Prescribing in Type 2 Diabetes Patients With and Without Cardiovascular Disease History: a Descriptive Analysis in the UK CPRD

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ABSTRACT

Purpose: Some classes of glucose-lowering medications, including sodium-glucose co-transporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1-receptor agonists (GLP1-RAs) have cardio-protective benefit, but it is unclear whether this influences prescribing in the United Kingdom (UK). This study aims to describe class-level prescribing in adults with type 2 diabetes mellitus (T2DM) by cardiovascular disease (CVD) history using the Clinical Practice Research Datalink (CPRD).

Methods: Four cross-sections of people with T2DM aged 18−90 and registered with their general practice for >1 year on 1st January 2017 (n = 166,012), 1st January 2018 (n = 155,290), 1st January 2019 (n = 152,602) and 31st December 2019 (n = 143,373) were identified. Age-standardised proportions for class use through time were calculated separately in those with and without CVD history and by total number of medications prescribed (one, two, three, four+). An analysis by UK country was also performed.

Findings: Around 31% of patients had CVD history at each cross-section. Metformin was the most common treatment (>70% of those with and without CVD had prescriptions across all treatment lines). Overall use of SGLT2is and GLP1-RAs was low, with slightly less use in patients with CVD (SGLT2i: 9.8% and 13.8% in those with and without CVD respectively; GLP1-RA: 4.3% and 4.9%, December 2019). Use of SGLT2is as part of dual therapy was low but rose throughout the study. In January 2017, estimated use was 8.0% (95% CI 6.9−9.1%) and 8.9% (8.6−9.3%) in those with and without CVD. By December 2019 this reached 18.3% (17.0−19.5%) and 21.2% (20.6−21.7%) for those with and without CVD respectively. SGLT2i use as triple therapy increased: 22.7% (21.0−24.4%) and 25.9% (25.2−26.6%) in January 2017 to 41.3% (39.5−43.0%) and 45.5% (44.7−46.3%) in December 2019. GLP1-RA use also increased, but observed usage remained lower than SGLT2 inhibitors. Insulin use remained stable throughout, with higher use observed in those with CVD (16% vs 9.7% Dec 2019). Time trends in England, Wales, Scotland and Northern Ireland were similar, although class prevalence varied.

Implications: Although use of SGLT2is and GLP1-RAs has increased, overall usage remains low with slightly lower use in those with CVD history, suggesting there is opportunity to optimise use of these medicines in T2DM patients to manage CVD risk. Insulin use was substantially more prevalent in those with CVD despite no evidence of CVD benefit. Further investigation of factors influencing this finding may highlight strategies to improve patient

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access to the most appropriate treatments, including those with evidence of cardiovascular benefit. (*Clin Ther*. xxxx;xxx:xxx)

Keywords: cardiovascular disease, observational cohort study, prescribing, real-world data, type 2 diabetes mellitus.

INTRODUCTION

Cardiovascular disease (CVD) is a common comorbidity of type 2 diabetes mellitus (T2DM) globally[1] as well as in the United Kingdom, with ~35% of people with T2DM estimated to have CVD.[2] Recently, large-scale cardiovascular outcome trials have reported that sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1-receptor agonists (GLP1-RAs) have significant cardioprotective benefits in people with T2DM[3–13] in addition to metabolic benefits such as blood pressure control and weight loss.[14,15] The first of these trials, EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients),[3] was published in 2015, with the remaining trials reported between 2016 and 2019. For the SGLT2 inhibitors, the EMPA-REG OUTCOME and CANVAS (Canagliflozin Cardiovascular Assessment Study) trials both showed a significant reduction in the primary end point of 3-point major adverse cardiovascular events (MACE), including CV death, nonfatal myocardial infarction, and nonfatal stroke, in a population with T2DM and increased risk for CVD, and empagliflozin showed a significant reduction in cardiovascular death.[3,4] The DECLARE-TIMI-58 (*Dapagliflozin Effect on Cardiovascular Events*—Thrombolysis in Myocardial Infarction *58*) and VERTIS-CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Diabetes Mellitus Participants With Vascular Disease) trials showed noninferiority in 3-point MACE, but did not show superiority, versus placebo.[5] All SGLT2 inhibitors showed a significant reduction in hospitalization for heart failure and the composite end point of hospitalization for heart failure or cardiovascular death.[3–6] For the GLP1-RAs, 4 of the 7 cardiovascular outcome trials (LEADER [Liraglutide Effect and Action in Diabetes], SUSTAIN-6 [Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes], HARMONY Outcomes, and REWIND [Researching Cardiovascular Events with a Weekly Incretin in Diabetes]) have shown significant reductions in 3-point MACE.[7–13]

As a result of these trials, the focus of international guidelines for T2DM has started to shift beyond a sole emphasis on glycemic control to managing the cardiovascular complications of diabetes, beginning with the 2018 consensus report by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) and the 2019 European Society for Cardiology guidelines.[16–19] At the time of writing, the National Institute for Health and Care Excellence (NICE) do not include consideration of CVD history or risk in their treatment guideline, although data from the cardiovascular outcome trials are under review, and a guideline update is expected.[20]

The ADA/EASD and the European Society for Cardiology guidelines recommend that prescribers consider early use of medication with demonstrated CVD benefit in people with high CVD risk.[18,19] However, it is unclear if and how treatment patterns are changing to reflect these updated recommendations. In particular, the use of treatment classes with cardioprotective benefit in patients with T2DM is unknown, including extent of use and stage of initiation, as well as how use varies between those with and without CVD.

Although data exist on prescribing patterns for diabetes, existing studies do not stratify according to CVD history,[21,22] or do not reflect the period post-2017, during which the evidence of CVD benefit for SGLT2 inhibitors and GLP1-RAs has begun to accrue.[23]

The goal of the present study was to describe prescribing of glucose-lowering medications, over 4 years since 2017, in people with T2DM with and without a history of CVD in the United Kingdom. The main interest was whether the presence of CVD history seems to influence prescribing over time, in light of the new evidence and updated guidelines.

PATIENTS AND METHODS

Study Design

This observational cohort study included nested cross-sectional analyses. Data were taken from the Clinical Practice Research Datalink (CPRD; https://www.cprd.com/) using CPRD GOLD. The CPRD holds de-identified data from 50 million patients in general practices across the United Kingdom and is a well-recognized source for publications on the use of medicines. The research was approved under Independent Scientific Advisory Committee protocol number 20_061A.

Population

The population of interest was adults with a T2DM code contributing at least 1 day of eligible data to the CPRD during the study period (January 1, 2017−December 31, 2019). T2DM was defined as a relevant diagnosis code at any time in the patient's record before the end of the study (see Supplemental Table I in the online version at doi:XXXXXXXXXX). Included individuals also had to have no prescription for insulin in the first 6 months of diabetes diagnosis, be aged >18 years, and have nonmissing data on their sex. All patients also had to have research-acceptable data, a metric defined by CPRD based on the quality of the patient record and the practice's data recording.

Patients were eligible to contribute data from their index date, defined as the latter of: January 1, 2017; first T2DM record; one year after practice data were considered research standard; or one year after patient registration (see Supplemental Fig. 1 in the online version at doi:XXXXXXXXXX). This ensured at least 1 year of accrued data for all individuals in the cohort before their index date. Patients were censored from the cohort at the earliest of: transfer out of practice; date of death; last collection date for the practice; or end of study period (December 31, 2019). Four cross-sectional populations were identified from the base cohort, consisting of those alive and under follow-up (as defined earlier) on the following: January 1, 2017; January 1, 2018; January 1, 2019; and December 31, 2019. This was to emulate four annual "audits" within all practices contributing to the CPRD on these dates, thus providing representative denominators for estimating the point prevalence for use of each medication class of interest. Patients were excluded at this point for the following: recent type 1 diabetes, secondary, or gestational diabetes codes; evidence of pregnancy; or age ≥90 years at the cross-section date.

Outcomes and Covariates

The outcome of interest was prescription of any of the following classes of routinely used glucose-lowering medication at the cross-section date: biguanides/metformin, sulfonylureas (SUs), dipeptidyl peptidase-4 (DPP4) inhibitors (including sitagliptin, saxagliptin, alogliptin, linagliptin, vildagliptin, and combinations), SGLT2 inhibitors (including dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, and combinations), thiazolidinediones, GLP1-RAs (including dulaglutide, semaglutide, exenatide, liraglutide, lixisenatide, and albiglutide), insulin, and other (acarbose and glinides). A full list of product codes is available in the Supplemental Information in the online version at doi:XXXXXXXXXX. A prescription was assumed to be current if the number of days' supply (calculated by using data on quantity and daily dose where specified, detailed in the Supplemental Information in the online version at doi:XXXXXXXXXX) plus a grace period equal to the number of days' supply, was sufficient to cover the period up to the cross-section date. If number of days' supply was missing, a 28-day supply was assumed as this was the most frequent prescription duration when specified.

The proportion of individuals with a current prescription for each class of glucose-lowering medication was compared according to CVD status at each cross-section. History of CVD was defined as a Read code indicating any of the following before the cross-section date: myocardial infarction, unstable angina, coronary atherosclerosis, or other forms of ischemic heart disease, and history of coronary artery procedures, congestive heart failure, stroke, transient ischemic attack, or peripheral arterial disease. All codes are provided in the Supplemental Information (see the online version at doi:XXXXXXXXXX). As with any database, research quality is dependent on the quality of data entry. It is possible that missing data (eg, codes relating to CVD history) could lead to a misclassification of patients in the cohort,

particularly for binary outcomes such as CVD history. However, patient populations with a chronic disease such as T2DM are likely to be more closely monitored than the general population due to the presence of Quality and Outcomes Framework targets. As such, missed coding of comorbidities is likely to be less problematic than in the general population.

Treatments prescribed were categorized into "treatment stages" based on the total number of distinct classes of glucose-lowering medications concurrently prescribed (none, 1, 2, 3, or ≥4). For simplicity of reporting, we also refer to those on 2 and 3 classes as being on dual and triple therapy, respectively. A comparison according to UK geographic region, as defined in CPRD, was also conducted.

Other covariates of interest included age, sex, ethnicity, most recent estimated glomerular filtration rate (eGFR) calculated by using the Chronic Kidney Disease Epidemiology Collaboration formula,[24] and years since diabetes diagnosis (if available). All covariates, except for ethnicity, UK region, and sex, were time updated for the respective cross-section date if a patient contributed to multiple cross-sections. The Chronic Kidney Disease Epidemiology Collaboration formula was not adjusted for ethnicity due to high levels of missingness; it has been previously reported that this omission has minimal impact on results.[25] Ethnicity was determined by using preexisting methodology for the CPRD.[26]

All clinical code lists that contributed to the definition of the study population and derivation of covariates are provided in Supplemental Table I though XIV in the online version at doi:XXXXXXXXXX and were reviewed by 2 clinical experts for accuracy.

Statistical Analysis

Descriptive summary statistics for each cross-section were calculated for covariates of interest, including the proportions of missingness. Point prevalence of medication use by calendar year was calculated as the proportion of individuals with a current prescription for each class of glucose-lowering medication at each treatment stage. Exact 95% CIs for proportions were calculated separately according to CVD status and treatment stage to quantify sampling error.

The main analysis used age-standardized prevalence to reduce any potential confounding by an aging cohort or by differences in age between those with and without a history of CVD; the age distribution of T2DM from the latest National Diabetes Audit for England was used for the analysis.[27] Age groupings used in the standardization were <40 years, 40−64 years, 65−79 years, and ≥80 years.

A sensitivity analysis to test the robustness of the definition of "current prescription" was also performed, by changing the grace period to a fixed 30 days rather than a length of time equal to the number of days' supply of the medicine. A further analysis assuming that any prescriptions in the 3 months before the cross-section date were current was also conducted. Finally, a sensitivity analysis restricted to patients whose most recent eGFR level was ≥60 mL/min/1.73 m^2 was conducted, as some glucose-lowering medications should not be initiated in patients with eGFR levels <60 mL/min/1.73 m^2. In this final sensitivity analysis, those with missing eGFR data were also excluded.

All analyses were conducted by using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina) and Stata version 15 (StataCorp, College Station, Texas).

RESULTS

Population

A total of 219,128 people with T2DM were identified for the base cohort (Figure 1). After applying cross-section−specific exclusions, there were 166,012, 155,290, 152,602, and 145,373 individuals for the January 2017, January 2018, January 2019, and December 2019 cross-sections, respectively. Cohort characteristics remained broadly stable over the 4 years of the study (Table I), including the proportion of patients with a history of CVD (31%). Glycosylated hemoglobin levels and body mass index were similar across cross-sections and in those with and without CVD history. The mean age of included individuals was 65 years in those without CVD history and 73 years in those with CVD.

Medication Classes Prescribed

Table II presents the number of current glucose-lowering medication classes prescribed to each patient according to CVD history. The proportions of patients receiving none, 1, 2, 3, or ≥4 classes of glucose-lowering medications were similar in patients

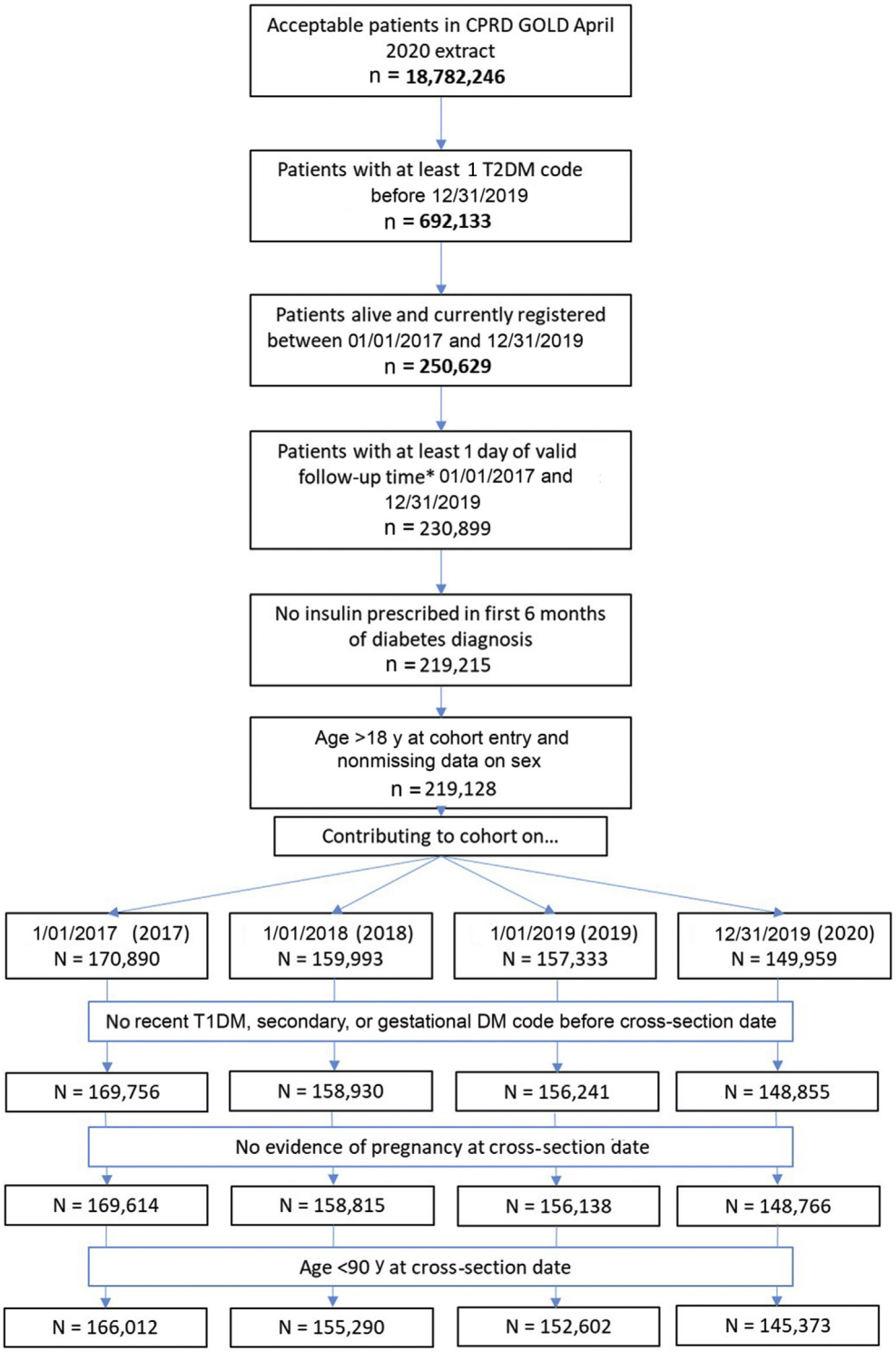

Figure 1. Population flow diagram for the overall population and cross-sections. CPRD = Clinical Practice Research Datalink; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus. *Valid follow-up time defined as having accrued at least 1 year of research quality data since registration with their general practice.

Table I. Patient demographic characteristics according to cross-section.

Characteristic	2017 (N = 166,012)		2018 (N = 155,290)		2019 (N = 152,602)		2020 (N = 145,373)	
	No CVD	CVD	No CVD	CVD	No CVD	CVD	No CVD	CVD
N	115,123	50,889	107,937	47,353	105,906	46,696	100,565	44,808
Age at cross-section								
Mean (SD), y	64.5 (12.5)	72.7 (10.1)	64.6 (12.5)	72.7 (10.1)	64.8 (12.5)	72.8 (10.1)	65.0 (12.5)	72.8 (10.2)
Median (IQR), y	65.0 (56.0, 74.0)	74.0 (66.0, 81.0)	65.0 (56.0, 74.0)	74.0 (66.0, 81.0)	65.0 (56.0, 74.0)	74.0 (66.0, 81.0)	66.0 (56.0, 74.0)	74.0 (66.0, 81.0)
Male sex, no. (%)	62,260 (54.1)	31,993 (62.9)	58,567 (54.3)	29,868 (63.1)	57,541 (54.3)	29,577 (63.3)	54,627 (54.3)	28,420 (63.4)
Diabetes duration								
Mean (SD), y	7.4 (5.7)	9.3 (6.5)	7.7 (5.8)	9.6 (6.7)	8.0 (6.0)	9.8 (6.8)	8.1 (6.1)	10.0 (7.0)
Median (IQR), y	6.4 (2.9, 10.8)	8.3 (4.0, 13.3)	6.6 (3.0, 11.2)	8.6 (4.2, 13.8)	6.8 (3.1, 11.6)	8.9 (4.3, 14.3)	7.0 (3.2, 11.9)	9.0 (4.3, 14.6)
Missing, no. (%)	24,327 (21.1)	11,516 (22.6)	23,553 (21.8)	10,961 (23.1)	23,689 (22.4)	10,980 (23.5)	22,620 (22.5)	10,464 (23.4)
Body mass index								
Mean (SD), kg/m^2	31.8 (6.7)	30.8 (6.1)	31.9 (6.7)	30.8 (6.1)	31.8 (6.7)	30.7 (6.2)	31.9 (6.7)	30.8 (6.2)
Median (IQR)), kg/m^2	30.9 (27.2, 35.4)	30.0 (26.6, 34.1)	30.9 (27.2, 35.4)	30.0 (26.6, 34.1)	30.8 (27.2, 35.4)	30.0 (26.5, 34.0)	30.9 (27.3, 35.5)	30.0 (26.6, 34.1)
Missing, no. (%)	6008 (5.2)	2917 (5.7)	6198 (5.7)	2951 (6.2)	6503 (6.1)	2944 (6.3)	6366 (6.3)	2878 (6.4)
Glycosylated hemoglobin								
Mean (SD), %	7.4 (1.5)	7.4 (1.5)	7.4 (1.5)	7.4 (1.5)	7.5 (1.5)	7.4 (1.5)	7.5 (1.5)	7.5 (1.5)
Median (IQR), %	7.0 (6.4, 8.0)	7.0 (6.4, 8.0)	7.1 (6.5, 8.1)	7.0 (6.4, 8.0)	7.1 (6.5, 8.1)	7.1 (6.5, 8.0)	7.1 (6.5, 8.2)	7.1 (6.5, 8.1)
Missing, no. (%)	12,564 (10.9)	4869 (9.6)	12,260 (11.4)	4684 (9.9)	11,761 (11.1)	4438 (9.5)	11,593 (11.5)	4320 (9.6)
Estimated GFR								
Mean (SD), mL/min/1.73 m^2	81.1 (20.1)	68.5 (21.3)	80.8 (20.1)	68.3 (21.3)	81.2 (20.0)	68.8 (21.4)	81.6 (20.1)	69.4 (21.6)
Median (IQR), mL/min/1.73 m^2	83.8 (68.2, 95.7)	69.8 (53.2, 85.3)	83.6 (67.8, 95.4)	69.7 (52.9, 85.2)	84.2 (68.4, 95.8)	70.3 (53.2, 85.9)	84.5 (68.8, 96.1)	71.2 (53.7, 86.5)
Missing, no. (%)	6217 (5.4)	1869 (3.7)	6669 (6.2)	2143 (4.5)	7120 (6.7)	2136 (4.6)	7336 (7.3)	2312 (5.2)
Ethnicity, no. (%)								
White	51,842 (45.0)	23,638 (46.5)	48,255 (44.7)	21,853 (46.1)	47,732 (45.1)	21,639 (46.3)	45,055 (44.8)	20,576 (45.9)
South Asian	4171 (3.6)	1191 (2.3)	4046 (3.7)	1112 (2.3)	3672 (3.5)	1030 (2.2)	3284 (3.3)	944 (2.1)
Black	1533 (1.3)	249 (0.5)	1445 (1.3)	232 (0.5)	1163 (1.1)	191 (0.4)	1044 (1.0)	174 (0.4)

Table I. (*Continued*)

Characteristic	2017 (N = 166,012)		2018 (N = 155,290)		2019 (N = 152,602)		2020 (N = 145,373)	
	No CVD	CVD	No CVD	CVD	No CVD	CVD	No CVD	CVD
Other	978 (0.8)	240 (0.5)	945 (0.9)	235 (0.5)	970 (0.9)	242 (0.5)	900 (0.9)	223 (0.5)
Mixed	438 (0.4)	69 (0.1)	428 (0.4)	65 (0.1)	411 (0.4)	62 (0.1)	399 (0.4)	64 (0.1)
Missing	56,161 (48.8)	25,502 (50.1)	52,818 (48.9)	23,856 (50.4)	51,958 (49.1)	23,532 (50.4)	49,883 (49.6)	22,827 (50.9)
UK geographic region, no. (%)								
North East	669 (0.6)	395 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
North West	6233 (5.4)	2785 (5.5)	5615 (5.2)	2453 (5.2)	5764 (5.4)	2508 (5.4)	5764 (5.7)	2489 (5.6)
Yorkshire and Humberside	757 (0.7)	311 (0.6)	238 (0.2)	93 (0.2)	244 (0.2)	99 (0.2)	252 (0.3)	101 (0.2)
West Midlands	7682 (6.7)	2867 (5.6)	6551 (6.1)	2409 (5.1)	6433 (6.1)	2359 (5.1)	5023 (5.0)	1903 (4.2)
East of England	2122 (1.8)	1031 (2.0)	1585 (1.5)	609 (1.3)	513 (0.5)	248 (0.5)	245 (0.2)	137 (0.3)
South West	4342 (3.8)	1794 (3.5)	3023 (2.8)	1212 (2.6)	2481 (2.3)	971 (2.1)	1658 (1.6)	675 (1.5)
South Central	4871 (4.2)	1570 (3.1)	3421 (3.2)	1094 (2.3)	2884 (2.7)	922 (2.0)	1266 (1.3)	428 (1.0)
London	6415 (5.6)	2098 (4.1)	5964 (5.5)	1936 (4.1)	4442 (4.2)	1512 (3.2)	3490 (3.5)	1183 (2.6)
South East Coast	11,506 (10.0)	4152 (8.2)	10,246 (9.5)	3628 (7.7)	9886 (9.3)	3449 (7.4)	7457 (7.4)	2474 (5.5)
Northern Ireland	6163 (5.4)	3415 (6.7)	6428 (6.0)	3531 (7.5)	6735 (6.4)	3677 (7.9)	6976 (6.9)	3756 (8.4)
Scotland	35,146 (30.5)	17,177 (33.8)	35,212 (32.6)	17,036 (36.0)	35,879 (33.9)	17,410 (37.3)	36,962 (36.8)	17,838 (39.8)
Wales	29,217 (25.4)	13,294 (26.1)	29,654 (27.5)	13,352 (28.2)	30,645 (28.9)	13,541 (29.0)	31,472 (31.3)	13,824 (30.9)
CVD subtypes, no. (%)								
Angina	–	17,463 (10.5)	–	47,353 (30.5)	–	46,696 (30.6)	–	14,302 (9.8)
MI	–	13,500 (8.1)	–	15,810 (10.2)	–	15,222 (10.0)	–	12,138 (8.3)
Heart failure	–	9606 (5.8)	–	12,715 (8.2)	–	12,630 (8.3)	–	9101 (6.3)
Other IHD	–	24,968 (15.0)	–	9165 (5.9)	–	9308 (6.1)	–	20,715 (14.2)
Coronary procedure	–	11,806 (7.1)	–	22,701 (14.6)	–	21,969 (14.4)	–	10,449 (7.2)
PAD	–	8930 (5.4)	–	11,056 (7.1)	–	10,911 (7.1)	–	7648 (5.3)
Stroke	–	12,271 (7.4)	–	8156 (5.3)	–	7949 (5.2)	–	11,250 (7.7)
TIA	–	6417 (3.9)	–	11,679 (7.5)	–	11,719 (7.7)	–	5772 (4.0)
Unspecified	–	5180 (3.1)	–	5985 (3.9)	–	5979 (3.9)	–	4449 (3.1)

CVD = cardiovascular disease; IHD = ischemic heart disease; IQR = interquartile range; MI = myocardial infarction; PAD = peripheral arterial disease; TIA = transient ischemic attack; UK = United Kingdom.

Table II. Total number of currently prescribed classes of glucose-lowering medication according to cardiovascular disease (CVD) status.

Class	2017		2018		2019		2020	
	No CVD	CVD	No CVD	CVD	No CVD	CVD	No CVD	CVD
None	31,810 (27.6%)	13,988 (27.5%)	29,982 (27.8%)	13,369 (28.2%)	30,007 (28.3%)	13,153 (28.2%)	28,428 (28.3%)	12,851 (28.7%)
1	42,327 (36.8%)	18,690 (36.7%)	38,926 (36.1%)	16,775 (35.4%)	37,379 (35.3%)	16,471 (35.3%)	34,846 (34.6%)	15,427 (34.5%)
2	25,557 (22.2%)	11,908 (23.4%)	23,615 (21.9%)	11,004 (23.2%)	22,830 (21.5%)	10,680 (22.9%)	21,601 (21.5%)	10,050 (22.5%)
3	13,385 (11.6%)	5512 (10.8%)	13,144 (12.2%)	5330 (11.3%)	13,146 (12.4%)	5453 (11.7%)	12,974 (12.9%)	5414 (12.1%)
≥4	2044 (1.8%)	791 (1.6%)	2270 (2.1%)	875 (1.8%)	2544 (2.4%)	939 (2.0%)	2716 (2.7%)	1066 (2.4%)

with or without CVD history. Changing the definition of current use in the sensitivity analyses had a negligible impact on the proportions (see Supplemental Tables XV and XVI in the online version at doi:XXXXXXXXXX). Approximately 30% of the included patients had no current prescriptions for any glucose-lowering therapy; patient characteristics for this group are provided in Supplemental Table XVII in the online version at doi:XXXXXXXXXX.

Overall, as expected, the most commonly used glucose-lowering medication across all treatment stages was metformin (Table III), followed by SUs and DPP4 inhibitors. Use of both the SGLT2 inhibitor and GLP1-RA classes increased through time but remained low compared with the aforementioned classes, irrespective of CVD status.

Figure 2 presents the age-standardized proportions of patients receiving each class of glucose-lowering therapy at each cross-section according to history of CVD. Results are shown separately according to the total number of classes prescribed. "Other classes" were excluded from the figures because the proportion of patients taking these was <1% (Table III). Tabulated point estimates with 95% CIs and non–age-standardized results are presented in the Supplemental Information in the online version at doi:XXXXXXXXXX.

Metformin was the most common monotherapy, with >70% of monotherapy patients with and without a history of CVD having a current prescription. This finding remained consistent throughout the study period. Use of SUs declined since 2017 in patients with and without CVD. DPP4 inhibitor use increased for dual therapy and remained broadly constant at ~55% for triple therapy, with little difference between those with and without CVD history.

Use of SGLT2 inhibitors increased over time for all stages other than monotherapy. Again, there was little difference between patients with and without a history of CVD; although there appears to be slightly lower use in people with a history of CVD, the differences are small. In January 2017, SGLT2 inhibitor use as dual therapy was estimated to be 8.0% (95% CI, 6.9–9.1) in those with a history of CVD and 8.9% (95% CI, 8.6–9.3) in those without CVD. By December 2019, this had increased to 18.3% (95% CI, 17.0–19.5) and 21.2% (95% CI, 20.6–21.7) for

Table III. Total number of adults with type 2 diabetes mellitus currently prescribed each class of glucose-lowering medication according to cardiovascular disease (CVD) status. Denominator includes those on no classes of medication.

Variable	2017		2018		2019		2020	
	No CVD	CVD	No CVD	CVD	No CVD	CVD	No CVD	CVD
Metformin	72,235 (62.7%)	28,940 (56.9%)	67,430 (62.5%)	26,522 (56%)	65,719 (62.1%)	26,202 (56.1%)	62,377 (62%)	24,982 (55.8%)
Sulfonylureas	25,902 (22.5%)	12,255 (24.1%)	23,012 (21.3%)	10,845 (22.9%)	20,939 (19.8%)	10,051 (21.5%)	18,640 (18.5%)	8989 (20.1%)
DPP4i	15,867 (13.8%)	7500 (14.7%)	15,713 (14.6%)	7514 (15.9%)	15,911 (15.0%)	7756 (16.6%)	15,586 (15.5%)	7721 (17.2%)
SGLT2i	7736 (6.7%)	2192 (4.3%)	9906 (9.2%)	2855 (6.0%)	12,017 (11.3%)	3577 (7.7%)	13,852 (13.8%)	4388 (9.8%)
GLP1-RA	3776 (3.3%)	1413 (2.8%)	3863 (3.6%)	1454 (3.1%)	4185 (4.0%)	1636 (3.5%)	4948 (4.9%)	1941 (4.3%)
Insulin	11,917 (10.4%)	8509 (16.7%)	11,136 (10.3%)	7939 (16.8%)	10,636 (10%)	7736 (16.6%)	9772 (9.7%)	7180 (16.0%)
TZD	4239 (3.7%)	1309 (2.6%)	3560 (3.3%)	1074 (2.3%)	3247 (3.1%)	952 (2.0%)	2708 (2.7%)	814 (1.8%)
Other	210 (0.2%)	122 (0.2%)	163 (0.2%)	108 (0.2%)	143 (0.1%)	80 (0.2%)	120 (0.1%)	68 (0.2%)

DPP4i = dipeptidyl peptidase-4 inhibitors; GLP1-RA = glucagon-like peptide 1-receptor agonists; SGLT2i = sodium-glucose co-transporter 2 inhibitors; TZD = thiazolidinediones.

those with and without CVD, respectively. In those taking 3 classes of medication, use of SGLT2 inhibitors was at 22.7% (95% CI, 21.0–24.4) and 25.9% (95% CI, 25.2–26.6) at the beginning of 2017 for those with/without CVD, increasing to 41.3% (95% CI, 39.5–43.0) and 45.5% (95% CI, 44.7–46.3) in December 2019 (Figure 2).

GLP1-RAs exhibited smaller changes through time, with the proportion of patients on this class of medication ~6% for dual therapy and ~17% for triple therapy in December 2019. Use of thiazolidinediones remained constant over time for those with and without CVD. The only class of medication to show differences according to CVD history was insulin, with greater use observed in patients with a history of CVD at all treatment stages. In December 2019, the proportion of patients on insulin as monotherapy was 15% (95% CI, 14.1–15.9) in those with CVD and 8.2% (95% CI, 7.9–8.5) in those without. Analogous proportions for dual and triple therapy were 25.5% (95% CI, 24.5–26.4) and 16.2% (95% CI, 15.7–16.7), respectively, in those with CVD history, and 29.3% (95% CI, 27.7–30.8) and 19.4% (95% CI, 18.6–20.1) in those without (Figure 2).

Results According to Country

Similar trends over time were observed across England, Wales, Scotland, and Northern Ireland, although the prevalence of different classes varied (see Supplemental Figs. 3 and 4 in the online version at doi:XXXXXXXXXX). For example, use of SUs in those on dual therapy was estimated to be higher in Scotland than in other countries, and lower in Northern Ireland (see Supplemental Fig. 3 in the online version at doi:XXXXXXXXXX).

Use of GLP1-RAs in dual therapy was comparable across all countries and CVD history, remaining below 10% at the end of 2019. For triple therapy, the data suggest that use of GLP1-RAs has not increased at the same speed as SGLT2 inhibitors since 2017, with usage still below 20% at the end of 2019 in the majority of country/CVD status strata (Figure 3; Supplemental Figs. 3 and 4 in the online version at doi:XXXXXXXXXX).

Use of SGLT2 inhibitors was observed to be highest in Northern Ireland. By the end of 2019, in patients with no history of CVD, 29.5% (95% CI, 27.3–31.7) and 51.1% (95% CI, 47.9–54.1) of

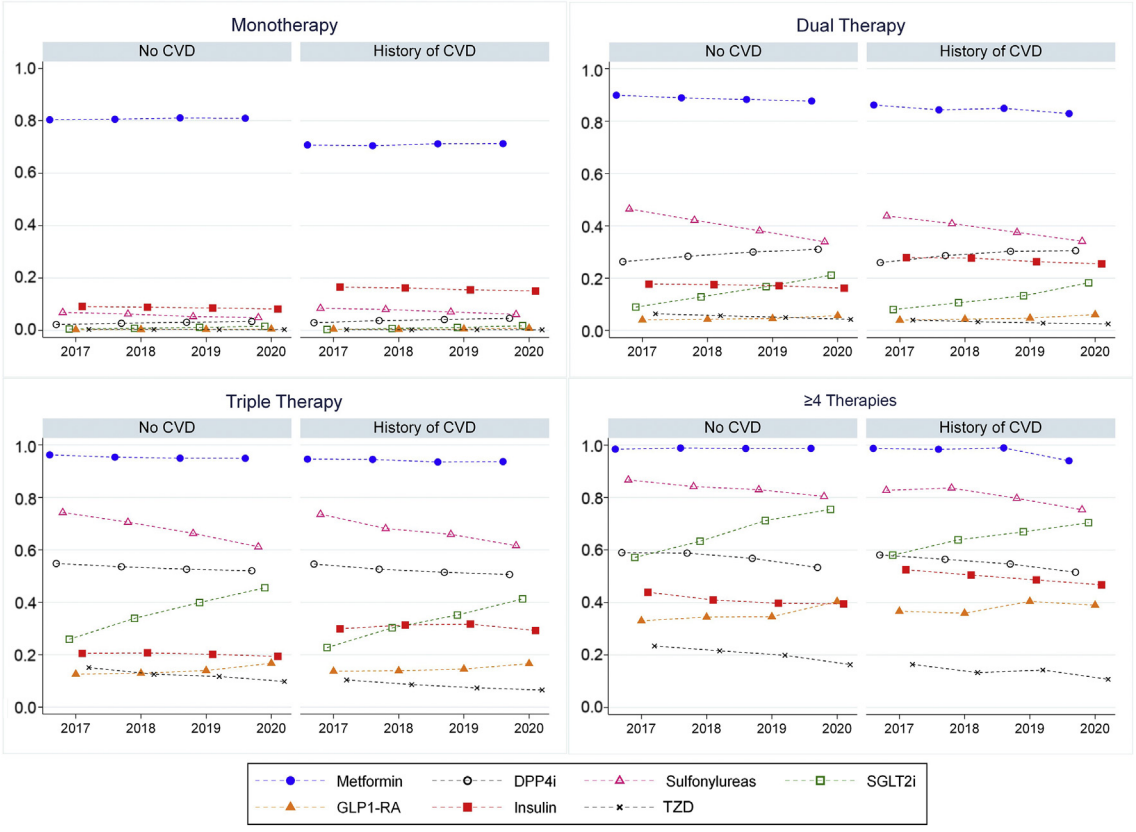

Figure 2. Age-standardized proportions of current classes used according to cardiovascular disease (CVD) status and total number of currently prescribed glucose-lowering medication classes. DPP4i = dipeptidyl peptidase-4 inhibitors; GLP1-RA = glucagon-like peptide 1-receptor agonists; SGLT2i = sodium-glucose co-transporter 2 inhibitors; TZD = thiazolidinediones.

individuals on dual and triple therapy, respectively, had a current prescription for an SGLT2 inhibitor. The analogous proportions in those with a history of CVD were slightly lower, a trend that was also observed for other countries, although in many cases the absolute observed differences were small (Figure 3). England had the lowest estimated proportion of patients with CVD currently taking an SGLT2 inhibitor as both dual and triple therapy.

Regional analysis within England was condensed to the North, West Midlands, East of England, South West and Central, and London and Southeast due to data sparsity. Crude results for this analysis are provided in the Supplemental Information in the online version at doi:XXXXXXXXXX. Small variations in prescribing between regions were observed; however, the small numbers resulted in wide CIs, making interpretation difficult.

Results in Patients With eGFR Levels ≥60 mL/min/1.73 m^2

Those with eGFR levels ≥60 mL/min/1.73 m^2 were slightly younger, had shorter duration of diabetes, and were slightly less likely to have a history of CVD compared with the overall population (25% vs 31%) (see Supplemental Table XIX and XX in the online version at doi:XXXXXXXXXX). Overall, results were similar to those seen in the main analysis, again with little difference between those with and without a

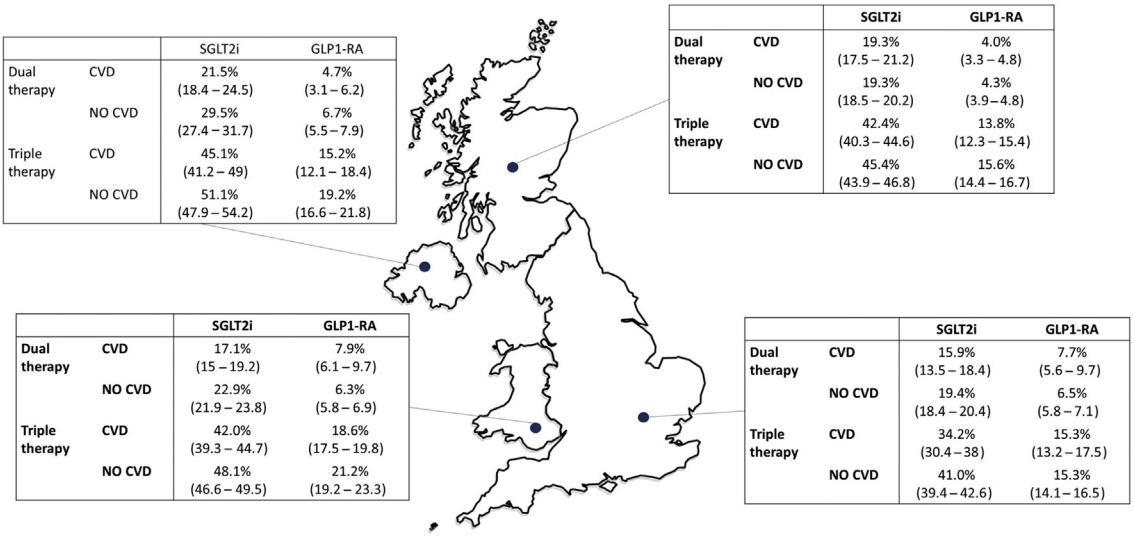

Figure 3. Age-standardized proportion (95% CI) of people with type 2 diabetes mellitus (T2DM) receiving sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1-receptor agonists (GLP1-RA) as part of dual or triple therapy according to UK country in December 2019. CVD = cardiovascular disease.

history of CVD. The observed proportion of patients using SGLT2 inhibitors was consistently between 1 and 6 percentage points higher in those with eGFR levels ≥60 mL/min/1.73 m^2, with a maximum observed usage of just below 50% of those on triple therapy in December 2019, regardless of CVD status (see Supplemental Fig. 5 in the online version at doi:XXXXXXXXXX).

DISCUSSION

Overall, between 2017 and 2020, there has been a shift in prescribing glucose-lowering medication characterized by reduced usage of SUs, and increased usage of newer classes, SGLT2 inhibitors and GLP1-RAs, with greater increases observed for SGLT2 inhibitors. As expected, metformin remains the most frequently prescribed medication as monotherapy and in combination with other therapies as per NICE guideline NG28.[20] The common use of metformin, decrease in use of SUs, and increase in use of SGLT2 inhibitors are broadly consistent with trends reported in other studies of prescribing in UK patients with T2DM, although use of GLP1-RAs seem to be higher in our study than previously reported.[21,22] Approximately 30% of people included in our study had a history of CVD; this finding was consistent across all years of the study and agrees with findings from 2 other recent studies of patients with T2DM and history of CVD in the United Kingdom and Scotland.[2,23]

At a population level, the data provide limited evidence of differences in prescribing of glucose-lowering medications based on a history of CVD. Although there were some differences, (eg, less use of metformin as monotherapy, slightly lower use of SGLT2 inhibitors in patients with a history of CVD), these absolute differences were small and had little impact on the overall proportions of medications prescribed. The most notable difference was observed for insulin, with greater use in patients with a history of CVD. Age standardization and the sensitivity analysis in patients with eGFR levels >60 mL/min/1.73 m^2 suggest that these findings are not explained by older age or renal impairment. The prescribing patterns we observed are consistent with a previous study examining CVD prevalence and risk factors in people with T2DM in Scotland in 2016, which also found high usage of metformin but

low use of SGLT2 inhibitors and GLP1-RAs, the classes that have been shown to reduce CVD risk and mortality.[23]

Although use of SGLT2 inhibitors and GLP1-RAs increased throughout the study period, use of these classes remained low overall. Of all adults with T2DM sampled, only 12.5% and 4.7% overall (9.8% and 4.3% in those with a history of CVD) had a current prescription for an SGLT2 inhibitor or GLP1-RA, respectively, in December 2019. In addition, the proportion of individuals on dual therapy receiving these classes remained low compared with those receiving triple therapy, suggesting a delay in use of these treatments to later stages of the treatment pathway. SGLT2 inhibitors and GLP1-RAs are the only classes that show reductions in MACE. As such, the lack of observed differences in prescribing of these classes between those with and without a history of CVD may suggest that UK practice has not yet been able to change to reflect the new evidence and guideline recommendations, such as those from the ADA and the EASD.[16,18]

This lack of change may occur for a number of reasons. First, it could reflect a more historical viewpoint that medications for T2DM are used for controlling glucose levels, rather than other end points observed in randomized controlled trials. There may be a lack of understanding of the results of the cardiovascular outcomes trials for the SGLT2 inhibitors and GLP1-RAs, including their implications for clinical practice. It could be that UK clinical practices are following the current NICE guideline, which has not yet been updated to include the results of the previously mentioned cardiovascular outcome trials.[20] Alternatively, it could be that medication formularies have not been updated to reflect the latest evidence, and thus a barrier to physicians prescribing the SGLT2 inhibitors and GLP1-RAs exists. Finally, there may be individual patient contraindications or tolerability issues preventing the use of these classes, which mask any shift in prescribing behavior at the population level. It is worth noting that the population with history of CVD in our study is considerably older, and with lower eGFR levels, than the population enrolled in cardiovascular outcomes trials, which may have affected prescribers' decisions.

This study was not designed to identify the drivers for these prescribing decisions, although a sensitivity analysis in those with an eGFR level $\geq$60 mL/min/1.73 m^2 provided similar results, suggesting that the increased risk of renal impairment (a key contraindication for some classes of glucose-lowering medication) in those with a history of CVD does not explain our findings. Other determining factors are clearly important if we are to understand if treatment of T2DM at both the patient and population level in the United Kingdom is optimal. Further research is ongoing to describe and compare the characteristics of those initiating different classes of glucose-lowering medication by CVD history as well as by treatment stage, including which characteristics seem to be associated with medication choice.

Similarly to a previous study,[23] we observed greater insulin use in people with a history of CVD compared with those without CVD history. This finding may be a result of older research that suggested insulin use was beneficial in patients after a myocardial infarction,[28] although these findings were not replicated in a subsequent study and the previous findings are likely to have been due to good glycemic control rather than intensive insulin use.[29,30] More recently, SGLT2 inhibitors have shown further benefits in people with heart failure without diabetes.[31,32] Whether this scenario further increases uptake in the subset of T2DM patients with comorbid heart failure, and also if it encourages prescribers to move away from insulin in patients with a history of CVD, will be an important subject for future research.

The overall UK trends were reflected in each country included in the study (England, Scotland, Wales, and Northern Ireland), but there were small differences in terms of proportions prescribed for each class, with England showing the lowest usage of SGLT2 inhibitors. This may be due to clinicians in each devolved nation following different guidelines, or it could be due to other clinical considerations. Investigating the factors affecting prescribing decisions in each country may show unwarranted variations and reveal ways in which these could be addressed.

Although there are a number of possible reasons why patients may not be prescribed SGLT2 inhibitors and GLP1-RAs, the evidence of their benefits in CVD risk reduction for patients with T2DM has now been accumulating for >5 years. Randomized

cardiovascular outcome trials are now supported by real-world evidence studies such as *CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors*) and EMPRISE (Empagliflozin Comparative Effectiveness and Safety), which show that the reductions in mortality and hospitalization for heart failure seen in clinical trials are consistent in the real world.[33,34] SGLT2 inhibitors have been assessed and found to be cost-effective by NICE in monotherapy and in combination therapy, and are therefore recommended as treatment options.[35–41] The GLP1-RAs have not undergone NICE technology appraisals but are recommended as triple therapy in NICE guideline NG28.[20] Both medication classes have been in use for a number of years and have well-understood safety profiles; thus, it is unlikely that prescriptions should be limited by concerns related to adverse events, although there may be individual contraindications or intolerances.

It is difficult to determine a specific proportion of patients who should be prescribed either an SGLT2 inhibitor or GLP1-RA, as their use should be considered in discussion with patients' health care professionals, leading to individualized treatment decisions. There is a proportion of patients for whom these classes will not be appropriate, although this is difficult to quantify. However, it is important that practitioners consider the presence of CVD in their selection of glucose-lowering medication and in particular consider the use of these 2 classes with demonstrable CVD benefit in this group of patients. The data we present here suggest this is currently not the case and therefore highlight a key area of practice that is not keeping pace with the current clinical evidence. Published literature suggests that 65% of men and 68% of women with T2DM have $\geq$2 risk factors for CVD.[23] In addition, 67% of men and 58% of women with T2DM are expected to develop CVD by 80 years of age.[42] This information suggests that the proportion of people with T2DM, with or without CVD, receiving SGLT2 inhibitors and GLP1-RAs should perhaps be higher than we observed.

A major strength of the present analysis is that it used real-world data from a validated source of primary care records. The CPRD has previously been shown to be representative of the UK population in terms of age, sex, and ethnicity.[43] The CPRD also conducts basic quality checks on data before release; this fact, and the use of only research-quality patients in our study, means that the data quality should be appropriate for this type of research. All prescriptions are identifiable by using British National Formulary and Gemscript coding, as well as drug name, allowing accurate classification of all diabetes medications into their respective classes. Because CPRD includes primary care data only, we do not have information on prescriptions from secondary or private care. However, because T2DM medications are prescription only and predominantly prescribed in primary care, there is likely to be minimal misclassification of the drugs prescribed. Two clinical experts validated the codes used in this study, including those used to identify the patient cohort and CVD history, to ensure these were accurate. Although we do not have data on whether the prescription was collected or taken, the record represents the physician's decision to treat, which is the relevant measure for this study. It is possible that prescribing at our cross-section dates (beginning of January or end of December) could be affected by the Christmas period; however, sensitivity analyses showed that varying definitions, including a simple definition of any prescription in the previous 3 months, made little difference to the results, suggesting that the impact of disruption is likely to be limited.

As discussed earlier, the present study was not designed to identify the factors behind prescribing decisions, which may include formulary and guideline restrictions, or numerous clinical variables such as body mass index, achievement of glycemic targets, renal function, or other individual contraindications. These factors are important in understanding how prescribing may be optimized in the United Kingdom and are the subject of ongoing work.

Some patient characteristics are known to be poorly completed in CPRD, notably ethnicity, with ~50% missing data in our study. The coronavirus disease 2019 pandemic, and in particular the increased risk of poorer outcomes in those in Black, Asian, and minority ethnic groups, has shown the importance of this type of information, which is sometimes considered to be of secondary importance when completing data records. The proportions of missing

data have been recorded for transparency in our study; however, because the effect of these characteristics is not being directly analyzed, this is unlikely to change the conclusions of this analysis.

CONCLUSIONS

Overall and early use (ie, monotherapy and dual therapy) of SGLT2 inhibitors and GLP1-RAs remains low, and there seems to be some country-level variation in usage, despite broadly similar trends over time. Although use of these classes, particularly SGLT2 inhibitors, is increasing, they are currently used slightly less in people with a history of CVD despite this group being likely to benefit. Although further investigations into drivers of class choice are warranted, it is likely that further opportunity remains to optimize use of these treatments to manage CVD risk as well as glycemic control in patients with T2DM.

CONFLICTS OF INTEREST

Dr. Farmer, Mr. Beard, Mr. Raza, Ms. Tebboth, and Dr. Ternouth are employees of Boehringer Ingelheim Ltd, the study sponsor. The study sponsor therefore had input into study design, analysis, data interpretation, mauscript preparation and the decision to submit. Dr. Gollop is an employee of Boehringer Ingelheim GmbH. Dr. Patel is a former employee of Boehringer Ingelheim. Dr. McGovern has received research funding from Eli Lilly, Pfizer, and AstraZeneca; and consultancy fees from Boehringer Ingelheim Ltd. Dr. Kanumilli has received consultancy fees from Boehringer Ingelheim Ltd for this work; serves as the Clinical Champion for Diabetes UK, the Clinical Network Lead for Diabetes—Greater Manchester, and the Diabetes Research Lead for Greater Manchester Clinical Research Network; is a member of the Primary Care Diabetes Society Committee and a Community Diabetes Consultant for the Manchester University Foundation Trust; has received educational speaking honoraria from AstraZeneca, Novo Nordisk, Sanofi, Napp, and Takeda; has received educational and travel grants from AstraZeneca and Novo Nordisk; and has served on advisory boards for Ascensia, AstraZeneca, Novo Nordisk, Roche, and Sanofi. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Dr. Farmer, Mr. Beard, Mr. Raza, Dr. Gollop, Dr. Patel, Dr. McGovern, Dr. Kanumilli, and Dr. Ternouth contributed to the plan and design of the study. Dr. Farmer completed the data analysis, and all remaining authors provided data interpretation. Ms. Tebboth drafted the manuscript, which was reviewed and approved by all authors.

The programming codes used in the analysis of this study are available from the corresponding author on reasonable request. The data for this study were obtained under licence from the UK Medicines and Healthcare products Regulatory Agency and therefore unfortunately cannot be shared.

This study was based on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. The study was approved by the Independent Scientific Advisory Committee (approval number: 20_061A).

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2020.12.015.

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