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Adherence and persistence to novel glucose-lowering medications in persons with type 2 diabetes mellitus undergoing routine care

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ABSTRACT

Aims: To assess adherence and persistence to sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP1-RA), and dipeptidyl peptidase-4 inhibitors (DPP4i) in routine care.
Methods: Using retrospective healthcare data from the Stockholm region, Sweden, we evaluated new-users of these agents during 2015–2020. We investigated adherence (≥80 % of days covered by an active supply), persistence (no treatment gap ≥ 60 days), and predictors for non-adherence and non-persistence.
Results: We identified 24,470 new-users of SGLT2i (10,743), GLP1-RA (10,315), and/or DPP4i (9,488). Over 2.8 years median follow-up, the proportion demonstrating adherence was higher for SGLT2i (57 %) than DPP4i (53 %, comparison $p < 0.001$), and for GLP1-RA than DPP4i (54 % vs 53 %, $p < 0.001$). Similarly, persistence was higher for both SGLT2i and GLP-RA than DPP4i (respectively, 50 % vs 44 %, $p < 0.001$; 49 % vs 44 %, $p < 0.001$). Overall adherence was better among users who were older, had a history of high blood pressure, used more non-diabetic medications, had lower Hba1c, had better kidney function, and had completed secondary schooling or university. Women had worse adherence to SGLT2i and GLP1-RA than DPP4i.
Conclusions: We report adherence and persistence to SGLT2i, GLP1-RA and DPP4i in routine care, and identify prognostic factors that could inform implementation interventions to improve uptake of these important therapies.

1. Introduction

Diabetes is a worldwide problem, expected to affect more than 1 in 10 adults worldwide by 2035 [1]. Among people with diabetes the relative risk of heart failure and death is doubled compared to the age-matched general population [2,3], while the risk of myocardial infarction is increased up to 4.5-fold [2], and the risk of stroke is 6.5-fold greater [2]. Approximately half of all those with diabetes develop diabetic kidney disease, the most common cause of end-stage kidney disease worldwide, and an amplifier of cardiovascular risk [1]. The burden of these complications on individuals is reflected in a large economic impact, with diabetes associated with an estimated global annual cost of USD$1.3 trillion in 2015, comprising 1.8 % of the total global gross domestic product, and with costs expected to rise to $2.1 trillion by 2030 [4].

For many years, glycaemia-directed treatment has been based on lifestyle modification and metformin followed by second-line therapies as needed for glycaemic control [5,6]. In recent years, two medication classes, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1-RA), have been found to directly reduce the risk of adverse cardiovascular events and chronic kidney disease progression through apparent class-specific effects in

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pivotal trials [7,8]. In contrast, the other common guideline-recommended second-line class of medications, dipeptidyl peptidase-4 inhibitors (DPP4i), has not clearly demonstrated such direct benefits.

Benefits observed in clinical trials may not be completely realised in real-world care. The challenge of implementing evidence-based care has been clearly demonstrated with the slow uptake of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs), which were demonstrated more than two decades ago to significantly reduce the risk of kidney failure among patients with diabetic kidney disease [9–11], yet are only employed for 25–40 % of eligible patients [12]. Although some under-utilisation is due to under-prescribing, with many patients not being assessed for eligibility criteria [13], it is also due to sub-optimal medication adherence and persistence [14]. Adherence studies across a range of chronic disease medications have demonstrated non-adherence of 40–60 %, indicating that as many as 1 out of every 2 medication doses is not being taken as prescribed [15]. Studies of adherence to glucose-lowering therapies have reported a wide range of adherence proportions, between 36 % and 93 % [16], suggesting that adherence is highly context-dependent.

In this retrospective cohort study, we examine adherence and persistence for three glucose-lowering agents, commonly used as second-line options after the guideline-indicated first-line use of metformin, in the region of Stockholm, Sweden. We selected three second-line treatment options to allow comparison between agents employed in similar contexts. We speculated that the uptake of these agents would increase over the time studied, reflecting greater familiarity with their use, and that adherence and persistence for SGLT2i and GLP1-RA may be higher than for DPP4i due to greater evidence of cardiovascular and kidney protection, and hence greater clinician and patient enthusiasm for their use. We also studied prognostic factors of non-adherence and non-persistence to better identify those at highest risk.

2. Subjects and Methods

2.1. Data sources

The Stockholm CREAtinine Measurements (SCREAM) project is a database collecting continually updated information of healthcare contacts from all residents in the region of Stockholm (with a population of approximately 2.3 million citizens) between the 1st of January 2006 and the 31st of December 2021 [17,18]. Sweden has a policy of universal healthcare access, where the Government covers almost the totality of the cost of prescribed medications. Swedish citizens are asked for co-payment of up to approximately 200 EUR per year for the totality of medications prescribed, and thereafter all subsequent prescriptions are provided for free. There is also an exemption from co-payment for those with financial difficulty. By linking laboratory data with other administrative databases and national registries, we were able to ascertain, among other things, demographics, complete collection of filled prescriptions at Swedish pharmacies, comorbidities, and vital and socioeconomic status.

2.2. Study Design, exposure and time zero

We included all patients $\geq$ 18 years old with a first-ever dispensation of either an SGLT2i, a GLP1-RA, or a DPP4i between the 1st of January 2015 and the 31st of December 2020, which allowed a minimum of 12 months of retrospective administrative follow-up for all included participants before the study end-date of 31st December 2021. The first dispensation for a drug of interest served as the index date and start of follow-up (time zero) for each participant. We excluded patients with the following conditions: (i) not residents of Stockholm at time of drug initiation; (ii) history of diabetes mellitus type 1 or two recorded diagnoses of gestational diabetes; (iii) history of kidney replacement therapy (iv) history of end-stage illness (v) history of severe pancreatic disorder, (vi) history of recreational drug misuse; and (vii) those who died on the day of drug initiation. In addition, among GLP1-RA initiators, we excluded individuals using liraglutide if the primary indication for therapy was obesity rather than diabetes. Cohorts were non-mutually exclusive, such that the same individual may have started one agent and then started another agent later during the observation period, and would therefore be included in each cohort, with a separate index date for each agent that was initiated. Detailed definitions of eligibility are presented in Table S1 of the Supplementary Appendix.

2.3. Covariates

Covariates were derived at the time of drug initiation and included age, sex, laboratory tests (baseline estimated glomerular filtration rate [eGFR], hemoglobin A1c [HbA1c,] and albuminuria levels), comorbidities (history of cardiovascular disease, diagnosis of high blood pressure, heart failure and diabetes complications), ongoing use of selected diabetes and non-diabetes drugs, time since first-ever diabetes drug recorded, number of prescription drugs in the previous year, calendar year, and a range of socioeconomic factors (highest attained level of education, living status of cohabitating or living alone, and income above or below the stratum median). Definitions for these covariates are also detailed in Table S1. Baseline HbA1c was calculated as the average of all HbA1c measurements in the year prior to the index date. Baseline eGFR was the average eGFR of all outpatient creatinine measurements in the year prior to the index date and determined using the 2009 CKD-EPI formula without the coefficient of race [19]. Baseline eGFR was thereafter categorised according to Kidney Disease: Improving Global Outcomes (KDIGO) G stages[20]. Baseline albuminuria assessment considered the most recent measurement of urinary albumin to creatinine ratio (ACR) or urinary dipstick prior to the index date, and was categorised according to KDIGO A stages [20].

2.4. Study outcomes

The primary study outcomes were adherence and persistence over the full duration of follow-up. We also assessed these outcomes over the first 12 and 24 months of therapy to better allow comparison to existing literature, which are predominantly limited to 12 months adherence data.

We also examined the trends in the number of new-users over time, the baseline prognostic factors for non-adherence and non-persistence, and the proportion restarting within 3 months after therapy discontinuation. Patients were followed from index date until event, emigration, death, or administrative censoring (December 31st 2021). Emigration, death or administrative censoring were not counted as non-persistence events.

2.5. Defining adherence and persistence

We defined adherence as achieving $\geq$ 80 % proportion of days covered (PDC) by an active medication supply [15] determined from repeated dispensations at Swedish pharmacies. An adherence definition of $\geq$ 80 % PDC is an established threshold in pharmacoepidemiology to define "good adherence" [21]. Non-adherence was defined as a PDC of $<$ 80 %. We assumed the standard dose of one pill per day for SGLT2i and DPP4i, and determined package durations for each of the commercial formulations of GLP1-RA. Details on unit supply per medication package can be found in Table S2. Medication switching within the same class was considered as continuation of that class.

Persistence, i.e. continuing drug treatment without a long-term interruption, was defined as the absence of a gap in dispensed medication supply of 60 days or more (referred to as the grace period), which is a common definition in diabetes medication adherence studies [14]. Non-persistence (i.e. discontinuation) was defined when such a treatment gap was observed. The date of non-persistence was defined as 60 days after the estimated end of the patient's drug supply. Among

discontinuers, we investigated the proportion who restarted treatment, defined as dispensation of the drug of interest again within 3 months after the estimated date of therapy non-persistence.

2.6. Assessment of prognostic factors for Non-Adherence and Non-Persistence

Prognostic factors of interest for non-adherence and non-persistence were age (in increments of 10 years), sex, baseline eGFR (in increments of 10 mL/min/1.73 m^2), baseline HbA1c (in increments of 3.1 % / 10 mmol/mol), baseline ACR categories, history of cardiovascular disease, diagnosis of high blood pressure, or history of diabetes complications; metformin use, sulfonylurea use, insulin use, use of other diabetes drugs, number of non-diabetic drugs dispensed in the past year (including short- and long-term medication use), highest level of attained education, living status, and income.

2.7. Statistical analyses

Categorical variables are presented as proportions and continuous variables are presented either as the mean (standard deviation) or median (interquartile range), depending on the distribution. Adherence and persistence were presented as unadjusted proportions with 95 % confidence intervals (CI). The comparison of adherence between agents, and therapy restart between agents, were studied using logistic regression models yielding odds ratios (OR) with 95 %CI. Persistence comparisons between agents were studied using Cox regression models yielding hazard ratios (HR) with 95 % CI. When comparing adherence, persistence, and restarting between drugs, DPP4i served as the reference group, as these agents have been in clinical use for a longer period of time but do not show the same cardiovascular and kidney benefits demonstrated by SGLT2i and GLP1-RA. Robust regressions were used to take into account that individuals could occur in both compared groups. Multivariable analyses assessed differences in adherence, persistence or therapy restart while adjusting for all covariates. For multivariable analyses of restarting, robust estimation was not possible due to dimensionality of data, as the limited sample size did not allow robust standard error estimation. Cumulative incidence functions were used to graphically depict discontinuation over time, accounting for the competing risk of death using an Aalen-Johansen estimator.

Prognostic factors for non-adherence and non-persistence were assessed through univariable logistic regression and Cox regression, respectively.

As a sensitivity analysis, we used a non-persistence grace period of 30 rather than 60 days. As supporting analysis, we computed results stratified on whether individuals initiated therapy in the period 2015–2017 or in the period 2018–2020. We hypothesised that adherence and persistence would be higher in the later period after the first years of unfamiliarity with the medications. All analyses were performed in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) [22]. All annotated R codes can be found at https://github.com/rjjanse.

3. Results

3.1. Baseline characteristics

We included 24,470 unique individuals, of whom 10,743 initiated an SGLT2i, 10,315 initiated an GLP1-RA, and 9,488 initiated a DPP4i (Figure S2) including 5,397 new-users represented in more than one group. Baseline characteristics are presented in Table 1 and S3. The mean age of our population was 63 years, but was higher among DPP4i users (67 years). Overall, 38 % of participants were women, but this proportion was lower among SGLT2i new-users (33 %) and higher among GLP1-RA new-users (42 %). The median eGFR was 88 mL/min/1.73 m^2 and 76 % had an eGFR of $\geq$ 60 mL/min/1.73 m^2. A fifth (19 %) of participants had an HbA1c $\geq$ 9 % (Hba1c $\geq$ 75 mmol/mol) at time of therapy initiation. The majority had a diagnosis of high blood pressure (71 %) and about half had a history of diagnosed diabetes complications (49 %). The most frequently used concomitant drug was metformin (77 %).

3.2. Medication class use over time

The numbers of new-users of these medications increased substantially throughout the study period. The initially stronger growth of DPP4i tapered towards the end of the study period while the growth in SGLT2i and GLP1-RA (Table 1 and Fig. 1) showed no signs of abating. By 2020 there were more than twice the number of new-users for SGLT2i and GLP1-RA than for DPP4i.

3.3. Adherence

The median length of follow-up was 2.8 years (interquartile range 1.8–4.1). Over the total duration of observation, the proportion of people demonstrating adherence was 57 % for SGLT2i (95 % CI 56–58 %), 54 % for GLP1-RA (95 %CI 53–55 %), and 53 % for DPP4i (95 %CI 52–54 %; Table 2). Adherence at 12 and 24 months are presented in Table 2. Figures S3-S5 show the adherence distribution across medication classes. On multivariable analysis, both SGLT2i and GLP1-RA were associated with better odds of non-adherence at 24 months and over the full duration of follow-up (Table 2).

3.4. Persistence

Over the total duration of observation, 50 % (95 %CI 49–51 %) of patients using SGLT2i remained on therapy, compared to 49 % (48–50 %) of patients using GLP1-RA and 44 % (43–45 %) of patients using DPP4i (Table 2). Of note, persistence could be higher than adherence if individuals had treatment gaps not exceeding the 60-day grace period, which would impact adherence without meeting non-persistence criteria. Non-persistence was observed primarily during the first year of therapy, where persistence dropped to 65 % (64–66 %) for SGLT2i, 66 % (65–67 %) for GLP1-RA and 68 % (67–69 %) for DPP4i (Table 2 and Fig. 2 and S6). The risk of therapy discontinuation was similar across agents throughout, with no difference over the duration of follow-up, but was greater for SGLT2i or GLP1-RA compared to DPP4i on univariable analysis at 12 months (Table 2). Multivariable analysis, however, showed better persistence for these agents compared to DPP4i at 24 months and at the end of follow-up.

3.5. Restarting after therapy discontinuation

Among those who stopped therapy, the proportions of re-starters within 3 months were 26 % for SGLT2i (95 %CI 25–27 %), 34 % for GLP1-RA (33–36 %) and 20 % for DPP4i (19–21 %). (Table S5). Restarting of therapy was more likely to occur for SGLT2i (univariable OR 1.39, 95 %CI 1.27–1.53, $p < 0.001$) and GLP1-RA new-users (univariable OR 2.06, 95 %CI 1.89–2.25, $p < 0.001$) compared with DPP4i.

3.6. Prognostic factors for Non-Adherence and Non-Persistence

Worse adherence and persistence for all three medications was seen among those who were younger, with no history of high blood pressure, with fewer non-diabetes medications, and lower attained education, as well at those with a higher baseline HbA1c (Table 3). For new-users of SGLT2i and GLP1-RA worse adherence and persistence were observed among females, those not using metformin, and those who had an income lower than the median. For new-users of SGLT2i and DPP4i, the absence of a history of atherosclerotic cardiovascular disease and heart failure were associated with worse adherence and persistence. Lower eGFR was associated with non-adherence for all three agents and non-

Table 1
Baseline characteristics of new-users of SGLT2i, GLP1-RA, or DPP4i in Sweden between 2015 and 2020*.

	Overall Unique Individuals	SGLT2i New-Users	GLP1-RA New-Users	DPP4i New-Users
Number of individuals	24,470	10,743	10,315	9,488
Age, mean (SD), y	63 (13)	63 (11)	60 (12)	67 (13)
Age group, n (%)				
<50 years	3,460 (15)	1,286 (13)	1,987 (20)	923 (10)
50–59	5,745 (25)	2,739 (27)	2,809 (28)	1,788 (20)
60–69	6,436 (28)	3,213 (31)	2,721 (27)	2,247 (25)
70–79	5,618 (24)	2,447 (24)	2,037 (20)	2,544 (28)
≥80	2,081 (9)	559 (6)	362 (4)	1,485 (16)
Women, n (%)	9,373 (38)	3,579 (33)	4,294 (42)	3,711 (39)
eGFR, median [IQR], ml/min/1.73 m^2	88 [71, 100]	90 [77, 100]	91 [75, 102]	82 [60, 96]
eGFR category, n (%)				
G1 (≥90 ml/min/ 1.73 m^2)	10,174 (42)	4,882 (45)	4,841 (47)	3,104 (33)
G2 (60–89 ml/min/ 1.73 m^2)	8,340 (34)	4,051 (38)	3,199 (31)	3,256 (34)
G3a (45–59 ml/min/ 1.73 m^2)	2,087 (8)	602 (6)	725 (7)	1,265 (13)
G3b (30–44 ml/min/ 1.73 m^2)	1,078 (4)	149 (1)	401 (4)	746 (8)
G4 (15–29 ml/min/ 1.73 m^2)	201 (1)	14 (0)	61 (1)	153 (2)
G5 (<15 ml/min/ 1.73 m^2)	10 (0)	0 (0)	3 (0)	9 (0)
Missing	2,580 (10)	1,045 (10)	1,085 (10)	955 (10)
HbA1c, median (IQR), %	7.7 [7.0, 8.7]	7.9 [7.2, 8.9]	7.9 [7.1, 9.0]	7.5 [6.9, 8.5]
HbA1c category, n (%)				
<7.0 % (<53 mmol/ mol)	5,497 (22)	1,943 (18)	2,046 (20)	2,305 (24)
7.0–7.4 % (53–57 mmol/mol)	3,508 (14)	1,506 (14)	1,234 (12)	1,590 (17)
7.5–7.9 % (58–63 mmol/mol)	3,718 (15)	1,752 (16)	1,516 (15)	1,579 (17)
8.0–8.4 % (64–68 mmol/mol)	2,320 (10)	1,199 (11)	1,021 (10)	910 (10)
8.5–8.9 % (69–74 mmol/mol)	2,172 (9)	1,077 (10)	1,088 (10)	750 (8)
≥9.0 % (≥75 mmol/ mol)	4,614 (19)	2,212 (21)	2,334 (23)	1,426 (15)
Missing	2,641 (11)	1,054 (10)	1,076 (10)	928 (10)
ACR, median [IQR], mg/ mmol	2 [1,5]	2 [1,4]	2 [1,5]	2 [1,6]
ACR category, n (%)				
A1 (<3 mg/mmol)	9,130 (37)	4,257 (40)	3,983 (39)	3,464 (36)
A2 (3–30 mg/mmol)	3,669 (15)	1,549 (14)	1,601 (16)	1,541 (16)
A3 (>30 mg/mmol)	963 (4)	381 (4)	394 (4)	428 (4)
Missing	10,708 (44)	4,556 (42)	4,337 (42)	4,055 (43)
Comorbidities, n (%)				
Atherosclerotic cardiovascular disease, composite of:	6,622 (27)	3,341 (31)	2,385 (23)	2,651 (28)
Acute coronary syndrome	2,723 (11)	1,600 (15)	927 (9)	974 (10)
Other ischemic heart disease	4,561 (19)	2,464 (23)	1,624 (16)	1,743 (18)
Stroke	1,591 (6)	689 (6)	562 (5)	733 (8)
Other cerebrovascular disease	1,593 (6)	694 (6)	555 (5)	729 (8)
Peripheral vascular disease	984 (4)	466 (4)	353 (3)	425 (4)
Heart failure	2,589 (11)	1,292 (12)	839 (8)	1,096 (12)
High blood pressure	17,300 (71)	7,783 (72)	7,290 (71)	6,811 (72)
Diabetic complications	12,066 (49)	5,653 (53)	5,088 (49)	4,909 (52)
Diabetes medication, n (%)				
Any	20,283 (83)	9,545 (89)	8,830 (86)	7,814 (82)
Metformin	18,786 (77)	8,694 (81)	7,697 (75)	7,128 (75)
Sulfonylureas	4,743 (19)	2,104 (20)	1,790 (17)	2,086 (22)
GLP1-RAs	8,379 (34)	1,677 (16)	10,315 (100)	277 (3)
SGLT2i	8,120 (33)	10,743 (100)	1,181 (11)	526 (6)
DPP4i	10,120 (41)	2,181 (20)	1,878 (18)	9,488 (100)
Insulin	5,291 (22)	2,434 (23)	3,172 (31)	1,445 (15)
Other drugs for diabetes (glitazones, glinides, acarbose)	712 (3)	330 (3)	327 (3)	289 (3)
Time since first-ever diabetes drug, n (%)				
<1 year	1,780 (9)	658 (7)	720 (8)	706 (9)
1–3 years	3,264 (16)	1,364 (14)	1,387 (16)	1,311 (16)
3–5 years	2,989 (15)	1,330 (14)	1,304 (15)	1,192 (15)
5–7 years	2,766 (14)	1,343 (14)	1,159 (13)	1,132 (14)
>7 years	9,459 (47)	4,800 (51)	4,089 (47)	3,689 (46)
No. of prescribed drugs in previous year, n (%)				
0–5	3,353 (14)	1,221 (11)	1,175 (11)	1,303 (14)
6–10	9,144 (37)	4,004 (37)	3,637 (35)	3,508 (37)
11–15	6,588 (27)	2,961 (28)	2,957 (29)	2,541 (27)
>15	5,385 (22)	2,557 (24)	2,546 (25)	2,136 (22)
Calendar year of medication initiation, n (%)				
2015	2,313 (10)	455 (4)	716 (7)	1,209 (13)
2016	2,755 (11)	785 (7)	839 (8)	1,403 (15)
2017	3,370 (14)	1,145 (11)	1,229 (12)	1,618 (17)
2018	4,582 (19)	2,067 (19)	1,828 (18)	1,778 (19)
2019	5,354 (22)	2,748 (26)	2,443 (24)	1,927 (20)
2020	6,096 (25)	3,543 (33)	3,260 (32)	1,553 (16)
Socioeconomic characteristics, n (%)				
Highest Educational Level				
Compulsory school	5,860 (24)	2,584 (24)	2,282 (22)	2,448 (26)
Secondary school	10,352 (42)	4,543 (42)	4,571 (44)	3,856 (41)
vUniversity	7,296 (30)	3,178 (30)	3,172 (31)	2,718 (29)
Missing	962 (4)	438 (4)	290 (3)	466 (5)
Living status				
Living alone	9,871 (40)	4,201 (39)	4,032 (39)	4,016 (42)
Cohabitating	14,263 (58)	6,394 (60)	6,172 (60)	5,311 (56)

(*continued on next page*)

Table 1 (*continued*)

	Overall Unique Individuals	SGLT2i New-Users	GLP1-RA New-Users	DPP4i New-Users
Missing	336 (1)	148 (1)	111 (1)	161 (2)
Income				
Below stratum median	12,094 (49)	5,296 (49)	5,101 (50)	4,661 (49)
Above stratum median	12,040 (49)	5,299 (49)	5,103 (50)	4,666 (49)
Missing	336 (1)	148 (1)	111 (1)	161 (2)

SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase-4 inhibitors; SD, standard deviation; eGFR, estimated glomerular filtration rate; ACR, albumin-creatine ratio.
*Individuals may be present in more than one group.

persistence for GLP1-RA and DPP4i.

3.7. Differences in outcomes between 2015–2017 and 2018–2020

The proportions demonstrating adherence, persistence, and medication restarting at 12 and 24 months remained similar between individuals who initiated SGLT2i, GLP1-RA, or DPP4i in the early period of 2015–2017 or during 2018–2020 (Figures S9-10 and S12).

4. Discussion

We investigated patterns of adherence and persistence for SGLT2i, GLP1-RA and DPP4i in Stockholm, Sweden, during 2015–2021. This period saw increasing use of SGLT2i and GLP1-RA, reflecting their integration into routine clinical practice. Over half of the population showed non-adherence or discontinued treatment over a median observation period of 2.8 years. There was an initial greater drop for SGLT2i and GLP1-RA adherence and persistence compared to DPP4i, but over the full duration of follow-up there was better adherence with SGLT2i on univariable analysis, and better adherence and persistence for both SGLT2i and GLP1-RA compared to DPP4i after adjustment for covariates. It was not clear which covariates most significantly contributed to this adjustment, although new-users of SGLT2i and GLP1-RA tended to be younger and to have higher HbA1c at baseline, which were both prognostic indicators for worse adherence and persistence that may have been negated during adjustment. The identification of factors associated with non-adherence and non-persistence may help identify those at risk but does not necessarily explain the causative factors leading to non-adherence or non-persistence. Other sub-populations at greater risk of non-adherence included younger patients, women, those with fewer indicators of chronic disease burden, and those with lower educational level and income.

Non-adherence with diabetes medications is associated with worse glycaemic control, a greater risk of diabetes complications, and increased healthcare costs [14]. While the optimum adherence level to achieve clinical benefit has not been clearly defined, studies of medications for cardioprotection or glycaemic management have suggested that each 10 % increase in adherence can have a statistically important effect on patient-important outcomes such as cardiovascular events and death [23–26]. The adherence proportions observed in our cohort are lower than those typically reported in large randomised controlled trials. For example, the dedicated SGLT2i diabetic kidney disease trial CREDENCE reported adherence of 84 % over a median of 2.6 years [27], while the SUSTAIN-6 trial of semaglutide reported 87 % adherence [28].

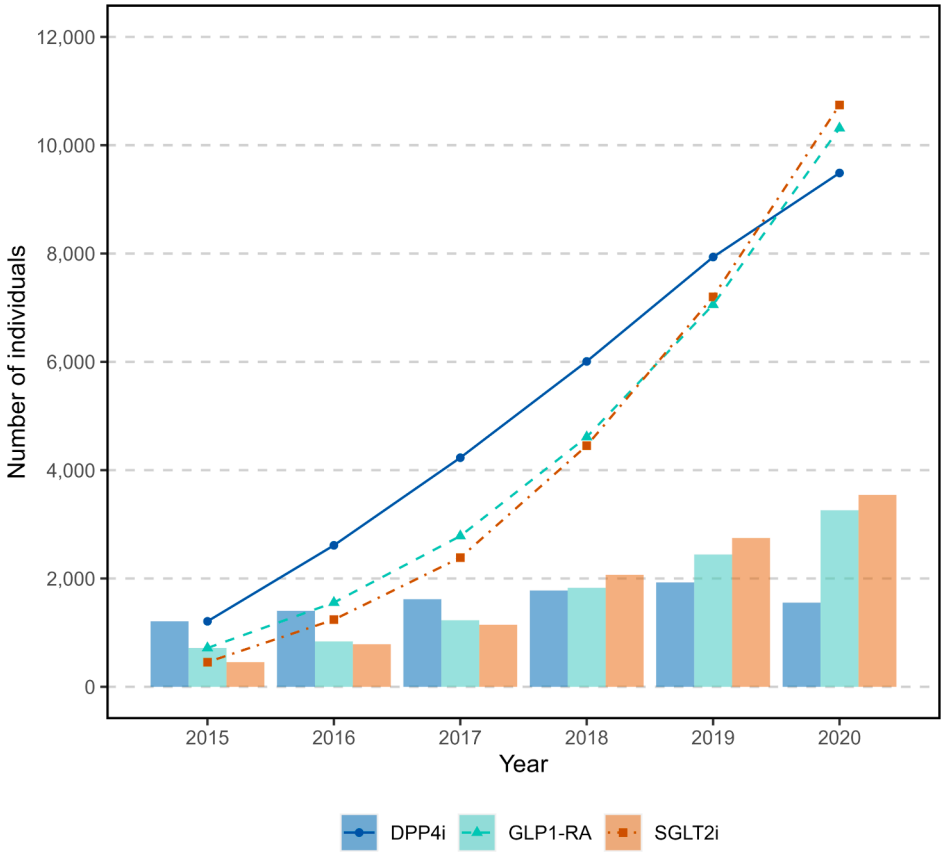


Fig. 1. Number of new-users of SGLT2i, GLP1-RA, or DPP4i by calendar year from 2015 to 2020, and cumulative count of new users* SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase-4 inhibitors *Lines show cumulative count, bars show individuals initiated per year.

Table 2
Number of events, proportion, and odds ratios for non-adherence (<80 % of days covered by an active supply) to SGLT2i, GLP1-RA, or DPP4i, and number of events, proportion and hazard ratios for non-persistence (treatment gap ≥ 60 days).

Non-Adherence

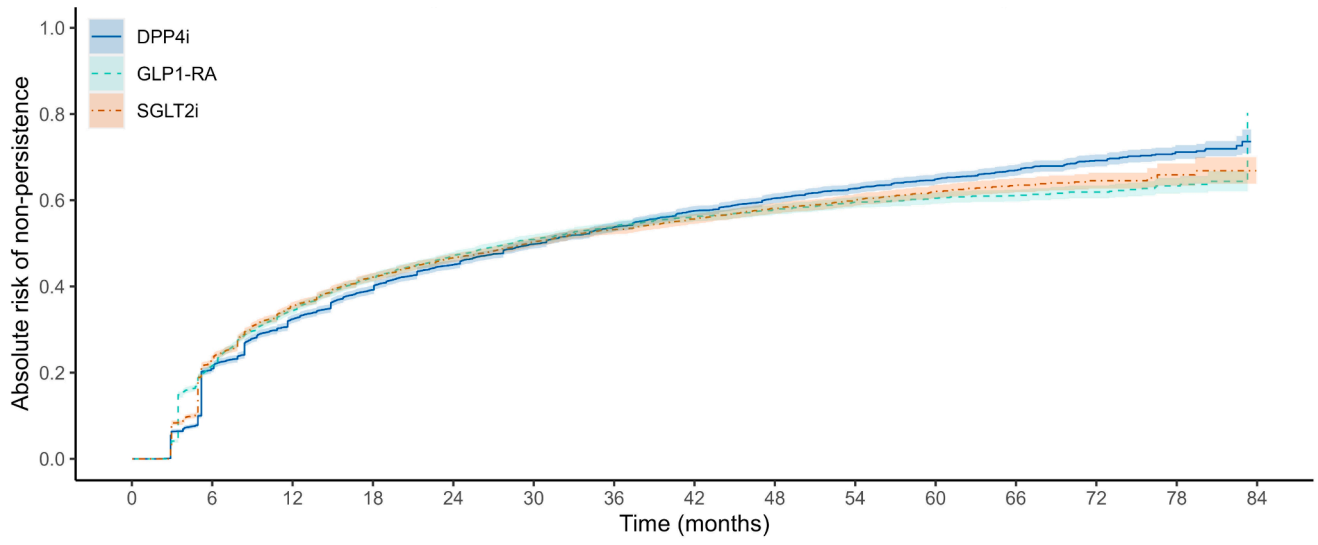
Drug	Number of Individuals	Non-Adherence	% (95 % CI) *	Univariable OR Relative to DPP4i (95 % CI; p value)	Multivariable OR Relative to DPP4i** (95 % CI; p value
SGLT2i	10,743				
Over 12 months		3,786	35 (34–36)	1.23 (1.16–1.30; p < 0.001)	0.98 (0.79–1.21; p = 0.84)
Over 24 months		4,278	40 (39–41)	1.06 (1.00–1.12; p = 0.041)	0.73 (0.60–0.90; p = 0.003)
Over full follow-up		4,574	43 (42–44)	0.83 (0.78–0.88; p < 0.001)	0.67 (0.54–0.82; p < 0.001)
GLP1-RA	10,315				
Over 12 months		4,008	39 (38–40)	1.43 (1.35–1.52; p < 0.001)	0.75 (0.57–0.99; p = 0.04)
Over 24 months		4,396	43 (42–44)	1.19 (1.12–1.26; p < 0.001)	0.51 (0.39–0.67; p < 0.001)
Over full follow-up		4,737	46 (45–47)	0.95 (0.90–1.00; p = 0.064)	0.44 (0.34–0.57; p < 0.001)
DPP4i	9,488				
At 12 months		2,916	31 (30–32)	1 (Reference)	1 (Reference)
At 24 months		3,645	38 (37–39)	1 (Reference)	1 (Reference)
Over full follow-up		4,482	47 (46–48)	1 (Reference)	1 (Reference)

Non-Persistence

Drug	Number of Individuals	Non-Persistence	% (95 % CI) *	Univariable HR Relative to DPP4i (95 % CI; p value)	Multivariable HR Relative to DPP4i** (95 % CI; p value)
SGLT2i	10,743				
Over 12 months		3,789	35 (34–36)	1.12 (1.07–1.18; p < 0.001)	0.90 (0.77–1.06; p = 0.2)
Over 24 months		4,780	44 (44–45)	1.07 (1.02–1.11; p < 0.001)	0.80 (0.70–0.92; p < 0.001)
Over full follow-up		5,376	50 (49–51)	0.99 (0.95–1.03; p = 0.66)	0.77 (0.68–0.87; p < 0.001)
GLP1-RA	10,315				
Over 12 months		3,535	34 (33–35)	1.09 (1.04–1.14; p < 0.001)	0.66 (0.54–0.81; p < 0.001)
Over 24 months		4,625	45 (44–46)	1.07 (1.02–1.11; p < 0.001)	0.61 (0.51–0.73; p < 0.001)
Over full follow-up		5,248	51 (50–52)	0.98 (0.94–1.02; p = 0.24)	0.57 (0.48–0.66; p < 0.001)
DPP4i	9,488				
Over 12 months		3,063	32 (31–33)	1 (Reference)	1 (Reference)
Over 24 months		4,158	44 (43–45)	1 (Reference)	1 (Reference)
Over full follow-up		5,357	56 (55–57)	1 (Reference)	1 (Reference)

CI, confidence interval; OR, odds ratio; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP1-RA, glucagon-like peptide-1 receptors agonists; dipeptidyl peptidase 4 inhibitors.
* Based upon number of events divided by participants.
** Adjusted for age, sex, average HbA1c, average eGFR, acute coronary syndrome, other ischemic heart disease, stroke, other cerebral vascular disease, peripheral vascular disease, heart failure, high blood pressure, diabetic complications, valve disorders, atrial fibrillation, other arrhythmias, chronic obstructive pulmonary disease, other lung disease, venous thromboembolism, cancer in previous year, liver disease, fracture in previous year, use of any diabetes medication, metformin, sulfonylureas, GLP1-RA, SGLT2i, DPP4i, insulin, other diabetes drugs, beta-blockers, calcium channel blockers, diuretics, ACEi/ARBs, lipid-lowering drugs, digoxin, nitrates, antiplatelets, anticoagulants, beta-2 agonist inhalants, anticholinergic inhalants, glucocorticoid inhalants, oral glucocorticoids, NSAIDs, and opioids, time since first ever diabetes medication, number of prescription drugs in previous year, healthcare access for inpatient cardiovascular causes, inpatient type 2 diabetes related causes, inpatient non-cardiovascular/type 2 diabetes related causes, outpatient cardiovascular causes, outpatient type 2 diabetes related causes, and outpatient non-cardiovascular/type 2 diabetes related causes, year of initiation, education, living status, and income.

Clinical trial settings differ from real-world settings, in the selection of patients with the opportunity and willingness to participate, and the benefit of dedicated follow-up support structures [29]. Real-world adherence studies in chronic disease medications commonly report adherence of 40–60 % [15]. However, results vary between different settings, including in other diabetes adherence cohorts examining SGLT2i, GLP1-RA and DPP4i. Among a cohort of new-users of these three medications in Hungary in 2014–2016, the proportions demonstrating adherence at 12 months were comparable to the present study [30], while a study of Italian new-users of SGLT2i or GLP1-RA in 2007–2017 found higher persistence than what we observed in our cohort at 71 % and 76 %, respectively [31]. In comparison, persistence at 12 months in a cohort of people in the US in 2014–2015 was lower than in our study at 57–68 % for SGLT2i, 52 % for GLP1-RA, and 54 % for DPP4i, while adherence was even lower than persistence [32]. As with our study, the US study demonstrated superior adherence with SGLT2i compared to the other agents. While differences in medication subsidisation costs between countries can play a major role in medication use [33], adherence is the result of a complex interplay of factors related to the medications, individuals, clinicians and healthcare



At risk															
SGLT2i	10,743	8,157	6,763	4,948	3,615	2,654	1,912	1,381	820	536	344	239	107	41	1
GLP1-RA	10,315	8,022	6,638	4,853	3,622	2,747	2,023	1,520	1,052	743	506	355	210	100	2
DPP4i	9,488	7,339	6,147	4,976	4,021	3,176	2,421	1,844	1,378	1,016	717	492	267	119	1

Fig. 2. Cumulative incidence function of non-persistence (treatment gap ≥ 60 days) to SGLT2i, GLP1-RA, or DPP4i after drug initiation, over the duration of follow-up. SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase-4 inhibitors.

systems, producing a range of potential systematic differences between settings.

The prognostic factors for non-adherence and non-persistence seen in our study have clinical implications. The finding of worse adherence among women are consistent with other chronic disease adherence studies [34]. The management of barriers that may disproportionately affect women, such as the increased risk of genital fungal infections with SGLT2i [35], may help address the adherence gap for these particular agents. The worse adherence in younger persons is also consistent with findings in some [32,36,37], but not all [30,38], cohorts of people with diabetes. Together with the findings of worse adherence among those without hypertension and with fewer non-diabetes medications, the lower adherence in younger individuals may indicate people less accustomed to managing multi-agent chronic disease regimens, who may need additional education and support. The association between poor adherence and lower educational level is consistent with existing evidence [39] and warrants ongoing efforts to engage those with lower health literacy.

While we were able to identify overall factors indicating greater risk of non-adherence and non-persistence, the study did not examine reasons for discontinuation at the patient level, or the interventions most likely to address this. Existing literature provides valuable insights; the primary reasons for missing or stopping chronic disease medications can include forgetfulness, competing priorities, and a lack of information [40]. Potential mitigating strategies include further communication skills training for prescribers [41], efforts to improve patient health literacy, strengthen the therapeutic alliance between patients and doctors, and provide long-term monitoring and follow-up of medication-taking behaviours [42]. Medication side effects may also be a significant barrier to adherence [40]. We were not able to ascertain why patients discontinued medications and so can only speculate at the reasons underscoring the greater initial decline in SGLT2i and GLP1-RA adherence compared to DPP4i. Further studies could investigate whether discontinuation is associated with the occurrence of adverse events and whether these are more common with these two agents, suggesting a need for improved patient follow-up and support during this time. There may be drug-specific factors to address, such as counselling about genital hygiene and the importance of maintaining hydration for SGLT2i [43,44], or the provision of advice about dose titration, potential gastrointestinal side effects and complementary dietary changes, as well as reviewing cost subsidization [45], and considering a weekly dosing schedule [31], for GLP1-RA.

The main strengths of the study were the complete and contemporary coverage of health trajectories for nearly all citizens with diabetes in the region of Stockholm, which ensures representativeness, and which provides the opportunity to study medication-taking behaviours with less bias from medication access issues. Another strength is the richness and granularity of clinical information to identify prognostic predictors and evaluate study outcomes with precision, including the use of dispensation data which is a more effective source to ascertain adherence than prescription claims. The duration of follow-up is another advantage over other studies, which primarily limited their analysis to the first 12 months of therapy. Nonetheless, the study also had some limitations. We were unable to identify patients with primary non-adherence, defined as being prescribed these medications but never filling the first prescription at the pharmacy, which was observed among 30–34 % of patients in a US study of these agents [46]. The study also did not include combination formulations (metformin combined with a DPP4i or an SGLT2i, or a DPP4i combined with an SGLT2i), and may therefore have falsely attributed non-adherence or non-persistence to switching to combination therapy. In Sweden, however, combination formulations comprise a minority of all prescriptions, at 2.5 % of all SGLT2i prescriptions and 12.4 % of all DPP4i prescriptions; no combination therapy exists for GLP1-RA [47]. The reasons for medication discontinuation were also not available, including whether the decision was initiated by the patient or clinician. Analysis of the adherence and persistence patterns associated with different HbA1c trajectories may be insightful, but was beyond the scope of the study. Medication use may also have been influenced by intercurrent developments in diabetes care. For example, it is possible that the dissemination of guidelines supporting SGLT2i and GLP1-RA use, such as the consensus report of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes in 2019 [48], or the ADA Guidelines in January 2021 [49], or the results of SGLT2i and GLP1-RA kidney and cardiovascular outcome trials referenced in these guidelines, may have led to class switching to SGLT2i or GLP1-RA, or greater clinician

Table 3
Prognostic factors for non-adherence (<80 % of days covered by an active supply) and non-persistence (treatment gap ≥ 60 days) to SGLT2i, GLP1-RA, or DPP4i after initiation until end of follow-up*.

Non-Adherence; Univariable Odds Ratios (95%CI)			
Prognostic factor	**SGLT2i**	**GLP1-RA**	**DPP4i**
Age per +10 years	0.93 (0.90-0.96)	0.89 (0.86-0.92)	0.81 (0.78-0.83)
Women vs. men	**1.22 (1.13-1.33)**	**1.16 (1.07-1.26)**	1.03 (0.95-1.13)
eGFR per -10 mL/min/1.73m^2	**1.02 (1.01-1.04)**	**1.04 (1.03-1.05)**	**1.06 (1.05-1.07)**
HbA1c per +3.1% (+10 mmol/mol)	**1.04 (1.02-1.05)**	**1.06 (1.04-1.07)**	**1.06 (1.05-1.08)**
ACR category A2 vs. A1	**1.21 (1.08-1.37)**	1.08 (0.96-1.22)	1.06 (0.93-1.20)
ACR category A3 vs. A1	0.80 (0.64-1.01)	**1.35 (1.09-1.67)**	0.86 (0.69-1.08)
ACR category missing vs. A1	1.03 (0.94-1.12)	**1.32 (1.21-1.45)**	1.06 (0.96-1.17)
Atherosclerotic CVD	0.88 (0.80-0.96)	0.96 (0.88-1.06)	0.83 (0.75-0.92)
Heart failure	0.82 (0.73-0.93)	1.03 (0.89-1.19)	0.68 (0.58-0.78)
High blood pressure	0.82 (0.75-0.90)	0.67 (0.62-0.73)	0.70 (0.63-0.76)
DM complications	0.93 (0.86-1.01)	0.89 (0.82-0.96)	0.94 (0.86-1.02)
Metformin use	0.82 (0.74-0.91)	0.65 (0.59-0.71)	1.10 (0.99-1.22)
SU use	0.94 (0.85-1.04)	0.75 (0.67-0.83)	**1.13 (1.02-1.25)**
Insulin use	0.96 (0.87-1.06)	0.92 (0.84-1.00)	1.06 (0.94-1.19)
Other DM medication use	0.97 (0.77-1.22)	0.93 (0.74-1.17)	1.02 (0.79-1.31)
Number of non-diabetic drugs per +1 drug	0.92 (0.90-0.94)	0.92 (0.91-0.94)	0.90 (0.88-0.92)
Secondary vs. compulsory school	0.88 (0.80-0.98)	0.85 (0.77-0.94)	0.88 (0.79-0.99)
University vs. compulsory school	0.82 (0.73-0.91)	0.88 (0.79-0.99)	0.80 (0.71-0.90)
Missing education vs. compulsory school	1.14 (0.93-1.40)	**1.74 (1.36-2.22)**	1.20 (0.98-1.48)
Cohabitating vs. living alone	0.87 (0.80-0.94)	0.98 (0.90-1.06)	1.06 (0.97-1.16)
Missing living status vs. living alone	1.06 (0.76-1.48)	**1.47 (1.01-2.15)**	**1.47 (1.06-2.03)**
Income above vs. below stratum median	0.71 (0.66-0.77)	0.73 (0.67-0.79)	0.94 (0.86-1.03)
Income missing vs. income below stratum median	0.98 (0.70-1.37)	1.28 (0.88-1.87)	1.38 (1.00-1.90)
Non-Persistence; Univariable Hazards Ratios (95%CI)			
Prognostic factor	**SGLT2i**	**GLP1-RA**	**DPP4i**
Age per +10 years	0.96 (0.94-0.99)	0.92 (0.89-0.94)	0.85 (0.83-0.87)
Women vs. men	**1.17 (1.09-1.25)**	**1.14 (1.07-1.22)**	1.04 (0.97-1.12)
eGFR per -10 mL/min/1.73m^2	1.01 (1.00-1.03)	**1.03 (1.02-1.04)**	**1.05 (1.04-1.06)**
HbA1c per +3.1% (+10 mmol/mol)	**1.03 (1.01-1.04)**	**1.05 (1.04-1.06)**	**1.05 (1.04-1.07)**
ACR category A2 vs. A1	**1.16 (1.05-1.27)**	1.11 (1.00-1.22)	1.02 (0.92-1.13)
ACR category A3 vs. A1	0.83 (0.69-1.01)	**1.29 (1.09-1.53)**	0.86 (0.71-1.04)
ACR category missing vs. A1	1.02 (0.95-1.10)	**1.30 (1.21-1.40)**	1.07 (0.98-1.15)
Atherosclerotic CVD	0.92 (0.86-0.99)	0.98 (0.90-1.06)	0.86 (0.80-0.94)
Heart failure	0.89 (0.81-0.99)	1.05 (0.93-1.18)	0.73 (0.65-0.83)
High blood pressure	0.89 (0.83-0.95)	0.72 (0.68-0.78)	0.74 (0.69-0.80)
DM complications	0.96 (0.90-1.03)	0.91 (0.85-0.97)	0.96 (0.89-1.03)
Metformin use	0.84 (0.77-0.90)	0.67 (0.62-0.72)	1.06 (0.98-1.15)
SU use	0.95 (0.88-1.04)	0.79 (0.72-0.86)	**1.10 (1.01-1.20)**
Insulin use	0.97 (0.90-1.05)	0.96 (0.89-1.03)	1.08 (0.98-1.19)
Other DM medication use	0.95 (0.79-1.15)	0.93 (0.76-1.12)	1.01 (0.82-1.24)
Number of non-diabetic drugs per +1 drug	0.94 (0.93-0.96)	0.95 (0.93-0.96)	0.91 (0.89-0.93)
Secondary vs. compulsory school	0.90 (0.83-0.97)	0.84 (0.77-0.91)	0.91 (0.83-0.99)
University vs. compulsory school	0.84 (0.77-0.91)	0.88 (0.81-0.97)	0.85 (0.77-0.94)
Missing education vs. compulsory school	1.11 (0.95-1.30)	**1.48 (1.24-1.77)**	**1.20 (1.02-1.40)**
Cohabitating vs. living alone	0.88 (0.83-0.94)	1.00 (0.94-1.07)	1.03 (0.96-1.11)
Missing living status vs. living alone	1.01 (0.77-1.32)	**1.39 (1.04-1.84)**	**1.30 (1.01-1.68)**
Income above vs. below stratum median	0.74 (0.70-0.79)	0.78 (0.73-0.83)	0.93 (0.86-1.00)
Income missing vs. income below stratum median	0.95 (0.72-1.23)	1.23 (0.92-1.63)	1.23 (0.96-1.59)

CI, confidence intervals: SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; ACR, albumin-creatinine ratio; CVD, cardiovascular disease; DM, diabetes mellitus; SU, sulfonylureas.

* Shaded cells indicate a statistically significant reduction in the odds of non-adherence, while bolded cells indicate a statistically significant increase in the odds. A 95 % confidence interval that does not cross unity reflects a P value < 0.05.

reinforcement of their importance. Of note, however, there was no significant difference in 12-month adherence between those newly initiating treatment in 2015–2017 compared to 2018–2020. Lastly, the results represent the Stockholm health service and socioeconomic setting, and extrapolation to other settings should be done with caution.

5. Conclusion

We observe adherence proportions of 53–57 % for three key glucose-lowering agents over a median follow-up of 2.8 years, and persistence proportions of 44–50 %, indicating important challenges in the delivery of evidence-based care in diabetes. Interventions that support people to improve their medication adherence behaviours are required, particularly (as identified in our study) among women, younger patients, and those with lower education and income levels.

Ethics

The Regional Ethical Review Board in Stockholm approved the study, including a waiver of patient consent as all data were de-identified.

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CRediT authorship contribution statement

Daniel V. O'Hara: . **Roemer J. Janse:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Writing – original draft, Writing – review & editing. **Edouard L. Fu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Meg J. Jardine:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Juan-Jesus Carrero:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: . Juan-Jesus Carrero reports a relationship with Amgen, Astellas, AstraZeneca, NovoNordisk, Viforpharma, Boehringer Ingelheim, Nestle, Abbott that includes: funding grants and speaking and lecture fees. Professor Jardine is responsible for research projects that have received unrestricted funding from Amgen, Baxter, CSL, Eli Lilly, Gambro, and MSD; has served on advisory boards and steering committees sponsored by Akebia, Astra Zeneca, Baxter, Bayer, Boehringer Ingelheim, CSL, Janssen, MSD and Vifor; has spoken at scientific meetings sponsored by Amgen, Janssen, Roche and Vifor, with any consultancy, honoraria, or travel support paid to her institution. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111745.

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