West Yorkshire Healthy Hearts

Improving CVD outcomes in diabetic patients

Background Information

West Yorkshire Health and Care Partnership

Yorkshire & Humber AHSN

West Yorkshire and Harrogate
HEALTHY HEARTS

Improving CVD outcomes in diabetic patients
Clinical Rationale Background Document

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Summary

- Cardiovascular disease (CVD) is a major complication and the most common cause of death in adults with type 2 diabetes.

- CV death accounts for 52% of deaths in type 2 diabetes. Diabetes increases the risk of CVD by nearly 50% (reference: National Diabetes Audit UK 2012). Patients with diabetes are two and half times more likely to develop heart failure.

- Sodium-glucose co-transporter-2 inhibitor (SGLT2i) therapies have robust evidence for significantly reducing CVD outcomes in people with type 2 Diabetes who have either established CVD or are at risk of developing CVD.

1. Introduction

1.1. Cardiovascular disease is a major complication and the most common cause of death in adults with type 2 diabetes. CV death accounts for 52% of deaths in type 2 diabetes1 and patients with diabetes are two and half times more likely to develop heart failure[2]. Diabetes increases the risk of CVD by nearly 50% (reference, National Diabetes Audit, 2012)

1.2. Sodium/glucose cotransporter-2 inhibitors (SGLT2i) are a new type of glucose-lowering drug that can reduce blood glucose by inhibiting its reabsorption in proximal tubules and by promoting urinary glucose excretion. Evidence shows that they can lower HBA1c levels significantly, reduce weight and lower blood pressure[3]

1.3. Cardiovascular disease (CVD), including heart failure (HF), is a leading cause of morbidity and mortality in people with type 2 diabetes mellitus (T2DM). CVD and T2DM share common risk factors for development and progression, and there is significant overlap between the conditions in terms of worsening outcomes. In assessing the cardiovascular (CV) profiles of anti-diabetic drugs, sodium-glucose co-transporter-2 inhibitor (SGLT2i) therapies have emerged with robust evidence for significantly reducing the risk of adverse CVD outcomes in people with T2DM who have either established CVD or are at risk of developing CVD. [4]

1.4. There have been four major trials on SGLT2 inhibitors:

- EMPA-REG[5] (Empagliflozin)
- DECLARE–TIMI 58[6] (Dapagliflozin)
- CREDENCE[7] (Canagliflozin)
- CANVAS[8] (Canagliflozin)

1.5. These trials show various benefits for each of the SGLT2i across key areas, with Empagliflozin particularly showing good outcomes across all-cause mortality, CVD mortality, MI, stroke and Heart Failure hospitalisation (see page 10)

[1] https://journals.lww.com/cardiovascularendocrinology/Fulltext/2017/03000/Epidemiology_in_diabetes_mellitus_and.4.aspx
[2] https://www.ncbi.nlm.nih.gov/pubmed/15277411
[3] https://care.diabetesjournals.org/content/37/6/1650
[4] https://link.springer.com/article/10.1007%2Fs13300-019-0657-8
[5] https://www.nejm.org/doi/full/10.1056/NEJMoa1504720
[6] https://www.thelancet.com/journals/landia/article/PIIS2213-8587(19)30180-9/fulltext
[7] https://www.nejm.org/doi/full/10.1056/NEJMoa1811744
[8] https://www.nejm.org/doi/full/10.1056/NEJMoa1611925

2. Brief Background / Context

2.1. The West Yorkshire and Harrogate Healthy Hearts project met with key stakeholders across Primary, Community and Secondary Care (26th February 2020) to scope phase three of the project – improving CVD outcomes in Diabetes patients.

2.2. Discussion on the evidence for cardiometabolic drugs was presented[9] by Dr Rob Sapsford – Cardiologist (Leeds Teaching Hospitals NHS Trust) and Professor Stephen Wheatcroft - Professor of Cardiometabolic Medicine (University of Leeds) / Consultant Cardiologist (Leeds Teaching Hospitals NHS Trust).

2.3. Agreement was reached that it would be of benefit to Primary Care to develop simple treatment guidance, similar to that developed for Hypertension and Cholesterol as part of WY&H Healthy Hearts and adapted from the work that has started to be developed in Leeds and other regions across the country.

2.4. A follow up meeting was arranged with representation from across Primary, Community and Secondary Care (18th December) to agree the treatment guidance. This will then be subject to robust governance through West Yorkshire and Harrogate in order to gain sign off.

3. Evidence

3.1. The evidence on the clinical effectiveness and safety of SGL2Ti has been increasing both internationally and nationally. These include randomised control trials, meta-analyses and evidence reviews. NICE have also carried out a number of reviews. One of the most significant trials is EMPA-REG.

3.2. *EMPA-REG, a large randomised controlled study…investigates empagliflozin compared with placebo on cardiovascular morbidity and mortality in people with type 2 diabetes at high risk for cardiovascular events who were receiving standard care …The results of this trial showed a showed a significant reduction in cardiovascular and all-cause mortality Based on extrapolation of EMPA-REG OUTCOME trial data using a participant-level simulation model, empagliflozin in addition to standard of care is projected to be highly cost-effective using UK healthcare costs*.[10]

3.3. Cardiovascular risk reduction using various drug interventions shows SGLT2i also as an effective method in terms of numbers needed to treat.

Table 1 CVD Risk Reduction from various drugs - Source Professor Stephen Wheatcroft (Leeds Teaching Hospitals NHS Trust)

[9] Diabetes Scoping Event Feb 20 FINAL.pptx
[10] https://www.ncbi.nlm.nih.gov/pubmed/31295358

Option	Intervention	Trial	Number needed to treat to prevent one death
Statins	Simvastatin for 5.4 years	4S	30
ACE inhibitors	Ramipril for 5 years	HOPE	53
SGLT2i	Empagliflozin for 3 years	EMPA-REG	39
GLP1 RA	Liraglutide for 3.8 years	LEADER	71

4. NICE Guidance

4.1. NICE have conducted various reviews of the evidence, with SGL2i being referenced in numerous guidance documents including (but not limited to):

- Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes Technology appraisal guidance [TA390] May 2016
- Empagliflozin in combination therapy for treating type 2 diabetes Technology appraisal guidance [TA336] March 2015
- Type 2 diabetes in adults: management Evidence reviews for SGLT-2 inhibitors and GLP-1 mimetics NICE guideline NG28 Evidence reviews March 2018

NG28 included a detailed assessment of the CVD data for SGLT2is. "The committee highlighted that in previous years, diabetes management was driven by the prescription of drugs on the basis of HbA1c benefits. However, diabetes management is now moving towards the prescription of drugs based on cardiovascular benefits"

NICE does recommend the use of SGLT2is as a second-line agent if HbA1c remains >58 with metformin

4.2. The current NICE guidance on SGLT2i is as follows:

4.3. Canagliflozin, dapagliflozin and empagliflozin as monotherapies are recommended as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- *a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and*
- *a sulfonylurea or pioglitazone is not appropriate.*11

4.4. Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- *a sulfonylurea is contraindicated or not tolerated, or*
- *the person is at significant risk of hypoglycaemia or its consequences.*

11 https://www.nice.org.uk/guidance/ta390/chapter/1-Recommendations

4.5. Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

4.6. metformin and a sulfonylurea or metformin and a thiazolidinedione.

4.7. *Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.*[12]

[12] https://www.nice.org.uk/guidance/ta336/chapter/1-Guidance

5. European Society Guidance

5.1. The European Society of Cardiology (ESC) (in collaboration with the European Association for the Study of Diabetes (EASD)) produced new guidelines in 201913 which have taken into account the CVD trials on SGLT2i and issued clear evidence-based guidance on their role in CVD prevention. The following recommendations are made in the new ESC guidelines

Glucose-lowering treatment
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or very high/high CV risk, to reduce CV events
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce the risk of death
Saxagliptin is not recommended in patients with T2DM and a high risk of HF

5.2. The recommendation on the use of Empagliflozin is concluded from the EMPA-REG trial evidence, and ESC interpretation is as follows:

In EMPA-REG OUTCOME….Empagliflozin significantly reduced the risk of the three-point composite primary outcome (CV death, non-fatal MI, or non-fatal stroke) by 14% compared with placebo. This reduction was driven mainly by a highly significant ***38% reduction in CV death*** *(P < 0.0001), with separation of the empagliflozin and placebo arms evident as early as 2 months into the trial. In a secondary analysis, empagliflozin was associated with a* ***35% reduction in hospitalization for HF*** *(P < 0.002), with separation of the empagliflozin and placebo groups evident almost immediately after treatment initiation, suggesting a very early effect on HF risk. Empagliflozin also* ***reduced overall mortality by 32%*** *(P < 0.0001), a highly significant effect, translating into a number needed to treat of 39 over 3 years to prevent one death*.

For the first time in the history of DM, we have data from several "Cardiovascular Outcome Trials" (CVOTs) that indicate CV benefits from the use of glucose-lowering drugs in patients with CVD or at very high/high CV risk. The recommendation for empagliflozin is supported by a recent meta-analysis which found high heterogeneity between CVOTs in mortality reduction. [I.e. each SGLT2i has different results]

6. Cost Effectiveness

6.1. There have been numerous evaluations on the cost effectiveness of SGLT2i. Cost effectiveness of SGLT2 inhibitors has been demonstrated by NICE through technology appraisals. NICE in 2018 suspended their planned appraisal of "Empagliflozin for reducing the risk of cardiovascular events in type 2 diabetes". They state 'Empaglifozin is already recommended for people with type 2 diabetes (TA336) and the population for which this additional appraisal would be aimed at (poorly controlled diabetes plus cardiovascular risk) is already included in the population previously appraised14.

6.2. However, in one cost effectiveness evaluation the use of empagliflozin was shown to have a positive cost effectiveness ratio:

[13] https://academic.oup.com/eurheartj/article/41/2/255/5556890#191172082
[14] https://www.nice.org.uk/guidance/indevelopment/gid-ta10177

6.3. The model predicted an 18% relative increase (by 2.1 life-years) in survival for empagliflozin (14.0 life-years) vs. standard of care (11.9 life-years), attributable to direct treatment effect on cardiovascular mortality, and to indirect effect via reductions in other events. Participants treated with empagliflozin may experience improved quality of life (1.0 QALY) … yielding an incremental cost-effectiveness ratio (ICER) of £4083/QALY15.

7. Rationale for the Local Clinical Guidance

Although there have been numerous trials and studies on SGLT2i, it is not always clear to health professionals which is the most appropriate drug for an individual or a particular group of patients.

7.1. The [NICE] committee agreed that evidence showed a clinically significant reduction in cardiovascular and all-cause mortality with empagliflozin but not with canagliflozin. Therefore, benefits on cardiovascular and all-cause mortality cannot be assumed for all SGLT-2 inhibitors as a class until more evidence is available.

7.2. *The committee [also] agreed that …. historically, the focus has been on glucose control. The committee agreed that, of all the antidiabetic drugs and combination of drugs, healthcare professionals and patients do not know which drug or combination of drugs is best at improving macrovascular [heart attacks and strokes] and microvascular outcomes [eye, kidney and foot disease]*.[16]

7.3. In addition to this, across each of the CCGs within West Yorkshire and Harrogate, there are no consistent prescribing recommendations for SGLT2i. *Appendix 2 - SGLT 2 Formulary choices in West Yorkshire* shows the current prescribing recommendations for SGLT2i.

7.4. This highlights the need to create local treatment guidance which, similar to the work already conducted on the West Yorkshire and Harrogate Healthy Hearts project for Hypertension and Cholesterol, has proved welcome.

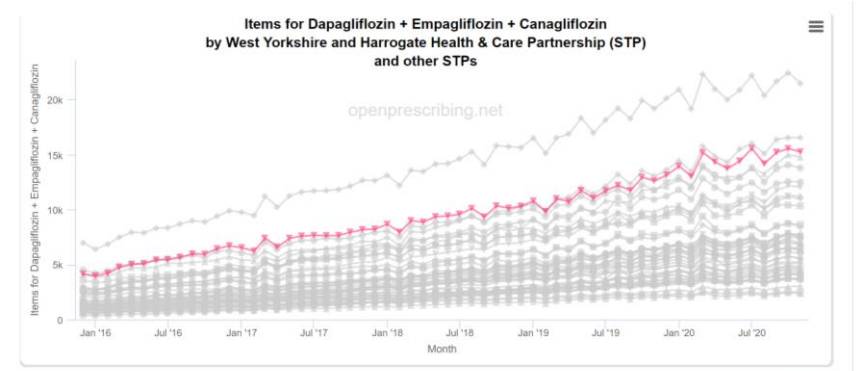
7.5. This treatment guidance will be targeted at specific patient cohorts – for example, those who are going on to a second line drug with HBA1c levels >58- 75 . This will be achieved by creating clinical searches to help Primary Care identify only suitable patients for this treatment regime. A list of the inclusion and exclusion criteria can be found (Appendix 2)

7.6. A copy of the draft treatment guidance can be found Appendix A. This will be taken through the appropriate clinical governance routes across West Yorkshire and Harrogate in order to gain sign off. As with previously developed guidance – clinical discretion can always be used.

[15] https://pubmed.ncbi.nlm.nih.gov/31295358/
[16] https://www.nice.org.uk/guidance/ng28/evidence/march-2018-evidence-reviews-for-sglt2-inhibitors-and-glp1-mimetics-pdf-4783687597

8. Current Local Prescribing

8.1. Current prescribing of SGLT2i is increasing, and across WY&H it is the third highest of all STPs[17] across the country, with Leeds CCG and Bradford and Craven CCG having higher prescribing numbers[18] – reflecting population sizes. However, further work to improve CVD outcomes in diabetes patients is needed and so the further use of SGLT2i is considered an important strategy to achieve this objective.



Total prescribing for *Dapagliflozin + Empagliflozin + Canagliflozin* across West Yorkshire and Harrogate Health & Care Partnership (STP)

	Nov '20	Financial YTD (Apr—Nov '20)	Last 12 months (Dec '19—Nov '20)
Cost (£)	555,907	4,316,230	6,374,984
Items	15,237	118,136	173,397

Figure 1 - SGLT2i prescribing by STP - source www.openprescribing.net

Table 2 - Figure 2 - Figure 1 - SGLT2i item prescribing by CCG - source www.openprescribing.net

	2015	2016	2017	2018	2019	2020
NHS BRADFORD DISTRICT AND CRAVEN CCG	1060	1812	22539	27412	32755	39813
NHS CALDERDALE CCG	505	7735	10927	12591	15185	16713
NHS GREATER HUDDERSFIELD CCG	266	4155	7187	9630	11898	12275
NHS LEEDS CCG	1229	17750	23633	31310	41465	50399
NHS NORTH KIRKLEES CCG	550	8579	11705	14452	16302	16867
NHS WAKEFIELD CCG	533	8254	12999	17597	21785	24191
Grand Total	**4143**	**64595**	**88990**	**112992**	**139390**	**160258**

[17] https://openprescribing.net/analyse/#org=stp&orgIds=E54000005&numIds=0601023AN,0601023AG,0601023AM,0601023AR,0601023AL,0601023AP&denom=nothing&selectedTab=map

[18] https://openprescribing.net/analyse/#org=CCG&orgIds=03J,15F,02W,02R,03R,03E,02T,03A,02N&numIds=0601023AN,0601023AG,0601023AM,0601023AR,0601023AL,0601023AP&denom=nothing&selectedTab=chart

9. Clinical Searches

In order to target the most appropriate patients for the locally developed treatment guidance, a number of clinical searches have been developed based on a safety and clinical effectiveness. These searches will also help ensure that Primary Care are not overwhelmed with high numbers of patients and can therefore target those with the greatest risk. Existing treatment guidance and care will therefore apply to any patients outside of the following criteria.

Inclusion criteria:

- Type 2 Diabetes with existing CVD or high / very high risk of CVD
- No history of PAD / Lower limb amputation
- Age: 40-79 (the expert advisory committee suggested avoiding prescribing in younger patients who were more likely to have type 1 diabetes and suggested avoiding routine searches in the elderly since this group was less represented in the studies and there would be an increased risk of polypharmacy and frailty. Standard medical care would remain for these age groups, as would individual clinician discretion)
- HBa1c: 58-75mmol
- On Metformin and/or 2-3 agents – Excluding Insulin
- eGfr:60+
- Excluding all Amber and Red clinical situations (see Appendix 2)

10. Author

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- Primary Care Lead, National Rapid Uptake Products (RUP) programme for Lipid Management, NHS England & Accelerated Access Collaborative
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Appendix 1 - EMPA REG Trial – Graphs and Tables

Table 3 - All cause mortality

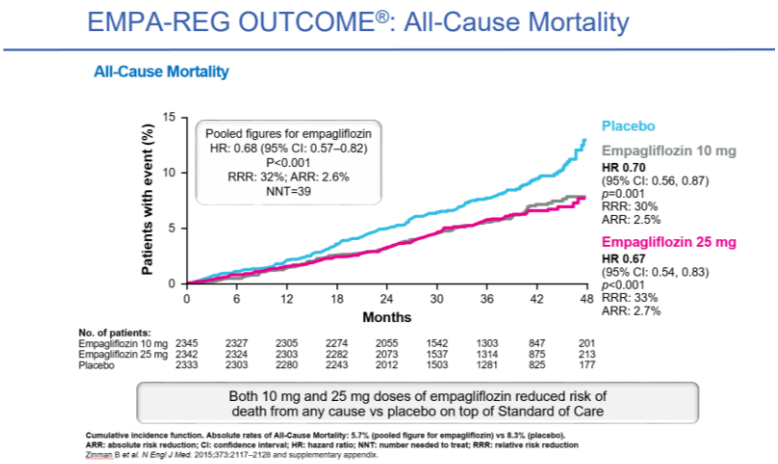


Table 4 - Cardiovascular Death

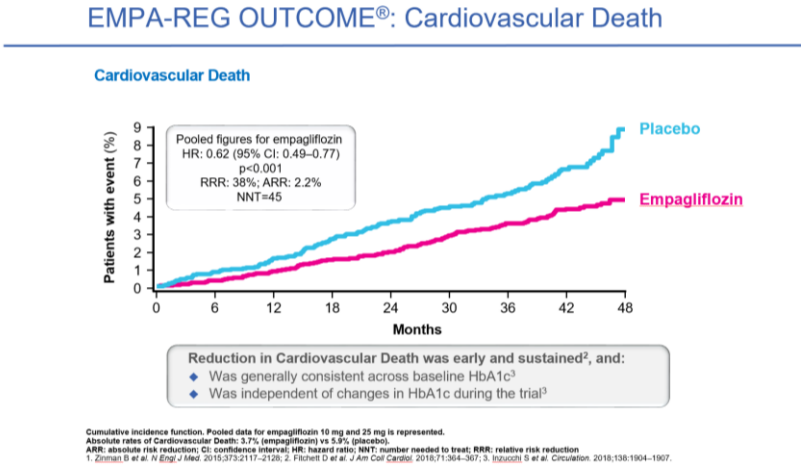
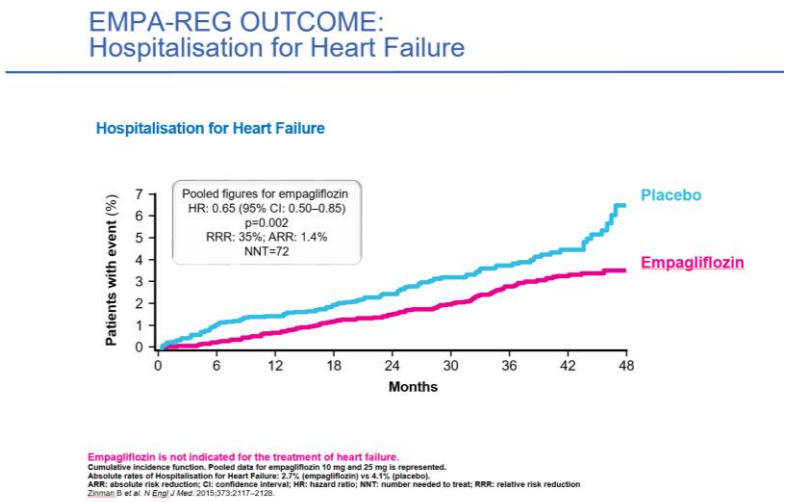


Table 5 - Heart Failure Hospitalisation



Appendix 2 - Prescribing Safety – Clinical Situations

The following tables are taken from the SGLT2i Prescribing Tool which has been prepared by the UK Improving Diabetes Steering Committee. To see the full document please see https://adisjournals.figshare.com/articles/dataset/SGLT2_Inhibitors_in_Type_2_Diabetes_Management_Key_Evidence_and_Implications_for_Clinical_Practice/6621683?file=24683327

- T2DM
- Age: above 40-80
- HBa1c = 58-75
- On Metformin and/or 2-3 agents (BNF groups of Diabetes) Exclude Insulin
- eGfr – 60+
- Include Red (do not prescribe below)

Do not prescribe SGLT2i

Clinical Situation	**Potential Implications**
Stage 3 CKD/eGFR <60 mL/min/1.73m2	Outside of licensed indication
DKA (or previous episode of DKA)	DKA risk
Eating disorders	DKA risk
Rapid progression to insulin (within 1 year)	DKA risk
Latent autoimmune diabetes	DKA risk
Excessive alcohol intake	DKA risk/outside of licensed indication
Diabetes due to pancreatic disease	DKA risk/outside of licensed indication
Genetic diabetes	Outside of licensed indication
Acute illness	Outside of licensed indication
Pregnancy (or suspected pregnancy), planning pregnancy or breastfeeding	Outside of licensed indication
Recent major surgery	Outside of licensed indication
Past history of necrotising fasciitis of the perineum (Fournier's gangrene)	Fournier’s gangrene risk

Appendix 2 - SGLT 2 Formulary choices in West Yorkshire

CCG	1st choice	2nd choice
Bradford Districts and Craven	Canagloflozin Empagloflozin	None listed
Calderdale (CHFT)	Ertugloflozin	Dapagloflozin Canagloflozin Empagloflozin
Greater Huddersfield	No information available	No information available
Kirklees	No information available	No information available
Harrogate	Dapagloflozin Canagloflozin Empagloflozin Ertugloflozin (no preference)	
Leeds	Empagloflozin	None listed
Wakefield (MYHT)	Dapagloflozin Canagloflozin Empagloflozin Ertugloflozin (no preference)	

Correct as of 6/3/2020 Complied by Tracey Gaston (Head of Optimisation – NHS Bradford District and Carven CCG)