

# Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitor: Comparing Trial Data and Real-World Use

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Received: February 9, 2017  
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## ABSTRACT

**Introduction:** The first cardiovascular safety trial in the sodium-glucose co-transporter-2 (SGLT2) inhibitor drug class, the Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial, demonstrated significant cardiovascular risk reduction with empagliflozin. It is currently not clear what proportions of people with type 2 diabetes (T2DM) have the same high cardiovascular risk as those included in the trial, and will therefore be likely to experience the same cardiovascular benefit. We aimed to identify and describe the proportion of people with T2DM from a

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**Electronic supplementary material** The online version of this article (doi:10.1007/s13300-017-0254-7) contains supplementary material, which is available to authorized users.

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representative English national population who have the comparable high cardiovascular risk to those included in the EMPA-REG trial.

**Method:** A cross-sectional analysis of cardiovascular risk in people with T2DM and a subgroup prescribed SGLT2 inhibitors. Patients were identified from the Royal College of General Practitioners Research and Surveillance Centre database. Cardiovascular risk factors were identified from electronic patient records.

**Results:** From 1,238,909 patients at 128 GP practices, we identified 60,327 adults with T2DM (mean age 66.1 years, SD 13.9) of whom 55.6% were male. From these 1642 (2.7%) people had been initiated on an SGLT2 inhibitor (mean age 58.1 years, SD 10.4; 58.8% male). In the complete T2DM group only 15.7% (95% CI 15.5–16.0%) had the same high cardiovascular risk as those included in the EMPA-REG trial. In those already initiated on SGLT2 inhibitors this proportion was 11.1% (95% CI 9.8–12.4%). Whilst the proportion was higher in the oldest age groups, in those 70+ years old less than a quarter met the EMPA-REG trial high cardiovascular risk criteria.

**Conclusions:** The EMPA-REG trial results are applicable only to a small proportion of people with T2DM and a smaller proportion of those currently treated with SGLT2 inhibitors. Additional data are required to identify any cardiovascular benefit in people with lower cardiovascular risk.

**Funding:** AstraZeneca.

**Keywords:** Cardiovascular disease; Cross sectional analysis; Empagliflozin; EMPA-REG OUTCOME; Type 2 diabetes; SGLT2

## INTRODUCTION

Until recently there was little evidence for cardiovascular risk reduction with glucose-lowering therapies in type 2 diabetes (T2DM). However, within the last year the results of two trials have demonstrated substantial cardiovascular benefit with two agents: the sodium glucose co-transporter 2 (SGLT2) inhibitor empagliflozin and then glucagon-like peptide-1 (GLP-1) analogue liraglutide. These landmark diabetes trials were the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial and the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, respectively [1, 2]. Whilst ground-breaking, it will take some time before the full clinical application of these trials is realized. The EMPA-REG trial was designed as a non-inferiority randomized placebo-controlled trial to investigate cardiovascular outcomes and mortality with empagliflozin in a selected group at very high risk of cardiovascular disease (Table 1). Unexpectedly, the trial demonstrated substantial cardiovascular benefit with empagliflozin in this cohort.

Sodium glucose co-transporter 2 (SGLT2) inhibitors, also known as gliflozins, improve glycaemic control through inhibition of glucose reuptake by SGLT2 in the proximal tubule of the kidney [3, 4]. This induces glucosuria which lowers serum glucose and also induces diuresis [5]. The cardiovascular risk reduction in the EMPA-REG trial was observed to occur very early, with survival curves, compared with placebo, separating almost immediately after randomization [6]. This has led some commentators to speculate that the survival benefit is achieved not from glucose lowering but due to the diuretic effect of SGLT2 inhibition as these survival curves appear similar to those for trials of diuretics in people with heart failure [7, 8]. However, the limited data available do not support this hypothesis [9]. Alternative mechanisms have

since been suggested including a reduction in cardiac preload and afterload, or shift towards myocardial tissue use of a more efficient fuel (possibly ketone bodies) [10–13]. Additional experimentation is needed, however, to explore these further. Given this uncertainty, it is unknown if the cardiovascular benefits observed in EMPA-REG can be expected in all people with T2DM or just those with a similar, high cardiovascular risk profile to those people included in the EMPA-REG trial [10].

The aims of the study were to provide a description of the cardiovascular risk profile of a large nationally representative sample of people with T2DM treated with SGLT2 inhibitors in England and compare this to the EMPA-REG trial inclusion criteria. Additionally, we compare those treated with SGLT2 inhibitors with the wider T2DM population.

## METHODS

We performed a cross-sectional analysis of all people with T2DM included in the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database based in England, in order to identify people initiated on SGLT2 inhibitors and describe their cardiovascular risk profile. In accordance with our explicit aim to create high-quality and transparent real-world evidence [14, 15], we have reported the planned methods in full in the study protocol [16].

We described the proportion of people with T2DM currently using SGLT2 inhibitors who had a similar cardiovascular risk profile to those included in the EMPA-REG trial. For comparison we also reported the number of people from the complete T2DM group who had the same high cardiovascular risk. The use of English electronic health records for this purpose enabled the identification of a high-quality population denominator as all individuals are registered with a single GP practice and have a unique national identifier, the NHS number [17]. This enabled capture of an almost complete population without double counting.

At the time of this study, the RCGP RSC database contained the electronic health

**Table 1** Inclusion criteria for the EMPA-REG trial Excerpted from the supplementary material included in the EMPA-REG trial manuscript by Zinman et al. [1]

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**Inclusion criteria**

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History of myocardial infarction

History of myocardial infarction >2 months prior to informed consent

Coronary artery disease

Evidence of multi-vessel coronary artery disease, i.e., in  $\geq 2$  major coronary arteries or the left main coronary artery, documented by any of the following:

Presence of significant stenosis:  $\geq 50\%$  luminal narrowing during angiography (coronary or multi-slice computed tomography)

Previous revascularization (percutaneous transluminal coronary angioplasty  $\pm$  stent or coronary artery bypass graft >2 months prior to consent

The combination of revascularization in one major coronary artery and significant stenosis ( $\geq 50\%$  luminal narrowing) in another major coronary artery

Evidence of single-vessel coronary artery disease,  $\geq 50\%$  luminal narrowing during angiography (coronary or multi-slice computed tomography) not subsequently successfully revascularized, with at least 1 of the following:

A positive non-invasive stress test for ischemia

Hospital discharge for unstable angina  $\leq 12$  months prior to consent

Unstable angina

Unstable angina >2 months prior to consent with evidence of single- or multi-vessel coronary artery disease

History of stroke

History of stroke (ischemic or hemorrhagic) >2 months prior to consent

Peripheral artery disease

Occlusive peripheral artery disease documented by any of the following:

Limb angioplasty, stenting, or bypass surgery

Limb or foot amputation due to circulatory insufficiency

Evidence of significant peripheral artery stenosis ( $>50\%$  on angiography, or  $>50\%$  or hemodynamically significant via non-invasive methods) in 1 limb

Ankle brachial index  $<0.9$  in  $\geq 1$  ankle

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records from 128 GP practices distributed across England (1.7% of all practices in England). The RCGP RSC provided a sample which is representative of the UK population [18]. Included data are recorded using the Read code 5-byte version 2 coding hierarchy; this comprises comprehensive diagnosis and treatment information, prescriptions, and laboratory data [19].

We used data from all the included GP practices collated after 1 January 2016. We included all patients with a diagnosis of T2DM over 18 years old on or before this date. In those with T2DM we identified all those people initiated on SGLT2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) at any time before 1 January 2016.

We used a two-stage informatics ontology-based process [20] to identify people with T2DM which we have reported in detail elsewhere [21]. The two stages were

1. Identification of all people with diabetes using diabetes diagnosis codes, glucose and HbA1c test results, or the use of diabetes therapies
2. Categorization by diabetes type based on their medication usage history, diabetes type codes, and other key clinical characteristics

The clinical characteristics of the whole T2DM group and subset of people using SGLT2 inhibitors were reported. These comprise age, gender, body mass index (BMI), glycated hemoglobin (HbA1c), blood pressure, diagnosis of hypertension, renal function, duration of diabetes, and current diabetes medications.

BMI was defined using the most recently recorded values. Where data on BMI were missing, we calculated BMI from the most recent weight and height measurements. HbA1c was defined using the most recent value prior to the initiation of SGLT2 inhibitor in those on SGLT2 inhibitors. Blood pressure values were taken from the most recent measurements. A diagnosis of hypertension was identified using diagnostic codes for hypertension only (not blood pressure measurements).

Renal function was reported as the proportion of people with an estimated glomerular filtration rate (eGFR) measurement of less than 60 ml/min/1.73 m<sup>2</sup>. Duration of diabetes was defined as the time since the first diabetes-defining event. These events comprise first diabetes diagnostic code, first investigation result consistent with diabetes, or date of first prescription of glucose-lowering medication. We have reported the number of people with missing data for all variables.

The high cardiovascular risk inclusion criteria for the EMPA-REG study are demonstrated in Table 1. We identified people with each of these cardiovascular risk factors using clinical diagnostic codes, or other codes which identified a diagnosis of the risk factor (a complete description of these codes is provided in Supplementary Tables S1 to S6). It is possible that

recording of unstable angina is limited in primary care data. As a measure of sensitivity we have also described the number of people with any recorded code for angina of any severity. We have considered a person to have the cardiovascular risk factor of interest if they have any of the disease-defining codes at any time in their clinical record.

We have reported the number of people with each risk factor and proportions with 95% confidence intervals in those with T2DM and also in those prescribed SGLT2 inhibitors. We have also performed subgroup analyses of these proportions stratified by age group, duration of diabetes, type of SGLT2 inhibitor, and by number of current diabetes therapies. Current diabetes therapies are grouped into none, oral monotherapy, oral dual therapy, oral triple therapy (or greater), insulin therapy (any regime which involves insulin use).

### Compliance with Ethics Guidelines

All data to be used was anonymized at the point of data extraction. No clinically identifiable information was made available to researchers. The study has been tested against the Health Research Authority (HRA)/Medical Research Council (MRC) "is this research" tool [22] and was considered to be an audit of current practice when compared to best available evidence. The study therefore did not require specific ethical approval. Approval for this work was granted by the RCGP RSC study approval committee. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## RESULTS

Data were available for analysis from 1,238,909 electronic patient records at 128 general practices. From these we identified 60,327 adults with T2DM. This group was slightly older than the EMPA-REG trial cohort, with a shorter duration of diabetes, but similar mean BMI (Table 2). Within this group 1642 (2.7%) people

**Table 2** Characteristics of with T2DM and a subgroup of people using SGLT2 inhibitors in the real world compared with those in the EMPA-REG trial

Characteristic	RCGP RSC total T2DM group (N = 60,327)	RCGP RSC SGLT2 user group (N = 1642)	EMPA-REG trial participants* (N = 4687)
Age (years)	66.1 (±13.9)	58.1 (±10.4)	63.1 (±8.6)
Male	33,535 (55.6)	966 (58.8)	3336 (71.2)
Race			
White	42,284 (70.1)	1194 (72.2)	3403 (72.6)
Asian	5706 (9.5)	155 (9.4)	1006 (21.5)
Black	2648 (4.4)	40 (2.4)	237 (5.1)
Other	1109 (1.8)	24 (1.5)	36 (0.8)
Missing	8580 (14.2)	229 (13.9)	5 (0.1)
BMI (kg/m <sup>2</sup> )	30.7 (±6.5)	34.0 (±6.4)	30.6 (±5.3)
BMI not recorded	1284 (2.1)	9 (0.5)	0 (0.0)
SBP (mmHg)	132.0 (±14.7)	130.2 (±13.4)	135.3 (±16.9)
DBP (mmHg)	75.0 (±9.6)	76.0 (±8.6)	76.6 (±9.7)
BP not recorded	221 (0.4)	2 (0.1)	0 (0.0)
Diagnosed hypertension	35,659 (59.1)	901 (54.9)	NR
Uncontrolled hypertension <sup>†</sup>	16,950 (28.1)	373 (22.7)	NR
eGFR <60 ml/min/1.73 m <sup>2</sup>	11,167 (18.5)	76 (4.6)	0 (0.0)
Duration of diabetes			
≤1 years	5320 (8.8)	45 (2.7)	128 (2.7)
>1–5 years	17,911 (29.7)	314 (19.1)	712 (15.2)
>5–10 years	18,963 (31.4)	604 (36.8)	1175 (25.1)
>10 years	18,133 (30.1)	679 (41.4)	2672 (57.0)
Other glucose-lowering therapy			
Metformin	35,146 (58.3)	1416 (30.2)	3459 (73.8)
Insulin	8128 (13.5)	447 (9.5)	2252 (48.0)
Sulfonylurea	14,765 (24.5)	800 (17.1)	2014 (43.0)
Dipeptidyl peptidase-4 inhibitor	7236 (12.0)	605 (12.9)	529 (11.3)
Thiazolidinedione	1875 (3.1)	144 (3.1)	198 (4.2)
Glucagon-like peptide-1 agonist	1983 (3.3)	360 (7.7)	126 (2.7)
Monotherapy	21,284 (35.3)	89 (5.5)	1380 (29.4)

**Table 2** continued

Characteristic	RCGP RSC total T2DM group (N = 60,327)	RCGP RSC SGLT2 user group (N = 1642)	EMPA-REG trial participants* (N = 4687)
Dual therapy	11,375 (18.9)	448 (27.5)	2259 (48.2)

Data are presented as *n* (%) or mean (SD)

*BMI* body mass index, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *NR* not reported, *SBP* systolic blood pressure, *SD* standard deviation

\* Pooled empagliflozin participants (10 and 25 mg doses)

† Most recent systolic blood pressure  $\geq 140$  mmHg

**Table 3** Proportion of people with major cardiovascular risk factors amongst all those with type 2 diabetes (N = 60,327) and those prescribed an SGLT2 inhibitor (N = 1642)

Cardiovascular risk factor	RCGP RSC total T2DM group (N = 60,327)		RCGP RSC SGLT2 user group (N = 1642)	
	Risk factor present <i>n</i> (%)*	95% confidence intervals %*	Risk factor present <i>n</i> (%)*	95% confidence intervals %*
Myocardial infarction	2978 (4.9)	4.8–5.1	65 (4.0)	3.2–4.8
Coronary artery disease	3542 (5.9)	5.7–6.0	78 (4.8)	3.9–5.6
Unstable angina	528 (0.9)	0.8–0.9	22 (1.3)	0.9–1.8
Stroke	2607 (4.3)	4.2–4.5	44 (2.7)	2.1–3.3
Peripheral artery disease	2679 (4.4)	4.3–4.6	56 (3.4)	2.7–4.1
Any major cardiovascular risk factor	9481 (15.7)	15.5–16.0	182 (11.1)	9.8–12.4

\* Percentage of people within group

had been initiated on an SGLT2 inhibitor. The majority of these were dapagliflozin (1123), followed by canagliflozin (422), and empagliflozin (160), including 63 people who had a prescription for two different SGLT2 inhibitors. People initiated on an SGLT2 inhibitor were younger than those in the EMPA-REG trial, had a higher BMI, and a broadly similar distribution of diabetes duration (Table 2). The mean HbA1c at SGLT2 initiation was 80.0 mmol/mol (SD 17.3). Twenty-eight people (1.7%) had no HbA1c recorded prior to initiating an SGLT2 inhibitor.

Only a small proportion of people with T2DM had the same cardiovascular risk factors as people included in the EMPA-REG trial (Table 3). Similarly, only a small proportion of those treated with SGLT2 inhibitors had the same cardiovascular risk factors as people

included in the EMPA-REG trial (Table 3). A larger proportion had angina of any severity (all people with T2DM: 4970 people; 8.2%; 95% CI 8.1–8.4%, those treated with SGLT inhibitors: 128 people; 7.8%; 95% CI 13.2–16.1%) or any major risk factor or angina of any severity (all people with T2DM: 11,704 people; 19.4%; 95% CI 19.1–19.7%, those treated with SGLT inhibitors: 240 people; 14.6%; 95% CI 13.2–16.1%).

In subgroup analyses, the proportion of people with major cardiovascular risk factors increased with age but still represented a minority of people even in the oldest age groups, i.e., less than a quarter of those over 70 years old (Table 4 and Supplementary Table S7). The proportion of people with major cardiovascular risk factors varied little by number of current oral therapies (none, one, two, three or more: 14.6%, 14.9%, 14.8%, and

**Table 4** Proportion of people with one or more major cardiovascular risk factor, by age group, amongst all those with type 2 diabetes ( $N = 60,327$ )

Age group	Number of people	Number of people with one or more major cardiovascular risk factor $n$ (%*)	95% confidence interval %*
18–49	7526	225 (3.0)	2.7–3.3
50–59	11,145	988 (8.9)	8.4–9.3
60–69	15,643	2273 (14.5)	14.1–15.0
70+	25,971	5995 (23.1)	22.7–23.5

\* Percentage of people within age group

**Table 5** Proportion of people with one or more major cardiovascular risk factor, by duration of diabetes, amongst all those with type 2 diabetes ( $N = 60,327$ )

Duration of diabetes	Number of people	Number of people with one or more major cardiovascular risk factor $n$ (%*)	95% confidence interval %*
≤1 years	5320	613 (11.5)	10.8–12.3
>1–5 years	17,911	2341 (13.1)	12.7–13.5
>5–10 years	18,963	2818 (14.9)	14.4–15.3
>10 years	18,133	3709 (20.5)	20.0–21.0

\* Percentage of people within diabetes duration group

12.2%, respectively) but was higher in people on insulin therapy (23.5%) (Supplementary Table S8). The proportion of people with a major cardiovascular risk factor was higher in people with a longer duration of diabetes (Table 5) with just over 20% prevalence in those with a history of diabetes longer than 10 years. The proportion of people with a major cardiovascular risk factor was higher in those on empagliflozin (16.3%) than dapagliflozin (10.2%) or canagliflozin (12.8%), although the difference was only significant between empagliflozin and dapagliflozin (Supplementary Table S9).

## DISCUSSION

In a large sample of people with T2DM in England only a small proportion (15.7%; 95% CI 15.5–16.0%) had the same high cardiovascular risk as those included in the EMPA-REG trial. In

those already initiated on SGLT2 inhibitors the proportion was smaller still (11.1%; 95% CI 9.8–12.4%) and this was a younger group. Whilst the proportion was higher in the oldest age groups, even in those 70 years old and over, this still comprised less than a quarter. Similarly, the proportion was higher in those with the longest duration of diabetes, but only comprised just over 20% in those with a duration of diabetes longer than 10 years.

## Implications of the Findings

The cardiovascular benefits identified by the EMPA-REG trial were a surprising but very welcome finding. However, it is important to be clear that the trial's participants were selected on the basis of very high cardiovascular risk. We can therefore only expect similar cardiovascular benefits in the same high risk group in the real world. Our data suggest that this makes up only a small but not insubstantial proportion of

those with T2DM. It also suggests that current SGLT2 inhibitor use occurs in a subgroup of people with T2DM who are of a younger age and have a lower cardiovascular risk than most people with T2DM. Any cardiovascular benefit in these people is uncertain. There are also a large proportion of people with high cardiovascular risk who are not currently treated with an SGLT2 inhibitor. Therefore, there is some scope to consider extending the use of empagliflozin in people with high cardiovascular risk if clinically appropriate.

The presence of cardiovascular risk factors was found, unsurprisingly, to be highest in the oldest age groups. It is therefore likely that this group is most likely to gain the largest cardiovascular risk reduction from SGLT2 inhibitor use. However, the use of SGLT2 inhibitors in this group can be problematic as the elderly are more likely to experience volume depletion, more likely to have baseline renal impairment, and have more significant sequelae from urinary tract infections [23–27].

Other cardiovascular safety trials are still ongoing and will help to explore questions around whether these benefits are a class effect and whether they can also be seen in lower cardiovascular risk groups. The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58) and CANagliflozin cardiovascular Assessment Study (CANVAS) trials with dapagliflozin and canagliflozin, respectively, are the two major ongoing trials with currently approved SGLT2 inhibitors [28, 29]. Their inclusion criteria are somewhat broader than those of the EMPA-REG trial, with lower cardiovascular risk participants enrolled. Whilst these trial results are awaited, a comparison of the characteristics of people treated with T2DM in clinical practice with those of the EMPA-REG trial is important to enable an understanding of how the existing data can be applied in practice. We provide a description of the cardiovascular risk profile of a large national sample of people with T2DM treated with SGLT2 inhibitors in England and compare this to the EMPA-REG trial inclusion criteria. We also provide a comparison with the complete denominator group (all people with identified T2DM).

It should be clearly stated that SGLT2 inhibitors have benefits beyond cardiovascular risk reduction: predominantly improved glycemic control and weight loss [30]. Our real-world data demonstrate that people prescribed SGLT2 inhibitors have a higher BMI than others with T2DM. This trend suggests that the weight loss benefits of the class are a key consideration in prescribing. Whilst our analysis demonstrates that the cardiovascular benefit identified in the EMPA-REG trial can only be extrapolated to a small proportion of those currently prescribed SGLT2 inhibitors, this group will still experience glycemic and weight loss benefits.

The SGLT2 inhibitor class of medication is costlier than older therapies. The National Institute for Health and Care Excellence (NICE) in the UK has previously undertaken an economic analysis of the use of SGLT2 inhibitors and considers their use to be below the cost-effectiveness thresholds [31–33]. Otherwise analyses also suggest SGLT2 inhibitors provide cost-effective benefit [34–36]. The benefits in these analyses are based on the glucose-lowering potential and do not consider the additional cardiovascular benefits seen in the EMPA-REG trial. Although we show that the trial findings can be only applied directly to a small proportion of those with T2DM, incorporation of the additional cardiovascular risk reduction into existing economic models is still likely to improve the cost-benefit estimates.

## Future Research

Our data highlight the importance of further research to identify any cardiovascular benefit from SGLT2 inhibitors in lower-risk groups which make up the majority of SGLT2 inhibitor use currently. This leads to several important clinically relevant questions: Are there any cardiovascular benefits with canagliflozin and dapagliflozin (which makes up the majority of SGLT2 inhibitor prescriptions currently)? What, if any, is the degree of cardiovascular benefit afforded in the lower cardiovascular risk groups? The ongoing cardiovascular safety trials with canagliflozin (CANVAS) and dapagliflozin (DECLARE-TIMI 58) will go some way to

answering these questions [28, 29]. The CANVAS trial is estimated to complete in 2017 and DECLARE-TIMI 58 in 2019. These trials should be supported by real-world analyses of cardiovascular outcomes in people currently treated with SGLT2 inhibitors.

The EMPA-REG, CANVAS, and DECLARE-TIMI 58 trials also exclude people with certain comorbidities. Many of those excluded may have had significant cardiovascular risk. Additional real-world evidence may also be needed to clarify whether the use of SGLT2 inhibitors in those with multimorbidity confers cardiovascular benefit.

### Comparison with Similar Studies

Only one other similar study comparing the EMPA-REG trial inclusion criteria against a large sample of people with diabetes has been performed. The study in initial reporting, and not yet published in a complete manuscript, compared the criteria against a large registry-based population in the USA (the Diabetes Collaborative Registry) [37]. The authors used prior myocardial infarction, any coronary artery disease, any coronary revascularization, or peripheral artery disease to approximate the EMPA-REG criteria. They found that only 16% of those with T2DM met these approximate criteria. These results agree closely with those presented here. Our present study may provide a more representative sample of the general population with T2DM than this registry-based analysis. We were also able to provide a closer mapping of disease codes to the EMPA-REG inclusion criteria than was possible for this study.

### Strengths and Limitations

The key strengths and limitations of the data source used for the study (RCGP RSC network of practices) have previously been described [21, 38] in accordance with European Federation for Medical Informatics Primary Care Informatics Working Group consensus recommendations [39]. Key strengths include the large sample size, high level of data

completeness, and the broadly representative nature of the population sample. However, the RCGP RSC group of practices are a somewhat self-selecting group of GP practices with a slightly more affluent population than the UK average [38]. Despite this, given the size of the population analyzed (ca. 1.7% of the English population), we feel that these data provide a reasonable approximation of the UK population.

Identification of the EMPA-REG inclusion criteria risk factors from routine primary care data may be limited by a number of factors. Firstly, the possibility of missing data (either because of failure to record known diagnoses or failure to identify risk factors in clinical practice) may have led us to underestimate the number of people who meet these criteria. As mentioned, our previous analyses of this dataset have demonstrated a high level of data completeness, particularly in those with diabetes which somewhat mitigates this limitation [21, 38]. Identification of specific inclusion criteria is limited by the clinical coding system used in UK primary care (Read codes) which does not have a code which mapped directly onto each EMPA-REG criterion. We have therefore used non-specific/broader clinical codes where no more specific code was available. This approach may have slightly overestimated the number of people meeting each inclusion criteria. Generally the Read coding system is an extensive system which facilitates very detailed coding of diagnoses and other code domains [19] such that this mapping mismatch is limited. Additional limitations of using routinely collected primary care data in research have also previously been described and include the loss of information recorded in the record as free text [40] which may have led to some missing cases in our data.

## CONCLUSIONS

Extrapolation of the EMPA-REG trial cardiovascular benefits to people with T2DM in the real world should be performed with extreme caution. In a large nationally representative sample of people with T2DM we found that only a

small proportion of people had the same high cardiovascular risk as those people included in the EMPA-REG trial. Additionally, an even smaller proportion of those currently treated with SGLT2 inhibitors had the same high risk. It remains to be seen whether people with T2DM, multimorbidity, and high cardiovascular risk (who were excluded from the trials) similarly benefit from treatment with SGLT2 inhibitors. Further data are also needed to identify possible cardiovascular benefit in the remaining lower cardiovascular risk group.

## ACKNOWLEDGEMENTS

This publication has been supported by a grant from AstraZeneca including funding for publication charges and medical editorial assistance.

All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. The authors thank Reza Hajhosseiny, who provided medical editorial assistance on behalf of Spotlight Research Ltd. Funding for medical editorial support was provided by AstraZeneca Europe.

Andrew McGovern conceived the idea. Andrew McGovern, Michael Feher, Neil Munro, and Simon de Lusignan designed the study. Andrew McGovern undertook the data analysis. Andrew McGovern, Michael Feher, Neil Munro, and Simon de Lusignan contributed to the manuscript and approved the final draft.

**Disclosures.** Andrew McGovern receives research funding from Eli-Lilly and AstraZeneca. Simon de Lusignan receives research funding from Eli-Lilly, GlaxoSmithKline, Takeda, and AstraZeneca. Neil Munro has received financial support for research, speaker meetings, and consultancy from MSD, Merck, BMS, AstraZeneca, Pfizer, Novo, Eli-Lilly, and Sanofi-Aventis.

Michael Feher has received financial support for research, speaker meetings, and consultancy from MSD, Merck, BMS, AstraZeneca, Pfizer, Novo, Eli-Lilly, and Sanofi-Aventis.

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**Data Availability.** The datasets generated during and/or analyzed during the current study are not publicly available as per the conditions of study approval by the RCGP RSC study approval committee, in order to protect patient confidentiality. The data can be made available to bona fide researchers on a case-by-case basis; please contact the corresponding author for further details.

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