ORIGINAL ARTICLE

Enrolment criteria for diabetes cardiovascular outcome trials do not inform on generalizability to clinical practice: The case of glucagon-like peptide-1 receptor agonists

Veronica Sciannameo¹ | Paola Berchialla² | Emanuela Orsi³ | Olga Lamacchia⁴ |
Susanna Morano⁵ | Fabrizio Querci⁶ | Agostino Consoli⁷ | Angelo Avogaro⁸ |
Gian Paolo Fadini on behalf of the DARWIN-T2D study

¹Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy

²Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

³Unit of Endocrinology and Metabolic Diseases, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico di Milano, Milan, Italy

⁴Unit of Endocrinology, Department of Medical and Surgical Sciences, University Hospital of Foggia, Foggia, Italy

⁵Unit of Diabetes Complications, V Clinica Medica, Department of Experimental Medicine, University of Rome "La Sapienza", Rome, Italy

⁶Unit of Diabetology, ASST Bergamo Est, Alzano Lombardo, Italy

⁷Department of Medicine and Aging Science, "G. D'Annunzio" University of Chieti, Chieti, Italy

⁸Department of Medicine, University of Padova, Padova, Italy

Correspondence

Gian Paolo Fadini, MD, Associate Professor of Endocrinology, Department of Medicine, University of Padova, Via Giustiniani 2, 35128 Padova, Italy.
Email: gianpaolofadini@hotmail.com

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Abstract

Aim: To evaluate the generalizability of cardiovascular outcome trials (CVOTs) on glucagon-like peptide-1 receptor agonists (GLP-1RAs), we assessed what proportion of real-world patients with type 2 diabetes (T2D) constitute true CVOT-like populations.

Materials and Methods: We applied inclusion/exclusion (I/E) criteria of each GLP-1RA CVOT to a cross-sectional database of 281 380 T2D patients from Italian diabetes outpatient clinics. We calculated the proportion of patients eligible for each CVOT and compared their clinical characteristics with those of trial patients. In addition, we used a Bayesian network-based method to sample the greatest subsets of real-world patients yielding true CVOT-like populations.

Results: Between 98 725 and 124 164 T2D patients could be evaluated for CVOT eligibility. After excluding patients who were already on GLP-1RAs and applying I/E criteria, 35.8% of patients would be eligible for REWIND, 34.1% for PIONEER-6, 13.4% for EXSCEL, 10.1% for SUSTAIN-6, 9.5% for HARMONY and 9.4% for LEADER. Overall, 45.4% of patients could be eligible for at least one of the CVOTs. These patients, however, were extremely different to trial patients in most of the clinical characteristics, including demographics, concomitant medications and complications. The greatest CVOT-like subsets of real-world patients were 0.5% for SUSTAIN-6, 1.0% for EXSCEL, 1.2% for LEADER, 1.8% for PIONEER-6 and 7.9% for REWIND.

Conclusions: A very small proportion of real-world patients constitute true CVOT-like populations. These findings question whether any meaningful information can be drawn from applying trial enrolment criteria to real-world T2D patients.

KEYWORDS

cardiovascular disease, glucagon-like peptide-1 analogue, pharmaco-epidemiology, population study, type 2 diabetes

1 | INTRODUCTION

In the field of diabetes pharmacotherapy, cardiovascular outcome trials (CVOTs) have been designed to test the cardiovascular safety of glucose-lowering medications (GLMs) against placebo.¹ Although designed primarily to show non-inferiority, some CVOTs have shown that active treatment was superior to placebo in reducing the rates of major adverse cardiovascular outcome events (MACE) in patients with type 2 diabetes (T2D). Results of these CVOTs have been incorporated into consensus algorithms, which now prioritize certain GLMs for the prevention of cardiovascular complications.²

This is the case for glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2is). Among GLP-1RAs, dedicated CVOTs showed the superiority of liraglutide (LEADER), semaglutide (SUSTAIN-6), albiglutide (HARMONY) and dulaglutide (REWIND) versus placebo in reducing the rates of three-point MACE (cardiovascular death, non-fatal myocardial infarction or stroke).^{3–6} The CVOTs on exenatide once-weekly (exeOW) and oral semaglutide showed nominal reductions in mortality rates.^{7,8} Therefore, there is general agreement that GLP-1RAs as a class improve the cardiovascular outcomes of T2D.⁹

However, the generalizability of CVOT findings to clinical practice may be hampered by the many differences between trial settings and routine care. CVOTs recruit patients based on rigorous inclusion/exclusion (I/E) criteria and closely follow them at regular intervals within strict trial experimental protocols. CVOTs are event-driven, and their I/E criteria allow rapid collection of the desired number of events by selecting T2D patients with a prior history of cardiovascular disease and/or multiple risk factors. Because only ~30% of T2D patients in routine care show signs of macroangiopathy, to what extent the results of CVOTs can be translated to T2D patients at lower cardiovascular risk is a matter of debate. Positive results from REWIND, in which ~30% of patients had established cardiovascular disease,³ suggest that the benefit of GLP-1RAs may be independent from the baseline cardiovascular risk.^{9,10}

A few studies have examined what proportion of T2D patients from various clinical care settings would satisfy I/E criteria to be enrolled in specific CVOTs,^{11–14} but no study to date has examined what the proportion is of real-world patients that corresponds to CVOT populations. Indeed, applying CVOT enrolment criteria to real-world T2D patients yields subgroups that are substantially different from the actual CVOT populations, thereby leaving the question of generalizability unanswered.

In this study, we aimed to resolve this issue. After applying I/E criteria for GLP-1RA CVOTs to a T2D real-world population, we show by how much the eligible population of patients differs from those of CVOTs, and calculate what proportion of patients from routine care would generate a true CVOT-like population.

2 | METHODS

2.1 | Data source

The DARWIN-T2D (DAta for Real World evldeNce in Type 2 Diabetes) study was conducted by the Italian Diabetes Society and was initially designed to evaluate dapagliflozin in the real world. Protocol details and primary analysis have been reported previously.^{15,16} The DARWIN-T2D database contains cross-sectional information on ~281 000 T2D patients from 46 diabetes outpatient clinics across Italy. Data were collected at each centre at the last available appointment attended by each patient in 2015 and 2016. Each clinic used the same electronic chart system to store patients' data (MyStar Connect/Smart Digital Clinic, Meteda Srl, San Benedetto del Tronto, Italy). The relevant data were extracted by dedicated software (Meteda) without manual intervention.

We recorded the following information: demographics (age, sex, diabetes duration), anthropometrics (height, weight, body mass index [BMI], waist circumference), cardiovascular risk factors (smoking, blood pressure values, lipid profile), estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration Equation¹⁷) and other laboratory data (including urinary albumin excretion rate and liver enzymes), and medications for the treatment of diabetes and other cardiovascular risk factors or conditions. In addition, detailed information was collected on diabetic complications from ICD-9 codes in the electronic chart, including: presence and stage of retinopathy and diabetic macular oedema; presence or absence of somatic or autonomic diabetic neuropathy; history of stroke, transient ischaemic attack or carotid endoarterectomy/stenting; history of angina, myocardial infarction or coronary revascularization; presence/absence of left ventricular hypertrophy and history of heart failure; history of claudication, limb ischaemia or amputation; presence of asymptomatic atherosclerosis of coronary, carotid or leg arteries. Codes to define prevalent cardiovascular disease have been standardized in the electronic chart, which is routinely used to monitor the quality of diabetes care in Italy.¹⁸

Not all of the records were complete for all of the patients: the degree and distribution of missing variables have been reported previously.¹⁵

2.2 | Data analysis

From the respective publications, we retrieved I/E criteria regarding the following CVOTs on GLP-1RAs: LEADER (liraglutide),⁶ SUSTAIN-6 (semaglutide),⁵ EXSCEL (exeOW),⁷ REWIND (dulaglutide),³ PIONEER-6 (oral semaglutide)⁸ and HARMONY (albiglutide).⁴ Details of these trials were published during 2015–2019, a timeframe which partially overlaps with our data collection period (2015–2016). Specific I/E criteria had to be adapted to the available data in the DARWIN-T2D database with some modifications (Table S1). For instance, the following information used for CVOT I/E criteria was not available: myocardial ischaemia stress test or imaging; diastolic dysfunction;

ankle-brachial index; calcitonin levels; and history of cancer and pancreatitis. The timings of prior cardiovascular events and revascularization were not available so as to exclude patients with recent events. Because no information concerning contraception was available, women of childbearing potential were excluded. Patients with missing information for key I/E variables were also excluded from the analysis.

We therefore identified T2D patients who would be eligible to participate in each of the considered CVOTs and calculated the respective proportion over the total background population of patients with available data. Then we compared the average clinical characteristics of eligible patients with average clinical characteristics of patients in the database who were already on GLP-1RAs, and also with those of patients actually enrolled in CVOTs (from the respective publications).

Finally, from the DARWIN-T2D database, we extracted the largest subgroup of patients who had average clinical characteristics superimposable on those of CVOTs. Because no specific tool was already available for this case-sampling procedure, we devised an analytical strategy, which is described below.

2.3 | Statistical analysis

For descriptive purposes, continuous variables are expressed as means and standard deviations, whereas categorical variables are expressed as percentages. To evaluate to what extent two groups of patients were similar, we computed the absolute standardized mean difference (SMD) for each variable. Conventionally, an SMD value of 0.1 or less is considered indicative of a good balance. For example, for continuous variables, an SMD of <0.1 indicates that the difference between the means of the two groups is <10% of the pooled standard deviation. Because of the very large sample size in each comparison, *P*-values were not calculated, as several minor and clinically irrelevant differences would yield *P*-values of <0.05.

2.4 | Sampling CVOT-like populations

Continuous variables in the DARWIN-T2D database were categorized into five classes, on the basis of each trial's summary statistics, and assuming a normal distribution. Observations with at least one missing value were removed. A Bayesian network (BN) was constructed for each randomized controlled trial (RCT), because each variable was preprocessed (continuous variables were categorized) according to the specific RCT's summary statistics, on the case complete dataset to obtain the conditional probability distributions, which reflect the dependencies among variables. All of the available variables were included in the construction of the BN. Then the Peter-Clark stable algorithm with a 100-fold bootstrap was employed for the structural learning of the BN (ie, for identifying the relationships among variables).¹⁹ A more robust BN was obtained by averaging the 100 BNs learned, considering only the relationships among variables present in at least 95% of times.²⁰ Bootstrap was performed to address the

sample variability. Finally, a maximum a posteriori estimation was used to compute the set of probabilities for conditional nodes, whereas for unconditional nodes, probabilities were assigned computing the ratio between CVOT frequency and DARWIN-T2D frequency, for each variable category, and then normalizing to 1. This was carried out to take into account the different distribution of patients' characteristics between DARWIN-T2D and CVOTs, and to increase the probability of the patients selected being less represented in DARWIN-T2D than CVOTs, and to decrease the probability of the patients selected being more represented in DARWIN-T2D than CVOTs. The decomposition of the joint probability into the product of conditional and unconditional probabilities was used to achieve a final probability of inclusion in a CVOT for each patient in DARWIN-T2D.²¹ The balancing between the patients sampled and each trial's patients was evaluated through SMD. To achieve an SMD smaller than 0.1 we proceeded as follows: first, we balanced the two groups according to an SMD smaller than 0.2 for each variable. To obtain this result, for each variable with an SMD greater than 0.2, 2% of patients with values in the tails of the distribution were sampled and removed from the DARWIN-T2D dataset. This procedure was iterated until SMD was less than 0.2.

The entire procedure was repeated to achieve a new random sample of patients balanced according to an SMD smaller than 0.2. Finally, all of the balanced groups obtained were joined together, and, for each variable, to once again obtain an SMD smaller than 0.1, the same procedure was applied. A sensitivity analysis on different thresholds of SMD was carried out, and the choice of the double threshold 0.2 and 0.1 produced the best balanced group. All of the analyses were performed using R version 3.5.0 (R Development Core Team).

3 | RESULTS

The original dataset was composed of 281 380 patients. Because the minimum requirement to enter the database was T2D diagnosis, many patients had missing values for several of the variables needed to evaluate CVOT I/E criteria. Among 130 380 patients with available information on GLMs, 6699 (5.1%) were being treated with a GLP-1RA (73.8% liraglutide, 23.5% exenatide, 2.7% lixisenatide). The numbers of patients who could be evaluated for CVOT eligibility were 124 164 for EXSCAL, 116 553 for PIONEER-6, 107 040 for HARMONY, 106 606 for LEADER, 105 074 for REWIND and 98 725 for SUSTAIN-6.

Patients being examined who were already taking a GLP-1RA at the visit were considered separately, because ongoing GLP-1RA therapy was an exclusion criterion in CVOTs. After applying I/E criteria (as outlined in Table S1), we calculated that the percentages of patients who were eligible for CVOTs were 35.8% for REWIND, 34.1% for PIONEER-6, 13.4% for EXSCAL, 10.1% for SUSTAIN-6, 9.5% for HARMONY and 9.4% for LEADER. Overall, 45.4% of patients were eligible for at least one of the CVOTs being considered.

The clinical characteristics of patients treated with GLP-1RAs and of those who were eligible for CVOTs are provided in Table 1.

TABLE 1 Clinical characteristics of patients treated with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and of those eligible for cardiovascular outcome trials (CVOTs)

	GLP-1RA users in DARWIN-T2D	LEADER	SUSTAIN-6	EXSCEL	REWIND	PIONEER-6	HARMONY
Number	6699	10 061	9942	16 544	37 574	39 726	10 208
Percentage ^a	5.1	9.4	10.1	13.4	35.8	34.1	9.5
Age, years	61.7 ± 9.5	74.2 ± 8.4	74.2 ± 8.5	70.8 ± 8.6	70.8 ± 7.1	73.7 ± 8.3	73.6 ± 9.1
Male, %	54.9	56.5	55.8	67.3	59.0	57.6	68.4
Diabetes duration, years	11.3 ± 7.5	13.6 ± 9.1	13.6 ± 9.1	15.4 ± 9.8	10.7 ± 8.2	14.3 ± 10.0	17.9 ± 10.2
Active smoker, %	19.8	13.5	13.6	17.1	14.3	14.0	16.1
Body mass index, kg/m ²	34.8 ± 6.2	29.1 ± 5.1	29.2 ± 5.2	29.1 ± 4.9	29.8 ± 4.7	29.3 ± 5.2	29.1 ± 4.9
Waist circumference, cm	114.7 ± 13.6	103.9 ± 12.2	104.1 ± 12.4	104.2 ± 11.9	104.5 ± 11.3	104.5 ± 12.6	104.6 ± 11.9
Systolic blood pressure, mmHg	138.3 ± 18.3	139.1 ± 18.6	139.2 ± 18.7	137.5 ± 18.4	138.4 ± 17.9	138.1 ± 18.7	137.5 ± 18.6
Diastolic blood pressure, mmHg	80.3 ± 9.9	76.9 ± 9.3	77.0 ± 9.4	76.5 ± 9.2	77.8 ± 9.1	76.3 ± 9.5	75.8 ± 9.2
Heart rate, bpm	78.8 ± 11.9	73.3 ± 11.9	73.5 ± 11.8	71.7 ± 11.6	73.3 ± 11.8	72.8 ± 11.8	70.2 ± 11.0
Fasting plasma glucose, mg/dl	151.2 ± 42.7	151.3 ± 36.9	155.6 ± 42.1	150.2 ± 42.2	136.8 ± 33.7	146.4 ± 47.7	160.4 ± 50.5
HbA1c, %	7.5 ± 1.1	7.8 ± 0.6	8.0 ± 1.0	7.6 ± 0.8	6.9 ± 0.9	7.4 ± 1.3	8.1 ± 1.0
Total cholesterol, mg/dl	169.3 ± 37.5	168.2 ± 38.2	169.0 ± 38.8	160.5 ± 38.3	170.0 ± 37.4	166.8 ± 38.8	158.2 ± 39.6
HDL cholesterol, mg/dl	45.9 ± 12.6	48.7 ± 13.6	48.4 ± 13.5	47.1 ± 13.6	49.8 ± 13.8	49.0 ± 14.5	45.7 ± 13.4
Triglycerides, mg/dl	160.2 ± 87.5	141.5 ± 74.2	144.2 ± 76.5	140.9 ± 85.3	134.6 ± 71.7	137.4 ± 77.6	146.9 ± 88.5
LDL cholesterol, mg/dl	91.9 ± 32.3	91.4 ± 32.2	91.9 ± 32.7	85.3 ± 31.7	93.3 ± 32.1	90.5 ± 32.6	83.1 ± 32.2
eGFR, ml/min/1.73 m ²	87.7 ± 24.1	68.3 ± 21.5	68.5 ± 21.9	73.3 ± 21.6	76.2 ± 19.4	66.7 ± 20.5	68.9 ± 22.1
Albumin excretion rate, mg/g	51.5 ± 147.7	59.5 ± 98.7	61.2 ± 109.5	42.5 ± 108.7	45.3 ± 66.0	57.1 ± 155.0	43.4 ± 132.1
Glucose-lowering medications, %							
Insulin	24.9	25.7	27.8	41.0	14.6	43.3	56.4
Metformin	85.9	75.2	73.8	67.8	83.4	62.1	59.5
Sulphonylurea/repaglinide	26.4	52.9	52.0	28.7	32.1	28.0	30.9
Acarbose	2.0	3.5	2.7	1.8	2.2	2.6	2.4
Pioglitazone	9.0	5.8	3.5	3.7	4.0	3.7	3.1
DPP-4 inhibitors	0.2	0.0	0.0	27.6	0.0	0.0	28.0
GLP-1RAs	100.0	0.0	0.0	0.0	0.0	0.0	0.0
SGLT-2 inhibitors	0.7	5.7	5.4	4.5	3.4	3.6	5.4
Other therapies, %							
Antiplatelet agents	46.4	58.5	58.5	74.6	51.3	60.9	84.0
Statin	62.9	64.3	63.9	76.1	63.4	64.8	79.4
Renin-angiotensin system blockers	74.5	71.2	71.3	74.0	70.7	72.1	75.9

(Continues)

TABLE 1 (Continued)

	GLP-1RA users in DARWIN-T2D	LEADER	SUSTAIN-6	EXSCEL	REWIND	PIONEER-6	HARMONY
Calcium channel blockers	25.6	27.0	27.1	28.6	25.7	27.4	29.4
Beta-blockers	31.5	36.4	36.6	44.5	32.7	36.9	49.7
Diuretics	15.8	21.4	21.6	23.7	15.0	25.2	30.5
Complications, %							
Chronic kidney disease	10.0	40.7	40.7	29.1	20.9	44.9	37.4
Albuminuria >30 mg/g	37.3	59.0	59.7	33.5	40.7	57.6	32.1
Retinopathy	15.6	16.1	16.6	24.9	11.4	17.9	31.2
Peripheral neuropathy	14.8	21.2	21.8	25.9	17.2	23.5	30.4
Atherosclerosis obliterans	12.4	27.2	27.7	48.3	13.8	26.1	60.9
Peripheral revascularization	1.2	3.0	3.0	5.2	1.3	2.8	6.4
Diabetic foot	7.6	13.0	13.6	15.9	10.0	12.4	19.3
Stroke/transient ischaemic attack	2.2	9.5	9.8	11.3	4.8	9.3	14.4
Carotid atherosclerosis	39.1	47.5	47.6	51.4	42.1	45.3	54.7
Ischaemic heart disease	8.2	20.9	20.9	44.2	11.7	21.0	56.7
Coronary revascularization	6.0	13.5	13.5	29.9	7.5	13.6	37.9
Microangiopathy	43.1	85.4	85.6	61.6	56.5	87.1	69.0
Macroangiopathy	30.4	52.3	52.5	79.8	37.2	50.3	98.2

Abbreviations: DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; SGLT-2, sodium-glucose co-transporter-2.

^aThe percentage refers to the % of patients who were on GLP-1RAs in the DARWIN-T2D database (first column) and to the % of patients who would be eligible for each trial in the other columns.

FIGURE 1 Real-world patients and cardiovascular outcome trials (CVOTs). (A) For each CVOT, the panels show the absolute standardized mean difference (SMD) between the actual trial population (retrieved from respective publications) and real-world patients selected based on inclusion/exclusion criteria (I/E) or for being CVOT-like (Like). In each plot, a dashed line indicates the SMD threshold of 0.1, indicating good balance. Fractions in brackets refer to the number of key clinical characteristics that are matched between real-world patients selected by I/E and trial characteristics. By design, all characteristics were balanced between CVOT-like patients and the respective CVOT population. (B) Proportion of real-world patients eligible for each CVOT based on I/E or sampled for being CVOT-like. BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; N/A, not available; SBP, systolic blood pressure

We observed that the average clinical characteristics of patients who could be eligible for CVOTs were substantially different from the average clinical characteristics of patients who composed each CVOT population (Figure 1A). For instance, patients selected from the real-world database were older than in CVOTs. In addition, despite 80%–100% of patients in LEADER and SUSTAIN-6 having established cardiovascular disease, application of the I/E criteria to the real-world population yielded patients with a 70%–80% prevalence of microangiopathy (mostly chronic kidney disease) and a lower prevalence of macroangiopathy (40%–50%). Most other clinical characteristics were imbalanced between patients enrolled in CVOTs and real-world patients eligible for the same CVOTs (Table 2). Out of 11 key clinical variables, eligible patients matched the trial characteristics with an absolute SMD of <0.1 for just two or three variables, with the notable exception of REWIND. Real-world patients eligible for REWIND were matched with the REWIND population for 6/11 variables.

Patients who were already on a GLP-1RA showed substantially different clinical characteristics when compared with both those satisfying CVOT I/E criteria and those actually enrolled in CVOTs.

We then evaluated what proportion of real-world patients would constitute a population of individuals with key average characteristics similar to those enrolled in CVOTs. The largest datasets of real-world patients yielding CVOT-like populations were 0.5% for SUSTAIN-6, 1.0% for EXSCEL, 1.2% for LEADER, 1.8% for PIONEER-6 and 7.9% for REWIND. We were unable to obtain a meaningful dataset of real-world patients who would match the population of the HARMONY study (Figure 1B).

4 | DISCUSSION

Although 10%–35% of real-world T2D patients could be enrolled in GLP-1RA CVOTs, their clinical characteristics were markedly different from those of CVOT populations. For the first time, we calculated that

TABLE 2 Key clinical characteristics of real-world patients compared with cardiovascular outcome trial (CVOT) patients. For each CVOT, we show the average clinical characteristics extracted from the respective publications, the characteristics of real-world patients who would be recruited into the CVOT based on inclusion/exclusion (I/E) criteria, and the characteristics of real-world patients sampled for being CVOT-like (Like). For both subgroups of real-world patients, we calculated the absolute standardized mean difference (SMD) as a measure of balance between groups; an SMD ≤ 0.10 is conventionally considered indicative of a good balance

Variable	LEADER	I/E	SMD	Like	SMD
Number	9340	10 061		1132	
Age, years	64.3 (7.2)	74.2 (8.4)	1.26	64.6 (7.6)	0.05
Male, %	64.2	56.5	0.16	65.0	0.02
Diabetes duration, years	12.8 (8.0)	13.6 (9.1)	0.09	13.5 (8.4)	0.09
HbA1c, %	8.7 (1.5)	7.8 (0.6)	0.80	8.5 (0.8)	0.10
BMI, kg/m ²	32.5 (6.3)	29.1 (5.1)	0.60	32.7 (5.8)	0.03
SBP, mmHg	135.9 (17.7)	139.1 (18.6)	0.18	137.8 (18.7)	0.10
DBP, mmHg	77.1 (10.2)	76.9 (9.3)	0.02	78.2 (9.3)	0.10
Heart failure, %	17.9	2.5	0.53	16.0	0.05
Established CVD, %	81.4	55.7	0.58	81.4	0.001
CVD risk factors, %	18.7	28.7	0.24	22.3	0.09
eGFR, ml/min/1.73 m ²	80.4 (21.0)	68.3 (21.5)	0.57	78.0 (26.5)	0.10
Variable	REWIND	I/E	SMD	Like	SMD
Number	9901	37 574		7280	
Age, years	66.2 (6.5)	70.8 (7.1)	0.66	66.7 (6.2)	0.08
Male, %	53.9	59.0	0.10	59.3	0.10
Diabetes duration, years	10.5 (7.2)	10.7 (8.2)	0.02	10.8 (7.1)	0.05
HbA1c, %	7.3 (1.1)	6.9 (0.9)	0.42	7.4 (1.2)	0.06
BMI, kg/m ²	32.3 (5.7)	29.8 (4.7)	0.51	31.9 (5.3)	0.10
SBP, mmHg	137.0 (17.0)	138.4 (18.0)	0.08	137.2 (15.5)	0.01
DBP, mmHg	78.0 (9.9)	77.8 (9.1)	0.02	78.7 (8.1)	0.08
Heart failure, %	8.7	1.0	0.36	7.3	0.05
Established CVD, %	31.4	28.2	0.07	30.6	0.02
CVD risk factors, %	68.6	19.9	1.12	63.8	0.10
eGFR, ml/min/1.73 m ²	75.0 (22.1)	75.2 (21.2)	0.009	77.4 (22.2)	0.10
Variable	SUSTAIN-6	I/E	SMD	Like	SMD
Number	3297	9942		476	
Age, years	64.6 (7.4)	74.2 (8.5)	1.16	65.1 (6.7)	0.07
Male, %	60.7	55.8	0.10	64.1	0.07
Diabetes duration, years	13.9 (8.1)	13.6 (9.1)	0.00	14.5 (6.8)	0.07
HbA1c, %	8.7 (1.5)	8.0 (1.0)	0.61	8.6 (0.7)	0.08
BMI, kg/m ²	32.8 (6.2)	29.2 (5.2)	0.66	32.8 (5.9)	0.004
SBP, mmHg	135.6 (17.2)	139.2 (18.7)	0.20	136.8 (17.5)	0.07
DBP, mmHg	77.0 (10.0)	77.0 (9.4)	0.00	77.8 (9.7)	0.08
Heart failure, %	23.6	2.6	0.65	19.5	0.10
Established CVD, %	83.0	55.7	0.62	80.5	0.07
CVD risk factors, %	17.0	29.0	0.29	14.1	0.08
eGFR, ml/min/1.73 m ²	N/A	N/A	N/A	N/A	N/A
Variable	PIONEER-6	I/E	SMD	Like	SMD
Number	3183	39 726		1663	
Age, years	66.0 (7.0)	73.7 (8.3)	0.94	66.6 (7.2)	0.09
Male, %	68.4	57.6	0.23	72.9	0.10

(Continues)

TABLE 2 (Continued)

Variable	LEADER	I/E	SMD	Like	SMD
Diabetes duration, years	14.9 (8.5)	14.3 (10.0)	0.06	14.0 (8.6)	0.10
HbA1c, %	8.2 (1.6)	7.4 (1.3)	0.60	8.2 (0.7)	0.01
BMI, kg/m ²	32.3 (6.5)	29.3 (5.2)	0.57	32.0 (3.7)	0.05
SBP, mmHg	136.0 (18.0)	138.1 (18.7)	0.11	135.7 (14.0)	0.01
DBP, mmHg	74.0 (21.0)	76.3 (9.5)	0.21	77.0 (8.0)	0.10
Heart failure, %	12.2	2.7	0.37	8.7	0.10
Established CVD, %	84.7	58.1	0.62	80.7	0.10
CVD risk factors, %	15.3	27.8	0.31	19.1	0.10
eGFR, ml/min/1.73 m ²	76.0 (10.0)	66.2 (21.3)	0.47	71.6 (26.0)	0.10
Variable	EXSCEL	I/E	SMD	Like	SMD
Number	14 752	16 544		915	
Age, years	62.0 (16.3)	70.8 (8.6)	0.69	62.3 (5.6)	0.02
Male, %	62.0	67.3	0.11	62.4	0.008
Diabetes duration, years	12.0 (7.4)	15.4 (9.8)	0.39	11.5 (6.9)	0.06
HbA1c, %	8.0 (1.2)	7.6 (0.8)	0.40	7.9 (0.7)	0.10
BMI, kg/m ²	31.8 (5.9)	29.1 (4.9)	0.50	31.8 (5.9)	0.006
SBP, mmHg	N/A	N/A	N/A	N/A	N/A
DBP, mmHg	N/A	N/A	N/A	N/A	N/A
Heart failure, %	16.2	2.9	0.46	12.6	0.10
Established CVD, %	73.1	64.5	0.19	72.3	0.02
CVD risk factors, %	26.9	27.9	0.02	22.3	0.10
eGFR, ml/min/1.73 m ²	76.3 (22.9)	70.5 (25.5)	0.24	78.4 (31.5)	0.09
Variable	HARMONY	I/E	SMD	Like	SMD
Number	9463	10 208			
Age, years	64.1 (8.7)	73.6 (9.1)	1.07	N/A	N/A
Male, %	69.0	68.4	0.01	N/A	N/A
Diabetes duration, years	14.1 (8.7)	17.9 (10.3)	0.40	N/A	N/A
HbA1c, %	8.7 (1.5)	8.1 (1.0)	0.47	N/A	N/A
BMI, kg/m ²	32.3 (5.9)	29.1 (4.9)	0.59	N/A	N/A
SBP, mm Hg	134.7 (16.5)	137.5 (18.6)	0.16	N/A	N/A
DBP, mm Hg	76.8 (10.1)	75.8 (9.2)	0.10	N/A	N/A
Heart failure, %	20.0	4.3	0.50	N/A	N/A
Established CVD, %	100.0	85.4	0.58	N/A	N/A
CVD risk factors, %	0.0	33.6	1.00	N/A	N/A
eGFR, ml/min/1.73 m ²	79.0 (25.5)	68.9 (22.1)	0.42	N/A	N/A

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; N/A, not available; SBP, systolic blood pressure.

Established CVD and CVD risk factors are defined as described in each trial publication and slightly modified (as illustrated in Table S1).

the proportion of real-world patients who have true CVOT-like characteristics is much smaller, ranging from 0.5% to 7.9%.

CVOTs have shown the notable capacity of some GLP-1RAs to reduce the rate of adverse cardiovascular outcomes in patients with T2D.⁹ The generalizability of such findings to clinical practice is challenging, in particular because the populations investigated in CVOTs are markedly different from real-world T2D patients. CVOTs select patients whose characteristics are intended to maximize the

probability of trial success, whereas the representativeness of the real-world T2D population is rarely an issue considered in CVOT design.

Prior studies have examined what proportion of patients from clinical practice databases would be eligible for CVOTs on GLP-1RAs or SGLT-2is. By analysing US adult T2D databases, Boye et al¹³ reported proportions of patients eligible for LEADER, SUSTAIN-6, EXSCEL and REWIND that were quite similar to those shown in our

study. This comparison is important because the proportion of patients eligible for CVOTs would be expected to be higher in US than in European databases, since CVOTs were conducted in the US. While small differences were probably a result of regional variations (eg, in BMI), no major difference emerged, suggesting a limited impact of geographical and cultural factors.

Similar analyses have been performed on CVOTs for SGLT-2is.^{12,14} Nicolucci et al¹¹ showed that real-world T2D patients eligible for CVOTs on SGLT-2is were different to trial populations in many instances.¹¹ To date, however, no study has been able to calculate what proportion of real-world patients truly constitute CVOT-like populations.

By analysing GLP-1RA CVOTs, we found substantial differences between the eligible real-world populations and trial populations. The high proportion of patients eligible for PIONEER-6⁸ in our study reflects enrolment criteria that, different to those of EXSCeL,⁷ lacked constraint on the ratio between patients with established cardiovascular disease and those with multiple cardiovascular risk factors. However, the resulting PIONEER-6 eligible subset was greatly imbalanced compared with the true PIONEER-6 population.⁸ We therefore examined what proportion of patients from the real-world database would generate CVOT-like populations. To this end, we used a Bayesian method to sample patients from a large dataset based on given average clinical characteristics. We found that the greatest subset of patients with CVOT-like characteristics was much smaller than the proportion of eligible patients. Interestingly, we found no subset of real-world patients matching the HARMONY trial population, probably because HARMONY patients had established cardiovascular disease at a young age.⁴ Notably, REWIND was confirmed as the CVOT mostly represented within the T2D population, although only 7.9% of real-world patients were truly REWIND-like. On the contrary, the apparently large generalizability of PIONEER-6 based on I/E criteria was not confirmed. This important finding highlights that CVOT populations are extremely specific and that they are poorly represented by real-world T2D patients.

We acknowledge that, in view of the potentially wide cardiovascular benefits of GLP-1RAs, this class of GLMs is substantially underutilized among T2D patients.²² However, our data argue that the generalizability of trial populations to clinical practice should not be based on trial I/E criteria. It is important to remember that the representativeness of trial populations is only one aspect of trial-finding generalizability. Observational studies, although unable to substitute for CVOTs,²³ complement CVOT findings and can provide an estimate of true effectiveness in real-world patients often not represented in CVOTs. Real-world studies on the glycaemic and extra-glycaemic effectiveness of GLP-1RAs have confirmed findings from phase III RCTs,²⁴⁻²⁶ but there is still a paucity of cardiovascular real-world studies.²⁷ In a small study from the UK, the intensification of oral therapy by adding GLP-1RAs was associated with a lower cardiovascular events rate than the intensification with insulin.²⁸ A study using the Swedish and Danish diabetes registries reported that liraglutide, compared with dipeptidyl peptidase-4 inhibitors, only exerted significant cardiovascular protection in patients with established cardiovascular disease.²⁹

In parallel to observational studies, alternative methods have recently been developed to transport trial findings to target populations using an inverse odds weighting approach^{30,31}.

Our study has limitations inherent to the nature of the data being analysed. Real-world databases often lack some of the information required to address trial I/E criteria, leading to the need for simplifications (Table S1). Exclusion of patients with missing data can lead to deviations from the target population, potentially affecting generalizability analysis.³² Under-reporting may be another issue in the data collected for clinical purposes, possibly leading to an underestimation of the proportion of patients eligible for CVOTs. Finally, we excluded prevalent GLP-1RA users from the analysis of generalizability because it was expected that GLP-1RAs would have already determined at least part of their benefits in those patients. However, the clinical characteristics of the small group of patients on GLP-1RAs did not resemble those of CVOT populations, suggesting that excluding prevalent GLP-1RA users was unlikely to affect the generalizability findings in a meaningful manner.

In conclusion, we show that applying CVOT enrolment criteria to real-world populations leads to a huge overestimation of patients who resemble CVOT populations, thereby leaving open the issue of generalizability.

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CONFLICT OF INTEREST

G.P.F. received grant support, lecture or advisory board fees from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Mundipharma, NovoNordisk, Sanofi, Genzyme, Servier, Abbott, Novartis and Merck Sharp & Dohme. E.O. received lecture fees from Eli Lilly and NovoNordisk. O.L. has received speaker fees from Eli-Lilly and NovoNordisk; she also received research grants from AstraZeneca and advisory board fees from NovoNordisk. S.M. received lecture or advisory board fees from AstraZeneca, Sanofi and Takeda. A.C. has received consultancy or speaker fees from Abbott, AstraZeneca, Boehringer-Ingelheim, Bruno Farmaceutici, Janssen, Eli-Lilly, Merck Sharp & Dohme, Novartis, NovoNordisk, Roche, Sanofi-Aventis, Servier and Takeda; he also received research grants From Eli-Lilly and NovoNordisk. A.A. received research grants, lecture or advisory board fees from Merck Sharp & Dome, AstraZeneca, Novartis, Boehringer-Ingelheim, Sanofi, Mediolanum, Janssen and NovoNordisk. V.S., P.B. and F.Q. have nothing to disclose.

AUTHOR CONTRIBUTIONS

Study design: V.S., P.B., A.C., A.A. and G.P.F. Data collection and analysis: V.S., P.B., E.O., O.L., S.M., F.Q. and G.P.F. Manuscript writing: V.S., P.B., A.C., A.A. and G.P.F. Manuscript revision: E.O., O.L., S.M. and F.Q. All of the authors approved the final version of the manuscript.

COMPOSITION OF THE DARWIN-T2D DATABASE

Agostino Consoli and Gloria Formoso (Dipartimento di Medicina e Scienze dell'Invecchiamento - Università Degli studi G. D'Annunzio di Chieti-Pescara); Giovanni Grossi (Ospedale San Francesco di Paola - Azienda Sanitaria Provinciale di Cosenza); Achirpita Pucci (Azienda Sanitaria Provinciale di Cosenza); Giorgio Sesti and Francesco Andreozzi (Azienda Ospedaliero Universitaria di Catanzaro); Giuseppe Capobianco (Azienda Sanitaria Locale Napoli 2 Nord); Adriano Gatti (Ospedale San Gennaro dei Poveri - Azienda Sanitaria Locale Napoli 1 Centro); Riccardo Bonadonna, Ivana Zavaroni and Alessandra Dei Cas (Azienda Ospedaliero Universitaria di Parma); Giuseppe Felace (Ospedale di Spilimbergo - Azienda per l'Assistenza Sanitaria n.5 Friuli Occidentale); Patrizia Li Volsi (Ospedale di Pordenone - Azienda per l'Assistenza Sanitaria n.5 Friuli Occidentale); Raffaella Buzzetti and Gaetano Leto (Ospedale Santa Maria Goretti - Azienda Sanitaria Locale di Latina); Gian Pio Sorice (Fondazione Policlinico Universitario A. Gemelli, Roma); Paola D'Angelo (Ospedale Sandro Pertini - Azienda Sanitaria Locale Roma 2); Susanna Morano (Azienda Ospedaliera Universitaria Policlinico Umberto I, Roma); Antonio Carlo Bossi (Ospedale di Treviglio - Azienda Socio Sanitaria Territoriale Bergamo Ovest); Edoardo Duratorre (Ospedale Luini Confalonieri di Luino - Azienda Socio Sanitaria Territoriale Sette Laghi); Ivano Franzetti (Ospedale Sant'Antonio Abate di Gallarate - Azienda Socio Sanitaria Territoriale Valle Olona); Paola Silvia Morpurgo (Ospedale Fatebenefratelli - Azienda Socio Sanitaria Territoriale Fatebenefratelli Sacco); Emanuela Orsi (Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico di Milano); Fabrizio Querci (Ospedale Pesenti Fenaroli di Alzano Lombardo - Azienda Socio Sanitaria Territoriale Bergamo Est); Massimo Boemi† and Federica D'Angelo (Presidio Ospedaliero di Ricerca INRCA-IRCCS di Ancona); Massimiliano Petrelli (Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona); Gianluca Aimaretti and Ioannis Karamouzis (Azienda Ospedaliero Universitaria Maggiore della Carità di Novara); Franco Cavalot (Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano); Giuseppe Saglietti† (Ospedale Madonna del Popolo di Omegna - Azienda Sanitaria Locale Verbano Cusio Ossola); Giuliana Cazzetta (Casa della Salute, Ugento - Distretto Socio Sanitario Gagliano del Capo - Azienda Sanitaria Locale di Lecce); Silvestre Cervone (Presidio ospedaliero San Marco in Lamis - Distretto Socio Sanitario San Marco in Lamis - Azienda Sanitaria Locale di Foggia); Eleonora Devangelio (Distretto Socio Sanitario di Massafra - Azienda Sanitaria Locale di Taranto); Olga Lamacchia (Azienda Ospedaliero Universitaria Ospedali Riuniti di Foggia); Salvatore Arena (Ospedale Umberto I - Azienda Sanitaria Provinciale di Siracusa); Antonino Di Benedetto (Azienda Ospedaliera Universitaria Policlinico G. Martino di Messina); Lucia Frittitta (Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi di Catania); Carla Giordano (Azienda Universitaria Policlinico Paolo Giaccone di Palermo); Salvatore Piro (Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi di Catania); Manfredi Rizzo, Roberta Chianetta and Carlo Mannina (Azienda Universitaria Policlinico Paolo Giaccone di Palermo); Roberto Anichini (Ospedale San Jacopo di Pistoia - Azienda USL Toscana Centro); Giuseppe Penno (Azienda Ospedaliero Universitaria Pisana); Anna Solini (Azienda Ospedaliera

Universitaria Pisana); Bruno Fattor (Comprensorio Sanitario di Bolzano - Azienda Sanitaria della Provincia Autonoma di Bolzano); Enzo Bonora and Massimo Cigolini (Azienda Ospedaliero Universitaria Integrata di Verona); Annunziata Lapolla and Nino Cristiano Chillelli (Complesso Socio Sanitario Ai Colli - Azienda ULSS n.6 Euganea); Maurizio Poli (Ospedale Girolamo Fracastoro di San Bonifacio - Azienda ULSS n.9 Scaligera); Natalino Simioni and Vera Frison (Ospedale di Cittadella - Azienda ULSS n.6 Euganea); Carmela Vinci (Azienda ULSS n.4 Veneto Orientale).

ORCID

Angelo Avogaro <https://orcid.org/0000-0002-1177-0516>

Gian Paolo Fadini <https://orcid.org/0000-0002-6510-2097>

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SUPPORTING INFORMATION

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

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