Diabetes and Heart Disease

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Potential for conflicts of interest: None
Mitigating Potential Bias

• While we have received unrestricted educational grants from several pharmaceutical companies, most presentations have no mention of specific products and are unrelated to the supporting companies or their products. No specific presentations will be supported or sponsored by a specific company.

• Information on specific products will be presented in the context of an unbiased overview of all products related to treating patients.

• All scientific research related to, reported or used in this CME activity in support or justification of patient care recommendations conforms to the generally accepted standards.

• Clinical medicine is based in evidence that is accepted within the profession.
Objectives

• To discuss the correlation between diabetes and cardiovascular disease.

• Highlight the recent CV outcome studies performed with newer agents for treating diabetes and their implications for the clinician.

• Understand the burden of heart failure in patients with diabetes
Background
Question #1

Which of the following is true?

1. Diabetes increases the risk of developing CV disease by 2-3 times
2. Prevalence of most macrovascular complications of diabetes has been declining
3. Only half of Canadians living with diabetes have adequate glycemic control
4. All of the above
Impact of Diabetes in Canada

1 in 10 deaths in Canadian adults was attributable to diabetes

3X more likely to be hospitalized with cardiovascular disease

12X more likely to be hospitalized with end-stage renal disease

Life Expectancy is Reduced By 12 Years in People With Diabetes and Previous CVD

T2DM Confers Highest Lifetime Risk For CHD of Any Risk Factor Studied

### Link Between Diabetes and CVD:

Vascular outcome in people with T2D vs. without T2D: T2D confers excess CVD risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>26505</td>
<td>2.0 (1.8;2.2)</td>
<td>64 (54;71)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11556</td>
<td>2.3 (2.1;2.6)</td>
<td>41 (24;54)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>14741</td>
<td>1.8 (1.6;2.0)</td>
<td>37 (19;51)</td>
</tr>
</tbody>
</table>

**Stroke subtypes**

<table>
<thead>
<tr>
<th>Stroke subtype</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>3799</td>
<td>2.3 (2.0;2.7)</td>
<td>1 (0;20)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1183</td>
<td>1.6 (1.2;2.1)</td>
<td>0 (0;26)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4973</td>
<td>1.8 (1.6;2.1)</td>
<td>33 (12;48)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3826</td>
<td>2.3 (2.0;2.7)</td>
<td>0 (0;26)</td>
</tr>
</tbody>
</table>

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**T2D confers 2-fold excess risk for CVD independently of other risk factors**

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CI, confidence interval; CVD, cardiovascular disease; HRs, hazard ratios; T2D, type 2 diabetes

Patients with DM but no history of prior MI experience a similar rate of MI as patients with prior history of MI without DM.

DM=Diabetes mellitus, MI=Myocardial infarction

*Fatal or non-fatal MI
Intensive Glucose Lowering Provides Modest, But Significant, Macrovascular Benefits

- **Meta-analysis**
  - ACCORD | ADVANCE | UKPDS | VADT

- **27,049 participants**
  - 2,370 major vascular events

- **Average follow-up = 4.4 years**

- **Intensive vs. conventional**

- **A1C ↓**
  - Mean 0.88% greater decrease

- **Relative risk reduction:**
  - **MACE** 9% (HR 0.91, 95% CI 0.84–0.99)
  - **MI** 15% (HR 0.85, 95% CI 0.76–0.94)

A1C = glycated hemoglobin; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; UKPDS = UK Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

Link Between Hypoglycemia and Acute CV Events in T2DM

- Retrospective, observational study assessing association between hypoglycemia and acute CV events
- 3.1% patients had hypoglycemia during evaluation period
- Patients with hypoglycemia had 79% higher odds for acute CV events vs. patients with no hypoglycemia

Johnston SS et al. Diabetes Care 2011; 34:1164-70
Hypoglycemia May Affect CV Events


**Hypoglycemia**

- Neutrophil activation
- Platelet activation
- Factor VII

**Blood coagulation abnormalities**

**Inflammation**

- CRP
- VEGF
- IL-6

**Sympathoadrenal response**

- Heart rate variability
- Adrenaline
- Oxygen consumption
- Contractility
- Heart workload

**Endothelial dysfunction**

- Vasodilation
Question #2

In your clinical practice, which is your go-to agent after metformin for most patients with diabetes and no h/o CV disease?

1. DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin)
2. GLP-1 RAs (dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide)
3. Insulin (basal, mixed, bolus)
4. SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)
5. Sulfonylureas (gliclazide, glimeperide, glyburide)
6. TZD (pioglitazone)
Main Classes of Glucose-lowering Medications

**α-glucosidase inhibitors**
(delay digestion and absorption of intestinal carbohydrate)

**DPP-4 inhibitors**
(prolong GLP-1 action, stimulate insulin secretion, suppress glucagon release)

**Metformin**
(reduce hepatic glucose production and intestinal absorption of glucose; increase peripheral glucose uptake)

**SGLT2 inhibitors**
(reduce renal reabsorption of glucose)

**Insulin secretagogues (SUs and Meglitinides)**
(stimulate insulin secretion)

**Metformin**
(reduce hepatic glucose production and intestinal absorption of glucose; increase peripheral glucose uptake)

**DPP-4 inhibitors**
(prolong GLP-1 action, stimulate insulin secretion, suppress glucagon release)

**Insulin**
(improves insulin secretion and peripheral insulin sensitivity)

**TZDs**
(reduce insulin resistance in target tissues)

**GLP-1R agonists**
(increase GLP-1 action, stimulate insulin secretion, suppress glucagon release, decrease appetite, delay gastric emptying)

**Lipase inhibitors**
(inhibit absorption of dietary fat)

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A Comparison of SGLT2i, DPP-4i and GLP-1RA

<table>
<thead>
<tr>
<th></th>
<th>SGLT2i</th>
<th>DPP-4i</th>
<th>GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C Reduction</td>
<td>↓↓ to  ↓↓</td>
<td>↓↓</td>
<td>↓↓ to  ↓↓</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>↓↓</td>
<td>Neutral</td>
<td>↓↓</td>
</tr>
<tr>
<td>Risk of Hypoglycemia</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>BP Reduction</td>
<td>↓↓</td>
<td>No</td>
<td>↓</td>
</tr>
</tbody>
</table>

Data are not based on head to head comparisons

SUs May Increase CV Risk in Patients with T2D: Meta-analysis of 33 Studies

In a meta-analysis of 33 studies (12 RCTs, 17 cohort, 4 case-control) representing 1,345,446 patients, SUs were associated with a significantly increased risk of CV death and of a CV composite compared with other oral diabetes drugs.

### CV Mortality
- Cohort Studies (n=20)
- SU vs MET (n=17)

### CV Composite
- All Observational Studies (n=32)
- Cohort Studies (n=28)
- SU vs MET (n=16)

Relative Risk (95% Confidence Interval)

- CV Mortality: 1.26 (1.18, 1.34)
- CV Composite: 1.11 (1.05, 1.18)

n = the total number of comparisons for that analysis one study may contribute more than one comparison to the analysis CV composite = MI, stroke, CV-related hospitalization or CV death.
SGLT2 inhibitors and DPP4-inhibitors least likely to cause hypoglycemia

<table>
<thead>
<tr>
<th>Comparators</th>
<th>MH-OR</th>
<th>p</th>
<th># trials</th>
<th>patient/yr</th>
<th># events</th>
<th>Yearly incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2i</td>
<td>18.69 [10.58;33.02]</td>
<td>&lt;0.001</td>
<td>1</td>
<td>401/400</td>
<td>162/14</td>
<td>40.4/3.5</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>6.76 [4.27;10.69]</td>
<td>&lt;0.001</td>
<td>7</td>
<td>6,445/6,436</td>
<td>998/171</td>
<td>15.5/2.7</td>
</tr>
<tr>
<td>alfa-GI</td>
<td>5.82 [2.66;12.70]</td>
<td>&lt;0.001</td>
<td>6</td>
<td>225/362</td>
<td>77/33</td>
<td>34.2/9.2</td>
</tr>
<tr>
<td>GLP-1RA</td>
<td>4.05 [2.43-6.75]</td>
<td>&lt;0.001</td>
<td>5</td>
<td>2,376/2,702</td>
<td>532/327</td>
<td>22.4/12.1</td>
</tr>
<tr>
<td>Glitazones</td>
<td>4.34 [3.40-5.55]</td>
<td>&lt;0.001</td>
<td>29</td>
<td>21,284/21,670</td>
<td>1,913/551</td>
<td>9.0/2.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.34 [1.70-6.57]</td>
<td>&lt;0.001</td>
<td>4</td>
<td>13,866/10,113</td>
<td>353/141</td>
<td>2.5/1.4</td>
</tr>
<tr>
<td>Metformin</td>
<td>2.74 [1.57-4.79]</td>
<td>&lt;0.001</td>
<td>8</td>
<td>8,305/8,409</td>
<td>604/195</td>
<td>7.3/2.3</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.37 [0.63-2.97]</td>
<td>0.42</td>
<td>4</td>
<td>13,898/10,388</td>
<td>371/403</td>
<td>2.7/3.9</td>
</tr>
<tr>
<td>Glinides</td>
<td>1.35 [1.01-1.75]</td>
<td>0.041</td>
<td>6</td>
<td>1,036/1,482</td>
<td>130/156</td>
<td>12.5/10.5</td>
</tr>
</tbody>
</table>

Monami M et al. Diabetes, Obesity & Metabolism. 2014; doi: 10.111/dom.12287
Safety Concerns About Antihyperglycemic Agents

1. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus
   - Steven E. Nissen, M.D.
   - Kathy Wolski, M.P.H.
   - Erie J. Topol, M.D.
   - 2005

2. Long-term Risk of Cardiovascular Events With Rosiglitazone: A Meta-analysis
   - 2007

3. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes
   - Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.
   - 2007
Antidiabetes Therapies and CV Risk – Maintaining the Balance

- Selecting a glucose lowering medication to treat T2DM is a balance between tight glycemic control and long-term CV safety

CV, cardiovascular; T2DM, Type 2 diabetes mellitus
Ferrannini E, DeFronzo RA. *Eur Heart J* 2015;36:2288–2296
Regulatory guidance requires CV Safety Data for New Antidiabetes Agents

FDA Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

“To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk…over a minimum of 2 years”

EMA Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

“For future developments, it is expected that the development programme provides sufficient information supporting the lack of a drug-induced excess cardiovascular risk…with at least 18–24 months of follow-up”
Question #3

In your clinical practice, which is your go-to agent after metformin for patients with h/o CV disease?

1. Canagliflozin
2. Dapagliflozin
3. Dulaglutide
4. Empagliflozin
5. Gliclazide
6. Insulin
7. Linagliptin
8. Liraglutide
9. Semaglutide
10. Saxagliptin
11. Sitagliptin
# High Risk Population in Recent CVOTs

## Proportion of patients with established CVD (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADER</td>
<td>81.2%</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>83%</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>73.1%</td>
</tr>
<tr>
<td>ELIXA</td>
<td>100% ACS</td>
</tr>
<tr>
<td>SAVOR-TIMI</td>
<td>78.5%</td>
</tr>
<tr>
<td>TECOS</td>
<td>100%</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>100% ACS</td>
</tr>
<tr>
<td>EMPA-REG</td>
<td>99%</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>64.8%</td>
</tr>
</tbody>
</table>

**GLP-1 RA studies**

**DPP-4 inhibitor studies**

**SGLT-2 inhibitor studies**
Duration of CVOTs
### DPP-4i CVOTs

Neutral for MACE | Increased Risk for CHF with Saxagliptin

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary endpoint</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53 (saxagliptin)</td>
<td>3P-MACE</td>
<td>1.00 (0.89, 1.12)</td>
<td>0.99</td>
</tr>
<tr>
<td>EXAMINE (alogliptin)</td>
<td>3P-MACE</td>
<td>0.96 (≤1.16*)</td>
<td>0.32</td>
</tr>
<tr>
<td>TECOS (sitagliptin)</td>
<td>4P-MACE</td>
<td>0.98 (0.88, 1.09)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Studies showing cardiovascular superiority
EMPA-REG
Primary Endpoint

Time to the first occurrence of CV death, non-fatal MI or non-fatal stroke

HR 0.86
(95.02% CI 0.74, 0.99)
P = 0.04

Empagliflozin was superior to placebo with respect to the primary endpoint

CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

No. of patients

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>4687</td>
<td>4580</td>
<td>4455</td>
<td>4328</td>
<td>3851</td>
<td>2821</td>
<td>1534</td>
<td>370</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>2333</td>
<td>2256</td>
<td>2194</td>
<td>2112</td>
<td>1875</td>
<td>1380</td>
<td>1161</td>
<td>741</td>
<td>166</td>
</tr>
</tbody>
</table>
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk


Simvastatin\(^1\)
for 5.4 years

30

High CV risk
5% diabetes, 26% hypertension

Pre-statins era

1994

Ramipril\(^2\)
for 5 years

56

High CV risk
38% diabetes, 46% hypertension

Pre-ACEi/ARB era

2000

Empagliflozin
for 3 years

39

T2DM with high CV risk
92% hypertension

Pre-ACEi/ARB era

2015

<29% statin

>80% ACEi/ARB

>75% statin
LEADER®: Primary outcome
CV death, non-fatal myocardial infarction, or non-fatal stroke

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

CI: confidence interval; CV: cardiovascular; HR: hazard ratio.
LEADER®: Number needed to treat to prevent one…

MACE

All-cause death

66

98

for 3 years

MACE, major adverse cardiovascular event.
CANVAS Program Primary MACE Outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Hazard ratio 0.86 (95% CI, 0.75-0.97)
\[ p < 0.0001 \text{ for noninferiority} \]
\[ p = 0.0158 \text{ for superiority} \]

No. of patients
- Placebo: 4347, 4153, 2942, 1240, 1187, 1120, 789
- Canagliflozin: 5795, 5566, 4343, 2555, 2460, 2363, 1661

Years since randomization
SUSTAIN 6 Primary outcome
TIME TO FIRST OCCURRENCE OF CV DEATH OR NON-FATAL MI OR NON-FATAL STROKE

HR, 0.74 (95% CI, 0.58; 0.95)
Events: 108 semaglutide; 146 placebo
P<0.001 for non-inferiority
P=0.02 for superiority*

Number of subjects at risk

<table>
<thead>
<tr>
<th></th>
<th>Semaglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1648</td>
<td>1649</td>
</tr>
<tr>
<td></td>
<td>1619</td>
<td>1616</td>
</tr>
<tr>
<td></td>
<td>1601</td>
<td>1586</td>
</tr>
<tr>
<td></td>
<td>1584</td>
<td>1567</td>
</tr>
<tr>
<td></td>
<td>1568</td>
<td>1534</td>
</tr>
<tr>
<td></td>
<td>1543</td>
<td>1508</td>
</tr>
<tr>
<td></td>
<td>1524</td>
<td>1479</td>
</tr>
<tr>
<td></td>
<td>1513</td>
<td>1466</td>
</tr>
</tbody>
</table>

*Not prespecified. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
### SGLT2i and GLP1RA overall outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Hazard Ratios for 3-pt MACE and Components</th>
<th>Hazard Ratios for Secondary and Exploratory Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-pt MACE</td>
<td>CV Death</td>
</tr>
<tr>
<td>EMPA-REG Outcome(^{15})</td>
<td>0.86</td>
<td>0.62</td>
</tr>
<tr>
<td>(empagliflozin 10mg, 25mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program(^{16})</td>
<td>0.86</td>
<td>0.87</td>
</tr>
<tr>
<td>(canagliflozin 100mg, 300 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEADER(^{17})</td>
<td>0.87</td>
<td>0.78</td>
</tr>
<tr>
<td>(liraglutide 1.8 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUSTAIN-6(^{18})</td>
<td>0.74*</td>
<td>0.98</td>
</tr>
<tr>
<td>(semaglutide 0.5, 1.0 mg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CJC In press
DOI: [https://doi.org/10.1016/j.cjca.2018.07.010](https://doi.org/10.1016/j.cjca.2018.07.010)
Recommendations for Individuals with Clinical CVD

In adults with T2DM 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 antihyperglycemic agent with demonstrated CV outcome benefit should be added.

- MACE reduction
  - Canagliflozin
  - Empagliflozin
  - Liraglutide

- HF hospitalization reduction
  - Canagliflozin
  - Empagliflozin

- Proven Renal Benefit
  - Canagliflozin
  - Empagliflozin

Question #4

Which of the following is true?

1. Due to their increased CV risk, all patients with diabetes should be on Aspirin therapy for primary prevention
2. It is preferable to have relaxed glycemic targets (A1c 7-8%) in all patients with previous history of CV events
3. All patients with type 2 diabetes over the age of 40 years should be on statin therapy
4. All patients over age 55 and with retinopathy should be on ACEi/ARB agents
5. Options 3 and 4
6. Options 1 and 2
Question #5

Which complication of diabetes causes the maximum morbidity and mortality?

1. Retinopathy
2. Nephropathy
3. Neuropathy
4. MI
5. Heart Failure
6. Stroke
7. Amputations
Diabetes and Heart Failure

• Heart failure is
  • one of **most common** CV complications of diabetes
  • the **most disabling and deadly** complication of diabetes

• There is a very high rate of sub-clinical heart failure and left ventricular diastolic dysfunction in diabetes

CHF in DM
The elephant in the room
Diabetes-Related Complications in the US 1990 – 2010: Rates of Diabetes Complications

- The magnitude of reduction was greatest for cardiovascular disease (CVD), particularly acute MI, which is now about as common as stroke.
- The rates of all five major complications in the population of adults with diabetes declined significantly.
- Reductions in rates were smallest for ESRD, which actually increased among older adults.

Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored

John J V McMurray, Hertzel C Gerstein, Rury R Holman, Marc A Pfeffer

Lancet Diabetes Endocrinol 2014

Heart Failure

The frequent, forgotten, and often fatal complication of diabetes

Heart Failure and Diabetes Mellitus

Each 1% increase in A1C

8% increased risk of heart failure

A1C = glycated hemoglobin
Diabetes and Heart Failure: Multifactorial Etiology

Vascular
- Coronary atherosclerosis
- Impaired angiogenesis
- Endothelial dysfunction

Aggravating Risk Factors
- Hypertension
- Obesity

Central and Paracrine
- Autonomic dysfunction
- SNS activation
- Neurohumoral activation
- Cardiorenal activation
- Resistance to ANP

Myocardial
- Glucotoxicity
- Insulin resistance
- Lipotoxicity
- Myocardial fibrosis
- Altered myocardial energetics

Diabetic Myopathy

HFPEF

• Aging
• Hypertension
• Diabetes

HFREF

• Male gender
• Myocardial infarction
• Genetic myopathies

LVH and fibrosis

LV dilation and cell loss

Systolic dysfunction

Diastolic dysfunction

LVEF (SV/EDV)

85%
65%
45%
25%
5%
Incidence of CV disease in T2DM patients treated with insulin

Mortality in diabetic-patients developing HF vs. not developing HF in LIFE and RENAAL

Carr A et al Am J Cardiol 2005;96:1530 – 1536
Hospitalisation for heart failure in patients with diabetes in LIFE and RENAAL

Carr A et al Am J Cardiol 2005;96:1530–1536
CV outcomes in patients with diabetes and nephropathy

**RENAAL**

- MI: [Graph showing MI percentages]
- HF: [Graph showing HF percentages]
- Stroke: [Graph showing Stroke percentages]
- CV death: [Graph showing CV death percentages]

**IDNT**

- MI: [Graph showing MI percentages]
- HF: [Graph showing HF percentages]
- Stroke: [Graph showing Stroke percentages]
- CV death: [Graph showing CV death percentages]

**ALTITUDE**

- MI: [Graph showing MI percentages]
- HF: [Graph showing HF percentages]
- Stroke: [Graph showing Stroke percentages]
- CV death: [Graph showing CV death percentages]
Importance of co-morbidity as a predictor of outcome

1. Age
2. Sex
3. Diabetes
4. COPD
5. BMI
6. Smoker
7. NYHA class
8. Diagnosis ≤18 months
9. Creatinine
10. SBP
11. LVEF
12. ACEi/ARB
13. Beta-blocker
PARADIGM-HF: Outcome according to baseline glycemic status

Relation between LVEF and CV death/HHF stratified by glycemic status
Effect of More vs Less Intensive Glycemic Control on MI and HF resulting in Admission to Hospital or Death

<table>
<thead>
<tr>
<th></th>
<th>More intensive</th>
<th>Less intensive</th>
<th>ΔA1C (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>198 (1.18)</td>
<td>245 (1.51)</td>
<td>-1.01</td>
<td>0.77 (0.64–0.93)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>310 (1.18)</td>
<td>337 (1.28)</td>
<td>-0.72</td>
<td>0.92 (0.79–1.07)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>150 (1.20)</td>
<td>76 (1.40)</td>
<td>-0.66</td>
<td>0.81 (0.62–1.07)</td>
</tr>
<tr>
<td>VADT</td>
<td>72 (1.65)</td>
<td>87 (1.99)</td>
<td>-1.16</td>
<td>0.83 (0.61–1.13)</td>
</tr>
<tr>
<td>Overall</td>
<td>730</td>
<td>745</td>
<td>-0.88</td>
<td>0.85 (0.76–0.94)</td>
</tr>
</tbody>
</table>

(Q=2.25, p=0.52, I²=0.0%)

| **Admission to hospital/fatal heart failure** |                |                |          |                     |
| ACCORD              | 152 (0.90)     | 124 (0.75)     | -1.01    | 1.18 (0.93–1.49)    |
| ADVANCE             | 220 (0.83)     | 231 (0.88)     | -0.72    | 0.95 (0.79–1.14)    |
| UKPDS               | 8 (0.06)       | 6 (0.11)       | -0.66    | 0.55 (0.19–1.60)    |
| VADT                | 79 (1.80)      | 85 (1.94)      | -1.16    | 0.92 (0.68–1.25)    |
| Overall             | 459            | 446            | -0.88    | 1.00 (0.86–1.15)    |

(Q=3.59, p=0.31, I²=16.4%)

FDA guidance – what endpoints?

• The events **should** include cardiovascular mortality, myocardial infarction and stroke.

• …and **can** include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.
Hospitalization for Heart Failure: EMPA-REG

Empagliflozin-treated individuals demonstrated significantly lower risk of hospitalization for heart failure vs. placebo.

HR 0.65  
(95% CI 0.50, 0.85)  
P = 0.0017

Recommendations for Individuals with Clinical CVD

In adults with T2DM 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 antihyperglycemic agent with demonstrated CV outcome benefit should be added.

Diabetes Canada 2018 Suggested Algorithm

When adding a second antihyperglycemic agent

Clinical CVD?

Yes

Canagliflozin
Empagliflozin
Liraglutide

No

Incretins or SGLT2i
(When avoiding hypoglycemia and weight gain are priorities)

Summary

- Cardiovascular disease occurs earlier and is associated with worse outcomes in patients with diabetes.
- Hypoglycemia significantly increases the CV risk in patients with diabetes.
- Heart Failure is the biggest driver of CV death in those with diabetes.
- Long term CV outcome studies show that MACE is not increased with newer diabetes medications and there is CV benefit seen so far with empagliflozin, canagliflozin, semaglutide and liraglutide.