Cardiovascular Outcome Trials of Diabetes Medications: Translating Results into Practice

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Complications of Diabetes

Diabetic Retinopathy
Leading cause of blindness in adults

Diabetic Nephropathy
Leading cause of end-stage renal disease

Stroke
2- to 4-fold increase in cardiovascular mortality and stroke

Cardiovascular Disease
8/10 individuals with diabetes die from CVD

Diabetic Neuropathy
Leading cause of non-traumatic lower extremity amputations

Diabetes & prior CVD begets premature mortality

Improvements in Diabetes-Related Complications in the USA, 1990-2010

Acute myocardial infarction
Reduction in events from 1990 to 2010 - 67.8%
(95% CI: 76.2% to 59.3%)

Reduction in events from 1990 to 2010 - 32.3%
(95% CI: 42.7% to 22.5%)

Population with Diabetes
Population with or without Diabetes

ADA Recommendations for Statin Therapy

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No Risk Factors</th>
<th>ASCVD Risk Factorsa</th>
<th>With ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>None</td>
<td>Moderate or high intensity</td>
<td>High intensity</td>
</tr>
<tr>
<td>40-75</td>
<td>Moderate intensity</td>
<td>High intensity</td>
<td>High intensity</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>Moderate intensity</td>
<td>Moderate or high intensity</td>
<td>High intensity</td>
</tr>
</tbody>
</table>

If ACS is present and LDL-C ≥ 100 mg/dL or statin intolerant, use moderate-intensity statins + ezetimibe.
- For every 30 mg/dL reduction in LDL-C, 21% reduction in MACE, 9% reduction in all-cause mortality
- PCSK9 inhibitors may be considered in patients at high risk of ASCVD events who are intolerant of high-intensity statin therapy

a) LDL-C ≥ 100 mg/dL, HTN, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

b) ≈ 1% annual risk of major CV event; BL LDL-C = 127.8 mg/dL, diabetes prevalence ≈ 6%.

Pharmacologic Interventions

- Treatment for hypertension should include drug classes demonstrated to reduce CV events in patients with diabetes:
  - ACE inhibitors
  - Angiotensin receptor blockers (ARBs)
  - Thiazide-like diuretics
  - Dihydropyridine calcium channel blockers

SBP target: <140 most, <130 select but relax in elderly (? <150 when >80 yrs)

- For most outcomes, risk reduction max <140 SBP
- <130 SBP further reductions in high risk for CVD, stroke, retinopathy and albuminuria
- BP < 130/70 associated with increased mortality in older adults


Heart Failure after MI Associated with High Mortality

- Retrospective chart review of all patients with first myocardial infarction, without previous diagnosis of heart failure – N = 2,596
- mean follow up 7.6 years
- Results:
  - 902 developed heart failure (58/1000 pt years)
  - Risk factors: older, female, HTN, DM
  - 535 developed recurrent MI
  - 1,116 died
  - >50% of deaths occurred after diagnosis of HF (5-fold higher in those without HF)

Diabetes and Heart Failure

- Second most common presentation of heart disease in diabetes (after peripheral vascular disease)
- 12% of all cases of HF attributable to DM
  - RF: older, long duration DM, insulin treatment, poor glycemic control
- When coexists with HF, diabetes associated with 53% higher risk of hospitalization and 50% higher mortality.
  - Median survival 50% in 5 years.
- Costs in 2012: 31 billion, primarily hospitalizations
  - #1 reason for hospitalization in those > 65 yrs

Cardiovascular Risk in Type 2 Diabetes: Intensive vs less intensive glycemic control

<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular events</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td></td>
<td>▲</td>
</tr>
<tr>
<td>ADVANCE</td>
<td></td>
<td>▲</td>
</tr>
<tr>
<td>UKPDS</td>
<td></td>
<td>▲</td>
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<tr>
<td>VADT</td>
<td></td>
<td>▲</td>
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</table>

Gerber Y et al. Circ Heart Fail. 2016;9:e002460. DOI: 10.1161/CIRCHEARTFAILURE.115.002460
McDonald MR et al. Eur Heart J, 2008

Completed and ongoing CVOTs

Cardiovascular Outcome Trials: Reported Studies to Date

<table>
<thead>
<tr>
<th>Study</th>
<th>Cardiovascular events</th>
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<tbody>
<tr>
<td>SAVOR-TIMI 53 (DPP4i - saxagliptin)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>EXAMINE (DPP4i - alogliptin)</td>
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<tr>
<td>TECOS (DPP4i - exenatide)</td>
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</tr>
<tr>
<td>ELIXA (GLP-1 RA - lixisenatide)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>LEADER (GLP-1 RA - liraglutide)</td>
<td>6</td>
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</tr>
<tr>
<td>CANVAS (SGLT2i - canagliflozin)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME (SGLT2i - empagliflozin)</td>
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<td></td>
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<tr>
<td>SUSTAIN-6 (GLP-1 RA - semaglutide)</td>
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Cardiovascular Outcome Trials: Reported Studies to Date

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Approved SGLT-2 Inhibitors With Proven Benefit on Cardiovascular Outcomes in Prospective RCTs (Rates per 100 patient-years)

<table>
<thead>
<tr>
<th>Drug</th>
<th>MACE</th>
<th>HF Hospitalization</th>
<th>CV Mortality</th>
<th>Total Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA</td>
<td>RR: -16%</td>
<td>RR: -37%</td>
<td>RR: -34%</td>
<td>RR: -42%</td>
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<tr>
<td>CANA</td>
<td>RR: -14%</td>
<td>RR: -10%</td>
<td>RR: -48%</td>
<td>RR: -75%</td>
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</table>

Approved GLP-1 Receptor Analogues With Proven Benefit on Cardiovascular Outcomes in Prospective RCTs (Rates/100 pt years)

<table>
<thead>
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<th>CV Mortality</th>
<th>Total Mortality</th>
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<tr>
<td>LIRA</td>
<td>RR: -13%</td>
<td>RR: -19%</td>
<td>RR: -15%</td>
<td>RR: -10%</td>
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<tr>
<td>SEMA</td>
<td>RR: 0%</td>
<td>RR: 0%</td>
<td>RR: 0%</td>
<td>RR: 0%</td>
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Number Needed to Treat to Avoid One Event

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<thead>
<tr>
<th>LEADER</th>
<th>EMPA-REG</th>
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<tr>
<td>3-point MACE</td>
<td>53</td>
</tr>
<tr>
<td>CVD Death</td>
<td>77</td>
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<tr>
<td>CHF Hospitalization</td>
<td>NA</td>
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CVOT: Review of Primary and Secondary Outcomes
Baseline Characteristics of CV Outcomes Trials (SGLT-2 Inhibitors and GLP-1 RA)

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>EXPA</th>
<th>LEADER</th>
<th>SUSTAIN</th>
<th>EXSCEL</th>
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<td>Mean age, y</td>
<td>63</td>
<td>63</td>
<td>60</td>
<td>64</td>
<td>65</td>
<td>62</td>
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<tr>
<td>Diabetes duration, y</td>
<td>12</td>
<td>14</td>
<td>9</td>
<td>13</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>% with prior HF</td>
<td>10</td>
<td>14</td>
<td>22</td>
<td>14</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>% with prior CVD</td>
<td>100</td>
<td>66</td>
<td>100</td>
<td>81</td>
<td>83</td>
<td>73</td>
</tr>
<tr>
<td>% with CKD 3+</td>
<td>25</td>
<td>20</td>
<td>23</td>
<td>25</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.1</td>
<td>8.2</td>
<td>7.6</td>
<td>8.7</td>
<td>8.7</td>
<td>8.0</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>77</td>
<td>75</td>
<td>64</td>
<td>75</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Premature discontinuation, %</td>
<td>25</td>
<td>29</td>
<td>25</td>
<td>NR (17)</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>Antihyperglycemic therapy, %</td>
<td>• MET 77</td>
<td>• SU 43</td>
<td>• TZD 4</td>
<td>• INS 49</td>
<td>• MET 77</td>
<td>• SU 43</td>
</tr>
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</table>


ORIGIN: Composite Outcomes & their Components

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P</th>
<th>Insulin /200 py</th>
<th>Standard /200 py</th>
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</thead>
<tbody>
<tr>
<td>1st Caprimary</td>
<td>1.02 (0.94, 1.11)</td>
<td>0.63</td>
<td>2.54</td>
</tr>
<tr>
<td>2nd Caprimary</td>
<td>1.04 (0.97, 1.11)</td>
<td>0.27</td>
<td>5.52</td>
</tr>
<tr>
<td>Microvascular</td>
<td>0.97 (0.90, 1.05)</td>
<td>0.43</td>
<td>3.87</td>
</tr>
<tr>
<td>Death</td>
<td>0.98 (0.90, 1.08)</td>
<td>0.70</td>
<td>2.57</td>
</tr>
<tr>
<td>MI</td>
<td>1.02 (0.88, 1.19)</td>
<td>0.49</td>
<td>0.95</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.03 (0.80, 1.32)</td>
<td>0.83</td>
<td>0.91</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.00 (0.88, 1.16)</td>
<td>0.24</td>
<td>1.57</td>
</tr>
<tr>
<td>CHF Hospital</td>
<td>0.90 (0.77, 1.05)</td>
<td>0.16</td>
<td>0.85</td>
</tr>
<tr>
<td>Revascularized</td>
<td>1.06 (0.96, 1.16)</td>
<td>0.24</td>
<td>2.69</td>
</tr>
</tbody>
</table>

NEJM 2012;367:319

Microvascular Outcomes

Microvascular Complications in the CVOT studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Nephropathy (HR)</th>
<th>Retinopathy (HR)</th>
<th>Amputation (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG</td>
<td>0.61</td>
<td>NR</td>
<td>p†</td>
</tr>
<tr>
<td>CANVAS</td>
<td>0.82</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>LEADER</td>
<td>0.78</td>
<td>1.15*</td>
<td>NR</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>0.54*</td>
<td>7.10*</td>
<td>NR</td>
</tr>
</tbody>
</table>

- In the SUSTAIN study: 79 events/3297 pts. 83% gave hx of DR, 29% hx of PDR
- In the CANVAS study: 125 events/10,142 pts. 71% “minor”. Highest with hx of amputation & PVD

* Enrolled patients with higher A1C – monitored nephropathy as event of interest
† Events/1000 patient years 6.5/1000 in treatment groups in both studies. Differences noted in placebo event rate. EMPA – not collected during study

DEVOTE: Degludec vs Glargine
Time to first 3-point MACE

Microvascular Complications

Other Adverse Events of Interest

NEJM 2012;367:319
**CANVAS Program: Fractures**

### Event rates per 1000 patient-years

<table>
<thead>
<tr>
<th>Study</th>
<th>Fractures</th>
<th>Fractures, Fibulae</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS Program</td>
<td>15</td>
<td>8.3</td>
</tr>
<tr>
<td>CANVAS (n = 2785)</td>
<td>13</td>
<td>8.3</td>
</tr>
<tr>
<td>CANVAS (n = 2600)</td>
<td>7.9</td>
<td>10</td>
</tr>
</tbody>
</table>

### Hypoglycemia

- Despite all studies showed a lower A1c with active treatment, only LEADER reported lower risk of hypoglycemia:
  - Confirmed: HR 0.80
  - Severe: HR 0.69

### Other Adverse Events of Interest

- In the studies with GLP-1 RA, the adverse profile was as expected: GI SE, injection site reactions (n = 27,389)
  - In LEADER, there was increase in gallbladder disease
  - Despite increases in lipase and amylase, there was no evidence of increase in risk for pancreatitis nor pancreatic cancer.
  - There was no evidence of increased risk for medullary cancer of the thyroid
- In the studies with SGLT-2 inhibitors, there was increased risk for genital mycotic infections and symptoms of volume depletion (n = 17,162)
  - Volume depletion was reported in 26 and 17/1000 pt-years in CANVAS and EMPA-REG respectively
  - There was no increase in risk for UTI, DKA, acute kidney injury, hyperkalemia.

### Mechanism of Action for Reduction of CV Risk

- Changes in traditional CVRF did not explain the outcomes in LEADER nor EMPA-REG.
- EMPA-REF: Changes in Hct of about 5% (as a measure of volume status) explained about 52% of the effect, followed by FBG at 22% and uric acid at 18%.
  - Similar changes in Hct seen with canagliflozin, but not reported in CANVAS paper
- Direct anti-atherogenic actions postulated for CV effects of liraglutide

### Potential Pathways Linking Empagliflozin With CV Benefits: Volume and Hemodynamics

(Sattar N et al. Diabetologia 2016; epub ahead of print. Michael A. Nauck et al. Circulation. 2017;136:849–870 Copyright © American Heart Association, Inc. All rights reserved.)
Carl

- 69 year old white male type 2 DM x15 yrs History of myocardial infarction, albuminuria, neuropathy, and nonproliferative retinopathy.
- OS: chronic dyspnea on exertion, diarrhea while on metformin
- SH: lives alone, doesn’t like to cook
- PE: Ht 77, TC 275, HDL 33, LDL 33, ALT 40.5, BP 149/85 + S4 gallop, 2+ pedal edema, absent pedal sensation
- A1c 8.0%, eGFR – 77, TC-186, TG-94, HDL-C-33, LDL-C-63, AL-T-21, UAE – 74 mg/g Cr.

What is your A1c goal for Carl?
A. <6.0%
B. <6.5%
C. <7.0%
D. <7.5%
E. <8.0%

What is your primary concern for Carl?
A. Lower his A1c
B. Lower his triglycerides
C. Weight management
D. Lower his risk for recurrent cardiovascular events &/or death from CVD

In addition to lowering the dose of insulin, what would you suggest for improving his glycemic control?
A. Add glimepiride
B. Add a DPP-4 inhibitor
C. Add liraglutide
D. Add SGLT-2 inhibitor.
E. Suggest bariatric surgery

Treatment considerations for Carl
- Signs of CHF and adequate GFR – good candidate for SGLT-2 inhibitor
- If SGLT-2 inhibitor is started:
  - Minimize hypoglycemia – consider 20 - 30% reduction in insulin dose (both basal and prandial)
  - DC HCTZ due to expected 5+ mmHg reduction in BP with SGLT-2 inhibitor
  - Encourage increased fluid intake
  - Advise about risk for balanitis, if not circumsized
Janice

- A 62-year-old woman with a 14 year history of T2D is seen for diabetes management. She has a 40 pack/year history of smoking, but quit after CVA.
- BP 142/90, BMI 36 kg/m²
- PE: unremarkable
- Labs: HbA₁c 8.5%, eGFR 40 mL/min/1.73m², LDL 90, HDL 37, TG 224; ALT normal; UACR 45
- SMBGs high 100s AM, 200s rest of the day

Medications
- Metformin 1000 mg BID
- Glimepride 2 mg BID
- Glargine insulin 65 units at bedtime
- Lisinopril 20 mg daily
- HCTZ 25 mg daily
- Atorvastatin 40 mg daily
- ASA 81 mg daily

What is your A1c goal for Janice?

A. <6.0%
B. <6.5%
C. <7.0%
D. <7.5%
E. <8.0%

What is the best next step to improve glycemic control?

A. Increase glimepiride to 4 mg BID
B. Add linagliptin 5 mg daily
C. Add lispro with each meal
D. Add canagliflozin 100 mg daily
E. Add liraglutide up to 1.8 mg daily

Treatment Considerations for Janice

- Due to age and serious comorbidities, I would be satisfied with an A1c in the 7’s.
- With her low GFR, I would opt for substituting liraglutide for glimepiride
  - Ensure up to date on eye exam
  - Advise about GI SE: slow titration
  - Advise about risk for gallbladder disease
- With history of CVA, lower target BP might be indicated, if tolerated
  - Consider an orthostatic BP/P
  - Helpful to know the carotid anatomy
- Consideration for increasing atorvastatin vs adding ezetimibe

Jacinta

- 58 year old Hispanic female with type 2 DM x 6 yrs, and recent diagnosis of PVD and small, healing noninfected foot ulcer.
- ROS: Neg
- SH: Non-smoker. Works as a manager for the state
- PE: HT 65”, WT 166 lbs, BMI
- 1+ pedal edema, diminished pedal sensation
- A1c 6.8%, eGFR ~ 75, TC 137, TG 238, HDL-C 36, LDL-C 63, ALT 21, UAE 155 mg/g Cr.

Medications
- Metformin 1000 mg BID
- Canagliflozin 300 mg QD
- Lisinopril 20 mg
- Metoprolol 50 mg BID
- Atorvastatin 40 mg
- Fish oil 2000 mg BID
- Aspirin 81 mg QD

What is your A1c goal for Jacinta?

A. <6.0%
B. <6.5%
C. <7.0%
D. <7.5%
E. <8.0%
What is your primary concern for Jacinta?

A. Lower her triglycerides
B. Weight management
C. Lower her risk for recurrent cardiovascular events &/or death from CVD
D. Management of her foot ulcer

What would you do with her medications?

A. Nothing
B. Change canagliflozin to empagliflozin
C. Change canagliflozin to liraglutide
D. Stop metoprolol and continue other medications.

Albert

• 70 year old white male type 2 DM x11 yrs, history of stent placement after a myocardial infarction 2 years ago. He denies hypoglycemia. He has Medicare Part D
• ROS: Neg
• SH: lives with his wife. Nonsmoker
• PE: Ht-71", Wt-244 lbs, BMI- 34, BP-132/70 1+ pedal edema, normal pedal sensation
• A1c-6.9%, eGFR – 57, TC-127, TG-188, HDL-C-36, LDL-C-63, ALT-21, UAE – 74 mg/g Cr.

What is your A1c goal for Albert?

A. <6.0%
B. <6.5%
C. <7.0%
D. <7.5%
E. <8.0%

What is your primary concern for Albert?

A. Lower his A1c
B. Lower his triglycerides
C. Weight management
D. Lower his risk for recurrent cardiovascular events &/or death from CVD

Is he a candidate for addition of a GLP-1 RA or SGLT-2 inhibitor?

A. No, his A1c is at target
B. No, they are too expensive
C. Yes, add liraglutide
D. Yes, add an SGLT-2 inhibitor
Treatment considerations for Albert

• He would be a candidate for either SGLT-2 inhibitor or GLP-1 receptor agonist
• Cost can be managed by using lower doses:
  – Do not titrate > 1.2 mg of liraglutide
  – Use ½ tablet of max dose of empagliflozin or canagliflozin

Cost of Liraglutide vs SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lowest cost for 30 days</th>
</tr>
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<tbody>
<tr>
<td>Liraglutide 1.8 mg</td>
<td>$993/662 (1.2 mg)</td>
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<tr>
<td>Empagliflozin 25 mg</td>
<td>$415/208 (1/2 tab)</td>
</tr>
<tr>
<td>Canagliflozin 300 mg</td>
<td>$443/222 (1/2 tab)</td>
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Source: GoodRx.com for zip 99203, accessed 9/11/17

Large CV Outcomes Trials in Diabetes (Non-Insulin)

<table>
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<th>Comparator</th>
<th>N</th>
<th>Results</th>
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<td>SAVOR</td>
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<td>16,500</td>
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</tr>
<tr>
<td>EXAMINE</td>
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<tr>
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Rates of All Complications of Diabetes are Decreasing

Summary: Lowering Risk for CVD events in Diabetes

• Clear evidence of CVD mortality in T2DM over several decades, but there remains a large gap over the risk for patients without diabetes
  – Better management of CVD risk factors have a major role, but many sub-optimally treated
    - BP and LDL-C reduction > glucose reduction
    - Smoking reduction
  – Best time to prevent CVD with glucose control is at diagnosis
  – Cardiovascular outcome trials show safety of DPP-4 inhibitors, insulin glargine, insulin degludec, lixisenatide and exenatide QW
  – Data from cardiovascular outcome trials support role of SGLT-2 inhibitors (empagliflozin and canagliflozin) and 2 of the long-acting GLP-1 receptor agonists (liraglutide and semaglutide) for reduction of CVD events in patients with established CVD
Differences within Class: GLP-1 RA

- Only two with demonstrated CV benefit: liraglutide and semaglutide
- Exenatide QW – barely missed significance – likely related to high medication discontinuation
- Lixisenatide – ND – likely related to short duration of action

Differences within Class: SGLT-2 inhibitor

- Greater impact on CV death with Empagliflozin – in part related to higher CV risk
  - Impact on primary endpoint and CHF similar
- Significant increase in amputations and traumatic fractures seen in CANVAS trial
  - Both likely related to greater risk for volume depletion reported in CANVAS (26/1000 pt-yr) compared to EMPA-REG (18/1000 pt yr)

Type 2 DM & ASCVD: Reducing Risk

Special precautions:
- retinopathy, especially with semaglutide
- PVD, especially with canagliflozin