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ORIGINAL ARTICLE

Generalizability of glucagon-like peptide-1 receptor agonist cardiovascular outcome trials to the overall type 2 diabetes population in the United States

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Aim: To examine the generalizability of results from glucagon-like peptide-1 receptor agonist (GLP-1 RA) cardiovascular outcome trials (CVOTs) in the US type 2 diabetes (T2D) population.

Materials and methods: Patients enrolled or eligible for inclusion in four CVOTs (EXSCEL, LEADER, REWIND, and SUSTAIN-6) were examined in reference to a retrospective clinical database weighted to match the age and sex distribution of the US adult T2D population. We descriptively compared key baseline characteristics of the populations enrolled in each trial to those of the reference population and estimated the proportions of individuals in the reference population represented by those in the trials for each characteristic. We also estimated the proportions of individuals in the reference population that might have been enrolled in each trial based upon meeting the trial inclusion and exclusion (I/E) criteria.

Results: No trial's enrolled population perfectly matched the reference population in key characteristics. The EXSCEL population most closely matched in mean age (62.7 vs. 60.5 years) and percentage with estimated glomerular filtration rate <60 (18.6 vs. 17.3%), while REWIND most closely matched in HbA1c, sex distribution, and proportion with a prior myocardial infarction. Based on I/E criteria, 42.6% of the reference population were eligible for enrolment in REWIND, versus 15.9% in EXSCEL, 13.0% in SUSTAIN-6, and 12.9% in LEADER.

Conclusions: Although none of the trials are fully representative of the general population, among the four trials examined, results from baseline REWIND were found to be more generalizable to the US adult T2D population than those of other GLP-1 RA CVOTs.

KEYWORDS

CVOTs, dulaglutide, GLP-1 receptor agonist, type 2 diabetes

1 | INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality for individuals with diabetes.[1] To address this concern, in 2008 the U.S. Food and Drug Administration (FDA) issued guidelines for the pharmaceutical industry suggesting sponsors show that any new therapy for type 2 diabetes (T2D) will not result in an unacceptable increase in cardiovascular risk.[2] According to these FDA guidelines,

Phase 2 and Phase 3 trials should examine cardiovascular events, including cardiovascular mortality, myocardial infarction (MI), and stroke, and be designed to facilitate the performance of a meta-analysis at completion.[2] In practice, cardiovascular outcome trials (CVOTs) are subsequently conducted in order for the drug to continue to be available to patients.[3]

In response to this guidance, new T2D drug therapies, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs), are being

tested in CVOTs. Because the designs of these trials favour enrolment of patients with unusually high cardiovascular risk, including some with prior cardiovascular events or renal disease, it is unclear whether the results are applicable to the majority of patients with T2D who have no more than moderate risk of developing cardiovascular complications.[4] We therefore evaluated the extent to which the populations of patients enrolled in GLP-1 RA trials of agents used in the United States, or eligible to be enrolled, reflect the general population of adult patients with T2D.

2 | METHODS

2.1 | Databases

The primary source for representative US data was IQVIA Real World Data Adjudicated Claims (United States, Copyright © 2018, IQVIA, All Rights Reserved). This source contains information from insurance claims, diagnoses, procedures, and filled outpatient prescriptions. These data are linked to electronic medical records to provide additional information on laboratory test results and vital statistics for individual patients, which are fully deidentified and Health Insurance Portability and Accountability Act (HIPAA)-compliant. Data for the present study were analyzed for the time interval from 1 October 2012 through 30 September 2017.

Patients were identified as having T2D if they were aged ≥18 years with a diagnosis of T2D, and no diagnosis of type 1 diabetes, gestational diabetes, or pregnancy. Candidates were also required to have at least one recorded HbA1c and estimated glomerular filtration rate (eGFR) laboratory result. A total of 113 079 T2D patients were included in this cohort. Supporting Information Appendix A illustrates how each of the inclusion and exclusion (I/E) criteria affected the sample size of the T2D population.

Whereas the IQVIA database is generally representative of a commercially insured population < 65 years of age in the United States,[5] it may not perfectly reflect the distribution of the general population.[5,6] Information on age and sex of individuals with T2D from the 2013 to 2014 National Health and Nutrition Examination Survey (NHANES)[7] was therefore applied to the IQVIA data in order to more accurately represent all adults with T2D. This was conducted in the following fashion. First, adults with T2D in the NHANES database were identified using published algorithms,[8–10] and NHANES sampling weights for this population were saved to provide an unbiased representation of the US Census civilian non-institutionalized population.[11] Next, these sampling weights were then applied to the IQVIA data by sex and 5-year age group strata to impute a final representative population of 26 110 573 individuals with the same age and sex distribution as found in the NHANES adult T2D population.

Cardiovascular outcome trials testing the effects of GLP-1 RAs were selected from the U.S. Clinical Trials Registry[12] according to the following criteria. Trials were required to have a randomized interventional design; to compare a GLP-1 RA marketed in the United States with placebo; to study medically stable ambulatory patients with T2D; and to have a cardiovascular outcome as the primary endpoint.

2.2 | Analyses

The generalizability of findings from these CVOTs was examined in two ways. First, the participants actually enrolled into the trials were compared with the representative population with respect to six key patient characteristics: age, sex, body mass index (BMI), HbA1c, eGFR category, and prior MI. Selection of these characteristics was based upon them being reported in at least three of the trials of interest as well as in the reference population. Comparisons employed t-statistics to examine differences in continuous variables and chi-square statistics for differences in categorical variables. Additional analyses estimated the percentage of individuals in the representative population who matched each of the specific characteristics of people recruited into the several trials. For continuous variables (age, BMI and HbA1c), the number (and percentage) of people in the reference population who matched those enrolled in each trial was defined as the number for whom the continuous variables value was within the 95% confidence interval of the trial's value.[13] For categorical variables (sex, eGFR category and prior MI), the number (and percentage) of people in the reference population who matched those enrolled in each trial was estimated by applying the percentage of people with that characteristic in each trial (±5%) to the reference population.

We also examined how each of the CVOT I/E criteria affected the number of patients included in the reference population, based on the assumption that people included in each trial would have been randomly chosen from the subgroup of people in the reference population who met key I/E criteria. These six commonly measured key criteria include age, prior cardiovascular disease, HbA1c, renal function, BMI, and prescription medication use.[9,14] Table 1 lists the key I/E criteria and Supporting Information Appendix B provides a detailed summary of how the cardiovascular criteria for each of the studies were mapped to our retrospective population.

3 | RESULTS

The CVOT study search criteria identified four clinical trials: EXSCEL (EXenatide Study of Cardiovascular Event Lowering),[18] LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results),[19] REWIND (Researching cardiovascular Events with a Weekly INcretin in Diabetes),[14] and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes).[20] Two cardiovascular trials were excluded: the ELIXA trial because it enrolled exclusively T2D patients hospitalized with an acute coronary syndrome event in the past 180 days[21] and the HARMONY trial because albiglutide is not marketed in the United States.[22]

3.1 | Analysis based on the enrolled populations

Table 2 summarizes descriptive data for age, sex, BMI, HbA1c, eGFR, and prior MI, in the reference population and upon enrolment into each of the CVOTs. The mean age of the T2D population was 60.5 years, and 55.5% were male; mean HbA1c was 7.2%; 17.3% had a recorded eGFR value <60 mL/min/1.73m^2; the mean BMI was 33.2 kg/m^2; and 5.5% had a recorded diagnosis of MI in the previous

TABLE 1 Inclusion and exclusion criteria for cardiovascular outcome trials

| Criteria | Inclusion criteria (unless otherwise stated) | | | |
	EXSCEL[15]	LEADER[16]	REWIND[14]	SUSTAIN-6[17]
Cardiovascular	60% with ECVD[a]	ECVD or CV risk	ECVD, SCVD or CV risk	ECVD or CV risk
Age (years)	≥18	≥50 if ECVD or ≥60 if CV risk	≥50 if ECVD, ≥55 if SCVD or ≥60 if CV risk	≥50 if ECVD or ≥60 if CV risk
BMI (kg/m^2)	None	None	≥23	None
HbA1c (%)	≥7 and ≤10	≥7	≤9.5	≥7
Medication	Exclude patients who use insulin within 2 weeks of index or >3 oral classes in 3 months prior to index	Exclude patients who use a GLP-1 RA, DPP-4 inhibitor or pramlintide within 3 months of index[b]	Exclude patients who use premix or bolus insulin or >2 oral classes in 3 months prior to index	Exclude patients who use a GLP-1 RA or pramlintide within 3 months of index; exclude if use a DPP-4 inhibitor within 1 month of index; exclude if being treated with >2 classes of orals at index
eGFR (mL/min/1.73m^2)	≥30	# of patients with eGFR <30 restricted to 2.5% of population	≥15 and not on dialysis	None

Abbreviations: BMI, body mass index; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; ECVD, established cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SCVD, subclinical vascular disease.
[a]Proportion of patients with established cardiovascular disease is provided in the original study protocol. However, the amended protocol changes this to "approximately 70%". Use of the original protocol percentage will bias the estimate of the generalizability of EXSCEL upward.
[b]The trial also excluded insulin other than human NPH insulin or long-acting analogue within 3 months prior to screening. However, since they allowed for short-term use of insulin for intercurrent illness at investigator discretion, we did not use this criterion.

5 years. The patients in each trial significantly differed from those in the reference population with respect to all six of the baseline characteristics ($P < 0.05$). Patients in EXSCEL most closely matched the overall T2D population in mean age and percentage of individuals with eGFR <60 mL/min/1.73m^2. In contrast, patients in REWIND most closely matched the T2D population in mean baseline HbA1c, sex distribution, and the percentage of individuals with a prior MI. Patients in all three trials with information regarding a prior MI had a significantly higher percentage than those in the reference population. Specifically, >30% of those patients in SUSTAIN-6 and LEADER had a history of a prior MI compared with 16.2% in REWIND, and 5.5% in the reference population.

Estimates of the number and percentage of patients in the reference population who were similar to those enrolled in each of the four CVOTs with respect to age, sex, BMI, HbA1c, eGFR and prior MI are tabulated in Supporting Information Appendix C. Whereas the sex, BMI and HbA1c distribution of all four CVOTs yielded comparable numbers and percentages of patients in the reference population, the age distribution of patients enrolled in the EXSCEL trial, and proportion of patients with a prior MI enrolled in the REWIND trial, yielded the highest numbers and percentages of patients in the reference population compared with the other CVOTs. In contrast, the proportion of patients with an eGFR <60 mL/min/1.73m^2 in the SUSTAIN-6 trial yielded the lowest percentage of patients in the reference population compared with the other CVOTs. Finally, the number and

TABLE 2 Patient characteristics for adults with type 2 diabetes and adults enrolled in cardiovascular outcome trials (CVOTs) with GLP-1 RA use

| Characteristic | Adult T2D population | Patient characteristics from CVOTs | | | |
		EXSCEL[23]	LEADER[24]	REWIND[14]	SUSTAIN-6[17]
Age, years (mean ± SD)	60.5 ± 13.5	62.7 ± 9.9[a]	64.3 ± 7.2	66.2 ± 6.5	64.6 ± 7.4
Sex (%)					
Male	55.5%	62.0%	64.3%	53.7%	60.7%
Female	44.5%	38.0%	35.7%	46.3%	29.3%
BMI, kg/m^2 (mean ± SD)	33.2 ± 6.7	31.8 ± 5.9[a]	32.5 ± 6.3	32.3 ± 5.7	32.8 ± 6.2
HbA1c, % (mean ± SD)	7.2 ± 1.6	8.0 ± 1.2[a]	8.7 ± 1.5	7.3 ± 1.1	8.7 ± 1.5
eGFR, mL/min/1.73m^2 (%)					
<60	17.3%	18.6%	23.1%	22.2%	28.5%
≥60	82.7%	81.4%	76.9%	77.8%	71.5%
Prior myocardial infarction (%)	5.5%	Not reported	30.7%	16.2%	32.5%
Sample size	26 110 573	14 752	9340	9901	3297

This table compares the characteristics of the adult T2D population with reported characteristics from patients enrolled in each of the CVOTs. All differences between adult T2D population and the CVOTs are statistically significant ($P < 0.05$).
Abbreviations: BMI, body mass index; CVOT, cardiovascular outcome trial; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SD, standard deviation; T2D, type 2 diabetes.
[a]Data provided as means and interquartile ranges were converted to means and standard deviations assuming a normal distribution.[25]

percentage of patients in the reference population who were similar to those enrolled in the REWIND trial exceeded those in the other CVOTs examined when two or more of the six enrolment criteria had to be met (Supporting Information Appendix C).

3.2 | Analysis based on inclusion and exclusion criteria

Figure 1 displays the proportion of the reference population that might have been enrolled in the four trials if all of their main I/E criteria were met. Results indicate that REWIND would have included >2.5 times more T2D patients than EXSCEL and >3 times more T2D patients than LEADER and SUSTAIN-6. A total of 42.6% of the reference population might have been enrolled in REWIND, compared with 15.9% in EXSCEL, 13.0% in SUSTAIN-6, and 12.9% in LEADER. When each of the six I/E criteria were considered separately (Figure 2), the greatest proportion would have been included using the age criteria of EXSCEL, the HbA1c criteria of REWIND, and the prior cardiovascular disease criteria of REWIND.

3.3 | Sensitivity analysis

Similar results were noted when the analyses were repeated for the 113 074 patients in the IQVIA database without any adjustment to match the US T2D population in age and sex (Supporting Information Appendices D1–D3).

4 | DISCUSSION

This analysis estimates the proportion of all adults in the United States with T2D who could have been included in the four GLP-1 RA CVOTs. Application of key characteristics of patients actually enrolled in each trial suggested that the greatest proportion of the general population would have been included in each trial if they satisfied two or more enrolment criteria from the REWIND trial. Application of the I/E criteria based on key characteristics suggested that among the CVOTs examined, the REWIND trial criteria would have included the greatest proportion of the general population.

A quantitative analysis of the percentages of the general population matching those in the trial populations with regard to enrolment characteristics suggested differences among these groups. The analysis of the percentages of the general population matching those actually enrolled in the trials indicated that ~75% of the general population was represented by participants enrolled in SUSTAIN-6 with respect to renal function, compared with ~95% to 100% for the other CVOTs. With respect to prior MI, ~20% of the general population was represented in LEADER and SUSTAIN-6, and ~50% in REWIND.

Analysis of the potential generalizability of results from the same studies if all individuals in a general population who matched the entry criteria for each trial had been enrolled randomly suggested qualitatively similar but quantitatively more extreme patterns. Notably, when I/E criteria for each trial were applied to the general population, 42.6% would have been eligible for the REWIND trial, 15.9% for EXSCEL, 13.0% for SUSTAIN-6, and 12.9% for LEADER. A previous analysis using somewhat different methods found that 47.2% of the population might have been represented by randomly enrolled EXSCEL patients, 22.4% for REWIND, 12.8% for LEADER and 11.8% for SUSTAIN-6.[9] However, this analysis did not account for the EXSCEL protocol requirement that at least 60% of patients should have established cardiovascular disease.[15] Furthermore, the study exclusively used NHANES data, which do not include information on cardiovascular procedures, peripheral vascular disease, or episodes of hyperglycaemia and hypoglycaemia.[9]

Our analyses have several strengths. First, they considered and included all four of the CVOTs of GLP-1 RAs currently available in the United States that were conducted in ambulatory patients with T2D and have been completed. Second, they compared these CVOTs to all adults with T2D in the United States by combining two broadly representative databases. Third, unlike previous reports, our analyses compared the populations actually enrolled in the trials with the reference population and also assessed what proportion of patients in the reference population might have qualified for each trial based on the I/E criteria. The fact that both approaches, as well as a sensitivity analysis, yielded similar conclusions, support the robustness of the findings.

Notwithstanding these strengths, the analyses were limited by the data available in the two databases used to construct the reference population (IQVIA and NHANES), which limited the enrolment and I/E
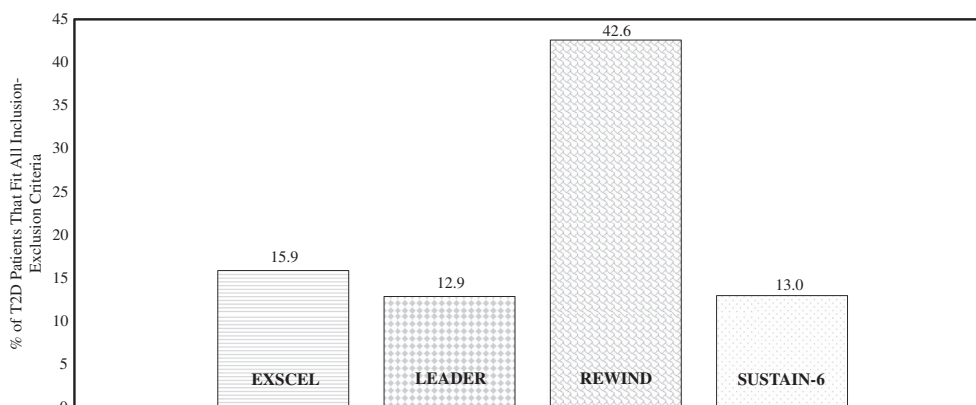
Illustrates the percentage of T2D adult patients that fit all of the inclusion-exclusion criteria. See Table 1 for a description of these criteria.

FIGURE 1 Overall generalizability of cardiovascular outcome trials inclusion–exclusion criteria
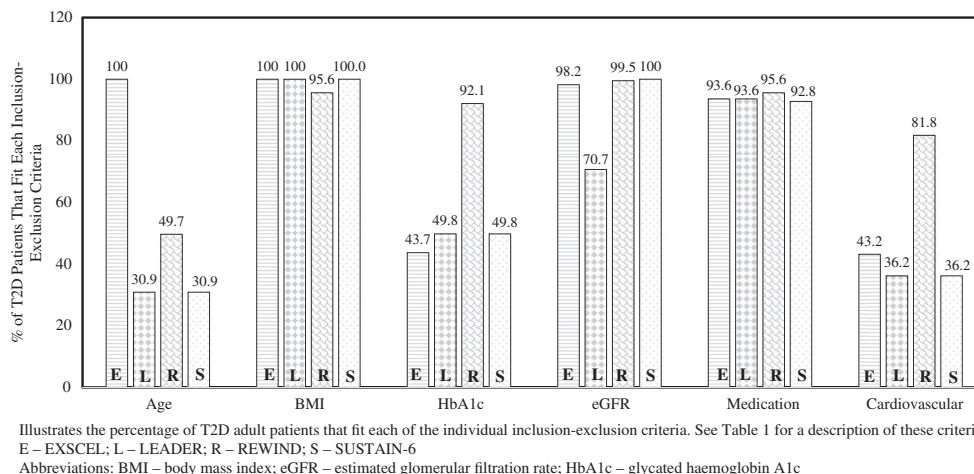
Illustrates the percentage of T2D adult patients that fit each of the individual inclusion-exclusion criteria. See Table 1 for a description of these criteria.
E – EXSCEL; L – LEADER; R – REWIND; S – SUSTAIN-6
Abbreviations: BMI – body mass index; eGFR – estimated glomerular filtration rate; HbA1c – glycated haemoglobin A1c

FIGURE 2   Generalizability of individual cardiovascular outcome trials inclusion–exclusion criteria

criteria that were considered. Clearly, an analysis that considered a greater number of enrolment and I/E criteria may have yielded different findings. Nevertheless, the criteria used were typical of those used to recruit patients to CVOTs, and data regarding them were available for this analysis. These analyses are also limited by the possibility that the reference database may not have accurately represented the entire population of people with T2D in the United States, and by the fact that the percentage of patients with prior MI in the EXSCEL trial was not available for consideration. In addition, the quantitative analyses of data for the enrolled populations assumed that the key characteristics assessed were normally distributed within each trial, an assumption that could not be tested because the individual-participant data from these trials were not available. Moreover, this assumption may not be true because study I/E criteria may have truncated distribution of some of these variables. Finally, the analysis did not examine all alternative methods of examining generalizability of clinical trial results.[26,27]

In conclusion, the CVOTs studied differ in their I/E criteria, in other factors affecting enrolment, and thus in the generalizability of their results to a representative population with T2D. None of them fully represents the population of adults with T2D in the United States, and they differ in specific clinical characteristics of their participants. Of the CVOTs analyzed, the greatest proportion of the general population of adults in the United States with T2D would have been included in the REWIND trial, but all four trials are relevant to important percentages of the T2D general population.

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CONFLICT OF INTEREST

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Author contributions

M.J.L. was responsible for the statistical considerations in the analysis. M.J.L. and K.S.B. are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the design of this analysis and participated in critical reviewing and interpreting the data for the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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SUPPORTING INFORMATION

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