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

DPC Cardiovascular Clinic

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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.

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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

Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

American Diabetes Association.

EASD European Association for the Study of Diabetes

ESC European Society of Cardiology

Case study, 2019

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

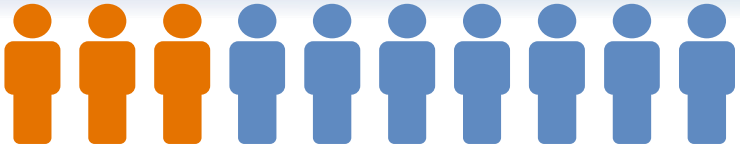
Patient suffers a Cardiovascular Death

Could we have done more?

BD: twice daily; BMI: body mass index; eGFR: estimated glomerular filtration rate; OD: once daily

Not an actual patient.

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]*

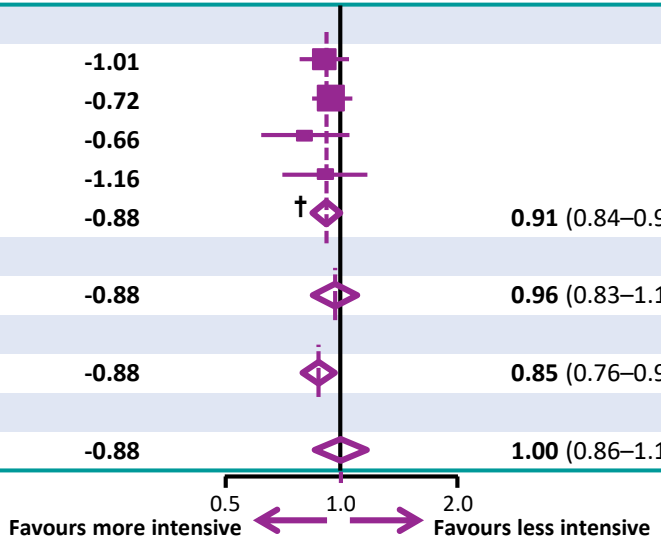
*Time to first Myocardial Infarction event or first heart failure hospitalisation.

1. Tancredi M *et al. N Engl J Med*. **2015**;373:1720–1732; 2. Einarson TR *et al. Cardiovasc Diabetol.* 2018;17:83;
3. Lautsch D *et al. Diabetes Ther*. **2019**; epub ahead of print. doi: 10.1007/s13300-019-00698-9; 4. Fisher M, Shaw KM. *Pract Diab Int*. **2001**;18:183–184;
5. Malmberg K et al. *Circulation*. **2000**;102:1014–1019; 6. Booth GL *et al. Lancet*. **2006**;368:29–36; 7. McMurray JJ *et al. Lancet Diabetes Endocrinol*. **2014**;2:843–851.

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

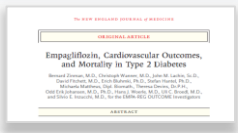
Meta-analysis including 27,049 participants and 2370 major Cardiovascular events

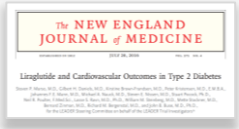
Trials	Number of events (annual event rate, %)		ΔHbA1c (%)	Hazard ratio (95% CI)	Overall HR (95% CI)
	More intensive	Less intensive			
Major Cardiovascular events*					
ACCORD	**352** (2.11)	**371** (2.29)	**-1.01**		
ADVANCE	**557** (2.15)	**590** (2.28)	**-0.72**		
UKPDS	**169** (1.30)	**87** (1.60)	**-0.66**		
VADT	**116** (2.68)	**128** (2.98)	**-1.16**		
Overall	**1194**	**1176**	**-0.88**	†	**0.91** (0.84–0.99)
Stroke					
Overall	**378**	**370**	**-0.88**		**0.96** (0.83–1.10)
Myocardial Infarction					
Overall	**730**	**745**	**-0.88**		**0.85** (0.76–0.94)
Hospitalised/fatal heart failure					
Overall	**459**	**446**	**-0.88**		**1.00** (0.86–1.16)

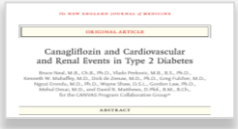


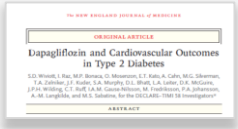
*Major Cardiovascular events = Cardiovascular Death, non-fatal stroke or non-fatal Myocardial Infarction.
†Diamonds incorporate point estimate (vertical dashed line) and encompass 95% CI of overall effect for each outcome.
CI: confidence interval; HR: hazard ratio.
Turnbull FM *et al. Diabetologia*. **2009**;52:2288–2298.

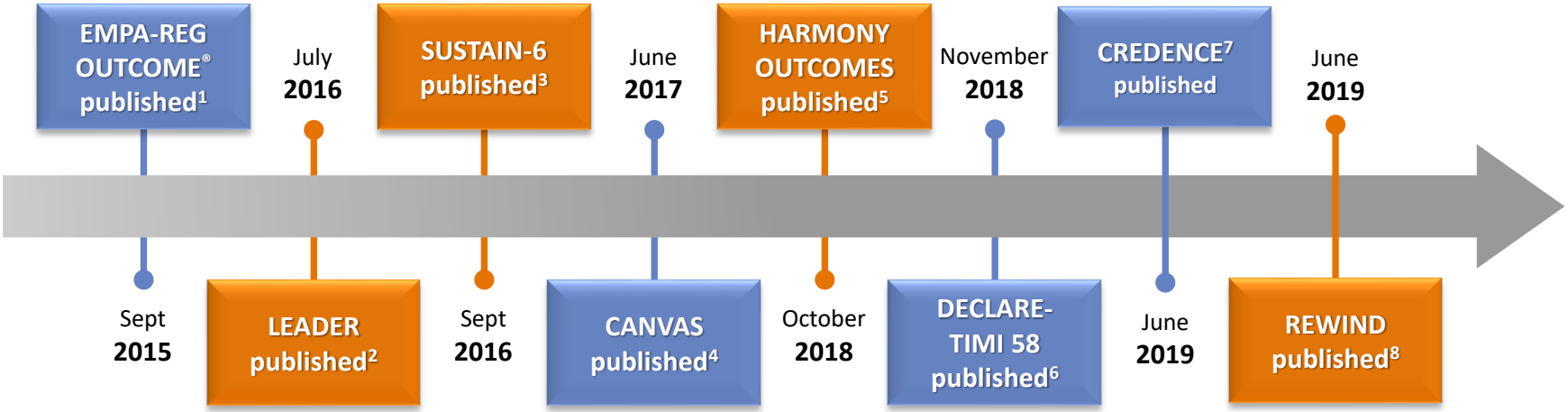
We now have an evidence base of Cardiovascular benefit with specific Type 2 Diabetes medications











1. Zinman B *et al. N Engl J Med*. **2015**;373:2117–2128; 2. Marso SP *et al. N Engl J Med*. **2016**;375:311–322; 3. Marso SP *et al. N Engl J Med*. **2016**;375:1834–1844;
4. Neal B *et al. N Engl J Med*. **2017**;377:644–657; 5. Hernandez AF *et al. Lancet*. **2018**;392:1519–1529. 6. Wiviott SD *et al. N Engl J Med*. **2019**;380:347–357;
7. Perkovic V *et al. N Engl J Med*. **2019**;380:2295–2306; 8. Gerstein HC *et al. Lancet*. **2019**;394:121–130.

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

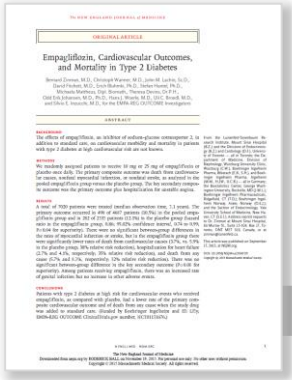
EMA: European Medicines Agency; SmPC: summary of product characteristics

Jardiance (empagliflozin) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/5441 (accessed October 2019).

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[1]

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[1]


Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

EMPA-REG OUTCOME® published[1] — Sept 2015

EMA approves an update to the SmPC for empagliflozin to include a change to the indication statement[2] — Jan 2017

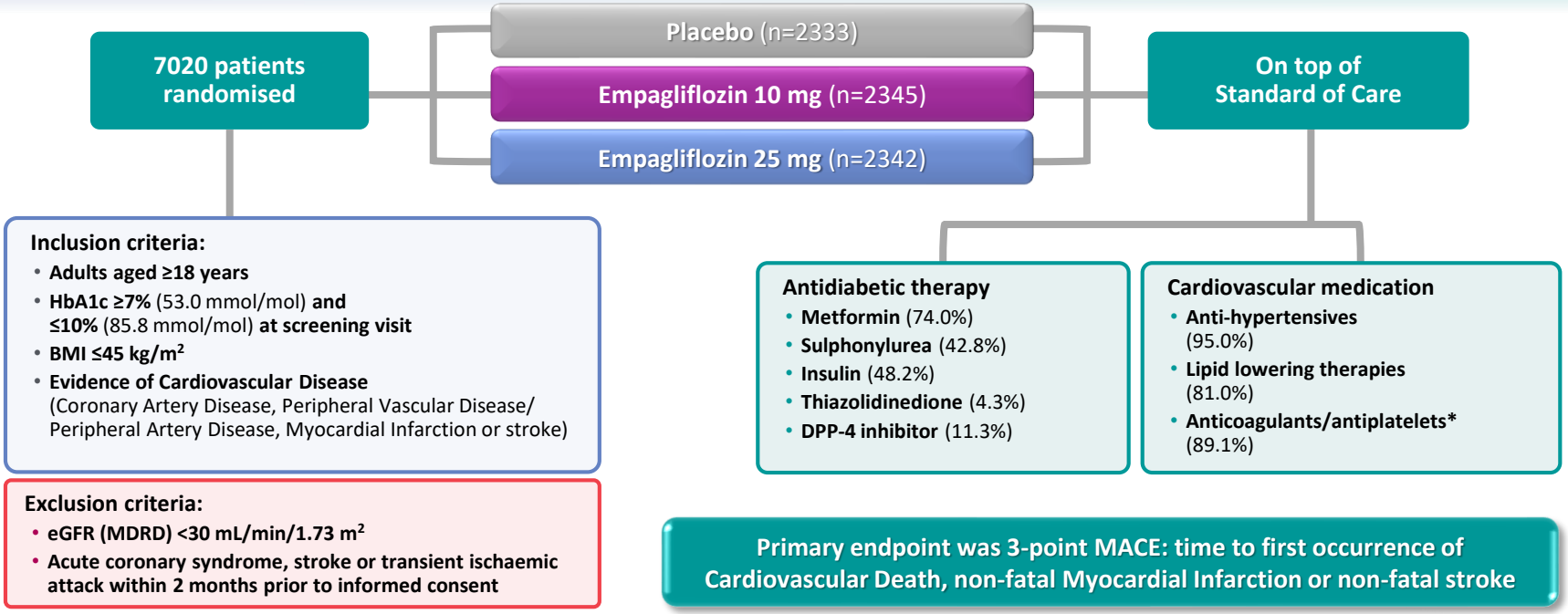
Addition of data on HHF and renal outcomes from EMPA-REG OUTCOME® to empagliflozin SmPC[2] — July 2018

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

1. Zinman B *et al. N Engl J Med*. **2015**;373:2117–2128; 2. Jardiance (empagliflozin) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/5441 (accessed October 2019).

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



Patients were followed for a median of 3.1 years.

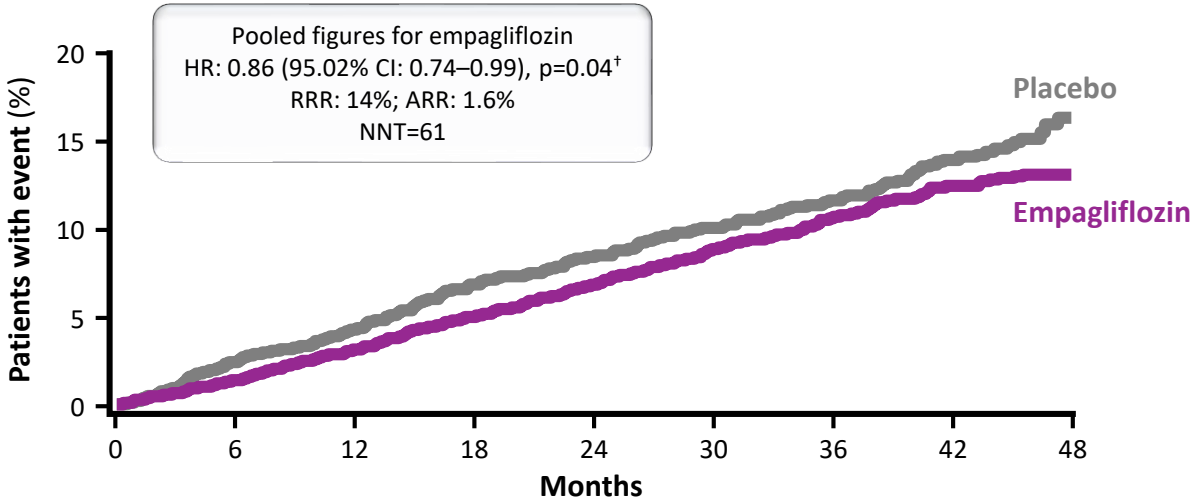
*82.7% on acetylsalicylic acid, 10.6% on clopidogrel, 6.0% on vitamin K antagonists.

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

Zinman B *et al. N Engl J Med*. **2015**;373:2117–2128 and supplementary appendix.

EMPA-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

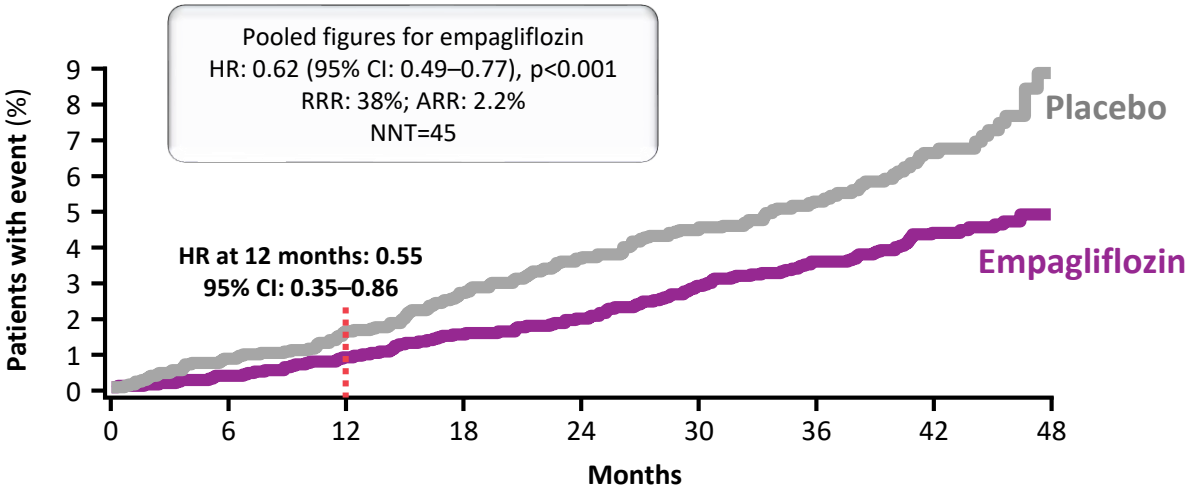


The reduction in the rate of 3P-MACE was driven by lower rates of death from Cardiovascular causes with empagliflozin vs placebo

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
Zinman B *et al. N Engl J Med.* **2015**;373:2117–2128.

EMPA-REG OUTCOME®: Cardiovascular Death

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



Reduction in Cardiovascular Death was early and sustained[2], and:

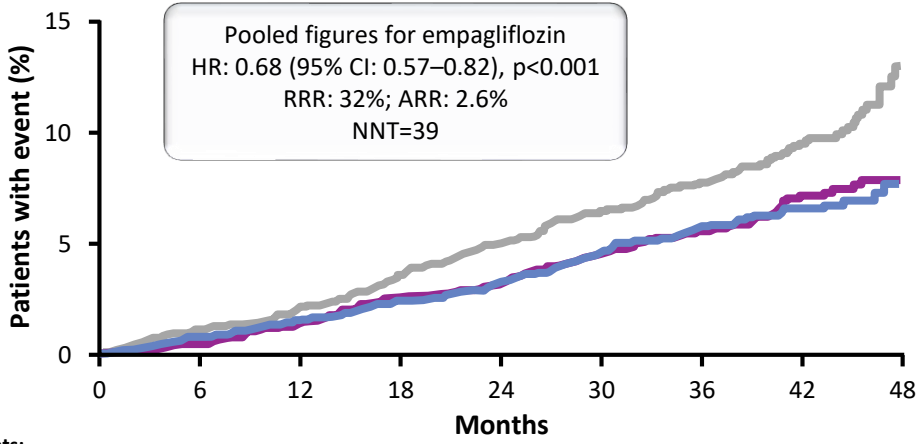
- Was generally consistent across baseline HbA1c[3]
- Was independent of changes in HbA1c during the trial[3]

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

1. Zinman B *et al. N Engl J Med*. **2015**;373:2117–2128; 2. Fitchett D *et al. J Am Coll Cardiol*. **2018**;71:364–367; 3. Inzucchi S *et al. Circulation*. **2018**;138:1904–1907.

EMPA-REG OUTCOME®: All-Cause Mortality

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



No. of patients:

Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Placebo

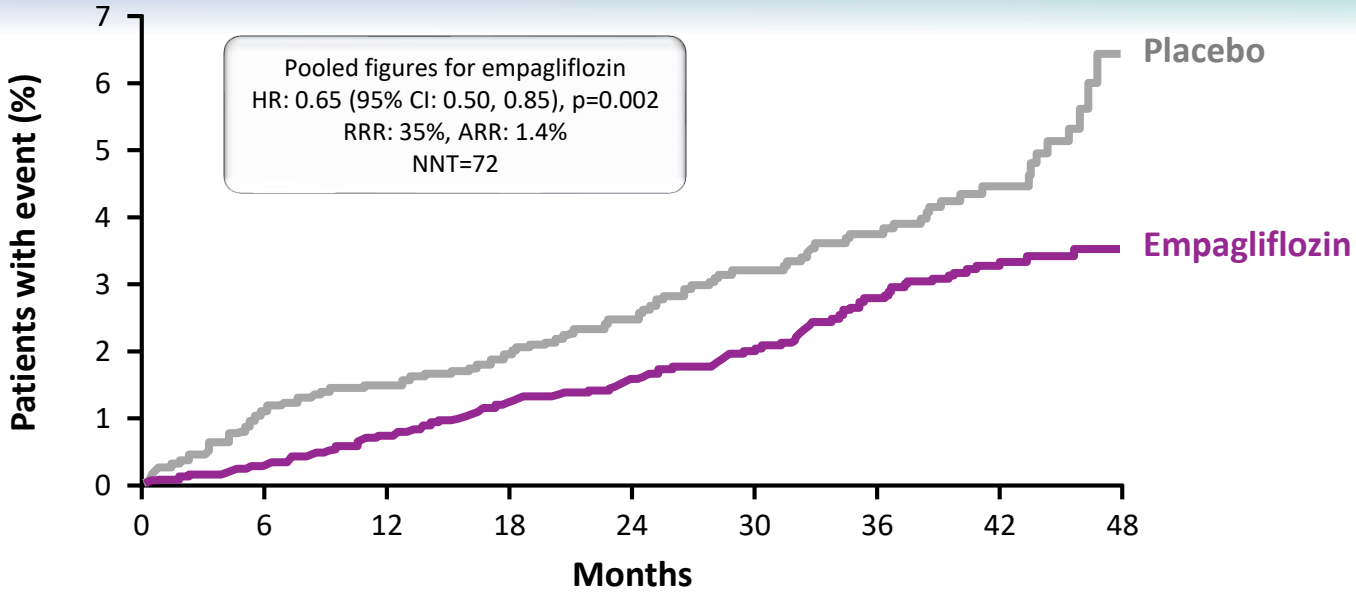
Empagliflozin 10 mg
HR 0.70
(95% CI: 0.56, 0.87)
p=0.001
RRR: 30%
ARR: 2.5%

Empagliflozin 25 mg
HR 0.67
(95% CI: 0.54, 0.83)
p<0.001
RRR: 33%
ARR: 2.7%

Both 10 mg and 25 mg doses of empagliflozin reduced risk of death from any cause vs placebo on top of Standard of Care

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
Zinman B *et al. N Engl J Med*. **2015**;373:2117–2128 and supplementary appendix.

EMPA-REG OUTCOME®: Hospitalisation for Heart Failure



No. of patients:									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

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

Zinman B, *et al. N Engl J Med.* **2015**;373:2117–2128.

EMPA-REG OUTCOME®: Cardiovascular Outcomes

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

Zinman B *et al. N Engl J Med*. **2015**;373:2117–2128.

Cardiovascular benefits seen with SGLT2 inhibitors

Primary safety endpoint: 3P-MACE	EMPA-REG OUTCOME empagliflozin[1]	CANVAS Program canagliflozin*[2]	DECLARE-TIMI 58 dapagliflozin*[3]
Major Adverse Cardiovascular Events	**>99%** Cardiovascular Disease (n=7020)	**65.6%**: Cardiovascular Disease (n=6656) **34.4%**: Multiple risk factors (n=3486)	**40.6%**: Cardiovascular Disease (n=6974) **59.4%**: Multiple risk factors (n=10,186)
Non-Inferiority	✓	✓	✓
Superiority	✓	✓	✗
1) Cardiovascular Death	✓	✗	✗
2) Non-fatal Myocardial Infarction	✗	✗	✗
3) Non-fatal Stroke	✗	✗	✗

✓ 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

1. Zinman B *et al. N Engl J Med*. **2015**;373:2117–2128; 2. Neal B *et al. N Engl J Med*. **2017**;377:644–657; 3. Wiviott SD *et al. N Engl J Med*. **2019**;380:347–357.

The Lancet. 2019; Volume 393

'[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…'

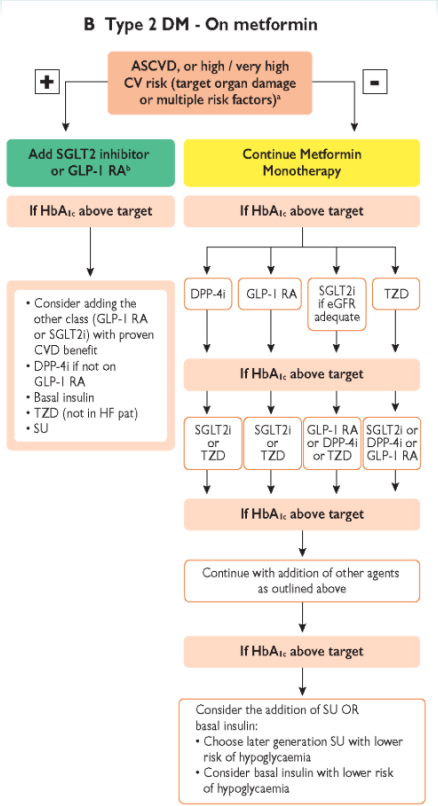
- Zelniker *et al*. performed a systematic review and meta-analysis of randomised, placebo-controlled, Cardiovascular Outcome Trials of SGLT2 inhibitors in patients with Type 2 Diabetes

SGLT2i: sodium–glucose co-transporter 2 inhibitor

Verma S, Jüni P, Mazer D. *Lancet*. **2019**;393:3–5. Comment on: Zelniker TA *et al. Lancet*. **2019**;393:31–39.

2019 ESC Guidelines on diabetes, pre-diabetes and Cardiovascular Disease

- 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**



ESC: European Society of Cardiology; GLP-1 RA: glucagon-like peptide 1 receptor agonist; SGLT2: sodium–glucose co-transporter 2

Cosentino F *et al. Eur Heart J.* **2019**. epub ahead of print. doi:10.1093/eurheartj/ehz486.

2019: ESC Guidelines on diabetes, pre-diabetes and Cardiovascular Disease – what's new (selected)

Change in recommendations 2013 to 2019

Glucose-lowering treatment	
Metformin should be considered as first-line therapy in patients with diabetes	Metformin should be considered in overweight patients with Type 2 Diabetes without Cardiovascular Disease and at moderate Cardiovascular risk

New recommendations in 2019

Glucose-lowering treatment
Empagliflozin, canagliflozin or dapagliflozin are recommended in patients with Type 2 Diabetes and Cardiovascular Disease, or at very high/high Cardiovascular risk, to reduce Cardiovascular events
Empagliflozin is recommended in patients with Type 2 Diabetes and Cardiovascular Disease to reduce the risk of death
Liraglutide, semaglutide or dulaglutide are recommended in patients with Type 2 Diabetes and Cardiovascular Disease, or at very high/high Cardiovascular risk, to reduce Cardiovascular events
Liraglutide is recommended in patients with Type 2 Diabetes and Cardiovascular Disease, or at very high/high Cardiovascular risk, to reduce this risk of death
Saxaglitpin is not recommended in patients with Type 2 Diabetes and a high risk of Heart Failure

Diabetes treatment to reduce Heart Failure risk
SGLT2 inhibitors (empagliflozin, canagliflozin or dapagliflozin) are recommended to lower risk of Heart Failure hospitalisation
Metformin should be considered in patients with diabetes and Heart Failure if eGFR >30 ml/min/1.73 m^2
GLP-1 RAs and DPP-4 inhibitors sitagliptin and linagliptin have a neutral effect on risk of Heart Failure and may be considered
Insulin treatment in Heart Failure may be considered
DPP-4 inhibitor saxagliptin in Heart Failure is not recommended
Thiazolidinediones (pioglitazone and rosiglitazone) in Heart Failure are not recommended
Management of chronic kidney disease
SGLT2 inhibitors are recommended to reduce the progression of diabetic kidney disease

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

Adapted from: Cosentino F *et al. Eur Heart J*. **2019**. epub ahead of print. doi:10.1093/eurheartj/ehz486.

EMPA-REG OUTCOME®: safety

Specific adverse events

Specific adverse events[1]	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
	n (%)	**n** (%)	**n** (%)
Diabetic ketoacidosis*	1 (<0.1)	3 (0.1)	1 (<0.1)
Acute renal failure†‡	155 (6.6)	121 (5.2)	125 (5.3)
Event consistent with volume depletion§	115 (4.9)	115 (4.9)	124 (5.3)
Thromboembolic event‖	20 (0.9)	9 (0.4)	21 (0.9)
Bone fractures¶	91 (3.9)	92 (3.9)	87 (3.7)

Note: in patients aged 75 years and older, an increased risk for volume depletion should be taken into account[2]

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.[2]

Patients should be advised on the symptoms and need to seek medical attention. Please refer to the Jardiance SmPC for further information.[2]

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
1. Zinman B *et al. N Engl J Med.* **2015**;373:2117–2128.
2. Jardiance (empagliflozin) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/5441 (accessed October 2019).

EMPA-REG OUTCOME®: safety

Urinary tract and genital infection

Specific adverse events	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
	n (%)	**n** (%)	**n** (%)
Event consistent with urinary tract infection*	423 (18.1)	426 (18.2)	416 (17.8)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)
Female patients†	265 (40.6)	246 (35.5)	246 (37.3)
Event consistent with genital infection‡§	42 (1.8)	153 (6.5)	148 (6.3)
Male patients	25 (1.5)	89 (5.4)	77 (4.6)
Female patients	17 (2.6)	64 (9.2)	71 (10.8)

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
Zinman B *et al. N Engl J Med.* **2015**;373:2117–2128.

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 m^2, dose should be adjusted or maintained at 10 mg
- Empagliflozin should not be initiated in patients with eGFR <60 mL/min/1.73 m^2 and should be discontinued when eGFR is persistently <45 mL/min/1.73 m^2
- 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 m^2.
eGFR: estimated glomerular filtration rate
Jardiance (empagliflozin) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/5441 (accessed October 2019).

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/m^2
- eGFR: 72 ml/min/1.73 m^2
- 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/m^2**
- **eGFR: 65 ml/min/1.73 m^2**
- **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
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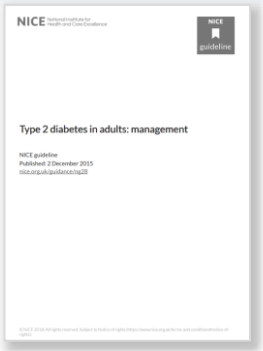
How could we have managed this patient?

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

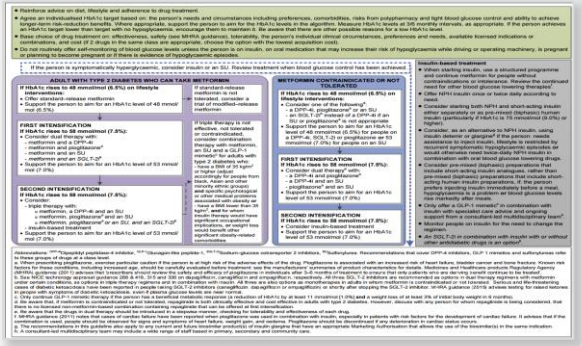

NICE

Type 2 diabetes in adults: management

NICE guideline

Published 2 December 2015

nice.org.uk/guidance/ng28



Dec 2015

May 2017

2020

NG28 published

NG28 updated

NG28: review due (new guidance TBC)

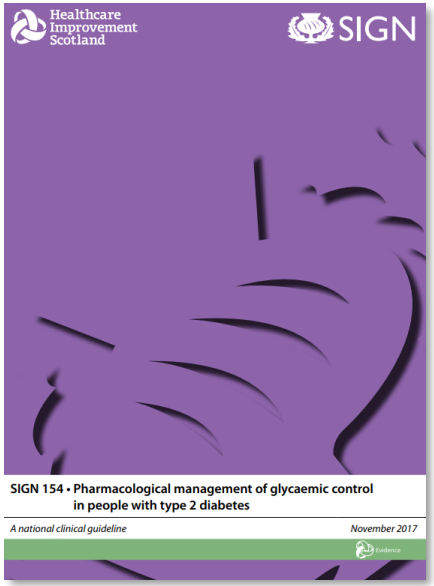
NICE guidance is prepared for the National Health Service in England and is subject to regular review and may be updated or withdrawn.

NG: NICE guideline

NICE Guideline 28. Type 2 diabetes in adults: management. December 2015 (last updated August 2019). Available at: www.nice.org.uk/guidance/ng28 (accessed October 2019).

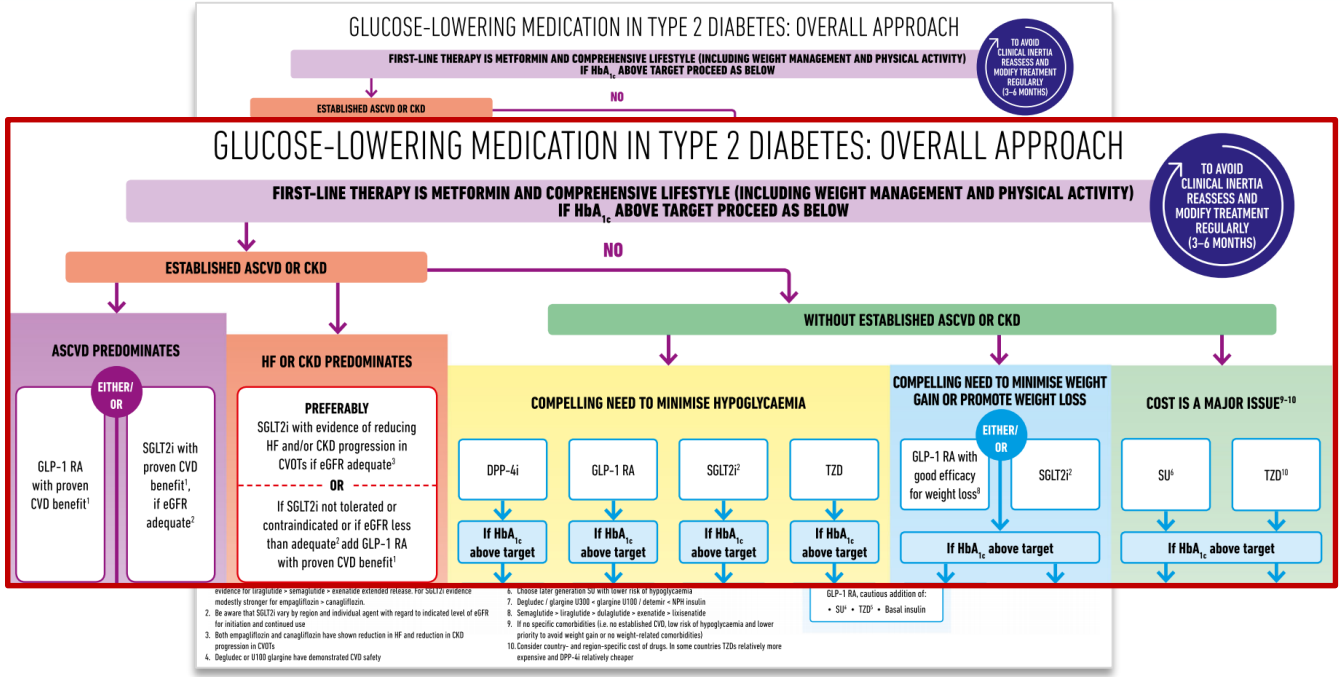
Clinical practice in the UK, 2017: SIGN Guideline 154 issued incorporating Cardiovascular Outcome Trial Data

- 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
SIGN 154. Pharmacological management of glycaemic control in people with Type 2 Diabetes. November 2017. Available at: www.sign.ac.uk/assets/sign154.pdf (accessed October 2019).

ADA/EASD, 2018: consensus report published incorporating Cardiovascular Outcome Trial Data

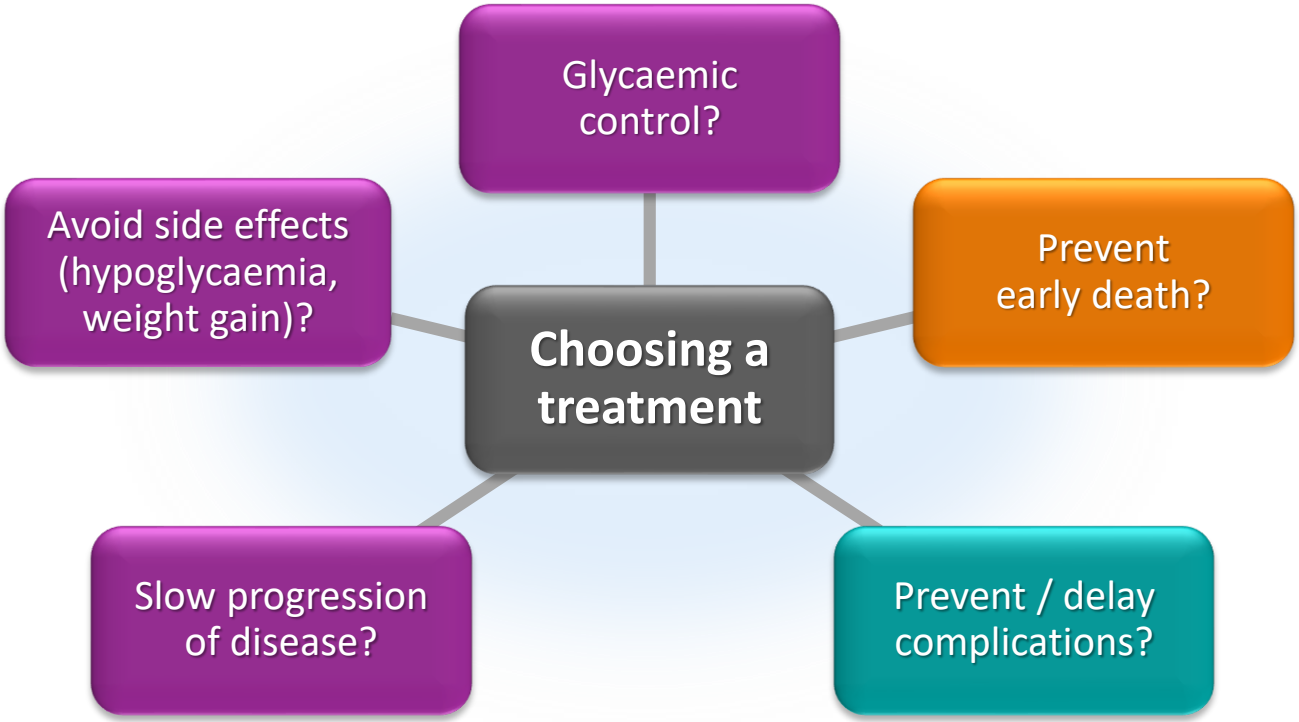


SGLT2 inhibitors are not indicated for the treatment of kidney disease or the treatment of heart failure.

ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes

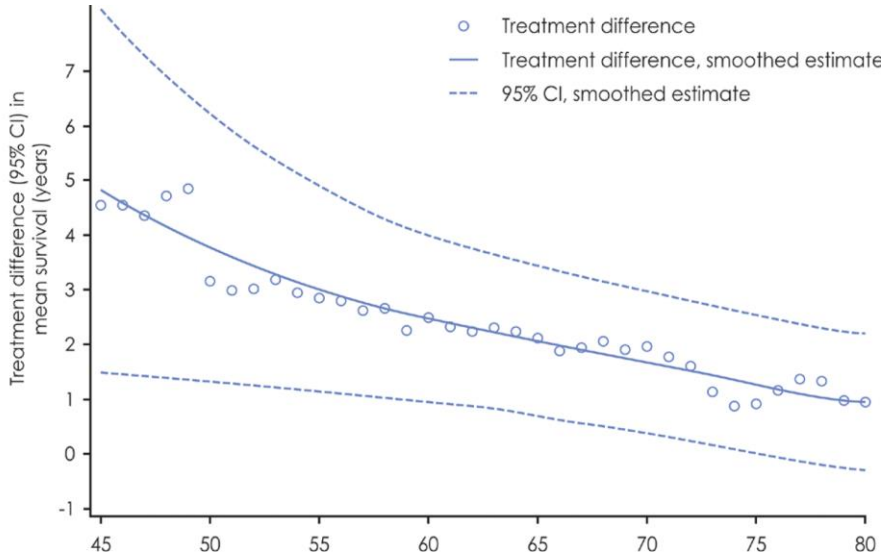
Davies MJ et al. *Diabetologia*. **2018**;61:2461–2498.

What are we trying to achieve when we decide on a treatment option for our patient?



What do these data mean for patients?

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



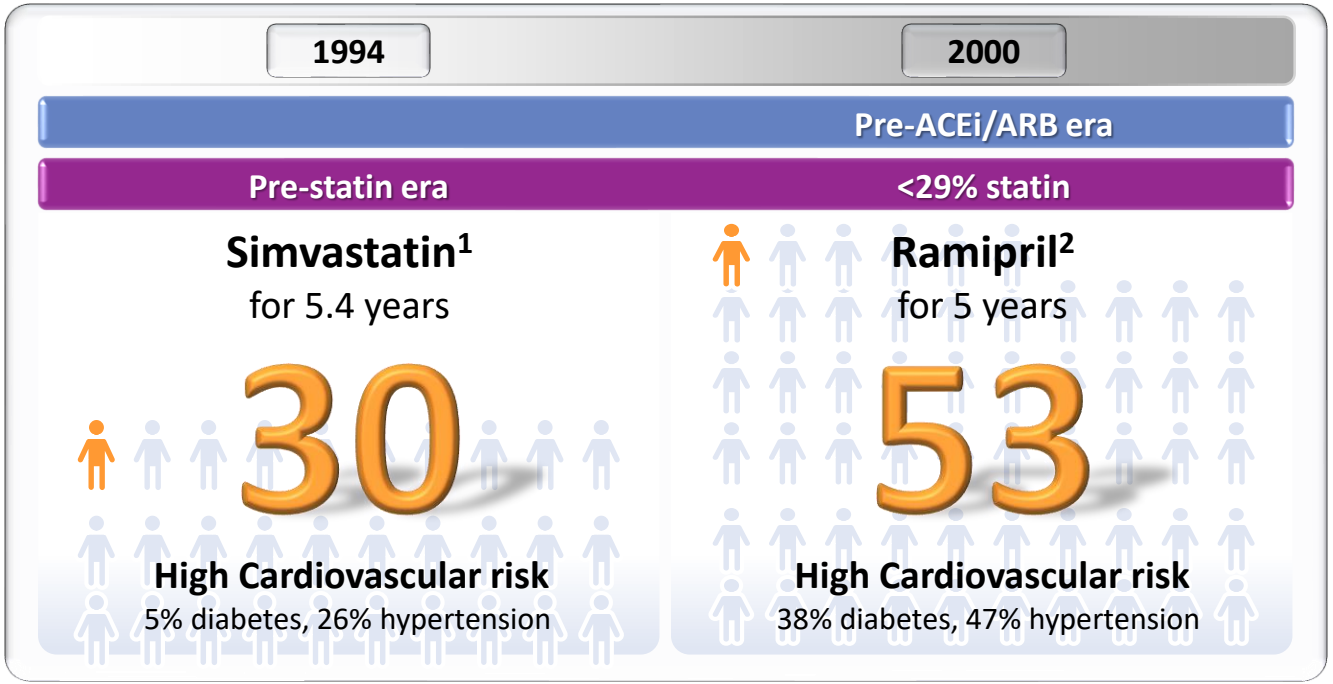
A 45-year-old patient with Type 2 Diabetes and Cardiovascular Disease could gain 4.5 years of life with empagliflozin

A 60-year-old could gain 3.1 years

CI: confidence interval

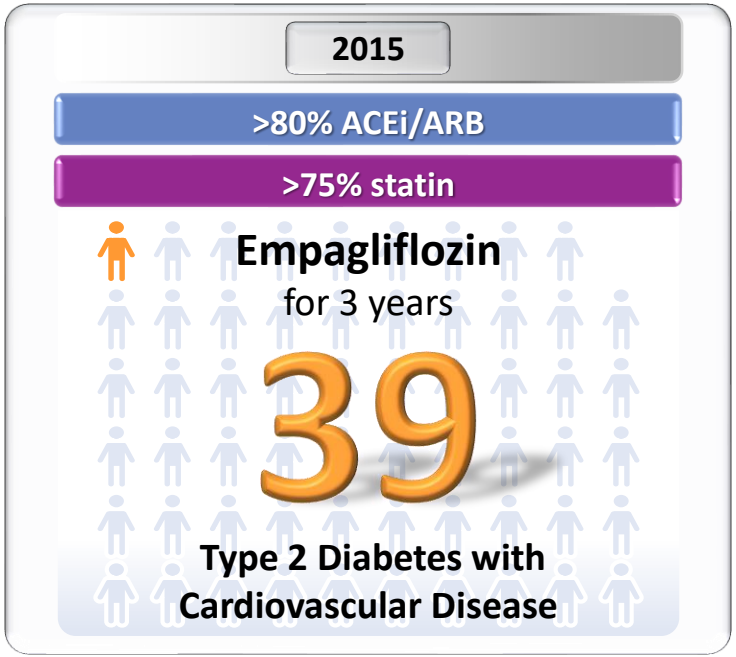
Claggett B *et al. Circulation*. **2018**;138:1599–1601.

Number needed to treat to prevent one death in landmark trials in patients with high Cardiovascular risk



Absolute risk reduction cannot be compared directly across different trials.
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker
1. 4S investigators. *Lancet*. **1994**;344:1383–1389; 2. HOPE investigators. *N Engl J Med*. **2000**;342:145–153.

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

Zinman B *et al. N Engl J Med*. **2015**;373:2117–2128 and supplementary appendix.

Summary

- 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

Healthcare Improvement Scotland | SIGN Evidence-based clinical guidelines

American Diabetes Association®

EASD European Association for the Study of Diabetes

ESC European Society of Cardiology

Is it time to think beyond HbA1c to tackle Cardiovascular morbidity and mortality in our patients with Type 2 Diabetes?

Prescribing Information (UK) JARDIANCE® (empagliflozin)

JARDIANCE® (empagliflozin)
Film-coated tablets containing 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 eGFR ≥ 60 ml/min/1.73 m^2 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 m^2 or CrCl ≥60 ml/min. Do not initiate in patients with an eGFR <60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m^2 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 m^2 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 the patient remembers; however, a double dose should not be taken on the same day. **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, including empagliflozin. 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 preferred to urine. Treatment with empagliflozin may be restarted when the 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. Haematocrit 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 anti hypertensive 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 Fournier's gangrene is suspected, Jardiance should be discontinued and prompt treatment should be instituted. An increase 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 footcare. Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies 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-treatment with known inducers of UGT enzymes 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, torasemide 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 (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), 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, haematocrit increased. Rare: DKA. Not known: necrotising fasciitis of the perineum (Fournier's gangrene), angioedema. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 10 mg; 28 tablets £36.59, 25 mg: 28 tablets £36.59. **Legal category:** POM. **MA numbers:** 10 mg/28 tablets EU/1/14/930/013; 25 mg/28 tablets EU/1/14/930/004. **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).