Putting EMPA-REG into practice: a data-driven intervention

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Abstract

This project aimed to establish community sodium-glucose co-transporter-2 inhibitor (SGLT2i) prescription rates in people with diabetes (PWD) who meet the EMPA-REG trial criteria. We established eligibility of PWD in two GP practices through primary care electronic record searches and a review of their medical notes. A total of 81 PWD were eligible for the EMPA-REG trial (8.2% of PWD); 46 were not prescribed an SGLT2i (56.8%). These individuals were contacted in a standardised way to discuss medication changes or offered a full diabetic review. The prescription rates obtained from review of medical notes were compared to the GP practice's national therapeutic indicator (NTI) for drugs indicative of cardiovascular disease and an SGLT2i or glucagon-like peptide 1 agonist. SGLT2i prescription rates obtained from this project are similar to NTIs, validating our data extrapolation. If PWD eligible for an SGLT2i, as per EMPA-REG criteria, but not currently prescribed one were commenced on treatment, we calculated that 74 (85.1 – 53.9) all-cause deaths could be prevented over 3.1 years in the Greater Glasgow and Clyde health board.

The rates of SGLT2i prescription in the community are suboptimal. Data-driven targeted reviews of at-risk PWD are a simple, time-efficient way to increase SGLT2i prescription rates, preventing some deaths with minimal additional workload.

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Background

The prevalence of type 2 diabetes (T2DM) is increasing in Scotland; prevalence is currently approximately 6%.[1] Despite high rates of vascular disease in people with T2DM, evolving treatment options are improving outcomes.[2] In 2015, the EMPA-REG trial showed that empagliflozin (a sodium-glucose co-transporter-2 inhibitor [SGLT2i]) use in people with diabetes (PWD) and established arterial disease (cardiovascular [CV], peripheral vascular, cerebrovascular disease) or heart failure (HF) significantly lowered overall mortality and the risk of non-fatal CV events at 3.1 years.[3] Two other SGLT2i (dapaglifozin and canagliflozin) have since been proven to have a similar benefit on CV outcomes in this target population.[4,5] Consequently, NICE and SIGN guidelines recommend that PWD and established CV disease or HF should be offered an SGLT2i once they have been established on metformin.[6,7]

Not only do SGLT2i improve CV outcomes in this population, they also delay the onset of diabetic kidney disease, improving quality of life.[3-5] Additionally, SGLT2i have been shown to be cost-effective: one study showed an 18% relative increase in survival, with an incremental cost-effectiveness, directly attributable to empagliflozin.[8] Therefore, it would be best practice to ensure that all individuals meeting EMPA-REG trial criteria are on an SGLT2i or have a reason for not being on one documented. This has not yet been evaluated in a primary care setting in the UK.

Objectives

This project aimed to describe SGLT2i prescription rates for people who met EMPA-REG trial criteria in the community and to assess interventions to improve SGLT2i prescription rates in line with the EMPA-REG trial. Additionally, this project aimed to quantify the potential benefit of improved SGLT2i prescription rates, by extrapolating findings to the Greater Glasgow and Clyde (GG&C) health board population.

Methods

Study design and participants

People coded as having T2DM and either ischaemic heart disease, cerebrovascular disease, peripheral vascular disease or HF were identified from two GP practices using EMIS (primary care electronic health record) searches. This list was considered the absolute truth for established diagnoses. A second list of PWD who met the biochemical EMPA-REG trial criteria was obtained from SCI diabetes (SCI-D), the Scottish database for diabetes care, using the 'flexible query' function. The medical notes of individuals on the GP lists were subsequently reviewed to establish EMPA-REG trial eligibility as per the inclusion and exclusion criteria listed in Appendix C and D of EMPA-REG.[3]

PWD who met the EMPA-REG trial criteria were assessed for suitability of medication changes and contacted in a

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standardised way. Those who had had an HbA_{1c} checked in the last 12 months were contacted via telephone, while those who had not were offered a face-to-face (F2F) appointment at their GP practice.

Scotland has developed a national therapeutics indicator (NTI). This online tool calculates the percentage of PWD prescribed a medication indicative of CV disease (nitrate, nicorandil, aspirin or clopidogrel) in the same annual quarter (October 2022 – December 2022) as an SGLT2i or glucose-like peptide-1 (GLP-1) agonist (GLP-1 A). It was used to assess the generalisability of the calculated rates prior to data extrapolation and to compare the included GP practices to others in GG&C.

The number needed to treat (NNT) for all-cause mortality, EMPA-REG primary and secondary outcomes and hospitalisation for HF was calculated from EMPA-REG trial results. To minimise variation in patient demographics, data extrapolation was carried out for GG&C using the cumulative prescription rate. The numbers of events preventable by telephone or F2F review were calculated using the new cumulative SLGT2i prescription rates following intervention.

Data sources/measurements

The review of EMIS and medical notes was carried out by one individual. The telephone and F2F reviews were carried out by three individuals of different professions (medical, nursing, pharmacy).

Study size

Due to time constraints only two practices were included. These practices were chosen due to their variability in size and staffing level, detailed further below.

Quantitative variables

Blood results prior to 20.05.23 were considered when defining individuals as ‘eligible for EMPA-REG'. During the interventions up-to-date blood results were considered when discussing medication changes.

Results

Practice and participant characteristics

Practice 1 has a patient population of 10,657; 49% of their patient population live in the 15% most deprived areas, as per public health data from 2022.[9] This practice had no dedicated member of staff to conduct diabetic reviews until recently, when the practice nurse took over. Practice 2 has a patient population of 5,309; 65% of their patients live in the 15% most deprived areas.[9] A pharmacist with an interest in diabetes care conducts diabetic reviews in this practice. T2DM prevalence is consistent with national rates in both practices.

Table 1 portrays the number of people in each practice at each stage of data collection. The final row represents individuals who met trial criteria following a review of their medical notes. Across both practices a total of 992 individuals have T2DM. The GP search for T2DM and arterial disease/HF identified 273 individuals: of these 81 (29.7%) were eligible for an SGLT2i as per the EMPA-REG trial criteria, accounting for 8.2% of the PWD population. The statin prescription rates for PWD who are older than 50 are 66.3% and 67.6% in Practice 1 and Practice 2, respectively. These prescription rates, obtained from SCI-D, are lower than that of the population of the EMPA-REG trial (77.5%).[3]

Table 2 provides a breakdown of the reasons why individuals on the GP list were excluded. The most common reason for exclusion was an haemoglobin A1 (HbA_{1c}) outside the trial inclusion range (53–85 mmol/mol), followed by not meeting criteria for established CV disease as per EMPA-REG Appendix C.[3] 192 people from the GP lists were excluded.

Table 3 summarises personal characteristics of individuals who met trial criteria. Regarding anti-diabetic medications: 8 people were on no anti-diabetic medications, 24 on one, 24 on two, 23 on three, and 3 on four (including an SGLT2i). Only 1 of the 9 people prescribed a GLP-1 A was not prescribed an SGLT2i.

Prescription rates

As summarised in Table 1, 52 individuals in Practice 1 met the trial criteria, 18 of whom were already prescribed an SGLT2i (34.6%). In Practice 2, 29 individuals met the trial criteria, 17 of whom were already prescribed an SGLT2i (58.6%). Compared to Practice 1, Practice 2 had a higher SGLT2i prescription rate cumulatively, and a higher SGLT2i prescription rate when looking at those who did and did not meet the EMPA-REG trial criteria separately (Figure 1). In both practices, the rate of SGLT2i prescription was higher in the group of PWD who met the EMPA-REG trial criteria. Cumulatively, 35 of the 81 (43.2%) individuals who met trial criteria were on an SGLT2i.

Interventions and data extrapolation

A summary of the encounter outcomes can be found in table 4. Of the 46 individuals who were not on an SGLT2i, two died

Table 1. Breakdown of number of individuals at each stage. The numbers of individuals in each practice and those with a diagnosis of T2DM were obtained from GP records and are listed in row 1 and 2. The prevalence of T2DM in both practices is in line with the Scottish national prevalence, as seen in row 2. A total of 81 patients met the trial criteria for review of patient notes.

Characteristic	Combined count	Practice 1 count	Practice 2 count
Total number of Individuals	15,966	10,657	5,309
Number of PWD (% of patient population)	992 (6.2%)	657 (6.2%)	335 (6.3%)
Number of patients identified by GP search	273	175	98
Number of patients who met trial criteria	81	52	29

Table 2. Summary of reasons why individuals on the GP lists did not meet the EMPA-REG trial criteria. A raised HbA_{1c} was the most common reason for exclusion. Individuals who met more than one exclusion criterion are counted in more than one row. The CV criteria and the other exclusion criteria were defined as per Section C and Section D of the supplementary appendix of the EMPA-REG trial.[3]

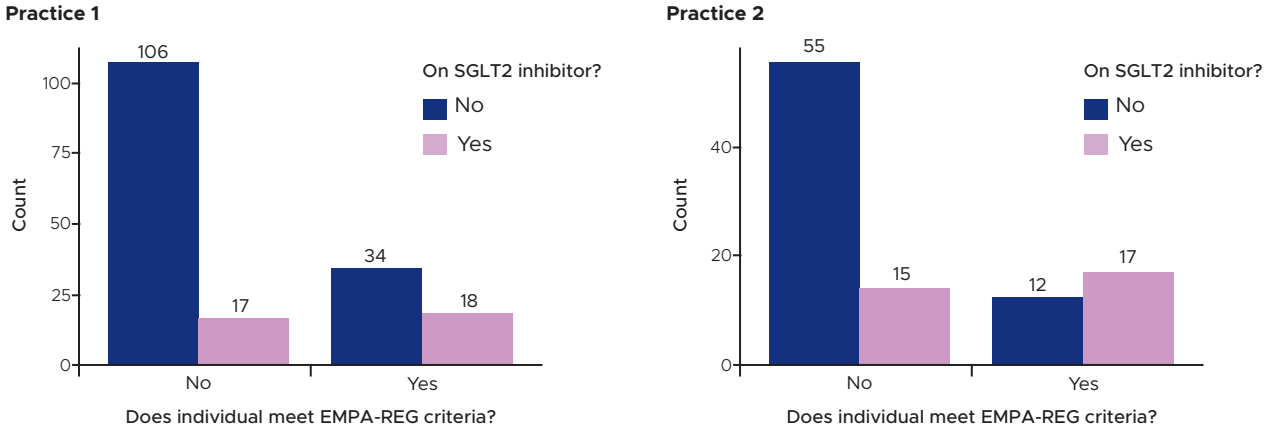
Reason not eligible for EMPA-REG	Combined total 192 excluded)	Practice 1 (total 123 excluded)	Practice 2 (total 69 excluded)
HbA^{1c} <53mmol/mol	130 (67.7%)	85 (6.9%)	45 (65.2%)
HbA^{1c} >85mmol/mol	17 (8.9%)	10 (8.1%)	7 (10.1%)
eGFR <30ml/min	11 (5.7)	10 (8.1%)	1 (1.4%)
Deranged LFTs	3 (1.6%)	2 (1.6%)	1 (1.4%)
BMI >45 kg/m^2	10 (5.2%)	7 (5.7%)	3 (4.3%)
Did not meet CV criteria	41 (21.6%)	28 (22.8%)	13 (18.8%)
Diagnosis of cancer	17 (8.9%)	13 (10.5%)	4 (5.8%)
Diagnosis of dementia	21 (10.9%)	8 (6.5%)	13 (18.8%)
Poor mental health	4 (2.1%)	4 (3.3%)	0
Recent diagnosis of T2DM	5 2.6%)	3 (2.4%)	2 (2.9%)
Transplant patient	1 (0.5%)	1 (0.8%)	0
On steroids	2 (1.0%)	1 (0.8%)	1 (1.4%)

Table 3. Summary of personal characteristics. Descriptive characteristics regarding the 81 individuals who met the EMPA-REG trial criteria from both practices. Those who had more than one type of arterial disease/HF have been accounted for more than once in the last four rows.

Characteristic		Combined count	Practice 1 count	Practice 2 count
Sex:	Female	29	21	8
	Male	52	31	21
Age:	40–60 years	17	12	5
	60–80	51	32	19
	80–100	13	8	5
Median BMI (IQR)		29.4 (26.6 – 35.2)	29.9 (26.6 – 35.4)	28 (26.1 – 32.2)
Median HbA_{1c} (IQR) (mmol/mol)		62 (56 – 70)	63 (56 – 69.8)	53 (47 – 67.8)
Time since diagnosis	<5 years	13	6	7
	5-10 years	21	12	9
	>10 years	47	34	13
Anti-platelet	Yes	62	42	20
	No	19	10	9
Anti-hypertensives	Yes	64	40	24
	No	17	12	5
Anti-diabetic medications				
Metformin		57	37	20
Sulfonyluea		22	14	8
DPP4-inhibitor		20	18	2
GLP-1 A		9	3	6
Insulin		8	6	2
PPAR agonist		1	1	0
SGLT2i		35	18	17
None		8	5	3
Type of arterial disease/HF				
Cardiovascular disease		51	34	17
Stroke		30	19	11
Heart failure		19	14	5
Peripheral vascular disease		11	7	4

Figure 1. Number of individuals who met the EMPA-REG criteria by practice.

These bar charts include all the individuals identified by the GP lists. The cluster of bars represent individuals who did not meet EMPA-REG trial criteria on the left of each graph and those who did on the right. Individuals who are prescribed an SGLT2i are represented in purple and those who are not are represented in blue. Practice 1 had a total of 52 patients who met the trial criteria, 18 (34.6%) of whom were already on an SGLT2i. In Practice 2, 29 individuals met the trial criteria, 17 (58.6%) of whom were already on an SGLT2i. The numbers represent the number of individuals in each group.



and 11 were not suitable for medication changes due to frailty, hospital admission or previous intolerance. Telephone interventions alone resulted in 11 SGLT2i prescriptions, increasing SGLT2i prescription from 43.2% to 58.2%. F2F reviews alone resulted in 10 SGLT2i prescriptions and increased SGLT2i prescription rate to 57.0%. The combination of both interventions increased the prescription rate to 70.9%. The final prescription rates calculations excluded those who died.

Within GG&C the median NTI for October 22 to December 22 (most recent data) was 41.62% (IQR: 34.98 – 48.80). The prescription rate of each GP practice was compared with their NTI. Practice 1 is below the 1st quartile of the GG&C NTI range (~30%), while Practice 2 is above the 3rd quartile (~50%). These percentages are similar to the calculated SGLT2i prescription rate. NTI does not provide individual GP practice percentages; these were estimated from the graphs in Figure 2.[10]

Figure 3 depicts data extrapolation for the number of preventable events if SGLT2i prescription was 100% for PWD who meet EMPA-REG trial criteria in GG&C. The 2021 Scottish Diabetes Survey recorded 61,126 PWD in GG&C.[1] In line with our data, we estimated 8.2% would meet EMPA-REG trial criteria (5,012.3 individuals) and of these 56.8% (2,847.0) would not be prescribed an SGLT2i. Assuming all of these individuals are started on an SGLT2i, we calculated a total of 74.0 (85.1–53.9) deaths could be prevented within GG&C over 3.1 years. Targeted telephone or F2F reviews of at-risk individuals could reduce the number of deaths by 19.6 and 18, respectively, in GG&C over 3.1 years.

Table 4. Outcomes of telephone and F2F interventions. This table excludes the patients who were deemed not eligible for intervention and were not contacted due to frailty, current IP stay or previous medication intolerance. The further specialty referrals were to diabetic nurses/secondary care MDT, renal or cardiology teams.

Encounter outcome		Practice 1	Practice 2	Total
Telephone consultation				
SGLT2i started		6	3	9
Failed to engage		1	0	1
Refused		1	1	2
Specialist referral required	SGLT2i started	1	1	2
	SGLT2i not started	1	2	3
F2F consultation				
SGLT2i started		10	1	11
Failed to engage		3	0	3
Refused		0	0	0
Specialist referral required	SGLT2i started	0	0	0
	SGLT2i no started	2	0	2

Validation of search criteria

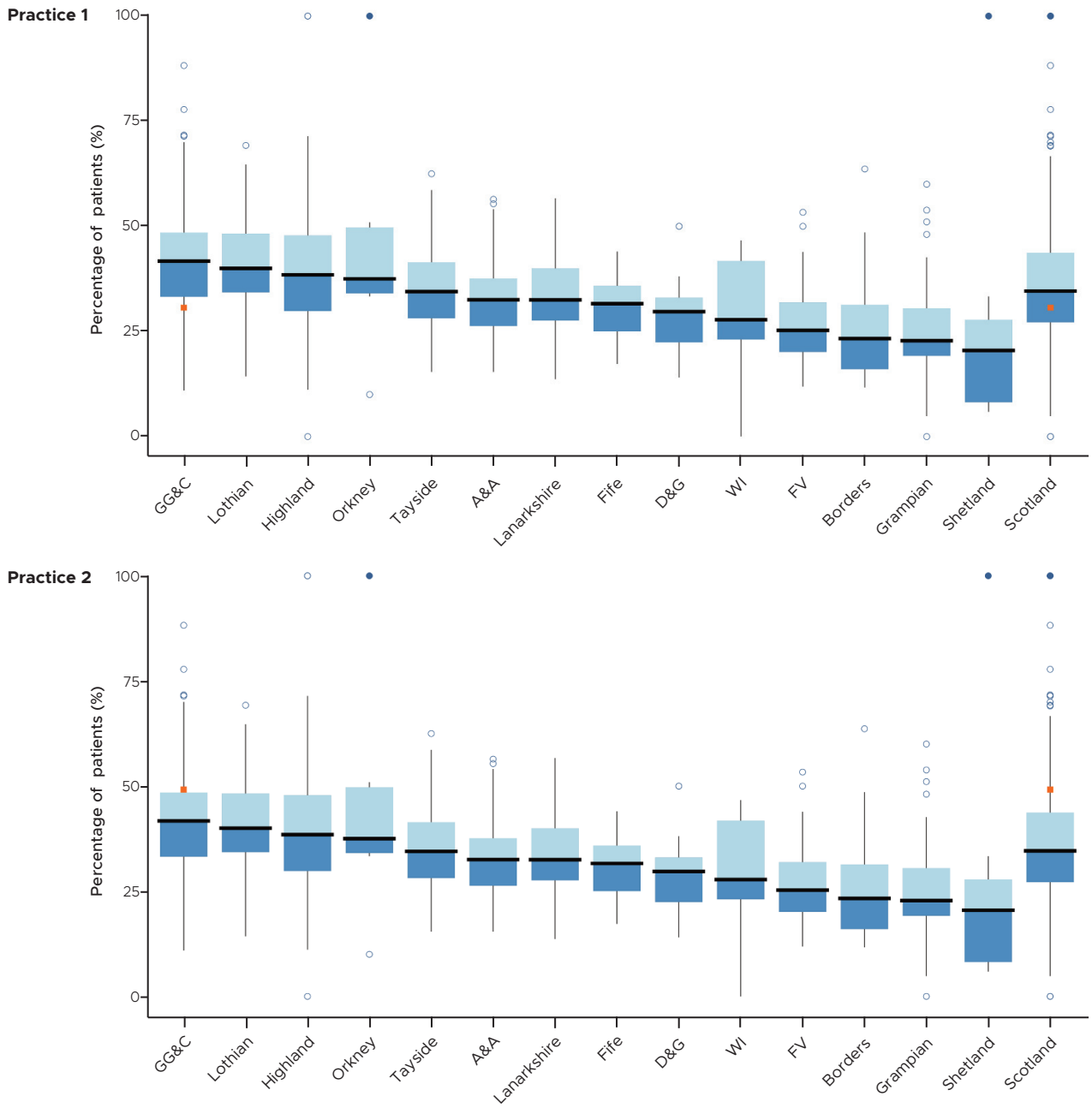
Of the 81 PWD who met the EMPA-REG criteria, 97.5% were on the SCI-D list. The 81 patients accounted for 20% of the SCI-D list, suggesting high sensitivity and poor specificity of the flexible query function. There is no option to input HF data in SCI-D.

Discussion

The two GP practices included showed some baseline variability (see Table 1) and variability in SGLT2i prescription rate, which is likely to be multifactorial in origin. Both practices have a T2DM prevalence in line with national rates, and a relatively high proportion of patients who live in the 15% most deprived areas.[9]

Figure 2. Position of Practice 1 (top graph) and Practice 2 (bottom graph) compared to the GGC percentage of individuals prescribed on SGLT2 or GLP-1 in the same annual quarter as a medication indicative of cardiovascular disease.

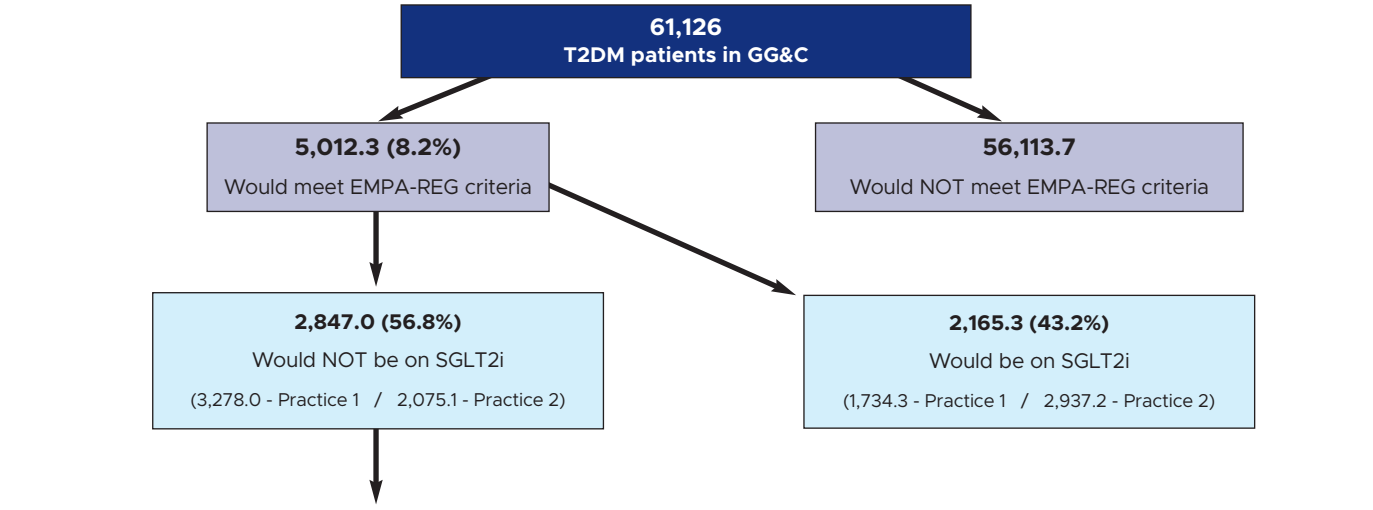
The National Therapeutic Indicator (NTI) tool uses a prescription of a nitrate, nicorandil, aspirin or clopidogrel as a proxy for cardiovascular disease and calculates the proportion of those patients who were prescribed a GLP-1 agonist or SGLT2 in the same quarter. The graphs represent all the deaneries in Scotland, with GGC on the far left of each individual graph and Scotland on the far right. The orange dot in the top graph shows where Practice 1 (rate ~30%) is compared to GGC. The orange dot in the bottom graph represents Practice 2 (rate ~50%) compared to GGC. The graphs are data from the final quarter of 2022, most recent data available, while date for this study was collected in May 2023.



Graphs obtained from National Therapeutic Indicators.[10]

Figure 3. Flow diagram representing data extrapolation to GG&C.

All numbers were rounded to 1 decimal place. The NNTs were calculated from the EMPA-REG trial results at 3.1 years.[3] The average calculation was carried out on the basis of the cumulative SGLT2i prescription rate across both practices, and the range was derived from each practice individually. The ranges in the third column represent the number of events prevented if every practice in GGC had rates as seen in Practice 1 and Practice 2, respectively. The subsequent columns represent the number of events which could be prevented with each intervention, given the new cumulative prescription rate following interventions. Individuals who died were excluded from the new prescription calculations.



Outcome	NNT	No. of events prevented in GG&C (Practice 1 – Practice 2)	No. of events prevented in GG&C with telephone consultation	No. of events prevented in GG&C with F2F consultation	No. of events prevented in GG&C with both interventions
All-cause mortality	38.5	74.0 (85.1 - 53.9)	19.6	18	36.1
Death from cardiovascular causes, non-fatal MI (excluding silent MI), or non-fatal stroke (primary outcome)	62.5	45.6 (52.4 - 33.2)	12.1	11.1	22.3
Primary outcome plus hospitalisation for unstable angina (secondary outcome)	50	57.0 (65.7 - 41.5)	15.1	13.9	27.8
Hospitalisation for HF	71.4	39.9 (45.9 - 29.1)	10.6	9.7	19.5

However, until recently, Practice 1 had no dedicated staff member conducting diabetic reviews. The practice nurse has now taken on this role, while in Practice 2 a pharmacist with an interest in diabetes conducts diabetic reviews. Practice 1 has a greater workload; this is reflected by the higher number of F2F reviews required, as more individuals had missed their last annual review. This may represent a lack of patient engagement as well as staffing issues; both of these pose a barrier to medication changes. An updated HbA_{1c} in individuals who engage poorly may uncover more patients eligible for an SGLT2i, highlighting the importance of regular reviews and engagement with PWD. None of the updated HbA_{1c} in patients reviewed excluded them from SGLT2i eligibility.

The NTIs and SGLT2i prescription rates calculated following review of medical notes mirror each other although interpretation of NTIs is limited by the misalignment of dates and inclusion of GLP-1 A. However, within our sample population, only 1 of the 9 individuals prescribed GLP-1 A was not also prescribed an SGLT2i, making this a negligible factor. Given the similarities between study findings and NTIs, we assumed that the cumulative prescription rate across both practices might be representative of GG&C GP practices. As such, if all individuals eligible for EMPA-REG were started on an SGLT2i 74 all-cause deaths could be prevented in GG&C at 3.1 years. When taking into account frailty, co-morbidities and patient choice, targeted interventions could decrease the number of deaths from all-cause mortality by almost half (36.1). A higher proportion of F2F reviews culminated in SGLT2i prescription; however, these are more time-consuming. Half of the telephone reviews, which can be more easily accommodated by GP practices, resulted in SGLT2i prescription. The higher proportion of SGLT2i prescription following F2F reviews may be due to a longer interval since previous diabetic review.

Key messages

- SGLT2i use in people with T2DM is recommended by both SIGN and NICE guidelines.
- SGLT2i prescription is suboptimal in the community and could be improved by telephone and/or face-to-face interventions.
- Consideration of HF and CVD should be made when prescribing for individual with T2DM to improve outcomes.

While there is an option to input data regarding arterial disease in SCI-D, there is no place for HF diagnosis. This addition might prompt healthcare professionals to consider the diagnosis of HF when discussing therapeutic options with PWD, resulting in fewer at-risk individuals missing therapeutic opportunities.

Limitations

The study size was limited by time. However, given the difference in prescription rates between both practices, and similarity to NTI, we feel the cumulative prescription rate may be representative of GP practices across GG&C. The use of the cumulative prescription rate across both practices for data extrapolation minimised skew.

The EMPA-REG criteria were used to ensure that the sample resembled that of the trial. Although this may have limited the number of individuals included, it allowed for data extrapolation. Data extrapolation was limited to GG&C to minimise variability in demographics. Data regarding individuals' ethnicity were not collected, and data regarding statin prescription rates were generalised from the practice prescription data from SCI-D.

The telephone and F2F reviews were conducted by three individuals of different professions. This element of variability was minimised by a pre-determined, standardised proforma to contact patients.

Conclusions

Community SGLT2i prescription rates are suboptimal, and an improvement in these could benefit outcomes in high-risk PWD. Data-driven telephone and F2F reviews are a simple way to improve SGLT2i prescriptions, improving CV outcomes and potentially reducing the risk of all-cause mortality. Although F2F consultations result in higher SGLT2i uptake they are more labour-intensive; a combination of F2F and telephone encounters may be more practical. Targeting GP practices identified as having a low NTI could have the greatest impact on SGLT2i prescription rates in at- risk groups.

The addition of HF diagnosis in SCI-D might improve SGLT2i prescription in this at-risk demographic. The database is being updated, with the potential to add HF diagnosis data.

Conflict of interest The authors have no conflicts of interest to declare.
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