New Approaches for Treating Challenging Patients with Diabetes

Anne Peters, MD
Professor, USC Keck School of Medicine
Director, USC Clinical Diabetes Programs
Disclosure of Potential Conflicts of Interest

Consultantship
- Abbott Diabetes Care
- Amgen/Astra Zeneca
- BD, BI
- CVS/Caremark
- FDA
- Janssen, Lexicon, Lilly
- Medscape, Merck
- NovoNordisk
- OptumRX
- Sanofi

Research Funding
- Janssen
- Medtronic Foundation
Healthy eating, weight control, increased physical activity & diabetes education

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>high</td>
<td>moderate risk</td>
<td>low risk</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>edema, HF, fxS</td>
<td>neutral</td>
<td>neutral</td>
<td>low loss</td>
<td>gain</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>neutral</td>
<td>low risk</td>
<td>GI, dehydration</td>
<td>hypoglycemia</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of triple therapy and patient:
(1) on oral combination, move to injectables,
(2) on GLP-1 RA, add basal insulin, or
(3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin.
In refractory patients consider adding TZD or SGLT2-i.
GLP-1 Secretion and Inactivation

GLP-1 Agonists
- Exenatide
- Liraglutide
- Albiglutide
- Dulaglutide

DPP-4 Inhibitors
- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

- A1c reduction
- Weight loss
- No hypos
- Injectable
- GI side effects

- A1c reduction
- Weight neutral
- No hypos
- Few SE's/pill

The GLP-1 RA Class: Pharmacokinetic Properties

GLP-1 RA

Short-acting (<24 hours)
- Exenatide BID
- Lixisenatide OD

Long-acting (≥24 hours)
- Liraglutide OD
- Dulaglutide OW
- Albigrutide OW
- Semaglutide OW
- Exenatide OW

BID, twice daily; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; OD, once daily; OW, once weekly

Structure of US Approved GLP-1 RAs

Diabetes Metab Syndr Obes. 2009 May 15;2:37
Albiglutide

GLP-1

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG

(7-37) amide

Site of proteolytic inactivation (DPP-4)

7 10 15 20 25 30 35 37

Albiglutide

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

Albumin

• 2 GLP-1 molecules in tandem
• Covalently bound to albumin
• DPP-4 resistant
• Half-life ~ 6-7 days

Dulaglutide

- Dulaglutide is a recombinant fusion protein linking a human GLP-1 peptide analog and a variant of a human IgG4 Fc fragment

- Dulaglutide was engineered for:
  - Duration of pharmacodynamic activity
  - DPP-IV inactivation
  - Solubility
  - Reduced immunogenic potential
Use of Dulaglutide

1 UNCAP THE PEN

2 PLACE AND UNLOCK

3 PRESS AND HOLD

5-10 Seconds
DUAL-1 Study Design

Inclusion criteria
• Type 2 diabetes
• Insulin-naïve, treated with metformin ± pioglitazone
• HbA1c 7.0–10.0%
• BMI ≤40 kg/m²
• Age ≥18 years*

N=1663, Randomized 2:1:1 Open-label

- Liraglutide OD (1.8 mg) + metformin ± pioglitazone (n=415)
- Degludec OD + metformin ± pioglitazone (n=414)
- IDegLira OD† + metformin ± pioglitazone (n=834)

Titration algorithm: IDegLira and Basal

<table>
<thead>
<tr>
<th>Mean fasting PG</th>
<th>Dose change</th>
<th>mg/dL</th>
<th>mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;72</td>
<td>-2</td>
<td>&lt;4.0</td>
<td></td>
</tr>
<tr>
<td>72–90</td>
<td>0</td>
<td>4.0–5.0</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>+2</td>
<td>&gt;5.0</td>
<td></td>
</tr>
</tbody>
</table>

†Not FDA approved

DUAL-1 Study Results

Mean values (±SEM) based on FAS and LOCF-imputed data; EOT = end of trial; ADA/EASD HbA1c target <7.0%; AACE HbA1c target ≤6.5%


*Not FDA approved
Intarcia Exenatide Sustained Delivery Device: ITCA 650
Extension 1: Sustained Efficacy Over 65 Weeks – Change From Baseline HbA1c by Visit (mITT Population)

Mean (SE) HbA1c (%) Change From Baseline

ITCA 650 60 mcg/day
(N=38)
In healthy individuals, the renal glomeruli filter approximately 162 g of glucose per day. Virtually all of the filtered glucose is reabsorbed in the proximal tubules through the sodium glucose cotransporters SGLT2 and SGLT1. Glucose homeostasis depends on reabsorption in the kidney.

Filtered glucose load ≈ 180 g/day

Virtually all of the filtered glucose is reabsorbed in the proximal tubules through the sodium glucose cotransporters SGLT2 and SGLT1.

SGLT1 = sodium glucose cotransporter 1; SGLT2 = sodium glucose cotransporter 2.

No Glycosuria
In the presence of SGLT-2 inhibitor, the less glucose is reabsorbed. The result is glycosuria.

Inhibitors of SGLT-2 Co-Transporter Increases Renal Glucose Excretion

SGLT-2

~90% SGLT1

~10%

Glycosuria
SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion ($RT_G$)

Adapted with permission from Abdul-Ghani MA, DeFronzo RA. T2DM = type 2 diabetes mellitus.
Canagliflozin/Dapagliflozin/Empagliflozin

Warnings and Precautions

- Hypoglycemia: risk with secretagogues and/or insulin
- Genital mycotic infections
- Volume depletion/orthostatic changes
- Hypersensitivity
- Increased LDL
- Bladder cancer: don’t use if active; use with caution if prior history of bladder cancer (dapagliflozin only)
Dapa/Cana/Empa in Patients with Renal Impairment

**Canagliflozin**

Contraindicated in patients with eGFR <45 ml/min/1.73 m²

Dose is limited to 100 mg daily if eGFR 45-<60 ml/min/1.73 m²

**Dapagliflozin**

Contraindicated in patients with eGFR <60 ml/min/1.73 m²

**Empagliflozin**

Contraindicated if eGFR <45 ml/min/1.73 m²
Meta-analysis of intensive glucose control in T2DM: major CV events including heart failure

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of events</th>
<th>Difference in HbA1c (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>378</td>
<td>-0.88</td>
<td>0.96 (0.83, 1.10)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>730</td>
<td>-0.88</td>
<td>0.85 (0.76, 0.94)</td>
</tr>
<tr>
<td>Hospitalisation for or death from heart failure</td>
<td>459</td>
<td>-0.88</td>
<td>1.00 (0.86, 1.16)</td>
</tr>
</tbody>
</table>

Favours more intensive Favour less intensive

- Meta-analysis of 27,049 participants and 2370 major vascular events from:
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

HR, hazard ratio; CV, cardiovascular
Turnbull FM et al. Diabetologia 2009;52:2288–2298
EMP A-REG OUTCOME®

• Randomised, double-blind, placebo-controlled CV outcomes trial

• Objective
  To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events
Trial design

- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event
Key inclusion and exclusion criteria

• Key inclusion criteria
  – Adults with type 2 diabetes
  – BMI ≤ 45 kg/m²
  – HbA1c 7–10%*
  – Established cardiovascular disease
    • Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease

• Key exclusion criteria
  – eGFR <30 mL/min/1.73m² (MDRD)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
*No glucose-lowering therapy for ≥12 weeks prior to randomisation or no change in dose for ≥12 weeks prior to randomisation or, in the case of insulin, unchanged by >10% compared to the dose at randomisation
Pre-specified primary and key secondary outcomes

• Primary outcome
  – **3-point MACE**: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

• Key secondary outcome
  – **4-point MACE**: Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina

CV, cardiovascular; MI, myocardial infarction; MACE, Major Adverse Cardiovascular Event
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.2 (8.8)</td>
<td>63.0 (8.6)</td>
<td>63.2 (8.6)</td>
</tr>
<tr>
<td>Male</td>
<td>1680 (72.0)</td>
<td>1653 (70.5)</td>
<td>1683 (71.9)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>959 (41.1)</td>
<td>966 (41.2)</td>
<td>960 (41.0)</td>
</tr>
<tr>
<td>North America*</td>
<td>462 (19.8)</td>
<td>466 (19.9)</td>
<td>466 (19.9)</td>
</tr>
<tr>
<td>Asia</td>
<td>450 (19.3)</td>
<td>447 (19.1)</td>
<td>450 (19.2)</td>
</tr>
<tr>
<td>Latin America</td>
<td>360 (15.4)</td>
<td>359 (15.3)</td>
<td>362 (15.5)</td>
</tr>
<tr>
<td>Africa</td>
<td>102 (4.4)</td>
<td>107 (4.6)</td>
<td>104 (4.4)</td>
</tr>
</tbody>
</table>

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

*Includes Australia and New Zealand
## Baseline characteristics: type 2 diabetes

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<thead>
<tr>
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<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>8.08 (0.84)</td>
<td>8.07 (0.86)</td>
<td>8.06 (0.84)</td>
</tr>
<tr>
<td><strong>Time since diagnosis of type 2 diabetes, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>423 (18.1)</td>
<td>406 (17.3)</td>
<td>434 (18.6)</td>
</tr>
<tr>
<td>&gt;5 to 10</td>
<td>571 (24.5)</td>
<td>585 (24.9)</td>
<td>590 (25.2)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1339 (57.4)</td>
<td>1354 (57.7)</td>
<td>1318 (56.3)</td>
</tr>
<tr>
<td><strong>Glucose-lowering medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>1734 (74.3)</td>
<td>1729 (73.7)</td>
<td>1730 (73.9)</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>992 (42.5)</td>
<td>985 (42.0)</td>
<td>1029 (43.9)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>101 (4.3)</td>
<td>96 (4.1)</td>
<td>102 (4.4)</td>
</tr>
<tr>
<td>Insulin</td>
<td>1135 (48.6)</td>
<td>1132 (48.3)</td>
<td>1120 (47.8)</td>
</tr>
<tr>
<td>Mean daily dose, U**</td>
<td>65 (50.6)</td>
<td>65 (47.9)</td>
<td>66 (48.9)</td>
</tr>
</tbody>
</table>

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*Medication taken alone or in combination

**Placebo, n=1135; empagliflozin 10 mg, n=1132; empagliflozin 25 mg, n=1120
### Baseline characteristics: CV risk factors

<table>
<thead>
<tr>
<th></th>
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<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>30.7 (5.2)</td>
<td>30.6 (5.2)</td>
<td>30.6 (5.3)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>86.6 (19.1)</td>
<td>85.9 (18.8)</td>
<td>86.5 (19.0)</td>
</tr>
<tr>
<td><strong>Waist circumference, cm</strong></td>
<td>105.0 (14.0)</td>
<td>104.7 (13.7)</td>
<td>104.8 (13.7)</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mmHg</strong></td>
<td>135.8 (17.2)</td>
<td>134.9 (16.8)</td>
<td>135.6 (17.0)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mmHg</strong></td>
<td>76.8 (10.1)</td>
<td>76.6 (9.8)</td>
<td>76.6 (9.7)</td>
</tr>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td>70.7 (0.2)</td>
<td>71.0 (0.2)</td>
<td>70.5 (0.2)</td>
</tr>
<tr>
<td><strong>LDL cholesterol, mg/dL</strong></td>
<td>84.9 (35.3)</td>
<td>86.3 (36.7)</td>
<td>85.5 (35.2)</td>
</tr>
<tr>
<td><strong>HDL cholesterol, mg/dL</strong></td>
<td>44.0 (11.3)</td>
<td>44.7 (12.0)</td>
<td>44.5 (11.8)</td>
</tr>
<tr>
<td><strong>eGFR, mL/min/1.73m² (MDRD)</strong></td>
<td>73.8 (21.1)</td>
<td>74.3 (21.8)</td>
<td>74.0 (21.4)</td>
</tr>
<tr>
<td><strong>≥90 mL/min/1.73m²</strong></td>
<td>488 (20.9%)</td>
<td>519 (22.1%)</td>
<td>531 (22.7%)</td>
</tr>
<tr>
<td><strong>60 to &lt;90 mL/min/1.73m²</strong></td>
<td>1238 (53.1%)</td>
<td>1221 (52.1%)</td>
<td>1204 (51.4%)</td>
</tr>
<tr>
<td><strong>&lt;60 mL/min/1.73m²</strong></td>
<td>607 (26.0%)</td>
<td>605 (25.8%)</td>
<td>607 (25.9%)</td>
</tr>
</tbody>
</table>

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

*Mean (SE). LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease equation
Baseline characteristics: CV complications

<table>
<thead>
<tr>
<th></th>
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<th>Empagliflozin 10 mg (n=2345)</th>
<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV risk factor</td>
<td>2307 (98.9%)</td>
<td>2333 (99.5%)</td>
<td>2324 (99.2%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1763 (75.6%)</td>
<td>1782 (76.0%)</td>
<td>1763 (75.3%)</td>
</tr>
<tr>
<td>Multi-vessel coronary artery disease</td>
<td>1100 (47.1%)</td>
<td>1078 (46.0%)</td>
<td>1101 (47.0%)</td>
</tr>
<tr>
<td>History of MI</td>
<td>1083 (46.4%)</td>
<td>1107 (47.2%)</td>
<td>1083 (46.2%)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>563 (24.1%)</td>
<td>594 (25.3%)</td>
<td>581 (24.8%)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>553 (23.7%)</td>
<td>535 (22.8%)</td>
<td>549 (23.4%)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>479 (20.5%)</td>
<td>465 (19.8%)</td>
<td>517 (22.1%)</td>
</tr>
<tr>
<td>Single vessel coronary artery disease</td>
<td>238 (10.2%)</td>
<td>258 (11.0%)</td>
<td>240 (10.2%)</td>
</tr>
<tr>
<td>Cardiac failure*</td>
<td>244 (10.5%)</td>
<td>240 (10.2%)</td>
<td>222 (9.5%)</td>
</tr>
</tbody>
</table>

Data are n (%) in patients treated with ≥1 dose of study drug

*Based on narrow standardised MedDRA query “cardiac failure”
Baseline characteristics: CV medication (1)

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</tr>
</thead>
<tbody>
<tr>
<td>Anti-hypertensive therapy</td>
<td>2221 (95.2%)</td>
<td>2227 (95.0%)</td>
<td>2219 (94.7%)</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>1868 (80.1%)</td>
<td>1896 (80.9%)</td>
<td>1902 (81.2%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1498 (64.2%)</td>
<td>1530 (65.2%)</td>
<td>1526 (65.2%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>988 (42.3%)</td>
<td>1036 (44.2%)</td>
<td>1011 (43.2%)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>788 (33.8%)</td>
<td>781 (33.3%)</td>
<td>748 (31.9%)</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists</td>
<td>136 (5.8%)</td>
<td>157 (6.7%)</td>
<td>148 (6.3%)</td>
</tr>
<tr>
<td>Renin inhibitors</td>
<td>19 (0.8%)</td>
<td>16 (0.7%)</td>
<td>11 (0.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>191 (8.2%)</td>
<td>193 (8.2%)</td>
<td>190 (8.1%)</td>
</tr>
</tbody>
</table>

Data are n (%) in patients treated with ≥1 dose of study drug

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers
Baseline characteristics: CV medication (2)

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<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-lowering drugs</td>
<td>1864 (79.9%)</td>
<td>1926 (82.1%)</td>
<td>1894 (80.9%)</td>
</tr>
<tr>
<td>Statins</td>
<td>1773 (76.0%)</td>
<td>1827 (77.9%)</td>
<td>1803 (77.0%)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>199 (8.5%)</td>
<td>214 (9.1%)</td>
<td>217 (9.3%)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>81 (3.5%)</td>
<td>95 (4.1%)</td>
<td>94 (4.0%)</td>
</tr>
<tr>
<td>Niacin</td>
<td>35 (1.5%)</td>
<td>56 (2.4%)</td>
<td>35 (1.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>175 (7.5%)</td>
<td>172 (7.3%)</td>
<td>193 (8.2%)</td>
</tr>
<tr>
<td>Anti-coagulants and anti-platelets</td>
<td>2090 (89.6%)</td>
<td>2098 (89.5%)</td>
<td>2064 (88.1%)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>1927 (82.6%)</td>
<td>1939 (82.7%)</td>
<td>1937 (82.7%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>249 (10.7%)</td>
<td>253 (10.8%)</td>
<td>241 (10.3%)</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>156 (6.7%)</td>
<td>141 (6.0%)</td>
<td>125 (5.3%)</td>
</tr>
</tbody>
</table>

Data are n (%) in patients treated with ≥1 dose of study drug.
All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).

X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements.
Weight

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)

X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements
All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat).

X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements.
Primary outcome: 3-point MACE

HR 0.86
(95.02% CI 0.74, 0.99)
p = 0.0382*

* Two-sided tests for superiority were conducted (statistical significance was indicated if p ≤ 0.0498)
CV death

HR 0.62
(95% CI 0.49, 0.77)
p < 0.0001

Cumulative incidence function. HR, hazard ratio
CV death

Empagliflozin 10 mg
HR 0.65
(95% CI 0.50, 0.85)
p=0.0016

Empagliflozin 25 mg
HR 0.59
(95% CI 0.45, 0.77)
p=0.0001

Cumulative incidence function. HR, hazard ratio
CV death, MI and stroke

Patients with event/analysed
Empagliflozin  Placebo  HR  (95% CI)  p-value

3-point MACE  490/4687  282/2333  0.86  (0.74, 0.99)*  0.0382
CV death  172/4687  137/2333  0.62  (0.49, 0.77)  <0.0001
Non-fatal MI  213/4687  121/2333  0.87  (0.70, 1.09)  0.2189
Non-fatal stroke  150/4687  60/2333  1.24  (0.92, 1.67)  0.1638

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI
Fatal and non-fatal stroke

Patients with event/analysed
Empagliflozin  Placebo  HR  (95% CI)  p-value

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</thead>
<tbody>
<tr>
<td>Intent-to-treat population</td>
<td>164/4687</td>
<td>69/2333</td>
<td>1.18</td>
<td>(0.89, 1.56)</td>
</tr>
</tbody>
</table>

**Numerical difference largely driven by events occurring >30 days after treatment stop**

On-treatment analysis*

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</thead>
<tbody>
<tr>
<td>On-treatment analysis*</td>
<td>141/4607</td>
<td>66/2308</td>
<td>1.04</td>
<td>(0.78, 1.40)</td>
</tr>
</tbody>
</table>

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; *Excluding events >30 days after last intake of study drug and patients who received study drug for <30 days (cumulative)
Hospitalisation for heart failure

**HR 0.65**
(95% CI 0.50, 0.85)

\[ p=0.0017 \]

Cumulative incidence function. HR, hazard ratio.
All-cause mortality

HR 0.68
(95% CI 0.57, 0.82)
p<0.0001

Kaplan-Meier estimate. HR, hazard ratio
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin\(^1\) for 5.4 years
- High CV risk
  - 5% diabetes, 26% hypertension
  - NNT: 30

Ramipril\(^2\) for 5 years
- High CV risk
  - 38% diabetes, 46% hypertension
  - NNT: 56

Empagliflozin for 3 years
- T2DM with high CV risk
  - 92% hypertension
  - NNT: 39

EMPAA-REG OUTCOME®: Therapeutic considerations

• Empagliflozin, as used in this trial, for 3 years in 1,000 patients with type 2 diabetes at high CV risk:

  – 25 lives saved (82 vs 57 deaths)
    • 22 fewer CV deaths (59 vs 37)
  – 14 fewer hospitalisations for heart failure (42 vs 28)
  – 53 additional genital infections (22 vs 75)
Technosphere Inhaler

Tools for Treating Diabetes

- Technology ever increasing
- Pace always far slower than any of us desire
- Each device approved is still one or two or three versions behind what is possible
- Tools are only as good as the user can use them—education/follow-up/realtime and retrospective interpretation vital elements
Diabetes Care in the 1970s
Diabetes Care in 2015
Monitoring
Abbott Freestyle Libre
Easier Communication
Bolus Calculator

1. Test Blood Sugar
   - bG Result: 106 mg/dL
   - 8:02 am, 2 Feb 14

2. Enter Carbs
   - Meal Time: 40 g
   - Active Insulin: 0.0 U
   - Bolus Advice: 3 U

3. Confirm Advice
   - Bolus: 3 U
   - Basal: 20 U
   - Exercise 1: -1.0 U
   - 106 mg/dL
   - 0.0 U
   - 4.0 U
Medtronic Pump
Patch Pumps
Patch Pumps
The Value of Continuous Glucose Monitoring
CGM: Dexcom Gen 5
Closed Loop “Automatic” Systems (Pump-Sensor)
Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia

Richard M. Bergenstal, M.D., David C. Klonoff, M.D., Satish K. Garg, M.D., Bruce W. Bode, M.D., Melissa Meredith, M.D., Robert H. Slover, M.D., Andrew J. Ahmann, M.D., John B. Welsh, M.D., Ph.D., Scott W. Lee, M.D., and Francine R. Kaufman, M.D., for the ASPIRE In-Home Study Group

ABSTRACT

BACKGROUND
The threshold-suspend feature of sensor-augmented insulin pumps is designed to minimize the risk of hypoglycemia by interrupting insulin delivery at a preset sensor glucose value. We evaluated sensor-augmented insulin-pump therapy with and without the threshold-suspend feature in patients with nocturnal hypoglycemia.
Sensor Glucose Values During Threshold-Suspend Events

Patient: Minimed 530G Threshold Suspend
Infusion Site Issues Another Understudied Factor
Infusion Site Issues: Another Understudied Factor
Technosphere Inhaler: Initial and Gen2 Device

## Dosing of Inhaled Insulin

<table>
<thead>
<tr>
<th>Injected Mealtime Insulin Dose</th>
<th>AFREZZA® Dose</th>
<th># of 4 unit (blue) cartridges needed</th>
<th># of 8 unit (green) cartridges needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 4 units</td>
<td>4 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
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</tbody>
</table>

Afrezza Prescribing information.
WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

- Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA. [see Warnings and Precautions (5.1)].

- AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD. [see Contraindications (4)].

- Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV₁) to identify potential lung disease in all patients [see Dosage and Administration (2.5), Warnings and Precautions (5.1)].
Glucose-Infusion Rate and Serum Insulin Concentrations in T1D

(A) GIR (mg/kg/min) vs Time (minutes)
(B) Insulin (U/mL) vs Time (minutes)

* Despite the faster absorption of insulin (PK) from Afrezza, the onset of activity (PD) was comparable to insulin lispro.

Afrezza Prescribing information.
Technosphere Inhaled Insulin: Clinical Features of Note

• Compared with Aspart 70/30, inhaled insulin was associated with reduced risk for
  – Hypoglycemia (0.41 vs 0.61 per patient/per month)
  – Weight gain (0.9 kg vs 2.5 kg)
• Increased risk for cough (33% vs 6%)
  – No change in FEV1
  – No difference in URI

Conclusions

- New treatments for diabetes continue to evolve
- The SGLT-2 inhibitor class holds great promise to improve CVD risk as well as BG outcomes.
- Always individualize treatment and care
THANK YOU