QUESTIONS
ABOUT DIABETES AND HF YOU WERE TOO AFRAID TO ASK
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Director, SBH Heart Failure and Transplant Clinics
Head, Medical Heart Failure Program
WRHA Cardiac Sciences Program
Winnipeg, MB

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Faculty

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St. Michael's Hospital
Scientist, Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute of St. Michael's Hospital
Professor of Surgery and Pharmacology & Toxicology
University of Toronto
Canada Research Chair in Atherosclerosis
Toronto, ON
# Speaker Disclosures

<table>
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<tr>
<th></th>
<th>SHELLEY ZIEROTH, MD, FRCPC</th>
<th>SUBODH VERMA, MD, PhD, FRCSC, FAHA</th>
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<th>KIM CONNELLY, MBBS, FRACP, PhD</th>
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<td>AstraZeneca, Boehringer</td>
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Disclosure of Commercial Support

Specific details of relationship:
- This program has received financial support from Boehringer Ingelheim and Eli Lilly Canada in the form of an educational grant.
- This program has received in-kind support from Canadian Heart Failure Society in the form of logistical support.

Potential for conflict(s) of interest:
- Speakers have received honoraria from Canadian Heart Failure Society.
- Boehringer Ingelheim/Eli Lilly Canada is the manufacturer 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

• Appreciate the increased risk of cardiovascular disease and heart failure in patients with type 2 diabetes and assess cardiovascular risk in these patients

• Describe the potential mechanisms of action for the heart failure benefit with clinical use of SGLT2i’s in diabetic and nondiabetic patients

• Explain the efficacy and safety of antihyperglycemic agents including SGLT2i’s with demonstrated CV and HF benefit

• Communicate to primary care providers practical recommendations and tips when starting SGLT2i’s
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>
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<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
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<tr>
<td>Welcome and introductions</td>
<td>Dr. Shelley Zieroth</td>
</tr>
<tr>
<td>Presentation: Mechanisms of action of SGLT2 inhibitors and why they work in heart failure</td>
<td>Dr. Subodh Verma</td>
</tr>
<tr>
<td>Panel discussion: Questions about heart failure and diabetes you were too afraid to ask</td>
<td>Dr. Shelley Zieroth, Dr. Vineeta Ahoota, Dr. Kim Connelly, Dr. Elizabeth Swiggum, Dr. Subodh Verma</td>
</tr>
<tr>
<td>Closing remarks</td>
<td>Dr. Shelley Zieroth</td>
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</tbody>
</table>
Housekeeping Details

• Please turn your phones to silent mode
• Please remember to complete your evaluation forms at the end of the session, by texting EVALUATION to (647) 696-5222
• Audience polling via text message...
  • Text HFUPDATE to 37607 ONE TIME at the beginning of the meeting and then text your answer to 37607 for subsequent questions
Audience Poll # 1

You are seeing Sam in your office. He is a 50-year-old male with HFrEF and Type 2 Diabetes for 4 years. What should his hgbA1c target be?

1. ≤ 6.5
2. ≤ 7
3. ≤ 8.5
4. I’m a cardiologist why are you asking me??
Question 1: What Does CV Protection Mean for People With Diabetes?

Dr. Vineeta Ahooja
Diabetes and Cardiovascular Disease (CVD) are Intertwined

- One of the most common conditions reported in Canadians with diabetes
- Most common cause of death in individuals with type 2 diabetes

People with diabetes are 2–4x more likely to develop CVD than those without
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>1</td>
</tr>
<tr>
<td>Acute myocardial infarction (heart attack)</td>
<td>3</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>4</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>6</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>10</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).
Diabetes and Heart Failure (HF)

• People with diabetes have 2-5-fold ↑ risk of developing HF
  • Concomitant CAD
  • Diabetic / ischemic cardiomyopathy
  • Hypertension
  • Extracellular fluid expansion
  • Concomitant renal disease

• Risk factors for hospitalization for HF:
  • Previous HF
  • Renal dysfunction (eGFR ≤60 mL/min)
  • Elevated NT-proBNP

• Presence of HF worsens outcomes of any ACS

HF: heart failure; CAD: coronary artery disease; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro b-type natriuretic peptide; ACS: acute coronary syndrome
A1C Targets

<table>
<thead>
<tr>
<th>≤6.5</th>
<th>Adults with type 2 diabetes to reduce the risk of CKD and retinopathy if at low risk of hypoglycemia</th>
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</thead>
<tbody>
<tr>
<td>≤7.0</td>
<td>MOST ADULTS WITH TYPE 1 OR TYPE 2 DIABETES</td>
</tr>
<tr>
<td>7.1</td>
<td>7.1-8.0%: Functionally dependent*</td>
</tr>
<tr>
<td></td>
<td>7.1-8.5%:</td>
</tr>
<tr>
<td></td>
<td>• Recurrent severe hypoglycemia and/or hypoglycemia unawareness</td>
</tr>
<tr>
<td></td>
<td>• Limited life expectancy</td>
</tr>
<tr>
<td></td>
<td>• Frail elderly and/or with dementia**</td>
</tr>
<tr>
<td>8.5</td>
<td>Avoid higher A1C to minimize risk of symptomatic hyperglycemia and acute and chronic complications</td>
</tr>
<tr>
<td>End of life</td>
<td>A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia</td>
</tr>
</tbody>
</table>

* Based on class of antihyperglycemic medication(s) utilized and person’s characteristics
** see Diabetes in Older People chapter
CKD; chronic kidney disease
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 type 2 DM 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
EMPA-REG Outcome: Primary Composite Endpoint
CV Death, MI, or Stroke

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>EMPA</th>
<th>HR</th>
<th>P</th>
<th>NNT3</th>
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<tbody>
<tr>
<td>CV death, MI, stroke (%)</td>
<td>12.1</td>
<td>10.5</td>
<td>0.86</td>
<td>0.04</td>
<td>63</td>
</tr>
<tr>
<td>CV deaths (%)</td>
<td>5.9</td>
<td>3.7</td>
<td>0.62</td>
<td>&lt;0.001</td>
<td>46</td>
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<tr>
<td>Nonfatal MI (%)</td>
<td>5.2</td>
<td>4.5</td>
<td>0.87</td>
<td>0.22</td>
<td></td>
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<tr>
<td>Nonfatal stroke (%)</td>
<td>2.6</td>
<td>3.2</td>
<td>1.24</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Hosp. heart failure (%)</td>
<td>4.1</td>
<td>2.7</td>
<td>0.65</td>
<td>0.002</td>
<td>72</td>
</tr>
<tr>
<td>All-cause mortality (%)</td>
<td>8.3</td>
<td>5.7</td>
<td>0.68</td>
<td>&lt;0.001</td>
<td>39</td>
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</table>

Placebo

Empagliflozin

HR 0.86
95.02% CI (0.74, 0.99)
P < 0.001 for non-inferiority
p=0.04 for superiority

EMPA-REG OUTCOME: Summary

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) decreased by 14%
- CV death (NNT 3y = 46) decreased by 38%
- All-cause mortality (NNT 3y = 39) decreased by 32%
- HF hospitalizations NNT 3y = 72 decreased by 35%
- New or worsening nephropathy (NNT 3y = 17) decreased by 39%

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

CANVAS PROGRAM: Primary Composite Endpoint
CV Death, MI, or Stroke


<table>
<thead>
<tr>
<th>Outcome (per 1000 pt-y)</th>
<th>PBO</th>
<th>CANA</th>
<th>HR</th>
<th>P or 95% CI</th>
<th>NNT5</th>
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<td>CV death, MI, stroke</td>
<td>31.5</td>
<td>26.9</td>
<td>0.86</td>
<td>0.02</td>
<td>44</td>
</tr>
<tr>
<td>CV deaths</td>
<td>12.8</td>
<td>11.6</td>
<td>0.87</td>
<td>(0.72-1.06)</td>
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<tr>
<td>Nonfatal MI</td>
<td>11.6</td>
<td>9.7</td>
<td>0.85</td>
<td>(0.69-1.05)</td>
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<tr>
<td>Nonfatal stroke</td>
<td>8.4</td>
<td>7.1</td>
<td>0.90</td>
<td>(0.71-1.15)</td>
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<tr>
<td>Hosp. heart failure</td>
<td>8.7</td>
<td>5.5</td>
<td>0.67</td>
<td>(0.52-0.87)</td>
<td>63</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>19.5</td>
<td>17.3</td>
<td>0.87</td>
<td>(0.74-1.01)</td>
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</table>

HR 0.86
95% CI (0.75, 0.97)
P < 0.001 for non-inferiority
p=0.02 for superiority

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%)

14%
↓ CV death, non-fatal MI, non-fatal stroke (P=0.02; NNT 5y = 44)

33%
↓ HF hospitalization (NNT 5y = 63)

40%
↓ eGFR, dialysis, renal death (NNT 5y = 58)

97%
↑ Lower extremity amputations (P<0.001; NNH 5y = 69)

26%
↑ Fractures (P=0.02; NNH 5y = 58)

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
### LEADER: Primary Outcome

**CV death, non-fatal myocardial infarction, or non-fatal stroke**

<table>
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<tr>
<th>Event</th>
<th>Placebo</th>
<th>Liraglutide</th>
<th>HR</th>
<th>P</th>
<th>NNT4</th>
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<td>CV death, MI, stroke (%)</td>
<td>14.9</td>
<td>13.0</td>
<td>0.87</td>
<td>0.01</td>
<td>53</td>
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<td>CV death (%)</td>
<td>6.0</td>
<td>4.7</td>
<td>0.78</td>
<td>0.007</td>
<td>77</td>
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<td>Nonfatal MI (%)</td>
<td>6.8</td>
<td>6.0</td>
<td>0.88</td>
<td>0.11</td>
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<td>Nonfatal stroke (%)</td>
<td>3.8</td>
<td>3.4</td>
<td>0.89</td>
<td>0.30</td>
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<tr>
<td>Hosp. heart failure (%)</td>
<td>5.3</td>
<td>4.7</td>
<td>0.87</td>
<td>0.14</td>
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<tr>
<td>All-cause mortality (%)</td>
<td>9.6</td>
<td>8.2</td>
<td>0.85</td>
<td>0.02</td>
<td>72</td>
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</table>

**HR 0.87**

95.02% CI (0.78, 0.97)

P < 0.001 for non-inferiority

p=0.01 for superiority

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SUSTAIN-6: Primary Outcome
CV death, non-fatal myocardial infarction, or non-fatal stroke

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<tr>
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<th>HR</th>
<th>P</th>
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<tr>
<td>CV death, MI, stroke (%)</td>
<td>8.9</td>
<td>6.6</td>
<td>0.74</td>
<td>0.02</td>
<td>44</td>
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<tr>
<td>CV death (%)</td>
<td>2.8</td>
<td>2.7</td>
<td>0.98</td>
<td>0.92</td>
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<tr>
<td>Nonfatal MI (%)</td>
<td>3.9</td>
<td>2.9</td>
<td>0.74</td>
<td>0.12</td>
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<tr>
<td>Nonfatal stroke (%)</td>
<td>2.7</td>
<td>1.6</td>
<td>0.61</td>
<td>0.04</td>
<td>91</td>
</tr>
<tr>
<td>Hosp. heart failure (%)</td>
<td>3.3</td>
<td>3.6</td>
<td>1.11</td>
<td>0.57</td>
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<tr>
<td>All-cause mortality (%)</td>
<td>3.6</td>
<td>3.8</td>
<td>1.05</td>
<td>0.79</td>
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HR, 0.74 (95% CI, 0.58; 0.95)
P<0.001 for non-inferiority
P=0.02 for superiority

Figure 1A. Kaplan Meier plot for first event adjudication committee-confirmed CV death, non-fatal MI and non-fatal stroke using ‘in-trial’ data from subjects in the full analysis set.

*Not prespecified. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Marso et al. NEJM, Published on September 16th, NEJM.org
AT DIAGNOSIS OF TYPE 2 DIABETES

Start healthy behaviour interventions (nutritional therapy, weight management, physical activity) +/- metformin

<table>
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<tr>
<th>A1C &lt;1.5% above target</th>
<th>A1C ≥1.5% above target</th>
<th>Symptomatic hyperglycemia and/or metabolic decompensation</th>
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</thead>
</table>

If not at glycemic target within 3 months, start/increase metformin

If not at glycemic target

Start metformin immediately
Consider a second concurrent antihyperglycemic agent

Initiate insulin +/- metformin

If not at glycemic target

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)

If not at glycemic target

NO
See next page

* Avoid in people with prior lower extremity amputation

2018 Diabetes Canada CPG – Chapter 23. Cardiovascular Protection in People with Diabetes
Antihyperglycemic Therapy Selection

In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with eGFR >30 mL/min/1.73m², an antihyperglycemic agent with demonstrated CV outcome benefit should be added to reduce the risk of major CV events [Grade A, Level 1A for empagliflozin; Grade A, Level 1A for liraglutide; Grade C, Level 2 for canagliflozin]
Choosing Between SGLT2i and GLP-1 RA Depends on Patient/Agent Characteristics

<table>
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<tr>
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<th>SGLT2i</th>
<th>GLP-1RA</th>
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<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</td>
<td>Liraglutide: Start at 0.6 mg OD and then titrate up to 1.8 mg OD</td>
</tr>
<tr>
<td></td>
<td>Canagliflozin: Start at 100 mg OD; increase to 300 mg OD if needed for glycemic control</td>
<td>Semaglutide: Start at 0.25 mg QW for 4 weeks; 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>
<tr>
<td>Reduction in MACE</td>
<td>EMPA REG OUTCOME: ↓14%; CANVAS Program: ↓14%*</td>
<td>LEADER: ↓13%; SUSTAIN-6: ↓26%**</td>
</tr>
<tr>
<td>Reduction in CV death</td>
<td>EMPA REG OUTCOME: ↓38%; CANVAS Program: ↓13%**</td>
<td>LEADER: ↓22%; SUSTAIN-6: ↓8%</td>
</tr>
<tr>
<td>NNT 3y (CV mortality)</td>
<td>EMPA REG OUTCOME: 46 to prevent 1 CV death</td>
<td>LEADER: 104 to prevent 1 CV death</td>
</tr>
</tbody>
</table>

Audience Poll # 1

You are seeing Sam in your office. He is a 50-year-old male with HFrEF and Type 2 Diabetes for 4 years. What should his hgbA1c target be?

1. ≤ 6.5
2. ≤ 7
3. ≤ 8.5
4. I’m a cardiologist why are you asking me??
Audience Poll #2

Cardiologists should consider starting SGLT2i's in diabetic patients with:

1. HFrEF
2. HFpEF
3. All of the above
4. None of the above
5. I don't know
Question 2: Are All SGLT2i the Same?

HF Outcomes

Dr. Elizabeth Swiggum
EMPA-REG OUTCOME
Hospitalization for Heart Failure

Investigators were encouraged to treat CV risk factors to achieve best available standard of care according to local guidelines.

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2333</td>
<td>4687</td>
<td>4614</td>
</tr>
<tr>
<td>6</td>
<td>2271</td>
<td>4523</td>
<td>4523</td>
</tr>
<tr>
<td>12</td>
<td>2226</td>
<td>4427</td>
<td>4427</td>
</tr>
<tr>
<td>18</td>
<td>2173</td>
<td>3988</td>
<td>3988</td>
</tr>
<tr>
<td>24</td>
<td>1932</td>
<td>2950</td>
<td>2950</td>
</tr>
<tr>
<td>30</td>
<td>1424</td>
<td>2487</td>
<td>2487</td>
</tr>
<tr>
<td>36</td>
<td>1202</td>
<td>1634</td>
<td>1634</td>
</tr>
<tr>
<td>42</td>
<td>775</td>
<td>395</td>
<td>395</td>
</tr>
<tr>
<td>48</td>
<td>168</td>
<td>163</td>
<td>163</td>
</tr>
</tbody>
</table>

HR 0.65 (95% CI 0.50, 0.85)  P = 0.002

HR 0.62 (95% CI, 0.45, 0.86), P = 0.004

HR 0.68 (95% CI, 0.50, 0.93), P = 0.02

Heart Failure Outcomes: EMPA-REG Outcome Trial

- **HHF or CV Death**
  - 5.7% v 8.5%

- 10.1% (706) of population had HF at baseline
  - 7020 patients

---

Outcomes With and Without HF at Baseline
EMPA-Reg Outcome Trial

Heart failure hospitalization or cardiovascular death
- All patients
- Heart failure at baseline
  - No
  - Yes

Hospitalization for heart failure
- All patients
- Heart failure at baseline
  - No
  - Yes

Cardiovascular death
- All patients
- Heart failure at baseline
  - No
  - Yes

All-cause mortality
- All patients
- Heart failure at baseline
  - No
  - Yes

HR (95% CI)
CV death in DM patients with and without HF

Empagliflozin reduces CV death in DM patients with HF, and in DM patients at HF risk

CV death rates in subgroups of HF risk and in HF patients

- **Empagliflozin**
  - 5-y HF risk <10%: HR: 0.65 (95%CI: 0.45-0.94)
  - 5-y HF risk 10-20%: HR: 0.57 (95%CI: 0.38-0.88)
  - 5-y HF risk >20%: HR: 0.49 (95%CI: 0.24-1.02)
  - HF burden*: HR: 0.67 (95%CI: 0.47-0.97)

- **Placebo**
  - 5-y HF risk <10%: 2.40%
  - 5-y HF risk 10-20%: 8.00%
  - 5-y HF risk >20%: 13.00%
  - HF burden*: 15.30%

(*') HF burden includes HF at baseline, HF during the study, and HF hospitalization

The 5-years HF risk was stratified according to the Health ABC HF risk score

CV: Cardiovascular; DM: diabetes mellitus; HF: heart failure; HR: hazard ratio; CI: confidence interval

Fitchett D et al., Eur Heart J 2018
CANVAS Program – Canagliflozin HHF

A Hospitalization for Heart Failure

- Hazard ratio, 0.67 (95% CI, 0.52–0.87)
- 5.5 vs 8.7 per 1000 patient-years
- \( P=0.002 \)

- 10 142 patients T2D
  - 188.2 weeks
  - Mean age 63.3
  - 35.8% women
- Mean duration of DM 13.5 yr
  - 65.6% Hx CV disease
  - 14.4% Hx of HF

Bruce Neal, NEJM 2017; 377:644-657
CANVAS
Baseline Characteristics With and Without Heart Failure

- History of HF
  - 1461 (14.4%)
- Without HF
  - 8681
# Canagliflozin for Primary and Secondary Prevention of CV Events

<table>
<thead>
<tr>
<th></th>
<th>Number of participants</th>
<th>Patients per 1000 patient-years</th>
<th>Hazard ratio (99% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, nonfatal MI, or nonfatal stroke</td>
<td>786</td>
<td>34.1 41.3</td>
<td>0.82 (0.72–0.95)</td>
<td>0.18</td>
</tr>
<tr>
<td>CV death</td>
<td>215</td>
<td>15.8 15.5</td>
<td>0.98 (0.74–1.30)</td>
<td></td>
</tr>
<tr>
<td>1011</td>
<td>26.9 31.5</td>
<td>0.86 (0.75–0.97)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>362</td>
<td>14.8 16.8</td>
<td>0.86 (0.70–1.06)</td>
<td>0.44</td>
</tr>
<tr>
<td>91</td>
<td>6.5 6.2</td>
<td>0.93 (0.69–1.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>453</td>
<td>11.6 12.8</td>
<td>0.87 (0.72–1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>304</td>
<td>12.5 16.0</td>
<td>0.79 (0.63–0.98)</td>
<td>0.10</td>
</tr>
<tr>
<td>70</td>
<td>5.5 4.4</td>
<td>1.21 (0.73–2.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>374</td>
<td>9.7 11.6</td>
<td>0.85 (0.69–1.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>209</td>
<td>8.8 10.4</td>
<td>0.88 (0.67–1.16)</td>
<td>0.83</td>
</tr>
<tr>
<td>65</td>
<td>4.5 5.0</td>
<td>0.97 (0.59–1.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>524</td>
<td>21.0 27.4</td>
<td>0.68 (0.51–0.90)</td>
<td>0.91</td>
</tr>
<tr>
<td>128</td>
<td>8.9 9.8</td>
<td>0.64 (0.35–1.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>652</td>
<td>16.3 20.8</td>
<td>0.67 (0.52–0.87)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression of albuminuria</th>
<th>Number of participants</th>
<th>Patients per 1000 patient-years</th>
<th>Hazard ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>840</td>
<td>77.7 116.0</td>
<td>0.69 (0.60–0.79)</td>
<td></td>
</tr>
<tr>
<td>2455</td>
<td>89.4 128.7</td>
<td>0.73 (0.67–0.79)</td>
<td></td>
</tr>
<tr>
<td>40% reduction in eGFR, renal replacement therapy, or renal death</td>
<td>Number of participants</td>
<td>Patients per 1000 patient-years</td>
<td>Hazard ratio (99% CI)</td>
</tr>
<tr>
<td>179</td>
<td>6.4 10.5</td>
<td>0.59 (0.44–0.79)</td>
<td>0.73</td>
</tr>
<tr>
<td>70</td>
<td>4.1 6.6</td>
<td>0.63 (0.39–1.02)</td>
<td></td>
</tr>
<tr>
<td>249</td>
<td>5.5 9.0</td>
<td>0.60 (0.47–0.77)</td>
<td></td>
</tr>
<tr>
<td>174</td>
<td>6.3 10.1</td>
<td>0.60 (0.44–0.81)</td>
<td>0.85</td>
</tr>
<tr>
<td>65</td>
<td>3.8 6.2</td>
<td>0.61 (0.37–1.00)</td>
<td></td>
</tr>
<tr>
<td>239</td>
<td>5.3 8.7</td>
<td>0.60 (0.47–0.79)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** CV = cardiovascular; MI = myocardial infarction; eGFR = estimated glomerular filtration rate.

---

Mahaffey et al Circ 2018
Are All SGLT2i the same?

<table>
<thead>
<tr>
<th>PRIMARY OUTCOME</th>
<th>EMPA-REG OUTCOME&lt;sup&gt;1&lt;/sup&gt; HR (95% CI)</th>
<th>CANVAS&lt;sup&gt;2&lt;/sup&gt; HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, Nonfatal MI, Nonfatal Stroke</td>
<td>0.86 (0.74, 0.99)</td>
<td>0.86 (0.75, 0.97)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECONDARY OUTCOMES</th>
<th>CV Death</th>
<th>Nonfatal MI</th>
<th>Nonfatal Stroke</th>
<th>Hospitalization for Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.62 (0.49, 0.77)</td>
<td>NS</td>
<td>NS</td>
<td>0.65 (0.50, 0.85)</td>
</tr>
<tr>
<td>CANVAS&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.67 (0.52, 0.87)</td>
</tr>
</tbody>
</table>

CV: cardiovascular; NS: not significant; MI: myocardial infarction

• Ongoing trials of SGLT-2 inhibitors will inform the use of the class of agents in patients with established HF

• Few patients in the EMPA-REG OUTCOME trial had HF at baseline (approximately 10%), however, patients with HF had results similar to those in the overall trial

• There are ongoing trials of SGLT-2 inhibitors specifically enrolling patients with HF that might inform future recommendations
What About the Real World?
Use of SGLT-2i in 400,000 patients: Real World Data

- Ipragliflozin*: 8.3%
- Empagliflozin: 9.0%
- Canagliflozin: 4.4%
- Dapagliflozin: 74.7%
- Luseogliflozin†: 1.0%
- Tofogliflozin†: 3.0%

- All-cause death
- Hospitalization for heart failure (HHF)
- All-cause death or HHF
- Myocardial infarction (MI)
- Stroke

*In South Korea and Japan; †In Japan only.

Kosiborod M et al. J Am Coll Cardiol. 2018;DOI: 10.1016/j.jacc.2018.03.009
## Composite of All-Cause Death or HHF

<table>
<thead>
<tr>
<th>Database</th>
<th>N</th>
<th># of events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korea</td>
<td>336,644</td>
<td>7990</td>
<td>0.81 (0.78, 0.85)</td>
</tr>
<tr>
<td>Japan</td>
<td>67,780</td>
<td>1061</td>
<td>0.65 (0.57, 0.74)</td>
</tr>
<tr>
<td>Singapore</td>
<td>2726</td>
<td>93</td>
<td>0.62 (0.41, 0.95)</td>
</tr>
<tr>
<td>Israel</td>
<td>19,472</td>
<td>313</td>
<td>0.45 (0.36, 0.57)</td>
</tr>
<tr>
<td>Canada</td>
<td>16,064</td>
<td>331</td>
<td>0.48 (0.39, 0.59)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>442,686</strong></td>
<td><strong>9788</strong></td>
<td><strong>0.60 (0.47, 0.76)</strong></td>
</tr>
</tbody>
</table>

P-value for SGLT2i vs. oGLD: p<0.001

Heterogeneity p-value: p<0.001

---

ITT, adjusted analysis

Kosiborod M et al. J Am Coll Cardiol. 2018;DOI: 10.1016/j.jacc.2018.03.009
# Hospitalization for Heart Failure

## ITT, adjusted analysis

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<th>N</th>
<th># of events</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Korea</td>
<td>336,644</td>
<td>5149</td>
<td>0.87 (0.82, 0.92)</td>
</tr>
<tr>
<td>Japan</td>
<td>67,780</td>
<td>565</td>
<td>0.75 (0.63, 0.89)</td>
</tr>
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<td>Singapore</td>
<td>2726</td>
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<td>Total</td>
<td>442,686</td>
<td>5997</td>
<td>0.64 (0.50, 0.82)</td>
</tr>
</tbody>
</table>

P-value for SGLT2i vs. oGLD: p=0.001

Heterogeneity p-value: p<0.001

Kosiborod M et al. J Am Coll Cardiol. 2018;DOI: 10.1016/j.jacc.2018.03.009
Audience Poll #2

Cardiologists should consider starting SGLT2i's in diabetic patients with:

1. HFrEF
2. HFpEF
3. All of the above
4. None of the above
5. I don't know
Question 3: What are Considerations in Patients with Renal Dysfunction?

Dr. Kim Connelly
In Canada, People with Diabetes Account For...

- 1/3 of all heart attacks & strokes
- 2/5 of all heart failure admissions
- 2/3 of all non-traumatic amputations
- 1/2 all patients starting dialysis

Chronic Kidney Disease Checklist

✓ **SCREEN** with random urine albumin creatinine ratio (ACR) and serum creatinine for estimated glomerular filtration rate (eGFR) at **diagnosis** then **annually** (T2D)

✓ **DIAGNOSE** with repeat confirmed ACR ≥2.0 mg/mmol and/or eGFR <60 mL/min/1.73m²

✓ **DELAY** onset and/or progression with glycemic and blood pressure control and ACEi or ARB

✓ **PREVENT** complications with dose adjustment, “sick day management” counselling and referral when appropriate

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker
ACR ≥2.0 mg/mmol
and / or
eGFR < 60 mL/min/1.73 m²

CKD in Diabetes

ACR, albumin to creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate
Antihyperglycemic Agents and Renal Function

CKD Stage eGFR (mL/min/1.73 m²):

- <15
- 15–29
- 30–44
- 45–59
- ≥ 60

**DPP-4 Inhibitors**

- Metformin
- Alogliptin: 6.25 mg daily
- Linagliptin: 15 mg daily
- Saxagliptin: 15 mg daily
- Sitagliptin: 25 mg daily

**GLP-1 Receptor Agonists**

- Exenatide: 30 mg QW
- Exenatide QW: 15 mg daily
- Liraglutide: 15 mg daily
- Semaglutide: 15 mg daily

**SGLT2 Inhibitors**

- Canagliflozin: 100 mg daily
- Dapagliflozin: 45 mg daily
- Empagliflozin: 45 mg daily

- Use alternative agent
- Caution
- Do not initiate
- Dose adjustment not required

*May be considered when indicated for CV and renal protection with eGFR < 60 but > 30 mL/min/1.73 m²*
Counsel all Patients About Sick Day Medication List

**Instructions for Health-Care Professionals:**

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)

Please complete the following card and give it to your patient.

People with diabetes should be instructed that increased frequency of self-blood glucose monitoring will be required, and adjustments to their doses of insulin or noninsulin antihyperglycemic agents may be necessary.

**Instructions for People with Diabetes**

When you are ill, particularly if you become dehydrated (e.g., vomiting or diarrhea), some medicines could cause your kidney function to worsen or result in side effects.

If you become sick and are unable to drink enough fluid to keep hydrated, you should **STOP** the following medications:

- Blood pressure pills
- Water pills
- Metformin
- Diabetes pills
- Pain medications
- Nonsteroidal anti-inflammatory drugs (see below)

Please be careful not to take nonsteroidal anti-inflammatory drugs (which are commonly found in pain medications [e.g., Advil] and cold remedies).

Please check with your pharmacist before using over-the-counter medications and discuss all changes in medication with your health-care professional.

Please increase the number of times you check your blood glucose levels. If they run too high or too low, contact your health-care professional.

If you have any problems, you can call:
Renal outcomes in patients on SGLT2i

Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
Diuretics and SGLT2 Inhibition

1. What is the volume status?

   - Hypervolemia
     - Continue diuretic and monitor BP, lytes/Cr/weight
     - Initiate SGLT2i if BP okay

   - Hypotensive
     - Caution, hold or reduce diuretic
     - Initiate SGLT2i but monitor BP closely

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

   - Volume Contraction
     - Stop diuretic and monitor
     - Initiate SGLT2i when euvolemic

2. What is the blood pressure?

   - Euvolemia
     - Continue diuretic therapy and monitor BP, lytes/Cr/weight
     - Initiate SGLT2i if BP okay

BP, blood pressure; Cr, creatinine.
Adapted from Cherney DZ, Udell JA. Circulation. 2016;134:1915-1917.
In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73 m², an SGLT2 inhibitor with proven renal benefit may be considered to reduce the risk of progression of nephropathy [Grade B, Level 2 (106) for empagliflozin; Grade C, Level 3 (107) for canagliflozin].

People with diabetes should be referred to a specialist with expertise in CKD in the following situations [Grade D, Consensus for each of the following]:

- Chronic, progressive loss of kidney function
- Urine ACR persistently >60 mg/mmol
- eGFR <30 mL/min
- Unable to remain on renal-protective therapies due to adverse effects, such as hyperkalemia or a >30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB
- Unable to achieve target BP
Question 4: What Should You Advise the Primary Care Doctor About Starting SGLT2 Inhibitors?

Panellists
Rapidfire Bonus Question Round
Questions

• Do all people with diabetes need an echo?

• Under what circumstances would you use SGLT2i’s in heart failure and stop it in heart failure?

• Do SGLT2i’s cause hypoglycemia? Do we need to watch for this?
Closing Remarks

Panellists
QUESTIONS
ABOUT DIABETES AND HF YOU WERE TOO AFRAID TO ASK

Thank you for attending!
Please fill out the evaluation form by texting EVALUATION to
(647) 696-5222