Cardiovascular risk profiles: A cross-sectional study evaluating the generalisability 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 UK

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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 of the CV outcome trials (CVOTs) of UK-marketed glucagon-like peptide-1 receptor agonists (GLP-1 RAs) 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 CVOTs' eligibility criteria. Data were analysed descriptively.

Results: The study cohort (N=33,118 patients with T2D) had a mean (SD) 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 CVOTs' 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 proportion of patients satisfying both CV and core criteria was 44.4% for REWIND, 13.3% for LEADER and 13.5% for SUSTAIN-6. Study findings remained consistent when restricted to GLP-1 RA users.

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

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality among people with type 2 diabetes (T2D).[1,2] In the UK, 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 co-transporter 2 (SGLT2) inhibitors and the glucagon-like peptide-1 receptor agonists (GLP-1 RAs), 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-1 RAs likely occurs through a variety of complex mechanisms, including CV risk factors modification, direct cardiac contractile impact and improvement in endothelial dysfunction.[11]

In the GLP-1 RA class, three commercially available drugs in the UK – 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 the categorisation 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 generalisability of the conclusions regarding CV benefit.

Observational studies can be utilised to determine if the populations included in randomised clinical trials are representative of real-world patient populations.[17] Several studies have addressed the question of the generalisability of the GLP-1 RA CVOTs' 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 focussing 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 this study was to determine what proportion of a large, nationally representative sample of T2D patients in the UK 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-1 RA users were considered.

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.

Databases

The CPRD is an ongoing database of anonymised medical records from UK general practitioners (GPs), with coverage, as of February 2021, of over 19.5 million patients from 949 practices in the UK.[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-Dec-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.

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 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 (e.g. consultation, prescription, etc.) in 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 on the assessment date; no death record before or on the assessment date; patient CPRD record of acceptable research quality (i.e. excluding patients with non-continuous 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.

Study analyses

The definitions of the core and CV inclusion and exclusion criteria for the three CVOTs are detailed in Supplementary Information Tables S1–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 operationalised for the purposes of this study.

Data for the study were derived either from the CPRD only, or from a combination of CPRD and HES. In cases where exact CVOT CV criteria could not be identified in CPRD or HES, approximations were used in line with a previous study[19] and clinically-informed proxies were used (e.g. 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.

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

A sensitivity analysis was carried out to determine the proportion of GLP-1 RA 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, non-comparative 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]

Results

Of 802,799 patients in the UK 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 (see Supplementary 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 number of patients who met each specific CV entry criterion are presented in Supplementary 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 of 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 ineligibility for LEADER and SUSTAIN-6, due to the requirement for HbA1c ≥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 established CVD (38.7%) compared with those classified as CV risk factors only (4.3%). When restricted to the subgroup of GLP-1 RA users (N=2,056; 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 number of patients who met each specific CV entry criterion are presented in Supplementary Information Tables S6 and S7. Slightly lower proportions of GLP-1 RA users were classified as established CVD and CV risk factors only for REWIND, LEADER and SUSTAIN-6 compared with the analysis of the full study cohort (Figure 3).

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-1 RA 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 US, which found that more than three times the number of T2D patients met REWIND eligibility criteria (42.6%) than the eligibility criteria from LEADER (12.9%) or SUSTAIN-6 (13.0%).[19] Also, 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]

Demographic characteristics of the 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 of REWIND was equivalent to the mean HbA1c of the study cohort. The higher baseline HbA1c among patients in LEADER and SUSTAIN-6 was likely a consequence of the core criterion requiring a HbA1c 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 generalisability 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 of CV benefit is the 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 standardised 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 ICD-10 codes, which could contain errors and result in misclassification bias. When operationalising the criteria for implementation into the study data (i.e. 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 practicing 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 against the REWIND criteria. That the methodology restricted the data set 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 of the rest of the UK and other developed nations.

Conclusions

The results of this study suggest that the patient population of REWIND was more representative of the real-world T2D patient population in the UK compared with 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 generalisability 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-1 RA 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 to design of data-driven therapeutic algorithms for the benefit of patients. The complexity introduced by the differences in study populations and sub-group definitions reinforces the importance of careful consideration of these in the design of future CVOTs conducted for diabetes therapies.

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Conflicts 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 Board or Advisory Boards for Eli Lilly and Company, Novo Nordisk and MSD.

Author contributions

Joanne Webb has made substantial contributions to the design of the work, the interpretation of data and critical revision of the manuscript.

Julie Mount has 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 has 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 has 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 has made substantial contributions to the design of the work, the analysis of data and critical revision of the manuscript.

Robert Wood has 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 has made substantial contributions to the design of the work, interpretation of data and critical revision of the manuscript.

Olivia Massey has made substantial contributions to the design of the work, the analysis of data, interpretation of data and critical revision of the manuscript.

Iskandar Idris has 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 give final approval of the manuscript to be submitted and have 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.

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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Figure Legends

Figure 1 Proportion of study cohort (N=33,118) meeting CV or CV/core criteria for the three CVOTs. CV, cardiovascular; CVOTs, CV outcome trials.

Figure 2 Proportion of the study cohort (N=33,118) meeting each criterion for the three CVOTs (A), and the proportion of patients who met 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 eGFR the criterion was ≥15 mL/min/1.73m^2 at most recent measurement on or prior to the assessment date.

* CVOT did not apply this core criterion.

BMI, body mass index; CV, cardiovascular; CVOTs, CV outcome trials; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

Figure 3 Patient subclassification per CVOT for ‘established CVD’ vs ‘CV risk factors’ of study cohort (N=33,118) (A), and for GLP-1 RA users (N=2,056) (B). For patients satisfying both ‘established CVD’ and ‘CV risk factors’ criteria, the former took precedence.

CV, cardiovascular; CVD, cardiovascular disease; CVOTs, CV outcome trials; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Table 1 Demographic and clinical characteristics of the study cohort and the CVOTs' patient populations

Demographic and clinical characteristics	Study cohort (N=33,118)	REWIND (N=9,901)[12]	LEADER (N=9,340)[13]	SUSTAIN-6 (N=3,297)[14]
Age (years), mean (SD)	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), mean (SD)	7.6 (5.2)[a]	10.0 (7.2)	12.7 (8.0)	13.9 (8.1)
BMI, kg/m^2, mean (SD)	30.8 (6.0)[b]	32.3 (5.7)	32.5 (6.3)	32.8 (6.2)
HbA1c (%), mean (SD)	7.3 (1.5)[b]	7.3 (1.1)	8.7 (1.5)	8.7 (1.5)
eGFR (mL/min/1.73 m^2)				
mean (SD)	77.8 (22.8)[b]	77.6 (24.1)	–	–
<60, %	20.2	22.2	21.8	28.5

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

BMI, body mass index; CVOTs, cardiovascular outcome trials; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SD, standard deviation; T2D, type 2 diabetes.

Figure 1

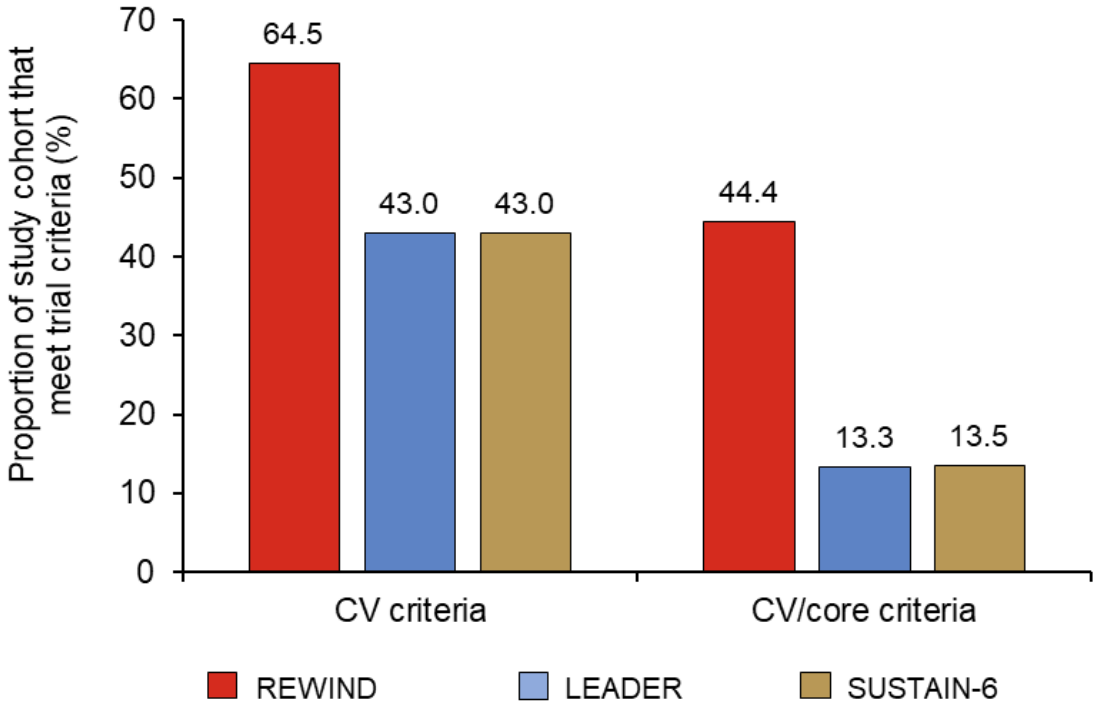

Proportion of study cohort that meet trial criteria (%)
70
60
50
40
30
20
10
0
64.5
43.0
43.0
44.4
13.3
13.5
CV criteria
CV/core criteria
REWIND
LEADER
SUSTAIN-6

Figure 2

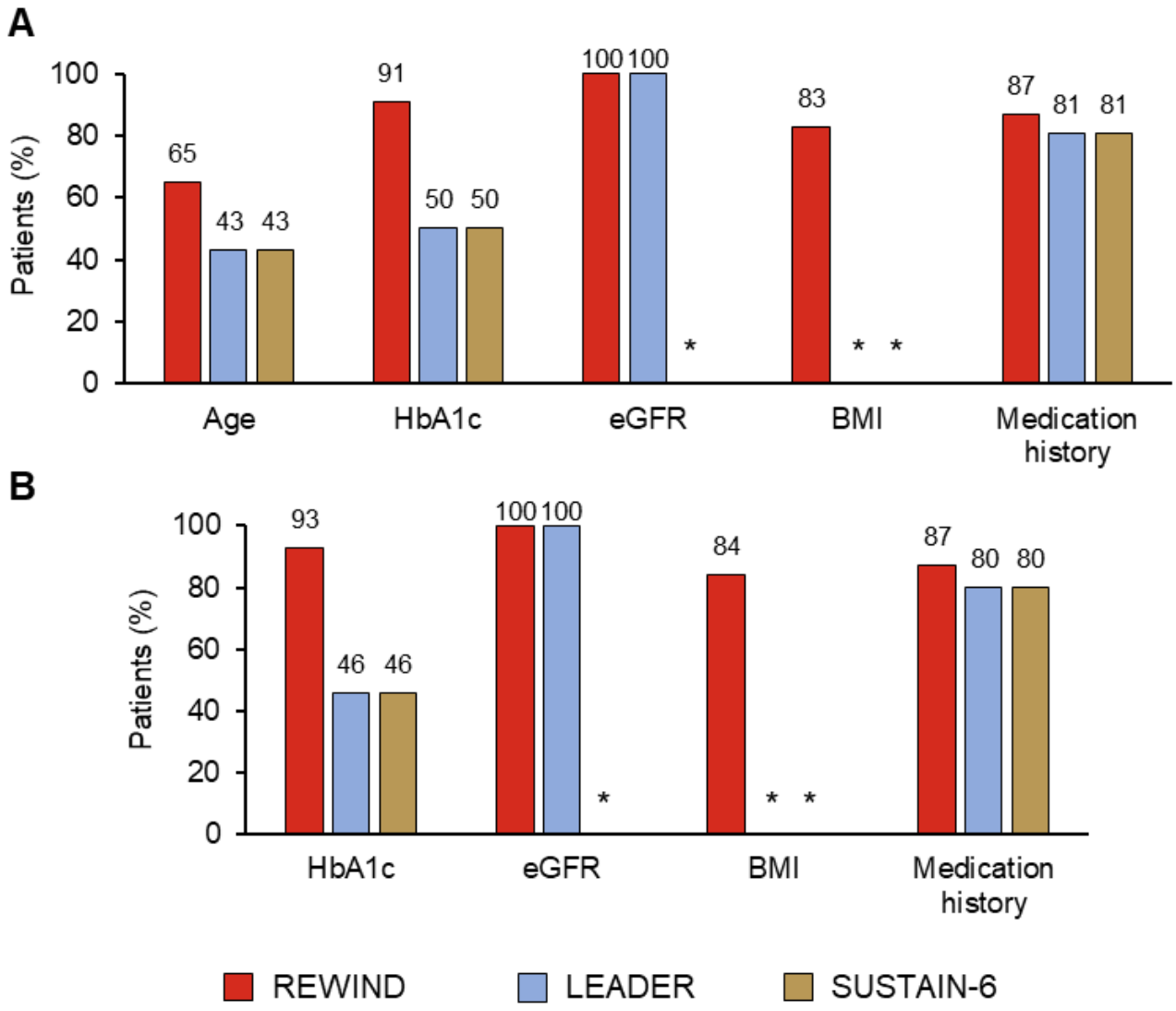
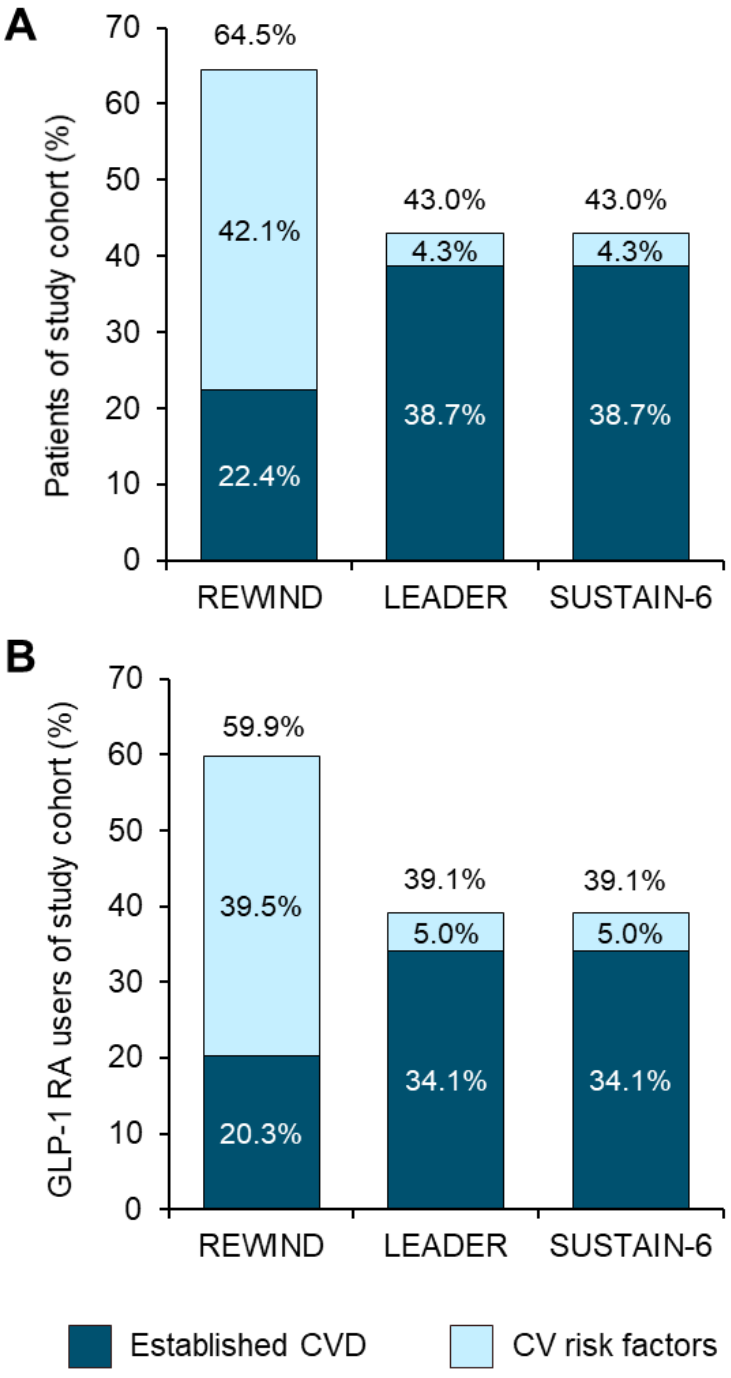

A
Patients (%)
100
80
60
40
20
0
65
43
43
91
50
50
100
100
*
83
*
*
87
81
81
Age
HbA1c
eGFR
BMI
Medication history
B
Patients (%)
100
80
60
40
20
0
93
46
46
100
100
*
84
*
*
87
80
80
HbA1c
eGFR
BMI
Medication history
REWIND
LEADER
SUSTAIN-6

Figure 3


A
Patients of study cohort (%)
70
60
50
40
30
20
10
0
64.5%
42.1%
22.4%
43.0%
4.3%
38.7%
43.0%
4.3%
38.7%
REWIND
LEADER
SUSTAIN-6
B
GLP-1 RA users of study cohort (%)
70
60
50
40
30
20
10
0
59.9%
39.5%
20.3%
39.1%
5.0%
34.1%
39.1%
5.0%
34.1%
REWIND
LEADER
SUSTAIN-6
Established CVD
CV risk factors

SUPPLEMENTARY INFORMATION

Table S1 Core and CV eligibility criteria for REWIND[30]

CORE CRITERIA	Inclusion: • Aged ≥50 years if 'established CVD'; ≥55 years if sub-clinical CVD; ≥60 years if 'at risk' • HbA1c ≤9.5% (at most recent measurement prior to or on the assessment date) • eGFR ≥15 mL/min/1.73m^2 (at most recent measurement prior to or on the assessment date) • BMI ≥23 kg/m^2 (at most recent measurement prior to or on the assessment date). Exclusion: • Use of premix or bolus insulin or >2 (concurrent) oral classes within 3 months prior to the assessment date.
CV CRITERIA	• If aged ≥50 years, at least one of the following criteria:[a] o prior MI o prior ischaemic stroke o coronary revascularisation ≥2 years earlier o carotid or peripheral revascularisation ≥2 months earlier o unstable angina hospitalisation o image-proven myocardial ischaemia or documented myocardial ischaemia by stress test or imaging[b,c] o PCI. • If aged ≥55 years, at least one of the following criteria: o ABPI <0.9 o eGFR persistently <60 mL/min/1.73m^2 o hypertension with LVH o persistent albuminuria (i.e. microalbuminuria or macroalbuminuria). • If aged ≥60 years, at least two of the following criteria: o any tobacco use o use of lipid-modifying therapy or a documented untreated LDL-C ≥3.4 mmol/L (130 mg/dL) within the past 6 months o HDL-C <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months o use of ≥1 blood pressure drug or untreated SBP ≥140 mmHg or DBP ≥95 mmHg o BMI categorised as 'overweight' (≥30 kg/m^2).[d]

[a] Patients satisfying any of the criteria in bold were classified as having 'established CVD', while all other patients were classified as 'at risk'.

[b] In REWIND this criterion (documented myocardial ischaemia by stress test or imaging) applies to the age ≥55 years group, rather than the age ≥50 years group as shown here.

[c] These criteria were combined into a single criterion as the medical coding systems were not sufficiently detailed to distinguish between the two criteria. In the REWIND protocol a patient was considered to have prior CV disease if they had a record of myocardial ischaemia; however, this

criterion did not differentiate how this diagnosis had been identified (i.e. ‘image proven’ or ‘stress test or image’). For the sake of this study, both criteria were considered indicative of established CVD.
[d] BMI used as a proxy for trial criterion defined as ‘waist-to-hip ratio >1.0 (men) or >0.8 (women)’.

ABPI, ankle–brachial pressure index; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

Table S2 Core and CV eligibility criteria for LEADER[13]

CORE CRITERIA	Inclusion: • Aged ≥50 years if 'established CVD'; ≥60 years if 'at risk' • HbA1c ≥7% (at most recent measurement prior to or on the assessment date) • eGFR ≥15 mL/min/1.73m^2 (at most recent measurement on or prior to the assessment date).[a] Exclusion: • Use of a GLP-1 RA, DPP-4 inhibitor, pramlintide or bolus insulin within 3 months prior to the assessment date.

CV CRITERIA	• If aged ≥50, at least one of the following criteria:[b]
	  ○ Prior MI
	  ○ Prior stroke or TIA
	  ○ Prior coronary, carotid or peripheral arterial revascularisation
	  ○ History of symptomatic CHD documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes OR asymptomatic cardiac ischemia documented by positive nuclear imaging test, exercise test or dobutamine stress echo[c]
	  ○ Chronic heart failure NYHA class II–III
	  ○ Chronic renal failure:
	  ▪ eGFR <60 mL/min/1.73m^2 (Modification of Diet in Renal Disease formula)
	  ▪ eGFR <60 mL/min (Cockcroft–Gault formula).
	• If aged ≥60, at least one of the following criteria:
	  ○ Microalbuminuria or proteinuria
	  ○ Hypertension and LVH by ECG or imaging
	  ○ Left ventricular systolic or diastolic dysfunction by imaging, ABPI <0.9.

[a] In the LEADER trial eligibility criteria 2.5% of patients were permitted to have eGFR <30mL/min/1.73m^2, with all other patients needing eGFR ≥30mL/min/1.73m^2. Because this eligibility criterion structure is incompatible with a generalisability study an operational definition was defined whereby patients were required to have eGFR ≥15mL/min/1.73m^2; this threshold was used to ensure that any patients with end-stage renal disease would be excluded.

[b] Patients satisfying any of the criteria in bold were classified as having 'established CVD', whilst all other patients were classified as 'at risk'

[c] These criteria were combined into a single criterion as the medical coding systems were not sufficiently detailed to distinguish between the two criteria.

ABPI, ankle–brachial pressure index; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Table S3 Core and CV eligibility criteria for SUSTAIN-6[14]

CORE CRITERIA	Inclusion: • Aged ≥50 years if 'established CVD'; ≥60 years if 'at risk' • HbA1c ≥7% (at most recent measurement prior to or on the assessment date) Exclusion: • Use of a GLP-1 RA or pramlintide within 3 months prior to the assessment date OR use of a DPP-4 inhibitor within 1 month prior to the assessment date OR treated with >2 (concurrent) classes of oral medication within 90 days prior to the assessment date OR use of bolus insulin within 90 days prior to the assessment date.
CV CRITERIA	• Aged ≥50 years with documented clinical evidence of CVD (established CVD)[a]: ○ prior MI ○ prior stroke or prior TIA ○ prior coronary, carotid or peripheral arterial revascularisation ○ history of symptomatic CHD documented by e.g. positive exercise stress test or any cardiac imaging or unstable angina with ECG changes or asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging[b] ○ chronic heart failure NYHA class II–III ○ chronic renal impairment: ▪ eGFR <60 mL/min/1.73m^2 (Modification of Diet in Renal Disease formula). • Aged ≥60 years with subclinical evidence of CVD (cardiovascular risk factors): ○ persistent microalbuminuria (30–299 mg/g) or proteinuria ○ hypertension and LVH by ECG or imaging ○ left ventricular systolic or diastolic dysfunction by imaging ○ ABPI <0.9.

[a] Patients satisfying any of the criteria in bold were classified as having 'established CVD', while all other patients were classified as 'at risk'.

[b] These criteria were combined into a single criterion as the medical coding systems were not sufficiently detailed to distinguish between the two criteria.

ABPI, ankle–brachial pressure index; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Table S4 Patients meeting specific REWIND CV entry criteria across entire study population, stratified by those in each age group who met age-group-specific criteria

REWIND CV entry operational criteria	Patient meeting eligibility criterion, N (%)			
	Patients in full study sample (N=21,369)	**Patients aged ≥50 and meeting ≥1 age-specific criterion[a] (N=7,414)**	**Patients aged ≥55 and meeting ≥1 age-specific criterion[a] (N=9,985)**	**Patients aged ≥60 and meeting ≥2 age-specific criteria[a] (N=18,130)**
Prior MI	3,130 (14.7)	3,130 (42.2)	1,614 (16.2)	2,409 (13.3)
Prior ischaemic stroke	1,121 (5.2)	1,121 (15.1)	606 (6.1)	863 (4.8)
Coronary revascularisation ≥2 years earlier	991 (4.6)	991 (13.4)	557 (5.6)	813 (4.5)
Carotid or peripheral revascularisation ≥2 months earlier	297 (1.4)	297 (4.0)	260 (2.6)	249 (1.4)
Unstable angina hospitalisation	1,219 (5.7)	1,219 (16.4)	617 (6.2)	956 (5.3)
Image proven myocardial ischaemia or documented myocardial ischaemia by stress test or imaging	6,232 (29.2)	6,232 (84.1)	3,184 (31.9)	4,827 (26.6)
PCI	1,992 (9.3)	1,992 (26.9)	925 (9.3)	1,516 (8.4)
ABPI <0.9	1,559 (7.3)	904 (12.2)	1,543 (15.5)	1,237 (6.8)
eGFR persistently <60 mL/min/1.73m^2	7,191 (33.7)	2804 (37.8)	7,164 (71.7)	5,789 (31.9)
Hypertension with LVH	215 (1.0)	99 (1.3)	213 (2.1)	185 (1.0)
Persistent albuminuria	3,871 (18.1)	1,436 (19.4)	3,834 (38.4)	2,971 (16.4)
Any tobacco use	4,260 (19.9)	1,492 (20.1)	1,806 (18.1)	3,816 (21.0)
Use of lipid-modifying therapy or a documented untreated LDL-C ≥3.4 mmol/L (130 mg/dL) within the past 6 months	17,385 (81.4)	6,242 (84.2)	7,769 (77.8)	15,711 (86.7)
HDL-C <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months	4,734 (22.2)	1,636 (22.1)	2,197 (22.0)	4,237 (23.9)
Use of ≥1 blood pressure drug or untreated SBP ≥140 mmHg or DBP ≥95 mmHg	17,263 (80.8)	5,790 (78.1)	8,282 (82.9)	15,465 (85.3)
BMI categorised as 'overweight' (≥30 kg/m^2)	11,714 (54.8)	3,880 (52.3)	5,061 (50.7)	10,712 (59.1)

[a] See Table S1 for age-specific criteria.

ABPI, ankle–brachial pressure index; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

Table S5 Patients meeting specific LEADER/SUSTAIN-6 CV entry criteria across entire study population, stratified by those in each age group who met age-group-specific criteria

SUSTAIN-6/LEADER CV entry operational criteria	Patient meeting eligibility criterion, N (%)		
	Patients in full study sample (N=14,236)	Patients aged ≥50 and meeting ≥1 age-specific criterion[a] (N=12,812)	Patients aged ≥60 and meeting ≥1 age-specific criterion[a] (N=5,382)
Prior MI	3,130 (22.0)	3,130 (24.4)	1,223 (22.7)
Prior stroke or TIA	2,638 (18.5)	2,638 (20.6)	829 (15.4)
Prior coronary, carotid or peripheral arterial revascularisation	3,010 (21.1)	3,010 (23.5)	1,156 (21.5)
History of symptomatic CHD documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes or asymptomatic cardiac ischemia documented by positive nuclear imaging test, exercise test or dobutamine stress echo	6,232 (43.8)	6,232 (48.6)	2,146 (39.9)
Chronic heart failure NYHA class II–III	1,972 (13.9)	1,972 (15.4)	1,170 (21.7)
Chronic renal failure	7,302 (51.3)	7,302 (57.0)	2,604 (48.4)
Microalbuminuria or proteinuria	3,676 (25.8)	2,622 (20.5)	3,450 (64.2)
Hypertension and LVH by ECG or imaging	210 (1.5)	158 (1.2)	195 (3.6)
Left ventricular systolic or diastolic dysfunction by imaging	1,200 (8.4)	1,154 (9.0)	1,105 (20.5)
ABPI <0.9	1,524 (10.7)	1,184 (9.2)	1,450 (26.9)

[a] See Tables S2 and S3 for age-specific criteria.

ABPI, ankle–brachial pressure index; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Table S6 GLP-1 RA users meeting specific REWIND CV entry criteria across entire study population, stratified by those in each age group who met age-group-specific criteria

REWIND CV entry operational criteria	Patient meeting eligibility criterion, N (%)			
	Patients in full study sample (N=1,231)	Patients aged ≥50 and meeting ≥1 age-specific criterion[a] (N=418)	Patients aged ≥55 and meeting ≥1 age-specific criterion[a] (N=601)	Patients aged ≥60 and meeting ≥2 age-specific criteria[a] (N=1,036)
Prior MI	183 (14.9)	183 (43.8)	93 (15.5)	135 (13.0)
Prior ischaemic stroke	52 (4.2)	52 (12.4)	24 (4.0)	36 (3.5)
Coronary revascularisation ≥2 years earlier	56 (4.6)	56 (13.4)	31 (5.2)	46 (4.4)
Carotid or peripheral revascularisation ≥2 months earlier	12 (1.0)	12 (2.9)	11 (1.8)	9 (0.9)
Unstable angina hospitalisation	92 (7.5)	92 (22.0)	43 (7.2)	66 (6.4)
Image proven myocardial ischaemia or documented myocardial ischaemia by stress test or imaging	366 (29.7)	366 (87.6)	185 (30.8)	279 (26.9)
PCI	134 (10.9)	134 (32.1)	71 (11.8)	100 (9.7)
ABPI <0.9	92 (7.5)	47 (11.2)	90 (15.0)	74 (7.1)
eGFR persistently <60 mL/min/1.73m^2	364 (29.6)	133 (31.8)	359 (59.7)	318 (30.7)
Hypertension with LVH	15 (1.2)	5 (1.2)	15 (2.5)	11 (1.1)
Persistent albuminuria	302 (24.5)	97 (23.2)	297 (49.4)	220 (21.2)
Any tobacco use	278 (22.6)	106 (25.4)	139 (23.1)	229 (22.1)
Use of lipid-modifying therapy or a documented untreated LDL-C ≥3.4 mmol/L (130 mg/dL) within the past 6 months	1,075 (87.3)	374 (89.5)	518 (86.2)	920 (88.8)
HDL-C <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women or triglycerides ≥2.3 mmol/L (200 mg/dL) within the past 6 months	385 (31.3)	138 (33.0)	200 (33.3)	323 (31.2)
Use of ≥1 blood pressure drug or untreated SBP ≥140 mmHg or DBP) ≥95 mmHg	996 (80.9)	345 (82.5)	497 (82.7)	854 (82.4)
BMI categorised as 'overweight' (≥30kg/m^2)	1,057 (85.9)	352 (84.2)	510 (84.9)	901 (87.0)

[a] See Table S1 for age-specific criteria.

ABPI, ankle–brachial pressure index; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

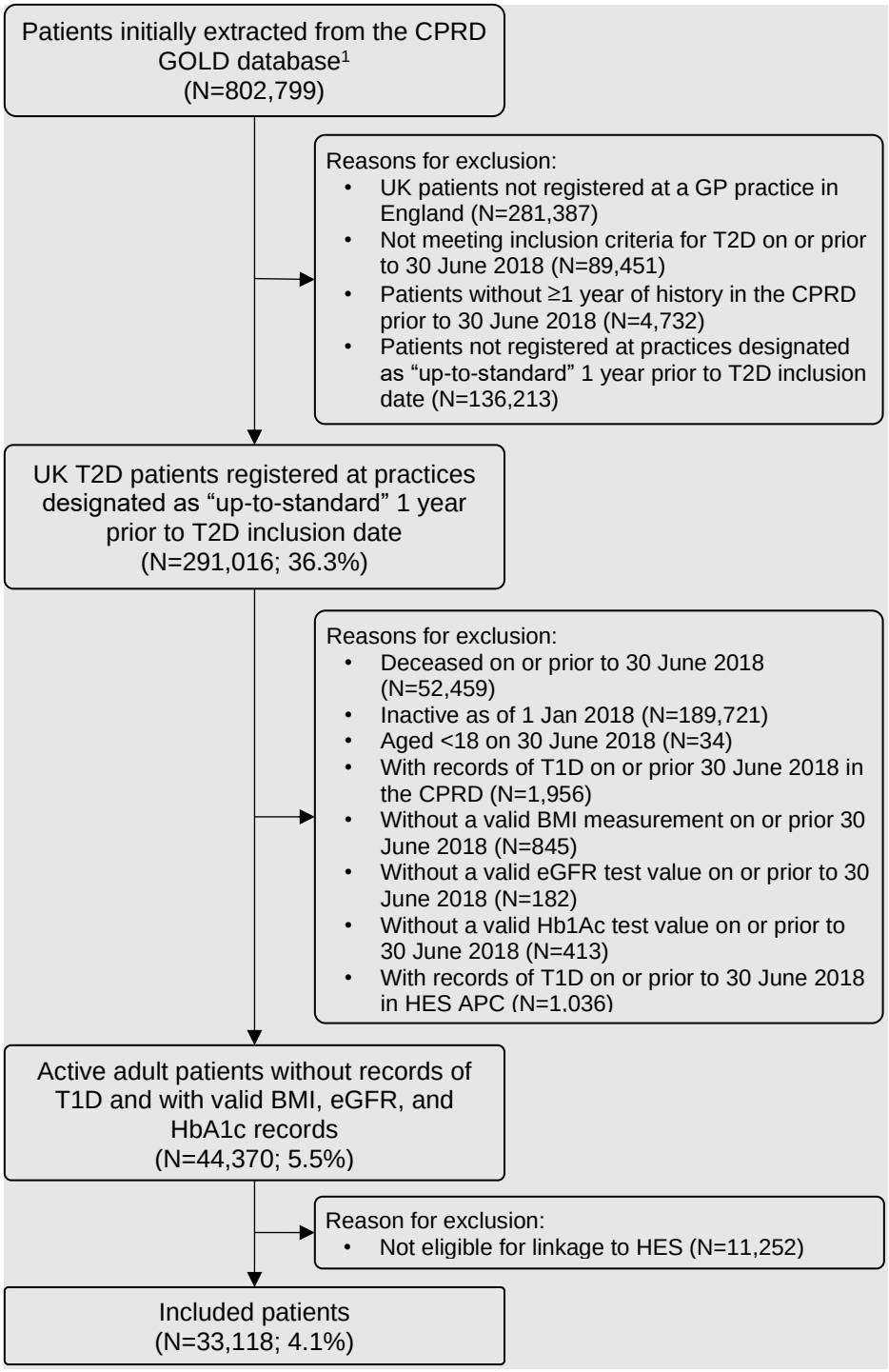
Table S7 GLP-1 RA users meeting specific LEADER/SUSTAIN-6 CV entry criteria across entire study population, stratified by those in each age group who met age-group-specific criteria

SUSTAIN-6/LEADER CV entry operational criteria	Patient meeting eligibility criterion, N (%)		
	Patients in full study sample (N=805)	Patients aged ≥50 and meeting ≥1 age-specific criterion[a] (N=702)	Patients aged ≥60 and meeting ≥1 age-specific criterion[a] (N=328)
Prior MI	183 (22.7)	183 (26.1)	67 (20.4)
Prior stroke or TIA	113 (14.0)	113 (16.1)	31 (9.5)
Prior coronary, carotid or peripheral arterial revascularisation	181 (22.5)	181 (25.8)	76 (23.2)
History of symptomatic CHD documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes or asymptomatic cardiac ischemia documented by positive nuclear imaging test, exercise test or dobutamine stress echo	366 (45.5)	366 (52.1)	124 (37.8)
Chronic heart failure NYHA class II–III	115 (14.3)	115 (16.4)	59 (18.0)
Chronic renal failure	375 (46.6)	375 (53.4)	130 (39.6)
Microalbuminuria or proteinuria	269 (33.4)	184 (26.2)	230 (70.1)
Hypertension and LVH by ECG or imaging	13 (1.6)	9 (1.3)	11 (3.4)
Left ventricular systolic or diastolic dysfunction by imaging	71 (8.8)	70 (10.0)	57 (17.4)
ABPI <0.9	88 (10.9)	66 (9.4)	78 (23.8)

[a] See Tables S2 and S3 for age-specific criteria.

ABPI, ankle–brachial pressure index; CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; TIA, transient ischaemic attack.

Figure S1 Patient selection



[1] Patients in the UK with at least one T2D diagnosis code or prescriptions of two classes of glucose-lowering medications.
APC, Admitted Patient Care; BMI, body mass index; CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; GP, general practitioner; HbA1c, glycated haemoglobin; HES, Hospital Episode Statistics; T1D, type 1 diabetes; T2D, type 2 diabetes