Thinking beyond HbA1c in Type 2 Diabetes
How can Cardiovascular morbidity and mortality be tackled?

DPC Cardiovascular Clinic

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The Boehringer Ingelheim and Lilly Diabetes Alliance has provided the funding for this sponsored session, including speaker honoraria and presentation development support. The presentation has been reviewed for medical accuracy and compliance with applicable laws and regulations.

Boehringer Ingelheim and Lilly Diabetes Alliance products will be discussed during this presentation.
Prescribing information for Jardiance® (empagliflozin) is available at the end of this presentation, or can be accessed online at: www.jardiancepi.co.uk

Adverse events should be reported. Reporting forms and further information can be found at: www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). Adverse events and product complaints should also be reported to Lilly: 01256 315 000.
Disclosures

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Objectives

- To consider the unmet clinical need
  - Cardiovascular morbidity/mortality in people with Type 2 Diabetes

- To discuss the results of EMPA-REG OUTCOME®
  - Use of empagliflozin to improve outcomes

- To understand new clinical guidance for Type 2 Diabetes
  - Updates reflect the results of Cardiovascular Outcome Trials

- To reflect on the goals of treatment for Type 2 Diabetes
  - Which patients could benefit from an SGLT2 inhibitor
Case study, 2019

- 68-year-old female
- **Diagnosed 10 years ago** with Type 2 Diabetes
- **HbA1c: 62 mmol/mol (7.8%)**
- BMI: 32 kg/m²
- eGFR: 65 ml/min/1.73 m²
- Dyslipidaemia, hypertension, hypothyroid
- Atorvastatin 20 mg OD, ramipril 5 mg OD, thyroxine 125 mcg OD, metformin 1000 mg BD, gliclazide 80 mg OD

Patient suffers a Cardiovascular Death

Could we have done more?
Excess mortality in diabetes is largely related to Cardiovascular Disease\(^1\)

Over **one third** of people with Type 2 Diabetes also have Cardiovascular Disease\(^2\)

Cardiovascular Disease is responsible for over **half of all deaths** in people with Type 2 Diabetes,\(^3\) with many of these deaths premature\(^4\)

Cardiovascular Disease can occur **10–15 years earlier** in patients with diabetes compared with those without diabetes\(^5,6\)

Diabetes accelerates the time to the first Cardiovascular event\(^7\)*

*Time to first Myocardial infarction event or first heart failure hospitalisation.

Meta-analysis shows modest benefit of intensive glycaemic control on macrovascular risk

Meta-analysis including 27,049 participants and 2370 major Cardiovascular events

<table>
<thead>
<tr>
<th>Trials</th>
<th>More intensive</th>
<th>Less intensive</th>
<th>∆HbA1c (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>Overall HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Cardiovascular events*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>352 (2.11)</td>
<td>371 (2.29)</td>
<td>-1.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>557 (2.15)</td>
<td>590 (2.28)</td>
<td>-0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS</td>
<td>169 (1.30)</td>
<td>87 (1.60)</td>
<td>-0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VADT</td>
<td>116 (2.68)</td>
<td>128 (2.98)</td>
<td>-1.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1194</td>
<td>1176</td>
<td>-0.88</td>
<td></td>
<td>0.91 (0.84–0.99)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>378</td>
<td>370</td>
<td>-0.88</td>
<td></td>
<td>0.96 (0.83–1.10)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>730</td>
<td>745</td>
<td>-0.88</td>
<td></td>
<td>0.85 (0.76–0.94)</td>
</tr>
<tr>
<td>Hospitalised/fatal heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>459</td>
<td>446</td>
<td>-0.88</td>
<td></td>
<td>1.00 (0.86–1.16)</td>
</tr>
</tbody>
</table>

*Major Cardiovascular events = Cardiovascular Death, non-fatal stroke or non-fatal Myocardial Infarction.
†Diamonds incorporate point estimate (vertical dashed line) and encompass 95% CI of overall effect for each outcome.
CI: confidence interval; HR: hazard ratio.
We now have an evidence base of Cardiovascular benefit with specific Type 2 Diabetes medications


**Timeline:**
- **EMPA-REG OUTCOME®** published¹: July 2016
- **LEADER published²**: Sept 2015
- **SUSTAIN-6 published³**: Sept 2016
- **CANVAS published⁴**: October 2018
- **HARMONY OUTCOMES published⁵**: June 2017
- **DECLARE-TIMI 58 published⁶**: June 2019
- **CREDENCE published⁷**: November 2018
- **REWIND published⁸**: June 2019

**Published Dates:**
- EMPA-REG OUTCOME®: Sept 2015
- LEADER: July 2016
- SUSTAIN-6: Sept 2016
- CANVAS: October 2018
- HARMONY OUTCOMES: June 2017
- DECLARE-TIMI 58: June 2019
- CREDENCE: November 2018
- REWIND: June 2019
The EMA has approved an update to the empagliflozin SmPC to include a change to the indication statement

‘Both improvement of glycaemic control and reduction of Cardiovascular morbidity and mortality are an integral part of the treatment of Type 2 Diabetes’

Therapeutic indication

Jardiance is indicated for the treatment of adults with insufficiently controlled Type 2 Diabetes mellitus as an adjunct to diet and exercise

- As monotherapy when metformin is considered inappropriate due to intolerance
- In addition to other medicinal products for the treatment of diabetes

For study results with respect to combinations, effects on glycaemic control and Cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1 of the SmPC

EMA: European Medicines Agency; SmPC: summary of product characteristics
EMPA-REG OUTCOME® is a landmark trial

The first dedicated Cardiovascular Outcome Trial to show a reduction in Cardiovascular risk and improved overall survival in adults with Type 2 Diabetes and Cardiovascular Disease

Trial objective: to examine the effects of empagliflozin, as compared with placebo, on Cardiovascular morbidity and mortality in patients with Type 2 Diabetes and Cardiovascular Disease who were receiving Standard of Care

SGLT2 inhibitors are not indicated for the treatment of heart failure or the treatment of kidney disease.

EMA: European Medicines Agency; HHF: hospitalisation for heart failure; SmPC: summary of product characteristics

EMPA-REG OUTCOME® was a randomised, double-blind placebo-controlled safety trial

Patients were followed for a median of 3.1 years.

*82.7% on acetylsalicylic acid, 10.6% on clopidogrel, 6.0% on vitamin K antagonists.

BMI: body mass index; DPP-4: dipeptidyl peptidase 4; eGFR: estimated glomerular filtration rate; MACE: major adverse cardiovascular events; MDRD: modification of diet in renal disease


Inclusion criteria:
- Adults aged ≥18 years
- HbA1c ≥7% (53.0 mmol/mol) and ≤10% (85.8 mmol/mol) at screening visit
- BMI ≤45 kg/m²
- Evidence of Cardiovascular Disease (Coronary Artery Disease, Peripheral Vascular Disease/Peripheral Artery Disease, Myocardial Infarction or stroke)

Exclusion criteria:
- eGFR (MDRD) <30 mL/min/1.73 m²
- Acute coronary syndrome, stroke or transient ischaemic attack within 2 months prior to informed consent

7020 patients randomised

Placebo (n=2333)

Empagliflozin 10 mg (n=2345)

Empagliflozin 25 mg (n=2342)

On top of Standard of Care

Antidiabetic therapy
- Metformin (74.0%)
- Sulphonylurea (42.8%)
- Insulin (48.2%)
- Thiazolidinedione (4.3%)
- DPP-4 inhibitor (11.3%)

Cardiovascular medication
- Anti-hypertensives (95.0%)
- Lipid lowering therapies (81.0%)
- Anticoagulants/antiplatelets* (89.1%)

Primary endpoint was 3-point MACE: time to first occurrence of Cardiovascular Death, non-fatal Myocardial Infarction or non-fatal stroke
EMPÁ-REG OUTCOME®: 3P-MACE

Significant improvements in the primary outcome 3P-MACE (time to first occurrence of Cardiovascular Death, non-fatal Myocardial Infarction or non-fatal stroke)* with empagliflozin vs placebo

Pooled figures for empagliflozin
HR: 0.86 (95.02% CI: 0.74–0.99), p=0.04†
RRR: 14%; ARR: 1.6%
NNT=61

The reduction in the rate of 3P-MACE was driven by lower rates of death from Cardiovascular causes with empagliflozin vs placebo

Absolute rates 10.5% (empagliflozin) vs 12.1% (placebo). Cumulative incidence function. Pooled data for empagliflozin 10 mg and 25 mg is represented.

*3P-MACE is the standard composite endpoint used in Cardiovascular Outcome Trials.
†Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498).
ARR: absolute risk reduction; CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular event; NNT: number needed to treat; RRR: relative risk reduction
Empagliflozin reduced the risk of Cardiovascular Death in patients with Type 2 Diabetes and Cardiovascular Disease on top of Standard of Care vs placebo

Empagliflozin: Cumulative incidence function. Pooled data for empagliflozin 10 mg and 25 mg is represented. Absolute rates of Cardiovascular Death: 3.7% (empagliflozin) vs 5.9% (placebo).

HR at 12 months: 0.55
95% CI: 0.35–0.86

RRR: relative risk reduction; ARR: absolute risk reduction; CI: confidence interval; HR: hazard ratio; NNT: number needed to treat.

Empagliflozin reduced the risk of All-Cause Mortality in patients with Type 2 Diabetes and Cardiovascular Disease on top of Standard of Care vs placebo

Cumulative incidence function. Absolute rates of All-Cause Mortality: 5.7% (pooled figure for empagliflozin) vs 8.3% (placebo).

ARR: absolute risk reduction; CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; RRR: relative risk reduction

Empagliflozin is not indicated for the treatment of heart failure.

Cumulative incidence function.

ARR: absolute risk reduction; CI: confidence interval; HR: hazard ratio; RRR: relative risk reduction

In adults with Type 2 Diabetes and established Cardiovascular Disease, empagliflozin, on top of Standard of Care, reduced Cardiovascular risk and improved overall survival compared with placebo and Standard of Care.

**Primary endpoint**

- **3P-MACE**
  - 14% (RRR)
  - ARR=1.6%, HR=0.86
  - 95% CI: 0.74–0.99
  - p<0.001 for non-inferiority
  - p=0.04 for superiority

**Other endpoints**

- **Cardiovascular Death**
  - 38% (RRR)
  - ARR=2.2%, HR=0.62
  - 95% CI: 0.49–0.77
  - p<0.001

- **All-Cause Mortality**
  - 32% (RRR)
  - ARR=2.6%, HR=0.68
  - 95% CI: 0.57–0.82
  - p<0.001

- **Hospitalisation for Heart Failure**
  - 35% (RRR)
  - ARR=1.4%, HR=0.65
  - 95% CI: 0.50–0.85
  - p=0.002

SGLT2 inhibitors are not indicated for the treatment of heart failure.

ARR: absolute risk reduction; CI: confidence interval; HR: hazard ratio; RRR: relative risk reduction; MACE: major adverse cardiovascular events

Cardiovascular benefits seen with SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Primary safety endpoint: 3P-MACE</th>
<th>EMPA-REG OUTCOME empagliflozin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>CANVAS Program canagliflozin*&lt;sup&gt;2&lt;/sup&gt;</th>
<th>DECLARE-TIMI 58 dapagliflozin*&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Adverse Cardiovascular Events</td>
<td>&gt;99% Cardiovascular Disease (n=7020)</td>
<td>65.6%: Cardiovascular Disease (n=6656)</td>
<td>40.6%: Cardiovascular Disease (n=6974)</td>
</tr>
<tr>
<td>Non-Inferiority</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Superiority</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>1) Cardiovascular Death</td>
<td>✓</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>2) Non-fatal Myocardial Infarction</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>3) Non-fatal Stroke</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

✓ statistical significance achieved  × statistical significance not achieved

These Cardiovascular Outcome Trials are not head-to-head trials and comparisons should be interpreted with caution due to differences in study design, populations and methodology.

*Please note absolute p-values for secondary outcomes were not reported in the CANVAS Program or DECLARE-TIMI 58.

MACE: major adverse cardiovascular events; SGLT2: sodium–glucose co-transporter 2

‘[Zelniker] and colleagues’ meta-analysis … provides compelling evidence that SGLT2i should now be considered as first-line therapy after metformin in most people with Type 2 Diabetes…’

- Zelniker et al. performed a systematic review and meta-analysis of randomised, placebo-controlled, Cardiovascular Outcome Trials of SGLT2 inhibitors in patients with Type 2 Diabetes.
Developed in collaboration with EASD

ESC extends previous recommendations to use SGLT2 inhibitors and GLP-1 RAs with proven benefit to reduce Cardiovascular events in patients with Type 2 Diabetes and atherosclerotic cardiovascular disease (ASCVD) also to those with Type 2 Diabetes and high/very high Cardiovascular risk.
2019: ESC Guidelines on diabetes, pre-diabetes and Cardiovascular Disease – what’s new (selected)

### Change in recommendations 2013 to 2019

#### Glucose-lowering treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2013 Recommendation</th>
<th>2019 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Should be considered as first-line therapy in patients with diabetes</td>
<td>Should be considered in overweight patients with Type 2 Diabetes without Cardiovascular Disease and at moderate Cardiovascular risk</td>
</tr>
</tbody>
</table>

### New recommendations in 2019

#### Glucose-lowering treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2019 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin, canagliflozin or dapagliflozin</td>
<td>Are recommended in patients with Type 2 Diabetes and Cardiovascular Disease, or at very high/high Cardiovascular risk, to reduce Cardiovascular events</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Is recommended in patients with Type 2 Diabetes and Cardiovascular Disease to reduce the risk of death</td>
</tr>
<tr>
<td>Liraglutide, semaglutide or dulaglutide</td>
<td>Are recommended in patients with Type 2 Diabetes and Cardiovascular Disease, or at very high/high Cardiovascular risk, to reduce Cardiovascular events</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Is recommended in patients with Type 2 Diabetes and Cardiovascular Disease, or at very high/high Cardiovascular risk, to reduce this risk of death</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Is not recommended in patients with Type 2 Diabetes and a high risk of Heart Failure</td>
</tr>
</tbody>
</table>

#### Diabetes treatment to reduce Heart Failure risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2019 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitors (empagliflozin, canagliflozin or dapagliflozin)</td>
<td>Are recommended to lower risk of Heart Failure hospitalisation</td>
</tr>
<tr>
<td>Metformin</td>
<td>Should be considered in patients with diabetes and Heart Failure if eGFR &gt;30 ml/min/1.73 m²</td>
</tr>
<tr>
<td>GLP-1 RAs and DPP-4 inhibitors</td>
<td>Sitagliptin and linagliptin have a neutral effect on risk of Heart Failure and may be considered</td>
</tr>
<tr>
<td>Insulin treatment</td>
<td>In Heart Failure may be considered</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>Saxagliptin in Heart Failure is not recommended</td>
</tr>
<tr>
<td>Thiazolidinediones (pioglitazone and rosiglitazone)</td>
<td>In Heart Failure are not recommended</td>
</tr>
</tbody>
</table>

#### Management of chronic kidney disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2019 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitors</td>
<td>Are recommended to reduce the progression of diabetic kidney disease</td>
</tr>
</tbody>
</table>

*SGLT2 inhibitors are not indicated for treatment of heart failure, treatment of kidney disease or reduction in early death.*

*SGLT2: sodium–glucose co-transporter 2*

**EMPA-REG OUTCOME®: safety**

### Specific adverse events

<table>
<thead>
<tr>
<th>Specific adverse events</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>Diabetic ketoacidosis*</td>
<td>1 (&lt;0.1)</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Acute renal failure†‡</td>
<td>155 (6.6)</td>
<td>121 (5.2)</td>
<td>125 (5.3)</td>
</tr>
<tr>
<td>Event consistent with volume depletion§</td>
<td>115 (4.9)</td>
<td>115 (4.9)</td>
<td>124 (5.3)</td>
</tr>
<tr>
<td>Thromboembolic event‖</td>
<td>20 (0.9)</td>
<td>9 (0.4)</td>
<td>21 (0.9)</td>
</tr>
<tr>
<td>Bone fractures‖</td>
<td>91 (3.9)</td>
<td>92 (3.9)</td>
<td>87 (3.7)</td>
</tr>
</tbody>
</table>

Note: in patients aged 75 years and older, an increased risk for volume depletion should be taken into account. In patients treated with SGLT2 inhibitors rare cases of diabetic ketoacidosis have been reported. Post-marketing cases of Fournier’s gangrene (outside clinical trials) have been reported with unknown incidence.

Patients should be advised on the symptoms and need to seek medical attention. Please refer to the Jardiance SmPC for further information.

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Patients treated with ≥1 dose of study drug. All events occurred within 7 days after the last receipt of the study drug.

* Based on 4 MedDRA preferred terms. †Based on 1 standardised MedDRA query. ‡p<0.01 for the comparison of pooled empagliflozin with placebo.

§ Based on 8 MedDRA preferred terms. †Based on 1 standardised MedDRA query. ‡Based on 62 MedDRA preferred terms.

MedDRA: Medical dictionary for regulatory activities
EMPA-REG OUTCOME®: safety
Urinary tract and genital infection

### Patients treated with ≥1 dose of study drug. All events occurred within 7 days after the last receipt of the study drug. Percentages were calculated as the proportions of all men and all women with the event.

*Based on 79 MedDRA preferred terms. †p<0.05 for the comparison of pooled empagliflozin with placebo.
‡Based on 88 MedDRA preferred terms. §p<0.001 for the comparison with placebo.

MedDRA: Medical dictionary for regulatory activities

<table>
<thead>
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<th>Placebo (n=2333)</th>
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<th>Empagliflozin 25 mg (n=2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Event consistent with urinary tract infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male patients</td>
<td>423 (18.1)</td>
<td>426 (18.2)</td>
<td>416 (17.8)</td>
</tr>
<tr>
<td>Female patients†</td>
<td>158 (9.4)</td>
<td>180 (10.9)</td>
<td>170 (10.1)</td>
</tr>
<tr>
<td><strong>Event consistent with genital infection</strong>‡§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male patients</td>
<td>42 (1.8)</td>
<td>153 (6.5)</td>
<td>148 (6.3)</td>
</tr>
<tr>
<td>Female patients</td>
<td>25 (1.5)</td>
<td>89 (5.4)</td>
<td>77 (4.6)</td>
</tr>
</tbody>
</table>
Empagliflozin – practicalities of prescribing

Starting dose 10 mg **once daily**

For patients who tolerate empagliflozin 10 mg once daily and need additional glycaemic control, the dose can be increased to 25 mg daily*

Empagliflozin can be taken:

- With or without food
- At any time of the day

**Precautions for use**

- If eGFR is persistently <60 mL/min/1.73 m², dose should be adjusted or maintained at 10 mg
- Empagliflozin should not be initiated in patients with eGFR <60 mL/min/1.73 m² and should be discontinued when eGFR is persistently <45 mL/min/1.73 m²
- Empagliflozin is not recommended for those aged <18 years
- Therapeutic experience in patients aged ≥85 years is limited; therefore, initiation is not recommended
- Avoid the use of empagliflozin during pregnancy or during breast-feeding

For full details see Summary of Product Characteristics.

*If eGFR is ≥60 mL/min/1.73 m².

eGFR: estimated glomerular filtration rate

20:20 hindsight
How has Standard of Care evolved in Type 2 Diabetes?
Case study: Turning back the clock
Could we have done more?

- 60-year-old female
- **Diagnosed 2 years ago** with Type 2 Diabetes
- **HbA1c: 60 mmol/mol (7.6%)**
- BMI: 31 kg/m²
- eGFR: 72 ml/min/1.73 m²
- BP: 148/90 mmHg
- LDL: 3.2 mmol/l
- Atorvastatin 20 mg OD, ramipril 5 mg OD, thyroxine 125 mcg OD, metformin 1000 mg BD

2019:
- **HbA1c: 62 mmol/mol (7.8%)**
- BMI: 32 kg/m²
- eGFR: 65 ml/min/1.73 m²
- Patient suffers a Cardiovascular Death

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; OD: once daily

Not an actual patient.
Case study: Turning back the clock
Could we have done more?

- 60-year-old female
- **Diagnosed 2 years ago** with Type 2 Diabetes
- **HbA1c: 60 mmol/mol (7.6%)**
- BMI: 31 kg/m²
- eGFR: 72 ml/min/1.73 m²
- BP: 148/90 mmHg
- LDL: 3.2 mmol/l
- Atorvastatin 20 mg OD, ramipril 5 mg OD, thyroxine 125 mcg OD, metformin 1000 mg BD

How could we have managed this patient?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; OD: once daily

Not an actual patient.
Clinical practice in the UK, 2015: NICE Guideline 28 does not include Cardiovascular Outcome Trial Data

NICE guidance is prepared for the National Health Service in England and is subject to regular review and may be updated or withdrawn.

NG: NICE guideline

Clinical practice in the UK, 2017: SIGN Guideline 154 issued incorporating Cardiovascular Outcome Trial Data

- Guidance on pharmacological management updated to include evidence from Cardiovascular Outcome Trials

- ‘The effects of glucose-lowering therapies on Cardiovascular morbidity and mortality are therefore of major importance and not necessarily related to glucose lowering’

- For individuals with Type 2 Diabetes and Cardiovascular Disease: advice to consider SGLT2 inhibitors and GLP-1 receptor agonists with proven Cardiovascular benefit

SIGN Guidelines are developed for use by the NHS in Scotland.
GLP-1: glucagon-like peptide 1; SGLT2: sodium–glucose co-transporter 2; SIGN: Scottish Intercollegiate Guidelines Network
SGLT2 inhibitors are not indicated for the treatment of kidney disease or the treatment of heart failure.
ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes
What are we trying to achieve when we decide on a treatment option for our patient?

- Prevent / delay complications?
- Choosing a treatment
- Slow progression of disease?
- Glycaemic control?
- Avoid side effects (hypoglycaemia, weight gain)?
- Prevent early death?
- Prevent / delay complications?
What do these data mean for patients?

Differences in mean survival by age with empagliflozin versus placebo estimated using data from EMPA-REG OUTCOME

A 45-year-old patient with Type 2 Diabetes and Cardiovascular Disease could gain 4.5 years of life with empagliflozin

A 60-year-old could gain 3.1 years

CI: confidence interval
Number needed to treat to prevent one death in landmark trials in patients with high Cardiovascular risk

<table>
<thead>
<tr>
<th></th>
<th>Pre-ACEi/ARB era</th>
<th>Pre-statin era</th>
<th>&lt;29% statin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1994</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>Pre-ACEi/ARB era</td>
<td>Simvastatin&lt;sup&gt;1&lt;/sup&gt; for 5.4 years</td>
<td>Ramipril&lt;sup&gt;2&lt;/sup&gt; for 5 years</td>
<td></td>
</tr>
<tr>
<td>High Cardiovascular risk</td>
<td>30</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>5% diabetes, 26% hypertension</td>
<td></td>
<td>38% diabetes, 47% hypertension</td>
<td></td>
</tr>
</tbody>
</table>

Absolute risk reduction cannot be compared directly across different trials.

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker
Number needed to treat to prevent one death with empagliflozin on top of Standard of Care in patients with Type 2 Diabetes and Cardiovascular Disease

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker
Historically, treatment of Type 2 Diabetes has focused on glycaemic control.

Excess mortality in diabetes is largely related to Cardiovascular Disease.

EMPA-REG OUTCOME® was the first Cardiovascular Outcome Trial to show a reduction in Cardiovascular events, including a 38% RRR (2.2% ARR) in Cardiovascular Death.

Internationally, clinical guidelines are now placing a greater emphasis on Cardiovascular risk.

Is it time to think beyond HbA1c to tackle Cardiovascular morbidity and mortality in our patients with Type 2 Diabetes?
Prescribing Information (UK) JARDIANE® (empagliflozin)

JARDIANE® (empagliflozin)

Information for healthcare professionals

Recommended Starting Dose

- Treatment of diabetes: 10 mg or 25 mg empagliflozin.

Indication

- Jardiance is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise: as monotherapy when metformin is considered inappropriate due to intolerance; in addition to other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, refer to the Summary of Product Characteristics.

Dose and Administration

- The recommended starting dose is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥ 60 ml/min/1.73 m² and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg. When used with sulphonylurea or insulin a lower dose of these may be considered to reduce the risk of hypoglycaemia. Renal impairment: The glycaemic efficacy is dependent on renal function. No dose adjustment is required for patients with an eGFR ≥ 60 ml/min/1.73 m² or CrCl ≥ 60 ml/min. Do not initiate in patients with an eGFR < 60 ml/min/1.73 m² or CrCl < 60 ml/min. In patients tolerating empagliflozin, if the eGFR is persistently below 60 ml/min/1.73 m² or CrCl below 60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Discontinue when eGFR is persistently below 45 ml/min/1.73 m² or CrCl persistently below 45 ml/min. Not for use in patients with end stage renal disease (ESRD) or on dialysis. Hepatic impairment: No dose adjustment is required for patients with hepatic impairment. Not recommended in severe hepatic impairment. Elderly patients: No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account. Not recommended in patients 85 years or older. Paediatric population: No data are available. Method of administration: The tablets can be taken with or without food, swallowed whole with water. If a dose is missed, it should be taken as soon as possible, with or without food. If a dose is missed, do not take any extra tablets to make up for the missed dose.

Clinical Pharmacology

- Contraindications: Hypersensitivity to the active substance or to any of the excipients. Warnings and Precautions: Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors. Consider the risk of DKA in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness and assess patients for ketoacidosis immediately, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment should be discontinued immediately. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is very useful in monitoring patients with uncontrolled ketosis. Normal ketone values are normal and the patient’s condition has stabilised. Before initiating empagliflozin, consider factors in the patient history that may predispose to ketoacidosis. Use with caution in patients who may be at higher risk of DKA. Renal impairment: See under Dose and Administration; Monitor renal function prior to initiation and at least annually. Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established. Haematoctit increase was observed with empagliflozin treatment. Osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients with known cardiovascular disease, patients on antihypertensive therapy with a history of hypotension or patients aged 75 years and older. In case of conditions that may lead to fluid loss (e.g., gastrointestinal illness), careful monitoring of volume status and electrolytes is recommended. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected. Elderly See under Dose and Administration; special attention should be given to volume intake of elderly patients in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE-inhibitors). Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections. Cases of necrotising fasciitis of the perineum (Fournier’s gangrene), have been reported in patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fourmer’s gangrene is suspected, the patient should be managed as for any other serious infection. Amputation in cases of foot gangrene may need to be considered in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor, counsel patients on routine preventative footwear. Experience in New York Heart Association (NYHA) class II-IV and type 1 diabetes patients treated with empagliflozin in NYHA class III-IV. Due to its mechanism of action, patients taking Jardiance will test positive for glucose in their urine. The tablets contain lactose and should not be used in patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption. Interactions: Use with diuretics may increase the risk of dehydration and hypotension. Insulin and insulin secretagogues may increase the risk of hypoglycaemia therefore, a lower dose of insulin or an insulin secretagogue may be required. The effect of UGT induction on empagliflozin has not been studied. Co-administration with known inducers of UGT should be avoided due to a potential risk of decreased efficacy. Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by coadministration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torsemide and hydrochlorothiazide. Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives. Fertility, pregnancy and lactation: There are no data from the use of empagliflozin in pregnant women. As a precautionary measure, it is preferable to avoid the use of Jardiance during pregnancy. No data in humans are available on excretion of empagliflozin into milk. Jardiance should not be used during breast feeding. No studies on the effect on human fertility have been conducted for Jardiance. Undesirable effects: Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (≥1/100000), not known (cannot be estimated from the available data). Very common: hypoglycaemia (when used with sulphonylurea or insulin). Common: vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, urinary tract infection (including pyelonephritis and urosepsis), thirst, pruritus (generalised), rash, increased urination, serum lipids increased. Uncommon: urticaria, volume depletion, dysuria, blood creatinine increased/glomerular filtration rate decreased, haematoctit increased. Rare: DKA. Not known: necrotising fasciitis of the perineum (Fourmer’s gangrene), angioedema. Prescribers should consult the Summary of Product Characteristics for further information on side effects. Pack size and NHS price: 28 tablets £36.59, 56 tablets £36.59. Legal category: POM. MA numbers: 10 mg/28 tablets EU/1/14/930/013; 25 mg/28 tablets EU/1/14/930/014. Marketing Authorisation Holder: Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. Prepared in October 2019.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).