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ORIGINAL ARTICLE

Real-world adherence, persistence, and in-class switching during use of dipeptidyl peptidase-4 inhibitors: a systematic review and meta-analysis involving 594,138 patients with type 2 diabetes

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Abstract

Aims Medication adherence and persistence are important determinants of treatment success in type 2 diabetes mellitus (T2DM). This systematic review and meta-analysis evaluated the real-world adherence, persistence, and in-class switching among patients with T2DM prescribed dipeptidyl peptidase-4 (DPP4) inhibitors.

Methods MEDLINE, EMBASE, Cochrane Library, PsychINFO, and CINAHL were searched for relevant observational studies published in the English language up to 20 December 2019. This was supplemented by manual screening of the references of included papers. Random-effects meta-analysis was performed.

Results Thirty-four cohort studies involving 594,138 patients with T2DM prescribed DPP4 inhibitors from ten countries were included. The pooled proportion adherent (proportion of days covered (PDC) or medication possession ratio (MPR) ≥ 0.80) was 56.9% (95% confidence interval [CI] 49.3–64.4) at one year and 44.2% (95% CI 36.4–52.1) at two years. The proportion persistent with treatment decreased from 75.6% (95% CI 71.5–79.5) at six months to 52.8% (95% CI 51.6–59.8) at two years. No significant differences in adherence and persistence were observed between individual DPP4 inhibitors. At one year, just 3.2% (95% CI 3.1–3.3) of patients switched from one DPP4 inhibitor to another. Switching from saxagliptin and alogliptin to others was commonest.

Conclusions Adherence to and persistence with DPP4 inhibitors is suboptimal but similar across all medications within the class. While in-class switching is uncommon, saxagliptin and alogliptin are the DPP4 inhibitors most commonly switched. Interventions to improve treatment adherence and persistence among patients with T2DM prescribed DPP4 inhibitors may be warranted.

Keywords DPP4 inhibitors · Dipeptidyl peptidase-4 inhibitors · Gliptins · Adherence · Persistence · Switching · Discontinuation · Hypoglycemic agents

Introduction

The American Diabetes Association and the European Association for the Study of Diabetes recommend dipeptidyl peptidase-4 (DPP4) inhibitors as potential second-line treatment for type 2 diabetes mellitus (T2DM) after metformin in patients at low cardiovascular risk or as third-line in those at high risk or with established cardiovascular disease who have inadequate glycemic control following the use of therapies with proven cardiovascular benefits (such as sodium glucose co-transporter 2 (SGLT2) inhibitors or Glucagon-like peptide-1 (GLP) receptor agonists) [1, 2].

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Beyond their effect on glycemic control, DPP4 inhibitors have minimal side-effects, are weight neutral [1], and may delay the progression of albuminuria [3]. Additional benefits of DPP4 inhibitors include their low risk of hypoglycemia and complementary mechanism of action to metformin [3], all of which have contributed to the increased prescribing of DPP4 inhibitors in many countries [4, 5]. However, there is limited insight of the patterns of use among patients with T2DM prescribed these drugs. In particular, the clinical effectiveness of DPP4 inhibitors may be influenced by the extent of patients' adherence to (extent of complying with drug schedule [6]) and persistence with (time from initiation until discontinuation [6]) treatment. Regardless, comprehensive insight of real-world adherence and persistence patterns among patients with T2DM prescribed DPP4 inhibitors is lacking. Moreover, while current clinical guidelines do not provide explicit advice regarding in-class switching of DPP4 inhibitors, such therapeutic changes may be undertaken due to efficacy or safety issues with a particular DPP4 inhibitor [7, 8] or as a means of reducing treatment cost [9, 10]. For example, in Canada, in 2015, the annual cost of treatment differed by about 3–17% across individual DPP4 inhibitors [11]). However, to our knowledge, no meta-analysis has quantified the extent of in-class switching among patients with T2DM prescribed DPP4 inhibitors.

Thus, in the present study, we performed a systematic review and meta-analysis to characterize the real-world adherence, persistence, and in-class switching among patients with T2DM prescribed DPP4 inhibitors. Furthermore, we compared the adherence, persistence, and switching rates among individual DPP4 inhibitors.

Methods

Our study followed the recommendations outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Table S1) [12] and the Cochrane collaboration handbook. The review process was defined a priori, and the protocol was registered in PROSPERO (ID: CRD42019153850). Searches were performed in MEDLINE, EMBASE, Cochrane Library, PsychINFO, and CINAHL from their inception up to 20 December 2019, for cohort studies published in the English language that reported data on adherence, persistence, or switching among adults aged ≥ 18 years with T2DM prescribed DPP4 inhibitors. The key terms used for the search included 'DPP4 inhibitors' or 'dipeptidyl-peptidase 4 Inhibitors' or 'gliptins' and 'adherence' or 'compliance' or 'persistence' or 'discontinuation' (Table S2). Two independent reviewers (OO and RO) screened articles, extracted relevant data, and cross-checked for consistency. Any disagreements were resolved via consensus-based discussions. If studies assessed adherence using multiple measures, the proportion of days covered (PDC) was preferred as the more robust metric [13]. Persistence was not restricted to a specific definition in order to reflect the heterogeneity in assessment methods in the literature [6]. We also collected information on the reasons for switching, nonpersistence, and nonadherence if reported. The methodological quality of each study was assessed using the Newcastle–Ottawa scale (NOS) for nonrandomized studies (https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Studies were ineligible for exclusion if they scored < 5 on the NOS.

Pooled adherence, persistence, and switching rates were obtained via meta-analysis using the Freeman–Tukey double arcsine transformed proportions to account for variance instability [14]. Where data existed from at least two studies that compared switching, adherence, or persistence among different DPP4 inhibitors, these were pooled with the effect measure expressed as odds ratio (OR). All meta-analyses were performed using random-effects model due to the anticipated between-study heterogeneity. Statistical heterogeneity was quantified via the I^2 statistic [14]. Publication bias was assessed through funnel plot asymmetry and quantified with the Egger's test. The robustness of pooled estimates was tested through leave-one-out sensitivity analyses. To explore the potential sources of heterogeneity, meta-regression was performed to examine the influence of study mean age, proportion of females, country (USA *versus* other), year of publication (recent [2017–2019] *versus* other [< 2017]), and techniques for measuring adherence (PDC versus medication possession ratio [MPR]) and persistence (gap ≥ 90-days versus other). All analyses were performed with STATA SE (Version 16). A p value of < 0.05 was considered statistically significant.

Results

Study characteristics

The electronic searches retrieved 8453 citations. After screening (Fig. 1), a total of 34 studies involving 594,138 patients with T2DM prescribed DPP4 inhibitors were included. The studies were published during 2012–2019 and were from ten countries [USA ($n = 16$); Japan ($n = 6$); UK ($n = 2$); France ($n = 2$); Hungary ($n = 2$); Spain ($n = 1$); Italy ($n = 1$); Australia ($n = 1$); Germany ($n = 1$); Saudi Arabia ($n = 1$), and one study involving data from Germany and France]. The median sample size was 8,221 (interquartile range 2858–26,064). The mean age ranged from 50.8 to 73.6 years, and 25.1–59.5% of participants were females. No study was excluded on the basis of the NOS assessment (Table S3).

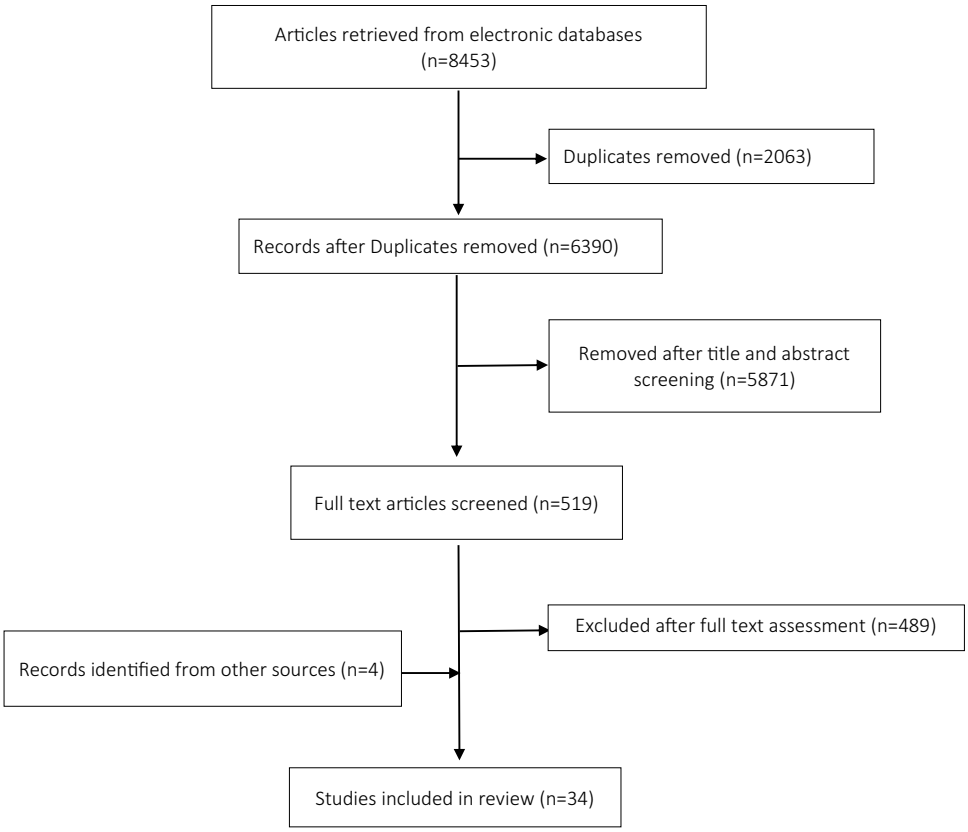

Fig. 1 PRISMA flowchart of studies' selection process

Adherence to DPP4 inhibitors

Across eighteen studies involving 299,121 patients, the reported mean MPR/PDC at one year ranged from 0.59 to 0.97, the pooled estimate being 0.72 (95% CI 0.68–0.77: $I^2 = 99.5\%$). Twenty studies involving 302,911 patients reported the proportion adherent (MPR/PDC ≥ 0.80) at one year; the pooled estimate was 56.9% (95% CI 49.3–64.4: $I^2 = 99.9\%$) (Figure S1). Across four studies involving 65,602 patients, the pooled proportion adherent at two years was 44.2% (95% CI 36.4–52.1; $I^2 = 99.5\%$). Seven studies involving 176,385 patients reported comparative data on one-year adherence rates among different DPP4 inhibitors. No significant differences in one-year adherence were noted among individual DPP4 inhibitors (Table 1 and Figure S2). None of the studies reported reasons for patients' non-adherence.

Persistence to DPP4 inhibitors

Fourteen studies involving 254,133 patients reported proportion persistent at six months; the pooled estimate was 75.6% (95% CI 71.5–79.5; $I^2 = 99.8\%$). The pooled proportion of patients persistent at one year across 26 studies involving 577,085 patients was 60.0% (95% CI 57.0–62.0; $I^2 = 99.8\%$) (Figure S3). Among fourteen studies involving 338,059 patients, the pooled proportion persistent at two years was 52.8% (95% CI 51.6–59.8; $I^2 = 99.8\%$) . In two studies involving 52,363 patients, the pooled proportion persistent at three years was 31.4 (95% CI 31.0–31.8; $I^2 = 0\%$). Pooled data from nine studies involving 238,541 patients revealed no significant differences in the one-year persistence among individual DPP4 inhibitors (Table 1 and Figure S4). Only two studies reported reasons for nonpersistence. In the first study [15], the most commonly cited reasons for drug discontinuation were inadequate glycemic control (52.1%) and intolerance (21.8%). Similarly, in the second study [16], the most commonly cited reasons for nonpersistence were poor efficacy (39.7%) and tolerability issues (39.1%). Regardless, these reasons were from physicians' perspectives.

Patterns of in-class switching

Three studies involving 76,222 patients reported data on in-class switching. The pooled proportion of patients who switched from one DPP4 inhibitor to another at one year was 3.2% (95% CI 3.1–3.3: $I^2 = 0\%$). Patients prescribed sitagliptin were less likely to switch compared to other DPP4 inhibitors (Fig. 2). Saxagliptin was associated with higher likelihood of switching compared to linagliptin and vildagliptin but no significant difference in comparison with alogliptin. Alogliptin was also associated with higher

Table 1 Results of multivariable random-effects meta-regression of the potential sources of between-study heterogeneity

Outcome	β (95% CI)	P value	Adjusted R^2 (%)
Mean PDC/MPR at 1-year			
Mean age (per unit increase)	0.002 (−0.007 to 0.012)	0.665	51.5
Proportion of female (per unit increase)	−0.0003 (−0.013 to 0.012)	0.948	
Country of study			
Other	Reference	–	
USA	−0.164 (−0.333 to 0.007)	0.058	
Publication year			
< 2017	Reference	–	
2017–2019	0.035 (−0.059 to 0.129)	0.438	
Measurement method			
MPR	Reference	–	
PDC	0.058 (−0.096 to 0.213)	0.423	
Proportion adherent[a] at 1 year			
Mean age (per unit increase)	0.002 (−0.005 to 0.010)	0.546	74.1
Proportion of female (per unit increase)	0.002 (−0.006 to 0.009)	0.607	
Country of study			
Other	Reference	–	
USA	**−0.352 (−0.463 to − 0.241)**	**< 0.001**	
Publication year			
< 2017	Reference	–	
2017–2019	0.011 (−0.06 to 0.086)	0.766	
Measurement method			
MPR	Reference	–	
PDC	−0.010 (−0.105 to 0.084)	0.825	
Proportion persistent at 1-year			
Mean age (per unit increase)	**−0.012 (−0.020 to −0.003)**	**0.012**	68.1
Proportion of female (per unit increase)	0.005 (−0.003 to 0.013)	0.194	
Country of study			
Other	Reference	–	
USA	**−0.301 (−0.429 to −0.174)**	**< 0.001**	
Publication year			
< 2017	Reference	–	
2017–2019	0.003 (−0.077 to 0.084)	0.934	
Measurement method			
Gap ≥ 90 days	Reference	–	
Other	−0.031 (−0.108 to 0.0458)	0.410	

CI confidence interval, *MPR* medication possession ratio, *PDC* proportion of days covered,

[a]Adherent represents MPR/PDC greater than or equal to 0.80

switching compared to vildagliptin and linagliptin, whereas no significant difference was noted between linagliptin and vildagliptin (Figure S5). None of the studies reported the reasons for switching.

Sensitivity analyses, publication bias, and meta-regression

The pooled adherence, persistence, and switching rates were unchanged during leave-one-out sensitivity analyses. There was no evidence of publication bias (Egger's test results: mean PDC/MPR at 1-year, $p = 0.971$; proportion adherent at one year, $p = 0.550$; proportion persistent at six months, $p = 0.254$; proportion persistent at one year, $p = 0.503$), except for proportion persistent at two years where slight asymmetry in funnel plot was noted ($p = 0.021$). Funnel plots are presented in supplementary Figures S7–S10. Studies involving US patients tended to report lower adherence and persistence. Increasing mean age was found to be associated with lower persistence. The variables in the meta-regression collectively explained

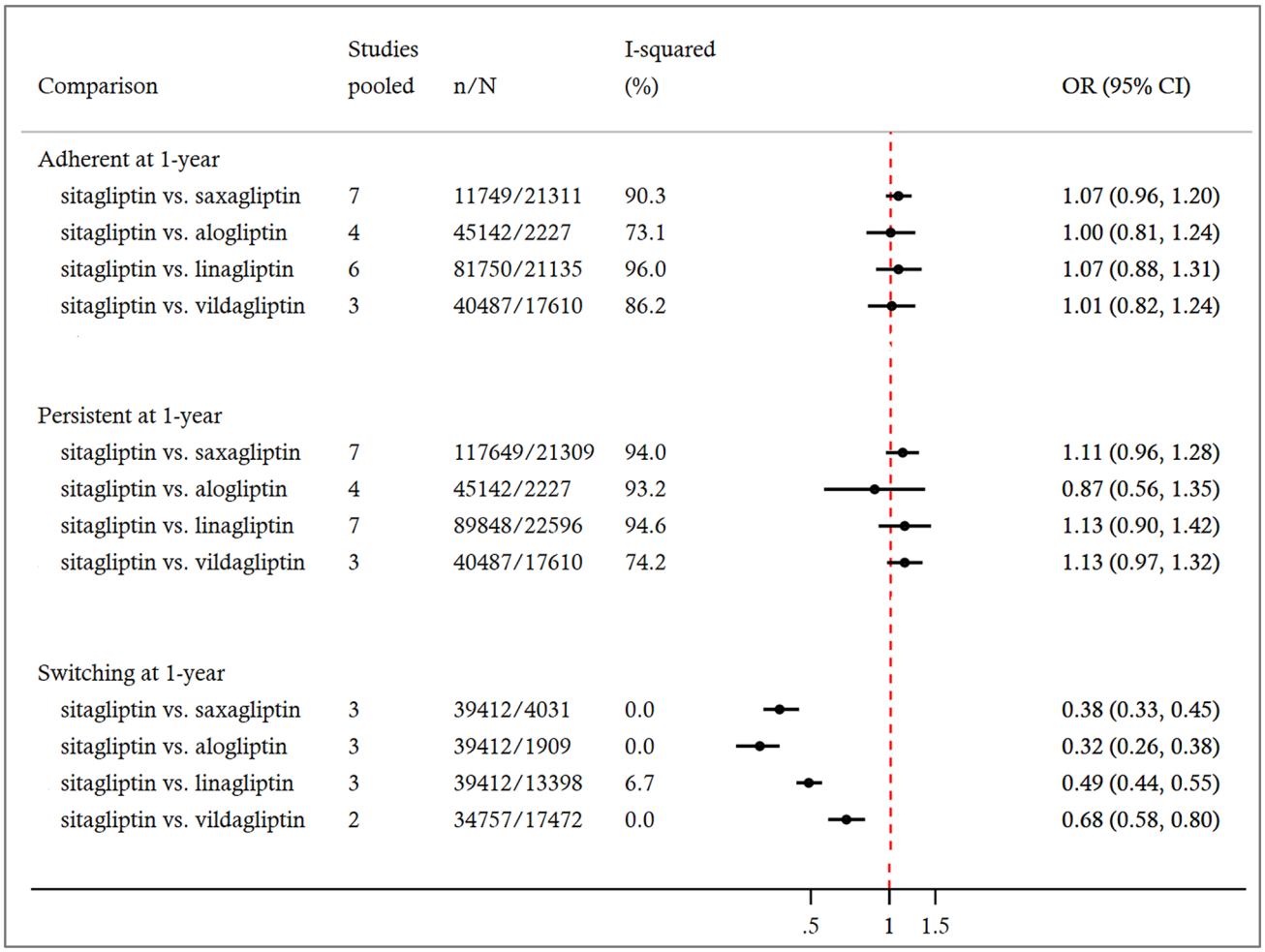

Fig. 2 Comparisons of the likelihood of being adherent, persistent, and switching between sitagliptin and other DPP4-inhibitors. *OR* odds ratio, *CI* confidence interval, *n* number of patients prescribed sitagliptin, *N* number of patients prescribed saxagliptin, alogliptin, or linagliptin

74.1% and 68.1% of the between-study variance relative to one-year adherence and persistence, respectively (Table 1).

DISCUSSION

Our study characterized the real-world adherence, persistence, and switching patterns among patients with T2DM prescribed DPP4 inhibitors. Fifty-seven percent of patients were adherent at one year. The proportion persistent with treatment decreased from 76% at six months to 53% at two years. There were no significant differences in adherence and persistence rates across individual DPP4 inhibitors. Only a small proportion (< 5%) of patients switched from one DPP4 inhibitor to another within one year. The likelihood of switching was highest with saxagliptin and alogliptin. Treatment persistence tended to decrease with increasing mean age and was lower in US studies compared to those from elsewhere.

The low rate of in-class switching among patients prescribed DPP4 inhibitors may be attributed to the fact that when patients using a DPP4 inhibitor fail to achieve adequate glycemic control, better improvement in glucose control is likely to be gained via addition of another therapeutic class rather than switching within the class or to another class [17]. Moreover, there is a lack of obvious clinical differences among the individual DPP4 inhibitors, particularly with respect to their effect on outcomes such as HbA1c, weight, hypoglycaemia risk, or adverse drug events such as acute pancreatitis [18, 19]. Thus, clinicians and patients may perceive little gain in changing from one DPP4 inhibitor to another. Cardiovascular outcomes trials of DPP4 inhibitors have also shown them to be generally safe [3], with the exception of saxagliptin for which an excess risk

of hospitalization for heart failure (hazard ratio 1.27, 95% CI 1.07–1.51; $p=0.007$) compared to placebo was observed in the SAVOR-TIMI 53 (Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications) study [20]. Our analysis suggested that patients prescribed saxagliptin were more likely to switch to another DPP4 inhibitor compared to those prescribed sitagliptin, linagliptin, or vildagliptin. Regardless, as to whether heart failure-related safety issues contributed to this trend is unclear.

Within randomized clinical trial (RCT) settings, compliance to DPP4 inhibitors is high. For example, in the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) trial [21], the discontinuation rate of linagliptin was 2.8% per year which is significantly lower than our pooled real-world data in which 40% of patients were nonpersistent at one year. The clinical implications of the discrepancies between RCT and real-world adherence have been widely discussed in the literature [22, 23]. A recent analysis based on data from a US commercial database showed that discrepancy in adherence could account for about three quarters of the gap between real-world effectiveness and RCT efficacy of DPP4 inhibitors [24]. In general, better adherence and persistence to antidiabetic medications have been associated with improved glycemic control, reduced risk of disease-related events, hospitalizations, mortality, and healthcare costs [22, 23]. Thus, interventions to improve adherence and persistence among patients with T2DM are essential. In particular, interventions addressing key modifiable risk factors for non-adherence and nonpersistence (e.g., health literacy, and quality of the relationship between patient and healthcare providers) are required [25, 26]. Interventions implemented need to be patient tailored to address specific challenges. For example, older adults may face issues with polypharmacy, increased susceptibility to adverse events, as well as declining executive cognitive functioning (hence, may benefit from services such as short message service (SMS) reminders) [27]. As our analysis also revealed temporal declines in adherence and persistence, continuous monitoring of patients' drug taking behaviors is necessary to promptly identify and address any issues.

The differences in adherence and persistence reported in studies from the US and other jurisdictions were not necessarily due to methodological variations. Thus, we ascribe this to multiple factors including healthcare system differences such as patient cost-sharing mechanisms [28]. Moreover, other issues such as non-medical switching (where a patient's treatment regimen is changed for reasons other than efficacy or side effects such as due to drug formulary changes aimed at reducing drug costs) which is more common in the US [29] could contribute to the observed low adherence and persistence. However, further investigations are warranted to provide deeper understanding.

Our study has limitations. First, there was high statistical heterogeneity that was not entirely explained by study characteristics such as mean age, proportion of females, year of publication, country, or adherence/persistence assessment methods. Qualitative evaluation provided additional insights. For example, while different studies measure adherence/persistence using similar methods, some included only patients with ≥ 2 dispensations, whereas others included all patients with ≥ 1 dispensation. Thus, comparisons of the results in different countries/settings should be interpreted cautiously. Second, none of the included studies reported reasons for switching or non-adherence. Two studies provided reasons for nonpersistence from clinician perspectives. In those studies, nonpersistence was ascribed to poor drug efficacy and tolerability issues, thus may not be entirely unwarranted. Nonetheless, to appropriately design interventions, better insight into patient-reported reasons for non-adherence and nonpersistence are needed. Third, as most studies relied on indirect measurements, it was impossible to ascertain whether patients actually took the medication. Fourth, we did not compare adherence/persistence against other antidiabetic drug classes. A previous meta-analysis by McGovern et al. suggested that DPP4 inhibitors had better adherence than sulfonylureas and thiazolidinediones [30], but comparisons to other novel therapies such as sodium glucose co-transporter 2 (SGLT2) inhibitors could not be made. Regardless, our recent meta-analysis involving > 120,000 patients prescribed SGLT2-inhibitors estimated that 61.8% were persistent at one year [31], which is comparable to the 60% rate found in this study. Similarly, using data from a National Health Insurance Fund in Hungary, Jermendy et al. [32] found that the 2-year persistence rate differed only slightly among patients prescribed DPP4 inhibitors (57.3%), SGLT2 inhibitors (56.8%), and GLP-1 agonists (52.1%), which further highlight the need for improvement in adherence/persistence for all antidiabetic medications. Fifth, our analysis did not estimate the rate of switching to a different class. Thus, future studies should examine this in detail. Finally, by restricting our review mainly to articles in the English language, the generalizability of the findings may be limited.

Conclusions

Adherence to and persistence with DDP4 inhibitors in the real world is suboptimal but is similar across all medications within the class. A very small proportion of patients switch from one DPP4 inhibitor to another, but switching was more common with saxagliptin and alogliptin.

Interventions to improve adherence and persistence among patients with T2DM prescribed DPP4 inhibitors may be necessary.

Author contributions RO conceived the study. OO and RO were responsible for articles' screening and data collection. DG, AM, and GJ supplied additional data. RO performed the statistical analysis and drafted manuscript. OO, MM, KLC, DG, AM, BSW, GJ, MJK, BA, ZA, MLDB, and DL critically reviewed the manuscript for intellectual content.

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Compliance with ethical standards

Conflict of interest DL reports past participation in advisory boards and/or receiving honoraria from Abbvie, Astellas, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer, Sanofi, and Shire for work unrelated to this study. RO and MLDB are employees of the Copenhagen Centre for Regulatory Sciences (CORS). CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, LEO pharma) as well as patient organizations (Rare Diseases Denmark). The center is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus, and the research is not company-specific product or directly company related and has received funding from Novo Nordisk, Ferring Pharmaceuticals, LEO pharma and Lundbeck for projects not related to this study. AM reports research funding from Eli Lilly, AstraZeneca, Boehringer Ingelheim, and Pfizer for work unrelated to this study. All others declare no relevant conflicts of interest.

Ethical approval This article does not contain any studies with human or animal performed by any authors.

Informed consent Informed consent is not required.

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