REPORT

Eligibility Varies Among the 4 Sodium-Glucose Cotransporter-2 Inhibitor Cardiovascular Outcomes Trials: Implications for the General Type 2 Diabetes US Population

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In 2015, more than 23 million adults in the United States had a diagnosis of diabetes, with an estimated 95% of cases being type 2 diabetes (T2D).[1] Patients with T2D are at increased risk of cardiovascular disease (CVD),[2] and therefore, improvement of cardiovascular (CV) outcomes is a goal of diabetes management.[3,4] Good glycemic control in T2D has been associated with a reduced risk of microvascular complications,[5,6] but its effects on the risk of CVD are less clear.[7-9] However, findings from a number of studies have shown that the use of certain classes of antihyperglycemic agents and some intensive glucose-lowering treatment regimens were associated with an increased risk of CV events or death.[10-13] As a result of such reports, the FDA issued guidance in 2008 on the evaluation of novel agents for the treatment of T2D with respect to major adverse cardiac events.[14,15] Studies of newer T2D therapies, such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors, for example, have shown a reduction in the risk of CV events in certain patient groups.[16-21]

SGLT2 inhibitors lower blood glucose by preventing reabsorption of glucose from the proximal renal tubule in the kidney, with the consequent excretion of excess glucose in the urine having additional beneficial effects on body weight and blood pressure,[22] as demonstrated in clinical trials of canagliflozin,[23] dapagliflozin,[24-26] and empagliflozin.[27] SGLT2 inhibitors do not act on insulin or related pathways and could therefore be used in combination with agents such as glucagon-like peptide-1 receptor agonists in patients who require additional glycemic control.[28] As with other novel antihyperglycemic medications, the CV safety of SGLT2 inhibitors has been evaluated in randomized, controlled CV outcomes trials (CVOTs), as in the case of empagliflozin,[16,29] and canagliflozin,[20,21,30] or such studies are ongoing, as they are for dapagliflozin[31,32] and ertugliflozin.[33] Although the FDA has provided some guidance on the design, primary outcomes, and patient populations for CVOTs of T2D medications,[15,34] there are some differences in these 4 randomized, controlled studies. For example, such differences include the number of patients to be recruited, and inclusion and exclusion criteria, such as patients' ages at enrollment, glycated hemoglobin (A1C) values at baseline, and histories of CVD and presence of CVD

ABSTRACT

Objectives: Guidance to industry from the FDA requires studies to evaluate the cardiovascular safety of novel type 2 diabetes (T2D) medications. Although the objectives of such cardiovascular outcomes trials (CVOTs) are similar, differences in features such as enrollment criteria present a challenge when trying to assess the applicability of these studies to real-world T2D populations. This study evaluated the proportions of US adults with T2D who met the eligibility criteria for each of the 4 sodium-glucose cotransporter-2 (SGLT2) inhibitor CVOTs.

Study Design: A cross-sectional retrospective study was conducted using data from the National Health and Nutrition Examination Survey (NHANES) and published patient eligibility criteria for completed or ongoing SGLT2 inhibitor CVOTs.

Methods: Data on T2D diagnosis and other relevant clinical and demographic characteristics were extracted from the NHANES (2009-2010 and 2011-2012). Weighted analysis of these data was used to estimate the percentage of US adults with T2D who met the eligibility criteria for the CANVAS program (CANagliflozin cardioVascular Assessment Study) (canagliflozin; NCT01032629, NCT01989754), and the DECLARE-TIMI 58 (dapagliflozin; NCT01730534), EMPA-REG OUTCOME (empagliflozin; NCT01131676), and VERTIS-CV (ertugliflozin; NCT01986881) trials.

Results: The weighted analysis identified a population of 23,941,512 US adults from data on key inclusion criteria and information indicating a diagnosis of T2D. Of these, 4.1% met the criteria for EMPA-REG OUTCOME, 4.8% for VERTIS-CV, 8.8% for the CANVAS program, and 39.8% for the DECLARE-TIMI 58 trial.

Conclusions: There were considerable differences in the proportions of US adults with T2D who met the eligibility criteria for these studies. The DECLARE-TIMI 58 trial criteria were the most generalizable to the US T2D population.

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TABLE 1. Eligibility Criteria For Cardiovascular Outcomes Trials of the SGLT2 Inhibitors[16,20,21,29-33,37]

Study	EMPA-REG OUTCOME (empagliflozin)[16,29]	CANVAS Program (CANVAS, CANVAS-R) (canagliflozin)[20,21,30]	
		Primary Prevention	Secondary Prevention
Key inclusion criteria data required from NHANES[a]	Age, A1C level, BMI, and a response of Yes or No to at least 1 of the following: "Ever been told you had congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke?"	Age, A1C level, and a response of Yes or No to "Ever told you had congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke?"	Age, A1C, a response of Yes or No to the CV questions in the columns to the left, and evaluable responses for at least 2 of any of the following: a response of Yes or No to "Are you taking any prescription medication for hypertension?," or non-missing values for SBP, LDL-C level, HDL-C level, or duration of diabetes
Age (years)	≥18	≥30	≥50 and 2 or more risk factors for CVD
Hypertension	No criterion	No criterion	If no heart disease or stroke history, antihypertensive use as determined by a response of Yes to "Are you taking any prescription drug for hypertension?" or SBP ≥140 mm Hg
Cholesterol	No criterion	No criterion	If no heart disease or stroke history, LDL-C level ≥154 mg/dL or HDL-C level ≤39 mg/dL
CV events: heart failure/CHD/angina/MI	High risk for CV events as determined by a response of Yes to "Ever been told you had congestive heart failure, coronary heart disease, angina/angina pectoris, or heart attack?" Patients with ACS <2 months prior to screening were excluded, but this may not be identifiable.	Heart failure/CHD/angina/MI as determined by a response of Yes to "Ever been told you had congestive heart failure, coronary heart disease, angina/angina pectoris, or heart attack?"	Not applicable to this subgroup
Stroke	Stroke as determined by a response of Yes to "Ever been told you had a stroke?"	Stroke as determined by a response of Yes to "Ever been told you had a stroke?"	Not applicable to this subgroup

(continued)

risk factors.[16,29-31,33] These differences in study populations, assessments of SGLT2 inhibitors to placebo rather than active therapies, and potential issues with statistical power may prevent meaningful comparisons between their findings and present a barrier to uniform extrapolation of outcomes when assessing the potential CV safety of a particular treatment in a real-world T2D population.

An understanding of the generalizability of the eligibility criteria of a particular CVOT can aid clinicians when evaluating the applicability of its findings to their patients. It is likely that the less generalizable the study design, the less similar the study participants to patients encountered in clinical practice and, therefore, the less applicable the study results. To investigate the generalizability of the eligibility criteria for these 4 SGLT2 inhibitor CVOTs to US adults with T2D, an analysis was undertaken to estimate the proportions of this patient population who would be eligible for enrollment in each of these studies.

Study Design

This was a cross-sectional retrospective cohort study. Data on T2D prevalence in the United States were derived from the National Health and Nutrition Examination Survey (NHANES),[35,36] and analyzed against the published patient eligibility criteria for CVOTs that were in progress or completed at the time of the study for the SGLT2 inhibitors canagliflozin (the CANVAS program [CANagliflozin cardioVascular Assessment Study]; CANVAS; NCT01032629, CANVAS-R; NCT01989754),[20,21,30] dapagliflozin (DECLARE-TIMI 58; NCT01730534),[31,32] empagliflozin (EMPA-REG OUTCOME; NCT01131676),[16,29] and ertugliflozin (VERTIS-CV; NCT01986881).[33,37]

Methods

The primary outcomes of the present analysis were an estimate of the number of US adults with T2D, and the numbers and percentages of adults in this US T2D population who would meet the criteria for inclusion in each of the 4 SGLT2 inhibitor CVOTs, and for participation in any, all, or none of these studies. The eligibility criteria for each of the four SGLT2 inhibitor CVOTs are shown in **Table 1**.[16,29-33] Information on the SCORED study of sotagliflozin (NCT03315143) was not available at the time of the present analysis.

TABLE 1. ***(continued)*** Eligibility Criteria For Cardiovascular Outcomes Trials of the SGLT2 Inhibitors[16,20,21,29-33,37]

Study	EMPA-REG OUTCOME (empagliflozin)[16,29]	CANVAS Program (CANVAS, CANVAS-R) (canagliflozin)[20,21,30]	
		Primary Prevention	Secondary Prevention
A1C level	≥7.0% and ≤10.0%	≥7.0% and ≤10.5%	
Prescription medications	Excludes patients treated with anti-obesity drugs or systemic steroids	No criterion	Treatment with a statin or fibrate qualifies as a cardiac risk factor
Other criteria	BMI ≤45 kg/m^2 Exclusion criteria: 1. eGFR <30 mL/min/1.73 m^2 2. Response of Yes to either "Ever been told you had weak/failing kidneys?" or "Have you received dialysis in past 12 months?" 3. Indication of liver disease as identified by a response of Yes to "Do you still have a liver condition?" 4. Medical history of cancer as identified by a response of Yes to "Ever been told you had cancer or malignancy?" 5. Patients with uncontrolled hyperglycemia as determined by FPG level >240 mg/dL; however, patients with missing values for FPG were included in the analysis.	Patients with a history of ≥1 severe hypoglycemic episode within 6 months before screening are excluded as determined by a FPG level <70 mg/dL.[b] However, patients with missing FPG values were included in the analysis.	If no heart disease or stroke history, then LDL-C level ≥154 mg/dL or HDL-C level ≤39 mg/dL is a qualifying risk factor. Qualifying risk factors also include: duration of T2D ≥10 years and smoking ≥½ pack per day of cigarettes. Hypoglycemia exclusion criterion was imposed for the Primary Prevention cohort. However, patients with missing FPG levels were included in the analysis.
T2D definition applied to NHANES dataset[c]	A1C level >7.0%	A1C level >7.0%	

Study	VERTIS-CV Study (ertugliflozin)[33,37]	DECLARE-TIMI 58 (dapagliflozin)[31,32]	
		Cardiovascular Disease	Multiple Risk Factors
Key inclusion criteria data required from NHANES[a]	Age, A1C level, BMI, and a response of Yes or No to ≥1 of the following: "Ever been told you had congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke?"	Age, a response of Yes, No, or Borderline to "Doctor ever told you that you have diabetes?" and a response of Yes or No to ≥1 of the following: "Ever been told you had congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke?"	Age, sex, a response of Yes, No, or Borderline to "Doctor ever told you that you have diabetes?" and a response of Yes or No to the CV questions for the ≥40 yrs subgroup and a response of Yes or No to "Are you taking any prescription medication for hypertension?" or non-missing SBP or LDL-C level
Age (years)	≥40	≥40	>55 yrs for men, >60 yrs for women, no known history of CVD and at least 1 risk factor for CVD
Hypertension	No criterion	No criterion	If no heart disease or stroke history, antihypertensive use as determined by a response of Yes to "Are you taking any prescription medication for hypertension?" or SBP ≥140 mm Hg or DBP >90 mm Hg[d]

(continued)

The NHANES is a nationally representative health survey of the US population. It incorporates objective health data from patients in combination with field surveys about health and health behaviors.[36] The NHANES questionnaire data are obtained through a range of survey questions, including participant self-reports of past diagnoses of a variety of diseases and conditions. If available, it also includes prescription medication data based on patient self-reports and examination of pill bottles. At the time of the present study, the 2 most recent waves of the NHANES with available data relevant to the study objectives were from 2009 to 2010 and 2011 to 2012. These comprised data on patient characteristics, medications, examinations, and laboratory results.[35] The NHANES files used to obtain data for this analysis are listed in **Appendix 1**.

TABLE 1. ***(continued)*** Eligibility Criteria For Cardiovascular Outcomes Trials of the SGLT2 Inhibitors[16,20,21,29-33,37]

Study	VERTIS-CV Study (ertugliflozin)[33,37]	DECLARE-TIMI 58 (dapagliflozin)[31,32]	
		Cardiovascular Disease	Multiple Risk Factors
Cholesterol	No criterion	No criterion	If no heart disease or stroke history, LDL-C level >130 mg/dL
CV events: heart failure/ CHD/ angina/MI	Evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems as determined by a response of Yes to "Ever been told you had coronary heart disease, angina/ angina pectoris, or heart attack?" Excludes patients with heart failure as determined by a response of No to "Ever been told you had congestive heart failure?"	High risk for CV events as determined by a response of Yes to "Ever been told you had congestive heart failure, coronary heart disease, angina/ angina pectoris, or heart attack?"	Not applicable to this subgroup
Stroke	Stroke as determined by a response of Yes to "Ever been told you had a stroke?"	Stroke as determined by a response of Yes to "Ever been told you had a stroke?"	Not applicable to this subgroup
A1C level	≥7.0% and ≤10.5%	6.5%-12.0%	
Prescription medications	Excludes patients using prandial insulin alone without basal insulin	No criterion	Treatment with lipid-lowering or antihypertensive therapies is a cardiac risk factor
Other criteria	BMI ≥18 kg/m^2	Not applicable to this subgroup	Excludes patients with a history of bladder cancer as determined by a value of "10"[e] to "What kind of cancer?" If no heart disease or stroke history, LDL-C level >130 mg/dL is a qualifying CV risk factor. Smoking ≥5 cigarettes per day is a qualifying CV risk factor, as determined by a response of "≥5" to "Average # cigarettes/day during past 30 days" or "# cigarettes smoked per day" or a response of "Every Day" or "Some days" to "Do you now smoke cigarettes?"
T2D definition applied to NHANES dataset[c]	A1C level >7.0%	A response of Yes to "Doctor ever told you that you have diabetes?" or an A1C level >6.5% or FPG level >126 mg/dL	

A1C indicates glycated hemoglobin; ACS, acute coronary syndrome; BMI, body mass index; CANVAS, CANagliflozin cardioVascular Assessment Study; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.
[a]The denominator patient population for all trials was determined by including only those patients having evaluable (non-missing) values for all key inclusion criteria.
[b]It may not be possible to determine the specific time point of a hypoglycemic event (eg, if it occurred within 6 months of screening); all available NHANES laboratory data will be used.
[c]These were the criteria used to identify the potentially eligible population of patients with T2D from the NHANES to be applied to each individual trial for this analysis.
[d]A blood pressure reading of 140/90 mm Hg was a cardiovascular risk factor for patients in these subgroups of the DECLARE-TIMI 58 trial. As NHANES examination data lists SBP and DBP separately, blood pressure cutoffs of an SBP >140 mm Hg or a DBP >90mm Hg were used.
[e]Where 10 is the numerical code ascribed to bladder cancer in the NHANES responses to the question "What kind of cancer?"

Data were extracted from the NHANES for adults aged at least 18 years who had information available on their T2D status. For the purposes of this analysis, individuals in this group were categorized as having T2D if they responded to survey questions that they had been diagnosed with diabetes or had a recorded fasting plasma glucose (FPG) value of at least 126 mg/dL or an A1C value greater than 6.5%. If a patient's responses indicated that they had been diagnosed with diabetes at less than 18 years of age, a diagnosis of type 1 diabetes was considered likely and they were excluded from the T2D analysis. Patients were also excluded if they responded "yes" to questions about pregnancy at the time of participation in the NHANES.

To estimate the total number of US adult patients with T2D and the numbers and percentages of this population who would have met the criteria for each study, weighted analyses of the

TABLE 2. NHANES-Weighted Variables Analyzed For Adult Patients With Type 2 Diabetes Identified From NHANES Data for 2009-2010 and 2011-2012 (N = 23,941,512)

Weighted Variable	
Mean age (years ± SD)	59.6 ± 13.5
Mean body mass index (kg/m^2 ± SD)	33.3 ±7.6
	Percentage of this population
Sex	
Men	52.2
Women	47.8
Race	
Non-Hispanic white	57.2
Non-Hispanic black	16.7
Mexican American	9.9
Other Hispanic	6.8
Other races (including multiracial)	9.4
Smoking status	
Smoker	32.5
Nonsmoker	67.5
Blood pressure status	
Hypertension	69.7
Normotensive	30.3
Cholesterol status	
Hypercholesterolemia	67.4
No hypercholesterolemia	32.6
CVD	
Evidence of CVD	23.7
No CVD	76.3
CKD	
Evidence of CKD	13.6
No CKD	86.4

CKD indicates chronic kidney disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

NHANES-derived datasets were undertaken according to the estimation and weighting procedures and analytic guidelines specified by the NHANES.[38-40] For the analysis of each CVOT, patients in the NHANES-derived T2D dataset were required to have non-missing data for the various key trial inclusion criteria (eg, age, A1C level, history of and risk factors for CVD; Table 1). Differences among the inclusion criteria for the 4 CVOTs meant that there were different requirements as to what data were available for the NHANES-derived T2D population to evaluate potential eligibility for each CVOT (see Table 1 "Key Inclusion Criteria").

Where information on certain eligibility for a given CVOT were not collected as part of the NHANES, the investigators agreed on methods to substitute equivalent data that were collected or they adjudged that the analysis could proceed with the data missing (**Appendix 2**). For example, an FPG value of less than 40 mg/dL recorded in the NHANES was used as an indicator of a severe hypoglycemic episode, while criteria that required data regarding recurrent urinary tract infections or durations of use of certain medications were ignored (Appendix 2). Heart failure data were extracted from the NHANES as it was not only considered to be an indicator of CVD, but also, New York Heart Association class IV heart failure was an exclusion criterion for the CANVAS program and the VERTIS-CV Study.[20,21,30,33,37] Data on coronary artery bypass graft surgery or percutaneous coronary interventions could not be obtained from the NHANES.

Results

Information on T2D status was available for 10,537 participants from the NHANES 2009 to 2010 and for 9756 from the NHANES 2011 to 2012. The weighted analysis using these data identified a US population of up to 203,090,000 adults who had non-missing data on the key inclusion criteria of any trial (eg, non-missing data for A1C values, age; Table 1). Of those, 23,941,512 had evidence supporting a diagnosis of T2D, giving a prevalence of T2D of 11.8% in this population. The mean age of these patients was 59.6 years, with a slightly lower proportion of women than men (**Table 2**). Patients were generally overweight or obese (mean body mass index, 33.3 kg/m^2). Approximately three-fourths of the T2D population had no evidence of CVD, although about two-thirds had hypertension and hypercholesterolemia.

The 4 CVOTs evaluated are described in detail elsewhere and summarized in Table 1.[16,20,21,29-31,33,41] All CVOTs were multisite, multinational studies. They included patients from 24 to 42 countries, and each included centers in the United States. **Table 3** summarizes the baseline characteristics of the 4 CVOTs.[38]

Table 4 shows the numbers of US adults with T2D, as calculated using the NHANES-weighted criteria, who had evaluable (ie, non-missing) data for all key inclusion criteria. The numbers and percentages of adults with T2D in this population who met the specific criteria for each of the 4 SGLT2 inhibitor CVOTs are shown in the **Figure**. Among the US adult T2D population identified, 40.8% would have met the eligibility criteria for at least 1 of the 4 CVOTs, but just 1% would have met the criteria for all 4. DECLARE-TIMI 58 had the most inclusive criteria, with 39.8% of this US adult T2D population meeting the inclusion criteria for this study. By contrast, of the other 3 CVOTs, the CANVAS program had the broadest criteria at 8.8% inclusivity and the other 2 studies at less than 5% each.

Discussion

This retrospective study assessed the extent to which the results of completed or ongoing (at the time of the analysis) studies of CV safety for the SGLT2 inhibitor class of antihyperglycemic medications could be generalized to adults in the United States with T2D. Data

TABLE 3. Baseline Characteristics of Patients Included in the CANVAS Program, DECLARE-TIMI 58, EMPA-REG OUTCOME, and VERTIS-CV Trials[37]

	CANVAS Program	DECLARE-TIMI 58	EMPA-REG OUTCOME	VERTIS-CV
Number randomized	10,142	17,160	7020	8237
Age (mean, yrs)	63	65	63	64
A1C level (mean, %)	8.2	8.3	8.1	8.3
CV status	• 34% primary prevention • 66% secondary prevention	• 41% established CVD • 59% multiple risk factors	• >99% established CVD	• >99% established CVD

A1C indicates glycated hemoglobin; CANVAS, CANagliflozin cardioVascular Assessment Study; CVD, cardiovascular disease.

for this study were derived from the NHANES, which is a nationally representative survey of health in the United States.[32] The calculated prevalence of T2D of 11.8% was similar to that reported by the CDC for 2015 (9.4% of US adults with diagnosed diabetes, with virtually all of these having T2D).[1] The slight disparity in prevalence observed could be due to various factors, such as the requirement for data on key eligibility criteria for those patients included in the denominator population in the present study.

This study found substantial differences in the extent to which the eligibility criteria, and hence the CV findings, of these CVOTs could be generalized to a real-world adult T2D patient population. Approximately 40% of the US adult T2D population identified via the weighted analysis of the NHANES data would have been eligible to participate in at least 1 of these 4 studies, but only the DECLARE-TIMI 58 study of dapagliflozin[31,41] had eligibility criteria that would have included more than 10% of this population.

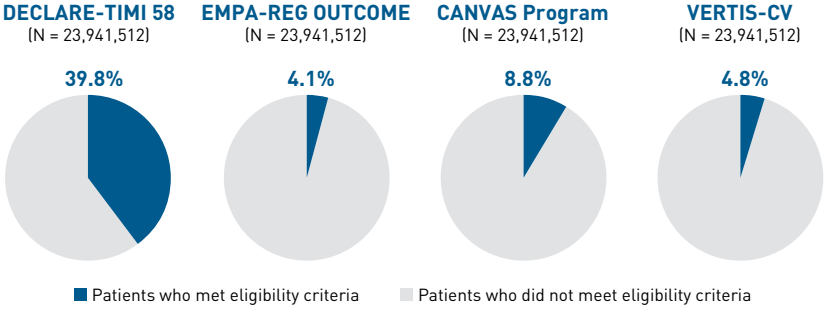
The 2008 FDA Guidance for Industry recommends that CV safety studies of novel T2D therapies include patients who are representative of those likely to receive the agent being investigated.[14] It is recommended that participants include those at higher risk of CV events, including the elderly, and those with relatively advanced T2D or with some level of renal impairment.[14] This is important, as patients with T2D are at a disproportionately high risk of death from CVD, with more than two-thirds of those at least 65 years of age dying from heart disease and approximately 15% from stroke,[2,42] and they are also more likely than the general population to have risk factors for CVD, such

TABLE 4. Percentages of Adults With Type 2 Diabetes In the United States Who Would Have Met Inclusion Criteria for CVOTs With Canagliflozin,[20,30] Dapagliflozin,[31,32] Empagliflozin,[16,29] or Ertugliflozin[33] and for Any, All, or None of These Trials[a]

Study (Agent)	Adult Population With a Diagnosis of T2D (N)[a]	Adults With T2D Who Would Meet All Inclusion Criteria (N)	Adults With T2D Who Would Meet All Inclusion Criteria (% of All Adults With T2D)
Any SGLT2 inhibitor CVOT	23,941,512	9,766,031	40.8
Any SGLT2 inhibitor CVOT excluding DECLARE-TIMI 58	23,941,512	2,760,334	11.5
DECLARE-TIMI 58 (dapagliflozin)	23,941,512	9,540,711	39.8
CANVAS Program (canagliflozin)	23,941,512	2,112,939	8.8
EMPA-REG OUTCOME (empagliflozin)	23,941,512	986,003	4.1
VERTIS-CV (ertugliflozin)	23,941,512	1,136,829	4.8
All SGLT2 inhibitor CVOTs	23,941,512	239,261	1.0
No SGLT2 inhibitor CVOT	23,941,512	14,175,480	59.2

CANVAS indicates CANagliflozin cardioVascular Assessment Study; CV, cardiovascular; CVOT, cardiovascular outcomes trial; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.
[a]Data were derived from weighted analyses of a dataset of patients with T2D derived from the National Health and Nutrition Examination Survey.

FIGURE. Percentages of Adults With Type 2 Diabetes in the United States Who Would Have Met Inclusion Criteria for Cardiovascular Outcomes Trials With Canagliflozin,[20,30] Dapagliflozin,[31,32] Empagliflozin,[16,29] or Ertugliflozin[33,a]



[a]Data were derived from weighted analyses of a dataset of patients with type 2 diabetes derived from the National Health and Nutrition Examination Survey.

as hypertension, dyslipidemia, or chronic kidney disease, in addition to diabetes.[43] However, when CVOTs in T2D are planned, ideally the inclusion criteria should not be so restrictive as to jeopardize the applicability of findings from the study to patient populations that are encountered in real-world clinical practice.

As estimated by analyses of the NHANES data, the inclusion criteria in 3 of the studies were applicable to less than 10% of the US adult T2D population. All 3 of these CVOTs focused on patients who had a history of prior CVD or were considered to be at high risk of CV events (Table 1).[29,30,33] The original CANVAS study included 2 subgroups of patients, one in those at least 30 years of age with a history of symptomatic atherosclerotic vascular disease and one in those at least 50 years of age without a history of known CVD, but with 2 or more prespecified risk factors in addition to T2D.[30] More than 10,000 adults (mean age, 63 years) were included in the combined CANVAS and CANVAS-R analysis,[31] of whom 66% had a history of macrovascular atherosclerotic disease before the study.[32] Adults aged at least 18 years could participate in the EMPA-REG OUTCOME trial, but only if they were at a high risk of CV events, which were defined by various criteria (including a history of myocardial infarction, and the presence of multivessel coronary artery disease [CAD] or of single-vessel CAD plus evidence, for example, of prior unstable angina, stroke, or peripheral artery disease).[29] The study included more than 7000 patients at high risk of CV events with a mean age of 63 years.[16,29] The VERTIS-CV Study included patients with T2D at least 40 years of age, but again with specific CVD-related criteria, which specified a history of coronary, cerebral, or peripheral atherosclerotic disease;[33,37] data for the recruited patient population were not available at the time of writing this paper. By contrast, DECLARE-TIMI 58 included 2 subgroups, 1 of patients at least 40 years of age with a high risk of CV events because of a history of heart disease or stroke, and a broader subgroup group of women at least 60 years of age and men at least 55 years of age without a known history of CVD, but with at least 1 risk factor (dyslipidemia, hypertension, or tobacco smoking) in addition to T2D.[31,40] More than 17,000 patients (mean age, 64 years) were randomized for this study; of these, almost 7000 (41%) had established CVD prior to enrollment, and the remainder had multiple CV risk factors.[40] In DECLARE-TIMI 58, the definition of a T2D diagnosis was also broader than that in the other 3 studies (see Table 1). Patients were required to have been told by a physician that they had T2D and an A1C level of 6.5% to 12.0%.[32] However, participation in the EMPA-REG OUTCOME trial required patients to have an A1C level of 7.0% to 9.0% if T2D-treatment–naïve or 7.0% to 10.0% if they were already taking antihyperglycemic medication,[16] and for both CANVAS and VERTIS-CV, an A1C value of 7.0% to 10.5% was stipulated (Table 1).[20,37] Therefore, the DECLARE-TIMI 58 study population comprised a broad population of middle-aged and older adults with T2D, including patients with established CVD or CVD risk factors.

The present analysis included available data for key study criteria from a representative sample of the US population. The results demonstrated that broader patient selection criteria allow enrollment of a study population that is more generalizable to a substantial proportion of US adults with T2D.

Study Limitations

As a retrospective database analysis, this study had a number of limitations. A selection bias of patients who volunteered to participate in the survey, who may not be representative of the general US patient population, could have resulted in inaccurate estimation of T2D prevalence in this analysis of the NHANES data. Although the present analysis excluded patients who were pregnant, and therefore those who could have currently had gestational diabetes, it did not exclude patients who might have had gestational diabetes during a previous pregnancy. Data on CHF were extracted from the present analysis as it can be indicative of CVD; however, this could have also captured CHF unrelated to CVD, although this would have probably impacted findings on generalizability equally across all 4 trials. Furthermore, diabetes diagnoses were allocated from self-reported data rather than from diagnosis or confirmation by treating physicians, and application of the trial definitions of T2D to the NHANES data may also have been imprecise (eg, where there were differences in the criteria used in each CVOT to define T2D and the data collected for the NHANES).

Data on some study eligibility criteria were not available from the NHANES, and guidelines for resolving issues of missing or differing ways of defining/recording criteria were therefore included in the analysis protocol (Appendix 2). However, in such cases, the omission or estimation of certain criteria using data acquired in other formats or from other survey responses would be expected to give only approximations for the numbers meeting the CVOT criteria in question. It is likely that such an approach would have had disproportionate effects on estimation of those meeting key CV eligibility criteria. Finally, this analysis did not consider differences in CVOT size, duration, or design.

Conclusions

There were considerable differences among the 4 SGLT2 inhibitor CVOTs in the proportions of patients in the US adult T2D population who would have met the eligibility criteria and, therefore, in the generalizability and applicability of these trials. The DECLARE-TIMI 58 trial was by far the most generalizable, with approximately 40% of this population potentially being eligible for inclusion; however, only 12% of US adult T2D patients would have been eligible for inclusion in any of the other trials. This analysis shows that it is important to bear in mind the differences in eligibility criteria when considering the generalizability and applicability of CVOTs for T2D medications to real-world populations. ■

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