Implications of Recent Cardiovascular Outcome Trials for Clinical Practice

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Disclosures

Consultant—AstraZeneca, Boehringer-Ingelheim, Janssen Pharmaceuticals, Inc., Lilly, Merck, Novo-Nordisk, Pfizer

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Speaker—Novo-Nordisk

All honoraria directed toward a non-profit that supports education and research
Learning Objectives

- Compare and contrast the results of recent cardiovascular outcomes studies in patients with diabetes mellitus
- Discuss various treatments and whether they address comorbid cardiovascular events
- Assess new ADA/EASD recommendations for managing patients with diabetes mellitus at heightened risk of cardiovascular disease
Outline

- Rationale for CVOTs in diabetes mellitus
- Cardiovascular safety of new diabetes drugs: evidence to date
  - TZDs
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - GLP-1 receptor agonists
  - Insulin
- Implications of CVOTs for clinical practice
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.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,285 (0.43)</td>
<td>22/6106 (0.36)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td>9/2634 (0.34)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td>41/2895 (1.42)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,845 (0.36)</td>
<td>7/3980 (0.18)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,635 (0.46)</td>
<td>10/2634 (0.38)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td>5/2895 (0.17)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
2008 FDA Guidance for Industry on Evaluating the Cardiovascular Risk of New Antidiabetic Therapies

For completed studies prior to NDA

- Integrated meta-analysis of phase 2/3 trials to compare CV events in patients randomized to investigational drug vs control

- Demonstrate new therapy will not result in an unacceptable CV risk
  - Evaluated by MACE
  - Estimated risk ratio for upper bound of the 2-sided CI for the investigational drug should be <1.8
  - If upper CI = 1.3 - 1.8, post-marketing CV surveillance trial may be required

CV = cardiovascular; MACE = major adverse cardiovascular events.
Cardiovascular Outcome Trials in Diabetes Mellitus

ALECARDIO (Aleglitazar, PPAR-αγ) n=7226; follow-up ~2 yrs
Termin. Q3 2013 – RESULTS

TECOS (Sitagliptin, DPP-4i) n=14,671; duration ~3 yrs Q4 2014 – RESULTS

DEVOTE (Insulin degludec, insulin) n=7637; duration ~2 yrs Q4 2017 – RESULTS

CARMELINA (Linagliptin, DPP-4i) n=7003; duration ~4 yrs Q3 2018 – RESULTS

POINTER 6 (Oral semaglutide, GLP-1RA) n=3176; duration ~1.5 yrs Completion Q3 2018

AMELIE-O (Ertugliflozin, SGLT-2i) n=8000; duration ~6 yrs Completion Q3 2019

CANVAS-R (Canagliflozin, SGLT-2i) n=5826; duration ~3 yrs Q2 2017 – RESULTS

CREDENCE (cardio-renal) (Canagliflozin, SGLT-2i) n=4964; duration ~5.5 yrs Q3 2018 – CANCELLED (+ve efficacy)

HARMONY OUTCOMES (Albiglutide, QW GLP-1RA) n=9574; duration ~4 yrs Q3 2018 – RESULTS

VERTIS CV (Ertugliflozin, SGLT-2i) n=8000; duration ~6 yrs Completion Q3 2019

SCORED (Sotagliflozin, SGLT-1i & SGLT-2i) n=10,500*; duration ~4.5 yrs Completion Q1 2022

EXSCEL (Exenatide ER, QW GLP-1RA) n=14,752; follow-up ~3 yrs Q3 2017 – RESULTS

REVIND (Dulaglutide, QW GLP-1RA) n=9622; duration ~6.5 yrs Completion Q3 2018

SOLIOST-WHF (Sotagliflozin, SGLT-1i & SGLT-2i) n=4000; duration ~2.7 yrs Completion Q1 2021

DEVOTE-MACE (Acarbose, AGI) n=6522; duration ~8 yrs Q2 2017 – RESULTS

ACE (Acarbose, AGI) n=6522; duration ~8 yrs Q2 2017 – RESULTS

AMPLOIDE-O (Efpeglenatide, QW GLP-1RA) n=4000*; duration ~3 yrs Completion Q2 2021

EXAMINE (Alogliptin, DPP-4i) n=5380; follow-up ~1.5 yrs Q3 2013 – RESULTS

SOMTOC (Sitagliptin, DPP-4i) n=6000; duration ~2 yrs Q1 2015 – RESULTS

SUSTAIN 6 (Semaglutide, GLP-1RA) n=3297; duration ~2.8 yrs Q3 2016 – RESULTS

SADVOR-TIMI 53 (Saxagliptin, DPP-4i) n=16,492; follow-up ~2 yrs Q1 2015 – RESULTS

FREEDOM (ITCA 650, GLP-1RA in DUROS) n=4000; duration ~2 yrs Q2 2016 – TOPLINE RESULTS

CANVAS (Canagliflozin, SGLT-2i) n=4418; duration 4+ yrs Q2 2017 – RESULTS

CAROLINA (Linagliptin, DPP-4i vs SU) n=6103; duration ~8 yrs Completion Q1 2019

HARMONY OUTCOMES (Albiglutide, QW GLP-1RA) n=9574; duration ~4 yrs Q3 2018 – RESULTS

VENTIS CV (Ertugliflozin, SGLT-2i) n=8000; duration ~6 yrs Completion Q3 2019

CARMELINA (Linagliptin, DPP-4i) n=7003; duration ~4 yrs Q3 2018 – RESULTS

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SOLEIST-WHF (Sotagliflozin, SGLT-1i & SGLT-2i) n=4000; duration ~2.7 yrs Completion Q1 2021

TECOS (Sitagliptin, DPP-4i) n=14,752; follow-up ~3 yrs Q3 2017 – RESULTS

CREDENCE (cardio-renal) (Canagliflozin, SGLT-2i) n=4964; duration ~5.5 yrs Q3 2018 – CANCELLED (+ve efficacy)

SOLIOST-WHF (Sotagliflozin, SGLT-1i & SGLT-2i) n=4000; duration ~2.7 yrs Completion Q1 2021

DECLARE-TIMI 58 (Dapagliflozin, SGLT-2i) n=17,276; duration ~6 yrs Q3 2018 – COMPLETED

EXAMINE (Alogliptin, DPP-4i) n=5380; follow-up ~1.5 yrs Q3 2013 – RESULTS

SADVOR-TIMI 53 (Saxagliptin, DPP-4i) n=16,492; follow-up ~2 yrs Q1 2015 – RESULTS

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*n=5380; follow-up ~1.5 yrs Q3 2013 – RESULTS

†Estimated enrolment • Stopped early after a median follow-up of 57.4 months following futility analysis

Tiers with filled boxes are completed. Trials with a white background are ongoing.

AGI, alpha-glucosidase inhibitor; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; GLP-1RA, glucagon-like peptide 1 receptor agonist; ITCA 650, continuous subcutaneous delivery of exenatide; PPAR-αγ, peroxisome proliferator-activated receptors-α and γ; QW, once weekly; SGLT-1i, sodium-glucose co-transporter 1 inhibitor; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; SU, sulphonylureas; TZD, thiazolidinedione.

ClinicalTrials.gov. Accessed 08 October 2018
Patients with T2DM in CV Outcomes Trials

- 28 Trials Ongoing/Completed
- 8 classes of medications
- >200,000 planned participants

Outline

- Rationale for CVOTs in diabetes mellitus
- Cardiovascular safety of new diabetes drugs: evidence to date
  - TZDs
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - GLP-1 receptor agonists
  - Insulin
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PROactive: Nonsignificant Reduction in Primary Outcome

All-cause mortality, non-fatal MI,* ACS, stroke, coronary or peripheral revascularization, leg amputation

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10% RRR
HR 0.90 (0.80–1.02)
\( P=0.095 \)

*Including silent MI.
PROactive: Significant Reduction in Secondary Outcome

All-cause mortality, non-fatal MI*, stroke

*Excluding silent MI.

16% RRR
HR 0.84 (0.72–0.98)
*P* = .027

16% RRR
HR 0.84 (0.72–0.98)
*P* = .027

Pioglitazone
301 events

Placebo
358 events

0 6 12 18 24 30 36
Time from randomization (months)

0 5 10 15 20 25
Events (%)

# PROactive: HF Hospitalization and Mortality

N=5238

<table>
<thead>
<tr>
<th></th>
<th>Pioglitazone</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF leading to hospital admission*</td>
<td>149 (5.7)</td>
<td>108 (4.1)</td>
<td>.007</td>
</tr>
<tr>
<td>Fatal HF</td>
<td>25 (0.96)</td>
<td>22 (0.84)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Non-adjudicated.
Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

Philip D Home, Stuart J Pocock, Henning Beck-Nielsen, Paula S Curtis, Ramon Gomis, Markolf Hanefeld, Nigel P Jones, Michel Komajda, John J V McMurray, for the RECORD Study Team

5½-year study
338 centers
23 countries in Europe, Australia, and New Zealand
Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

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<table>
<thead>
<tr>
<th>Event</th>
<th>Rosiglitazone (N=2220)</th>
<th>Active control (N=2227)</th>
<th>HR</th>
<th>Rate difference per 1000 person-years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or CV hospitalisation</td>
<td>321</td>
<td>323</td>
<td>0.99 (0.85 to 1.16)</td>
<td>-0.2 (-4.5 to 4.1)</td>
<td>0.93</td>
</tr>
<tr>
<td>All-cause death</td>
<td>136</td>
<td>157</td>
<td>0.86 (0.68 to 1.08)</td>
<td>-1.7 (-4.3 to 0.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>CV death</td>
<td>60</td>
<td>71</td>
<td>0.84 (0.59 to 1.18)</td>
<td>-0.9 (-2.7 to 0.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>64</td>
<td>56</td>
<td>1.14 (0.80 to 1.63)</td>
<td>0.6 (-1.1 to 2.4)</td>
<td>0.47</td>
</tr>
<tr>
<td>Stroke*</td>
<td>46</td>
<td>63</td>
<td>0.72 (0.49 to 1.06)</td>
<td>-1.4 (-3.1 to 0.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>154</td>
<td>165</td>
<td>0.93 (0.74 to 1.15)</td>
<td>-1.0 (-3.9 to 1.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Heart failure*</td>
<td>61</td>
<td>29</td>
<td>2.10 (1.35 to 3.27)</td>
<td>2.6 (1.1 to 4.1)</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

Data are numbers, HR (95% CI), or rate differences (95% CI). CV=cardiovascular. MI=myocardial infarction. *Fatal and non-fatal.

Table 4: Deaths and hospitalisations from cardiovascular causes
Pioglitazone after Ischemic Stroke or Transient Ischemic Attack


**Eligibility**
- Recent TIA or Ischemic Stroke
- Non-diabetic
- Insulin Resistant (HOMA >3.0)
- No CHF

IRIS: Trial Design

- Placebo
- Pioglitazone 15 mg → 45 mg

5 years

Fatal/Non-fatal MI
Fatal/Non-fatal stroke

5 years

*90% power to detect a 20% RRR from 27% in the placebo group to 22% in the pioglitazone group at an alpha level of 0.05

IRIS: Primary Outcome

**Cumulative Event-Free Survival Probability**

- **Pioglitazone**: HR 0.76, 95% CI, 0.62 to 0.93, \( P = .007 \)
- **Placebo**: 11.8%*
- **Cumulative event rates.**

Summary: TZD Cardiovascular Outcomes Trials

- No apparent increased risk of MI or MACE
  - Some benefit apparent with pioglitazone
  - Cannot assume that this is a class effect

- Increased risk for heart failure
  - No increased risk for heart failure deaths

- Increased risk for fractures
Outline

- Rationale for CVOTs in diabetes mellitus
- Cardiovascular safety of new diabetes drugs: evidence to date
  - TZDs
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - GLP-1 receptor agonists
  - Insulin
- Implications of CVOTs for clinical practice
Saxagliptin in Patients with Type 2 Diabetes

Effekt of Saxagliptin on Outcomes in Patients with Type 2 Diabetes and a History of Cardiovascular Disease

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*
Cardiovascular Outcomes Trials for DPP-4 Inhibitors

SAVOR-TIMI 53

- **Primary Endpoint**: CV death, non-fatal MI, or non-fatal stroke
- **Hazard Ratio**: 1.00 (95% CI 0.89, 1.12) \( P = .99 \)
- **Follow-up**:
  - Saxagliptin: Median follow-up 2.1 years
  - Placebo: Median follow-up 2.1 years
- **Participants**: n=16,492

EXAMINE

- **Primary Endpoint**: CV death, non-fatal MI, or non-fatal stroke
- **Hazard Ratio**: 0.96 (upper boundary of 1-sided repeated CI 1.16) \( P = .315 \)
- **Follow-up**:
  - Alogliptin: Median follow-up 1.5 years
  - Placebo: Median follow-up 1.5 years
- **Participants**: n=5380

TECOS

- **Primary Endpoint**: CV death, non-fatal MI, or non-fatal stroke, or UA requiring hospitalization
- **Hazard Ratio**: 0.98 (95% CI 0.88, 1.09) \( P = .645 \) (superiority)
- **Follow-up**:
  - Sitagliptin: Median follow-up 3 years
  - Placebo: Median follow-up 3 years
- **Participants**: n=14,735

CVD = cardiovascular disease.
Cardiovascular Outcomes Trials for DPP-4 Inhibitors

Saxagliptin (SAVOR-TIMI 53 Trial)

N=16,492

Composite of CV death, MI, or ischemic stroke

Hazard ratio: 1.00 (95% CI: 0.89–1.12)
P < .001 (non-inferiority)

Alogliptin (EXAMINE Trial)

N=5380

Composite of CV death, non-fatal MI, or non-fatal stroke

Hazard ratio: 0.96 (upper boundary of one-sided repeated 95% CI: 1.16)

Sitagliptin (TECOS Trial)

N=14,671

Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina

Hazard ratio: 0.98 (95% CI: 0.89, 1.08)
P = .65

SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Study Drug n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI</td>
<td>289/8280 (3.5%)</td>
<td>228/8212 (2.8%)</td>
<td>1.27</td>
<td>1.07, 1.51</td>
<td>.009*</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>106/2701 (3.9%)</td>
<td>89/2679 (3.3%)</td>
<td>1.19</td>
<td>0.89, 1.58</td>
<td>.238</td>
</tr>
<tr>
<td>TECOS</td>
<td>228/7332 (3.1%)</td>
<td>229/7339 (3.1%)</td>
<td>1.00</td>
<td>0.83, 1.20</td>
<td>.983</td>
</tr>
</tbody>
</table>

*Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI.
CARMELINA Trial: Impact of Linagliptin on CV Safety and Kidney Outcomes

Patients (%) with CV Events, Decline in Kidney Function, or Hospitalization for HF - Linagliptin Compared to Placebo Added to Standard of Care. N=6980 patients randomized 1:1.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Linagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, Non-fatal MI, Non-fatal Stroke</td>
<td>12.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Decline in Kidney Function</td>
<td>9.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Hospitalization for Heart Failure</td>
<td>6.0%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

Data demonstrate no impact on cardiovascular (CV), heart failure, or renal events, even in those who already have kidney disease, when linagliptin is added to standard of care therapy.

CARMELINA Trial Results Summary. Available at: https://www.boehringer-ingelheim.com/CARMELINA.
Summary: DPP-4 Inhibitor Cardiovascular Outcomes Trials

- All trials met the primary goal of demonstrating that there is no increased risk of CVD
  - No benefit is apparent
  - Cannot assume that this is a class effect
  - There may be heterogeneity with respect to heart failure

- These large trials have been useful for evaluating other potentially beneficial effects of the drugs
  - Decreased rates of albuminuria

- More precise estimates of the risk of other rare events
Outline

- Rationale for CVOTs in diabetes mellitus
- Cardiovascular safety of new diabetes drugs: evidence to date
  - TZDs
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - GLP-1 receptor agonists
  - Insulin
- Implications of CVOTs for clinical practice
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators
EMPA-REG Outcomes Trial: Design

Key inclusion criteria
- Adults with T2DM
- BMI < 45 kg/m²
- HbA1c 7%-10%
- **Established CV disease**

Key exclusion criteria
- eGFR < 30 mg/min/1.73 m² (MDRD)

**Screening** (n=11531) ➔ **Randomized and treated** (n=7020) ➔

- **Placebo** (n=2333)
- **Empagliflozin 10 mg** (n=2345)
- **Empagliflozin 25 mg** (n=2342)

Median treatment duration = 2.6 years

Empa-Reg Outcomes Trial: Main Results

**Cumulative Incidence of the Primary Outcome**

- **Empagliflozin**:
  - Patients with event, %: 5
  - Hazard ratio, 0.86 (95% CI, 0.74–0.99)
  - P = .04 for superiority

- **Placebo**:
  - Patients with event, %: 10

**Cumulative Incidence of Death from CV Causes**

- **Empagliflozin**:
  - Patients with event, %: 3
  - Hazard ratio, 0.62 (95% CI, 0.49–0.77)
  - P < .001

- **Placebo**:
  - Patients with event, %: 6

**Hospitalization for Heart Failure**

- **Empagliflozin**:
  - Patients with event, %: 1
  - Hazard ratio, 0.65 (95% CI, 0.50–0.85)
  - P = .002

- **Placebo**:
  - Patients with event, %: 2

---

*aCumulative incidence of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke.

N=7020 patients with T2DM at high risk of CV events.

EMPA-REG Outcomes Trial: Renal Outcomes

- Lower rates of acute renal failure and kidney injury (5.2% vs 6.6% and 1.0% vs 1.6%, respectively; \(P<.05\) vs placebo)
- A1C reduction of –0.52% to –0.68% vs placebo in CKD stages 2-3 (eGFR ≥30 to <90 mL/min/1.73 m\(^2\)); \(P<.0001\)
- Equivalent adverse event rates as placebo in patients in CKD stages 2-3

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*
## Baseline Demographics and Disease History

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (n = 5795)</th>
<th>Placebo (n = 4347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Female, %</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>Mean duration of diabetes, y</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Heart failure (NYHA I-III), %</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>65</td>
<td>67</td>
</tr>
</tbody>
</table>
CANVAS: Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Hazard ratio 0.86 (95% CI, 0.75-0.97)

p < 0.0001 for noninferiority

p = 0.0158 for superiority

No. of patients

Placebo 4347 4153 2942 1240 1187 1120 789
Canagliflozin 5795 5566 4343 2555 2460 2363 1661

Years since randomization
CANVAS: MACE Components and HF

<table>
<thead>
<tr>
<th>Primary cardiovascular outcome</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>0.87 (0.72-1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.85 (0.69-1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.71-1.15)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.87 (0.74-1.01)</td>
</tr>
</tbody>
</table>

CANVAS: Renal Outcomes

Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death

Hazard ratio 0.60 (95% CI, 0.47-0.77)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% eGFR reduction</td>
<td>239</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease/renal death</td>
<td></td>
<td>21</td>
</tr>
</tbody>
</table>

Patients with an event (%)

No. of patients
Placebo 4347 4227 3029 1274 1229 1173 819
Canagliflozin 5795 5664 4454 2654 2576 2495 1781

Years since randomization

## CANVAS: Amputation Risk

### Highest Level of Amputation

<table>
<thead>
<tr>
<th></th>
<th>Event rate per 1000 patient-years</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td>All amputations (n = 187)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor amputation (71%)</td>
<td>4.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Toe</td>
<td>3.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Transmetatarsal</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Major amputation (29%)</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Ankle</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Below-knee</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Above-knee</td>
<td>0.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

Dapagliflozin: Major Cardiovascular and Renal Outcomes and Death from Any Cause

- 17,160 pts with T2DM
- A1c 8.3%
- BMI 32 kg/m²
- 40.5% with established ASCVD
- No apparent increased risk of amputation or fracture

Summary: SGLT-2 Inhibitor Cardiovascular Outcomes Trials

● All trials met the primary goal of demonstrating that there is no increased risk of CVD
  – MACE benefit with both empagliflozin and canagliflozin
  – Heart failure benefit with empagliflozin, canagliflozin and dapagliflozin
  – Mortality benefit with empagliflozin but not canagliflozin or dapa

● These large trials have been useful for evaluating other potentially beneficial effects of the drugs
  – Decreased rates of albuminuria, CKD progression

● More precise estimates of the risk of other rare events
  – Amputation and fracture risk with canagliflozin
Outline

- Rationale for CVOTs in diabetes mellitus
- Cardiovascular safety of new diabetes drugs: evidence to date
  - TZDs
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - GLP-1 receptor agonists
  - Insulin
- Implications of CVOTs for clinical practice
Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome

Marc A. Pfeffer, M.D., Ph.D., Brian Claggett, Ph.D., Rafael Diaz, M.D., Kenneth Dickstein, M.D., Ph.D., Hertzl C. Gerstein, M.D., Lars V. Køber, M.D., Francesca C. Lawson, M.D., Lin Ping, M.D., Xiaodan Wei, Ph.D., Eldrin F. Lewis, M.D., M.P.H., Aldo P. Maggioni, M.D., John J.V. McMurray, M.D., Ph.D., Jeffrey L. Probstfield, M.D., Matthew C. Riddle, M.D., Scott D. Solomon, M.D., and Jean-Claude Tardif, M.D., for the ELIXA Investigators*
ELIXA Study: Lixisenatide vs Placebo

6068 subjects with T2DM and recent ACS event randomized to lixisenatide vs placebo

Trial information
- Multi-center
- Double-blind
- Parallel-group
- Event-driven
- Randomized

Run-in period
- Patients were trained in self-administration of daily subcutaneous volume-matched placebo
- Glucose control was managed by site investigators’ judgment

Run-in
- Placebo
- Lixisenatide 10 μg

Titration
- Lixisenatide or matching placebo (1:1)
  - Initial dose 10 μg/d
  - Down- or up-titration permitted to maximum of 20 μg/d

Lixisenatide, 20 μg maximum dose

End of treatment
- 203±1 weeks

Randomization
- (1:1)

1 week
- Run-in
- Titration 2 weeks
- 2 weeks
ELIXA Study: Primary Composite Endpoint

Time to first occurrence of the primary CV event: CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*
LEADER: Liraglutide vs Placebo
Cardiovascular Outcomes Trial

**Key inclusion criteria**

- Adult patients with T2DM
- HbA1c ≥7.0%
- Antidiabetic drug naive, or
- Treated with one or more OADs, or
- Treated with basal or premix insulin (alone or in combination with OADs)
- High-risk CV profile

**Placebo* run-in period of ≥2 weeks**

Patients demonstrating ≥50% adherence to regimen and willingness to continue with injection protocol for duration of trial proceeded to randomization

**Randomization (1:1)**

N=9340

- Standard of care + liraglutide (0.6–1.8 mg once daily)
- Standard of care + placebo*

3.5–5-year follow-up

*Daily single-blind subcutaneous injection of placebo.
OAD = oral antidiabetic drug.
LEADER: Primary and Secondary Outcomes with Liraglutide

**Primary Outcome\(^a\)**
- Hazard ratio, 0.87 (95% CI, 0.78–0.97)
- \(P<.001\) for non-inferiority
- \(P=.01\) for superiority

**Cardiovascular-Related Death**
- Hazard ratio, 0.78 (95% CI, 0.66–0.93)
- \(P=.007\)

**Death from Any Cause**
- Hazard ratio, 0.85 (95% CI, 0.74–0.97)
- \(P=.02\)

\(^a\)Composite of death from CV causes, non-fatal MI, or non-fatal stroke.

N=9340 patients with T2DM and high CV risk.
LEADER: Time to First Renal Event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

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; ESRD: end-stage renal disease; HR: hazard ratio.

HR: 0.78
95% CI (0.67–0.92)
p=0.003

Patients at risk
Liraglutide 4668 4635 4561 4492 4400 4304 4210 4114 1632 454
Placebo 4672 4643 4540 4428 4316 4196 4094 3990 1613 433
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D.,
Freddy G. Eliašchewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D.,
Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D.,
Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D.,
Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D.,
and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*
SUSTAIN 6: Primary and Secondary Outcomes with Semaglutide

A Primary Outcome

- Hazard ratio, 0.74 (95% CI 0.58–0.95)
- P < 0.001 for noninferiority
- P = 0.02 for superiority

B Nonfatal Myocardial Infarction

- Hazard ratio, 0.74 (95% CI 0.51–1.08)
- P = 0.12

C Nonfatal Stroke

- Hazard ratio, 0.61 (95% CI 0.38–0.99)
- P = 0.04

D Death from Cardiovascular Causes

- Hazard ratio, 0.98 (95% CI 0.65–1.48)
- P = 0.92

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

EXSCEL: Primary and Secondary Outcomes with Exenatide QW

Primary Outcome (3-point MACE)
- Hazard ratio, 0.91 (95% CI, 0.83–1.00)
- \(P<.001\) for non-inferiority
- \(P=.06\) for superiority

Death from Any Cause
- Hazard ratio, 0.86 (95% CI, 0.77–0.97)

Death from CV Causes
- Hazard ratio, 0.88 (95% CI, 0.76–1.02)

Hospitalization for HF
- Hazard ratio, 0.94 (95% CI, 0.78–1.13)

### Study design and inclusion criteria

- **Albiglutide 30 mg† QW + standard of care**
- **Placebo QW + standard of care**

**Treatment period:** Assessed every 4 months (clinic visit)†

**Event driven:**
- Randomisation† (1:1)
- Trial continues until ≥611 confirmed MACE events
- Follow-up to continue until a median of ≥1.5 years
- End of treatment

**9,463 patients**
- T2D, ≥40 years old with HbA$_1c$ >7.0%
- Established CVD

### Primary endpoint

- Time from randomisation to first occurrence of a MACE, defined as CV death, non-fatal MI or non-fatal stroke

---

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

HR: 0.78
(95% CI: 0.68; 0.90)
Event rate per 100 person-years: albiglutide 4.57; placebo 5.87
*p*<0.0001 for non-inferiority
*p*=0.0006 for superiority

---

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
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</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>4731</td>
<td>4613</td>
<td>4503</td>
<td>4239</td>
<td>3148</td>
<td>2142</td>
<td>1064</td>
<td>-</td>
</tr>
<tr>
<td>Placebo</td>
<td>4732</td>
<td>4603</td>
<td>4460</td>
<td>4208</td>
<td>3074</td>
<td>2077</td>
<td>1030</td>
<td>-</td>
</tr>
</tbody>
</table>

---

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction,

Summary: GLP-1 Receptor Agonist Cardiovascular Outcomes Trials

- All trials met the primary goal of demonstrating that there is no increased risk of CVD
- LEADER (liraglutide), SUSTAIN 6 (semaglutide) and HARMONY (albiglutide) demonstrated a benefit on MACE and mortality (liraglutide)
- ELIXA (lixisenatide), EXSCEL (exenatide) and FREEDOM (exenatide) did not demonstrate a CV benefit
- These large trials have been useful for evaluating other potentially beneficial effects of the drugs
  - Decreased rates of albuminuria
- More precise estimates of the risk of other rare events
  - No increased rate of pancreatitis
Rationale for CVOTs in diabetes mellitus

Cardiovascular safety of new diabetes drugs: evidence to date
- TZDs
- DPP-4 inhibitors
- SGLT-2 inhibitors
- GLP-1 receptor agonists
- Insulin

Implications of CVOTs for clinical practice
Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes

DEVOTE: Trial Design

- Randomization: 7637 patients randomized
- Insulin degludec once daily (blinded vial) + standard of care
- IGlar U100 once daily (blinded vial) + standard of care
- Interim analysis (150 MACE accrued)
- End of treatment (633 MACE accrued)
- Follow-up period
- Follow-up period

Primary endpoint: Time from randomization to first occurrence of a 3-point MACE: CV death, non-fatal MI, or non-fatal stroke

Secondary endpoints:
- Rate of severe hypoglycemic episodes
- Incidence of severe hypoglycemic episodes

**DEVOTE: Time to First 3-Point MACE**

- **Insulin degludec**
  - Rate: 4.71/100 PYO
- **Iglar U100**
  - Rate: 4.29/100 PYO

**Patients with an Event**

- **Insulin degludec** (N)
  - 3818
  - 3765
  - 3721
  - 3699
  - 3611
  - 3563
  - 3504
  - 2851
  - 1767
  - 811
  - 217

- **Iglar U100 (N)**
  - 3819
  - 3758
  - 3703
  - 3655
  - 3595
  - 3530
  - 3472
  - 2832
  - 1742
  - 811
  - 205

**EAC = Event Adjudication Committee; N = number of patients at risk; PYO = patient-years of observation.**

DEVOTE: Glycemic Control and Severe Hypoglycemia

- Glycemic control (insulin degludec vs IGlar U100):
  - End of treatment mean HbA$_{1c}$ values 7.55% vs 7.50%
  - Change in FPG levels -39.9 mg/dL vs -34.9 mg/dL

- 27% fewer patients experienced severe hypoglycemia with insulin degludec

- 40% rate reduction of severe hypoglycemia

- 53% rate reduction of nocturnal severe hypoglycemia
Rationale for CVOTs in diabetes mellitus

Cardiovascular safety of new diabetes drugs: evidence to date
- TZDs
- DPP-4 inhibitors
- SGLT-2 inhibitors
- GLP-1 receptor agonists
- Insulin

Implications of CVOTs for clinical practice
DECISION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES

**GOALS OF CARE**
- Prevent complications
- Optimise quality of life

**REVIEW AND AGREE ON MANAGEMENT PLAN**
- Review management plan
- Mutual agreement on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid clinical inertia
- Decision cycle undertaken regularly (at least once/twice a year)

**ASSESS KEY PATIENT CHARACTERISTICS**
- Current lifestyle
- Comorbidities i.e. ASCVD, CKD, HF
- Clinical characteristics i.e. age, HbA₁c, weight
- Issues such as motivation and depression
- Cultural and socio-economic context

**ONGOING MONITORING AND SUPPORT INCLUDING:**
- Emotional well-being
- Check tolerability of medication
- Monitor glycaemic status
- Biofeedback including SMBG, weight, step count, HbA₁c, BP, lipids

**IMPLEMENT MANAGEMENT PLAN**
- Patients not meeting goals generally should be seen at least every 3 months as long as progress is being made; more frequent contact initially is often desirable for DSMES

**SHARE DECISION-MAKING TO CREATE A MANAGEMENT PLAN**
- Involves an educated and informed patient (and their family/caregiver)
- Seeks patient preferences
- Effective consultation includes motivational interviewing, goal setting and shared decision-making
- Empowers the patient
- Ensures access to DSMES

**CONSIDER SPECIFIC FACTORS WHICH IMPACT CHOICE OF TREATMENT**
- Individualised HbA₁c target
- Impact on weight and hypoglycaemia
- Side effect profile of medication
- Complexity of regimen i.e. frequency, mode of administration
- Choose regimen to optimise adherence and persistence
- Access, cost and availability of medication

ASCVD = Atherosclerotic Cardiovascular Disease  
CKD = Chronic Kidney Disease  
HF = Heart Failure  
DSMES = Diabetes Self-Management Education and Support  
SMBG = Self-Monitored Blood Glucose

Fig. 1  Decision cycle for patient-centred glycaemic management in type 2 diabetes
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY) IF HbA₁c ABOVE TARGET PROCEED AS BELOW

If HbA₁c above target
- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CVD benefit
  - DPP-4i (not saxagliptin) in the setting of HF not on GLP-1 RA
  - Basal insulin
  - SU

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin

HF OR CKD PREDOMINATES
- PREFERABLY SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

If HbA₁c above target

Without established ASCVD or CKD

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

- If HbA₁c above target
  - Continue with addition of other agents as outlined above

If HbA₁c above target

If HbA₁c above target
- Consider the addition of SU OR basal insulin:
  - Choose later generation SU with lower risk of hypoglycaemia
  - Consider basal insulin with lower risk of hypoglycaemia

If HbA₁c above target

If HbA₁c above target
- If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain
- PREFERABLY DPP-4i (if not on GLP-1 RA) based on weight neutrality
- OR Insulin therapy basal insulin with lowest acquisition cost
- OR Consider DPP-4i or SGLT2i with lowest acquisition cost

If HbA₁c above target

Fig. 2  Glucose-lowering medication in type 2 diabetes: overall approach

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.

2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.

3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs.

4. Degludec or U100 glargine have demonstrated CVD safety.

5. Low dose may be better tolerated though less well studied for CVD effects.

6. Choose later generation SU with lower risk of hypoglycaemia.

7. Degludec / glargine U300 > glargine U100 / detemir > NPH insulin

8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)

10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper.
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

Use metformin unless contraindicated or not tolerated
If not at HbA\textsubscript{1c} target:
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2 or GLP-1 RA with proven cardiovascular benefit\textsuperscript{1} (See below)
If at HbA\textsubscript{1c} target:
- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit\textsuperscript{1} (See below)
OR reconsider/adjust individualised target and introduce SGLT2i or GLP-1 RA
OR reassess HbA\textsubscript{1c} at 3 month intervals and add SGLT2i or GLP-1 RA if HbA\textsubscript{1c} goes above target

ASCVD predominates

EITHER/ OR

GLP-1 RA with proven CVD benefit\textsuperscript{1}  
SGLT2i with proven CVD benefit\textsuperscript{1,2}, if eGFR adequate\textsuperscript{2}

If HbA\textsubscript{1c} above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit\textsuperscript{1}
- DPP-4i if not on GLP-1 RA
- Basal insulin\textsuperscript{3}
- TZD\textsuperscript{4}
- SU\textsuperscript{7}

HF or CKD predominates

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate\textsuperscript{3}
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate\textsuperscript{2} add GLP-1 RA with proven CVD benefit\textsuperscript{1,4}

If HbA\textsubscript{1c} above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CVD benefit\textsuperscript{1}
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin\textsuperscript{5}
  - SU\textsuperscript{7}

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2 evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs
4. Caution with GLP-1 RA in EIRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects
7. Choose later generation SU to lower risk of hypoglycaemia
Completed long-term CV safety trials have demonstrated no increased risk of CV events associated with newer anti-hyperglycemic agents

- DPP-4 inhibitors not associated with an increased overall risk
- Potential for increased HF risk with some DPP-4 inhibitors

The LEADER trial (liraglutide), SUSTAIN-6 trial (semaglutide) and HARMONY trial (albiglutide) demonstrated CV benefit, whereas ELIXA (lixisenatide) EXSCEL and FREEDOM (exenatide) did not

- Label for liraglutide updated to reflect this

The EMPA-REG Outcomes Trial (empagliflozin), CANVAS (canagliflozin) and DECLARE (dapagliflozin) demonstrated a CV benefit, decreased mortality (empagliflozin), and less heart failure hospitalizations

- Label for empagliflozin and canagliflozin recently updated to reflect this

Guidelines are evolving rapidly to reflect the new evidence