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ORIGINAL ARTICLE

Patterns of initial and first-intensifying antidiabetic drug utilization among patients with type 2 diabetes mellitus in Scotland, 2010–2020: A retrospective population-based cohort study

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Abstract

Aim: To evaluate the utilization and prescribing patterns of antidiabetic drugs (ADDs) for patients with type 2 diabetes mellitus (T2DM) at treatment initiation and first intensification.

Methods: A retrospective cohort study was performed using linked routinely collected data of patients with T2DM who received ADDs between January 2010 and December 2020 in Scotland. The prescribing patterns were quantified using frequency/percentages, absolute/relative change, and trend tests.

Results: Overall, 145 909 new ADD users were identified, with approximately 91% ($N = 132\,382$) of patients receiving a single ADD at first treatment initiation. Metformin was the most often prescribed monotherapy ($N = 118\,737$, 89.69%). A total of 50 731 patients (39.40%) who were started on metformin ($N = 46\,730/118\,737$, 39.36%) or sulphonylurea (SU; $N = 4001/10\,029$, 39.89%) monotherapy had their treatment intensified with one or more additional ADD. Most initial-metformin (45 963/46 730; 98.36%) and initial-SU users (3894/4001; 97.33%) who added further drugs were intensified with single ADDs. SUs (22 197/45 963; 48.29%) were the most common first-intensifying monotherapy after initial metformin use, but these were replaced by sodium-glucose cotransporter-2 (SGLT2) inhibitors in 2019 (SGLT2 inhibitors: 2039/6065, 33.62% vs. SUs: 1924/6065, 31.72%). Metformin was the most frequently added monotherapy to initial SU use (2924/3894, 75.09%).

Although the majority of patients received a single ADD, the use of combination therapy significantly increased over time. Nevertheless, there was a significant increasing trend towards prescribing the newer ADD classes (SGLT2 inhibitors, dipeptidyl peptidase-4 inhibitors) as monotherapy or in combination compared with the older ones (SUs, insulin, thiazolidinediones) at both drug initiation and first intensification.

Conclusions: An overall increasing trend in prescribing the newer ADD classes compared to older ADDs was observed. However, metformin remained the most commonly prescribed first-line ADD, while SGLT2 inhibitors replaced SUs as the most common add-on therapy to initial metformin use in 2019.

KEYWORDS

antidiabetic drugs, drug utilization, prescribing pattern, treatment intensification, type 2 diabetes

1 | INTRODUCTION

Parallel with the continuing increase in the prevalence and burden of type 2 diabetes mellitus (T2DM) globally,[1,2] there have been considerable developments in the treatment options for T2DM.[3] This has been accompanied by changes in national[4,5] and international guidelines[6] for T2DM management, including the Scottish guideline,[7] especially after the approval of newer antidiabetic drug (ADD) classes that have additional proven cardiovascular and potential renal benefits, namely, sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs).[7–9] To ensure that guideline updates are translated into improving disease management and patient care, it is critical to evaluate the implementation of these updated clinical guidelines in clinical practice. The availability of electronic administrative databases provides a robust, reliable and efficient tool for evaluating changes in treatment selection over time in response to changes in treatment guidelines, including ADD utilization patterns.[10,11]

Although all clinical guidelines for treating T2DM recommend metformin as first-line therapy for newly diagnosed patients,[7–9] there are a considerable number of patients who might be started on a different ADD class for multiple reasons (e.g., contraindications).[12,13] In addition, some patients might need to be initiated on multiple ADDs, depending on disease severity.[8,14] Furthermore, given the progressive nature of T2DM and the limited durable effectiveness of ADDs, patients often fail to maintain their targeted glycaemic control over time; thus, initiation of additional ADDs is warranted to maintain glycaemic targets.[7–9] There is no clear recommendation, however, regarding selection of the initial alternative ADD to metformin, the initial combination therapy for patients with more severe disease, or the ADD that should be the first intensifying therapy.[7–9] In 2015, the Scottish Intercollegiate Guidelines Network (SIGN) guideline added SGLT2 inhibitors as a second-line therapy and beyond to the other available treatment options, which include sulphonylureas (SUs), dipeptidyl peptidase-4 (DPP-4) inhibitors and pioglitazone. As a result, a change in the prescribing patterns of ADDs over time in response to the change in the clinical guideline would be expected, however, data on this are limited.

Few studies have examined the prescribing patterns of ADDs over time in the United Kingdom,[14–16] and, to our knowledge, previous studies have not provided information about the utilization of ADDs as first-line and subsequent intensifying therapies in Scotland at a national level. In addition, little is known globally about the use of the newest ADD class (SGLT2 inhibitors) and combination regimens as first-line and add-on therapy. Most studies investigating combination regimens did not specify which stage of treatment was studied and reported only the overall consumption of combination regimens, without studying the prescribing trends over time. In addition, most studies investigated changes in the prescribing patterns at the first intensification stage either without standardizing the first-line treatment[17–20] or including only patients who received metformin as a first-line therapy.[12,14–16,21,22] Accordingly, this study aimed to provide a comprehensive evaluation of utilization and change in prescribing patterns of ADDs for patients with T2DM at both the drug initiation and first intensification stages as a proxy for the impact of the introduction of newer ADD classes and the recent updates in T2DM clinical guidelines.

2 | METHODS

2.1 | Study design and data source

A population-based retrospective cohort study was conducted using routinely linked data from five different national datasets in Scotland between January 2010 and December 2020 (Figure 1). The Scottish Care Information-Diabetes (SCI-Diabetes) was used to obtain the study cohort. SCI-Diabetes is a national register and database, launched in April 2002, collating all relevant information on all patients diagnosed with diabetes within the primary and secondary care settings across Scotland, covering over 99.5% of people with diabetes. This database was linked with the Prescribing Information

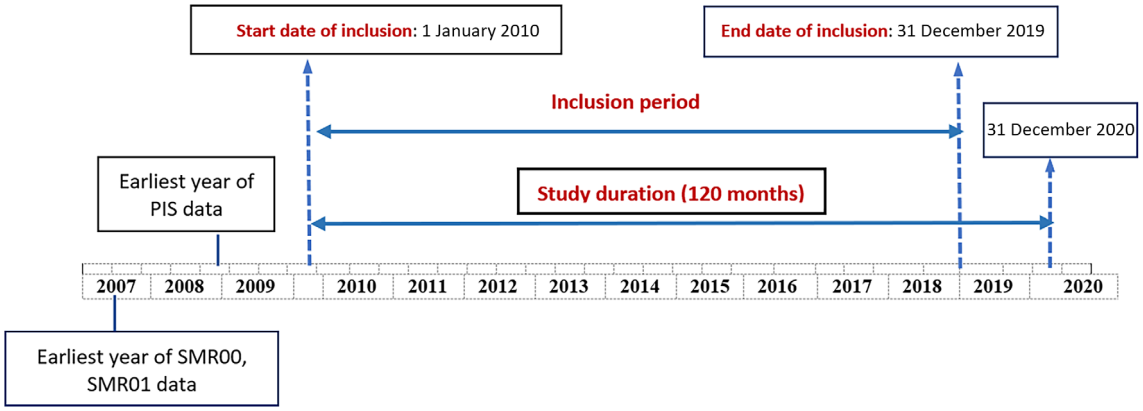

FIGURE 1 Illustration of the study timeline. Scottish Morbidity Records codes: SMR00, outpatient attendance; SMR01, general/acute inpatient and day case. PIS; prescribing information system.

System (PIS), Scottish Morbidity Records, and National Records of Scotland using the Community Health Index (CHI) unique identification number to retrieve information relevant to prescriptions (ADDs and other concomitant medications), patient demographics, and comorbidities.

2.2 | Study cohort

The study cohort comprised patients from the SCI-Diabetes database in Scotland who were diagnosed with T2DM between 1 January 2010 and 31 December 2019 and were prescribed at least one ADD during the study period (1 January 2010–31 December 2020). Only new ADD users were included; these were defined as those with no prescriptions of ADDs recorded within the year preceding cohort entry. Additionally, each patient had to have at least 1 year of follow-up to facilitate the study of change in T2DM management over time; therefore, the last date of patient inclusion was 31 December 2019. The inclusion/exclusion criteria are described in Appendix S1. The index ADD and the index date were defined as the first event of ADD prescribing for each patient, even if it was prescribed only once, and the corresponding prescription date for each included patient, respectively.

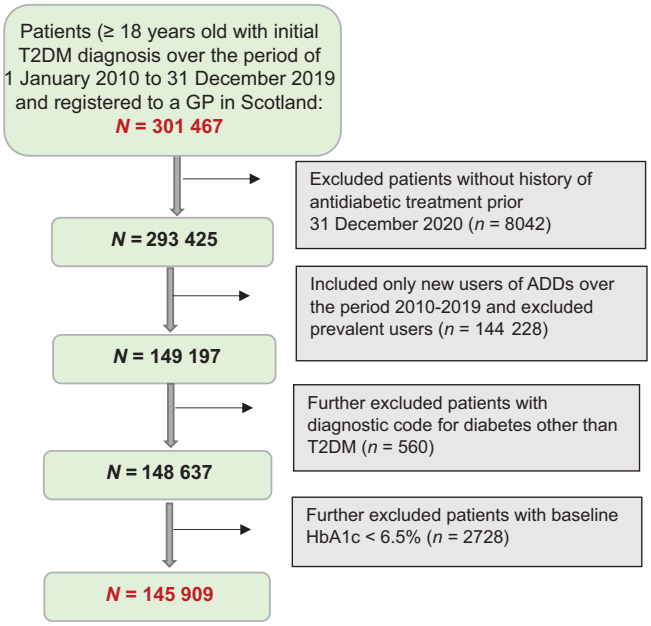

FIGURE 2 Flowchart of cohort identification process at the stage of drug initiation. HbA1c, glycated haemoglobin; T2DM, type 2 diabetes.

2.3 | Study outcome

The first study outcome was the change in prescribing patterns at drug initiation for drug-naïve patients with T2DM (new users of ADDs). The second study outcome was the prescribing patterns at the stage of first intensification, that is, instances where patients who initially received first-line metformin or an SU subsequently received one or more additional ADDs following at least 3 months of initial treatment. The identified cohort (both new users and patients whose treatment was intensified) was stratified into monotherapy or combination-therapy users based on the number of different ADD classes that were prescribed for the individual patient over a specific period, the initiation period. The initiation period was defined as the first 3 months following the earliest identified ADD in the PIS records. A 3-month interval was selected since clinical guidelines for T2DM management recommend reassessing glycaemic control after at least 3 months of starting an ADD. Accordingly, no change in drug therapy is expected to occur within 3 months of drug initiation based on the effectiveness of initiated treatment.

Each ADD was assigned to the appropriate antidiabetic class, providing a total of eight main classes. These included biguanides (metformin), TZDs, SUs, DPP-4 inhibitors, GLP-1RAs, SGLT2 inhibitors, insulin, and others (alpha-glucosidase inhibitors and meglitinide). Generally, monotherapy users were defined as patients who were started on a single ADD over the initiation period, while combination-therapy users comprised patients who started on two or more ADDs from different classes (including fixed-dose combination) over the defined

period. Appendix S2 lists the criteria established to classify the included patients into monotherapy or combination-therapy groups, with examples. These criteria were established based on three variables within the PIS dataset, including type of prescribed ADD, the corresponding prescription date, and prescribed quantity. The clinical relevance of all applied criteria was discussed with a specialist pharmacist and a diabetologist.

2.4 | Data analyses

Data are presented as frequency and percentage of patients started on a particular antidiabetic regimen or class per calendar year. The absolute and relative change in the use of ADDs was also calculated. Additionally, a Cochran–Armitage test for trend analysis was conducted, with a p value of less than 0.05 taken to indicate a significant change in the prescribing patterns of ADDs over the study period.

2.5 | Ethical considerations

The data used in this project were collated by the Public Health Scotland electronic Data Research and Innovation Service (eDRIS). They were made available in pseudonymized form and accessed in a secure environment to ensure patient privacy and confidentiality.

3 | RESULTS

3.1 | Prescribing patterns at the drug initiation stage

In Scotland, a total of 145 909 patients with T2DM (median [interquartile range] age: 61 [52–70] years, 57.94% male) were identified as new ADD users over the study period and included in the first-line study (Figure 2). The baseline characteristics of the included cohort are presented in Appendix S5. Approximately 91% of patients (N = 132 382/145 909) were started on a single ADD (monotherapy). However, the proportion of patients starting on combination therapy significantly increased during the study period by 25.29% (p < 0.001; Appendix S3). Among monotherapies, metformin was the most frequently prescribed ADD (89.96%, n = 18 737/132 382), followed by SUs (N = 10 029/132 382, 7.58%). Nevertheless, the share of DPP-4 inhibitors and SGLT2 inhibitors significantly increased over time (p < 0.001), while the use of older ADD classes as initial therapy (SUs, TZDs and insulin) significantly decreased (Table 1). Changes in the prescribing patterns of initial monotherapy by ADD class are summarized in Tables 1 and 2.

Similar to monotherapies, only the prescribing of those combination regimens that included DPP-4 inhibitors or SGLT2 inhibitors (metformin + DPP-4 inhibitors; metformin + SGLT2 inhibitors; DPP-4 inhibitors + SUs; and metformin + SGLT2 inhibitors + SUs)

TABLE 1 Frequency and percentage of the individual class of antidiabetic drugs prescribed as monotherapy at the stage of drug initiation over the study period.

Antidiabetic group	2010 (N = 14 438)	2011 (N = 12 991)	2012 (N = 13 579)	2013 (N = 13 591)	2014 (N = 11 940)	2015 (N = 13 551)	2016 (N = 12 976)	2017 (N = 12 831)	2018 (N = 12 762)	2019 (N = 13 723)	Total (N = 132 382)
Biguanides	12 600 (87.27%)	11 372 (87.54%)	12 070 (88.89%)	12 190 (89.69%)	10 732 (89.88%)	12 249 (90.39%)	11 775 (90.74%)	11 666 (90.92%)	11 591 (90.82%)	12 492 (91.03%)	118 737 (89.69%)
DPP-4 inhibitors	34 (0.24%)	48 (0.37%)	64 (0.47%)	80 (0.59%)	79 (0.66%)	96 (0.71%)	113 (0.87%)	125 (0.97%)	154 (1.21%)	151 (1.10%)	944 (0.71%)
GLP-1RAs	*	5 (0.00%)	*	0 (0.00%)	7 (0.06%)	*	*	*	*	5 (0.03%)	42 (0.03%)
Insulin	280 (1.94%)	214 (1.65%)	223 (1.64%)	200 (1.47%)	210 (1.76%)	218 (1.61%)	207 (1.60%)	229 (1.78%)	190 (1.49%)	200 (1.45%)	2171 (1.64%)
Other	*	6 (0.00%)	*	*	*	*	*	*	*	*	29 (0.02%)
SUs	1467 (10.16%)	1317 (10.14%)	1206 (8.88%)	1109 (8.16%)	903 (7.56%)	955 (7.05%)	837 (6.45%)	750 (5.85%)	733 (5.74%)	752 (5.48%)	10 029 (7.58%)
TZDs	47 (0.33%)	29 (0.22%)	10 (0.07%)	8 (0.06%)	*	6 (0.04%)	7 (0.05%)	6 (0.04%)	6 (0.05%)	*	127 (0.09%)
SGLT2 inhibitors	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	*	19 (0.14%)	32 (0.25%)	46 (0.35%)	83 (0.65%)	118 (0.86%)	303 (0.23%)

*Values were removed either because they are very small (<5) or in order not to disclose a very small value because of the high risk of patient identification. 'Other' includes alpha-glucosidase inhibitors and meglitinide.
Abbreviations: DPP-4 inhibitors, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide receptors agonist; SGLT2, sodium glucose co-transporter-2; SU, sulphonylurea; TZD, thiazolidinedione.

TABLE 2 The change in prescribing patterns of the individual class of antidiabetic drug prescribed as monotherapy at the stage of drug initiation: absolute change, relative change, and trend test.

Antidiabetic group	Absolute change	Relative change	Trend-test[a]
Biguanides	3.76%	4.31%	$Z = 14.92$, $p < 0.001$
DPP-4 inhibitors	0.86%	358.33%	$Z = 12.94$, $p < 0.001$
GLP-1RAs	0.01%	25.93%	$Z = 0.53$, $p = 0.599$
Insulin	−0.49%	−25.26%	$Z = -2.35$, $p = 0.019$
Other	−0.03%	−75.00%	$Z = -2.19$, $p = 0.029$
SGLT2 inhibitors	0.85%	8500.00%	$Z = 19.87$, $p < 0.001$
SUs	−4.68%	−46.06%	$Z = -22.63$, $p < 0.001$
TZDs	−0.30%	−90.91%	$Z = -8.52$, $p < 0.001$

[a]Using Cochran–Armitage test for trend (each group was compared to all other groups). 'Other' includes alpha-glucosidase inhibitors and meglitinide.
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide receptor agonist; TZD, thiazolidinedione; SGLT2, sodium-glucose cotransporter-2; SU, sulphonylurea.

significantly increased ($p < 0.001$), while the use of metformin + SUs decreased over the course of the study (Appendix S3).

Of the patients started on combination regimens ($N = 13\,527/145\,909$), 90.49% ($N = 12\,241/13\,527$) were started on dual therapy. For dual-therapy users, the majority of patients were prescribed metformin-based regimens, with more than two thirds (68.68%, $n = 8408/12\,241$) of patients receiving metformin + SUs, yet dual-therapy use significantly declined over time ($p < 0.001$). In contrast, the use of metformin + DPP-4 inhibitors and metformin + SGLT2 inhibitors significantly increased despite their low overall use during the 10-year study period (Appendix S3). Of the remaining 1286 patients (triple-therapy users), more than two thirds (71.70%, $n = 922/1286$) were treated with a metformin–SU-based triple regimen (Appendix S3). The use of SGLT2 inhibitors in triple combination with metformin and SUs significantly increased over time compared to other regimens that included three or more ADDs ($p < 0.001$).

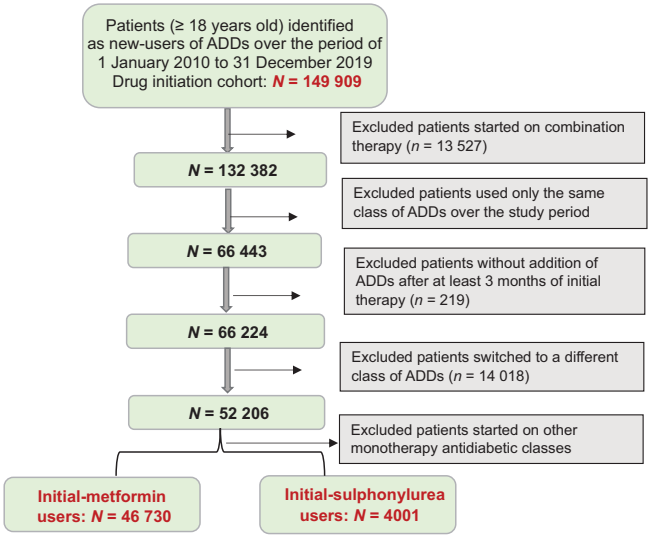

FIGURE 3 Flowchart of cohort identification at the stage of first drug intensification. ADD, antidiabetic drug.

3.2 | Prescribing patterns at the first treatment intensification stage

Of the 145 909 new ADD users identified in the first-line therapy study, a total of 50 731 patients were started on either metformin ($N = 46\,730$, median [interquartile range] age 59 [51–68] years, 60.05% male) or SUs ($N = 4001$, median [interquartile range] age 64 [54–73] years, 58.31% male) and intensified with one or more additional ADDs between January 2010 and December 2020 (Figure 3). The baseline characteristics of the included cohort are presented in Appendix S5. Most of the initial-metformin ($N = 45\,963/46\,730$, 98.36%) and initial-SU users ($N = 3894/4001$, 97.33%) were intensified with monotherapy (Appendix S4). The initial-metformin users who were intensified with monotherapy mostly received SUs ($N = 22\,197/45\,963$, 48.29%), followed by DPP-4 inhibitors ($N = 12\,986/45\,963$, 28.25%) and SGLT2 inhibitors ($N = 7850/45\,963$, 17.08%). In contrast, metformin accounted for 75.09% ($N = 2924/3894$) of the first-intensifying monotherapy to initial SU, followed by DPP-4 inhibitors ($N = 428/3894$, 10.99%) and insulin ($N = 342/3894$, 8.78%). Of the added combination regimens, metformin + a DPP-4 inhibitor was the most common combination regimen added to initial SU use ($N = 44/107$, 41.12%), while DPP-4 inhibitors + SUs comprised the joint highest proportion of combination regimens among the initial metformin users ($N = 249/767$, 32.46%). The prescribing trend analyses of the first-intensifying ADDs among the initial-metformin user cohort were consistent with the results of the first-line therapy study (Table 4 and Appendix S4). A significant rise was observed in SGLT2 inhibitor and DPP-4 inhibitor prescribing as monotherapy (Table 4), but only the SGLT2 inhibitor-based combinations (SGLT2 inhibitors + DPP-4 inhibitors, SGLT2 inhibitors + SUs) showed a substantial increment throughout the study (Appendix S4). In 2019, SGLT2 inhibitors replaced SUs as the most frequently prescribed first-intensifying monotherapy (Table 3), and SGLT2 inhibitors + SUs surpassed DPP-4 inhibitors + SUs as the most commonly prescribed add-on combination therapy to initial metformin use (Appendix S4). However, in the initial SU cohort, only the

TABLE 3 Frequency and percentage of the individual class of antidiabetic drugs prescribed as a monotherapy at stage of first intensification for patients starting on metformin over the study period.

Antidiabetic group	2010 (N = 624)	2011 (N = 2056)	2012 (N = 3121)	2013 (N = 3840)	2014 (N = 4061)	2015 (N = 5030)	2016 (N = 5090)	2017 (N = 5336)	2018 (N = 5442)	2019 (N = 6065)	2020 (N = 5298)	Overall (N = 45 963)
DPP-4 inhibitors	87 (13.94%)	380 (18.48%)	667 (21.37%)	890 (23.18%)	1139 (28.05%)	1548 (30.78%)	1596 (31.36%)	1759 (32.96%)	1744 (32.05%)	1811 (29.86%)	1365 (25.76%)	12 986 (28.25%)
GLP-1RAs	20 (3.21%)	35 (1.70%)	*	30 (0.78%)	*	49 (0.97%)	42 (0.83%)	*	54 (0.99%)	88 (1.45%)	90 (1.70%)	558 (1.21%)
Insulin	*	41 (1.99%)	75 (2.40%)	62 (1.61%)	79 (1.95%)	98 (1.95%)	*	89 (1.67%)	*	89 (1.47%)	113 (2.13%)	826 (1.80%)
SUs	408 (65.38%)	1385 (67.36%)	2160 (69.21%)	2688 (70.00%)	2561 (63.06%)	2822 (56.10%)	2519 (49.49%)	2231 (41.81%)	1918 (35.24%)	1924 (31.72%)	1581 (29.84%)	22 197 (48.29%)
TZDs	90 (14.42%)	209 (10.17%)	155 (4.97%)	138 (3.59%)	133 (3.28%)	185 (3.68%)	171 (3.36%)	170 (3.19%)	115 (2.11%)	114 (1.88%)	51 (0.96%)	1531 (3.33%)
SGLT2 inhibitors	0 (0.00%)	0 (0.00%)	0 (0.00%)	32 (0.83%)	113 (2.78%)	328 (6.52%)	680 (13.36%)	1032 (19.34%)	1528 (28.08%)	2039 (33.62%)	2098 (39.60%)	7850 (17.08%)
Other	*	6 (0.29%)	*	0 (0.00%)	*	0 (0.00%)	*	*	*	0 (0.00%)	0 (0.00%)	15 (0.03%)

*Those values were removed either because they are very small (<5) or to no disclose a very small value because of the high risk of patient's identification. 'Other' includes alpha-glucosidase inhibitors and meglitinide.Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide receptor agonist; SGLT2, sodium-glucose cotransporter-2; SU, sulphonylurea; TZD, thiazolidinedione.

prescribing patterns of SGLT2 inhibitors as add-on therapy showed a statistically significant rise over the study period, while the addition of metformin, insulin and TZDs significantly decreased (Table 6). The results of the prescribing pattern analysis of initial-metformin users and initial-SU users are presented in Tables 3–6 and Appendix S4.

4 | DISCUSSION

The aim of this study was to summarize comprehensively the prescribing patterns of ADDs at the drug initiation stage and first treatment intensification stage in Scotland between January 2010 and December 2019. The findings potentially reflect the impact of the currently available new ADD classes on the prescription of older ADDs.

The observed significant rise in the use of combination therapy at drug initiation and first treatment intensification could be related to the current availability of newer ADDs, which have different extra-glycaemic benefits (e.g., weight loss, renal/cardioprotective effects). This provides prescribers with more options not only to achieve glycaemic control but also to decrease the progression of diabetes-related complications. For instance, clinical guidelines have recommended using ADDs with proven cardiovascular benefits (e.g., SGLT2 inhibitors) in addition to metformin for patients with established cardiovascular disease or with risk factors for cardiovascular disease.[7–9] Furthermore, most patients presenting with a very high glycated haemoglobin level (≥9%, 75 mmo) need to be started on insulin.[8,9] However, because of the barriers associated with using insulin, patients and prescribers may prefer to use combination oral drugs over insulin.[23,24] Consistent with this study finding, Wang et al.[25] reported that 92% of participants in their study were started on single ADDs. The result was also in keeping with the studies by Lee et al.[26] (2021) and Chu et al.,[17] who showed a significant increase in combination-therapy prescribing for T2DM management in Korea (between 2000 and 2019) and Taiwan (between 2005 and 2012), respectively; however, it was not stated in these studies at which treatment stage the prescribing pattern was observed.

Metformin is the recommended drug for newly diagnosed T2DM patients because of its pleiotropic effects, including glycaemic control, weight-neutral to weight-loss effects, cardiovascular risk improvement, low cost, and low hypoglycaemic risk.[8,9] Consistently, this study showed that metformin was by far the most commonly used first-line ADD for newly treated patients in each studied year.

The dominant prescription of metformin as an initial therapy and add-on therapy to initial SU treatment could imply the concordance of clinical practice with guideline recommendations. This was also reflected in the greater proportion of patients receiving metformin as an initial therapy in this study relative to earlier studies conducted in various countries and regions, including the United Kingdom, the United States, Europe and Taiwan.[12,17,18,27,28] For instance, in 2016, 77% of patients received metformin as initial therapy in a study conducted in the United States[12] compared to 90.7% in this study.

Of non-metformin monotherapy users in this study, SUs represented the highest proportional share of prescribed ADDs at drug

TABLE 4 The change in prescribing pattern of the individual class of antidiabetic drug prescribed as monotherapy at stage of first intensification for patients starting on metformin.

Antidiabetic group	Absolute change	Relative change	Trend-test[a]
DPP-4 inhibitors	11.82%	84.79%	$Z = 12.48$, $\mathbf{p < 0.001}$
GLP-1RAs	−1.51%	−47.04%	$Z = -0.28$, $p = 0.783$
Insulin	−0.59%	−21.69%	$Z = -2.00$, $\mathbf{p = 0.045}$
SGLT2 inhibitors	38.77%	4671.08%	$Z = 77.70$, $\mathbf{p < 0.001}$
SUs	−35.54%	−54.36%	$Z = -61.25$, $\mathbf{p < 0.001}$
TZDs	−13.46%	−93.34%	$Z = -21.53$, $\mathbf{p < 0.001}$
Other	−0.32%	−100.00%	$Z = -4.94$, $\mathbf{p < 0.001}$

[a]Using Cochran–Armitage test for trend (each group was compared to all other groups). 'Other' includes alpha-glucosidase inhibitors and meglitinide.
Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide receptor agonist; SU, sulphonylurea; SGLT2, sodium-glucose cotransporter-2; TZD, thiazolidinedione.

initiation. Despite the low use of the remaining classes as initial therapy, a significant rise in the prescribing of DPP-4 and SGLT2 inhibitors was observed, accompanied by a significant decline in the use of SUs, TZDs and insulin. Similar observations in the prescribing trends of ADDs were observed at the stage of first treatment intensification after initial metformin use. The previous findings might reflect that the newer ADDs, particularly SGLT2 inhibitors, have indeed affected the use of the older ADD classes as the decline in prescribing of the older ADDs mainly commenced in 2013, the year in which the use of SGLT2 inhibitors began in Scotland.

The decline in SU prescribing might be related to the associated risk of hypoglycaemia and weight gain, with no potential benefits with regard to the incidence/progression of cardiovascular/renal complications.[29–31] Likewise, the improved awareness of TZD-related side effects (e.g., weight gain, fracture, and cardiovascular risk), might discourage prescribers from prescribing TZDs despite their effectiveness.[32–34] All the aforementioned drug characteristics were published before the start of this study (2010), suggesting a possible link between these characteristics and the observed change in prescribing patterns of ADDs.

In addition, only the use of SGLT2 inhibitors as a first-intensifying therapy after initial SU use showed a significant increment over the study period. This is likely attributable to the previous findings that the addition of an SGLT2 inhibitor to SU treatment enhances glycaemic control, reduces body weight, and improves blood pressure and cardiovascular risk, with no significant increase in the risk of hypoglycaemia.[35–37]

The study findings relevant to the change in the prescribing patterns of initial ADDs for newly treated patients were in line with previous studies conducted in the United Kingdom,[14,22,38–40] Europe,[18,27,28] the United States[12,41,42] and Taiwan.[17] These studies also reported a statistically significant reduction in the prescribing of older ADD classes (SUs, insulin and TZDs) as initial therapy, with a significant increase in the prescription of newer classes. Of the newer ADD classes, DPP-4 inhibitors were the most commonly investigated, while the prescribing trends for SGLT2 inhibitors were only examined in one study at drug initiation since most studies were conducted before or soon after the introduction of SGLT2 inhibitors.[12]

Furthermore, the changes identified in the prescribing patterns of the first-intensifying therapy after initial metformin use in this study were consistent with the findings of multiple United Kingdom-based studies[14,15,22,43] and international studies conducted in the United States,[12] Korea[21] and Canada.[44] These studies showed that the prescribing of SUs and TZDs as first-intensifying or second-line therapy decreased over time, while the use of DPP-4 and SGLT2 inhibitors markedly increased. For instance, Dennis et al.[22] and Wilkinson et al.[14] documented that SU prescribing fell from 53% in 2010 to 29% in 2017, and from 63.04% to 30.01% over a similar time interval, respectively, compared to a reduction in SU prescribing in this study from 65.4% in 2010 to 41.8% in 2017 (29.8% in 2020), suggesting a slower reduction in SU use as first-intensifying therapy in Scotland than in other United Kingdom-based studies. Additionally, the results relevant to the overall consumption of ADDs are quite variable. For example, the proportional share of SGLT2 and DPP-4 inhibitor prescriptions in this study was higher (2016: 13.4% and 31.4%, 2020: 39.6% and 25.8%) than that reported in the United States (2016: 7% and 20%) and Canada (2016: 23.2% and 14.8%, 2020: 20.2% and 8%).[12,44]

Notably, this study revealed that SGLT2 inhibitors have surpassed SUs as the most prescribed first-intensifying therapy since 2019. However, previous studies conducted in the United Kingdom reported that DPP-4 inhibitors replaced SUs as the most common second-line therapy.[14–16,21,22,45] This difference could be related to the difference in the study time periods, with previous studies being conducted up to 2016[15] or 2017[14,16] compared to up to December 2020 in this study; this study was therefore more likely to capture prescriptions of SGLT2 inhibitors, which were introduced in the United Kingdom, including Scotland, in 2013.

The prescribing patterns of first-intensifying ADDs after initial SU use were less frequently examined in the literature since the majority of patients are usually started on metformin. Nevertheless, Grimes et al.[39] reported a similar result, with metformin and DPP-4 inhibitors identified as the most common ADDs added to initial SU use. Some studies reported metformin and insulin as the most common first-intensifying treatment after initial SU use.[22,46,47] Furthermore, according to Moreno Juste et al., [47]none of the patients who were

TABLE 5 Frequency and percentage of the individual class of antidiabetic drugs prescribed as a monotherapy for patients starting on sulphonylurea over the study period.

Antidiabetic group	2010 (N = 104)	2011 (N = 272)	2012 (N = 401)	2013 (N = 438)	2014 (N = 438)	2015 (N = 413)	2016 (N = 446)	2017 (N = 396)	2018 (N = 382)	2019 (N = 372)	2020 (N = 232)	Overall (N = 3894)
Biguanides	78 (75.00%)	218 (80.15%)	309 (77.06%)	332 (75.79%)	328 (74.89%)	324 (78.45%)	329 (73.77%)	272 (68.9%)	300 (78.53%)	275 (73.92%)	159 (68.53%)	2924 (75.09%)
DPP-4 inhibitors	9 (8.65%)	14 (5.15%)	41 (10.22%)	48 (10.96%)	52 (11.87%)	44 (10.65%)	69 (15.47%)	57 (14.39%)	29 (7.59%)	40 (10.75%)	25 (10.78%)	428 (10.99%)
Insulin	14 (13.46%)	21 (7.72%)	38 (9.48%)	53 (12.10%)	47 (10.73%)	34 (8.23%)	26 (5.83%)	32 (8.08%)	33 (8.64%)	21 (5.65%)	23 (9.91%)	342 (8.78%)
TZD	*	*	*	*	*	*	*	*	*	*	*	61 (1.57%)
SGLT2 inhibitors	0 (0.00%)	0 (0.00%)	0 (0.00%)	*	*	7 (1.69%)	14 (3.14%)	27 (6.82%)	18 (4.71%)	29 (7.80%)	22 (9.48%)	124 (3.18%)
Other[a]	*	*	*	*	*	*	*	*	*	*	*	15 (0.39%)

[a]Includes glucagon-like peptide receptor agonists, alpha-glucosidase, meglitinide.
*Those values were removed either because they are very small (<5) or to no disclose a very small value because of the high risk of patient's identification. 'Other' includes alpha-glucosidase inhibitors and meglitinide.Abbreviations: DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; SGLT2-i, sodium glucose co-transporter-2 inhibitors; TZD, thiazolidinedione.

initially treated with SUs received SGLT2 inhibitors as a first-intensifying therapy.

All above mentioned differences between this study and the previous studies are likely attributable to the variability in the time intervals of data collection, the clinical guidelines of each country, the available treatment options, the time of introduction of ADDs onto the market, the sample size of the study, and the data sources used.

The economic and clinical consequences of starting patients on multiple ADDs rather than following a stepwise approach are still uncertain.[48,49] It has been suggested that combination of therapies with complementary mechanisms of action would be beneficial in delaying disease progression.[49] Nevertheless, as documented in this study, combination therapy was prescribed to a much lesser extent compared to monotherapy for patients newly diagnosed with T2DM. The majority of patients received a metformin-based combination as an initial and first-intensifying therapy (after initial SU use). As stated previously, metformin is the only drug recommended by all clinical guidelines as a first-line therapy for newly diagnosed patients with T2DM; therefore, it is not surprising that metformin was a core treatment in the majority of combination regimens.

One of the main strengths of this study is that the analysed data were obtained from five different datasets containing a wide range of high-quality routinely collected health and health-related data for all patients who were registered with a general practitioner across Scotland. The study population was identified from the SCI-Diabetes database, which covers over 99.5% of patients with T2DM in Scotland, largely representative of the diabetic population in Scotland. In addition, the data used in this project covered a long period (from January 2010 to December 2020), with several years covering the period after the use of the newest antidiabetic class (SGLT2 inhibitors) began in Scotland (2013); thus, a greater proportion of patients using these newer antidiabetic classes could be included in the study, enabling a more reliable measurement of the potential impact of newer ADDs on the utilization of the older ADDs. Having high-quality data with national coverage of the population of Scotland increases both the reliability of the study findings and the generalizability of the results. Furthermore, cohort identification and classification were conducted based on specific criteria, which were discussed with clinicians to ensure their relevance to clinical practice. The selection of a 12-month period prior to drug initiation to define new ADD users minimizes the risk of misclassification of a prevalent user as an incident user. In addition, the regular continuous collection of prescribing data on a monthly basis in Scotland decreases the potential of treatment stage misclassification.

Nevertheless, this study has some limitations that should be considered. First, treatment intensification was defined based on the presence of further prescriptions of initial therapy (metformin or SUs) with or after the addition of new drug(s); thus, there is a possibility of misclassifying an intensifying therapy as a switching therapy. However, the definition was used in previous literature and was discussed with a diabetologist and a diabetes specialist pharmacist, therefore, it is unlikely that this impacted the study findings significantly. Second, despite the fact that dosage escalation of the same drug could be

TABLE 6 The change in prescribing pattern of the individual class of antidiabetic drug prescribed as monotherapy at stage of first intensification for patients starting on sulphonylureas.

Antidiabetic group	Absolute change	Relative change	Trend-test[a]
Biguanides	−6.47%	−8.63%	$Z = -2.60$, $p = \mathbf{0.009}$
DPP-4 inhibitors	2.13%	24.62%	$Z = 1.54$, $p = 0.123$
Insulin	−3.55%	−26.37%	$Z = -2.31$, $p = \mathbf{0.021}$
TZDs	−2.45%	−85.069%	$Z = -4.82$, $p < \mathbf{0.001}$
SGLT2 inhibitors	8.80%	1294.12%	$Z = 10.27$, $p < \mathbf{0.001}$
Other	−0.20%	−10.42%	$Z = 1.45$, $p = 0.147$

[a]Using Cochran–Armitage test for trend (each group was compared to all other groups). 'Other' includes alpha-glucosidase inhibitors and meglitinide.
Abbreviations: DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter-2; TZD, thiazolidinedione.

considered a treatment intensification, this study only examined intensification defined as the addition of a second ADD class (the National Institute of Health and Care Excellence guideline definition of intensification) because our study aim was to assess prescribing patterns in terms of the addition of another drug class. Additionally, using dose escalation as a measure for intensification is complex and not always accurate because of the possible misclassification of patients who increase their dose for treatment intensification and those who start with a low dose and optimize this gradually to minimize side effects. Third, patients who switched their initial drug were excluded because they were beyond the scope of this study, which focused on intensification only, which is very different from switching. Fourth, the time from diagnosis until treatment initiation or from treatment initiation until intensification was not measured because data related to the time of disease diagnosis (obtained from the SCI-Diabetes database) were incomplete and it has been reported that the date of diabetes diagnosis could be unreliable. Lastly, although the impact of the update in the clinical guideline and the introduction of newer ADD classes were discussed in this paper, they were not measured quantitively by performing a time-series analysis. However, given the many overlapping changes in clinical guidelines and the introduction of newer agents, along with the continually evolving evidence around the effectiveness of these newer agents on cardiovascular and renal outcomes, it would be very challenging to undertake a time-series analysis, which requires a clear intervention time point with enough follow-up time before and after each event.

In conclusion, prescribing patterns of ADDs for T2DM are rapidly changing towards the use of newer agents. The majority of T2DM patients received a single ADD as an initial and first-intensifying therapy. Metformin was by far the most commonly prescribed ADD over the study period as both a first-line and add-on therapy after initial SU use. Although SUs were the second most frequently prescribed ADD, their use has significantly decreased over time. In contrast, the use of newer ADDs (SGLT2 inhibitors and DPP-4 inhibitors) has significantly increased. Interestingly, SGLT2 inhibitors have replaced SUs as the most common first-intensifying therapy after initial metformin use since 2019. These results might reflect that the newer classes of ADD do indeed influence the utilization of the older ADDs.

The findings of this study have significant implications for clinical practice and the management of T2DM progression. Firstly, the persistent predominance of metformin as the initial ADD of choice reinforces current clinical guidelines that favour metformin due to its proven efficacy, safety profile, and positive impact on cardiovascular outcomes. The shift towards prescribing newer classes of ADDs, such as SGLT2 inhibitors and DPP-4 inhibitors, as first-intensification options over SUs and insulin reflects a paradigm shift in the management of T2DM. This trend suggests an increasing recognition of the benefits of these newer agents, which include lower risk of hypoglycaemia, weight neutrality or weight loss, and, for SGLT2 inhibitors, cardiovascular and renal benefits.

The increase in the use of combination therapy over time highlights an evolving approach to T2DM management, aiming to address the multifactorial nature of the disease more effectively and potentially slow disease progression by utilizing the complementary mechanisms of action of different ADDs. This is particularly relevant as the disease progresses and monotherapy becomes insufficient to maintain glycaemic control. Importantly, the transition towards newer antidiabetic classes and the strategic use of combination therapy could lead to better disease progression control, reduced risk of diabetes-related complications, and improved patient outcomes. However, it also necessitates ongoing education and adaptation by healthcare professionals to keep abreast of emerging evidence and integrate new treatment paradigms into clinical practice effectively.

Furthermore, the study's insights into prescribing patterns over a decade in Scotland provide a valuable benchmark for evaluating the impact of national guidelines and healthcare policies on diabetes management. It underscores the importance of data-driven approaches to optimize T2DM treatment pathways, which could inform future guideline revisions and clinical decision-making processes. Overall, the observed trends in ADD prescribing patterns reflect a proactive and individualized patient management approach, which is crucial for enhancing quality of life and reducing the burden of T2DM on patients and healthcare systems.

AUTHOR CONTRIBUTIONS

The authors confirm their contributions to the paper as follows. Study concept and design: Fatema Mahmoud, Amanj Kurdi, Tanja Mueller, Alexander Mullen; data request, cleaning, and preparation: Fatema Mahmoud, Amanj Kurdi, Tanja Mueller; data analysis: Fatema Mahmoud; interpretation of results: Fatema Mahmoud, Amanj Kurdi, Tanja

Mueller, Christopher Sainsbury, Gordon F. Rushworth; draft manuscript preparation: Fatema Mahmoud, Amanj Kurdi, Tanja Mueller, Alexander Mullen, Christopher Sainsbury, Gordon F. Rushworth. All authors reviewed and revised the manuscript and approved the final version.

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The authors have nothing to disclose.

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DATA AVAILABILITY STATEMENT

Data subject to third party restrictions.

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