SGLT2i in Management of Diabetes

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**Consultant:** AstraZeneca, BMS, Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Novo Nordisk and Sanofi, Roche.

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**Speaker’s Bureau:** AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Novo Nordisk and Sanofi
Outline

• Update on the SGLT2 inhibitor class
• Cardiovascular Outcomes trials in Diabetes
• Real World Experience with SGLT2i

The idea that disease could be diagnosed goes back to writings of Gelen, a Greco-Roman doctor

“Piss Prophets”
ADA/EASD: position statement for managing hyperglycaemia

Healthy eating, weight control, increased physical activity

Initial monotherapy

Two-drug combinations

Three-drug combinations

More complex strategies

Metformin

SU

TZD

DPP-4i

SGLT2i

GLP-1 RA

Insulin

TZD DPP-4i SGLT2i GLP-1 RA Insulin

SU DPP-4i SGLT2i GLP-1 RA Insulin

SU TZD SGLT2i Insulin

SU TZD DPP-4i Insulin

SU TZD Insulin

TZD DPP-4i SGLT2i GLP-1 RA

Insulin (MDI)

Escalate therapy at 3 months if target not achieved.

DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MDI, multiple daily injection; SU, sulfonylurea; TZD, thiazolidinedione.

Reducing CV risk in T2D requires a multifactorial approach

- Control of LDL-cholesterol
- Antihypertensive therapy
- Antiplatelet therapy
- Weight loss and lifestyle intervention*
- Glycaemic control

*Includes smoking cessation.
The Ominous Octet: Eight core defects T2D
Multifactorial in origin, has a variable and progressive course, requires attention to attendant risk factors and co-morbidities on long term basis.

Adapted from DeFronzo, R.A., Diabetes. 2009; 58: 773–795
SGLT2 inhibitors inhibit SGLT2 by an insulin-independent mechanism to remove excess glucose in the urine\(^1\)

FORXIGA may be used without dosing reduction in patients with mild renal impairment, but is not recommended for use in patients with moderate-to-severe renal impairment (eGFR < 60 mL/min/1.73 m\(^2\) or CrCl < 60 mL/min).\(^1\) Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.\(^1\) CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; SGLT, sodium-glucose co-transporter.

1. FORXIGA. Summary of product characteristics, 2014.
SGLT2 inhibitors modulate a range of factors related to CV risk
Based on clinical and mechanistic studies

SGLT2 Inhibition addresses other important pathophysiologic process of T2DM

Effect of SGLT2i

- Improved Beta Cell Function
- Hyperglucagonemia
- ↑ Glucose production
- ?? Effect on Insulin Resistance
- Inhibit Glucose reabsorption
- ↑ Fat Oxidation
- ↑ Insulin Sensitivity
- ↓ Tissue Glucose Disposal
- ?? GLP-1 Response

SGLT2i: Sodium Glucose Co Transporter Inhibitors
Dapagliflozin
Change in HbA1c from baseline at Week 24, core placebo-controlled phase 3 studies

Add-on combinations with:

- DAPA 5 mg
- DAPA 10 mg

Baseline mean HbA1c (%)

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Baseline mean HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>7.92</td>
</tr>
<tr>
<td>61</td>
<td>7.92</td>
</tr>
<tr>
<td>65</td>
<td>8.06</td>
</tr>
<tr>
<td>133</td>
<td>7.93</td>
</tr>
<tr>
<td>132</td>
<td>8.11</td>
</tr>
<tr>
<td>223</td>
<td>8.38</td>
</tr>
<tr>
<td>142</td>
<td>8.53</td>
</tr>
<tr>
<td>150</td>
<td></td>
</tr>
<tr>
<td>140</td>
<td></td>
</tr>
<tr>
<td>140</td>
<td></td>
</tr>
<tr>
<td>210</td>
<td></td>
</tr>
<tr>
<td>192</td>
<td></td>
</tr>
</tbody>
</table>

Statistically significant vs placebo; adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF).

MET, metformin; SU, sulfonylurea; TZD, thiazolidinediones;

# Empagliflozin

## Change in HbA1c Phase 3 pooled efficacy placebo-corrected change\(^a\) from baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, n</th>
<th>Baseline mean HbA1c (%)</th>
<th>Adjusted mean (SE) difference versus placebo in change from baseline HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled data</td>
<td>831</td>
<td>7.98</td>
<td>-0.62 (-0.68)</td>
</tr>
<tr>
<td>Monotherapy2</td>
<td>821</td>
<td>7.96</td>
<td>-0.74 (-0.85)</td>
</tr>
<tr>
<td>MET3</td>
<td>224</td>
<td>7.87</td>
<td>-0.57 (-0.64)</td>
</tr>
<tr>
<td>PIO4</td>
<td>224</td>
<td>7.86</td>
<td>-0.48 (-0.61)</td>
</tr>
<tr>
<td>MET + SU5</td>
<td>217</td>
<td>7.94</td>
<td>-0.64 (-0.64)</td>
</tr>
<tr>
<td>Insulin 78 week6</td>
<td>213</td>
<td>8.07</td>
<td>-0.62 (-0.52)</td>
</tr>
<tr>
<td>Mild RI7</td>
<td>216</td>
<td>8.06</td>
<td>-0.59 (-0.68)</td>
</tr>
<tr>
<td>Insulin 25 mg q.d.</td>
<td>225</td>
<td>8.07</td>
<td>-0.64 (-0.64)</td>
</tr>
<tr>
<td>Insulin 10 mg q.d.</td>
<td>216</td>
<td>8.10</td>
<td>-0.59 (-0.62)</td>
</tr>
<tr>
<td>Insulin 25 mg q.d.</td>
<td>169</td>
<td>8.27</td>
<td>-0.68 (-0.62)</td>
</tr>
</tbody>
</table>

\(^a\) All statistically significant unless otherwise marked.  
RI, renal impairment.
Canagliflozin
HbA1c change from baseline (LOCF)\textsuperscript{1-6}

<table>
<thead>
<tr>
<th>Monotherapy\textsuperscript{1}</th>
<th>Dual therapy</th>
<th>Triple therapy</th>
<th>Add-on to insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET + CANA vs MET + SITA\textsuperscript{2}</td>
<td>MET + CANA vs MET + GLIM\textsuperscript{3}</td>
<td>MET + SU + CANA vs SITA\textsuperscript{4}</td>
<td>MET + PIO + CANA\textsuperscript{5} + CANA\textsuperscript{6}</td>
</tr>
</tbody>
</table>

-0.77 -0.73 -0.82

-1.03 -0.88 -0.93

-1.03 -0.98 -1.07

-0.65 -0.73

\textbf{N} 195 197 368 367 483 485 377 113 114 566 587

\textbf{BL mean HbA1c (\%)} 8.1 8.0 7.9 7.8 8.1 8.0 7.9 8.3

All at 52 weeks except monotherapy at 26 weeks and add-on to insulin at 18 weeks

Change from baseline in HbA1c at week 24 by baseline BMI: add-on to metformin study

Subjects with BMI <25 kg/m² at baseline
- n = 17, Mean baseline 7.61, SE (0.15)
- 19, Mean baseline 8.03, SE (0.22)
- 10, Mean baseline 8.45, SE (0.34)
- 14, Mean baseline 7.89, SE (0.20)
- 20, Mean baseline 7.97, SE (0.21)

Subjects with BMI ≥25 kg/m² at baseline
- 117, Mean baseline 7.94, SE (0.07)
- 116, Mean baseline 7.93, SE (0.07)
- 130, Mean baseline 7.98, SE (0.07)
- 123, Mean baseline 8.02, SE (0.09)
- 108, Mean baseline 8.03, SE (0.09)

Adjusted mean (SE) change from baseline in HbA1c (%)
- Subjects with BMI <25 kg/m² at baseline
  - Empa 25 mg / lina 5 mg: -1.21, p=0.004
  - Empa 10 mg / lina 5 mg: -1.30, p=0.051
  - Empa 25 mg: -0.82, p<0.001
  - Empa 10 mg: -0.88, p<0.001
  - Lina 10 mg: -0.55, p=0.016

- Subjects with BMI ≥25 kg/m² at baseline
  - Empa 25 mg / lina 5 mg: -1.19, p<0.001
  - Empa 10 mg / lina 5 mg: -1.05, p<0.001
  - Empa 25 mg: -0.56, p<0.001
  - Empa 10 mg: -0.36, p<0.001
  - Lina 10 mg: -0.36, p<0.001

ANOVA in FAS (LOCF). p=0.275 for treatment by baseline BMI interaction.

Khunti K et al 98th Annual Meeting of the Endocrine Society (ENDO), Boston, MA; April 1-4, 2016
## Change from baseline in HbA1c at week 24 by baseline eGFR: add-on to metformin study

### Adjusted mean (SE) change from baseline in HbA1c (%) by baseline eGFR

<table>
<thead>
<tr>
<th>Baseline eGFR 60 to &lt;90 mL/min/1.73 m²</th>
<th>Baseline eGFR ≥90 mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>77</td>
<td>57</td>
</tr>
<tr>
<td>78</td>
<td>60</td>
</tr>
<tr>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>Mean baseline</td>
<td>Mean baseline</td>
</tr>
<tr>
<td>7.81</td>
<td>7.96</td>
</tr>
<tr>
<td>(0.09)</td>
<td>(0.11)</td>
</tr>
<tr>
<td>-0.51</td>
<td>-0.78</td>
</tr>
<tr>
<td>-0.64</td>
<td>-0.72</td>
</tr>
<tr>
<td>-0.67</td>
<td>-0.72</td>
</tr>
<tr>
<td>Adjusted mean (SE) change from baseline in HbA1c (%)</td>
<td>Adjusted mean (SE) change from baseline in HbA1c (%)</td>
</tr>
<tr>
<td>-1.17</td>
<td>-1.24</td>
</tr>
<tr>
<td>0.0 (0.09)</td>
<td>0.0 (0.11)</td>
</tr>
<tr>
<td>0.66 p&lt;0.001</td>
<td>0.47 p&lt;0.001</td>
</tr>
<tr>
<td>0.50 p&lt;0.001</td>
<td>0.52 p&lt;0.001</td>
</tr>
<tr>
<td>0.31 p=0.011</td>
<td>0.51 p&lt;0.001</td>
</tr>
<tr>
<td>0.28 p=0.021</td>
<td>0.52 p&lt;0.001</td>
</tr>
</tbody>
</table>

**Empa 25 mg / lina 5 mg**  
**Empa 10 mg / lina 5 mg**  
**Empa 25 mg**  
**Empa 10 mg**  
**Lina 10 mg**

**ANCOVA in FAS (LOCF).** p=0.494 for treatment by baseline eGFR (MDRD) interaction.

Khunti K et al 98th Annual Meeting of the Endocrine Society (ENDO), Boston, MA; April 1-4, 2016
SGLT inhibitor as an add on to metformin versus SU:
Comparable HbA1c reductions sustained over 4 years\(^1\)

At 52 weeks, reductions in HbA\(_{1c}\) were statistically non-inferior to glipizide (−0.52% for both)\(^2\)

Data are adjusted mean change from baseline derived from a longitudinal repeated measures mixed model.
A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study with a double-blind extension to evaluate the efficacy and safety profile of FORXIGA 10 mg + metformin (1500–2000 mg/day) versus glipizide + metformin (1500–2000 mg/day) in patients with inadequate glycaemic control (HbA\(_{1c}\) >6.5% and ≤10%) on metformin alone.\(^1\)


Mentioned diagram is only for educational purpose. AstraZeneca is not responsible for data and copyrights
Dapagliflozin as add-on to metformin versus SU:
Weight loss sustained over 4 years

At 52 weeks, Dapagliflozin was associated with weight loss of –3.2 kg versus weight gain of +1.4 kg with glipizide (p<0.0001)

Dapagliflozin is not indicated for the management of obesity. Weight change was a secondary endpoint in clinical trials. A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study with a double-blind extension to evaluate the efficacy and safety of dapagliflozin 10 mg + metformin (1500–2000 mg/day) versus glipizide + metformin (1500–2000 mg/day) in patients with inadequate glycaemic control (HbA1c >6.5% and ≤10%) on metformin alone. Data are adjusted mean change from base line derived from a longitudinal repeated-measures mixed model.


Above diagram is only for educational purpose. AstraZeneca is not responsible for data and copyrights.
SGLT2 inhibitors as add-on to metformin: HbA\textsubscript{1c} reductions and hypoglycemia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Hypoglycemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2</td>
<td>SUL</td>
</tr>
<tr>
<td>DAPA\textsuperscript{1} (10 mg)</td>
<td>4\textdagger</td>
</tr>
<tr>
<td>EMPA\textsuperscript{2} (25 mg)</td>
<td>2\textdagger</td>
</tr>
<tr>
<td>CANA\textsuperscript{4} (300 mg)</td>
<td>5\textdagger</td>
</tr>
</tbody>
</table>

SGLT2i, sodium-glucose co-transporter 2 inhibitors; *Significant vs. all comparators; **p<0.0001 (non-inferiority); †p<0.0001 vs. placebo; NR, not reported.

SGLT2 inhibitors as add-on to metformin: body weight reductions

SGLT2is, sodium-glucose co-transporter 2 inhibitors; *Significant vs. all comparators; NR, not reported.

Effect of Dapagliflozin on Fat Loss

DXA, dual-energy X-ray absorptiometry.
Consistent BP Reductions with Dapagliflozin: 4-5 mmHg systolic

Mean changes in systolic blood pressure (mmHg)

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy$^1$</th>
<th>Add-on to Met$^2$</th>
<th>Add-on to SU$^3$</th>
<th>48 week add-on to insulin$^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24 or 48 mean change from baseline mmHg</td>
<td>-3.7</td>
<td>-0.9</td>
<td>-4.9</td>
<td>-5.9</td>
</tr>
<tr>
<td>Dapagliflozin (10 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$Ferrannini E, et al. Diabetes Care 2010;33:2217-2224;
Dapagliflozin as add-on to Metformin:

**Sustained Reductions in SBP are over 4 years**

- The primary endpoint was change from baseline to Week 208 in HbA$_{1c}$, with SBP and weight change as secondary endpoints.

At Week 208, Dapagliflozin + metformin reduced HbA$_{1c}$ by $-0.10\%$ versus an increase of $+0.20\%$ with SU + metformin.

---

FORXIGA is not indicated for the management of high blood pressure.

A Phase III, multicentre, randomised, double-blind, parallel-group, 52-week, glipizide-controlled, non-inferiority study with a double-blind extension to evaluate the efficacy and safety profile of FORXIGA 10 mg + metformin (1500–2000 mg/day) versus glipizide + metformin (1500–2000 mg/day) in patients with inadequate glycaemic control (HbA$_{1c}$ >6.5% and ≤10%) on metformin alone.\(^1\)

CI, confidence interval; SBP, systolic blood pressure; SU, sulphonylurea.


---

*Above diagram is only for educational purpose. AstraZeneca is not responsible for data and copyrights.*
Dapagliflozin real-world evidence: Data from routine clinical practice confirms efficacy seen in randomised clinical trials\textsuperscript{1–5}

- Dapagliflozin delivers comparable reductions in HbA\textsubscript{1c}, weight and blood pressure* in real-world clinical practice as seen in randomised clinical trials

\begin{align*}
\text{Clinical trial data}^{\text{++1,2}} \\
\text{As add-on to metformin and insulin at 24 weeks, Dapagliflozin delivers:}
\end{align*}

\begin{align*}
\text{HbA}\textsubscript{1c} &:
-0.84%^{1} \\
\text{Weight} &:
-2.9 \text{ kg}^{1} \\
\text{SBP} &:
-5.1 \text{ mmHg}^{1}
\end{align*}

\begin{align*}
\text{Add-on to insulin: } & \\
-0.96%^{2} \\
-1.6 \text{ kg}^{2} \\
-6.7 \text{ mmHg}^{2}
\end{align*}

\begin{align*}
\text{Real-world data}^{\text{§ ¶ **3–5}} \\
\text{As add-on to various agents including metformin and insulin over 6–12 months, Dapagliflozin delivers:}
\end{align*}

\begin{align*}
\text{HbA}\textsubscript{1c} &:
-0.80 \text{ to } -1.16%^{3–5} \\
\text{Weight} &:
-2.5 \text{ to } -4.6 \text{ kg}^{3,5} \\
\text{SBP} &:
-2.3 \text{ mmHg}^{3}
\end{align*}

* Dapagliflozin is not indicated for the management of weight loss or blood pressure, and any changes were secondary endpoints in clinical trials.

Study details are available in slide notes.
MET, metformin; SBP, systolic blood pressure.
**UTIs and genital infections**

- SGLT2 inhibitors work by eliminating excess glucose through the kidney and is associated with a higher incidence of genital infections and UTIs\(^1\)
- Most genital infections* and UTIs were mild to moderate in intensity, rarely led to discontinuation of medication and were generally resolvable with a single course of standard treatment\(^1\)
- Pyelonephritis was uncommon and occurred at a similar frequency to control\(^1\)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Placebo-controlled pool (short-term)(^2)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FORXIGA 10 mg (N=2360)</td>
<td>Placebo (N=2295)</td>
</tr>
<tr>
<td>UTIs</td>
<td>110 (4.7)</td>
<td>81 (3.5)</td>
</tr>
<tr>
<td>Genital infections</td>
<td>130 (5.5)</td>
<td>14 (0.6)</td>
</tr>
</tbody>
</table>

A comparable safety profile was also seen in real-world observational studies\(^3\)–\(^6\)

*Genital infection includes the preferred terms: Vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial and vulval abscess.

UTI, urinary tract infection.

Empa-Reg Outcomes: 3P-MACE

Empa-Reg Primary End Point: 3P-MACE*

Primary End Point: 3P-MACE*

CV death, nonfatal MI, nonfatal stroke.
Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio. Cumulative incidence function. MACE = Major Adverse Cardiovascular Event; HR = hazard ratio.

* CV death, nonfatal MI, nonfatal stroke
† Two sided tests for superiority were conducted (statistics of significance was indicated if $P=0.0498$)

Zinaman et al. Results of the EMPA-REG OUTCOME study. EASD 2015 Stockholm
Empa Reg CV death, MI and Stroke

<table>
<thead>
<tr>
<th>Event/Outcome</th>
<th>Patients with event/analysed</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86 (0.74, 0.99)*</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62 (0.49, 0.77)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87 (0.70, 1.09)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24 (0.92, 1.67)</td>
</tr>
</tbody>
</table>

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI
Zinamann et al. Results of the EMPA-REG OUTCOME study. EASD 2015 Stockholm
CV safety trials are being conducted for each compound within the Newer Classes

Timings represent estimated completion dates as per ClinicalTrials.gov. Adapted from Johansen OE. World J Diabetes 2015;6:1092–96. (references 1–19 expanded in slide notes)
Changes in HbA1c and weight in type 2 diabetes patients initiating dapagliflozin treatment in routine UK primary care

A retrospective study using data from the Clinical Practice Research Datalink, a subset of the ~40,000 UK patients receiving dapagliflozin

**Change in HbA1c at >180 days**

- Dual: \(-11.8\) mmol/mol (n = 101, 73.6\(^a\) mmol/mol (8.9%))
- Insulin: \(-13.4\) mmol/mol (n = 56, 83.4\(^a\) mmol/mol (9.8%))

**Change in weight at >180 days**

- Dual: \(-6.3\) kg (n = 95, 107.4\(^a\) kg)
- Insulin: \(-3.2\) kg (n = 52, 103.8\(^a\) kg)

Results from a subset of the 2401 patients prescribed dapagliflozin in CPRD (which represents ~9% of UK population).\(^a\) Baseline values

Real world data on canagliflozin: after 6 months

- Using retrospective claims data from the United States, patients with type 2 diabetes had clinically meaningful improvements in HbA1c during the 6 months following the first canagliflozin prescription.
- HbA1c reductions with canagliflozin were larger in patients with higher baseline A1C, and more patients achieved HbA1c treatment targets during the 6-month follow-up period.

Diabetic Ketoacidosis & SGLT2i

**AACE /ACE Scientific and Clinical Review**

Concluded that the prevalence of DKA is infrequent and the risk-benefit ratio overwhelmingly favors **continued use of SGLT2 inhibitors** with no changes in current recommendations.

**AACE recommends**
Consider halting SGLT2 inhibitors for at least 24 hrs. prior to surgeries, planned invasive procedures, or anticipated difficult physical activities.

For any extreme stress events such as emergency surgeries, the drug should be stopped immediately and appropriate clinical care should be provided.

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**Risk Factors for EuDKA**
Poor Nutrition, Post-operative period
Management is similar to DKA ( IV fluids, Insulin, K+ )

Summary

• T2DM Progressive disease
• Effective treatment of T2DM requires multiple drugs used in combination to correct multiple pathophysiological defects
• Selective inhibition of SGLT2 directly removes excess glucose and associated calories, along with sodium, resulting in blood glucose, weight, and blood pressure reductions
• SLGT2 inhibitors have the potential to help control hyperglycaemia at all stages of diabetes and improve macrovascular and microvascular outcomes
Thank you

“You said to bring a urine sample.”

www.leicesterdiabetescentre.org.uk
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@LDC_Tweets