Generalizability of Cardiovascular Safety Trials on SGLT2 Inhibitors to the Real World: Implications for Clinical Practice

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ABSTRACT

Introduction: Following the US Food and Drug Administration (FDA) guidance on the evaluation of novel agents for the treatment of type 2 diabetes mellitus (T2DM), a number of cardiovascular outcomes safety trials (CVOTs) on sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been conducted. These trials show similarities in study design and definition of primary endpoints, but differ in their eligibility criteria. The aim of the present study was to investigate the generalizability of CVOTs on SGLT2i to Italian adults with T2DM; we estimated the proportions of this patient population who would be eligible for enrollment in EMPA-REG OUTCOME (empagliflozin), CANVAS (canagliflozin), DECLARE-TIMI 58 (dapagliflozin), and VERTIS-CV (ertugliflozin) studies.

Methods: This observational, cross-sectional study was conducted in 222 Italian diabetes clinics. Data on 455,662 adult patients with T2DM seen during 2016 were analyzed against the published patient eligibility criteria for the four CVOTs. The current use of SGLT2i in potentially eligible patients was assessed.

Results: Among the population identified, the proportion of patients meeting major eligibility criteria was 11.7% for EMPA-REG OUTCOME, 29.4% for CANVAS, 55.9% for DECLARE-TIMI 58, and 12.8% for VERTIS-CV. Of the patients eligible for these CVOTs, only a minority (range 4.4–6.8%) was actually prescribed an SGLT2i. Compared with patients in the CVOTs, eligible patients in the real world showed older age and longer diabetes duration, lower BMI and HbA1c

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levels, lower prevalence of established cardiovascular and cerebrovascular disease, and higher rates of microvascular complications and peripheral arterial disease.

Conclusion: The percentage of patients potentially eligible for treatment with SGLT2i varies as a reflection of different eligibility criteria applied in the trials. A large number of patients that could benefit from SGLT2i in terms of not only cardiovascular protection but also renal protection do not receive the treatment.

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Keywords: Cardiovascular outcomes safety trials; Electronic medical records; Eligibility criteria; Endocrinology; Quality of care; Real-world data; Sodium-glucose cotransporter-2 inhibitors; Type 2 diabetes

INTRODUCTION

Cardiovascular complications represent the leading cause of morbidity and mortality among people with type 2 diabetes mellitus (T2DM) [1]. Improving cardiovascular outcomes thus represents a primary objective of diabetes management [2]. In recent years, following the US Food and Drug Administration (FDA) guidance on the evaluation of novel agents for the treatment of T2DM with respect to major adverse cardiac events [3], a number of cardiovascular outcomes safety trials (CVOTs) have been conducted. These trials have confirmed the cardiovascular safety of new drug classes such as GLP-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) [4–11]. In addition, several of these large randomized controlled trials reported statistically significant reductions in cardiovascular events for three of the FDA-approved SGLT2i (empagliflozin, canagliflozin, dapagliflozin) [4, 9, 10, 12] and three FDA-approved GLP-1 RAs (liraglutide, albiglutide, and semaglutide) [6, 7, 11]. The results of these trials are particularly relevant, since they suggest a paradigm shift in the management of patients with T2DM and established CV disease, from lowering HbA1c alone to a broader focus on lowering CV risk.

SGLT2 inhibitors lower blood glucose levels by preventing the reabsorption of glucose from the proximal renal tubule in the kidney, with the consequent excretion of excess glucose in the urine; they also show additional benefits on body weight and blood pressure [13] as demonstrated in clinical trials of canagliflozin [14], dapagliflozin [15–17], and empagliflozin [18].

Three large CVOTs on SGLT2i have been completed so far, EMPA-REG OUTCOME (empagliflozin) [4], CANVAS (canagliflozin) [9], and DECLARE-TIMI 58 (dapagliflozin) [12], while VERTIS-CV (ertugliflozin) [19] is still in progress. All these trials show similarities in study design and definition of primary endpoints, in accordance with FDA guidelines. However, eligibility criteria such as patients' ages, glycated hemoglobin (HbA1c) levels at baseline, history of CV disease, and presence of CV risk factors vary among trials (Table 1).

These differences in study populations may prevent meaningful comparisons between the findings of the different CVOTs, and pose problems when assessing the potential CV safety of a particular treatment in a real-world T2DM population. An understanding of the generalizability of the eligibility criteria of CVOTs can help clinicians evaluate the applicability of the findings to their patients. In fact, restrictive inclusion criteria make study results less applicable, due to the lack of similarity between study participants and the vast majority of patients encountered in clinical practice.

In Italy, since 2006 the Italian Association of Diabetologists (Associazione Medici Diabetologi, AMD) has promoted a monitoring and continuous quality of care improvement initiative called AMD Annals. This initiative is based on clinical data stored in electronic medical records (EMR) of a large network of diabetes clinics, which are periodically extracted and used to assess specific quality indicators of diabetes care [20–22]. The current availability of this large database can allow an accurate investigation of the generalizability of the four SGLT2 inhibitor CVOTs to Italian adults with T2DM. The aim of our study was to estimate the proportions of this patient population who would be eligible for enrollment in each of

Table 1 Main characteristics of the CVOTs considered

	EMPA-REG OUTCOME	CANVAS program	DECLARE-TIMI 58	VERTIS-CV
SGLT2i tested	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Control group	Placebo	Placebo	Placebo	Placebo
Number of patients	7020	10,142	17,160	8238
Primary endpoint	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke
Mean follow-up (years)	3.1	3.6	4.2	In progress
Inclusion criteria				
T2DM	×	×	×	×
Age (years)	≥ 18	≥ 30 plus established CVD	≥ 40 plus established CVD	≥ 18
		OR	OR	
		≥ 50 plus ≥ 2 CV risk factors	≥ 55 (M)/60 (F) plus ≥ 1 CV risk factor	
HbA1c	7–10%	7–10.5%	≥ 6.5%	7–10.5%
eGFR (ml/ min × 1.73 m^2)	≥ 30	≥ 30	–	–
BMI (kg/m^2)	≤ 45	–		≥ 18
Established CVD				
Myocardial infarction	×	×	×	×
CHD	×	–	×	×
PCI	×	×	×	×
CABG	×	×	×	×
Angina	×	×	×	–
Stroke	×	×	×	×
Peripheral arterial disease	×	×	×	×
Peripheral reperfusion/ revascularization	×	×	×	×
Peripheral bypass surgery	×	×	×	×
TIA	–	×	–	–
Amputation	–	×	×	×

Table 1 continued

	EMPA-REG OUTCOME	CANVAS program	DECLARE-TIMI 58	VERTIS-CV
CV risk factors				
Duration of diabetes (years)	–	≥ 10	–	–
Systolic blood pressure (mmHg)	–	≥ 140	Treated with antihypertensive agents	–
Smoking	–	×	×	–
Micro/macroalbuminuria	–	×	–	–
HDL cholesterol (mg/dl)	–	< 39	–	–
LDL cholesterol (mg/dl)	–	–	> 130	–
Main results (SGLT2i vs. placebo)				
MACE[a]	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	–
CV mortality[a]	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	–
Total mortality[a]	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.82–1.04)	–
Hospitalization for heart failure[a]	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	–

eGFR estimated glomerular filtration rate, *CVD* cardiovascular disease, *CHD* coronary heart disease, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft surgery, *TIA* transient ischemic attack, *MACE* death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

[a] Hazard ratio and 95% confidence intervals

these studies, and compare the characteristics of the CVOTs populations with those of everyday practice patients potentially eligible for these trials; we also evaluated which proportion of all potentially eligible patients was actually treated with an SGLT2i.

METHODS

This observational, cross-sectional study was conducted in a network of 222 Italian diabetes clinics participating in the last edition of AMD Annals initiative. These centers, accounting for approximately one-fourth of all the clinics operating within the national healthcare system, all share the same software for data extraction from electronic medical records. Data from participating centers are annually collected and centrally analyzed anonymously. For the purposes of the present study, data on all patients with T2DM seen during 2016 were analyzed against the published patient eligibility criteria for CVOTs on the SGLT2i canagliflozin (CANVAS) [9], dapagliflozin (DECLARE-TIMI 58) [12], empagliflozin (EMPA-REG OUTCOME) [4], and ertugliflozin (VERTIS-CV) [19] (Table 1).

The primary aim of the study was to estimate the proportion of adults with T2DM attending diabetes clinics in Italy who would meet the criteria for inclusion in each of the four SGLT2i CVOTs. We also compared the characteristics of the CVOTs populations with those of everyday practice patients potentially eligible for these trials, and evaluated which proportion of all potentially eligible patients was actually treated with an SGLT2i.
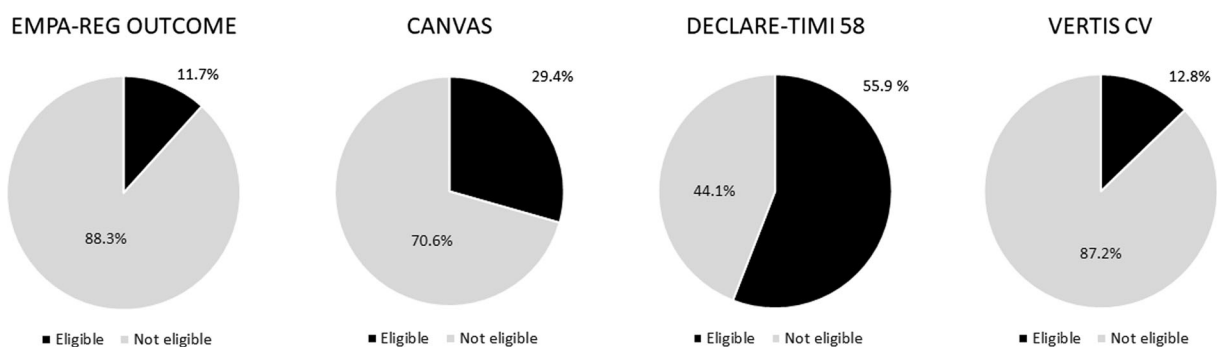
Fig. 1 Percentages of adults with type 2 diabetes in the AMD Annals database who would have met inclusion criteria for cardiovascular outcomes trials with empagliflozin, canagliflozin, dapagliflozin, or ertugliflozin

Table 2 Characteristics of patients in EMPA-REG and those of patients in the AMD Annals database eligible for the trial

Characteristics	Class	AMD Annals database	EMPA-REG OUTCOME
No.		40,039	7034
Gender (%)	Female	31.6	28.5
	Male	68.4	71.5
Age (years)		72.7 ± 9.0	63.1 ± 8.6
Smoking (%)		16.9	13.0
Body mass index (kg/m^2)		29.3 ± 4.8	30.6 ± 5.3
Duration of diabetes	≤ 5 years	12.5	18.0
	5–10 years	18.0	24.9
	> 10 years	69.5	57.1
HbA1c (%)		7.9 ± 0.7	8.1 ± 0.8
Glucose-lowering agents (%)	Metformin	54.1	73.8
	Secretagogues	28.3	42.7
	TZDs	3.2	4.3
	DPP-IV inhibitors	20.2	11.3
	GLP-1 RA	3.4	2.8
	Insulin	56.4	48.2
Lipid profile (mg/dl)	Total cholesterol	157.8 ± 37.3	162.2 ± 42.5
	LDL cholesterol	84.2 ± 30.8	84.9 ± 34.8
	HDL cholesterol	45.8 ± 12.7	46.3 ± 11.6
	Triglycerides	146.0 ± 86.9	168.0 ± 123.9
Lipid-lowering agents (%)	Statins	72.2	76.6
	Fibrates	2.7	9.0

Table 2 continued

Characteristics	Class	AMD Annals database	EMPA-REG OUTCOME
Blood pressure (mmHg)	Systolic	135.9 ± 18.4	135 ± 17
	Diastolic	75.4 ± 9.3	77 ± 10
Antihypertensive agents (%)		86.9	94.4
	Diuretics	47.4	–
	Beta-blockers	54.6	80.3
	Calcium channel blockers	27.1	30.1
	ACE inhibitors and/or ARBs	69.4	80.3
Antiplatelets (%)	Aspirin	62.8	85.2
Renal function	Micro/macroalbuminuria (%)	55.4	39.6
	eGFR (ml/min $\times$ 1.73 m^2)	69 ± 20	74 ± 21
	eGFR < 60 ml/min $\times$ 1.73 m^2 (%)	36.2	25.5
CVD (%)	CHD	44.2	57.3
	Myocardial infarction	17.8	46.6
	CABG	13.0	24.7
	Stroke	15.4	23.2
	Peripheral arterial disease	39.4	20.6

TZDs thiazolidinediones, *ARB* angiotensin receptor blocker, *eGFR* estimated glomerular filtration rate, *CVD* cardiovascular disease, *CHD* coronary heart disease, *CABG* coronary artery bypass graft surgery

Information collected included age, gender, diabetes duration, BMI, HbA1c, blood pressure, lipid profile, albuminuria, estimated glomerular filtration rate (CKD-EPI formula), presence of diabetic retinopathy, glucose-lowering drugs, antihypertensive drugs, lipid-lowering drugs, and antiplatelet agents. Major cardiovascular, cerebrovascular, and peripheral vascular events were classified using the ICD-9-CM coding system, as reported in Supplementary Table 1.

For patients with more than one clinic visit during the study period, the most recent visit was used for analysis.

Data are summarized as mean and standard deviation (continuous variables) or percentages (categorical variables).

The AMD Annals initiative has been approved by the ethics committees of all participating centers (Supplementary Table 2). On the basis of Italian regulations, the written informed consent from participants was not required, being extracted data anonymous. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

RESULTS

EMPA-REG OUTCOME

During 2016, 455,662 patients with T2DM were seen by the participating centers. Overall, 342,205 patients could be evaluated for eligibility (presence of information on all relevant inclusion criteria), of whom 50.2% had an HbA1c value between 7.0% and 10.0%, and 23.8% had established CV disease. Among the

adult T2DM population identified, 11.7% (40,039 patients) would have met the eligibility criteria for EMPA-REG OUTCOME (Fig. 1). Of these, only 2073 (5.2%) were actually treated with an SGLT2i.

Compared with patients in the trial, EMPA-REG OUTCOME eligible patients in the AMD Annals database were older, had a longer duration of diabetes and lower BMI and HbA1c levels, were less likely to have a diagnosis of myocardial infarction or stroke, but were more likely to have albuminuria and a diagnosis of peripheral arterial disease (Table 2). Furthermore, patients in the AMD Annals database were less likely to be treated with metformin and secretagogues, and more likely to be treated with DPP-IV inhibitors and insulin. Treatment with beta-blockers and ACE inhibitors or angiotensin II receptor blockers (ARBs) was also less frequently documented in the real-world population.

CANVAS

There were 149,064 patients with no missing information on all major eligibility criteria of CANVAS, of whom 50.2% had an HbA1c value between 7.0% and 10.0%, and 24.4% had established CV disease.

Among the T2DM population identified, 29.4% (43,883 patients) would have met the eligibility criteria for CANVAS (Fig. 1). Of these, only 2917 (6.6%) were actually treated with an SGLT2i.

CANVAS eligible patients in the AMD Annals database differed in many aspects from those in the trial. In particular, they were older, had a longer duration of diabetes, higher systolic blood pressure, and lower HbA1c and BMI. They were also less likely to have a diagnosis of coronary artery disease, cerebrovascular disease, and chronic heart failure, but were more likely to have albuminuria and diabetic retinopathy (Table 3). Furthermore, patients in the AMD Annals database were less likely to be treated with metformin and secretagogues, and more likely to be treated with DPP-IV inhibitors. Patients in CANVAS were more likely to be treated with beta-blockers and ACE inhibitors or ARBs.

DECLARE-TIMI 58

Overall, 257,694 patients could be evaluated for eligibility, of whom 74.8% had an HbA1c value $\geq 6.5\%$ and 25.1% had established CV disease. Among patients in the AMD Annals database, 55.9% (144,166 patients) would have met the eligibility criteria for DECLARE-TIMI 58 (Fig. 1). Of these, 6373 (4.4%) were actually treated with an SGLT2i.

Compared with patients in the trial, DECLARE-TIMI 58 eligible patients in the AMD Annals database were older, had a longer duration of diabetes, lower BMI and markedly lower HbA1c levels, were less likely to have coronary artery disease, but were more likely to have albuminuria, eGFR < 60 ml/min, diabetic retinopathy, and a diagnosis of peripheral arterial disease (Table 4). Furthermore, patients in the AMD Annals database were less likely to be treated with metformin and secretagogues, and more likely to be treated with DPP-IV inhibitors and insulin. Treatment with beta-blockers, calcium channel blockers, ACE inhibitors or ARBs, and statins was also less frequently documented in the AMD Annals population, while the use of diuretics was more common.

VERTIS-CV

There were 342,205 patients in the AMD Annals database evaluable for eligibility in VERTIS-CV, of whom 51.4% had an HbA1c value between 7.0% and 10.5%, and 23.6% had established CV disease. Among these patients, 12.8% (46,631 patients) would have been eligible for VERTIS-CV (Fig. 1), of whom 2148 (4.9%) were actually treated with an SGLT2i.

Compared with patients in the trial, eligible patients in the AMD Annals database were older, had a longer duration of diabetes, lower BMI and HbA1c levels, were less likely to have coronary artery disease, stroke, and congestive heart failure, but were more likely to have albuminuria, eGFR < 60 ml/min, diabetic retinopathy, and a diagnosis of peripheral arterial disease (Table 5). Furthermore, patients in the AMD Annals database were less likely to be treated with metformin and secretagogues, and

Table 3 Characteristics of patients in CANVAS and those of patients in the AMD Annals database eligible for the trial

Characteristics	Class	AMD Annals database	CANVAS
No.		43,883	10,142
Gender (%)	Female	36.3	35.8
	Male	63.7	64.2
Age (years)		70.8 ± 9.2	63.3 ± 8.3
Smoking (%)		22.9	17.8
Body mass index (kg/m^2)		29.9 ± 5.3	32.0 ± 5.9
Duration of diabetes (years)		16.4 ± 9.3	13.5 ± 7.8
HbA1c (%)		7.9 ± 0.8	8.2 ± 0.9
Glucose-lowering agents (%)	Metformin	60.5	77.2
	Secretagogues	30.1	43.0
	DPP-IV inhibitors	22.4	12.4
	GLP-1 RA	4.8	4.0
	Insulin	53.2	50.2
Lipid profile (mg/dl)	Total cholesterol	164.8 ± 37.9	170.1 ± 46.4
	LDL cholesterol	89.7 ± 31.5	88.9 ± 34.8
	HDL cholesterol	46.0 ± 13.1	46.4 ± 11.6
	Triglycerides	151.8 ± 92.4	177.1 ± 88.6
Lipid-lowering agents (%)	Statins	63.2	74.9
Blood pressure (mmHg)	Systolic	140.1 ± 19.2	136.6 ± 15.8
	Diastolic	77.6 ± 9.5	77.7 ± 9.7
Antihypertensive agents (%)		86.9	94.4
	Diuretics	43.6	44.3
	Beta-blockers	39.5	53.5
	ACE inhibitors and/or ARBs	69.2	80.0
Antiplatelets (%)		57.4	73.6
Renal function	Micro/macroalbuminuria (%)	63.8	30.2
	eGFR (ml/min × 1.73 m^2)	71.9 ± 20.5	76.5 ± 20.5
CVD (%)	Coronary disease	21.9	56.4
	Cerebrovascular disease	9.4	19.3
	Peripheral arterial disease	20.5	20.8
	CHF	3.7	14.4
	Amputation	0.9	2.3

ARB angiotensin receptor blocker, *eGFR* estimated glomerular filtration rate, *CVD* cardiovascular disease, *CHD* coronary heart disease, *CHF* chronic heart failure

Table 4 Characteristics of patients in DECLARE-TIMI 58 and those of patients in the AMD Annals database eligible for the trial

Characteristics	Class	AMD Annals database	DECLARE-TIMI 58
No.		144,166	17,160
Gender (%)	Female	42.3	37.4
	Male	57.7	62.6
Age (years)		71.9 ± 8.4	63.8 ± 6.8
Smoking (%)		17.5	14.5
Body mass index (kg/m^2)		29.7 ± 5.3	32.1 ± 6.0
Duration of diabetes (years)		13.9 ± 9.6	11.8 ± 7.8
HbA1c (%)		7.6 ± 1.1	8.3 ± 1.2
Glucose-lowering agents (%)	Metformin	59.5	78.5
	Secretagogues	27.5	41.1
	DPP-IV inhibitors	21.1	16.0
	GLP-1 RA	3.6	4.2
	Insulin	41.4	39.6
Lipid profile (mg/dl)	Total cholesterol	169.2 ± 39.5	169.8 ± 46.3
	LDL cholesterol	93.3 ± 33.6	88.8 ± 34.7
	HDL cholesterol	48.3 ± 13.3	46.3 ± 11.6
	Triglycerides	144.2 ± 84.6	177.0 ± 132.7
Lipid-lowering agents (%)	Statins	61.4	71.3
	Fibrates	3.2	8.3
	Omega-3	7.9	4.6
	Ezetimibe	3.5	7.4
Blood pressure (mmHg)	Systolic	137.6 ± 18.6	135.0 ± 15.5
	Diastolic	76.9 ± 9.5	78.0 ± 9.1
Antihypertensive agents (%)		88.5	89.4
	Diuretics	48.2	38.6
	Beta-blockers	40.7	46.2
	Calcium channel blockers	27.0	33.0
	ACE inhibitors and/or ARBs	72.1	77.1
Antiplatelets (%)	Aspirin	47.1	52.1
	Clopidogrel	6.1	10.9

Table 4 continued

Characteristics	Class	AMD Annals database	DECLARE-TIMI 58
Renal function	Micro/macroalbuminuria (%)	48.8	30.2
	eGFR (ml/min × 1.73 m^2)	70.1 ± 21.7	86.1 ± 21.8
	eGFR < 60 ml/min × 1.73 m^2 (%)	31.7	9.1
Retinopathy		28.2	12.4
CVD (%)	Myocardial infarction	6.6	20.9
	PCI	8.3	21.3
	CABG	4.4	9.8
	Stroke	5.4	6.5
	Peripheral arterial disease	14.6	6.0
	Peripheral revascularization	0.0	1.3
	Peripheral bypass surgery	0.6	1.6
	Amputation	0.6	0.6

ARB angiotensin receptor blocker, *eGFR* estimated glomerular filtration rate, *CVD* cardiovascular disease, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft surgery

Table 5 Characteristics of patients in VERTIS-CV and those of patients in the AMD Annals database eligible for the trial

Characteristics	Class	AMD Annals database	VERTIS-CV
No.		80,797	8238
Gender (%)	Female	32.2	30.0
	Male	67.8	70.0
Age (years)		72.9 ± 9.0	64.4 ± 8.1
Smoking (%)		29.5 ± 5.1	32.0 ± 5.4
Body mass index (kg/m^2)		16.9 ± 10.3	12.9 ± 8.3
Duration of diabetes (years)		7.9 ± 0.8	8.3 ± 0.9
HbA1c (%)		80.797	8.238
Glucose-lowering agents (%)	Metformin	50.3	76.3
	Secretagogues	26.9	41.1
	TZDs	3.1	1.9
	DPP-IV inhibitors	19.5	11.0
	GLP-1 RA	3.3	3.4
	Insulin	59.1	47.2

Table 5 continued

Characteristics	Class	AMD Annals database	VERTIS-CV
Lipid profile (mg/dl)	Total cholesterol	158.2 ± 37.8	169 ± 46.5
	LDL cholesterol	84.4 ± 30.9	89 ± 38.3
	HDL cholesterol	45.5 ± 12.7	44 ± 12.1
	Triglycerides	148.6 ± 88.9	181 ± 114.6
Lipid-lowering agents (%)	Statins	71.7	81.4
	Ezetimibe	4.5	3.6
Blood pressure (mmHg)	Systolic	135.9 ± 18.5	133 ± 13.8
	Diastolic	75.3 ± 9.4	77 ± 8.5
Antihypertensive agents (%)	Diuretics	49.7	40.6
	Beta-blockers	54.9	69.1
	Calcium channel blockers	27.8	–
	ACE inhibitors and/or ARBs	68.8	81.4
Antiplatelets (%)		73.0	84.6
Renal function	Micro/macroalbuminuria (%)	57.8	39.4
	eGFR (ml/min × 1.73 m^2)	65.5 ± 22.9	76.0 ± 20.9
	eGFR < 60 ml/min × 1.73 m^2 (%)	40.9	22.0
Retinopathy		39.4	16.8
CVD (%)	Myocardial infarction	18.1	47.9
	PCI	25.4	41.4
	CABG	13.3	22.0
	Stroke	15.5	21.0
	Peripheral arterial disease	40.2	18.8
	Peripheral revascularization	0.1	8.2
	Amputation	1.6	3.6
	CHF	6.2	23.1

TZDs thiazolidinediones, *ARB* angiotensin receptor blocker, *eGFR* estimated glomerular filtration rate, *CVD* cardiovascular disease, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft surgery

more likely to be treated with DPP-IV inhibitors and insulin. Treatment with beta-blockers, ACE inhibitors or ARBs, and statins was also less frequently documented in the AMD Annals population, while the use of diuretics was more common.

DISCUSSION

The aim of this retrospective analysis was to assess the extent to which eligibility criteria of CVOTs on SGLT2i could be generalized to adults with T2DM attending diabetes outpatient clinics in Italy. The study documented

substantial differences in the percentage of patients who would have met the major eligibility criteria of the different trials, ranging between 11.7% for the EMPA-REG OUTCOME and 55.9% for the DECLARE-TIMI 58. The difference in percentages closely reflects the inclusion of patients with established CV disease only, as in the case of EMPA-REG OUTCOME and VERTIS, or also patients carrying multiple CV risk factors, as in DECLARE-TIMI 58 and CANVAS. Of note, despite one in four patients in the AMD Annals database having established CV disease, many of them were not eligible for the trials, mainly because of HbA1c levels outside the allowed range. Since the positive CV effects of SGLT2i are largely independent of HbA1c levels, it is plausible to assume that in everyday practice a larger proportion of patients would benefit from the treatment.

Compared with a similar study conducted in the USA [23], percentages of patients eligible for the different CVOTs were higher in Italy (DECLARE-TIMI 58: 55.9% vs. 39.8%; EMPA-REG OUTCOME: 11.7% vs. 4.1%; CANVAS: 29.4% vs. 8.8%; VERTIS-CV 12.8% vs. 4.8%). However, in the US study information on complications and risk factors was derived from the NHANES survey and was self-reported by the participants. This could have resulted in inaccurate estimation of the eligibility criteria, thus leading to an underestimation of the real proportions of patients potentially eligible. Furthermore, the Italian sample was identified in diabetes centers. It is plausible that patients seen in secondary care present more severe diabetes, making this population more similar to that enrolled in CVOTs.

In another USA-based outpatient registry of individuals with type 2 diabetes from 313 sites that included cardiology, endocrinology, and primary care practices, 26.2% patients met major eligibility criteria for EMPA-REG OUTCOME [24]. In this case, the participation of a large number of cardiology practices may have increased the proportion of patients with established CV disease, thus leading to a higher eligibility rate.

This observation suggests that there are considerable differences in the characteristics of the patients among the real-world T2D populations in each study. The characteristics of patients in real-world practice may be different among areas or countries probably because of social background, age pyramid, healthcare system (public vs. private insurance; primary care vs. specialist care), and reimbursement limitations. As such, no real-world cohort can be considered as a reference standard for comparison.

Compared with patients in the CVOTs, eligible patients in the AMD Annals database differed in many aspects, including older age and longer diabetes duration, lower BMI and HbA1c levels, lower prevalence of established cardiovascular and cerebrovascular disease, higher rates of microvascular complications and peripheral arterial disease, and different glucose-lowering and cardiovascular background therapies. More advanced age and longer diabetes duration may justify the higher prevalence of retinopathy, albuminuria, and reduced eGFR. On the other hand, the lower prevalence of macrovascular disease suggests a better control of major CV risk factors in this population. The high prevalence of patients with peripheral vascular disease poses some problems of generalizability of trial results, considering that in CANVAS the use of canagliflozin was associated with a doubling in the risk of lower limb amputations [9, 25]. Although these findings were not confirmed in trials with other SGLT2i and no specific etiological mechanism has been identified, caution and close monitoring are required when prescribing these drugs to patients with peripheral vascular disease. On the other hand, the high prevalence of patients with albuminuria or reduced eGFR underlines another important potential benefit of SGLT2i. A recent meta-analysis documented that SGLT2i reduced the risk of progression of renal disease by 45%, with a similar benefit in patients with and without atherosclerotic cardiovascular disease [26]. These findings suggest the need to broaden the scope for treatment with SGLT2i, to include also the prevention or the delay in the progression of microvascular complications.

Despite the evidence supporting the efficacy and safety of SGLT2i, only a minority of patients in the AMD Annals database were

actually treated with these drugs. In Italy SGLT2i were introduced on the market in 2015, and the data analyzed referred to 2016, when only the results of EMPA-REG OUTCOME had been published. It is therefore plausible that the prescription of these drugs has increased in recent years, as a result of the accumulation of new evidence and the issuing of new guidelines for clinical practice [27].

Our findings also have implications for future research. In particular, eligibility criteria of future CVOTs should more closely reflect real-world populations to allow a greater generalizability of their results. The inclusion of larger numbers of patients without established cardiovascular disease, as already done in the DECLARE-TIMI 58, with more advanced age and lower BMI will certainly improve the external validity of the trials, thus increasing the relevance of their results for clinical practice.

Our study has strengths and limitations. Among the strengths, the large number of diabetes centers and patients involved make the study results highly generalizable. In this respect, it should be emphasized that in Italy SGLT2i can only be prescribed by diabetes specialists, making outpatient diabetes centers the ideal setting to perform the study. Furthermore, the adoption in all centers of the same electronic medical records system makes the information collected highly reliable and accurate. The study also has limitations. First, data analyzed refer to 2016 and they might not reflect actual practice in a rapidly evolving scenario. However, it is highly unlikely that the characteristics of patients attending diabetes clinics have changed in most recent years, thus making the results relating to the generalizability of CVOTs still valid. Second, information on major exclusion criteria (e.g., liver disease or other major comorbidities) was not available in the AMD Annals database. Therefore, the percentage of patients that would have been eligible for the different CVOTs could be overestimated.

CONCLUSIONS

Our study shows that the percentage of patients potentially eligible for treatment with agents that demonstrated CV risk reduction in recent

CVOTs varies as a reflection of different eligibility criteria applied in the trials. These differences should be taken into consideration when evaluating the generalizability and applicability of CVOTs to real-world populations. In any case, a large number of patients that could benefit from SGLT2i in terms of not only CV protection but also renal protection do not receive the treatment. Since existing CVOTs targeted high-risk populations, with either established CV disease or multiple CV risk factors, the treatment of choice when low-risk patients require therapy intensification remains to be established.

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Compliance with Ethics Guidelines. The AMD Annals initiative has been approved by the ethics committees of all participating centers (Supplementary Table 2). On the basis of Italian regulations, the written informed consent from participants was not required, being extracted data anonymous. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. All data generated or analyzed during the current study are available from the study sponsor (AMD scientific society) on reasonable request.

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