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Cardiovascular risk profiles: A cross-sectional study evaluating the generalizability of the glucagon-like peptide-1 receptor agonist cardiovascular outcome trials REWIND, LEADER and SUSTAIN-6 to the real-world type 2 diabetes population in the United Kingdom

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Abstract

Aims: To determine the proportion of UK patients with type 2 diabetes (T2D) who meet the cardiovascular (CV) or combined CV/core eligibility criteria used for the CV outcome trials (CVOTs) of UK-marketed glucagon-like peptide-1 receptor agonists (GLP-1RAs) showing CV benefit (dulaglutide in REWIND, liraglutide in LEADER and injectable semaglutide in SUSTAIN-6).

Materials and Methods: Adults with T2D on/before June 2018 were identified from the UK Clinical Practice Research Datalink GOLD primary care database and linked to Hospital Episode Statistics data (Protocol 19_262). Patient CV and clinical data were evaluated against the CVOT eligibility criteria. Data were analysed descriptively.

Results: The study cohort (N = 33 118 patients with T2D) had a mean (standard deviation) age of 66.0 (13.3) years and 56.6% were male. Almost two-thirds (64.5%) of the study cohort met the CV criteria for REWIND, versus 43.0% for both LEADER and SUSTAIN-6. The proportions of the study cohort who met the CVOT criteria of "established CV disease" and "CV risk factors only" for REWIND were 22.4% and 42.1%, respectively, versus 38.7% and 4.3%, respectively, for both LEADER and SUSTAIN-6. The proportions of patients satisfying both CV and core criteria were 44.4% for REWIND, 13.3% for LEADER and 13.5% for SUSTAIN-6. Study findings remained consistent when restricted to GLP-1RA users.

Conclusions: REWIND captured a trial population more representative of the real-world T2D population in the United Kingdom than LEADER or SUSTAIN-6 with regard to both CV and combined CV/core eligibility criteria.

KEYWORDS
cardiovascular disease, cardiovascular outcome trials, GLP-1RA, real-world evidence, type 2 diabetes

1 | INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality among people with type 2 diabetes (T2D).[1,2] In the United Kingdom, approximately one-third of patients with T2D have concomitant established CVD.[3] Reducing possible long-term cardiovascular (CV) complications is an important goal of diabetes management. To prevent an increase in CV risk with the introduction of new antidiabetic therapies, the US Food and Drug Administration and the European Medicines Agency issued guidelines to the pharmaceutical industry concerning evaluation of the CV safety of any new T2D drugs.[4,5] Multiple CV outcome trials (CVOTs) evaluating glucose-lowering therapies of various classes have been conducted to comply with these guidelines, with none reporting an increase in risk of CV events.[6,7] Some agents in two classes of glucose-lowering therapy, the sodium-glucose cotransporter 2 inhibitors and the glucagon-like peptide-1 receptor agonists (GLP-1RAs), showed not only CV safety, but also statistically significant reductions in CV events in patients with T2D when compared with placebo.[1,8-10] The reduction in risk of CV events associated with GLP-1RAs probably occurs through a variety of complex mechanisms, including CV risk factor modification, direct cardiac contractile impact and improvement in endothelial dysfunction.[11]

In the GLP-1RA class, three commercially available drugs in the United Kingdom—dulaglutide (REWIND trial, ClinicalTrials.gov identifier: NCT01394952),[12] liraglutide (LEADER trial, NCT01179048)[13] and injectable semaglutide (SUSTAIN-6 trial, NCT01720446)[14] —demonstrated statistically significant CV benefit in patients with T2D. All three CVOTs included patients with established CVD and patients with CV risk factors only. The "established CVD" groups all essentially included patients with established coronary heart disease, established cerebrovascular disease or established peripheral vascular disease, but differed in their categorization of patients with chronic kidney disease (CKD). In REWIND, patients with CKD were included in the "CV risk factors-only" group, whereas in LEADER and SUSTAIN-6, patients with CKD of stage 3 or greater were included in the established CVD group.[15] In REWIND, LEADER and SUSTAIN-6, according to each study's own definition, 31.5%, 81.3% and 83%, respectively, of the included patients had established CVD.[12-14] In REWIND, there was consistent benefit in patients with and without established CVD at baseline.[12] In contrast, in LEADER and SUSTAIN-6, although benefit was demonstrated for patients with established CVD,[13,14] there was no evidence of CV benefit in the 18.7% and 17% of patients, respectively, with CV risk factors only.[8]

The inclusion criteria of CVOTs are often aimed at enriching the study population with patients with high CV risk in order to accrue sufficient events in a timely manner.[6,16] While this approach is efficient, and not inappropriate given the primary safety-related purpose of the studies, a major limitation is that study populations that have been enriched with patients with particularly high CV risk could fail to represent patients in the general population, limiting generalizability of the conclusions regarding CV benefit.

Observational studies can be utilized to determine if the populations included in randomized clinical trials are representative of real-world patient populations.[17] Several studies have addressed the question of the generalizability of the GLP-1RA CVOT results to the general T2D population.[18-21] A large database study weighted to match the age and sex distribution of the US adult T2D population showed that 42.6% of the reference population were eligible for enrolment in REWIND, 12.9% in LEADER and 13.0% in SUSTAIN-6.[19] Comparable results were obtained from the analysis of a database based on Italian diabetes outpatient clinics.[20] However, these studies focused on the overall eligibility criteria of the CVOTs, rather than primarily on the CV criteria, which are the clear focus of the CVOTs, and did not differentiate between patients with established CVD or CV risk factors only. Furthermore, the extent of the applicability of the populations included in these studies to the UK population is uncertain.

The primary objective of the present study was to determine what proportion of a large, nationally representative sample of T2D patients in the United Kingdom would meet the CV risk profile delineated by the CV eligibility criteria of REWIND, LEADER and SUSTAIN-6. Other objectives of this study were to determine the proportion of T2D patients who met the core eligibility criteria (including CV eligibility criteria) in these trials, and to describe the basic clinical and demographic characteristics of the population with T2D in UK primary care. Also, we evaluated the proportion of patients with T2D who would meet the CV criteria for the subgroups with established CVD and CV risk factors only, and if the study findings were consistent when only GLP-1RA users were considered.

2 | MATERIALS AND METHODS

In this cross-sectional study, adult patients with a diagnosis of T2D in the primary care setting were assessed to establish the proportion who would meet the CV or combined CV/core entry criteria for REWIND, LEADER and SUSTAIN-6. Patients were identified using linked patient data from the UK Clinical Practice Research Datalink (CPRD) GOLD primary care database and the Hospital Episode Statistics (HES) Admitted Patient Care dataset. The CV and overall clinical profiles of the patients on/before 30 June 2018 were assessed.

2.1 | Databases

The CPRD is an ongoing database of anonymized medical records from UK general practitioners (GPs), with coverage, as of February

2021, of over 19.5 million patients from 949 practices in the United Kingdom.[22] The database contains a population that is broadly representative of the UK general population in terms of age, sex and ethnicity, and includes data on demographics, symptoms, tests, diagnoses, therapies and health-related behaviours.

To obtain more complete information on clinical history of past major CV events than would be available using only CPRD data, the study dataset included patients with CPRD data that could be linked to HES,* specifically the Admitted Patient Care dataset, which contains data from hospital admissions at all NHS hospitals in England. Data linkage between CPRD and HES Admitted Patient Care was performed by NHS Digital in accordance with an established and robust methodology.[23] Because this study only used T2D patients eligible for linkage to HES, the sample was restricted to patients in England only. The use of linked CPRD-HES data was approved by the CPRD Independent Scientific Advisory Committee (ISAC Protocol No. 19_262; approved 18 December 2019). The study population of patients with T2D was identified from the CPRD. Data from the CPRD were obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone.

2.2 | Patient population

Inclusion criteria for the study cohort from the CPRD database were: Patients with T2D on or before 30 June 2018 (selected as the cross-sectional assessment date), defined either by medical records in the CPRD with a diagnosis code indicative of T2D (read codes), or treatment with at least two classes of glucose-lowering medications from prescription records; at least 1 year of history in the CPRD ("registered in practice") prior to the assessment date; at least one record of activity (eg, consultation, prescription, etc.) in the CPRD after 1 January 2018 (patients meeting this criterion were assumed to be active in the database on the assessment date); data from a practice designated as "up to standard" at least 1 year prior to the date on which the patient met the T2D inclusion; aged ≥18 years on the assessment date; no death record before or on the assessment date; patient CPRD record of acceptable research quality (ie, excluding patients with noncontinuous follow-up, or patients with poor data recording that raises suspicion as to the validity of that patient's record); and eligibility for linkage to HES.

Patients were excluded if meeting any of the following criteria: at least one record of a diagnostic code indicative of type 1 diabetes before or on the assessment date; absence of at least one record of estimated glomerular filtration rate (eGFR), glycated haemoglobin (HbA1c) or body mass index (BMI) at any time on or before the assessment date.

2.3 | Study analyses

The definitions of the core and CV inclusion and exclusion criteria for the three CVOTs are detailed in Supporting Information Tables S1 to S3. Core eligibility criteria included age, HbA1c levels, eGFR, BMI, and prior medication use. However, these differed across trials: SUSTAIN-6 did not include eGFR, and LEADER and SUSTAIN-6 did not include BMI.

In the three CVOTs, CV eligibility criteria considered established CVD and CV risk factors only, but the definitions of these categories were based on each study's own definition and differed slightly. The CV eligibility criteria for LEADER and SUSTAIN-6 were identical once they were operationalized for the purposes of this study.

Data for the study were derived either from the CPRD only, or from a combination of the CPRD and HES. In cases where exact CVOT CV criteria could not be identified in the CPRD or HES, approximations were used in line with a previous study[19] and clinically informed proxies were used (eg, a diagnosis of peripheral artery disease was used as a proxy for ankle-brachial pressure index <0.9; a BMI of ≥30 kg/m^2 was used as a proxy for waist-to-hip ratio >1.0 [men] or >0.8 [women]). The criterion of >50% stenosis of coronary, carotid or lower extremity arteries, present in all three CVOTs, was omitted from the analyses due to insufficient data/medical codes available in the CRPD or HES.

TABLE 1 Demographic and clinical characteristics of the study cohort and the cardiovascular outcome trial patient populations

Demographic and clinical characteristics	Study cohort (N = 33 118)	REWIND (N = 9901)[12]	LEADER (N = 9340)[13]	SUSTAIN-6 (N = 3297)[14]
Age, years	66.0 (13.3)	66.2 (6.5)	64.3 (7.2)	64.6 (7.4)
Gender male, %	56.6	53.7	64.3	60.7
Time since T2D diagnosis, years	7.6 (5.2)[a]	10.0 (7.2)	12.7 (8.0)	13.9 (8.1)
BMI, kg/m^2	30.8 (6.0)[b]	32.3 (5.7)	32.5 (6.3)	32.8 (6.2)
HbA1c, %	7.3 (1.5)[b]	7.3 (1.1)	8.7 (1.5)	8.7 (1.5)
eGFR, mL/min/1.73 m^2	77.8 (22.8)[b]	77.6 (24.1)	—	—
eGFR <60 mL/min/1.73 m^2, %	20.2	22.2	21.8	28.5

Note: Data are presented as mean (standard deviation), unless otherwise stated.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; T2D, type 2 diabetes.

[a]As at assessment date.

[b]Most recently recorded test value as at assessment date.

Patients with a history of treatment with a GLP-1RA (exenatide, dulaglutide, liraglutide, lixisenatide or semaglutide) on or prior to the assessment date were considered GLP-1RA users.

A sensitivity analysis was carried out to determine the proportion of GLP-1RA users who met the CV criteria for the subgroups with established CVD and risk factors only separately, for REWIND, LEADER and SUSTAIN-6.

Given the descriptive, noncomparative nature of this study, no statistical testing was performed; all data were analysed descriptively. All data analysis was executed using STATA 16.1 statistical software.[24]

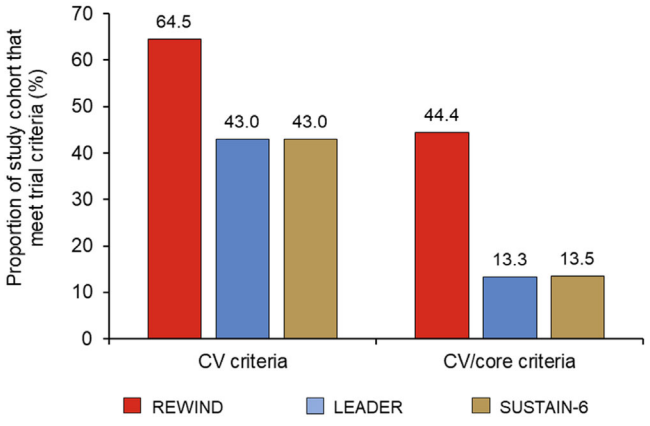

FIGURE 1 Proportion of study cohort (N = 33 118) meeting cardiovascular (CV) or CV/core criteria for the three CV outcome trials

3 | RESULTS

Of 802 799 patients in the United Kingdom with at least one T2D diagnosis code or prescriptions of two classes of glucose-lowering medications initially extracted from the CPRD, 33 118 patients (4.1%) were eligible for inclusion in the study cohort (Supporting Information, Figure S1). The study cohort had a mean (standard deviation [SD]) age of 66.0 (13.3) years, and 56.6% were male (Table 1). As at the assessment date, the mean (SD) duration of T2D was 7.6 (5.2) years.

The patient characteristics of the study cohort for age, gender and HbA1c levels were more closely aligned to the REWIND population than to the LEADER and SUSTAIN-6 populations (Table 1).

A comparison of the patient characteristics relating to CV criteria showed that 21 369 patients (64.5%) met the CV entry criteria for REWIND compared with 14 263 patients (43.0%) for both LEADER and SUSTAIN-6. The numbers of patients who met each specific CV entry criterion are presented in Supporting Information Tables S4 and S5. When considering both CV and core entry criteria, 44.4%, 13.3% and 13.5% of the study cohort met the entry criteria for REWIND, LEADER and SUSTAIN-6, respectively (Figure 1).

The proportion of patients in the study cohort that met each core criterion is shown in Figure 2A. Aside from the age criterion, which was determined by eligibility for the CV entry criteria, BMI was the greatest cause of ineligibility for REWIND, although this was in part driven by a large proportion of patients with missing BMI data in the 2 years prior to the assessment date (10.8%). Of those with BMI records in this period, 6.2% of patients had a BMI value considered ineligible (<23 kg/m^2). In contrast, HbA1c was the greatest cause of

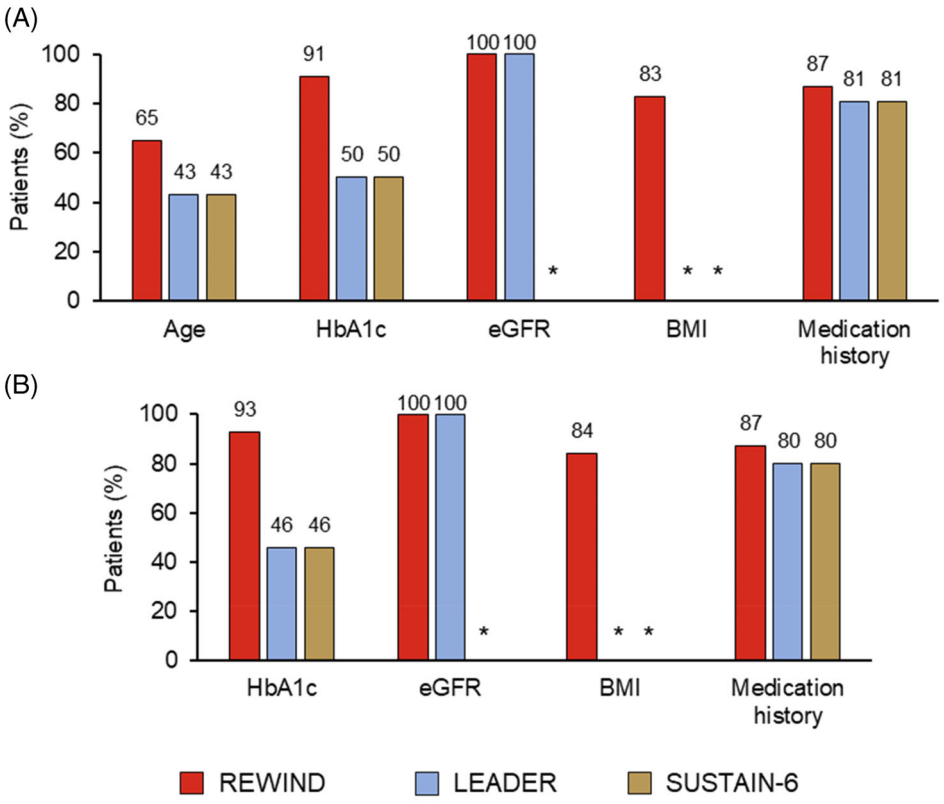

FIGURE 2 Proportion of the study cohort (N = 33 118) meeting each criterion for the three cardiovascular outcome trials (CVOTs) (A), and the proportion of patients who met cardiovascular (CV) entry criteria who also met each of the other core criteria (B). In (A) eligibility for the age core criterion was determined by eligibility for CV entry criteria. For estimated glomerular filtration rate (eGFR) the criterion was ≥15 mL/min/1.73 m^2 at most recent measurement on or prior to the assessment date. *CVOT did not apply this core criterion. BMI, body mass index; HbA1c, glycated haemoglobin

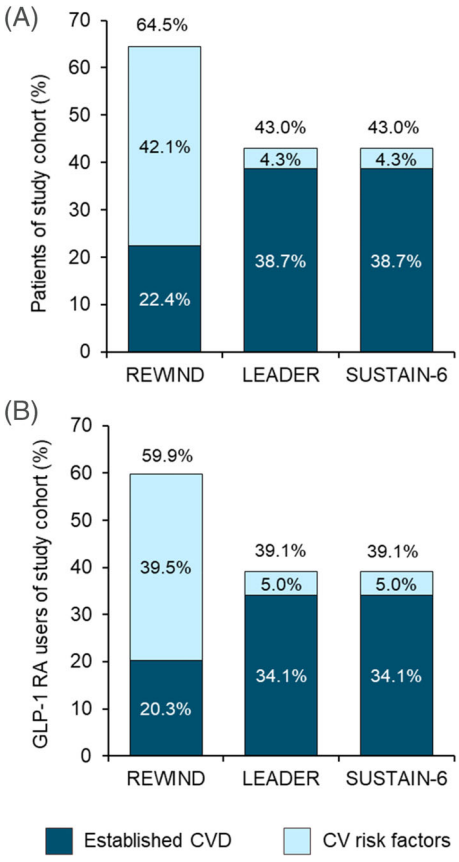

FIGURE 3 Patient subclassification per cardiovascular (CV) outcome trial for "established CV disease (CVD)" vs. "CV risk factors" of study cohort (N = 33 118) (A), and for glucagon-like peptide-1 receptor agonist (GLP-1RA) users (N = 2056) (B). For patients satisfying both 'established CVD' and 'CV risk factors' criteria, the former took precedence

ineligibility for LEADER and SUSTAIN-6, due to the requirement for HbA1c levels ≥7.0% (for REWIND the HbA1c criterion for eligibility was ≤9.5%). The proportion of the total number of patients who met all trial CV entry criteria is presented in Figure 2B.

The proportion of patients who met the CV inclusion criteria in the established CVD and CV risk factors-only subgroups for each study was determined (Figure 3). For REWIND, 22.4% met the established CVD criteria and 42.1% met the CV risk factors-only criteria, while for LEADER and SUSTAIN-6, a far greater proportion were classified as having established CVD (38.7%) compared with those classified as having CV risk factors only (4.3%). When restricted to the subgroup of GLP-1RA users (N = 2056; 6.2% of the patients in the study cohort), 59.9% of the patients met the CV entry criteria for REWIND and 39.1% of patients met the CV entry criteria for both LEADER and SUSTAIN-6. The numbers of patients who met each specific CV entry criterion are presented in Supporting Information Tables S6 and S7. Slightly lower proportions of GLP-1RA users were classified as having established CVD and CV risk factors only for REWIND, LEADER and SUSTAIN-6 compared with the analysis of the full study cohort (Figure 3).

4 | DISCUSSION

This descriptive study analysed the proportion of a nationally representative sample of UK patients with T2D who would have met the eligibility criteria for the three UK-marketed GLP-1RA CVOTs showing CV benefit: REWIND, LEADER and SUSTAIN-6. The results showed that a larger proportion of the real-world UK T2D patient population would meet the CV criteria for REWIND (64.5%) compared with LEADER and SUSTAIN-6 (both 43.0%). When both core eligibility criteria and CV criteria were considered, a larger proportion of the real-world UK T2D patient cohort met the criteria for REWIND (44.4%) than for both LEADER (13.3%) and SUSTAIN-6 (13.5%).

The results presented in this study are consistent with a similar study conducted in the United States, which found that more than three times the number of T2D patients met the REWIND eligibility criteria (42.6%) than the eligibility criteria from LEADER (12.9%) or SUSTAIN-6 (13.0%).[19] A recent study of Italian diabetes outpatient clinics also showed similar results: 35.8% of patients would have been eligible for REWIND, 9.4% for LEADER and 10.1% for SUSTAIN-6.[20]

The demographic characteristics of the present study cohort were broadly comparable to the demographic characteristics of the study populations of each of the three trials. However, unlike LEADER and SUSTAIN-6, the mean HbA1c level in REWIND was equivalent to the mean HbA1c level in the present study cohort. The higher baseline HbA1c among patients in LEADER and SUSTAIN-6 was probably a consequence of the core criterion requiring an HbA1c level of ≥7.0% in LEADER and SUSTAIN-6, compared with ≤9.5% in REWIND.[12-14]

In REWIND, a consistent benefit for both patients with established CVD and those with CV risk factors only was demonstrated, whereas LEADER and SUSTAIN-6 only showed benefit for those with established CVD. It should be noted that the populations included in LEADER and SUSTAIN-6 were more heavily enriched with patients with established CVD (81.3% and 83.0%, respectively) compared with REWIND (31.5%).[12-14] Almost two-thirds (64.5%) of the study cohort met the CV inclusion criteria for REWIND; 22.4% met the established CVD criteria and 42.1% met the CV risk factors-only criteria. For LEADER and SUSTAIN-6, 43.0% of the study cohort met the CV inclusion criteria; 38.7% met the established CVD criteria and 4.3% met the CV risk factors-only criteria.

This is the first study to report the representativeness of the "established CVD" and "CV risk factors-only" subgroups from the CVOTs, a particularly important distinction given the guidance that the generalizability of the REWIND data, but not the LEADER or SUSTAIN-6 data, extends to include a primary prevention population.[25-28]

A limitation of the comparative analysis of studies on CV benefit is differences in the criteria for the definition of established CVD or CV risk factors only. The proportion of eligible patients with established CVD, as defined in LEADER and SUSTAIN-6, was greater than in REWIND, and the inclusion of patients with CKD stage ≥3 in this subgroup in LEADER and SUSTAIN-6, but not in REWIND, is a likely explanation for this effect. These results highlight the need for objective and standardized definitions of CVD in the inclusion and

exclusion criteria of future trials, especially with respect to the presence of CKD.[29]

The findings presented in this study must be viewed within the limitations of the methodology employed. As with any database study, data could be missing, incomplete or inaccurate. For example, diagnoses were identified using Read and International Classification of Diseases 10th revision codes, which could contain errors and result in misclassification bias. When operationalizing the criteria for implementation into the study data (ie, linked CPRD-HES), validated code lists or algorithms were used, where available, but some had to be developed for the study. Code lists were developed and compiled after extensive analysis and validation by a medical team including a practising GP and a cardiologist. Also, BMI may have been only recorded in patients with prior weight issues or health conditions, thus biasing the global results. Although BMI assessment is a quality outcome criterion in T2D primary care management in the UK—hence measurements of BMI are expected to be available—a large proportion of patients (10.8%) were determined to have missing BMI data in the previous 2 years, and this was a leading cause of ineligibility due to BMI with regard to the REWIND criteria. That the methodology restricted the dataset to patients from England is a potential limitation; however, the standard of care for patients with T2D in England should not differ greatly from that in the rest of the United Kingdom and other developed nations.

In conclusion, the results of this study suggest that the patient population of REWIND was more representative of the real-world T2D patient population in the United Kingdom compared with those of LEADER and SUSTAIN-6, with 64.5% of the cohort meeting the CV entry criteria for REWIND compared with 43% for both LEADER and SUSTAIN-6. The study also provided insights into the representativeness of the "established CVD" and "CV risk factors-only" subgroups from each of the studies, a particularly important distinction given the guidance around broader generalizability of the REWIND data to include a primary prevention population. When applying additional core criteria, the proportions of patients eligible decreased to 44.4% for REWIND, 13.3% for LEADER and 13.5% for SUSTAIN-6. Study findings remained consistent when restricted to GLP-1RA users. The patient demographics more closely resembled the population baseline characteristics for REWIND, with a mean HbA1c of 7.3%. Understanding the differences and similarities of the study populations is critical for the correct interpretation of outcomes and ultimately for the design of data-driven therapeutic algorithms for the benefit of patients. The complexity introduced by the differences in study populations and subgroup definitions reinforces the importance of careful consideration of these in the design of future CVOTs conducted for diabetes therapies.

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CONFLICT OF INTEREST

Joanne Webb, Julie Mount, Lill-Brith von Arx, Jonathan Rachman are employees of Eli Lilly and Company. Joanne Webb and Julie Mount are minor shareholders of Eli Lilly and Company. Dionysis Spanopoulos is a former employee of Eli Lilly and Company. Robert Wood, Theo Tritton and Olivia Massey are employees of Adelphi Real World, who were funded by Eli Lilly and Company to conduct this research. Iskandar Idris has received payment and/or honoraria from Eli Lilly and Company, Novo Nordisk, Astra Zeneca, MSD, Boehringer Ingelheim, and has participated on Data Safety Monitoring Boards or Advisory Boards for Eli Lilly and Company, Novo Nordisk and MSD.

AUTHOR CONTRIBUTIONS

Joanne Webb made substantial contributions to the design of the work, the interpretation of data and critical revision of the manuscript. Julie Mount made substantial contributions to the conception of the work, the design of the work, the interpretation of data and critical revision of the manuscript. Lill-Brith von Arx made substantial contributions to the conception of the work, the design of the work, the analysis of data, the interpretation of data, the drafting and critical revision of the manuscript. Jonathan Rachman made substantial contributions to the conception of the work, the design of the work, the interpretation of data and critical revision of the manuscript. Dionysis Spanopoulos made substantial contributions to the design of the work, the analysis of data and critical revision of the manuscript. Robert Wood made substantial contributions to the design of the work, the analysis of data, the interpretation of data and critical revision of the manuscript. Theo Tritton made substantial contributions to the design of the work, interpretation of data and critical revision of the manuscript. Olivia Massey made substantial contributions to the design of the work, the analysis of data, interpretation of data and critical revision of the manuscript. Iskandar Idris made substantial contributions to the design of the work, interpretation of data, the analysis of data and critical revision of the manuscript. Joanne Webb, Julie Mount, Lill-Brith von Arx, Jonathan Rachman, Dionysis Spanopoulos, Robert Wood, Theo Tritton, Olivia Massey and Iskandar Idris gave final approval of the manuscript to be submitted and participated sufficiently in the work to agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ENDNOTE

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14580.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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