DISCLOSURES

Speaker For

- Abbvie
- Astra Zeneca
- Janssen
- Sanofi
OVERVIEW

Introduction/Background: Diabetes and CV Disease

Summary of the Effects of Older Glucose Lowering Agents on CV Risk

CV Outcome Trials with Newer Glucose Lowering Agents
OBJECTIVES

Present the significance of CV disease in the diabetic population

Present emerging cardiovascular and renal indications for anti-hyperglycemic medications

Present the implications of the data on the management of T2DM
Diabetes mellitus is a major risk factor for CV disease-related mortality and morbidity

Macrovascular complications account for

- Most of the hospitalizations among patients with diabetes
- A substantial part of the costs associated with diabetes

Prevalence of coronary artery disease, stroke, peripheral vascular disease, and mortality is higher in diabetic subjects compared to nondiabetic population

In addition, prevalence of risk factors for macrovascular disease is high among diabetic populations, these include

- Hypertension
- Lipid abnormalities
- Smoking
PREVALENCE OF TYPE 2 DIABETES MELLITUS IS INCREASING

Globally, 415 million people were living with diabetes in 2015; this will rise to 642 million by 2040\(^1\)

CV death rates are higher among adults with diabetes when compared to those without diabetes\(^2,3\)

\(^a\)Diabetes type (ie, type 1 or 2) was not specified in participant records; however, the age of the participants suggests that the majority of participants with diabetes would have had T2DM

CV disease is the major cause of morbidity and mortality for individuals with diabetes\(^1\)

Presence of these risk factors\(^a\) in diabetic patients results in increased incidence of coronary heart disease, CV disease, and mortality in this population\(^1\)

Life expectancy is reduced by \(\geq 12\) years in patients aged 60 years with diabetes and previous CV disease\(^b,3\)

- Estimated reductions in life expectancy were greater in younger patients

\(^a\)Risk factors analyzed were smoking, dyslipidemia, and hypertension

\(^b\)History of myocardial infarction or stroke

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DIABETES CONFERS SIGNIFICANT CV RISK; COMBINATION OF DIABETES AND HISTORY OF MI FURTHER INCREASES RISK

Data from Schramm et al. Circulation 2008;117:1945-54
MEDICATIONS PRIOR TO 2008

Metformin is indicated for the treatment of T2DM, and generally recommended as first-line therapy

- No conclusive evidence of CV risk reduction

Sulfonylureas

- In the US, SUs carry a special warning around increased risk of CV mortality

Insulin

- No CV risk reduction

TZD’s and CV Risks\(^1\)

- A large randomized controlled CV outcomes trial (PROactive study\(^2\)) provided strong evidence that pioglitazone does not increase the risk of coronary events
- Meta-analyses of long-term efficacy trials\(^3,4\) and a CV outcomes trial (RECORD study\(^5\)) suggest that rosiglitazone might increase the risk of ischemic cardiac events

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1 Schernthaner G and Chilton RJ. Diabetes Obes Metab. 2010;12:1023-35
5 Home PD et al. Lancet 2009;373:2122-32
FDA guidance (December 2008)¹

- Sponsors are required to demonstrate that a new anti-diabetic therapy does not increase CV risk to an unacceptable extent
- A comparison of CV events between investigational product and control, either a meta-analysis of Phase 2/3 studies or in a large RCT to show:

OVERVIEW OF CVOTS OF GLUCOSE LOWERING DRUGS

Timings represent estimated completion dates as per ClinicalTrials.gov

1. Johansen OE. 2015
2. White WB et al. 2013
3. Scirica BM et al. 2013
4. Green JB et al. 2015
5. Pfeffer MA et al. 2015
6. ORIGIN. 2012
7. Zinman B et al. 2015
10. Pfeffer MA et al. 2015
11. Marso SP et al. 2017
12. Neal B et al. 2017
13. NCT01144338
14. NCT01897532
15. NCT01144338
16. NCT02692716
17. NCT02479399
18. NCT00700856
19. NCT01243424
20. NCT01730534
21. NCT01394952
22. NCT01986881
23. NCT02692716
24. NCT02479399
**EMPA-REG OUTCOME: STUDY DESIGN AND OBJECTIVES**

**Eligibility Criteria**:  
- T2DM with HbA1c 7.0%-10.0%  
- Age ≥18 years  
- BMI ≤45 kg/m^2  
- GFR ≥30 mL/min/1.73 m^2  
- Had established CV disease

**Empagliflozin (10 mg or 25 mg QD) + Standard Care**  
- N=4687

**Placebo + Standard Care**  
- N=2333

**Primary Outcome**:  
- Composite of CV death, nonfatal MI, or nonfatal stroke

**Key Secondary Outcome**:  
- Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

**Study design**: Multicenter, randomized, double-blind, placebo-controlled study

**Primary objective**: To assess the effects of empagliflozin vs. placebo on CV morbidity and mortality in patients with T2DM who were at high risk for CV events and were receiving standard care

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1 HbA1c 7.0%-9.0% in patients who did not receive any glucose lowering agents ≥12 weeks prior to randomization
2 Pooled empagliflozin group

In patients with T2DM who are at high risk for CV events, empagliflozin added to standard care, compared to placebo, is associated with lower rates of

- The primary composite CV outcome (HR 0.86 [95.02% CI, 0.74-0.99]; p=.04)
  - This was driven by the significant reduction in CV death, with no significant between-group difference in risk of MI or stroke
- Death from any cause
- Hospitalization for heart failure

Proportion of patients reporting AEs, SAEs, and AEs leading to discontinuation was similar in the two groups
The primary outcome was a composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE); two-sided tests for superiority were conducted (statistical significance was indicated if $p \leq 0.0498$). Data from Zinman B et al. N Engl J Med 2015;373:2117-28.

**Empa-Reg Outcome: Primary Outcome (3-Point MACE)**

- **CI upper limit <1.3**
  - Empagliflozin met the noninferiority criterion (did not increase the risk of CV events versus placebo) (primary objective).

- **CI upper limit <1.0**
  - Empagliflozin met the superiority criterion (reduced risk for CV events vs. placebo).

**Cumulative Incidence Function**

A The primary outcome was a composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE); *Two-sided tests for superiority were conducted (statistical significance was indicated if $p \leq 0.0498$)*.

EMPÁ-REG OUTCOME: CV DEATH & HHF

CV Death

HR 0.62
(95% CI 0.49, 0.77)
p < .0001

Hospitalization for HF

HR 0.65
(95% CI 0.50, 0.85)
p = .002

Data from Zinman B et al. N Engl J Med 2015;373:2117-28
Study design: Multicenter, randomized, double-blind, placebo-controlled, parallel group study

Primary objective: To determine the effects of canagliflozin compared to placebo (against a background of standard care) on the risk of CV disease and to provide data on safety and tolerability

1. Increased CV risk defined as: Age ≥30 years with history of CV disease or age ≥50 years with ≥2 CV risk factors (≥10 years diabetes duration, systolic BP >140 mm Hg while receiving antihypertensive agent(s), current smoking, microalbuminuria or macroalbuminuria, or HDL-C <1 mmol/L [<38.7 mg/dL]).

### INTEGRATED CANVAS PROGRAM: PRIMARY AND SECONDARY OUTCOMES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of participants/1000 patient-years</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Canagliflozin (N=5795)</td>
<td>Placebo (N=4347)</td>
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<tr>
<td>Primary composite outcome*</td>
<td>26.9</td>
<td>31.5</td>
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<tr>
<td>CV death</td>
<td>11.6</td>
<td>12.8</td>
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<td>7.1</td>
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<td>Hospitalization for any cause</td>
<td>118.7</td>
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<td>8.7</td>
</tr>
<tr>
<td>Death from any cause</td>
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<td>19.5</td>
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<tr>
<td>Progression of albuminuria*</td>
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<td>128.7</td>
</tr>
<tr>
<td>Composite renal outcome*</td>
<td>5.5</td>
<td>9.0</td>
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</tbody>
</table>

*P<.001 for noninferiority and p=.02 for superiority

The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke.

Progression of albuminuria was evaluated with data from 9015 participants with normoalbuminuria or microalbuminuria at baseline.

The composite renal outcome was a sustained 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes.

The HRs and 95% CIs were estimated with the use of Cox regression models with stratification according to trial and history of CV disease for all canagliflozin groups combined vs. placebo.

Data from Neal B et al. N Engl J Med 2017
In patients with T2DM who were at increased risk for CV disease, cangliflozin treatment compared with placebo was associated with a significantly lower risk of a primary outcome event\(^a\)

- HR: 0.86 (95% CI, 0.75-0.97); \(p=.02\)

\(^a\)The primary outcome was a composite of CV death, nonfatal MI, and nonfatal stroke

The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The integrated CANVAS Program comprised two trials: CANVAS and CANVAS-Renal. The HRs and 95% CIs were estimated with the use of Cox regression models with stratification according to trial and history of CV disease for all canagliflozin groups combined vs. placebo.

Data from Neal B et al. N Engl J Med 2017
**Study design:** International, randomized, placebo-controlled study

**Primary objective:** To evaluate the effect of liraglutide compared to placebo on the incidence of CV events in adults with type 2 diabetes

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1. Coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD stage ≥3, chronic heart failure NYHA class II
2. Microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle-brachial index (the ratio of the systolic BP at the ankle to the systolic BP in the arm) of <0.9
3. Liraglutide was administered at 0.6 mg daily for 1 week, 1.2 mg/day for an additional week, and a potential maximum dosage of 1.8 mg/day thereafter
LEADER: CONCLUSIONS

Liraglutide added to standard of care demonstrated noninferiority, as well as superiority, vs. placebo + standard of care for the primary endpoint\(^a\)

- HR: 0.87 (95% CI, 0.78-0.97); \(p=0.01\)
- Liraglutide reduced the risk for 3-point MACE by 13%

- Nonfatal MI, nonfatal stroke and hospitalization for heart failure were numerically lower in the liraglutide group
- Liraglutide reduced the risk of CV death and all-cause death by 22% and 15%, respectively

\(^a\)The primary composite outcome included CV death, nonfatal MI, or nonfatal stroke

The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal 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 were truncated at 54 months, because <10% of the patients had an observation time beyond 54 months.

Liraglutide met the noninferiority criterion (did not increase the risk of CV events vs. placebo) (primary objective) and demonstrated superiority (reduced risk for CV events) vs. placebo.

No. at risk

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<th>Liraglutide</th>
<th>Placebo</th>
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HR: 0.87 (95% CI, 0.78-0.97)

p<.001 for noninferiority

p=.01 for superiority

CI upper limit <1.3

Liraglutide demonstrated superiority (reduced risk for CV events) vs. placebo

*The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal 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 were truncated at 54 months, because <10% of the patients had an observation time beyond 54 months.

**Study design:** Global, randomized, double-blind, placebo-controlled, event-driven study

**Primary objective:** To determine whether treatment with dulaglutide has a lower hazard of CV events compared with placebo

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**Gerstein et al. Diabetes Obes Metab 2018;20:42-49**

**CV=cardiovascular; eGFR=estimated glomerular filtration rate; MACE=major adverse cardiovascular event; MI=myocardial infarction; OAD=oral antihyperglycemic drug; R=randomization**
REWIND RESULTS

♦ Dulaglutide significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction or non-fatal stroke, meeting the primary efficacy objective of superiority of the REWIND trial.

♦ The study included a majority of patients without established CV disease at baseline, a first for the GLP-1 RA class. Only 31% of the patients had established CV disease.

♦ The REWIND study is distinct compared to other CV outcome trials, enrolling a limited number of people with established CV disease and following participants for 5.4 years, the longest follow-up period for a CV outcome trial in the GLP-1 RA class.

**CANVAS-RENAL: STUDY DESIGN AND OBJECTIVES**

**Study design:** Multicenter, randomized, double-blind, placebo-controlled, parallel group study

**Primary objective:** To assess the effect of canagliflozin compared to placebo on progression of albuminuria in participants with T2DM receiving standard care but with inadequate glycemic control and at elevated risk of CV events

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1. Increased CV risk defined as: Age ≥30 years with history of CV disease or age ≥50 years with ≥2 CV risk factors (≥10 years diabetes duration, systolic BP >140 mm Hg while receiving antihypertensive agent(s), current smoking, microalbuminuria or macroalbuminuria, or HDL-C <1 mmol/L [<38.7 mg/dL]).

2. Dose may be increased to 300 mg once daily after first 13 weeks of treatment.

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\(^*\)p<.001 for noninferiority and \(p=.02\) for superiority.

\(^a\)The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke.

\(^b\)Progression of albuminuria was evaluated with data from 9015 participants with normoalbuminuria or microalbuminuria at baseline.

\(^c\)The composite renal outcome was a sustained 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes.

The HRs and 95% CIs were estimated with the use of Cox regression models with stratification according to trial and history of CV disease for all canagliflozin groups combined vs. placebo.

Data from Neal B et al. *N Engl J Med* 2017
**CREDENCE: STUDY DESIGN AND OBJECTIVES**

**Study design:** Multicenter, randomized, double-blind, placebo-controlled study

**Primary objective:** To assess the effects of canagliflozin on renal and CV outcomes in participants with T2DM and diabetic nephropathy, who are receiving standard of care including a maximum tolerated daily dose of an ACEi or ARB

Study start - expected completion: February 2014 - June 2019

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**Eligibility Criteria:**
- T2DM with HbA1c ≥6.5% to ≤12.0%
- Age ≥30 years
- eGFR ≥30 to <90 mL/min/1.73 m²
- Receiving a stable MTD of an ACEi or ARB for ≥4 weeks prior to randomization
- UACR >300 mg/g and ≤5000 mg/g

**Primary Outcome:**
- Composite of end-stage renal disease, doubling of serum creatinine, renal or CV death

**Key Secondary Outcome**
- Composite CV endpoint
- Composite renal endpoint
- All-cause death

**Canagliflozin (100 mg) vs Placebo**

Duration of study: 5-5.5 years

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*The composite CV endpoint includes CV death, nonfatal MI, nonfatal stroke, hospitalized heart failure, and hospitalized UA
*The renal composite endpoint includes end-stage renal disease, doubling of serum creatinine, and renal death

https://clinicaltrials.gov/ct2/show/NCT02065791
CREDENCE: RESULTS

Figure 3a from Perkovic et al, NEJM 2019

Figure 3b from Perkovic et al, NEJM 2019
Composite of results of end-stage renal disease, doubling of serum creatinine, renal or CV death

- Significantly lower with cana
- 30% lower relative risk of these events
**DECLARE-TIMI 58: STUDY DESIGN AND OBJECTIVES**

**Study design:** Multicenter, randomized, double-blind, placebo-controlled, event-driven study

**Primary objective:** To test the hypothesis that in patients with type 2 diabetes mellitus long-term treatment with dapagliflozin will reduce the incidence of the composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke

Study start - expected completion: April 2013 - April 2019

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**Eligibility Criteria:**
- T2DM
- Age ≥40 years
- With known CV disease or at least 2 risk factors for CV disease

**R 1:1**

**Primary Outcome:**
- Composite of CV death, MI, or ischemic stroke

**Key Secondary Outcome**
- Composite of CV death, MI, stroke, hospitalization for heart failure, UA, or revascularization

**Median follow-up:** ~4.5 years

**Dapagliflozin (10 mg)**

**Placebo**
DECLARE-TIMI-58

Dapagliflozin was superior to placebo for hHF/CV Death: HR 0.83 (95% CI: 0.73, 0.95)
• Driven by a 27 % hHF risk reduction
• Similar effect size in patients with or without established CVD

Dapagliflozin was not superior to placebo for MACE: HR 0.93 (95% CI: 0.84, 1.03)

Secondary renal endpoint: HR 0.76 (95% CI: 0.82, 1.04)
• 47% risk reduction in renal composite endpoints

Reassuring safety results overall including for bladder cancer, amputation and fracture.
Events of DKA and genital infection were low with more events reported on Dapa compared to placebo.
SUMMARY

Data presented on SGLT2’s demonstrate CV and Renal risk reduction in patients with established disease.

Data on GLP1-RA’s demonstrate CV Risk reduction in patients with and without established CV disease.
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

ESTABLISHED ASCVD OR CKD

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

• GLP-1 RA with proven CV benefit
• SGLT2i with proven CV benefit

IF HbA1c above target

• If CV medication is required or patient is new to established CV risk profile
• Consider adding the other class
• SGLT2i in setting of HF

IF HbA1c above target

• Avoid TZD in setting of HF
• Consider adding the other class with proven CV benefit

IF HbA1c above target

IF further intensification is required or patient is new to established CV risk profile

IF HbA1c above target

PREFERABLY SGLT2i with evidence of reducing CV and/or CKD progression in CVOTs of aHFrEp adequate

IF DPP-4i or GLP-1 RA not tolerated or contraindicated or if eGFR less than adequate add SGLT2i

IF HbA1c above target

IF HbA1c above target

IF HbA1c above target

IF HbA1c above target

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i

GLP-1 RA

SGLT2i

TZD

GLP-1 RA with good efficacy for weight loss

SGLT2i

IF HbA1c above target

IF HbA1c above target

IF HbA1c above target

IF HbA1c above target

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA

SGLT2i

IF HbA1c above target

IF HbA1c above target

IF HbA1c above target

IF HbA1c above target

COST IS A MAJOR ISSUE

ESTABLISH

SIP

TZD

GLP-1 RA

SIP

TZD

GLP-1 RA with good efficacy for weight loss

GLP-1 RA

SIP

TZD

GLP-1 RA with good efficacy for weight loss

1. Proven CV benefit means: it has label indication of reducing CV events. For GLP-1 RA: evidence for SGLT2i stronger evidence for DPP-4i and incretin-monoid treatment. For SGLT2i evidence mainly stronger for mortality + cardiovascular death. Revascularisation benefit has also been demonstrated.

2. Not aware that SGLT2i vary by region and individual agent with respect to indication level of aHFrEp for initiation and continuation use.

3. Both regimens have demonstrated reduction in CV risk and reduction in CKD progression in CVOTs.

4. Degludec or U100 glargine have demonstrated CV safety.

5. Lower dose may be better tolerated throughout less well studied for CV effects.

6. Choose later generation SGLT2i with lower risk of hypoglycaemia.


8. Proven CV benefit means: it has label indication of reducing CV events. For GLP-1 RA: evidence for SGLT2i stronger evidence for DPP-4i and incretin-monoid treatment. For SGLT2i evidence mainly stronger for mortality + cardiovascular death. Revascularisation benefit has also been demonstrated.

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

10. Consider country- and region-specific COTs cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper.
CONCLUSIONS — ASCVS PREDOMINATES

If HbA1c is above target

liraglutide    canagliflozin
 dulaglutide    empagliflozin
 semaglutide    dapagliflozin
CONCLUSIONS – HF OR CKD PREDOMINATES

If HbA1c is 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 (if not on GLP-1 RA)
  - Basal insulin
  - SU

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

- If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

canagliflozin
empagliflozin