

Research: Treatment

Sodium–glucose co-transporter-2 inhibitor cardiovascular outcome trials and generalizability to English primary care

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Abstract

Aim To identify people in English primary care with equivalent cardiovascular risk to participants in the sodium–glucose co-transporter-2 inhibitor (SGLT-2i) cardiovascular outcome trials (CVOTs). A secondary objective was to report the usage of SGLT-2is.

Methods Cross-sectional analysis of people registered with participating practices in the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network on the 31 December 2016. We derived: (1) proportions of the primary care population eligible for inclusion in each SGLT-2i CVOT (CANVAS, DECLARE, EMPA-REG and VERTIS); (2) characteristics of the eligible population compared with trial participants (demographics, disease duration and vascular risk); and (3) differences within the eligible population prescribed SGLT-2is.

Results The proportions of people with type 2 diabetes ($N = 84\,394$) meeting the inclusion criteria for each CVOT were: DECLARE 27% [95% confidence interval (CI) 26.5–27.1]; CANVAS 17% (16.6–17.1); VERTIS 7% (7.1–7.4); and EMPA-REG 7% (6.5–6.8). Primary care populations fulfilling inclusion criteria were 5–8 years older than trial cohorts, and <10% with inclusion criteria of each trial were prescribed an SGLT-2i; a greater proportion were men, and of white ethnicity.

Conclusions There was variation in proportions of the primary care type 2 diabetes population fulfilling inclusion criteria of SGLT-2i CVOTs. The more stringent the inclusion criteria, the lower the proportion identified in a primary care setting. Prescription rates for SGLT-2is were low in this national database, and there were demographic disparities in prescribing.

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Introduction

Cardiovascular outcome trials (CVOTs) are randomized controlled trials (RCTs) developed after 2008 following guidance from the US Food and Drug Administration (FDA) to ensure the cardiovascular safety of glucose-lowering medications in type 2 diabetes [1]. CVOTs were principally designed to determine safety/non-inferiority of newer glucose-lowering drugs compared with placebo when added to standard care. The primary composite trial endpoint comprised death due to cardiovascular causes, non-fatal myocardial infarction and

non-fatal stroke. However, cardiovascular superiority has also been demonstrated in six CVOTs, with significant reductions for the primary composite endpoint for canagliflozin and empagliflozin from the sodium–glucose co-transporter-2 inhibitor (SGLT-2i) medication class, and liraglutide, albiglutide, semaglutide and dulaglutide, from the glucagon-like peptide-1 receptor agonist (GLP-1 RA) medication class [2–7].

Generalizability of these trials to real-world type 2 diabetes populations is challenging because each trial had different inclusion criteria. A national primary care comparison of the first SGLT-2i CVOT, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) trial, showed that only a small proportion of people with type 2 diabetes conformed to the trial inclusion criteria [8]. This was due to the high cardiovascular risk inclusion criteria of the

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What's new?

- It is unclear to what extent the findings of the sodium–glucose co-transporter-2 (SGLT-2) inhibitor cardiovascular outcomes trials (CVOTs) are generalizable to the real-world type 2 diabetes populations.
- Using a national primary care database, we found that the inclusion criteria of four SGLT-2 inhibitor CVOTs applied to between 7% and 27% of people with type 2 diabetes.
- Generalizability of the findings from CVOTs to a wider type 2 diabetes population may be restricted to groups defined by the inclusion criteria for each trial.
- Uniform inclusion criteria for trials would allow direct comparison to be made between trials.

trial. The rationale behind selecting people at high cardiovascular risk is that adverse cardiovascular events can be expected to occur in this group over the shortest period, limiting duration and costs of the trials [9]. More recently, several studies have reported that the proportion of people meeting inclusion criteria vary considerably between four SGLT-2i CVOTs [10–12]. Further analysis of other real-world clinical data is essential to determine how the differing inclusion criteria affect the generalizability of SGLT-2i CVOTs.

The aims of the present study were: (1) to describe differences between CVOT inclusion criteria; (2) their implications for the proportion of the diabetes population that this trial evidence would include; and (3) the proportions prescribed SGLT-2is, reporting any disparity in prescribing of SGLT-2is.

Methods

Study design and data source

We conducted a cross-sectional analysis of adults with type 2 diabetes in the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database to identify those that shared comparable cardiovascular risk to participants in each SGLT-2i CVOT: Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (collectively known as the CANVAS Program) [6,13]; Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58); EMPAREG OUTCOME; and eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS CV) [7,14,15]. The planned methods for this study have previously been reported [16].

The RCGP RSC is a sentinel network of primary care practices from across England. The network comprises > 200 practices, with a population in excess of 2 million people

[18], and is representative of the national population [18]. Data quality of the RCGP RSC, and for UK primary care in general, is particularly high since the introduction of a pay-for-performance scheme, the Quality and Outcomes Framework in 2004 [19].

In the UK, primary care medical records are computerized, and key data were recorded, at the time of this study using a comprehensive primary care terminology called the 'Read codes' [20]. The Read classification includes clinical codes for diagnosed conditions, treatments, processes of care and laboratory data. UK primary care is a registration-based system; citizens are registered with a single practice, and have a unique identifier, the National Health Service (NHS) number. This allowed us to determine an accurate denominator for the RCGP RSC population.

Data were extracted from the primary care records of all people registered with practices in the RCGP RSC database on 31 December 2016, and included those with type 2 diabetes aged 18 years or more on this date. We identified the proportion of people with type 2 diabetes that met the cardiovascular inclusion criteria across the four SGLT-2i CVOTs (Table 1). We then described the clinical characteristics of each identified group, and compared these with equivalent data from the trials. In addition, we determined the proportions of people in each group that had previously been prescribed an SGLT-2i, reporting gender, ethnicity and socio-economic status. Socio-economic status was determined at the individual level by converting individual postcode to Index of Multiple Deprivation (IMD) [21]; this is a machine processed activity at the point of data extraction, with researchers not having access to individual's postcodes. We then, converted IMD scores into a categorical variable, quintiles, with quintile 1 being the most, and quintile 5 the least deprived.

Identifying study groups

We used an established ontological and algorithmic approach to identify people with type 2 diabetes. In the first step, all people with diabetes were identified according to diagnosis of diabetes (excluding gestational diabetes and other types of secondary diabetes), clinical investigations (blood glucose and HbA_{1c}), and glucose-lowering medications (except metformin). These people were then categorized by diabetes type (type 1, type 2, undetermined) using a seven-step algorithm, which takes into account age, type of medication and BMI [22].

To identify groups of people with equivalent cardiovascular risk to the SGLT-2i CVOTs, we used the nearest matching Read codes available to determine cardiovascular risk factors [16]. These include codes for diagnosis, procedures and laboratory-based data. Wider criteria were used for particular conditions not recorded in primary care. For example, for hospital admission for unstable angina, we used diagnosis codes for unstable angina and codes indicating

Table 1 Inclusion criteria used in SGLT-2i cardiovascular outcomes trials

Criteria	Trial (drug)			
	CANVAS Program [6,13] (canagliflozin)	DECLARE-TIMI 58 [15] (dapagliflozin)	EMPA-REG OUTCOME [7] (empagliflozin)	VERTIS CV [14] (ertugliflozin)
Age (years)	≥ 30 and history of CVD, or ≥ 50 and with CV risk factors	≥ 40 and history of CVD, or ≥ 55 (males) or ≥ 60 (females) and with CV risk factors	≥ 18	≥ 40
HbA1c	mmol/mol % ≥ 53 and ≤ 91 ≥ 7.0 and ≤ 10.5	≥ 48 and ≤ 108 ≥ 6.5 and ≤ 12.0	≥ 53 and ≤ 86 ≥ 7.0 and ≤ 10.0	≥ 53 and ≤ 91 ≥ 7.0 and ≤ 10.5
Renal function	eGFR (ml min ⁻¹ 1.73 m ⁻²) CrCl (ml/min)	≥ 30 No criterion	≥ 30 No criterion	No criterion
BMI (kg/m ²)	No criterion	≥ 60 No criterion	No criterion ≤ 45	No criterion ≥ 18
History of CVD (≥ 1 of the following) Coronary	<ul style="list-style-type: none"> • Myocardial infarction • Hospital admission for unstable angina • CABG • Percutaneous coronary intervention (with or without stenting) 	<ul style="list-style-type: none"> • Myocardial infarction • Percutaneous coronary intervention • CABG • Coronary stenosis (> 50%) in at ≥ 2 coronary artery territories (i.e. left anterior descending, ramus intermedius, left circumflex, right coronary artery) involving the main vessel, a major branch, or a bypass graft) 	<ul style="list-style-type: none"> • Myocardial infarction > 2 months prior to informed consent • Multivessel coronary artery disease, i.e. in at ≥ 2 major coronary arteries or the left main coronary artery • Single-vessel coronary artery disease, ≥ 50% luminal narrowing during angiography • Unstable angina > 2 months prior to consent with evidence of single- or multivessel coronary artery disease 	<ul style="list-style-type: none"> • Myocardial infarction in which the most recent event occurred at least 90 days prior to screening • Coronary revascularization through a percutaneous coronary intervention at least 90 days prior to screening • CABG at least 90 days prior to screening
Cerebrovascular	Stroke	<ul style="list-style-type: none"> • Ischemic stroke (excluding transient ischemic attack, primary intracerebral hemorrhage or subarachnoid hemorrhage) • Carotid stenting or endarterectomy 	<ul style="list-style-type: none"> • Stroke (ischemic or hemorrhagic) > 2 months prior to consent 	<ul style="list-style-type: none"> • Ischemic stroke at least 90 days prior to screening • Carotid revascularization at least 90 days prior to screening visit
Peripheral	<ul style="list-style-type: none"> • Peripheral revascularization (angioplasty or surgery) • Symptomatic with documented hemodynamically significant carotid or peripheral vascular disease • Amputation secondary to vascular disease 	<ul style="list-style-type: none"> • Peripheral arterial intervention, stenting or surgical revascularization • Lower extremity amputation as a result of peripheral arterial obstructive disease • Current symptoms of intermittent claudication AND an ABI < 0.90 documented within last 12 months 	<ul style="list-style-type: none"> • ≥ 1 of the following: <ul style="list-style-type: none"> • Limb angioplasty, stenting, or bypass surgery • Limb or foot amputation due to circulatory insufficiency • Evidence of significant peripheral artery stenosis (>50% on angiography, or >50% or hemodynamically significant via non-invasive methods) in one limb • ABI < 0.9 in ≥ 1 ankle 	<ul style="list-style-type: none"> • Peripheral arterial disease as indicated by: <ul style="list-style-type: none"> • Angiographically documented peripheral vascular disease • Resting ABI of < 0.85 (measured by a certified vascular laboratory) plus symptoms of claudication • Amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia occurring at least 90 days prior to screening

Table 1 (Continued)

Criteria	Trial (drug)			
	CANVAS Program [6,13] (canagliflozin)	DECLARE-TIMI 58 [15] (dapagliflozin)	EMPA-REG OUTCOME [7] (empagliflozin)	VERTIS CV [14] (ertugliflozin)
No history of CVD				
Hypertension	≥ 2 of the following: SBP ≥ 140 mmHg while on ≥ 1 anti-hypertensive agents	≥ 1 of the following: Blood pressure >140/90 mm/Hg or on anti- hypertensive therapy	No criterion	No criterion
Dyslipidaemia	HDL cholesterol <1 mmol/l)	LDL- cholesterol >130 mg/dl (3.36 mmol/l) within last 12 months or on lipid lowering therapy for at least 12 months		
Duration of diabetes (years)	≥10	No criterion		
Renal function	Micro- or macroalbuminuria	No criterion		
Smoking status	Current smoker	Current smoker (5 cigarettes/day or more for at least 1 year)		

ABI, ankle : brachial index; CABG, coronary artery bypass graft; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; SBP, systolic blood pressure.

poor angina control (Table S1). For the DECLARE inclusion criteria we used $eGFR \geq 60 \text{ ml min}^{-1} 1.73\text{m}^{-2}$ as a surrogate marker for creatinine clearance ($CrCl \geq 60 \text{ ml/min}$).

Data analysis

The demographic and clinical characteristics of people meeting the inclusion criteria of each trial were compared with equivalent data for the previously published trials. These data included age, gender, ethnicity, HbA_{1c} , BMI, blood pressure (SBP and DBP), presence of hypertension, renal function using $eGFR$, duration of diabetes, presence of cardiovascular disease (CVD), and glucose-lowering medications.

Age was defined as of the end of the study period (31 December 2016), whereas BMI was taken from the most recently recorded values. For missing data, BMI was calculated using weight and height. HbA_{1c} and blood pressure were also defined using the latest recorded measurements.

To capture data on currently used medications, we took the most recent prescriptions in the 6 months before 31 December 2016. The $eGFR$ was calculated based on the latest serum creatinine value entered into the individual's medical record, with at least two values required that were recorded 90 days or more apart [23]. Duration of diabetes was determined from the first event that indicated diabetes, which included diagnosis codes, investigation results to indicate diabetes, or the date for a first prescription of a glucose-lowering drug. Presence of hypertension and CVD were captured from the first recorded diagnosis in the individuals' medical records.

Statistical analysis

We calculated the proportion of people that met the inclusion criteria for each trial. We described their clinical characteristics, using proportions for categorical variables, and mean (SD) and median (IQR) to report continuous data. These data were compared with the baseline characteristics described in the completed trials: CANVAS Program, DECLARE-TIMI 58 and EMPA-REG OUTCOME.

Finally, we report any disparity within the population eligible to start this class of medicines and those ever prescribed at least one SGLT-2i. The percentages of people prescribed an SGLT-2i were reported according to the areas of potential disparity (gender, ethnicity and socio-economic status), and 95% confidence intervals (CI) calculated to explore differences.

Sensitivity analysis

For sensitivity analysis, we restricted our analysis to complete cases. Because each trial had specific inclusion criteria, we created separate subsets of people with type 2 diabetes that were relevant to each CVOT in terms of specific variables to remove missing cases for (Appendix 1). Using the subsets with complete cases, we then recalculated the proportion of people that met the inclusion criteria of each CVOT.

Ethical considerations

This study was approved by the RCGP RSC Research Approval Committee (RSC_CLIN_0218), and was

Table 2 Characteristics of participants for SGLT-2i cardiovascular outcomes trials and people in the RCGP RSC population that met inclusion criteria for each trial

Characteristic*	CANVAS Program (canagliflozin)		DECLARE-TIMI 58 (dapagliflozin)		EMPA-REG OUTCOME (empagliflozin)		VERTIS CV (ertugliflozin)
	CANVAS participants† (N = 5795)	RCGP RSC – CANVAS inclusion criteria (N = 14 227)	DECLARE participants‡ (N = 8582)	RCGP RSC – DECLARE inclusion criteria (N = 22 651)	EMPA-REG participants§ (N = 4687)	RCGP RSC – EMPA-REG inclusion criteria (N = 5628)	RCGP RSC – VERTIS inclusion criteria (N = 6119)
Age (years)	63.2 ± 8.3	69.9 ± 10.7	63.9 ± 6.8	69.3 ± 8.8	63.1 ± 8.6	71.8 ± 10.5	71.8 ± 10.5
Men	3759 (64.9)	9298 (65.4)	5411 (63.1)	14 162 (62.5)	3336 (71.2)	3950 (70.2)	4311 (70.5)
HbA _{1c} %	8.2 ± 0.9	8.1 ± 0.9	8.3 ± 1.2	7.7 ± 1.3	8.1 ± 0.9	7.9 ± 0.8	8.0 ± 0.9
mmol/mol	66 ± 10	65 ± 10	67 ± 13	61 ± 14	65 ± 9	63 ± 8	64 ± 10
BMI (kg/m ²)	31.9 ± 5.9	31.1 ± 6.1	32.1 ± 6.0	31.1 ± 6.2	30.6 ± 5.3	30.3 ± 5.3	30.7 ± 5.9
SBP (mmHg)	136.4 ± 15.8	134.5 ± 15.4	135.1 ± 15.3	133.5 ± 14.1	135.3 ± 16.9	131.7 ± 15.2	131.9 ± 15.5
DBP (mmHg)	77.6 ± 9.6	74.0 ± 9.6	NR	74.5 ± 9.1	76.6 ± 9.7	72.4 ± 9.5	72.2 ± 9.7
Hypertension¶	5188 (89.5)	10 705 (75.2)	6977 (81.3)	18 525 (81.8)	4446 (94.9)	4046 (71.9)	4438 (72.5)
eGFR (ml min ⁻¹ 1.73 m ⁻²)	76.7 ± 20.3	76.0 ± 21.0	85.4 ± 15.8	83.8 ± 12.7	74.2 ± 21.6	72.7 ± 20.8	70.5 ± 23.0
Ethnicity							
White	4508 (77.8)	10 222 (71.8)	6843 (79.7)	16 152 (71.3)	3403 (72.6)	4142 (73.6)	4491 (73.4)
Non-white	1287 (22.2)	1896 (13.3)	1739 (20.3)	3095 (13.7)	1284 (27.4)**	609 (10.8)	679 (11.1)
Missing	–	2109 (14.8)	–	3404 (15.0)	–	877 (15.6)	949 (15.5)
Duration of diabetes (years)							
Mean duration	13.5 ± 7.7	13.5 ± 7.5	NR	10.4 ± 7.1	NR	13.0 ± 8.2	13.3 ± 8.4
Median duration (IQR)	NR	12.9 (8.8–17.1)	11.0 (6.0–16.0)	9.7 (5.1–14.4)	NR	12.1 (7.1– 16.9)	12.4 (7.3–17.5)

CVD, cardiovascular disease; NR, not reported.

*Unless specified, data are mean ± SD or n (%).

†Pooled canagliflozin participants (100 and 300 mg doses) in CANVAS or CANVAS-R trials.

‡Dapagliflozin participants (10 mg doses).

§Pooled empagliflozin participants (10 and 25 mg doses).

¶Previous hypertension or on antihypertensive therapy.

||Trial data includes Asian, black and other ethnicity; RCGP RSC includes Asian, black, mixed ethnicity, and other ethnicity.

**EMPA-REG trial included 41 participants categorised as 'other/missing' ethnicity.

determined by the Health Research Authority/Medical Research Council online tool as a clinical audit not requiring formal ethics committee review [24]. Data were pseudonymized at the point of extraction, so personal data were not identifiable to the researchers.

Results

Data were analysed from the computerized medical records of 1 595 445 people across 164 practices in the RCGP RSC network. Within this population, we identified 84 394 adults with type 2 diabetes. Of these, the following numbers of people met the inclusion criteria for cardiovascular risk in each trial: CANVAS 14 227 (17%; 95% CI 16.6–17.1); DECLARE 22 651 (27%; 26.5–27.1); EMPA-REG 5628 (7%; 6.5–6.8); VERTIS 6119 (7%; 7.1–7.4).

Participants in the CVOTs were younger than people in the RCGP RSC database with equivalent cardiovascular risk factors (CANVAS 63.2 vs. 69.9 years; DECLARE 63.9 vs. 69.3 years; EMPA-REG 63.1 vs. 71.8 years), but shared a similar mean BMI and eGFR (Table 2). Duration of diabetes and HbA_{1c} were also similar, except for longer duration of

disease (11.0 vs. 9.7 years) and higher HbA_{1c} in participants in the DECLARE trial than RCGP RSC individuals that met the inclusion criteria (67 vs. 61 mmol/mol; 8.3% vs. 7.7%). A higher proportion of participants in the CANVAS and DECLARE trials were of white ethnicity (CANVAS 78% vs. 72%; DECLARE 80% vs. 71%) than people eligible for each trial in the RCGP RSC database, but there were similar proportions for EMPA-REG (73% vs. 74%). Blood pressure values were marginally higher in the trial participants; however, hypertension was substantially more common in the CANVAS and EMPA-REG trials than in people that met the inclusion criteria for the CVOTs (CANVAS 90% vs. 75%; EMPA-REG 95% vs. 72%).

Differences in prevalence of CVD between the CVOTs and people meeting inclusion of each trial were also found. Approximately 25% more participants in the CANVAS trial had any type of CVD compared with people in the RCGP RSC database with equivalent CV risk factors (71% vs. 46%), whereas two-fifths (40%) of participants in the DECLARE trial had any type of CVD compared with only a quarter (25%) of people in the RCGP RSC database (Table 3). People who met the inclusion criteria for the

Table 3 Proportion of people according to type of cardiovascular disease in the RCGP RSC population that met inclusion criteria for SGLT-2i cardiovascular outcomes trial

History of CVD*	CANVAS Program (canagliflozin)		DECLARE-TIMI 58 (dapagliflozin)		EMPA-REG OUTCOME (empagliflozin)		VERTIS CV (ertugliflozin)
	CANVAS participants† (N = 5795)	RCGP RSC – CANVAS inclusion criteria (N = 14 227)	DECLARE participants‡ (N = 8582)	RCGP RSC – DECLARE inclusion criteria (N = 22 651)	EMPA-REG participants§ (N = 4687)	RCGP RSC – EMPA-REG inclusion criteria (N = 5628)	RCGP RSC – VERTIS inclusion criteria (N = 6119)
Coronary	3234 (55.8)	3750 (26.4)	2824 (32.9)	3773 (16.7)	3545 (75.6)	3506 (62.3)	3787 (61.9)
Cerebrovascular	1113 (19.2)	2307 (16.2)	653 (7.6)	1719 (7.6)	1084 (23.1)	1508 (26.8)	1637 (26.8)
Peripheral	1176 (20.3)	1630 (11.5)	522 (6.1)	1722 (7.6)	982 (21.0)	1545 (27.5)	1747 (28.6)
Any	4127 (71.2)	6489 (45.6)	3474 (40.5)	5555 (24.5)	4657 (99.4)	5628 (100.0)	6119 (100.0)

*Data are *n* (%).

†Pooled canagliflozin participants (100 and 300 mg doses) in CANVAS or CANVAS-R trials.

‡Dapagliflozin participants (10 mg doses).

§Pooled empagliflozin participants (10 and 25 mg doses).

EMPA-REG CVOT were equally likely to have CVD as the participants themselves.

Fewer than one in ten people who met the inclusion criteria of any of the CVOTs were prescribed an SGLT-2i (Fig. 1). Insulin use was at least 50% more common in the trial populations than in people that met trial inclusion criteria in the RCGP RSC database. Use of sulfonylureas and metformin was also more common in the trial populations (Table 4). A greater proportion of men compared with women, and people of white ethnicity compared with black ethnicity were prescribed SGLT-2is across each group identified as eligible for the CVOTs. Prescribing rates were also higher in the IMD quintile 1 (most deprived) compared with IMD quintile 5 (least deprived) in the eligible populations for the CANVAS and DECLARE trials (Table 5), but there was some intersection amongst the other quintiles.

Sensitivity analysis

Proportions of missing data for each variable are provided (Table S2). Between 6% and 23% of cases were removed from the type 2 diabetes cohort for the complete case analysis (Table S3). The proportions of people identified for each CVOT were slightly higher (Table S4) than those in our primary analysis, but DECLARE remained the most representative of the trials.

Discussion

This study in primary care confirmed that between 7% and 27% of the type 2 diabetes population fulfil the inclusion criteria of the SGLT-2i CVOTs. There are categorical differences in the inclusion criteria of the CVOTs for the SGLT-2is. The differences between inclusion criteria are related to the level of cardiovascular risk. The population eligible to participate seen in practice are similar; however, the practice population who meet the inclusion criteria are 5 to 8 years older. We also report that only ~10% of those

who meet the study criteria are currently prescribed SGLT-2is and how disparities may exist in prescribing, with a bias towards prescribing to men and white ethnicity.

When guidance for the CVOTs was first released in 2008, the FDA advised that the trials should comprise people at greater risk of cardiovascular events, including those with advanced duration of diabetes, older people and those with impaired kidney function [1]. These inclusion requirements are typical of RCT design, in which participants must be at high risk of experiencing the specific outcome in an appropriate amount of time; less than 5 years in the case of CVOTs [9]. A consequence of these inclusion criteria is that the findings only apply to a subset of the type 2 diabetes population. As yet, the findings of CVOTs cannot be applied to the wider type 2 diabetes population. Our study highlights the impact of the differences between inclusion criteria of each of the SGLT-2i CVOTs.

The eligibility criteria for CVOT trial recruitment followed what investigators of each CVOT deemed to be a high-risk population. The EMPA-REG OUTCOME trial had the most selective criteria of a history of CVD, and at least 18 years of age [7]. In the CANVAS trial, approximately two-thirds of participants were > 30 years of age with established CVD, the remaining participants were aged ≥ 50 years with at least two risk factors but no history of CVD [6]. The VERTIS-CV trial is yet to be completed, but includes only people aged ≥ 40 years with previous CVD [14]. The DECLARE trial had the broadest eligibility criteria, with just 41% of participants aged ≥ 40 years with established CVD, while the remaining participants were men ≥ 55 years and women ≥ 60 years with one or more risk factors [15]. The differences in the inclusion criteria were reflected in our study, with the lowest proportion of people identified using the EMPA-REG OUTCOME and VERTIS criteria (both 7%), followed by CANVAS (17%), and DECLARE (27%). These data support the findings of other CVOT eligibility-based studies, which also showed substantial differences between the proportions of people identified

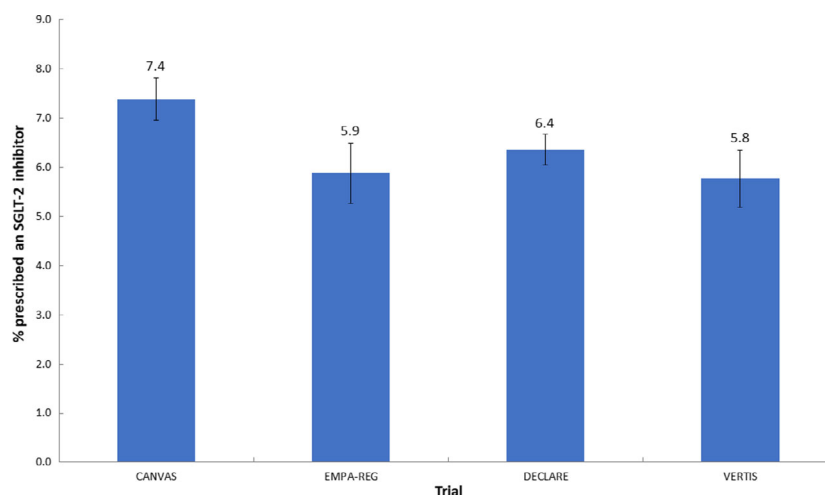


FIGURE 1 The proportion of people in the RCGP RSC database meeting trial eligibility criteria and were prescribed SGLT-2is.

Table 4 Proportion of people according to diabetes medication use in the RCGP RSC population that met inclusion criteria for each SGLT-2i cardiovascular outcomes trial

Glucose lowering therapies*	CANVAS Program (canagliflozin)		DECLARE-TIMI 58 (dapagliflozin)		EMPA-REG OUTCOME (empagliflozin)		VERTIS CV (ertugliflozin)
	CANVAS participants† (N = 5795)	RCGP RSC – CANVAS inclusion criteria (N = 14 227)	DECLARE participants‡ (N = 8582)	RCGP RSC – DECLARE inclusion criteria (N = 22 651)	EMPA-REG participants§ (N = 4687)	RCGP RSC – EMPA-REG inclusion criteria (N = 5628)	RCGP RSC – VERTIS inclusion criteria (N = 6119)
Metformin	4447 (76.7)	10 201 (71.7)	7020 (81.8)	16 103 (71.1)	3459 (73.8)	3752 (66.7)	3927 (64.2)
Insulin	2890 (49.9)	4437 (31.2)	3567 (41.6)	4042 (17.8)	2252 (48.0)	1753 (31.1)	2097 (34.3)
Sulfonylurea	2528 (43.6)	5509 (38.7)	3615 (42.1)	6862 (30.3)	2014 (43.0)	1921 (34.1)	2061 (33.7)
DPP-4 inhibitor	697 (12.0)	3400 (23.9)	1418 (16.5)	4080 (18.0)	529 (11.3)	1238 (22.0)	1363 (22.3)
Thiazolidinedione	NR	487 (3.4)	NR	688 (3.0)	198 (4.2)	136 (2.4)	146 (2.4)
GLP-1 RA	222 (3.8)	860 (6.0)	397 (4.6)	996 (4.4)	126 (2.7)	262 (4.7)	291 (4.8)

*Data are n (%).

†Pooled canagliflozin participants (100 and 300 mg doses) in CANVAS or CANVAS-R trials.

‡Dapagliflozin participants (10 mg doses).

§Pooled empagliflozin participants (10 and 25 mg doses).

according to inclusion criteria of each trial. In the retrospective cross-sectional study of 20 293 people in the National Health and Nutrition Examination Survey (NHANES), weighted analyses demonstrated between 4% and 40% of the US population were eligible for the SGLT-2i CVOTs [12]. A European-based observational study of 803 836 people from Germany, the Netherlands, Norway and Sweden, found that 17% to 59% met the main criteria for the CVOTs [10]. More recently, DISCOVER, a 3-year prospective cohort study of 15 992 people with type 2 diabetes from four regions of the world (Asia-Pacific, Europe, Latin America, and Middle East and Africa) identified 7% to 41% of the cohort as eligible for the CVOTs [11]. Again, DECLARE was the most representative CVOT in the above studies.

The implications of these data are that the findings of the SGLT-2i CVOTs may apply only to particular subgroups of people with type 2 diabetes – those with a history of CVD or

with risk factors for CVD. This feature is highlighted in the recent ADA and EASD joint guidelines for managing hyperglycaemia, which recommend SGLT-2is as a second line therapy only in people with previous atherosclerotic CVD or chronic kidney disease [25]. Moreover, the inclusion criteria of the trials vary, so that the more highly selective these were, the smaller proportion of people (from the RCGP RSC database) eligible. Comparing the findings from the trials themselves is complex because the eligibility of the trials differ, and this is demonstrated by this study in terms of the proportions of people identified and population characteristics. Uniformity in participant selection would make such comparisons more achievable.

When considering usage of SGLT-2is, prescribing rates were low (< 10%) in the subgroups of people with type 2 diabetes with equivalent risk for cardiovascular events to the trials. Given the positive results of the trials to date, this may

Table 5 Disparities in individuals prescribed SGLT-2is within the type 2 diabetes population who meet the cardiovascular outcomes trial inclusion criteria*

Characteristic	RCGP RSC – CANVAS inclusion criteria (N = 14 227)		RCGP RSC – DECLARE inclusion criteria (N = 22 651)		RCGP RSC – EMPA-REG inclusion criteria (N = 5628)		RCGP RSC – VERTIS inclusion criteria (N = 6119)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Gender								
Men	742	8.0 (7.43–8.54)	989	7.0 (6.57–7.41)	258	6.5 (5.77–7.32)	273	6.3 (5.61–7.07)
Women	309	6.3 (5.60–6.96)	452	5.3 (4.85–5.81)	73	4.4 (3.40–5.36)	80	4.4 (3.48–5.42)
Ethnicity								
White	789	7.7 (7.21–8.24)	1085	6.7 (6.33–7.11)	244	5.9 (5.19–6.62)	258	5.7 (5.08–6.44)
Asian	87	7.0 (5.60–8.40)	106	5.6 (4.62–6.69)	25	5.7 (3.65–7.99)	26	5.3 (3.50–7.41)
Black	12	2.6 (1.32–4.19)	22	2.4 (1.43–3.51)	2	1.9 (0.00–4.67)	2	1.7 (0.00–4.13)
Mixed	13	13.4 (7.22–20.62)	11	7.8 (3.55–12.77)	5	19.2 (3.85–34.62)	6	18.8 (6.25–34.38)
Other	9	9.5 (4.21–15.79)	11	7.0 (3.16–11.39)	3	7.9 (0.00–18.42)	4	10.0 (2.50–20.00)
Missing	141	6.7 (5.64–7.78)	206	6.1 (5.26–6.87)	52	5.9 (4.45–7.53)	57	6.0 (4.53–7.59)
IMD Quintile								
IMD quintile 5 (least deprived)	206	6.6 (5.72–7.48)	303	5.8 (5.15–6.43)	66	5.2 (4.05–6.51)	69	5.1 (4.01–6.31)
IMD quintile 4	220	7.4 (6.50–8.40)	322	6.7 (5.98–7.40)	81	6.8 (5.36–8.21)	89	6.9 (5.57–8.28)
IMD quintile 3	187	6.9 (5.95–7.82)	243	5.6 (4.91–6.26)	68	6.0 (4.67–7.41)	72	5.9 (4.59–7.30)
IMD quintile 2	186	7.2 (6.22–8.19)	252	6.4 (5.67–7.20)	52	5.2 (3.87–6.55)	57	5.1 (3.84–6.42)
IMD quintile 1 (most deprived)	250	8.9 (7.86–9.96)	319	7.5 (6.68–8.25)	63	6.1 (4.68–7.60)	65	5.8 (4.43–7.18)
Missing	2	8.0 (0.00–20.00)	2	5.1 (0.00–12.82)	1	14.3 (0.00–42.86)	1	10.0 (0.00–30.00)

*Proportions of people in the RCGP RSC population eligible for each cardiovascular outcomes trials (CVOT) ever prescribed SGLT-2is, stratified by gender, ethnicity and IMD quintile. For example, 7.7% (95% CI 7.21–8.24) of people of white ethnicity (N = 10 222) in the RCGP RSC – CANVAS cohort were ever prescribed an SGLT-2i compared with 2.6% (95% CI 1.32–4.19) of people of black ethnicity (N = 454).

seem surprising. Several factors are likely to have influenced these figures. First, prescribing of SGLT-2is is influenced by renal function; initiation of SGLT-2is is not licensed if eGFR < 60 ml min⁻¹ 1.73m⁻², and continuation only permitted if eGFR ≥ 45 ml min⁻¹ 1.73m⁻² [26]. Many people with type 2 diabetes have impaired kidney function, and therefore were not prescribed these drugs. In addition, the latest UK National Institute for Health and Care Excellence (NICE) guidelines for the management of type 2 diabetes were published in 2015 before evidence of cardiovascular safety/efficacy were available [27]. SGLT-2is are recommended by NICE as a third line therapy, an add on to metformin, pioglitazone or sulfonylurea, with a specific focus on improving blood glucose levels. More recently, other national and international guidelines have acknowledged the positive findings of CVOTs, and recommend medications with demonstrable cardiovascular benefit earlier in the treatment pathway for people with established CVD [25,28]. Updated analyses of these data, therefore, may show increased prescribing of SGLT-2is in people with a history of CVD.

Strengths and limitations

The RCGP RSC database contains a large nationally representative population, which has been demonstrated to have a high level of data completeness [18,22,29]. However, there may be some selection bias in terms of the volunteer practices

of the RCGP RSC network, and these are marginally in more affluent areas compared with the English population as a whole [18].

The data source used to identify people according to the inclusion criteria of each trial carries several limitations. There is some likelihood of missing data due to failure to enter key information into a person's medical record (such as diagnoses, key risk factors), and recording of data in different healthcare systems. For instance, incidence of myocardial infarction is lower in the RCGP RSC database than primary care data that are linked to hospital data such as Clinical Practice Research Datalink; crude rates: 96.9 and 186.7 per 100 000 respectively [29,30]. However, pay-for-performance for chronic disease management, which relies on coding for payment [19], encouraged coding.

Because of the nature of the data source, it is likely that the number of people identified was underestimated for some variables. For example, ankle-brachial index and peripheral revascularization are procedures that are not commonly used in primary care, and there may be a lag in case ascertainment in primary care. Identification of the inclusion criteria was restricted by the use of the clinical codes, Read codes, used in UK primary care. As such, the closest matching codes available were used to capture information on diagnosis or risks factors, which may have led to an overestimation of people that met the inclusion criteria.

The sensitivity analysis showed only slightly higher proportions of people met the inclusion criteria of the trials,

and these data supported our primary analysis. However, we were unable to remove missing data for different types of disease because the presence of a condition in primary care records was indicated only by the date an entry was made; unless a date is present in a person's record, it is assumed that the individual does not have the condition, when it may in fact be undiagnosed. This is a limitation of secondary use of observational data.

Conclusions

The CVOTs are important trials assessing cardiovascular safety of new classes of drugs used in the management of type 2 diabetes. The cardiovascular benefits of SGLT-2is from these trials were important new findings. However, the more stringent the inclusion criteria, the lower the proportion identified in a primary care setting. The generalizability of the findings to a wider type 2 diabetes population may be restricted to groups defined by the inclusion criteria for each trial. Direct comparability of CVOTs will only be possible if, in future, they move towards common inclusion criteria. Only a small proportion of those who meet trial inclusion criteria currently receive these medicines, although this may change as the outcomes of these trials become more widely known.

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Competing interests

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Author contributions

W.H. led the drafting of the manuscript. M.F., N.M., M.J. and S.d.L. reviewed the manuscript and study design and contributed to the final manuscript draft.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Variables used in the RCGP RSC database to match against the inclusion criteria of each SGLT-2 inhibitor CVOT (CANVAS Program, DECLARE-TIMI 58, EMPA-REG OUTCOME, and VERTIS CV).

Table S2. Proportion of missing data per variable excluded in complete case analysis.

Table S3. Proportion of complete cases in the T2DM population prior to creation of SGLT-2i CVOTs subsets.

Table S4. Proportion of people with complete cases that met the inclusion criteria of each SGLT-2i CVOT.

Appendix 1

Variables screened for missing data for analysis of complete cases only as part of a sensitivity analysis.

CANVAS

Age; HbA_{1c}; eGFR; Systolic blood pressure; High-density lipoprotein cholesterol; Microalbuminuria; Smoking status

DECLARE

Age; HbA_{1c}; eGFR; Systolic blood pressure; Diastolic blood pressure; Low-density lipoprotein cholesterol; Smoking status

EMPA-REG

Age; HbA_{1c}; eGFR; BMI

VERTIS

Age; HbA_{1c}; eGFR; BMI