BRIEF REPORT

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Eligibility of patients with type 2 diabetes for sodium-glucose co-transporter-2 inhibitor cardiovascular outcomes trials: An assessment using the Diabetes Collaborative Registry

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Abstract

Generalizability of findings from cardiovascular outcomes trials (CVOTs) to patients with type 2 diabetes (T2D) in clinical practice is unknown. We assessed the proportions of patients in the Diabetes Collaborative Registry who would have met enrolment criteria for pivotal CVOTs of sodium-glucose co-transporter-2 inhibitors (SGLT-2is): EMPA-REG OUTCOME, CANVAS, DECLARE and VERTIS CV. In 172 643 patients, mean [standard deviation (SD)] age and HbA1c were 68.1 (11.8) years and 7.8% (2.2), respectively; 56.8% of patients were men and SGLT-2i use was 4.4%. Atherosclerotic cardiovascular disease (ASCVD) prevalence was 64.3% and mean 10-year ASCVD risk was 28.6% in patients without ASCVD. Proportions of patients eligible for CVOTs ranged from 26% (EMPA-REG OUTCOME) to 44% (DECLARE); 48% of patients were ineligible for all CVOTs. Mean (SD) ASCVD risk was 25.4% (22.6), 32.1% (20.6) and 37.7% (19.4) in patients eligible for no, one or two CVOTs, respectively. SGLT-2i use was low in patients eligible for no CVOTs (3.5%) and at least one CVOT (5.2%). In conclusion, applicability of CVOT results to patients with T2D in clinical practice varies based on trial eligibility criteria.

KEYWORDS

cardiovascular disease, observational study, SGLT-2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Cardiovascular (CV) outcomes trials (CVOTs) are the standard approach to assessing CV safety and efficacy of type 2 diabetes (T2D) drugs, as mandated by US Food and Drug Administration (FDA) guidance from 2008.[1] Three CVOTs showed significant CV benefits of the sodium-glucose cotransporter-2 inhibitors (SGLT-2is) empagliflozin, canagliflozin and dapagliflozin in patients with T2D.[2-4] Real-world data from CVD-REAL studies suggest a class effect,[5] and one CVOT of ertugliflozin is ongoing.[6] However, in order to accrue a sufficient number of CV events in a timely manner, CVOTs generally enrol patients at higher CV risk than a patient with T2D seen in routine clinical practice. Therefore, the generalizability of CVOT findings to the broader population of patients with T2D is unknown.

The Diabetes Collaborative Registry (DCR) is the first US cross-specialty outpatient practice database designed to track and improve the quality of care for patients with diabetes across primary and specialty care settings.[7] Initiated in 2014 as a collaboration between endocrinology, primary care and cardiology professional societies, the registry collects relevant data from electronic health records of

patients within participating practices. Particular advantages of the DCR include the collection of patient-level clinical and laboratory data, as well as the enrolment of patients across the adult age spectrum. As of 31 March 2016, the DCR comprised 1 029 807 patients across 374 sites and 5114 providers. At this time point, general practice (including internal medicine, primary care or family practices), cardiology, endocrinology and obstetrics/gynaecology practices accounted for 50.1%, 74.9%, 2.1% and 9.4% of sites, respectively (sites could comprise multiple types of practice).

Understanding the applicability of CVOT findings to patients with T2D in clinical practice will help physicians make more informed treatment decisions for their patients. In this study, we assessed the proportions of adults with T2D in the DCR who would have met enrolment criteria for CVOTs of the four US-marketed SGLT-2is, empagliflozin, canagliflozin, dapagliflozin and ertugliflozin: EMPA-REG OUTCOME,[2] CANVAS,[3] DECLARE[4] and VERTIS CV[6], respectively.

2 | METHODS

This was a retrospective cross-sectional analysis of patients in the DCR. Adults with T2D who were seen in a DCR-participating practice between 1 January 2013 and 31 March 2016 were eligible for inclusion. Patients with type 1 diabetes, prediabetes or diet-controlled T2D, and patients without documented HbA1c measurements were excluded. A waiver of written informed consent and authorization for this study were granted by Chesapeake Research Review, Inc.,

because DCR participation does not require data collection beyond that of routine clinical care and data are de-identified.

Demographic and clinical characteristics of the analytic cohort were described. Selected data including A1C range and history of chronic kidney disease (CKD) and CV disease (CVD) (Table 1) were extracted from the analytic cohort. These data were cross-tabulated with major determinants of eligibility from the four CVOTs examined (Table S1), in order to estimate the percentages of patients who were eligible for individual, all, or none of the CVOTs. Where no value was recorded for CKD- and CVD-related variables, it was assumed that the condition was not present.

The 10-year atherosclerotic CVD (ASCVD) risk for patients without established CVD was calculated using the American College of Cardiology ASCVD risk estimator.[9] In addition, the 5-year risk of CVD, including coronary heart disease and stroke, was calculated using the method devised by Pocock et al.[8] Briefly, this method calculates a risk score based on 11 key risk factors: age, sex, smoking, systolic blood pressure, total cholesterol, height, creatinine, history of myocardial infarction, history of stroke, diabetes, and left ventricular hypertrophy. When calculating the 5-year risk of CVD, missing data were estimated using simple imputation. Data on left ventricular hypertrophy are not currently collected in the DCR, so this risk factor was set to zero for all patients.

3 | RESULTS

The analytic cohort consisted of 172 643 DCR patients with evaluable data who met the study inclusion criteria (Table 1). Within this cohort,

TABLE 1 Baseline characteristics of the overall study cohort and of patients eligible for individual cardiovascular outcomes trials

Characteristic	Overall population (N = 172 643)	Eligible for EMPA-REG OUTCOME (n = 44 570)	Eligible for CANVAS (n = 55 759)	Eligible for DECLARE (n = 75 445)	Eligible for VERTIS CV (n = 46 267)
Age, years, mean (SD)	68.1 (11.8)	69.5 (10.6)	68.9 (10.6)	68.8 (9.9)	69.5 (10.4)
Men (%)	56.8	64.0	62.0	60.9	63.9
A1C (%), mean (SD)	7.8 (2.2)	7.9 (0.8)	8.0 (0.9)	7.9 (1.3)	8.0 (0.9)
ASCVD, number (%)	110 959 (64.3)	44 570 (100.0)	47 119 (84.5)	53 864 (71.4)	46 267 (100.0)
10-year risk in patients without ASCVD[a], %, mean (SD)	28.6 (22.1)	NA	34.7 (20.7)	34.0 (20.2)	NA
5-year CVD Death risk[b], mean (SD)	6.7 (8.0)	7.6 (8.5)	7.1 (8.1)	6.2 (7.1)	7.5 (8.5)
CKD[c], number (%)	20 123 (11.7)	3579 (8.0)	4333 (7.8)	2037 (2.7)	3732 (8.1)
SGLT-2i use, %[d]	4.4	5.5	5.6	5.3	5.5
Canagliflozin	2.9	3.7	3.8	3.6	3.7
Dapagliflozin	1.0	1.2	1.3	1.2	1.2
Empagliflozin	0.7	0.8	0.8	0.8	0.8

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; NA, not applicable; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.
[a]Calculated using the American College of Cardiology (ACC) ASCVD risk estimator.
[b]Calculated using the method of Pocock et al.[8]
[c]Defined by the presence of a CKD diagnosis in patient records as well as eGFR values.
[d]Some patients were taking more than one type of SGLT-2i.

56.8% of patients were men; mean [standard deviation (SD)] age and A1C were 68.1 (11.8) years and 7.8% (2.2), respectively; 4.4% of patients were using SGLT-2is. In total, 64.3% of patients had ASCVD, and mean (SD) 10-year ASCVD risk was 28.6% in patients without established ASCVD. Overall, the mean (SD) risk of CVD death within 5 years was 6.7% (8.0).

The proportions of patients meeting CVOT inclusion criteria ranged from 26% for EMPA-REG OUTCOME to 44% for DECLARE (Figure 1A). Mean age, A1C and proportions of men and SGLT-2i use were similar between the cohorts of patients eligible for each CVOT (Table 1). All patients eligible for EMPA-REG OUTCOME and VERTIS CV had ASCVD, and the proportion of patients with ASCVD was 84.5% and 71.4% in patients eligible for CANVAS and DECLARE, respectively. The mean (SD) 10-year ASCVD risk in patients without established ASCVD was similar between patients eligible for CANVAS and DECLARE (34.7% and 34.0%, respectively). The proportion of patients with CKD was much lower in patients eligible for DECLARE compared with the other CVOTs (2.7%; range for other CVOTs, 7.8-8.1%), and 5-year CVD death risk was also lower in these patients (7.1; range for other CVOTs, 8.1-8.5%).

Almost half (48%) of patients did not meet eligibility criteria for any CVOT (Figure 1B). The mean (SD) ASCVD risk was lower in patients who were not eligible for any CVOTs than in patients eligible for one or two CVOTs [25.4% (22.6) vs. 32.1% (20.6) and 37.7% (19.4)] (Table S2). SGLT-2i use was 3.5% and 5.2% in patients eligible for no CVOTs and at least one CVOT, respectively.

4 | DISCUSSION

Data from the EMPA-REG OUTCOME, CANVAS, and DECLARE CVOTs showed a significant benefit of the SGLT-2is empagliflozin, canagliflozin and dapagliflozin in decreasing the risk of CV events in patients with T2D.[2-4] However, the applicability of the findings from CVOTs to patients with T2D in the real world is not certain, given the selective populations enrolled in CVOTs.

The inclusivity of all CVOTs assessed in our analysis was less than 50%. Despite DECLARE being the most inclusive CVOT, 56% of the DCR cohort in the present study did not meet eligibility criteria for this trial. Nonetheless, this finding suggests that the results from DECLARE may still be applicable to a large proportion of patients with T2D in the general population. The EMPA-REG OUTCOME and CANVAS eligibility criteria minimally reflected the general T2D population, which was probably attributable to these trials predominantly enrolling patients with prior CVD (the proportion of patients with a history of CVD was 99% and 66% in EMPA-REG OUTCOME and CANVAS, respectively).[2,3] In contrast, the majority of patients enrolled in DECLARE (59%) did not have established CVD.

Our results are similar to findings from a large European observational study where the proportions of patients eligible for EMPA-REG OUTCOME, CANVAS, DECLARE and VERTIS CV were 21%, 34%, 59% and 17%, respectively.[10] A recent meta-analysis of 34 322 patients from EMPA-REG OUTCOME, the CANVAS programme and DECLARE concluded that the collective modest benefit of SGLT-2is in
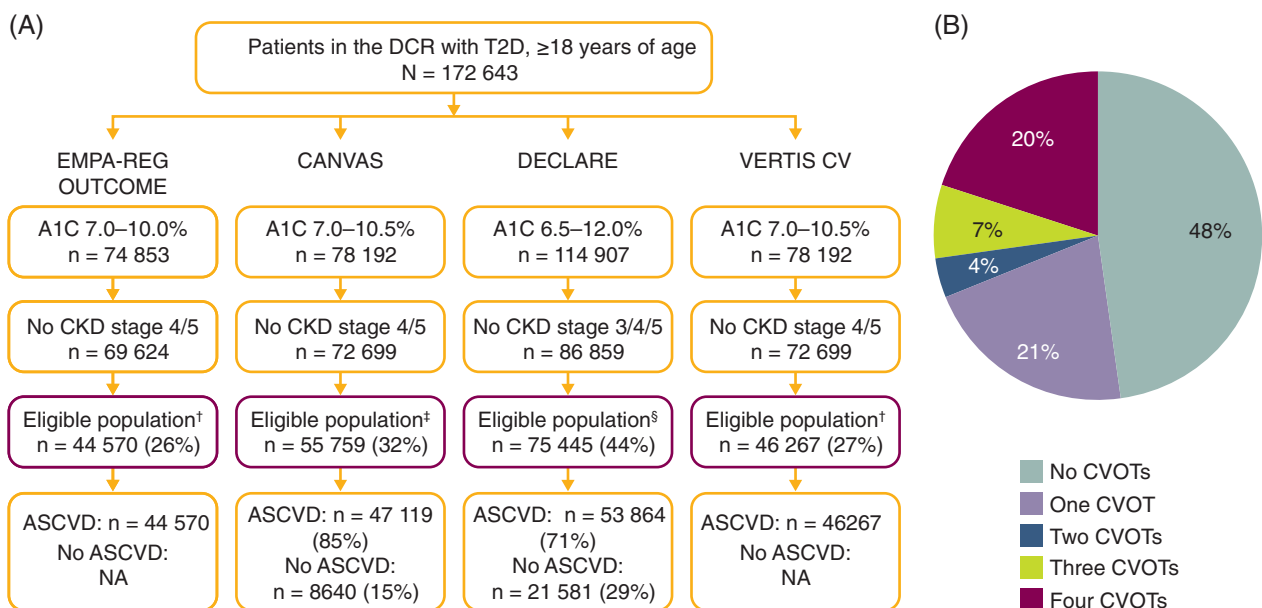
FIGURE 1 A, Flow diagram for estimation of Diabetes Collaborative Registry (DCR) patients potentially eligible for cardiovascular outcomes trial (CVOT) enrolment; B, proportions of patients meeting enrolment criteria for CVOTs. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DCR, diabetes collaborative registry; MI, myocardial infarction; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; T2D, type 2 diabetes. [†]History of CAD, MI, PCI, CABG, stable angina, PAD or stroke; [‡]history of CAD, MI, PCI, CABG, stable angina, PAD, stroke, TIA, carotid stenting or carotid endarterectomy, or no CV history in patients aged ≥50 years with two or more CV risk factors; [§]history of CAD, MI, PCI, CABG, stable angina, PAD, stroke, TIA, carotid stenting or carotid endarterectomy, or no CV history in patients aged >55 years (men) or >60 years (women) with at least one CV risk factor

the reduction of atherothrombotic CV events was primarily limited to patients with established CVD.[11] However, patients with T2D and a broad CV risk profile enrolled in DECLARE experienced significant reductions in the composite of CV death or heart failure hospitalizations when treated with dapagliflozin compared with placebo.[11] Further supporting these findings from CVOTs, the CVD-REAL 1 and 2 studies,[5,12,13] as well as other real-world studies,[14,15] also found a significantly lower risk of CV events associated with initiation of an SGLT-2i (vs other glucose-lowering agents). Although large pharmacoepidemiologic studies such as CVD-REAL have potential limitations (including a possibility of residual confounding), their findings are important and complementary to randomized controlled trials, as they include a population of patients with T2D that is much more representative of that seen in routine clinical practice, with a much broader CV risk profile (13-25% of patients had prior CVD in CVD-REAL).[5,12,13]

Ideally, CVOTs should not be conducted primarily in patients with high CV risk if broad applicability to clinical practice is desired, although inclusion of only low risk patients in CVOTs is problematic, because of low event rates, which could impair the feasibility of conducting CVOTs. Findings from the current study did not suggest any key factors beyond CV risk that were associated with ineligibility for CVOTs. Furthermore, they suggest that substantial variability exists in the degree to which SGLT-2i CVOTs represent the broader population of patients in clinical practice who may be prescribed these medications. Our results differ in some respects from a recently published analysis that used the National Health and Nutrition Examination Survey (NHANES) database to address a similar research question.[16] In both studies, DECLARE was the most inclusive CVOT, with similar percentages of patients eligible in NHANES and the DCR. However, in NHANES, eligibility for the other three CVOTs was very low (4.1-8.8%); moreover, 59.2% of patients did not meet eligibility criteria for any of the four CVOTs, compared with 48% of patients in the present analysis. This was probably because the patients included in NHANES are substantially younger and have fewer comorbidities than those in the DCR, in large part a result of cardiology practices representing the majority of sites (74.9%) in the DCR. Thus, the findings from the present analysis may be more representative of the broader population of patients with T2D than those from studies that utilized NHANES data.

Other notable findings from our study include the observation that 10-year ASCVD risk was high in patients without established ASCVD. Despite this, use of SGLT-2is was infrequent in the DCR, even among patients who would have been eligible for the CVOTs and in patients with established CVD. These findings suggest an unmet need for treatment in patients who could potentially benefit from SGLT-2is. It is worth noting that clinical guidelines that were current at the time these analyses were conducted recommended SGLT-2is as one of several potential options for second-line treatment in patients with T2D,[17,18] which may partially explain why SGLT-2i use was lower than we might have expected. A new joint consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes

(EASD), recommends SGLT-2is for the treatment of patients with T2D and established ASCVD, and also for patients with T2D and either heart failure or CKD.[19] Given that these guidelines may alter prescribing patterns in patients with T2D, SGLT-2i use should be evaluated over time to detect any change in the frequency of prescribing of these agents.

Study limitations include the high rates of missing data for some parameters (eg, urine albumin and high-density lipoprotein cholesterol) in the DCR, which could have led to underestimation of trial eligibility. Conversely, use of selected key CVOT inclusion criteria in the analysis and greater prevalence of CVD in patients from a mostly cardiology practice-based registry increased the probability of overestimating trial eligibility for the general population of patients with T2D. Given that the DCR is continually enrolling practices, the CV risk profile of patients may change in response to the proportion of cardiology practices in the registry. Future studies of a similar nature to this one will allow an assessment of whether the CVOT eligibility of DCR patients changes as a consequence.

In conclusion, the applicability of CVOT results to the broader population of patients with T2D in clinical practice varies based on trial eligibility criteria. Findings from the present study will assist clinicians in assessing the representativeness of CVOT trial populations to the overall population of patients with T2D in clinical practice.

CONFLICT OF INTEREST

E.W. and D.C. are employees of AstraZeneca. M.K. has received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Glytec Systems, Intarcia Therapeutics, Janssen, Merck, Novartis, Novo Nordisk and Sanofi, and he has received research support from AstraZeneca and Boehringer Ingelheim. S.V.A. and F.T. have no disclosures to declare.

AUTHOR CONTRIBUTIONS

E.W., D.C., S.V.A. and M.K. contributed to the study design. S.V.A. and M.K. collected the data. E.W., D.C., S.V.A. and F.T. contributed to the analysis. All authors contributed to the writing of the manuscript.

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SUPPORTING INFORMATION

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

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