Implementing the new NICE guidelines for type 2 diabetes (NG28): Focusing beyond HbA_{1c} targets and clinically phenotyping patients to the appropriate second-line agent

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Abstract

A significant number of cardiovascular outcome trials have been published to support decision-making regarding treatment options after or alongside metformin in people with type 2 diabetes (T2DM), specifically targeting prevention of adverse cardiovascular and renal outcomes. The latest NICE guidelines recommend the use of sodium-glucose transport inhibitors (SGLT2i) in patients with cardiovascular diseases, heart failure and chronic kidney disease with diabetes and recommends the use of glucagon-like polypeptide receptor agonists (GLP-1RA) only in a selected group of patients. A comprehensive summary of the various trials, structured around patient characteristics and clinical outcomes, can help to compare the various classes of drugs and drugs within the class. Since the drug acquisition cost within a class is generally the same in the UK, the drug with the best available evidence in the class should be chosen to maximise clinical benefit for the patient. Clinical phenotyping, a process of aligning a patient to the inclusion criteria and the desired clinical outcomes of a trial, can guide the choice of the best drug within a class.

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Introduction and methods

The management of type 2 diabetes (T2DM) should now include strategies to reduce adverse cardiovascular and renal outcomes concurrently alongside management of HbA_{1c}. There is an overwhelming evidence base available in patients with established atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) and chronic kidney disease (CKD) demonstrating reduction of significant clinical outcomes: major adverse cardiovascular events (MACE-cardiovascular deaths, non-fatal strokes or non-fatal myocardial infarction), hospitalisation for heart failure (hHF) and progression of CKD. The Association of British Clinical Diabetologists (ABCD) has published a comprehensive summary of the relevant cardiovascular outcome trials (CVOTs), dedicated CKD and HF trials in people taking glucagon-like polypeptide receptor agonists (GLP-1RA), sodium-glucose co-transporter inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP-4i) drugs.[1] The recently published National Institute for health and Care Excellence (NICE) guidelines on type 2 diabetes (NG28) recommends: "at any stage after they have started first-line treatment, if they have or develop chronic heart failure or established ASCVD, offer an SGLT2i with proven cardiovascular benefit in addition to current treatment or replace an existing drug with the SGLT2 inhibitor".[2] An SGLT2i is therefore prioritised as an add-on to metformin in people with high CV risk and as the second-line drug option for diabetes management.[3] A GLP-1RA is recommended only in a selected group of people with weight-related issues.

During a clinical consultation, once the choice of the class of drug has been decided based on the patient's clinical assessment (add-on SGLT2i therapy or GLP-1RA) there is scope also to choose a particular drug within that class. Though the CVOTs may appear similar in terms of establishing CV safety, there are differences in the inclusion criteria and the endpoints measured. For instance, in the EMPA-REG OUTCOME trial, presence of ASCVD was an essential inclusion criterion and the trial achieved significant improvement in MACE, whereas in DECLARE-TIMI 58 only 41% had ASCVD and the reduction in MACE was not significant.[4,5] Therefore, classifying the evidence base available based on the patient characteristics included and the clinical outcomes assessed can help to individualise the drug choice. The process of aligning a patient

to a clinical trial, referred as clinical phenotyping, would help to maximise evidence-based practice of medicine.

We previously published a step-wise, deliberations-based, approach to the consultation process based on patient characteristics, clinical phenotyping and a clinical cost calculator (YoDa – years of drug administration; calculated as a product of NNT, duration of trial and drug acquisition cost, as a cost estimate to derive a particular benefit) to compare various SGLT2i to achieve a similar endpoint.[6] The current paper provides a summary of the relevant clinical trials on SGLT2i, GLP-1RA and DPP-4i with their broad inclusion criteria and relevant clinical endpoints in a comparable format (Table 1) and a simplified summary to aid therapeutic decision-making by prescribers in clinical practice (Table 2). A summary of SGLT2i trials specifically in a patient-friendly format is also provided to facilitate patient involvement and shared-decision making (Table 3). The following approach could help in step-wise decision making process

Does the patient have ASCVD?

The main clinical intent of using an SGLT2i in treating patients with ASCVD [includes *established ASCVD* (myocardial infarction, stroke or peripheral vascular disease – angioplasty or amputation) or *very high risk for CV events* (unstable angina, angiographically proven significant vascular disease, positive stress test or high ankle-brachial pressure index)] is prevention of MACE. Among dedicated SGLT2i CVOTs on ASCVD, empagliflozin showed significant reduction in MACE; the trial involving ertugliflozin was only a non-inferiority trial. Of the GLP-1RA CVOTs, albiglutide (not available for clinical use now) showed clinical benefits and lixisenatide did not.[4,7-9]

A number of other CVOTs included patients with ASCVD and/or CV risk factors. Canagliflozin, liraglutide, semaglutide s/c (subcutaneous once weekly) and dulaglutide demonstrated significant reduction in MACE.[10-13] Dapagliflozin and oral semaglutide did not show this benefit.[5,14] However, post-hoc or exploratory analyses of CVOTs analysing the ASCVD cohort separately showed CV benefits with canagliflozin, dapagliflozin and liraglutide (Table 1).[15-18] The CV benefits with SGLT2i drugs were incremental over pre-established treatments with renin-angiotensin-aldosterone system (RAAS) drugs, statins and anti-platelet therapy. The DPP-4i did not show any benefit with CV outcomes.[19-22]

Does the patient have HF?

Empaglifozin and dapagliflozin have shown significant reduction in hHF or CV deaths in patients with HF with reduced ejection fraction (HFrEF), with or without diabetes.[23,24] A sub-study from CANVAS trial showed benefit for hHF with canagliflozin.[25] Other SGLT2i CVOTs have included patients with HF but the inclusion criteria were not comparable (Table 1, 2). Empagliflozin has also subsequently shown significant benefits in patients with preserved ejection fraction heart failure (HFpEF).[26] The DPP-4i or GLP-1RA CVOTs have not shown any significant benefit with respect to HF outcomes; the SAVOR-TIMI 53 trial demonstrated an increased signal for hHF with saxagliptin.[21]

Does the patient have CKD?

The renal composite endpoint assessed in the trials broadly includes doubling of serum creatinine, progression to renal replacement therapy or death from renal disease (with some marginal differences between trials). NICE recommends the use of an SGLT2i in patients with CKD with urine albumin creatinine ratio >30mg/mmol and consider its addition if this is between 3-30mg/mmol, to delay the progression of nephropathy.[2] Dapagliflozin and canagliflozin have shown significant renal benefits, with individual benefits for decline of eGFR and progression to renal replacement therapy (RRT) in patients with significant diabetic nephropathy.[27,28] CVOTs have also demonstrated benefit with the composite renal outcomes and/or more specific renal outcomes (Table 1).

In addition to CKD benefits, the CVOTs have also demonstrated CV benefits, with no heterogeneity noted across various GFR ranges. Further, analytical studies of CVOTs have also been published on empagliflozin, canagliflozin and liraglutide, demonstrating significant cardiovascular benefits among patients with low GFR.[29-31]

Addressing CV risk

High cardiovascular risk

NICE also advises consideration of an SGLT2i with a proven CV benefit at any stage of diabetes management in patients with high risk of CVD. This is defined as a QRISK2 score ≥10% (QRISK2 incorporates multiple CV risk factors under one metric [hypertension, smoking, dyslipidemia, obesity and family history of premature CVD]) or an elevated lifetime CV risk, defined as age <40 years and presence of 1 or more CV risk factors.[32] Most patients who are already established on statin therapy for primary prevention can be considered to belong to this category. A number of studies included patients with multiple risk factors in various combinations in their trials (table 1: ASCVD 1(b) and 4). The trials have generally demonstrated lack of heterogeneity amongst subgroups with or without ASVD; some trials have also published post-hoc analyses specifically on CV risk cohorts.[16-18,33] Clinical phenotyping, based on patient characteristics and desired clinical outcomes (Table 2,3), can help to choose among the SGLT2i.

Sub-optimal HbA_{1c} and low QRISK2 OR age > 40 with CV risk factors

This deliberation is relevant in choosing the appropriate second-line or third-line drug in diabetes. As per NICE, the choice here would be between SGLT2i, DPP-4i, sulphonylureas and pioglitazone for second-line therapy.2 SGLT2i have significant cardiovascular and renal benefits and hence must be ideal second-line drugs, ahead of the others in the class (Table 1 and 3). Clinical phenotyping can be relevant when choosing an appropriate SGLT2i to maximize the application of evidence-based medicine in practice (Table 3).

NICE has recommended the use of GLP-1RA in a selected group of patients - if triple therapy fails, one of the drugs could be substituted with GLP-1RA in patients with obesity, or where weight loss would provide desirable benefit or insulin initiation can have occupational implications. Again, clinical phenotyping could help to choose the best GLP-1RA for a particular patient, for a desired clinical outcome (Table 2). The following points could help to guide decision-making:

(a) Both SGLT2i and GLP-1RA have supporting data for renal com-

Table 1 Summary of CVOTs, clinical trials and post-hoc analysis on SGLT2i, GLP-1RA and DPP-4i; (CVOTs are shown in bold)

Trial Label	N=	Inclusion criteria – for clinical Phenotyping	MACE	MI (fatal or nonfatal)	Stroke (fatal or nonfatal)	hHF	CV deaths	CV deaths or hHF	All-cause mortality	Renal composite endpoint	Other Renal endpoints
1. ASCVD – 1(a) Exclusive ASCVD trials/ datasets											
EMPA-REG OUTCOME **Empagliflozin**	**7020** 100%, 10%	ASCVD	0.86 (0.74-0.99)	0.87 (0.70-1.09)	1.18 (0.89-1.56)	0.65 (0.50-0.85)	0.62 (0.49-0.77)	0.66 (0.55-0.79)	0.68 (0.57-0.82)	0.54 (0.40-0.75)	Albuminuria Progression 0.62 (0.54-0.72) Progression to ESRD 0.45 (0.21-0.97)
VERTIS CV **Ertugliflozin**	**8238** 100%, 24%	ASCVD	0.97 (0.85-1.11)	1.04 (0.86-1.26)	1.06 (0.82-1.37)	0.70 (0.54-0.90)	0.92 (0.77-1.11)	0.88 (0.75-1.03)	0.93 (0.80-1.08)	0.81 (0.63-1.04)	
ELIXA **Lixisenatide**	**6068** 100%, 22%	ASCVD – ACS within < 180 days	1.02 (0.89-1.17)	1.03 (0.87-1.22)	1.12 (0.79-1.58)	0.96 (0.75-1.23)	0.98 (0.78-1.22)	na	0.94 (0.78-1.13)	0.84 (0.68-1.02)	New macroalbuminuria 0.81 (0.66-0.99)
HARMONY **Albiglutide**	**9463** 100%, 20%	ASCVD	0.78 (0.68-0.90)	0.75 (0.61-0.90)	0.86 (0.66-1.14)	na	0.93 (0.73-1.19)	0.85 (0.70-1.04)	0.95 (0.79-1.16)	na	-
TECOS **Sitagliptin**	**14671** 100%, 18%	ASCVD	0.99 (0.89-1.11)	0.97 (0.81-1.11)	0.97 (0.79-1.19)	1.00 (0.83-1.20)	1.03 (0.89-1.19)	1.02 (0.90-1.15)	1.01 (0.90-1.14)	na	-
EXAMINE **Alogliptin**	**5380** 100%, 28%	ASCVD – ACS within <90 days	0.96 (<1.16)	1.08 (0.88-1.33)	0.91 (0.55-1.50)	na	0.85 (0.66-1.10)	na	0.88 (0.71-1.09)	na	-
Furtado *et al* DECLARE-TIMI 58 sub-study	**3584**	DECLARE TIMI 58 Patients with MI sub-study	0.84 (0.72-0.99)	0.78 (0.63-0.95)	0.93 (0.66-1.30)	0.71 (0.53-0.94)	0.84 (0.60-1.19)	0.81 (0.65-1.00)	0.83 (0.67-1.03)	0.80 (0.63-1.01)	
Mahaffey *et al* CANVAS sub-study	**6656**	CANVAS trial patients with ASCVD sub-study	0.82 (0.72-0.95)	0.79 (0.73-0.99)	0.88 (0.67-1.16)	0.68 (0.51-0.90)	0.86 (0.70-1.06)	0.77 (0.65-0.92)	0.89 (0.75-1.07)	0.59 (0.44-0.79)	-
Verma *et al* LEADER Sub-study	**3692**	LEADER with previous ASCVD (MI and stroke)	0.85 (0.73-0.99)	0.83 (0.67-1.03)	0.93 (0.73-1.23)	0.80 (0.62-1.03)	0.80 (0.63-1.02)	-	0.90 (0.74-1.09)	-	-
Leiter *et al* SUSTAIN 6 sub-study	**1262**	SUSTAIN 6 with previous ASCVD (MI and Stroke)	0.76 (0.55-1.05)	0.70 (0.44-1.11)	0.66 (0.35-1.23)	0.99 (0.58-1.68)	1.22 (0.70-2.11)	-	-	-	-
1. ASCVD - 1 (b) Trails including ASCVD or risk factors											
CANVAS **Canagliflozin**	**10142** 66%, 14%	ASCVD OR Age >50 AND two of DM >10 yrs, smoking, micro or macroalbuminuria, SBP>140mmHg on ≥1 HT drug, HDL<1mmol/L	0.86 (0.75-0.97)	0.89 (0.73-1.09)	0.87 (0.69-1.09)	0.67 (0.52-0.87)	0.87 (0.72-1.06)	0.78 (0.67-0.91)	0.87 (0.74-1.01)	0.6 (0.47-0.77)	Albuminuria Progression 0.73 (0.67-0.79)
DECLARE-TIMI 58 **Dapagliflozin**	**17160** 41%, 10%	ASCVD OR Men≥55 or women≥60 AND one of HT, smoking, dyslipidemia	0.93 (0.84-1.03)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.73 (0.61-0.88)	0.98 (0.82-1.17)	0.83 (0.73-0.95)	0.93 (0.82-1.04)	0.53 (0.43-0.66)	na
LEADER **Liraglutide**	**9340** 81%, 18%	Age>50+ASCVD/ HF/CKD3 OR Age>60 + one of MA/LVSD/HT&LVH/ABPI < 0.9	0.87 (0.78-0.97)	0.88 (0.75-1.03)	0.89 (0.72-1.11)	0.87 (0.73-1.05)	0.78 (0.66-0.93)	na	0.85 (0.75-0.97)	0.78 (0.67-0.92)	New macroalbuminuria 0.74 (0.60-0.91)
SUSTAIN-6 **Semaglutide s/c**	**3297** 72%, 24%	Age>50+ASCVD/HF/CKD3 OR Age>60 + one of MA/LVSD/HT&LVH/ABPI <0.9	0.74 (0.58-0.95)	0.74 (0.51-1.08)	0.61 (0.38-0.99)	0.86. (0.48-1.55)	0.98 (0.65-1.48)	na	1.05 (0.74-1.50)	0.64 (0.46-0.88)	New Macroalbuminuria 0.54 (0.37-0.77)
PIONEER 6 **Semaglutide PO**	**3183** 84%, 12%	ASCVD/HF/CKD3 OR Age>60 + one of MA/LVSD/HT&LVH/ABPI <0.9	0.79 (0.57-1.11)	1.18 (0.73-1.90)	0.74 (0.35-1.57)	0.86 (0.48-1.55)	0.49 (0.27-0.92)	na	0.51 (0.31-0.84)	na	na
REWIND **Dulaglutide**	**9901** 31%, 9%	Age>55 +ASCVD/LVH/CKD3/ Proteinuria OR Age>60 +smoking/dyslipidemia/ obesity/ HT	0.88 (0.79-0.99)	0.96 (0.79-1.15)	0.76 (0.62-0.94)	1.11 (0.77-1.61)	0.91 (0.78-1.06)	na	0.90 (0.80-1.01)	0.85 (0.77-0.93)	New Macroalbuminuria 0.77 (0.68-0.97)

Continued...

Table 1 continued Summary of CVOTs, clinical trials and post-hoc analysis on SGLT2i, GLP-1RA and DPP-4i; (CVOTs are shown in bold)

CARMELINA Linagliptin	**6991** 57%, 27%	ASCVD/high renal risk e:GFR 45-75+ UACR>200 or eGFR 15-45	1.02 (0.89-1.17)	1.12 (0.90-1.40)	0.91 (0.67-1.43)	0.90 (0.74-1.08)	0.96 (0.81-1.14)	na	0.98 (0.84-1.13)	1.04 (0.89-1.22)	Albuminuria progression 0.86 (0.78-0.95)
SAVOR-TIMI 53 Saxagliptin	**16492** 78%, 13%	ASCVD OR Men ≥55 or women ≥60 AND one of HT, Smoking, dyslipidemia	1.00 (0.89-1.12)	0.95 (0.80-1.12)	1.11 (0.88-1.39)	1.27 (1.07-1.51)	1.03 (0.87-1.22)	na	1.11 (0.96-1.27)	1.08 (0.88-1.32)	na
2.Heart failure 2(a) HfrEF											
DAPA HF Dapagliflozin	**4744**	T2DM or no DM, HF NYHA II-IV, EF ≤40, High BNP adjusted for AF/ recent hHF	na	na	na	0.70 (0.59-0.83)		0.75 (0.65-0.85)	0.83 (0.71-0.97)	0.71 (0.44-1.16)	na
EMPEROR -REDUCED Empagliflozin	**3730**	T2DM or no DM, HF NYHA II-IV, EF ≤40, High BNP adjusted for AF/NYHA	na	na	na	0.69 (0.59-0.81)	0.92 (0.75-1.12)	0.75 (0.65-0.86)	0.92 (0.77-1.10)	0.5 (0.32-0.77)	na
SOLOIST-WHF† Sotagliflozin	**1222**	T2DM, HF – symptoms and signs needing hHF and IV diuretics	na	na	na	0.64 (0.49-0.83)	0.84 (0.58-1.22)	0.67 (0.52-0.85)	0.82 (0.59-1.14)	na	na
Radholm *et al* CANVAS sub-study	**1461**	CANVAS patients with heart failure	0.80 (0.61-1.05)	1.11 (0.65-1.89)	0.84 (0.51-1.39)	0.51 (0.33-0.78)	0.72 (0.51-1.02)	0.61 (0.46-0.80)	0.70 (0.51-0.96)	0.67 (0.30-1.51)	na
2.Heart failure 2(b)HfpEF											
EMPEROR -PRESERVED Empagliflozin	**5988**	T2DM or no DM, HF NYHA II-IV, EF >40, High BNP adjusted for AF, recent hHF or LVH	na	na	na	0.73 (0.61-0.88)	na	0.79 (0.69-0.90)	1.00 (0.87-1.15)	0.95 (0.73-1.24)	eGFR decline higher in placebo 1.36 (1.06-1.66)
3.CKD - 3(a) Diabetic nephropathy with significant proteinuria											
CREDENCE Canagliflozin 100mg	**4401 50%, 15%**	T2DM, eGFR 30-<90, UACR >300mg/gm,	0.80 (0.67-0.90)	na	na	0.61 (0.47-0.80)	0.78 (0.61-1.00)	0.69 (0.57-0.83)	0.83 (0.68-1.02)	0.66 (0.53-0.81)	Progression to ESRD 0.68 (0.54-0.86)
DAPA-CKD Dapagliflozin 10mg	**4304 37%, 11%**	T2DM or no DM, eGFR 25-75, UACR >200mg/gm	na	na	na	na	0.81 (0.58-1.12)	0.71 (0.55-0.92)	0.69 (0.53-0.88)	0.56 (0.45-0.68)	Progression to ESRD 0.64 (0.50-0.82)
3.CKD 3(b) CKD with low GFR and/or proteinuria											
Wanner *et al* EMPA-REG OUTCOME sub-study	**2250**	EMPA-REG OUTCOME patients with CKD	na	na	na	0.61 (0.42-0.87)	0.71 (0.52-0.98)	0.76 (0.59-0.99)	na	na	na
Neuen *et al* CANVAS sub-study	**2039**	CANVAS trial patients with CKD	0.70 (0.55-0.90)	0.49 (0.22-1.07)	0.32 (0.11-0.96)	0.45 (0.23-0.88)	1.01 (0.57-1.81)	na	na	0.69 (0.28-1.45)	na
SCORED† Sotagliflozin	**10584**	T2DM, eGFR 25-60, age >18 with one major CV risk OR age >55 with 2 minor CV risk	0.77 (0.65-0.91)	na	na	0.67 (0.55-0.82)	0.90 (0.73-1.12)	0.74 (0.63-0.88)	0.99 (0.83-1.18)	0.71 (0.46-1.08)	na
Mann *et al* LEADER sub-study	**2158**	LEADER patients with eGFR<60	0.69 (0.57-0.85)	0.73 (0.55-0.98)	0.53 (0.36-0.79)	0.72 (0.54-0.96)	0.67 (0.50-0.90)	na	0.74 (0.60-0.92)	na	na
4. Multiple CV risk factors with sub-optimal HbA1c [also see ASCVD – 1(b)]											
Mahaffey *et al* CANVAS sub-study	**3486**	CANVAS trial patients without ASCVD	0.98 (0.74-1.39)	1.21 (0.73-2.00)	0.97 (0.59-1.61)	0.64 (0.35-1.15)	0.93 (0.60-1.43)	0.83 (0.58-1.19)	0.79 (0.58-1.07)	0.63 (0.39-1.02)	Albuminuria progression 0.69 (0.60-0.79)
Cahn*et al* DECLARE TIMI 58 sub-study	**10186**	DECLARE TIMI 58 patients without ASCVD	1.01 (0.86-1.20)	na	na	0.64 (0.46-0.88)	-	0.84 (0.67-1.04)	-	0.51 (0.37-0.69)	-
Verma *et al* LEADER sub-study	**2565**	LEADER patients without ASCVD	1.08 (0.84-1.38)	0.93 (0.63-1.36)	1.07 (0.68-1.69)	1.37 (0.92-2.05)	0.99 (0.67-1.46)	na	0.95 (0.72-1.27)	na	na
Leiter *et al* SUSTAIN 6 sub-study	**764**	SUSTAIN 6 patients without ASCVD	0.48 (0.23-0.99)	0.29 (0.08-1.05)	0.55 (0.16-1.89)	1.15 (0.39-3.41)	0.65 (0.18-2.30)	na	na	na	na

Note: All outcome statistics shown as Hazard ratio (95% confidence intervals) ; Green shaded boxes denote HR not crossing 1; orange shaded box denotes HR >1 and significant

Abbreviations: ABPI – ankle brachial pressure index; ACS – acute coronary syndrome; ASCVD – Atherosclerotic cardiovascular disease; BP – blood pressure; CV – cardiovascular; CKD – chronic kidney disease; ESRD – end stage renal disease; GFR – glomerular filtration rate (ml/min/1.73m2); HDL – high density lipoprotein; HF – heart failure; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; hHF – heart failure hospitalization; LVH – left ventricular hypertrophy; LVSD – left ventricular systolic dysfunction; MA – microalbuminuria; MI – myocardial infarction; na - not available; NYHA – New York Heart Association classification; SBP – systolic blood pressure; T2DM – Type 2 diabetes mellitus; UACR – urine albumin creatinine ratio

Table 2 Summary of clinical phenotypes vs evidence available from clinical trials for specific clinical outcomes (drugs tabulated as PO – per oral; S/c – subcutaneous drugs to facilitate decision making)

		Clinical Outcomes				
		MACE	hHF	CVD	All-cause mortality	Composite or other renal endpoint
Clinical Phenotype						
ASCVD	PO	Empagliflozin Dapagliflozin# Canagliflozin#	Empagliflozin Ertugliflozin Dapagliflozin#	Empagliflozin	Empagliflozin	Empagliflozin Canagliflozin#
	S/c	Albiglutide Liraglutide#				Lixisenatide$
ASCVD or Risk factors	PO	Canagliflozin	Canagliflozin Dapagliflozin	Semaglutide po	Semaglutide po	Canagliflozin Dapagliflozin Linagliptin$
	S/c	Liraglutide Semaglutide s/c Dulaglutide		Liraglutide	Liraglutide	Liraglutide Semaglutide s/c Dulaglutide
HFrEF	PO		Dapagliflozin Empagliflozin Canagliflozin#	Dapagliflozin		Empagliflozin
HfpEF	PO		Empagliflozin			
CKD with proteinuria	PO	Canagliflozin	Canagliflozin		Dapagliflozin	Canagliflozin Dapagliflozin
CKD	PO	Canagliflozin#	Empagliflozin# Canagliflozin#	Empagliflozin#		
	S/c	Liraglutide#	Liraglutide#	Liraglutide#	Liraglutide#	
CV risk factors	PO		Dapagliflozin#			Dapagliflozin# Canagliflozin$
	S/c	Semaglutide s/c#				

data from post-hoc trials; $ drugs with evidence for specific renal endpoints only (not for composite renal endpoint)

Abbreviations: ASCVD – atherosclerotic cardiovascular disease; CKD – chronic kidney disease; CV – cardiovascular; CVD – cardiovascular disease; HFrEF – Heart failure with reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; hHF – hospitalisation for heart failure; MACE – major adverse cardiovascular events; semaglutide po – per oral preparation of semaglutide; semaglutide s/c – once weekly subcutaneous preparation

posite endpoints: the former are more consistent with development of new macroalbuminuria and the latter with progression of albuminuria. Amongst GLP-1RA, lixisenatide, semaglutide s/c, liraglutide and dulaglutide showed reduction in incident new macroalbuminura.[9,11-13] Linagliptin, empagliflozin and canagliflozin showed evidence of reduction of albuminuria progression.[4,10,20]

(b) Both SGLT2i and GLP-1RA appear to have reasonable evidence towards reduction of MACE in this cohort. Canagliflozin, liraglutide and dulaglutide demonstrated this in CVOTs, and semaglutide s/c in both CVOT and post-hoc analyses.[16-18,33]

(c) SGLT2i have a better evidence base for reduction of hHF, whereas GLP-1RA and DPP-4i do not. Saxagliptin shows some signals towards worsening of HF. [21]

(d) Though the papers may quote a comparable clinical benefit, the cost associated in achieving this and the clinical running costs for GLP-1RA are significantly different and need to be taken into consideration.

Previously published data have shown a comparison of benefits of using SGLT2i and GLP-1RA in clinical practice, which provide some guidance on head-to-head comparison trials.[34] The NICE guidelines have provided a clear steer towards using SGLT2i ahead of GLP-1RA therapy, and this article can help to decide the best drug within the class for a given patient.[34]

Low-risk patient, to optimise individualized HbA_{1c} target

Most of the published trials looking at this specific cohort were conducted on an intention-to-treat basis and hence would not provide significant data on cardiovascular prevention. The choice of drugs in this cohort would generally be driven by factors such as cost, risk of weight gain, hypoglycaemia and clinician and patient preferences. CVD-REAL compared the efficacy of SGLT2i versus other oral glucose-lowering drugs in routine clinical practice and found comparable benefits in clinical endpoints irrespective of pre-existent CVD. EMPRISE published a comparative study on real-life use of empagliflozin in comparison to sitagliptin.[35-37] These studies showed the consistent effect of SGLT2i outside trial settings and reflect clinical practice, with a mixed combination of patient characteristics.

Discussion

Clinical phenotyping can help to broadly align a patient with T2DM to the trial evidence available based on his clinical characteristics, and can incorporate individualised decision-making into routine clinical practice. Our proposed approach helps to phenotype a patient as ASCVD, HF, CKD or high CV risk irrespective of their HbA_{1c}, providing an accessible summary of the trial evidence for the drugs that can be used as second-line agents after or alongside metformin (Table 3).

Table 3 Summary of Clinical Outcomes for SGLT2i Group of Drugs

DELIBERATIONS	1		2			3		4	
Choose Patient Group	**ASCVD** • Heart Attack or Angina • Stroke or TIA • Leg Vascular Disease • Bypass Surgery or Stents		**Heart Failure ± DM** Over 18 with: • NYHA Class II, III, or IV • HFrEF: LVEF ≤ 40% • Elevated NT-proBNP		Over 18: • NYHA II-IV • HFpEF • Elevated NT-proBNP	**Chronic Kidney Disease** • UACR at least 23-565 • eGFR reduced 23 to 75 • on ACE-I or ARB > 4 weeks		**ASCVD or High Risk CVD** ASCVD or Over ~50 with: • High Blood Pressure • Current Smoker • LDL >3.36 mmol/l or statin	
RCT Trial Name	**EMPA-REG**	**VERTIS CV**	**DAPA HF**	**EMPEROR** -REDUCED	**EMPEROR** -Preserved	**CREDENCE**	**DAPA-CKD ± DM**	**CANVAS**	**DECLARE-** TIMI 58
Median Duration	3.1 yrs	3.5yrs	1.5yrs	1.33 yrs	2.2 yrs	2.6yrs	2.4yrs	3.6yrs	4.2yrs
Special Considerations		Age ≥ 40 yrs			49% DM	Age ≥ 30 yrs eGFR: 30-89 UACR: 34-565	Age ≥ 18 yrs eGFR 25-75 UACR: 23-565	Micro-albuminuria or Low HDL	Men ≥ 55 yrs Women ≥ 60
	Empagliflozin 10 or 25mg	Ertugliflozin 5 or 15mg	Dapagliflozin 10mg	Empagliflozin 10mg	Empagliflozin 10mg	Canagliflozin 100mg	Dapagliflozin 10mg	Canagliflozin 100 or 300mg	Dapagliflozin 10mg
Baseline HbA_{1c} (in DM Patients)	65 mmol/mol (8.1%)	66 mmol/mol (8.2%)		64 mmol/mol 8.0%		67 mmol/mol (8.3%)		66 mmol/mol (8.2%)	67 mmol/mol (8.3%)
MI or Stroke or CVD Death^	-14%	-3%	Not reported	Not reported		-20%	Not reported	-14%	-7%
Heart Attack (MI: fatal or any)	-13%	+4%	Not reported	Not reported		Not reported	Not reported	-11%	-11%
Stroke (fatal or nonfatal)	+18%	+6%	Not reported	Not reported		Not reported	Not reported	-13%	+1%
Heart Failure hospitalization	-35%	-30%	-30%	-31%	-27%	-39%	Not reported	-33%	-27%
CV deaths	-38%	-8%	-18%	-8%		-22%	-17%	-13%	-2%
CV deaths + HF hospitalization	-34%	-12%	-25%	-25%	-21%	-31%	-29%	-22%	-17%
All-cause mortality	-32%	-7%	-17%	-8%		-17%	-31%	-13%	-7%
Renal Endpoint	-46%	-19%	-29%	-50%	eGFR decline reduced	-34%	-44%	-40%	-47%
Progression to ESRD	-55%	Not reported	Not reported	Not reported		-32%	-36%	Not reported	Not reported
Patient or HCP Choice									

Patient and HCP Can Indicate: 1st, 2nd and 3rd Choice Agent

Only Green Shaded Percentage Changes are significant and show benefit.

All statistics shown as % Changes from published HR (95% CI). Deemed as significant if HR did not cross 1.0 indicating ($p \leq 0.05$)
Partly adapted from Varadhan *et al*, Clinical Drug Investigations [3]

Abbreviations: ACE-I – angiotensin converting enzyme inhibitors; ARB – angiotensin receptor blockers; SCVD – atherosclerotic cardiovascular disease; CV – cardiovascular; CVD – cardiovascular disease; DM – type 2 diabetes mellitus; ESRD – end stage renal disease; HCP – health care professional; HF – heart failure; HFpEF – heart failure wih preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; LVEF – left ventricular ejection fraction; MI – myocardial infarction; NT-pro BNP – N terminal B Natriuretic peptide; NYHA – New York Heart association; TIA – transient ischaemic attack; UACR – Urine albumin creatinine ratio

There are a few factors to take into consideration with this approach.

(1) The NICE guidelines clearly steer clinicians towards the use of SGLT2i as a preferred second add-on drug in people with high CV risk. In the UK, with the drug acquisition cost within a class being generally the same, the choice of a drug within the class can be guided by the available evidence base. However, the heterogeneity seen in the trials of a particular class of drugs may not be due to drug inefficiency but merely due to trial design and inclusion criteria.

(2) The positive outcomes of a trial are not necessarily achievable in real-life clinical practice. Further, it cannot be assumed that clinical benefits will continue to increase or that they will be maintained beyond the duration of the trial.

(3) Patients may fit into more than one clinical phenotype and desired clinical outcome can be multiple. Individualising trial evidence to a particular patient can be challenging and HbA_{1c} optimisation always takes priority during clinical care.

(4) The cost of the drug to accrue a particular benefit does not equate to the cost of acquiring the drug. The numbers needed to treat, duration of the trials and time to reach the desired outcomes are different and hence have an implication for the cost involved to accrue particular benefit. These data are again grossly different between the trials and make this cost calculation challenging.[6]

The clinical evidence available from clinical trials, together with the steer from the new NICE guideline, will inevitably result in an increase in the number of prescriptions of second-line agents for diabetes care, particularly SGLT2i. It is important for reasons of cost efficiency and patient outcomes that agents with the best evidence are considered for CV protection in people with diabetes.

Key messages

- The NICE guidelines has provided a clear steer towards prioritizing use of SGLT2i as the second agent, as an add-on to metformin in patients with type 2 diabetes
- The cardiovascular and clinical benefits with SGLT2i are well proven in patients with atherosclerotic cardiovascular disease, heart failure and chronic kidney disease.
- Clinical phenotyping of a patient can help to reasonably align a given patient to the inclusion criteria of a trial and desired clinical outcomes, which could then guide to choose a class of drug and the best drug within the class to derive that outcome
- By using a step-wise consultation approach and tailoring the choice of the drug to a given patient, the clinical benefits could be maximised for the same acquisition cost and evidence-based decision making process incorporated into clinical practice

Conclusion

Clinical phenotyping can help to map a patient based on their clinical characteristics to particular trials, which would then help to choose a class of drug, and a drug within that class. The drug choices can be made according to the clinical endpoints desired. This approach would help to align management plans to current NICE guidelines and evidence-based medicine.

Conflict of interest VP has worked with a large number of Pharmaceutical companies in the field of diabetes care. This includes: AstraZeneca, Boehringer Ingelheim, Knapp, MSD, Lilly, Novo, Sanofi, Takeda, Mylan. Has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events / all major companies in Diabetes Care. All profits to Charity. Has had support for attending meetings and/or travel - Occasional funded travel. Max twice a year; SA is a consultant diabetologist on the NICE guidelines committee; WA Trustee Diabetes UK, Trustee South Asian Health Foundation, Non Executive Director BMJ, Chair DMMAG Birmingham. All other authors have nothing to declare.
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* Average additional time in range per day for study participants who used Control-IQ Technology. Brown SA, Kovatchev BP, Raghinaru D, et al. Six-month randomised, multicenter trial of closed-loop control in type 1 diabetes. N Eng J Med. 2019;381(18):1701-1717.