Learning Objectives

Upon completion of this program, participants will be better able to:

• Define chronic kidney disease (CKD) in diabetes and its prevalence
• Discuss current standards of care in the treatment of CKD in patients with diabetes and the need for new therapeutic interventions
• Apply evidence from recent clinical trials with renal outcomes
Unmet Needs: Chronic Kidney Disease in Diabetes
CKD in diabetes has high prevalence and burden

- **40-50%** of people with diabetes will develop CKD\textsuperscript{1,2}
  - CKD is more common than CVD in patients with T2DM (24.1% vs 21.6\%)\textsuperscript{3}

- Diabetes is the **leading cause of new cases of ESKD** in Canada\textsuperscript{4}
  - \textit{\~}50\% of adults **requiring dialysis or renal replacement** have ESKD attributable to diabetes\textsuperscript{2}

- **CKD in diabetes can lead to complications**, including significant reductions in both length and quality of life\textsuperscript{5}
  - Between 1990 and 2012, number of **deaths due to CKD in patients with T2DM rose by 94\%**\textsuperscript{1}

ESKD, End-stage kidney disease; CKD: Chronic kidney disease; CVD: cardiovascular disease; T2DM: type 2 diabetes mellitus

Despite these interventions, there has been little improvement in the rate of ESKD

- Rates of other major complications in diabetes have declined
- Rates of ESKD have actually increased among older adults

ESKD, end-stage kidney disease; MI: myocardial infarction

Over the last 20 years, Diabetes Canada (DC) has advocated three key targets for patients with diabetes and renal impairment

- **A1C Control**
  - \( \leq 7.0\% \)
  - (Grade A)

- **BP Control**
  - \(< 130/80 \text{ mmHg}\)
  - (Grade A)

- **ACEi or ARB Treatment**
  - (Grade A)

Grade A recommendations are supported by systematic overview or meta-analysis of high-quality randomized clinical trials (RCTs) or appropriately designed RCT(s) with adequate power to answer the question posed by the investigators.

CDA: Canadian Diabetes Association; T2D: type 2 diabetes; A1C: glycated hemoglobin; BP: blood pressure; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

ACEi or ARB: “Gold standard” for CKD in diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Albuminuria</th>
<th>Baseline renal function</th>
<th>2xCr, ESKD, Renal Death – # of events</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT¹ (irbesartan)</td>
<td>1715</td>
<td>Median 1900 mg/d (1000 – 3800 mg/d)</td>
<td>Mean Cr: 148 μmol/L</td>
<td>644</td>
<td>20% (p=0.006)</td>
</tr>
<tr>
<td>RENAAL² (losartan)</td>
<td>1513</td>
<td>Median ACR: ~140 mg/mmol</td>
<td>Mean Cr: 168 μmol/L</td>
<td>686</td>
<td>16% (p = 0.02)</td>
</tr>
<tr>
<td>ACEi Collaborative study group³ (captopril)</td>
<td>409</td>
<td>Mean proteinuria: 2500 mg/d</td>
<td>Mean Cr: 115 μmol/L</td>
<td>2xCrR: 68</td>
<td>43% (p = 0.007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death or ESKD: 65</td>
<td>46%</td>
</tr>
</tbody>
</table>

ACEi: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin receptor blocker

ACEi or ARB: “Gold standard” for CKD in diabetes


- Risk reduction associated with ACEi or ARB agents was an important development in primary care
- There is still a clear unmet need for new therapeutic interventions

Note that this does not represent a head-to-head comparison or of ARB and ACEi effects in patients with CKD and diabetes.
No new treatment for CKD in diabetes since the advent of ACEi or ARB 17 years ago

High blood pressure identified as risk factor for CKD in patients with diabetes

ACEIs and ARBs

- Captopril\textsuperscript{3} T1D
- IDNT\textsuperscript{4}, IRMA 2\textsuperscript{5} Irbesartan T2D
- RENAA\textsuperscript{6} Losartan T2D

<table>
<thead>
<tr>
<th>1980s</th>
<th>1990s</th>
<th>2000s</th>
<th>2010s</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>ß-blockers\textsuperscript{1}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine\textsuperscript{2}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; T1D, type 1 diabetes; T2D, type 2 diabetes; IDNT, Irbesartan Type 2 Diabetic Nephropathy Trial; RAAS, renin–angiotensin-aldosterone system; RENAAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan


Figure adapted from: Steele A. LMC Clinical Practice Update 2018 [in press].d
Turning Point:
EMPA-REG, CANVAS, DECLARE
SGLT2 inhibitors and cardiovascular disease: MACE

<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Patients (n)</th>
<th>Events (n)</th>
<th>Events per 1000 patient-years (n)</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4687</td>
<td>2333</td>
<td>772</td>
<td>37.4</td>
<td>0.86 (0.74–0.99)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>3756</td>
<td>2900</td>
<td>796</td>
<td>34.1</td>
<td>0.82 (0.72–0.95)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>1020</td>
<td>36.8</td>
<td>0.90 (0.79–1.02)</td>
</tr>
</tbody>
</table>

Fixed effects model for atherosclerotic cardiovascular disease (p=0.0002)

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Patients (n)</th>
<th>Events (n)</th>
<th>Events per 1000 patient-years (n)</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>215</td>
<td>15.8</td>
<td>0.98 (0.74–1.30)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>5108</td>
<td>5078</td>
<td>539</td>
<td>13.4</td>
<td>1.01 (0.86–1.20)</td>
</tr>
</tbody>
</table>

Fixed effects model for multiple risk factors (p=0.98)

Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0.94, p=0.63, I²=0%; multiple risk factors: Q statistic=0.03, p=0.86, I²=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0.0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.
SGLT2i-associated side effects

**COMMON**
- Genital infections

**LESS COMMON**
- Urinary tract infections
- Osmotic diuresis, hypovolemia, hypotension
- Mild LDL-C increase

**RARE**
- Diabetic ketoacidosis*
- Amputations†
- Possible increase in fractures‡
- Increase in bladder cancer§
- Pancreatitis

For the most current side effect information, please review each individual product monograph

* observed with all SGLT2 inhibitors; † avoid using canagliflozin in individuals with a history of lower extremity amputation(s); ‡ observed with canagliflozin; § dapagliflozin not to be used in patients with bladder cancer.

Turning Point: The Kidney
**EMPA-REG OUTCOME**

Change in eGFR* over 192 weeks

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Empagliflozin, 10 mg</th>
<th>Empagliflozin, 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>68</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>70</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>72</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>108</td>
<td>74</td>
<td>76</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>136</td>
<td>76</td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>164</td>
<td>78</td>
<td>80</td>
<td>108</td>
</tr>
<tr>
<td>7</td>
<td>124</td>
<td>108</td>
<td>108</td>
<td>136</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>136</td>
<td>136</td>
<td>164</td>
</tr>
<tr>
<td>9</td>
<td>94</td>
<td>164</td>
<td>164</td>
<td>192</td>
</tr>
</tbody>
</table>

**CANVAS Program**

Change in eGFR over 6.5 years

<table>
<thead>
<tr>
<th>Years since randomization</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>1</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>54</td>
</tr>
</tbody>
</table>

In CVOTs, eGFR initially drops and is stabilized over time


*CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; CVOTs: cardiovascular outcome trials
Kidney outcomes in SGLT2 inhibitor CV outcome trials

Comparisons of trials should be interpreted with caution due to differences in study design, populations and methodology

*Accompanied by eGFR ≤45 mL/min/1.73 m²; †Nominal p-value. See slide notes for abbreviations


<table>
<thead>
<tr>
<th>Trial</th>
<th>SGLT2i n event/N analysed (%)</th>
<th>Rate/1000 PY</th>
<th>Placebo n event/N analysed (%)</th>
<th>Rate/1000 PY</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME¹</td>
<td>81/4645</td>
<td>6.3</td>
<td>71/2323</td>
<td>11.5</td>
<td>0.54 (0.40, 0.75)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Doubling of serum creatinine, * RRT or death from kidney causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DECLARE-TIMI 58²</td>
<td>127/8582</td>
<td>3.7</td>
<td>238/8578</td>
<td>7.0</td>
<td>0.53 (0.43, 0.66)</td>
<td>NR</td>
</tr>
<tr>
<td>≥40% decrease in eGFR to &lt;60 mL/min/1.73 m², new ESRD or death from kidney causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS³</td>
<td>NR</td>
<td>1.5</td>
<td>NR</td>
<td>2.8</td>
<td>0.53 (0.33, 0.84)</td>
<td>NR</td>
</tr>
<tr>
<td>Doubling of serum creatinine, ESKD or death from kidney causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.25 Favours SGLT2i 0.5 1 2 Favours placebo
Recommendation 10

10. 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, a SGLT2 inhibitor with proven renal benefit may be considered to reduce the risk of progression of nephropathy [Grade B, Level 2 for empagliflozin; Grade C, Level 3 for canagliflozin]

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate
One trial of SGLT2i agents with primary renal outcomes has been completed

<table>
<thead>
<tr>
<th></th>
<th>CREDENCE(^1,2)</th>
<th>DAPA-CKD(^3)</th>
<th>EMPA-KIDNEY(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>4401</td>
<td>4000</td>
<td>5000</td>
</tr>
<tr>
<td>Treatment arms</td>
<td>CANA 100 mg vs. PBO</td>
<td>DAPA (5, 10 mg) vs. PBO</td>
<td>EMPA vs. PBO</td>
</tr>
<tr>
<td>Patient population</td>
<td>CKD + T2D <strong>Must</strong> be taking max. labelled or tolerated ACEi/ARB</td>
<td>CKD ± T2D May be taking ACEi/ARB</td>
<td>CKD ± T2D May be taking ACEi/ARB</td>
</tr>
<tr>
<td>Kidney function inclusion criteria (eGFR units: mL/min/1.73 m(^2))</td>
<td>eGFR ≥30 to &lt;90 (\text{AND}) UACR &gt;33.9 mg/mmol (60%) to have eGFR ≥30 to &lt;60</td>
<td>eGFR ≥25 to &lt;75 (\text{AND}) UACR ≥22.6 mg/mmol</td>
<td>eGFR ≥20 to &lt;45 (\text{OR}) eGFR ≥45 to &lt;90 with UACR ≥22.6 mg/mmol</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Composite of ESKD, doubling of sCr, renal or CV death</td>
<td>Composite of ≥50% sustained decline in eGFR, ESKD, CV or renal death</td>
<td>Composite of CV death, kidney disease progression (ESKD, renal death or a sustained decline of ≥40% in eGFR)</td>
</tr>
<tr>
<td>Start</td>
<td>2014</td>
<td>2017</td>
<td>2018</td>
</tr>
<tr>
<td>Completion</td>
<td><strong>Complete</strong>: Stopped early due to achievement of efficacy endpoint</td>
<td>2020</td>
<td>2022</td>
</tr>
</tbody>
</table>

CREDENCE
Primary Renal Outcomes for SGLT2i in Patients with CKD and Diabetes
**CREDENCE: Study design**

**Key inclusion criteria**
- ≥30 years of age
- T2DM and HbA1c 6.5–12.0%
- eGFR 30–90 mL/min/1.73 m²
- UACR 300–5000 mg/g (33.9–565 mg/mmol)
- Stable maximum tolerated or labelled dose of ACEi or ARB for ≥4 weeks

**Key exclusion criteria**
- ≥Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

**2-week placebo run-in**

Double-blind randomization (1:1)

**Canagliflozin 100 mg**

**Placebo**

Follow-up at Weeks 3, 13, and 26 (F2F) then every 13 weeks (alternating phone/F2F)

Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; UACR, urinary albumin-to-creatinine ratio

Primary Endpoint: Composite of ESKD, doubling of serum creatinine, and renal or CV death

Hazard ratio, 0.70 (95% CI, 0.59–0.82)
$P = 0.00001$

Secondary Endpoint: End-stage kidney disease

Hazard ratio, 0.68 (95% CI, 0.54–0.86)
P = 0.002

No. at risk
Placebo 2199 2182 2141 2063 1752 1152 641 178
Canagliflozin 2202 2182 2146 2091 1798 1217 654 199

Effects on eGFR

Placebo (mean baseline eGFR 56.0 mL/min/1.73 m²)
Canagliflozin (mean baseline eGFR 56.4 mL/min/1.73 m²)

Acute eGFR change (3 weeks)
Placebo: –0.55 ml/min/1.73 m²
Canagliflozin: –3.72 ml/min/1.73 m²
Difference: –3.17
(95% CI, –3.87, –2.47)

Chronic eGFR slope
Difference: 2.74/year
(95% CI, 2.37–3.11)

No. at risk
Placebo 2178 2084 1985 1882 1720 1536 1006 583
Canagliflozin 2179 2074 2005 1919 1782 1648 1116 652
Projected Effects on eGFR

Average CREDECE patient
Age = 63 years
eGFR = 56

- Placebo/SOC
  Age = 73 years
eGFR = 10

- Canagliflozin
  Age = 88 years
  eGFR = 10

eGFR < 10 mL/min/1.73 m²

15.1 years

-4.59/year

-1.85/year
Secondary Endpoint: CV death or hospitalization for heart failure

Hazard ratio, 0.69 (95% CI, 0.57–0.83)
P <0.001

No. at risk
Placebo 2199 2165 2123 2044 1736 1147 638 170
Canagliflozin 2202 2171 2132 2077 1789 1226 668 199

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
Secondary Endpoint: CV Death, MI, or stroke (major adverse cardiovascular events, or 3-point MACE)

Hazard ratio, 0.80 (95% CI, 0.67–0.95)
P = 0.01

Participants with an event (%)

Participants:
- Placebo: 269
- Canagliflozin: 217

Months since randomization:
- 0
- 6
- 12
- 18
- 24
- 30
- 36
- 42

No. at risk:
- Placebo: 2199, 2152, 2100, 2022, 1717, 1143, 635, 168
- Canagliflozin: 2202, 2163, 2106, 2047, 1756, 1196, 642, 198

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
Secondary Endpoint: Hospitalization for heart failure

Hazard ratio, 0.61 (95% CI, 0.47–0.80)  
P <0.001

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
# AEs and serious AEs

<table>
<thead>
<tr>
<th></th>
<th>Number of participants with an event, n</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin (N = 2200)</td>
<td>Placebo (N = 2197)</td>
</tr>
<tr>
<td>All AEs</td>
<td>1784</td>
<td>1860</td>
</tr>
<tr>
<td>All serious AEs</td>
<td>737</td>
<td>806</td>
</tr>
</tbody>
</table>

Includes all treated participants through 30 days after last dose.

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
## Renal safety

<table>
<thead>
<tr>
<th></th>
<th>Number of participants with an event, n</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin (N = 2200)</td>
<td>Placebo (N = 2197)</td>
</tr>
<tr>
<td>All renal-related AEs</td>
<td>290</td>
<td>388</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>151</td>
<td>181</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>86</td>
<td>98</td>
</tr>
</tbody>
</table>

Includes all treated participants through 30 days after last dose.

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
# Other AEs of interest

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of participants with an event, n</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male genital mycotic infections*</td>
<td>Canagliflozin (N = 2200) 28</td>
<td>Placebo (N = 2197) 3</td>
</tr>
<tr>
<td>Female genital mycotic infections†</td>
<td>Canagliflozin (N = 2200) 22</td>
<td>Placebo (N = 2197) 10</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Canagliflozin (N = 2200) 245</td>
<td>Placebo (N = 2197) 221</td>
</tr>
<tr>
<td>Volume depletion–related AEs</td>
<td>Canagliflozin (N = 2200) 144</td>
<td>Placebo (N = 2197) 115</td>
</tr>
<tr>
<td>Malignancies‡</td>
<td>Canagliflozin (N = 2200) 98</td>
<td>Placebo (N = 2197) 99</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Canagliflozin (N = 2200) 1</td>
<td>Placebo (N = 2197) 5</td>
</tr>
<tr>
<td>Breast†</td>
<td>Canagliflozin (N = 2200) 8</td>
<td>Placebo (N = 2197) 3</td>
</tr>
<tr>
<td>Bladder</td>
<td>Canagliflozin (N = 2200) 10</td>
<td>Placebo (N = 2197) 9</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Canagliflozin (N = 2200) 5</td>
<td>Placebo (N = 2197) 2</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Canagliflozin (N = 2200) 11</td>
<td>Placebo (N = 2197) 1</td>
</tr>
</tbody>
</table>

Includes all treated participants through 30 days after last dose except cancer, which includes all treated patients through the end of the trial.

*Includes male participants only (canagliflozin, n = 1439; placebo, n = 1466).
†Includes female participants only (canagliflozin, n = 761; placebo, n = 731).
‡Includes malignant tumors of unspecified type.
**AEs: Lower extremity amputation**

**Hazard ratio, 1.11 (95% CI, 0.79–1.56)**

- **Placebo**
  - 63 participants
  - No. at risk: 2197, 2169, 2131, 2065, 1766, 1177, 658, 182

- **Canagliflozin**
  - 70 participants
  - No. at risk: 2200, 2163, 2118, 2071, 1788, 1228, 667, 202

Mahaffey KW. Presented at ISN World Congress of Nephrology; April 12-15, 2019; Melbourne, Australia. Session O-361.
Canagliflozin renal benefits are additive to ACEi and ARB

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Albuminuria</th>
<th>Baseline renal function</th>
<th>Median Follow-up</th>
<th>2xCr, ESKD, Renal Death # of events</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT</td>
<td>1715</td>
<td>Median: 1900 mg/d</td>
<td>Mean Cr: 148 μmol/L</td>
<td>2.6 years</td>
<td>644</td>
<td>20%</td>
</tr>
<tr>
<td>RENAAL</td>
<td>1513</td>
<td>Median ACR: 140 mg/mmol</td>
<td>Mean Cr: 168 μmol/L</td>
<td>3.4 years</td>
<td>686</td>
<td>16%</td>
</tr>
<tr>
<td>ACEi Collaborative study group</td>
<td>409</td>
<td>Mean proteinuria: 2500 mg/d</td>
<td>Mean Cr: 115 μmol/L</td>
<td>3.0 years</td>
<td>2xCrR: 68 Death or ESKD: 65</td>
<td>43% 46%</td>
</tr>
<tr>
<td>CREDENCE*</td>
<td>4401</td>
<td>Median UACR: 105 mg/mmol</td>
<td>Mean eGFR: 56.2 mL/min/1.73 m²</td>
<td>2.6 years</td>
<td>377</td>
<td>34%</td>
</tr>
</tbody>
</table>

*NOTE: All patients enrolled in CREDENCE were taking maximal labelled or tolerated daily dose of ACEi or ARB in addition to being treated to target for blood pressure and A1C as part of the standard of care

GLP-1RA effects on a composite renal endpoint in CVOTs

- Meta-analysis of GLP-1RA CVOTs on composite renal endpoint:
  - **New-onset macroalbuminuria**, sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal cause

- REWIND trial (dulaglutide CVOT)
  - New-onset macroalbuminuria, sustained decline in eGFR ≥30%, or new chronic renal replacement therapy

### Meta-analysis

<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients</th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>5286</td>
<td>375</td>
<td>0.84 (0.68, 1.02)</td>
</tr>
<tr>
<td>LEADER</td>
<td>9340</td>
<td>605</td>
<td>0.78 (0.67, 0.92)</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>3297</td>
<td>162</td>
<td>0.64 (0.46, 0.88)</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>14752</td>
<td>773</td>
<td>0.88 (0.76, 1.01)</td>
</tr>
</tbody>
</table>

**Fixed Effects for GLP1-RA (P-value<0.001)** 0.82 (0.75, 0.89)

### REWIND

- **Cumulative risk (%)**
  - Placebo
  - Dulaglutide

- **No. at risk**
  - Placebo: 4952, 4756, 4475, 4145, 3887, 3169, 641
  - Dulaglutide: 4949, 4798, 4571, 4303, 4045, 3320, 667

One trial of SGLT2i agents with primary renal outcomes has been completed

<table>
<thead>
<tr>
<th></th>
<th>CREDENCE(^1,2)</th>
<th>DAPA-CKD(^3)</th>
<th>EMPA-KIDNEY(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>4401</td>
<td>4000</td>
<td>5000</td>
</tr>
<tr>
<td>Treatment arms</td>
<td>CANA 100 mg vs. PBO</td>
<td>DAPA (5, 10 mg) vs. PBO</td>
<td>EMPA vs. PBO</td>
</tr>
<tr>
<td>Patient population</td>
<td>CKD + T2D</td>
<td>CKD + T2D</td>
<td>CKD + T2D</td>
</tr>
<tr>
<td></td>
<td><strong>Must</strong> be taking max. labelled or tolerated ACEi/ARB</td>
<td>May be taking ACEi/ARB</td>
<td>May be taking ACEi/ARB</td>
</tr>
<tr>
<td>Kidney function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inclusion criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(eGFR units: mL/min/1.73 m(^2))</td>
<td></td>
<td></td>
<td>eGFR ≥20 to &lt;45</td>
</tr>
<tr>
<td></td>
<td>60% to have eGFR ≥30 to &lt;60</td>
<td></td>
<td>OR eGFR ≥45 to &lt;90 with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UACR ≥22.6 mg/mmol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Composite of CV death, kidney disease progression (ESKD, renal death or a sustained decline of ≥40% in eGFR)</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Composite of ESKD, doubling of sCr, renal or CV death</td>
<td>Composite of ≥50% sustained decline in eGFR, ESKD, CV or renal death</td>
<td>Composite of CV death, kidney disease progression (ESKD, renal death or a sustained decline of ≥40% in eGFR)</td>
</tr>
<tr>
<td>Start</td>
<td>2014</td>
<td>2017</td>
<td>2018</td>
</tr>
<tr>
<td>Completion</td>
<td><strong>Complete</strong>: Stopped early due to achievement of efficacy endpoint</td>
<td>2020</td>
<td>2022</td>
</tr>
</tbody>
</table>

“AstraZeneca has announced that the phase 3 DAPA-CKD trial for dapagliflozin (Farxiga) in patients with chronic kidney disease has been halted early because of overwhelming efficacy of the drug, at the recommendation of an independent data monitoring committee.”
Time to update the guidelines

A1C Control

≤ 7.0%

(Grade A)

BP Control

< 130/80 mmHg

(Grade A)

ACEi or ARB

Treatment

(Grade A)

SGLT2i

Treatment

(Grade A)

Grade A recommendations are supported by systematic overview or meta-analysis of high-quality randomized clinical trials (RCTs) or appropriately designed RCT(s) with adequate power to answer the question posed by the investigators.

CDA: Canadian Diabetes Association; T2D: type 2 diabetes; A1C: glycated hemoglobin; BP: blood pressure; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

Time to update the guidelines

Canagliflozin indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of end-stage kidney disease, doubling of serum creatinine, and cardiovascular (CV) death in adult patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria

A1C Control
≤ 7.0%
(Grade A)

BP Control
< 130/80 mmHg
(Grade A)

ACEi or ARB
Treatment
(Grade A)

SGLT2i
Treatment
(Grade A)

Grade A recommendations are supported by systematic overview or meta-analysis of high-quality randomized clinical trials (RCTs) or appropriately designed RCT(s) with adequate power to answer the question posed by the investigators

CDA: Canadian Diabetes Association; T2D: type 2 diabetes; A1C: glycated hemoglobin; BP: blood pressure; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

Where do we go from here

• General principles:
  - **Address atherosclerotic risk factors**
  - On top of ACEi or ARB, SGLT2i are profoundly cardio and nephroprotective, especially in high-risk patients
  - Perhaps the most potent single intervention we can offer diabetics
  - Even in low-risk patients data support outcome benefits unseen in any other class – consider using SGLT2i as first add-on after metformin in all patients
  - SGLT2i have side affects
    - Properly counseled, all side affects seem acceptable given the benefits
Where do we go from here?

- Does my patient have CKD (with or without proteinuria)?
  - If yes:
    - Ensure patient is taking an ACE or ARB
    - For all patients with GFR > 30 ml/min, consider an SGLT2i
    - Scrutinize any internal or external decision not to prescribe
      - Warn about adverse effects (esp: DKA, amputation, GMI, diuretic effects)
    - For patients with marginal BP, consider reducing or removing all meds that do not have Grade A evidence for organ protection
      - Consider reducing (not removing) dose of organ protecting drugs to accommodate SGLT2i
Where do we go from here?

- Recommend SGLT2i or start them myself?
  - Will depend on comfort level for modifying insulin or AHA
  - I will start SGLT2i in patients:
    - On AHA which do not cause hypoglycemia
    - On AHA which do cause hypoglycemia if A1C greater than 8, especially if patient self-monitors blood glucose +/- reduces SU
Where do we go from here?

- I will not start (but will recommend) SGLT2i:
  - In patients on MDI insulin +/- larger doses of basal insulin especially if A1C <8% and patients do not self-monitor blood glucose
  - Type 1 DM
  - +/- prior amputation
  - Some uncertainty in patients with A1C at target
    - Start anyways?
    - Swap out AHA
Where do we go from here?

• For patients with residual proteinuria (ACR >50-70 mg/mmol)
  • Consider starting or recommending GLP1-RA
  • High dose ACEi/ARB
  • Consider MRA (Coming soon: Finerenone in diabetic CKD)
Where do we go from here

- Areas of further exploration:
  - SGLT2i in non-diabetes
  - MRA (finerenone) to improve renal outcomes
  - GLP-RA to improve renal outcomes
  - Endothelin antagonists to improve renal outcomes