question

- If you do prescribe SGLT2i’s is your recommendation for or against use influenced by:
  - Cost = 29%
  - CV benefits = 63%
  - Renal benefits = 6%
  - Presence of PVD = 2%
#Cardiotwitter Answer

Shelley Zieroht @Shelle... · 14 Apr.  
And a followup poll: @S_brimble @ChristosArgyrop @Msood99M @NavTangri @GBJohnMancini1 interested in your perspective: If you do prescribe SGLT2i's is your recommendation for or against use more influenced by:

- **Cost** 22%
- **CV benefits** 57%
- **Renal benefits** 22%
- **Presence of PVD** 0%

46 votes • Final results
Closing Remarks
Shelley Zieroth
MD, FRCPC, FCCS
@ShelleyZieroth