Treatment: Concepts and New Developments

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Disclosures

♦ None
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\(^2\)

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\(^1\) http://www.diabetesatlas.org/ National diabetes statistics report, 2014

Impact of Diabetes on Cardiovascular Mortality

CV disease is the major cause of morbidity and mortality for individuals with diabetes. Presence of these risk factors in diabetic patients results in increased incidence of coronary heart disease, CV disease, and mortality in this population.

Risk factors analyzed were smoking, dyslipidemia, and hypertension.

1. Data from ADA. *Diabetes Care* 1989;12:573-9
2. ADA. *Diabetes Care* 2016;39(Suppl 1):S60-71
Major Historic CV Outcomes Trials: Intensive vs. Conventional Glycemic Control

DCCT\textsuperscript{a,4}

EDIC\textsuperscript{a,5}

ADVANCE\textsuperscript{7}

UGDP\textsuperscript{1,2}

UKPDS\textsuperscript{3}

ACCORD\textsuperscript{8}

VADT\textsuperscript{6}

\textsuperscript{a}DCCT/EDIC study included patients with T1DM; all other studies included patients with T2DM

5. EDIC. Diabetes Care 1999;22:99-111
UKPDS: Myocardial Infarction

Fatal or Nonfatal MI, Sudden Death 573 of 3867 Patients (15%)

% of Patients With an Event

Years From Randomization

Risk Reduction 16% (0%-29%)  
\( p = .052 \)

Conventional therapy\(^a\)

Intensive therapy\(^b\)

\(^a\)Conventional policy: Patients received dietary advice to maintain FPG <15 mmol/L and near-normal body weight

\(^b\)Intensive policy: Patients received insulin or SU with an aim to maintain FPG <6 mmol/L

ACCORD: Intensive Glucose Lowering Associated With Higher Mortality vs. Standard Therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (n=5128)</th>
<th>Standard Therapy (n=5123)</th>
<th>Favors Intensive Therapy</th>
<th>Favors Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome&lt;sup&gt;a&lt;/sup&gt;</td>
<td>352 (2.11)</td>
<td>371 (2.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cause</td>
<td>257 (1.41)</td>
<td>203 (1.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV cause</td>
<td>135 (0.79)</td>
<td>94 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>67 (0.39)</td>
<td>61 (0.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal CHF</td>
<td>152 (0.90)</td>
<td>124 (0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>186 (1.11)</td>
<td>235 (1.45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>First occurrence of nonfatal MI or nonfatal stroke or death from CV causes.

Intensive therapy arm was terminated early (after 3.5 years) due to higher mortality.

Overview of CVOTs of Glucose-lowering Drugs

Timings represent estimated completion dates as per ClinicalTrials.gov

1. Johansen OE. 2015
2. Scirica BM et al. 2013
3. White WB et al. 2013
4. Pfeffer MA et al. 2015
5. Green JB et al. 2015
6. ORIGIN. 2012
7. Lincoff AM et al. 2014
8. Zinman B et al. 2015
10. NCT01959529
11. NCT01720446
12. NCT01989754
13. NCT01455896
14. NCT01032629
15. NCT01897532
16. NCT01959529
17. NCT01720446
18. NCT01989754
19. NCT01455896
20. NCT01032629
21. NCT01897532
22. NCT01243424
23. NCT01703208
24. NCT01144338
25. NCT00700856
26. NCT01730534
27. NCT01394952
28. NCT02065791
29. NCT02479399
30. NCT01986881
31. NCT01986881
32. NCT01243424
33. NCT01703208
34. NCT01144338
35. NCT00700856

SAVOR-TIMI 53 (n=16,492) 1,222 3P-MACE
EXAMINE 3 (n=5380) 621 3P-MACE
TECOS 5 (n=14,671) ≥ 1300 4P-MACE
ORIGIN 6 (n=12,537) 3P-MACE
AleCardio 7 (n=7226) 3P-MACE
DEVOTE 10 (n=7637) 3P-MACE
CANVAS 14 (n=4339) ≥ 420 3P-MACE
CARMELINA 15 (n=8300) 4P-MACE + renal
CAROLINA 16 (n=6041) ≥ 631 4P-MACE
OMNEON 17 (n=4000) 4P-MACE
DECLARE-TIMI 58 (n=17,150) ≥ 1390 3P-MACE
EMPA-REG OUTCOME 8 (n=7028) ≥ 691 3P-MACE
ELIXA 4 (n=6068) ≥ 805 4P-MACE
SUSTAIN-6 11 (n=3297) 3P-MACE
CANVAS-R 12 (n=5820) Albuminuria
LEADER 9 (n=9341) ≥ 611 3P-MACE
FREEDOM CVO 13 (n=4000) 4P-MACE
STELLA-LONG TERM 22 (n=11,412) 3P-MACE + Tumors
HARMONY Outcomes 24 (n=9400) 3P-MACE
CREDENCE 21 (n=4200) 4P-MACE + renal
OMNEON 17 (n=4000) 4P-MACE
EXSCEL 18 (n=14,000) ≥ 1591 3P-MACE
DECLARE-TIMI 58 19 (n=17,150) ≥ 1390 3P-MACE
REWIND 20 (n=9622) ≥ 1067 3P-MACE
CAROLINA 16 (n=8300) 4P-MACE + renal
Ertugliflozin CVOT 23 (n=3900) 3P-MACE
DEVOTE 10 (n=7637) 3P-MACE
CAROLINA® 16 (n=6041)

DPP-4 inhibitor
SGLT-2 inhibitor
GLP1 RA
Insulin
PPAR agonist
TZD
There was no significant between-group difference in the primary composite CV outcome.

Primary endpoint was composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA.

# Cardiovascular Outcome Trials for SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>SGLT-2 inhibitor</th>
<th>Study Phase</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME¹</td>
<td>Empagliflozin</td>
<td>3</td>
<td>2015</td>
</tr>
<tr>
<td>CANVAS²</td>
<td>Canagliflozin</td>
<td>3</td>
<td>2017</td>
</tr>
<tr>
<td>CANVAS-R³</td>
<td>Canagliflozin</td>
<td>4</td>
<td>2017</td>
</tr>
<tr>
<td>STELLA LONGTERM⁴</td>
<td>Ipragliflozin</td>
<td>Observational</td>
<td>2018</td>
</tr>
<tr>
<td>DECLARE-TIMI 58⁵</td>
<td>Dapagliflozin</td>
<td>3</td>
<td>2019</td>
</tr>
<tr>
<td>CREDENCE⁶</td>
<td>Canagliflozin</td>
<td>3</td>
<td>2020</td>
</tr>
<tr>
<td>Ertugliflozin CVOT⁷</td>
<td>Ertugliflozin</td>
<td>3</td>
<td>2020</td>
</tr>
</tbody>
</table>

2. [https://clinicaltrials.gov/ct2/show/NCT01032629](https://clinicaltrials.gov/ct2/show/NCT01032629)
5. [https://clinicaltrials.gov/ct2/show/NCT01730534](https://clinicaltrials.gov/ct2/show/NCT01730534)
**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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Eligibility Criteria¹:
- T2DM with HbA1c 7.0%-10.0%<sup>a</sup>
- Age ≥18 years
- BMI ≤45 kg/m²
- GFR ≥30 mL/min/1.73 m²
- Had established CV disease

**Empagliflozin (10 mg or 25 mg QD) + Standard Care**
- N=4687<sup>b</sup>

**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

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<sup>a</sup>HbA1c 7.0%-9.0% in patients who did not receive any glucose lowering agents ≥12 weeks prior to randomization

<sup>b</sup>Pooled empagliflozin group

EMPA-REG OUTCOME: Primary Outcome (3-point MACE)

**Primary Outcome (3-point MACE)**

**HR 0.86 (95.02% CI 0.74, 0.99); p=.04**

**No. at Risk:**
- Empagliflozin: 4687, 4580, 4455, 4328, 3851, 2821, 2359, 1534, 370
- Placebo: 2333, 2256, 2194, 2112, 1875, 1380, 1161, 741, 166

**Cumulative incidence function**

*Two-sided tests for superiority were conducted (statistical significance was indicated if p≤.0498)*

**EMPA-REG OUTCOME: 3-point MACE and 4-point MACE**

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin n/N</th>
<th>Placebo n/N</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-point MACE</strong></td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86</td>
<td>(0.74, 0.99)</td>
<td>.04</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>.22</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
<td>.16</td>
</tr>
<tr>
<td><strong>4-point MACE</strong></td>
<td>599/4687</td>
<td>333/2333</td>
<td>0.89</td>
<td>(0.78, 1.01)</td>
<td>.08</td>
</tr>
</tbody>
</table>

Cox regression analysis

*aPrimary outcome: Composite of CV death, nonfatal MI, and nonfatal stroke; b95.02% CI
*cSecondary outcome: Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

EMPA-REG OUTCOME: CV Death

HR 0.62
(95% CI 0.49, 0.77)
p < .001

Cumulative incidence function
EMPA-REG OUTCOME: Hospitalization for Heart Failure

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

No. at Risk:

<table>
<thead>
<tr>
<th>Empagliflozin</th>
<th>4687</th>
<th>4614</th>
<th>4523</th>
<th>4427</th>
<th>3988</th>
<th>2950</th>
<th>2487</th>
<th>1634</th>
<th>395</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2333</td>
<td>2271</td>
<td>2226</td>
<td>2173</td>
<td>1932</td>
<td>1424</td>
<td>1202</td>
<td>775</td>
<td>168</td>
</tr>
</tbody>
</table>

Cumulative incidence function
EMPA-REG OUTCOME: All-cause Mortality

Cumulative incidence function


HR 0.68
(95% CI 0.57, 0.82)
p<.0001

Patients With Event (%)

Time (Months)

No. at Risk:

Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414

Placebo 2333 2303 2280 2243 2012 1503 1281 825 177
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
  - 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

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

Primary objective: To evaluate the effects of lixisenatide on CV morbidity and mortality [composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalization for UA] compared to placebo in T2DM patients who recently experienced an ACS event

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Dose could be increased to a maximum of 20 µg/day at the investigator's discretion

ELIXA: Primary Outcome (CV Death, MI, Stroke, or UA)

No. at Risk:

<table>
<thead>
<tr>
<th></th>
<th>Lixisenatide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3034</td>
<td>2785</td>
<td>2759</td>
</tr>
<tr>
<td>484</td>
<td>1558</td>
<td>1566</td>
</tr>
</tbody>
</table>


HR, 1.02 (95% CI, 0.89-1.17); p=.81

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

**CI upper limit >1.0**
Lixisenatide did not demonstrate superiority (reduced risk for CV events vs. placebo)
LEADER: Study Design and Objectives

Eligibility Criteria:
- T2DM with HbA1c ≥7.0%
- Age ≥50 years with ≥1 coexisting CV condition\(^a\) or
- Age ≥60 years with ≥1 CV risk factor\(^b\)

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

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

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

\(^a\)Coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD stage ≥3, chronic heart failure NYHA class II/III

\(^b\)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

\(^c\)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

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.

LEADER: Expanded MACE\textsuperscript{a}
CV Death, Nonfatal MI, Nonfatal Stroke, Coronary Revascularization, or Hospitalization for UA

The expanded composite CV outcome included CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for UA or heart failure.

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 less than 10% of the patients had an observation time beyond 54 months.

Marso SP et al.\textit{N Engl J Med} 2016;(Ahead of print)

\begin{table}[h]
\centering
\begin{tabular}{lccccccccccc}
\hline
\textbf{No. at risk} & \multicolumn{11}{c}{Time From Randomization (Months)}
\hline
 & 0 & 6 & 12 & 18 & 24 & 30 & 36 & 42 & 48 & 54
\hline
\textbf{Liraglutide} & 4668 & 4515 & 4356 & 4221 & 4063 & 3914 & 3793 & 3682 & 1452 & 395
\textbf{Placebo} & 4672 & 4506 & 4336 & 4157 & 4002 & 3857 & 3697 & 3581 & 1410 & 366
\hline
\end{tabular}
\caption{No. at risk}
\end{table}

HR: 0.88 (95% CI, 0.81-0.96)
p=.005
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 less than 10% of the patients had an observation time beyond 54 months.

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 less than 10% of the patients had an observation time beyond 54 months. Marso SP et al. *N Engl J Med* 2016;(Ahead of print)
Liraglutide added to standard of care demonstrated noninferiority, as well as superiority, vs. placebo + standard of care for the primary endpoint

- 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

The primary composite outcome included CV death, nonfatal MI, or nonfatal stroke

Thesis

The role of ketone measurements which have been ignored in recent recommendations on diabetes care need to be reassessed.
Species of Ketones

- Beta Hydroxybutyrate (<0.3 mmol/L)
- Acetoacetate (<0.1 mmoles/L)
- Acetone (undetectable)

Standard urine ketone and serum testing only measured acetoacetate and acetone. Beta hydroxybutyrate is not measured.
Role of Ketone Measurements

Nutritional Status

Recognition and treatment of DKA

Cardiac impact
Schematic representation of the effect of SGLT2 inhibition on the stimulation of hepatic ketogenesis and ATP synthesis.

Giuseppe Daniele et al. Dia Care 2016;39:2036-2041

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The phenomenon of near euglycemic diabetic ketoacidosis

Individuals on SGLT-2 inhibitors with diabetes supposedly, Type 1 and Type 2, have presented with diabetic ketoacidosis despite serum glucose levels often less than 200 mg/dl. This has been confirmed by the presence of an anion gap acidosis and elevated ketone levels.
Glucose Clamps Studies in Patients on Dapaglifozin

- Increased Glucose Disposal by 36% \( p<0.01 \)
- Decreased Glucose Oxidation
- Increased Glycogen Formation
- Increased Lipid Oxidation
- Increased Ketone Formation (0.05mmol/L to 0.20 mmole/L \( p<0.01 \))
- Increased Glucagon (77 to 94 \( p < 0.01 \))

Diabetes Care 39:2036-2041, 2016
EMPA-REG Outcomes - Questions

• Game changer? Or incredibly preliminary?
• Class effect or drug specific?
• What happens with primary prevention?
• What is the mechanism?
• If osmotic diuresis is the mechanism, should Empagliflozin/SGLT2 be studied in non-diabetic patients with fluid overload states?
• Are the Glitazars (mura, tesa and aleglitazar) an acceptable comparator?
EMPA-REG POSSIBLE EXPLANATIONS

• Diuretic Effect
• Blood Pressure Effect
• Improved Glycemic control
• Weight Loss
• Decreased glucose fluctuations
• Increased levels and use of beta hydroxybutyrate as cardiac substrate
Effect of beta Hydroxybutyrate on Cardiac Myocytes

- Beta Hydroxybutyrate uptake is insulin independent
- Fractional extraction of 40%
- Contributes 15% of energy expenditure overnight
- Decreases lipid oxidation and subsequent oxygen demand
Fractional extraction of substrates by the human heart under basal (overnight fast) and systemic hyperinsulinemia (euglycemic-hyperinsulinemic clamp).

Ele Ferrannini et al. Dia Care 2016;39:1108-1114

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Postulated changes in myocardium fuel metabolism before and after SGLT2 inhibitor (SGLT2i) therapy.

Sunder Mudaliar et al. DiaCare 2016;39:1115-1122

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Postulated changes in whole-body and organ fuel energetics in T2DM before and after SGLT2 inhibitor (SGLT2i) therapy.

Sunder Mudaliar et al. DiaCare 2016;39:1115-1122

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Fuel Energetics in T2DM

Heart
- Without SGLT2i: ↑Fox, ↓Gox, ↔BHOB ox
- With SGLT2i: ↓Fox, ↑Gox, ↑↑BHOB ox

Muscle
- Without SGLT2i: ↑Fox, ↓Gox, ↔BHOB ox
- With SGLT2i: ↑Fox, ↓Gox, ↔Gox

Kidney
- Without SGLT2i: ↑Fox, ↓Gox, ↔BHOB ox
- With SGLT2i: ↓Fox, ↓Gox, ↑↑BHOB ox

Fox = fatty acid oxidation
Gox = glucose oxidation
BHOB ox = beta-hydroxybutyrate oxidation
↔ = no change
HYPOTHESIS

Should beta Hydroxybutyrate measurements be done routinely with the goal of preventing ketoacidosis in individuals with Type 1 diabetes if and when SGLT2 therapy is indicated and should these measurements also be done on individuals with Type 2 diabetes and cardiac disease to achieve safe but desirable levels of beta hydroxybutyrate?
Differences Between EMPA-REG and Leader

- Time to initial benefit
- Impact on Stroke
- Impact on Heart Failure
- Impact on Pulse Rate
Analysis of EMPA-REG and Leader

• Primary vs Secondary Prevention
• Same phenomenon or different
• Synergistic?
Thougths and Recommendations

• SGLT2 Treatment for all Diabetics with Heart Failure
• Testing for occult Heart Failure in all Diabetics
• Harm of GLP1 treatment on the benefits of SGLT2 treatment
• Need for Primary Prevention Study of both agents