New Diabetes Drugs
Consultant & advisory board activities
Agenda

• Review of epidemiology and pathophysiology
• Impact of glycemic control of vascular complications
• Treatment options in T2DM
  • Incretins
  • SGLT2 inhibitors
  • Future fixed combination options
• Cardiovascular outcome trials in diabetes
• Potential renal impact of SGLT2i
Agenda

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Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 Years or older

**Obesity (BMI ≥30 kg/m²)**

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;14.0%</th>
<th>14.0-17.9%</th>
<th>18.0-21.9%</th>
<th>22.0-25.9%</th>
<th>&gt;26.0%</th>
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</thead>
<tbody>
<tr>
<td>1994</td>
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</table>

**Diabetes**

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;4.5%</th>
<th>4.5-5.9%</th>
<th>6.0-7.4%</th>
<th>7.5-8.9%</th>
<th>≥9.0%</th>
</tr>
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<tbody>
<tr>
<td>1994</td>
<td></td>
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<td></td>
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<tr>
<td>2010</td>
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</tr>
</tbody>
</table>

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**FAST FACTS ON DIABETES**

- **29.1 million people or 9.3% of the U.S. population have diabetes.**
- **DIAGNOSED 21.0 million people**
- **UNDIAGNOSED 8.1 million people**
  (27.8% of people with diabetes are undiagnosed).

---

Economic costs of diabetes in the US in 2012

Average medical expenditures
$13,700/yr
($7,900 for diabetes)

43% Hospital inpatient care
18% Meds to treat complications
12% anti-DM agents & supplies
9% Physician office visits
8% Nursing/residential facilities

1 out of 5 healthcare dollars
Cardiovascular risks in adults with diabetes

CVD death rates ~1.7x higher among adults ≥18 years with diabetes

HTN 71%
Dyslipidemia 65%
ESRD 1.1%
Obesity 57%
Smoking 20%

Reduction in complications in people with diabetes over 2 decades

Type 2 DM Pathophysiology

HYPERGLYCEMIA

↓ glucose uptake

↑ lipolysis

↑ glucose reabsorption

↓ incretin effect

↑ glucose uptake

↓ insulin

β cell

↑ glucagon

α cell

↑ hepatic glucose output

neurotransmitter dysfunction

DeFronzo RA. Diabetes. 2009;58(4):773-795
Timeline of Diabetes Medications in USA

- **1920**: Iletin insulin
- **1930**: Ultralente, Lente & Semilente insulin
- **1940**: PZI insulin
- **1950**: NPH insulin
- **1960**: 1st gen. SU
- **1970**: glipizide, glyburide
- **1980**: Human insulin: Regular, NPH & U500
- **1990**: lispro, metformin, acarbose
- **2000**: NPH insulin, repaglinide
- **2005**: rosiglitazone, pioglitazone
- **2010**: sitagliptin, coleselam
- **2015**: exenatide weekly, liraglutide, linagliptin
- **2020**: empagliflozin, inhaled insulin, albiglutide, dulaglutide
- **2025**: dapagliflozin, degludec

Number of medications & classes:
- 1920: 1
- 1930: 2
- 1940: 3
- 1950: 4
- 1960: 5
- 1970: 6
- 1980: 7
- 1990: 8
- 2000: 9
- 2010: 10
- 2020: 11
- 2030: 12
- 2040: 13
- 2050: 14
- 2060: 15
- 2070: 16
- 2080: 17
- 2090: 18
- 2100: 19
Type 2 DM Treatment Targets

DeFronzo RA. Diabetes. 2009;58(4):773-795
Duration of T2DM and need for insulin replacement to maintain control

**UKPDS**: at 6 years, more than 50% of patients (newly diagnosed at start of study) need insulin to reach target (FPG ≤6.0 mmol/L)

- **Patients Requiring Insulin (%)**
  - Years from Randomization
    - 1
    - 2
    - 3
    - 4
    - 5
    - 6

FPG = fasting plasma glucose
Agenda

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• **Impact of glycemic control of vascular complications**
• Treatment options in T2DM
  • Incretins
  • SGLT2 inhibitors
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• Cardiovascular outcome trials in diabetes
• Potential renal impact of SGLT2i
### Glycemic Control & Vascular Complications in Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular Effect</th>
<th>Macrovascular Effect</th>
<th>Mortality Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT/EDIC</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>ACCORD</td>
<td>±</td>
<td>=</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>VADT</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
</tbody>
</table>

In ACCORD, progression of retinopathy in patients with mild baseline retinopathy was positively impacted; similar benefits were seen for fenofibrate use. In ACCORD, baseline CKD was associated with higher CV & overall mortality in the intensive group. In ADVANCE, the intensive group had lower rates of ESRD in both active trial and FU.

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GLP-1 Effects in Humans
Understanding the Natural Role of Incretins

GLP-1 secreted upon the ingestion of food

DPP-4 inhibitor

GLP-1 agonist

Inactive GLP-1 (GLP-1 t½ ~ 2 min)

Beta cells:
Enhances glucose-dependent insulin secretion

Alpha cells:
Postprandial glucagon secretion

Liver:
Glucagon reduces hepatic glucose output

Adapted from Nauck MA, et al. Diabetologia. 1996;39:1546-1553
Adapted from Drucker DJ. Diabetes. 1998;47:159-169
## Considerations for incretin selection

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>DPP-4 inhibitors</th>
<th>GLP1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycemic effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective A1C reduction</td>
<td>0.5 – 1.0% above target</td>
<td>1.0 – 1.5% above target</td>
</tr>
<tr>
<td>Fasting glucose reduction</td>
<td>0 – 30 mg/dl</td>
<td>20 – 70 mg/dl (long-acting &gt; short-acting)</td>
</tr>
<tr>
<td>Post-prandial glucose reduction</td>
<td>&lt; 60 mg/dl</td>
<td>60 – 100 mg/dl (short-acting &gt; long-acting)</td>
</tr>
<tr>
<td><strong>Non-glycemic effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>neutral</td>
<td>1– 3 kg decrease</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>neutral</td>
<td>0 - 3 mmHg decrease</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI side effects</td>
<td>none</td>
<td>5-20% nausea</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>alogliptin no dose adjustments</td>
<td>none indicated in severe renal insufficiency</td>
</tr>
<tr>
<td>Cost</td>
<td>$$</td>
<td>$$$</td>
</tr>
</tbody>
</table>

Adapted from Nauck M. Diabetes, Obesity and Metabolism 2016; 18: 203–216
GLP-1RA more clinically effective than DPP-4 inhibitor

HbA$_1C$

Hypoglycemia

Weight

Insulin + metformin + exenatide
Insulin + metformin + sitagliptin
Insulin + metformin

Arnolds et al. Diabetes Care 2010;33:1509–15
Clinically Approved GLP-1 Receptor Agonists

**SHORT-ACTING**
- Exenatide BID
- Lixisenatide QD (EU approved)

**LONG-ACTING**
- Exenatide extended release QW
- Albiglutide QW
- Liraglutide QD
- Dulaglutide QW

Exendin-4 derivatives (mimetics)

GLP1 analogs
A1C comparisons among GLP1 RA preparations

- Exenatide 10 ug BID
- Exenatide 2 mg QW
- Liraglutide 1.8 mg QD
- Lixisenatide 20 ug QD
- Albiglutide 50 mg QW
- Dulaglutide 1.5 mg QW

*Non-inferiority criteria met. †Non-inferiority criteria not met
Differential effects of short- vs long- acting GLP1 RA

Madsbad S. Diabetes, Obesity and Metabolism 2016; 18: 317–332
Differences in 24-hour glucose profiles for short- vs long- acting GLP1 RA

Madsbad S. Diabetes, Obesity and Metabolism 2016; 18: 317–332
Differences in 24-hour glucose profiles for short- vs long-acting GLP1 RA

Madsbad S. Diabetes, Obesity and Metabolism 2016; 18: 317–332
Differences in 24-hour glucose profiles for short- vs long- acting GLP1 RA

Madsbad S. Diabetes, Obesity and Metabolism 2016; 18: 317–332
Introducing incretins in the treatment paradigm

**Current treatment**
- OADs
- Basal insulin

**Current A1C level above target**
- < 1%
- > 1%

**Incretin options**
- DPP-4 i
- GLP1 RA

**Predominant glycemic burden**
- FPG > PPG
- FPG = PPG
- PPG > FPG

**GLP1 RA options**
- Long-acting
- Either
- Short-acting
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Renal glucose reabsorption in the kidney

Glucose

Proximal tubule
S1 segment

SGLT2
~90% glucose reabsorption

SGLT-1
~10% glucose reabsorption

S3 segment

Collecting ducts

Glycosuria & loss of calories
Clinical effects and characteristics of SGLT2i

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin</th>
<th>Canagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended dose</strong></td>
<td>10 mg</td>
<td>100 or 300 mg</td>
<td>10 or 25 mg</td>
</tr>
<tr>
<td></td>
<td>(5 mg in severe liver disease)</td>
<td>(100 mg in renal impairment)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean A1C reduction (%)</strong></td>
<td>-0.52 (-0.45 to -0.60)</td>
<td>-1.08 (-0.90 to -1.25) mono</td>
<td>-0.66 (-0.57 to -0.76)</td>
</tr>
<tr>
<td><strong>Mean weight loss (kg)</strong></td>
<td>-2.10</td>
<td>-2.81</td>
<td>-1.84</td>
</tr>
<tr>
<td><strong>Mean systolic reduction (mmHg)</strong></td>
<td>-3.78</td>
<td>-4.38</td>
<td>-4.19</td>
</tr>
<tr>
<td><strong>CKD contraindications</strong></td>
<td>eGFR &lt; 60</td>
<td>eGFR &lt; 45</td>
<td>eGFR &lt; 45</td>
</tr>
<tr>
<td><strong>Most common AE</strong></td>
<td>Genital/mycotic infections</td>
<td>Genital/mycotic infections</td>
<td>Genital/mycotic infections</td>
</tr>
</tbody>
</table>
Clinical comparisons among DPP-4i, GLP1 RA and SGLT2i

<table>
<thead>
<tr>
<th></th>
<th>DPP4i</th>
<th>GLP1 RA</th>
<th>SGLT2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction</td>
<td>0.5 – 0.7%</td>
<td>0.7 – 1.5%</td>
<td>0.5 – 1.0%</td>
</tr>
<tr>
<td>Weight</td>
<td>-</td>
<td>1 – 3 kg</td>
<td>1 – 3 kg</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>minimal</td>
<td>GI</td>
<td>GU/bone?</td>
</tr>
<tr>
<td>CV Outcomes</td>
<td>-</td>
<td>-/+</td>
<td>+/-?</td>
</tr>
</tbody>
</table>
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SGLT2i & GLP1 RA as add-on to insulin therapy

Adding Exenatide to Glargine in Insulin Treated Subjects

Two major hypoglycemic episodes in the placebo group

30-week double-blind study comparing twice-daily exenatide vs. placebo as add-on to insulin glargine ± OADs

Fixed dose combination degludec/liraglutide and glargine/lixisenatide

• Subcutaneous injection
  • Fixed ratio of IDeg (100 U/mL) and liraglutide (3.6 mg/mL)
  • Fixed ratio of IGlar (100 U/ml) and lixisenatide (50 ug/ml)

NOT FDA approved
Fixed dose combination (degludec/liraglutide) vs. glargine in patients with T2DM on basal insulin

A1C (%)  Body Weight (kg)  Hypoglycemia

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Cardiovascular Outcome Trials in Diabetes

**SUSTAIN 6** (Semaglutide, GLP-1RA)
- n=3297; duration ~2.8 years
- Completion Q4 2015

**EMPA-REG OUTCOME** (Empagliflozin, SGLT-2i)
- n=7000; duration up to 5 years Q2 2015

**CANVAS-R** (Canagliflozin, SGLT-2i)
- n=4330; duration 4+ years
- Completion Q2 2018

**RENEW** (Dulaglutide, QW GLP-1RA)
- n=3700; duration ~5.5 years
- Completion Q1 2019

**SAVOR TIMI-53** (Onglyza, DPP-4i)
- n=16,492; follow-up ~2 years
- Completion Q3 2019

**EXAMINE** (Januvia, DPP-4i)
- n=14,000; duration ~4–5 years
- Completion Q4 2015

**CAROLINA** (Tradjenta, DPP-4i vs. SU)
- n=6000; duration ~8 years
- Completion Q3 2018

**DECLARE – TIMI-58** (Forxiga, SGLT-2i)
- n=17,150; duration ~6 years
- Completion Q2 2019

**CANVAS** (Canagliflozin, SGLT-2i)
- n=4330; duration 4+ years
- Completion Q2 2018

**CREDENCE (cardio-renal)** (Canagliflozin, SGLT-2i)
- n=3700; duration ~5.5 years
- Completion Q1 2019

**EXSCEL** (Bydureon, QW GLP-1RA)
- n=14,000; duration ~7.5 years
- Completion Q2 2018

**DEVOTE** (Insulin degludec, insulin)
- n=7500; duration ~5 years
- Completion Q1 2019

**NCT01986881** (Ertugliflozin, SGLT-2i)
- n=3900; duration ~6.3 years
- Completion Q3 2021

**NCT01703208** (Omarigliptin, QW DPP-4i)
- n=4000; duration ~3 years
- Completion Q3 2019

**DECLARE – TIMI-58** (Forxiga, SGLT-2i)
- n=17,150; duration ~6 years
- Completion Q2 2019

**HARMONY OUTCOME** (Tanzeum, QW GLP-1RA)
- n=5000; duration ~4 years
- Completion Q2 2019

**CARMELINA** (Tradjenta, DPP-4i)
- n=8300; duration ~4 years
- Completion Q1 2018

**CAROLINA** (Tradjenta, DPP-4i vs. SU)
- n=6000; duration ~8 years
- Completion Q3 2018

** DECLARE – TIMI-58** (Forxiga, SGLT-2i)
- n=17,150; duration ~6 years
- Completion Q2 2019

**CREDENCE (cardio-renal)** (Canagliflozin, SGLT-2i)
- n=3700; duration ~5.5 years
- Completion Q1 2019

**EXSCEL** (Bydureon, QW GLP-1RA)
- n=14,000; duration ~7.5 years
- Completion Q2 2018

**DEVOTE** (Insulin degludec, insulin)
- n=7500; duration ~5 years
- Completion Q1 2019

**NCT01986881** (Ertugliflozin, SGLT-2i)
- n=3900; duration ~6.3 years
- Completion Q3 2021

**CREDENCE (cardio-renal)** (Canagliflozin, SGLT-2i)
- n=3700; duration ~5.5 years
- Completion Q1 2019


GLP-1RA  SGLT-2i  DPP-4i  Insulin  PPAR-αγ

Cardiovascular Outcome Trials in Diabetes

>150,000 patients have been or are being followed in CVOTs

**ALECARDIO**
(Aleglitazar, PPAR-αγ) n=7226; follow-up 2.0 years
Termin. Q3 2013 - RESULTS

**EMPA-REG OUTCOME**
(Empagliflozin, SGLT-2i)
n=7000; duration up to 5 years Q2 2015 - RESULTS

**SUSTAIN 6**
(Semaglutide, GLP-1RA)
n=3297; duration ~2.8 years
Completion Q1 2016

**CANVAS-R**
(Canagliflozin, SGLT-2i)
n=5700; duration ~3 years
Completion Q2 2017

**CANVAS**
(Canagliflozin, SGLT-2i)
n=4330; duration 4+ years
Completion Q2 2018

**DECLARE-TIMI-58**
(Forxiga, SGLT-2i)
n=17,150; duration ~6 years
Completion Q2 2019

**CARMELINA**
(Tradjenta, DPP-4i)
n=8300; duration ~4 years
Completion Q1 2018

**EMPA**
(Empagliflozin, SGLT-2i)
n=7000; duration up to 5 years Q2 2015 - RESULTS

**EXAMINE**
(Nesina, DPP4i) n=5380; follow-up ~1.5 years
Completion Q2 2013 - RESULTS

**TECOS**
(Januvia, DPP-4i)
n=14,000; duration ~4–5 years
Q4 2014 - RESULTS

**TECOS**
(Januvia, DPP-4i)
n=14,000; duration ~4–5 years
Q4 2014 - RESULTS

**ELIXA**
(Lyxumia, GLP-1RA)
n=6000; duration ~4 years
Completion Q1 2015

**FREEOM**
(ITCA 650, GLP-1RA in DUROS)
n=4000; duration ~2 years
Completion Q2 2018

**DECLARE**
(Forxiga, SGLT-2i)
n=17,150; duration ~6 years
Completion Q2 2019

**EXSCEL**
(Bydureon, QW GLP-1RA)
n=14,000; duration ~7.5 years
Completion Q2 2018

**FREEDOM**
(ITCA 650, GLP-1RA in DUROS)
n=4000; duration ~2 years
Completion Q2 2018

**DECLARE**
(Forxiga, SGLT-2i)
n=17,150; duration ~6 years
Completion Q2 2019

**CREDENCE**
(Empagliflozin, SGLT-2i)
n=3700; duration ~5.5 years
Completion Q1 2019

**REWIND**
(Dulaglutide, QW GLP-1RA)
n=9622; duration ~6.5 years
Completion Q2 2019

**CAROLINA**
(Tradjenta, DPP-4i vs. SU)
n=6000; duration ~8 years
Completion Q3 2018

**EXSCEL**
(Bydureon, QW GLP-1RA)
n=14,000; duration ~7.5 years
Completion Q2 2018

**SUSTAIN 6**
(Semaglutide, GLP-1RA)
n=3297; duration ~2.8 years
Completion Q1 2016

**CAROLINA**
(Tradjenta, DPP-4i vs. SU)
n=6000; duration ~8 years
Completion Q3 2018

**CREDENCE**
(Empagliflozin, SGLT-2i)
n=3700; duration ~5.5 years
Completion Q1 2019

**DECLARE**
(Forxiga, SGLT-2i)
n=17,150; duration ~6 years
Completion Q2 2019

**CANVAS**
(Canagliflozin, SGLT-2i)
n=4330; duration 4+ years
Completion Q2 2018

**DECLARE**
(Forxiga, SGLT-2i)
n=17,150; duration ~6 years
Completion Q2 2019

**CANVAS**
(Canagliflozin, SGLT-2i)
n=5700; duration ~3 years
Completion Q2 2017

**DECLARE**
(Forxiga, SGLT-2i)
n=17,150; duration ~6 years
Completion Q2 2019

**CREDENCE**
(Empagliflozin, SGLT-2i)
n=3700; duration ~5.5 years
Completion Q1 2019

**CANVAS**
(Canagliflozin, SGLT-2i)
n=5700; duration ~3 years
Completion Q2 2017

2013
GLP-1RA

2014
SGLT-2i

2015
DPP-4i

2016
Insulin

2017
PPAR-αγ

2018

2019

2020

2021

>150,000 patients have been or are being followed in CVOTs

Trial design of CVOTs of incretin-based therapies with publically available results

**EXAMINE**
- **DPP4i**
- T2D; HbA$_1c$ 6.5–11.0%; ACS within 15–90 days (n=5380)
  - Alogliptin (6.25, 12.5 or 25 mg/day) + standard of care
  - Placebo + standard of care

**SAVOR-TIMI-53**
- **DPP4i**
- T2D; HbA$_1c$ 6.5–12.0%; ≥40 years + CVD; ≥55 (men) or ≥60 (women) years + CV risk factors (n=16,492)
  - Saxagliptin (2.5 or 5 mg/day) + standard of care
  - Placebo + standard of care

**ELIXA**
- **GLP-1RA**
- T2D; HbA$_1c$ 5.5–11.0%; ACS within 180 days (n=6068)
  - Lixisenatide (10 or 20 μg/day) + standard of care
  - Placebo + standard of care

**TECOS**
- **DPP4i**
- T2D; HbA$_1c$ 6.5–8.0%; ≥50 years; CVD history (n=14,671)
  - Sitagliptin (100 or 50 mg/day) + standard of care
  - Placebo + standard of care

---

Trial design of CVOTs of incretin-based therapies with publically available results

EXAMINE
DPP4i
- T2D; HbA1c 6.5–12.0%
- ACS within 15–90 days (n=5380)
- Alogliptin (6.25, 12.5 or 25 mg/day) + standard of care
- Placebo + standard of care
- Neutral

SAVOR-TIMI-53
DPP4i
- T2D; HbA1c 6.5–12.0%
- ≥40 years + CVD (men) or ≥60 years + CV risk factors (women) (n=16,492)
- Saxagliptin (2.5 or 5 mg/day) + standard of care
- Placebo + standard of care
- Neutral but ↑ in hospitalization for CHF

ELIXA
GLP-1RA
- T2D; HbA1c 5.5–11.0%
- ACS within 180 days (n=6068)
- Lixisenatide (10 or 20 μg/day) + standard of care
- Placebo + standard of care
- Neutral

TECOS
DPP4i
- T2D; HbA1c 6.5–8.0%
- ≥50 years; CVD history (n=14,671)
- Sitagliptin (100 or 50 mg/day) + standard of care
- Placebo + standard of care
- Neutral

EMPA-REG OUTCOME Inclusion Criteria

- Type 2 diabetes age ≥18 years
- BMI ≤45.0 kg/m²
- eGFR ≥30 mL/min/1.73 m²
- Entry A1C 7-9% (drug-naïve) or 7-10% (stable anti-diabetes therapy)
- Established CVD

History of MI or CVA >2 months prior to informed consent
Evidence of multi-vessel CAD
Evidence of incompletely treated single-vessel CAD
Unstable angina >2 months prior to consent with evidence of CAD
Documented occlusive peripheral artery disease

EMPA-REG OUTCOME Trial Study Design

1° endpoint
Composite of CV death, non-fatal MI or non-fatal stroke

Key 2° endpoint
Composite of the 1° outcome plus hospitalisation for unstable angina

Empagliflozin 25 mg once daily (n=2342)
Empagliflozin 10 mg once daily (n=2345)
Placebo once daily (n=2333)

Screening  Placebo run-in  Randomisation  Treatment period  End of study  Follow-up
Median duration: 2.6 years
Median observation time: 3.1 years

EMPA-REG OUTCOME Trial Study Design

Key endpoints:
- Composite of CV death, non-fatal MI or non-fatal stroke
- Composite of the 1st outcome plus hospitalisation for unstable angina

Change in A1C over time:

EMPA-REG OUTCOME Trial Results

7020 Patients

Median observation time in years 3.1

Primary Outcome
10.5 vs 12.1%
↓14%

CVD Mortality
3.7 vs 5.9%
↓38%

CHF Hospitalization
2.7 vs 4.1%
↓35%

Overall mortality
5.7 vs 8.3%
↓32%

EMPA-REG OUTCOME Adverse Events: Pooled EMPA vs placebo

7020 Patients

Median observation time in years
3.1

Genital infections
6.4 vs 1.8%

Acute Renal Failure
5.2 vs 6.6%

Bone fractures
3.8 vs 3.9%

UTIs
18.0 vs 18.1%

DKA
0.2 vs <0.1%

Statistically significant

Agenda

• Review of epidemiology and pathophysiology
• Impact of glycemic control of vascular complications
• Treatment options in T2DM
  • Incretins
  • SGLT2 inhibitors
  • Future fixed combination options
• Cardiovascular outcome trials in diabetes
• Potential renal impact of SGLT2i
Tubular hypothesis of hyperfiltration & SGLT2i

TGF = TubuloGlomerular Feedback
Tubular hypothesis of hyperfiltration & SGLT2i

Hyperglycemia

↑ glucose at proximal tubule

↑ SGLT2 mRNA expression

Hyperfiltration

↑ Intraglomerular pressure
Albuminuria

↓ Renal function over time

TGF = TubuloGlomerular Feedback

Tubular hypothesis of hyperfiltration & SGLT2i

Potential reno-protective effects attributable to SGLT2 inhibitors

CREDENCE (cardio-renal)
(Canagliflozin, SGLT-2i)
n= 3700; duration ~5.5 years
Completion Q1 2019

Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy
