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Dynamics of switching, adherence, and persistence of dipeptidyl peptidase-4 inhibitors use: A nationwide cohort study

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ABSTRACT

Aims: To characterise the patterns of switching, adherence, and persistence among adults aged ≥18 years with diabetes prescribed dipeptidyl peptidase-4 inhibitors (DPP-4is) in Australia.

Methods: The analysis included 15,915 adults newly prescribed DPP-4is (sitagliptin = 9576; vildagliptin = 1130; saxagliptin = 1126; linagliptin = 3560; and alogliptin = 523). Multivariable logistic regression model was used to compare the non-adherence (proportion of days covered [PDC] <0.80) rates whereas Cox proportional hazards regression models were used to compare switching and non-persistence (≥90-day gap) among different DPP4-is over 12-months.

Results: Overall, 36.0% (5722/15,915) of DPP-4i users were non-adherent and 30.0% (4775/15,915) were non-persistent at 12-months. Compared to sitagliptin, vildagliptin, linagliptin, and alogliptin were not associated with higher non-adherence and non-persistence. However, saxagliptin was associated with a higher likelihood of being non-adherent (odds ratio 1.41, 95% confidence interval [CI] 1.23–1.60) or non-persistent (hazard ratio 1.27, 95% CI 1.15–1.42) compared to sitagliptin. Just 3.2% of people switched between different DPP-4is. Compared to sitagliptin, people initiated on vildagliptin, saxagliptin, alogliptin, and linagliptin were more likely to switch.

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Conclusions: We found no significant differences in the adherence and persistence rates between alogliptin, vildagliptin or linagliptin and sitagliptin. However, saxagliptin was associated with higher non-adherence and non-persistence compared to sitagliptin. Switching was lowest amongst users of sitagliptin.

1. Background

During the past decade, more than 40 new diabetes medications have been developed [1]. The efficacy of these new medications has been demonstrated in several randomised controlled trials (RCTs). Yet significant proportions of people with type 2 diabetes (T2D) prescribed these medications fail to achieve the desired clinical targets. Part of the challenge has been the poor adherence and persistence when medications are used in real-world settings [2,3]. Data from observational studies suggest that between 36% and 93% of people with T2D are adherent to their medications [4–6]. Beyond contributing to poor glycaemic control, medication non-adherence and non-persistence have been associated with adverse outcomes such as the increased risk of diabetes complications and death [7–9].

Dipeptidyl peptidase-4 inhibitors (DPP-4is), commonly called *gliptins*, are a relatively new class of oral medications for the treatment of T2D. DPP-4is act via inhibition of the degradation of the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [10–12]. Because DPP-4is improve insulin secretion in response to an increased level of blood glucose, it is deemed appropriate to pair them with T2D medications that have a different mechanisms of action, such as metformin [12]. Consequently, in Australia, DPP-4is are subsidised for use with either metformin or a sulfonylurea (dual therapy) under the Pharmaceutical Benefits Scheme (PBS) [13–15], the Australian government's strategy to providing timely and affordable access to a wide range of medicines for Australian citizens, permanent residents and people from countries with reciprocal healthcare [16]. Moreover, sitagliptin and linagliptin are approved by the Therapeutic Goods Administration (TGA) as monotherapy if metformin (and sulfonylureas for linagliptin) is not tolerated, but none of the gliptins are subsidised for use as a monotherapy under the PBS [14]. Thus, most T2D patients in Australia would have trialled metformin or a sulfonylurea prior to initiating a DPP-4is. Sitagliptin, saxagliptin, vildagliptin, linagliptin and alogliptin have been listed on the PBS since August 2008, June 2011, August 2010, March 2012, and December 2013, respectively.

A *meta*-analysis found that as second line therapy, DPP-4is were inferior to glucagon-like peptide-1 (GLP-1) agonists (weighted mean difference (WMD) 0.49, 95% confidence interval [CI] 0.31 to 0.67) but similar to pioglitazone (WMD 0.09, 95% CI −0.07 to 0.24) at reducing glycated haemoglobin (HbA1c) [17]. Moreover, there was no significant difference between sulfonylureas (SU) and DPP-4is in the attainment of a HbA1c level of less than 7% (risk ratio in favour of SU [RR] 1.06, 95% CI 0.98 to 1.14) [17]. Experimental and clinical data also suggest that aside from contributing to improved metabolic control, DPP4-is could potentially delay the onset and progression of diabetic microangiopathy [18].

The overall cardiovascular safety of DPP-4is has been demonstrated in major RCTs: SAVOR-TIMI 53 (Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications) [19], EXAMINE (Cardiovascular Outcomes Study of Alogliptin in Patients with Type 2 Diabetes and Acute Coronary Syndrome) [20], TECOS (Sitagliptin Cardiovascular Outcomes Study [MK-0431-082]) [21], CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients with Type 2 Diabetes Mellitus) [22] and CAROLINA (Cardiovascular Outcome of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) [23]. However, in the SAVOR-TIMI 53 trial, there was an increased risk of hospitalisation for heart failure among patients treated with saxagliptin compared to placebo (hazard ratio [HR] 1.27; 95% CI, 1.07 to 1.51; P = 0.007) [19].

DPP-4is are increasingly being prescribed to T2D patients, with the number of Australians dispensed DPP-4is more than doubling between August 2012 and July 2016 [24]. However, there is poor evidence of the adherence and persistence patterns among people with T2D prescribed DPP-4is in Australia. Such data may be useful for informing clinical practice and the management of people with T2D. In the present study, we utilised a very large, real-world contemporary dataset to characterise the patterns of adherence, persistence and switching of DPP-4is in Australia.

2. Subjects, materials and methods

2.1. *Study design and data sources*

This was a retrospective cohort study that used data drawn from the PBS records covering a 10% random sample of Australians dispensed PBS medications [25,26]. The data captured in the PBS records include item numbers of medications dispensed and strength, basic demographic information (sex, years of birth and death), dates of dispensing and quantity of medication supplied, pharmacy location (state), concession card status and prescriber details. As a medication acquisition database, clinical and diagnostic information such as fasting blood glucose (FBG) or HbA1c levels are not recorded in the PBS datasets. Furthermore, other data such as patients' socioeconomic status are not captured in the PBS dataset. The PBS datasets used in the study were provided by the Australian Government Department of Human Services. The data were anonymized, with everyone being ascribed a unique identifying code.

Table 1 – Baseline characteristics of the study cohort initiating DPP-4is between January 2015 and August 2017.

Variable	All	DPP-4i type					P-value[a]
		Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin	Alogliptin	
Number of people (*n*)	15,915	9,576	1,130	1,126	3560	523	
Mean age (±s.d)	62.7 (13.3)	61.6 (13.1)	60.8 (13.1)	61.7 (12.9)	66.8 (13.1)	62.0 (12.9)	0.926
Female Gender (n, %)	6804 (42.8)	4,078 (43.6)	498 (44.1)	446 (39.6)	1568 (44.0)	214 (40.9)	0.072
Pre-index Medication use (*n*, %)							
Insulin	2381 (15.0)	1345 (14.1)	113 (10.0)	100 (8.9)	763 (21.4)	60 (11.5)	<0.001
Blood pressure lowering agents	11,497 (72.2)	6785 (70.9)	738 (65.3)	794 (70.5)	2815 (79.1)	365 (69.8)	<0.001
Blood thinning agents	3596 (22.6)	1995 (20.8)	209 (18.5)	212 (18.8)	1096 (30.8)	84 (16.1)	<0.001
Antidepressants	3894 (24.5)	2386 (24.9)	253 (22.4)	247 (21.9)	896 (25.2)	112 (21.4)	0.025
Anti-anxiety agent	1187 (7.5)	715 (7.5)	81 (7.2)	73 (6.5)	280 (7.9)	38 (7.3)	0.632
Anti-dementia	87 (0.6)	44 (0.5)	4 (0.4)	8 (0.7)	30 (0.8)	1 (0.2)	0.047
Lipid-lowering therapy	10,729 (67.4)	6296 (65.8)	747 (66.1)	729 (64.7)	2620 (73.6)	337 (64.4)	<0.001
Drugs for reactive airway disease	1909 (12.0)	1131 (11.8)	114 (10.1)	136 (12.1)	476 (13.4)	52 (9.9)	0.013
Anti-epilepsy	507 (3.2)	312 (3.3)	26 (2.3)	30 (20.7)	122 (3.4)	17 (3.3)	0.319
Drugs for malignancy	230 (1.5)	127 (1.3)	14 (1.2)	9 (0.8)	75 (2.1)	5 (1.0)	0.003
Thyroid-related medication	1214 (7.6)	705 (7.4)	85 (7.5)	83 (7.4)	307 (8.6)	34 (6.5)	0.134
Antipsychotics	697 (4.4)	429 (4.5)	39 (3.5)	40 (3.6)	161 (4.5)	28 (5.4)	0.218
Nicotine dependence therapies	404 (2.5)	256 (2.7)	41 (3.6)	32 (2.8)	62 (1.7)	13 (2.5)	0.003
Concessional beneficiary (*n*, %)	9326 (58.6)	5442 (56.8)	618 (54.7)	658 (58.4)	2297 (64.5)	311 (59.5)	<0.001
Prescribed as FDC with metformin[b]	9968 (62.6)	6555 (68.5)	936 (82.8)	791 (70.3)	1315 (36.9)	371 (70.9)	<0.001

FDC = fixed dose combination; s.d = standard deviation;

[a] means compared by one-way analysis of variance (ANOVA), proportions compared with chi-square test;

[b] based on the index script.

2.2. Study cohort

We selected adults aged 18 years and older who were newly dispensed DPP-4is from 1 January 2015 to 31 August 2017, the first dispensing date being the index date. A new DPP-4i user was defined as any person who was dispensed a DPP-4is but had not had a DPP-4is dispensed in the previous 12 months [16]. We excluded people who died prior to 12 months post index date.

2.3. Exposure

DPP-4i dispensations were identified from the PBS data using their item codes and World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system codes [27]. We included both single active ingredient and fixed dose combinations (FDC)s of five DPP-4is; sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin. Supplemental Table S1 provides the item codes as well as the ATC codes for the included DPP-4is.

2.4. Outcomes

We assessed switching, non-adherence, and non-persistence as separate outcomes. Switching was defined as the first change from the index DPP-4i to another DPP-4i.

Medication adherence was measured using the proportion of days covered (PDC) during the 12-month follow-up period. The PDC was calculated by dividing the number of days the patient was 'covered' by the medication (i.e., had the medication 'on hand') during the follow-up period (numerator) by 365 days (denominator). People who achieved a PDC < 0.80 were considered to be non-adherent [28,29]. The dataset used for this study did not contain information on dosing. However, as per the PBS rules, for patients with chronic morbidities (including diabetes), the dispensing schedule is typically for one month [30,31]. Thus, in line with prior Australian studies [32–36], we used this interval as the supply days for each dispensation. Subsequently, this information was used to estimate the end date of each dispensation. If a patient refilled earlier than the estimated end date of the current dispensing schedule (i.e., overlapping refills), it was assumed that the person would continue using the medication at hand until completion before commencing the refill prescription [16,37]. Persistence was defined as continuous use of medication until a gap of 90 or more days without medication on hand. We calculated the 'gap' as the number days elapsed after the estimated end date of a DPP-4i dispensing and no refill had been made [16]. People who experienced a ≥90-day gap were classified as non-persistent. Adherence and persistence were first examined at a class level. However, when comparing adherence and persistence among the different DPP-4is, PDC and gap in therapy were estimated at the drug level.

2.5. Statistical analyses

Descriptive analyses were conducted to compare the baseline characteristics of patients initiated on the various DPP-4is. We used χ^2 test to compare proportions and one-way analysis of variance (ANOVA) to compare means. The following baseline characteristic were compared: age, sex, concession status and pre-index medication use. In Australia, concession card holders are eligible for lower, capped payments for medications than general beneficiaries [38]. There are strict requirements for meeting concession status, including meeting a minimum level of income and age as set out by the Department of Health. For the pre-index medication use, the following were assessed; insulin, blood pressure lowering (BPL) agents, lipid-lowering therapy (LLT), blood thinning agents (antiplatelets and anticoagulants), anti-dementia medication, antidepressants, anti-anxiety agents, thyroid-related medication (hypothyroidism and hyperthyroidism), medications for malignancy, anti-anxiety agents, antipsychotics, medications for reactive airway disease, and nicotine dependency therapies. The pre-index medication utilisation was obtained using the dispensing records of individuals in the 12 months preceding DPP-4is initiation (Supplemental Table S2).

Logistic regression models were fit to compare the likelihoods of being non-adherent (PDC < 0.80). Cox proportional hazards models were also used to compare the likelihoods of switching or being non-persistent between people initiated on the various DPP-4is. All models were adjusted for age, sex, concession status, pre-index medication use, and whether the index therapy was an FDC with metformin. All analyses were performed using STATA 15/IC and a P value of < 0.05 was considered statistically significant.

The study was approved by the Monash University Human research Ethics Committee. The analysis plan was approved, and the final manuscript noted by the Australian Government Department of Human Services.

3. Results

3.1. Baseline characteristics

A total of 15,915 adults who were initiated DPP-4is between January 2015 and August 2017 were identified. The mean age was 62.7 (standard deviation [S.D] ± 13.3) years and 42.8% were female. Of the cohort, 58.6% were concession card holders and 15.0% were being dispensed insulin prior to the commencement of DPP-4i therapy. In addition, 24.5%, 72.2%, 67.4%, 2.5% and 4.4% were being dispensed antidepressants, BPL agents, LLT, nicotine dependence therapies, and antipsychotics, respectively, prior to DPP4-is initiation. In all, 62.6% of people initiated DPP4-is as an FDC with metformin.

Table 1 summarises the baseline characteristics of the people prescribed sitagliptin (n = 9,576), vildagliptin (n = 1,130), saxagliptin (n = 1,126), linagliptin (n = 3,560), and alogliptin (n = 523). There were no statistically significant age and gender differences among the people initiated on the various DPP-4is. However, the pre-index uses of insulin, BPL, blood thinners, and LLT varied significantly across the groups of people initiated the various DPP-4is. While 64.5% of people initiated on linagliptin were concessional beneficiaries, 56.8%, 54.7%, 58.4% and 59.5% of people initiated on sitagliptin, vildagliptin, saxagliptin and alogliptin were concessional beneficiaries. Of people initiated on vildagliptin,

Table 2 – Patterns of in-class switching during 12 months among people prescribed DPP-4is.

Switch from (index DPP-4is)	Switch to (n, %)				
	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin	Alogliptin
Sitagliptin (n = 221)		28 (12.7%)	45 (20.3%)	126 (57.0%)	22 (10.0%)
Vildagliptin (n = 44)	25 (56.8%)		5 (11.4%)	13 (29.5%)	1 (2.3%)
Saxagliptin (n = 63)	39 (61.9%)	3 (4.8%)		17 (27.0%)	4 (6.3%)
Linagliptin (n = 144)	109 (75.7%)	9 (6.3%)	16 (11.1%)		10 (6.9%)
Alogliptin (n = 36)	21 (58.3%)	2 (5.6%)	3 (8.3%)	10 (27.8%)	

82.8% were dispensed an FDC with metformin, compared to 68.5%, 70.3%, 36.9% and 70.9% of people initiated on sitagliptin, saxagliptin, linagliptin and alogliptin, respectively.

3.2. *Overall adherence and persistence to DPP-4is*

When analysing medication use at a class level, the mean PDC of the cohort over the one-year follow-up period was 0.76 ± 0.32. In total, 36.0% (5,722/15,915) of people were non-adherent (PDC < 0.80) to their DPP-4is. The proportion of people who were non-persistent (i.e., experienced a gap of ≥90 days) in the 12-months follow up was 30.0% (4,775/15,915). The median time to non-persistence was 150 (interquartile range [IQR] 146–223) days.

3.3. *Comparison of switching, adherence and persistence among the individual DPP-4is*

Overall, just 3.2% (508/15,915) of people switched from one DPP-4is to another during the 12-month follow-up. The proportion of people who switched from sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin were 2.3% (221/9576), 3.9% (44/1130), 5.6% (63/1126), 4.0% (144/3560) and 6.9% (36/523), respectively. Table 2 presents the transition patterns among the people who switched from one DPP-4i to another. Of the switches, 38.2% involved a change from vildagliptin, saxagliptin, linagliptin or aloglitptin to sitagliptin. In the multivariable Cox regression model, vildagliptin (HR 1.60, 95% CI 1.08–2.37)), saxagliptin (HR 2.44, 95% CI 1.76–3.39), linagliptin (HR 1.38, 95% CI 1.05–1.81) and alogliptin (HR 2.42, 95% CI 1.53–3.82) were associated with higher likelihoods of switching compared to sitagliptin. The full results of the multivariable Cox model for switching between different DPP-4is are presented in Supplemental Table S3.

When adherence was evaluated at the medication level, the mean PDC of the people initiated on sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin were 0.76 (±0.32), 0.77 (±0.33), 0.70 (±0.34), 0.75 (±0.33) and 0.76 (±0.32), respectively. Fig. 1 presents the cumulative PDC distribution among people prescribed the various DPP-4is. The proportion of people prescribed sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin who were non-adherent (PDC < 0.80) were 36.3%, 34.2%, 43.4%, 37.2% and 38.0%, respectively. In the multivariable logistic regression model, compared to sitagliptin, people prescribed vildagliptin (odds ratio [OR] 0.99, 95% CI 0.86–1.13), linagliptin (OR 0.93, 95% CI 0.93 (0.85–1.01), and alogliptin (OR 1.13, 95% CI 0.93–1.36) were no more likely to be non-adherent. However, being prescribed saxagliptin (OR 1.41, 95% CI 1.23–1.60) was associated with a greater likelihood of being non-adherent compared to sitagliptin. Supplemental Table S4 presents the associations between various factors and non-adherence to DPP-4is from the multivariable logistic regression model.

During the 12-month follow-up, 29.6%, 31.7%, 35.9%, 31.2%, and 30.4% of people initiated on sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin, respectively, were non-persistent. In the multivariable Cox regression model, being dispensed vildagliptin (HR 1.11, 95% CI 0.98–1.24), linagliptin (HR 0.93, 95% CI (0.85–1.01) and alogliptin (HR 1.13, 95% CI 0.93–1.36) were not associated with a statistically significant increased likelihood of being non-persistent compared to sitagliptin (Table 3.). However, saxagliptin (HR 1.27, 95% CI 1.15–1.42) was associated with a greater likelihood of being non-persistent compared to sitagliptin. The associations between various factors and non-persistence to DPP-4is from the multivariable cox model are presented in Supplemental Table S5.

4. Discussion

In this study, we used nationwide Australian medication claims data to characterise the patterns of switching, non-adherence, and non-persistence of DPP-4is. We found that just 3.2% of people switched from one DPP-4i to another. Overall, 36.0% and 30.0% of the people dispensed DPP4-is were non-adherent or non-persistent, respectively, within the 12 months of follow up. Vildagliptin, linagliptin, and alogliptin were not associated with greater likelihoods of being non-adherent or non-persistent compared to sitagliptin. However, saxagliptin was associated with a greater likelihood of being non-adherent or non-persistent compared to sitagliptin.

We are unaware of any study that has presented detailed patterns of the in-class switching of DPP-4is. Thus, studies in other populations are needed to better understand the dynamics of switching among people prescribed these medications. Regardless, the generally low level of in-class switching of DPP-4is observed in our study may be due to the fact that there are no significant differences in clinical effectiveness between individual DPP-4is, particularly in terms of achieving change in HbA_{1c} levels or body weight, or their risk of hypoglycaemia, and adverse drug events such as acute pancreatitis [17,39–42]. Moreover, apart from saxagliptin, which was shown in the SAVOR-TIMI study to be associated

Table 3 – Comparison of switching, adherence and persistence between people initiated on individual DPP4-is over the 12-month follow up.

Outcome	DPP4i subtype					P-value[a]
	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin	Alogliptin	
Total no. of people	9,576	1,130	1,126	3,560	523	
Switching						
Number switched	221	44	63	144	36	
% switched	2.3	3.9	5.6	4.0	6.9	<0.001
Univariate HR (95% CI) for switching	1.0	1.58 (1.07–2.33)*	2.45 (1.77–3.40)*	1.49 (1.15–1.93)*	2.43 (1.55–3.83)*	
Multivariable HR (95% CI) for switching[b]	1.0	1.60 (1.08–2.37)*	2.44 (1.76–3.39)*	1.38 (1.05–1.81)*	2.42 (1.53–3.82)*	
Non-adherent (PDC < 0.80)						
Number non-adherent	3,478	386	489	1,324	199	
% non-adherent	36.3	34.2	43.4	37.2	38.0	<0.001
Univariate OR (95% CI) for being non-adherent	1.0	0.85 (0.74–0.96)*	1.35 (1.19–1.52)*	1.04 (0.96–1.13)**	1.07 (0.90–1.28)**	
Multivariable OR of being non-adherent[b]	1.0	0.99 (0.86–1.13)**	1.41 (1.23–1.60)*	0.93 (0.85–1.01)**	1.13 (0.93–1.36)**	
Non-Persistence (≥90 gap)						
Number non-persistent	2,837	358	404	1,112	159	
% non-persistent	29.6	31.7	35.9	31.2	30.4	<0.001
Univariate HR (95% CI) for non-persistence	1.0	1.06 (0.95–1.19)**	1.26 (1.14–1.41)*	1.07 (0.99–1.14)**	1.03 (0.88–1.21)**	
Multivariable HR for non-persistence[b]	1.0	1.11 (0.98–1.24)**	1.27 (1.15–1.42)*	1.01 (0.94–1.09)**	1.06 (0.90–1.24)**	

* $p < 0.05$;

** $p > 0.05$; PDC = proportion of days covered; HR = hazard ratio; OR = odds ratio;

[a] proportions were compared via a chi-square test;

[b] all logistic regression and cox models were adjusted for age, sex, concession status, pre-index medication use and whether the index therapy was a fixed-dose combination (FDC) with metformin

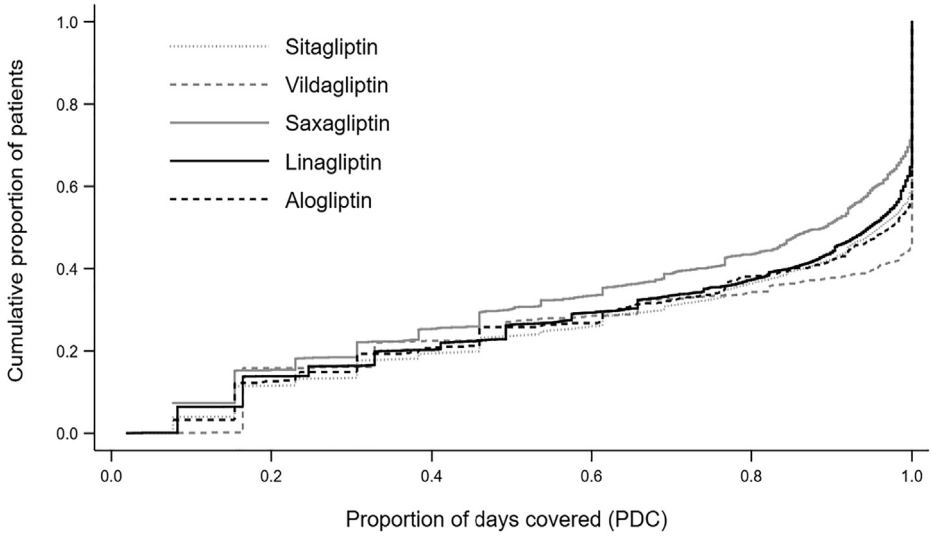

Fig. 1 – One-year cumulative PDC among the people prescribed various DPP4-is.

with an excess risk of hospitalisation for heart failure compared to placebo [19], the results of cardiovascular safety trials of sitagliptin (TECOS), linagliptin (CAROLINA) [23], and alogliptin (EXAMINE) [20] found them to be safe. Thus, overall, clinicians and patients may perceive low clinical utility in switching from one DPP-4is to another. However, we did find higher likelihoods of switching among people prescribed vildagliptin, linagliptin, alogliptin and saxagliptin compared to sitagliptin which deserves further exploration to better understand the contributory factors.

In prior studies DPP-4is have been found to be associated with better adherence and persistence than sulphonlyureas, thiazolidiones, meglitinides, α-glucosidase inhibitors and GLP-1 inhibitors [43–48]. Nonetheless, in these studies, up to 58.8% of people prescribed DPP-4is were non-adherent and 26.5–46.2% were non-persistent within 12 months [43–49]. In our study, we found that 36.0% and 30.0% of the people dispensed DPP4-is were non-adherent or non-persistent, respectively, in 12 months of follow-up. In RCTs, DPP-4is have been shown to be associated with improved glycaemic control (in a way similar to sulfonylureas or pioglitazone) in patients who previously were not achieving glycaemic targets with metformin [17]. However, these results have been reported against a background of high adherence and persistence. Carls and colleagues have shown that medication adherence contributes to about three-quarters of the gap between real world and expected RCT results for DPP-4is in terms of achieving reductions in HbA_{1c} levels [3]. Therefore, our results accord with those of earlier studies, and re-iterate the need for more efforts to improve adherence and persistence if the benefits of DPP-4is observed in RCTs are to be realised in routine clinical settings. In particular, interventions aimed at addressing the modifiable risk factors of non-adherence and non-persistence (such as health literacy, quality of the relationship between patient and physician) to DPP4-is are required [50,51].

Few studies have assessed the comparative adherence and persistence among people prescribed individual DPP-4is and to our knowledge, none included data on all the five DPP-4is as done in this study. Rascati and colleagues [49] analysed administrative claims data from Humana, a for-profit American health insurance company and found that among medicare advantage patients, those prescribed linagliptin were less likely to be adherent or persistent compared to people prescribed saxagliptin and sitagliptin. However, our study found no significant differences in the likelihoods of being non-adherent or non-persistent between the initiators of linagliptin and sitagliptin. Farr *et al.* [47] also using US data from the Truven Health MarketScan, found that compared to sitagliptin, initiators of saxagliptin were more likely to be adherent (adjusted OR 1.21, 95% CI 1.16–1.27), and sitagliptin initiators also had significantly greater likelihood of discontinuation (adjusted HR 1.16, 95% CI 1.12–1.20). In contrast, we found that the initiators of saxagliptin were more likely to be non-adherent or non-persistent compared to initiators of sitagliptin. We speculate that the differences in our findings and those of the US studies may be due to several factors, including variation in clinical practice, regulatory approvals, patients' expectations or preferences and health system factors including accessibility issues (e.g. co-payment) between Australia and the US [52]. For example, while DPP-4is may be used as monotherapy in the US [53], none of the DPP-4is is subsidised for use as a monotherapy under the PBS [14]. All of the gliptins are TGA-approved and PBS-subsidised for use in combination with either metformin or a sulfonylurea [13–15]. Saxagliptin is also TGA-indicated (but not PBS-subsidised) for use as initial combination therapy with metformin when appropriate (i.e. high initial HbA1c levels and where there is a high likelihood of poor response to monotherapy). Under the PBS there are further restrictions for the use of most gliptins, except alogliptin, among patients in whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated [14]. Regardless, the disparities in our results with the US-based studies deserve further investigation when comparative data become available.

Our study has important strengths. To our knowledge, this was the first study to describe in detail the patterns of switching, adherence, and persistence of DPP-4i among those with

type 2 diabetes in Australia. While studies in other jurisdictions have examined persistence and adherence among people prescribed DPP4-is, none have included data on all five DPP4-is as presented in this study. Moreover, our analysis was based on real world nationwide data from a 10% random sample of the PBS which has been used to study both the prescribing patterns and the effect of policy changes on the utilisation patterns of several medication classes including statins [16,26], BPL agents [54,55], antipsychotics [56], anxiolytics [57,58], and opioids [59], and has been shown to be highly reliable [25].

Our study also has some important limitations. In particular, the PBS datasets did not capture the reasons why people dispensed prescribed DPP-4is were non-adherent or non-persistent nor did it record adverse events. Thus, future studies need to investigate this to inform the design of interventions to improve adherence and persistence. The data also did not contain clinical information such as HbAIc or FBG, and therefore we could not ascertain the effect of medication adherence on clinical outcomes. Furthermore, the PBS datasets do not capture in-hospital medication use. Hence, for people hospitalised during the analysis period, it is possible that we may have overestimated non-adherence or non-persistence. Additionally, as our study was a single in-class analysis, we are unable to establish whether this population would exhibit similar adherence and persistence to other antihyperglycemic agents, and as such comparative analysis across different diabetes medication groups may be needed. The PBS dataset did not include dosage information, so we assumed as per the PBS guidelines that dispensations were for one month [30,31]. However, in rare cases such as among patients travelling overseas, supply may exceed one month. For such patients, the PDC over the one-year analysis period could likely be underestimated leading to misclassification as nonadherent or nonpersistent. However, such misclassification, if present, is likely to be non-differential and unlikely to significantly change our findings. Finally, the analysis presented are indirect measures of adherence and we could not confirm whether people actually took the dispensed medication [16].

5. Conclusion

In this large Australian cohort study using real world data, we found that about 1 in 3 people dispensed DPP-4is were non-adherent or non-persistent at 12 months. There were no significant differences in the adherence and persistence rates between alogliptin, vildagliptin or linagliptin and sitagliptin. However, saxagliptin was associated with greater likelihoods of being non-adherent or non-persistent compared to sitagliptin. Switching was lowest among users of sitagliptin. Interventions to improve adherence and persistence among people prescribed DPP-4is may be necessary.

Author contributions

RO, JI, and DL conceived the study. RO, JI, JSB, and DL acquired data; RO conducted the analysis. All authors contributed to data interpretation, manuscript preparation and revision for intellectual content. All authors approved the final version before submission.

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Declaration of Competing 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. EZ reports receiving study funds from Amgen, AstraZeneca, Pfizer and Shire for work unrelated to this study. DJM reports past participation in advisory boards and/or receiving honoraria from AstraZeneca, and Bayer for work unrelated to this study.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107909.

REFERENCES

[1] Edelman SV, Polonsky WH. Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control. Diabetes Care 2017;40:1425–32.
[2] Capoccia K, Odegard PS, Letassy N. Medication Adherence With Diabetes Medication: A Systematic Review of the Literature. The Diabetes educator. 2016;42:34–71.
[3] Carls GS, Tuttle E, Tan RD, Huynh J, Yee J, Edelman SV, et al. Understanding the Gap Between Efficacy in Randomized Controlled Trials and Effectiveness in Real-World Use of GLP-1 RA and DPP-4 Therapies in Patients With Type 2 Diabetes. Diabetes Care 2017;40:1469–78.
[4] Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. Diabet Med. 2015;32:725–37.
[5] McGovern A, Tippu Z, Hinton W, Munro N, Whyte M, de Lusignan S. Comparison of medication adherence and persistence in type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2018;20:1040–3.
[6] Cramer JA. A systematic review of adherence with medications for diabetes. Diabetes Care 2004;27:1218–24.
[7] Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Prevalence and economic consequences of medication adherence in diabetes: a systematic literature review. Managed care interface. 2006;19:31–41.
[8] Egede LE, Gebregziabher M, Dismuke CE, Lynch CP, Axon RN, Zhao Y, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. Diabetes Care 2012;35:2533–9.

[9] Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018;8 e016982.
[10] Singh AK. Dipeptidyl peptidase-4 inhibitors: Novel mechanism of actions. Indian J Endocrinol Metab. 2014;18:753–9.
[11] Omar B, Ahren B. Pleiotropic mechanisms for the glucose-lowering action of DPP-4 inhibitors. Diabetes 2014;63:2196–202.
[12] Bohannon N. Overview of the gliptin class (dipeptidyl peptidase-4 inhibitors) in clinical practice. Postgrad Med. 2009;121:40–5.
[13] Gunton J, Cheung N, Davis T, Colagiuri S, Zoungas S. A new blood glucose management algorithm for type 2 diabetes A position statement of the. Australian Diabetes Society. Australian Diabetes Society 2016.
[14] Newcastle Evaluation Group (NEG). Review of Diabetes Management Terms of Reference 3 : Final Report May 2014. Australian Government Department of Health; 2014.
[15] NPS MedicineWise. Sitagliptin, vildagliptin and saxagliptin — dipeptidyl peptidase-4 inhibitors ('gliptins') for add-on therapy in type 2 diabetes mellitus. NPS MedicineWise; 2011.
[16] Ofori-Asenso R, Ilomaki J, Tacey M, Zomer E, Curtis AJ, Bell JS, et al. Patterns of statin use and long-term adherence and persistence among older adults with diabetes. J Diabetes. 2018;10:699–707.
[17] Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344 e1369.
[18] Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. Diabetes Care 2014;37:2884–94.
[19] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–26.
[20] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369:1327–35.
[21] Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015;373:232–42.
[22] Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 2019;321:69–79.
[23] Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. JAMA. 2019. 2019 Sep 19. doi: 10.1001/jama.2019.13772. [Epub ahead of print]
[24] Drug utilisation sub-committee (DUSC). Medicines for the treatment of diabetes Department of Health; 2017.
[25] Mellish L, Karanges EA, Litchfield MJ, Schaffer AL, Blanch B, Daniels BJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. BMC research notes. 2015;8:634.
[26] Ofori-Asenso R, Ilomaki J, Tacey M, Si S, Curtis AJ, Zomer E, et al. Predictors of first-year nonadherence and discontinuation of statins among older adults: a retrospective cohort study. Br J Clin Pharmacol. 2019;85:227–35.
[27] Collaborating WHO. Centre for Drug Statistics Methodology. Purpose of the ATC/DDD system. Norwegian Institute for. Public Health 2018.
[28] Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin. 2009;25:2303–10.
[29] Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. 2015;2015 217047.
[30] The Department of Haealth. Pharmaceutical Benefits Scheme (PBS). 2015.
[31] Hynd A, Roughead EE, Preen DB, Glover J, Bulsara M, Semmens J. Increased patient co-payments and changes in PBS-subsidised prescription medicines dispensed in Western Australia. Aust N Z J Public Health. 2009;33:246–52.
[32] Dharan NJ, Radovich T, Che S, Petoumenos K, Juneja P, Law M, et al. HIV treatment regimens and adherence to national guidelines in Australia: an analysis of dispensing data from the Australian pharmaceutical benefits scheme. BMC Public Health. 2019;19:13.
[33] Arnet I, Greenland M, Knuiman MW, Rankin JM, Hung J, Nedkoff L, et al. Operationalization and validation of a novel method to calculate adherence to polypharmacy with refill data from the Australian pharmaceutical benefits scheme (PBS) database. Clin Epidemiol. 2018;10:1181–94.
[34] Warren JR, Falster MO, Fox D, Jorm L. Factors influencing adherence in long-term use of statins. Pharmacoepidemiol Drug Saf. 2013;22:1298–307.
[35] Warren JR, Falster MO, Tran B, Jorm L. Association of Continuity of Primary Care and Statin Adherence. PLoS ONE 2015;10 e0140008.
[36] Ofori-Asenso R, Liew D, Lalic S, Mazidi M, Magliano DJ, Ademi Z, et al. Adherence, Persistence, and Switching Among People Prescribed Sodium Glucose Co-transporter 2 Inhibitors: A Nationwide Retrospective Cohort Study. Adv Ther 2019.
[37] Ofori-Asenso R, Ilomaki J, Tacey M, Zomer E, Curtis AJ, Si S, et al. Switching, Discontinuation, and Reinitiation of Statins Among Older Adults. J Am Coll Cardiol. 2018;72:2675–7.
[38] Ofori-Asenso R, Ilomaki J, Tacey M, Zomer E, Curtis AJ, Bell JS, et al. Predictors of statin use among older adults: A nationwide cross-sectional study. J Clin Lipidol. 2019;13(156–62) e1.
[39] Li CJ, Liu XJ, Bai L, Yu Q, Zhang QM, Yu P, et al. Efficacy and safety of vildagliptin, Saxagliptin or Sitagliptin as add-on therapy in Chinese patients with type 2 diabetes inadequately controlled with dual combination of traditional oral hypoglycemic agents. Diabetology & metabolic syndrome. 2014;6:69.
[40] Craddy P, Palin HJ, Johnson KI. Comparative effectiveness of dipeptidylpeptidase-4 inhibitors in type 2 diabetes: a systematic review and mixed treatment comparison. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2014;5:1–41.
[41] Khalse M, Bhargava A. A Review on Cardiovascular Outcome Studies of Dipeptidyl Peptidase-4 Inhibitors. Indian J Endocrinol Metab. 2018;22:689–95.
[42] Pinto LC, Rados DV, Barkan SS, Leitao CB, Gross JL. Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: A meta-analysis with trial sequential analysis. Sci Rep. 2018;8:782.
[43] McGovern A, Hinton W, Calderara S, Munro N, Whyte M, de Lusignan S. A Class Comparison of Medication Persistence in People with Type 2 Diabetes: A Retrospective Observational Study. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2018;9:229–42.
[44] Cai J, Divino V, Burudpakdee C. Adherence and persistence in patients with type 2 diabetes mellitus newly initiating

canagliflozin, dapagliflozin, dpp-4s, or glp-1s in the United States. Curr Med Res Opin. 2017;33:1317–28.
[45] Cai J, Wang Y, Baser O, Xie L, Chow W. Comparative persistence and adherence with newer anti-hyperglycemic agents to treat patients with type 2 diabetes in the United States. Journal of medical economics. 2016;19:1175–86.
[46] Jermendy G, Kiss Z, Rokszin G, Abonyi-Toth Z, Wittmann I, Kempler P. Persistence to Treatment with Novel Antidiabetic Drugs (Dipeptidyl Peptidase-4 Inhibitors, Sodium-Glucose Co-Transporter-2 Inhibitors, and Glucagon-Like Peptide-1 Receptor Agonists) in People with Type 2 Diabetes: A Nationwide Cohort Study. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2018;9:2133–41.
[47] Farr AM, Sheehan JJ, Curkendall SM, Smith DM, Johnston SS, Kalsekar I. Retrospective analysis of long-term adherence to and persistence with DPP-4 inhibitors in US adults with type 2 diabetes mellitus. Adv Ther. 2014;31:1287–305.
[48] Nishimura R, Kato H, Kisanuki K, Oh A, Hiroi S, Onishi Y, et al. Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study. BMJ Open. 2019;9 e025806.
[49] Rascati KL, Worley K, Meah Y, Everhart D. Adherence, Persistence, and Health Care Costs for Patients Receiving Dipeptidyl Peptidase-4 Inhibitors. Journal of managed care & specialty pharmacy. 2017;23:299–306.
[50] Kirkman MS, Rowan-Martin MT, Levin R, Fonseca VA, Schmittdiel JA, Herman WH, et al. Determinants of adherence to diabetes medications: findings from a large pharmacy claims database. Diabetes Care 2015;38:604–9.
[51] Tiv M, Viel JF, Mauny F, Eschwege E, Weill A, Fournier C, et al. Medication adherence in type 2 diabetes: the ENTRED study 2007, a French Population-Based Study. PLoS ONE 2012;7 e32412.
[52] Jones PD, Seoane L, Deichmann Jr R, Kantrow C. Differences and similarities in the practice of medicine between australia and the United States of america: challenges and opportunities for the university of queensland and the ochsner clinical school. The Ochsner journal. 2011;11:253–8.
[53] Zhang Q, Rajagopalan S, Mavros P, Engel SS, Davies MJ, Yin D, et al. Baseline characteristic differences between patients prescribed sitagliptin vs. other oral antihyperglycemic agents: analysis of a US electronic medical record database. Curr Med Res Opin 2010;26:1697–703.
[54] Si S, Ofori-Asenso R, Briffa T, Sanfilippo FM, Ilomaki J, Qin X, et al. Long-term persistence and adherence to blood pressure lowering agents among older Australians. Pharmacoepidemiol Drug Saf 2019.
[55] Schaffer AL, Pearson SA, Buckley NA. How does prescribing for antihypertensive products stack up against guideline recommendations? An Australian population-based study (2006–2014). Br J Clin Pharmacol. 2016;82:1134–45.
[56] Hollingworth SA, Siskind DJ, Nissen LM, Robinson M, Hall WD. Patterns of antipsychotic medication use in Australia 2002–2007. The Australian and New Zealand journal of psychiatry. 2010;44:372–7.
[57] Schaffer AL, Buckley NA, Cairns R, Pearson SA. Interrupted Time Series Analysis of the Effect of Rescheduling Alprazolam in Australia: Taking Control of Prescription Drug Use. JAMA internal medicine. 2016;176:1223–5.
[58] Schaffer AL, Buckley NA, Cairns R, Pearson S. Comparison of Prescribing Patterns Before and After Implementation of a National Policy to Reduce Inappropriate Alprazolam Prescribing in Australia. JAMA Netw Open. 2019;2 e1911590.
[59] Lalic S, Ilomaki J, Bell JS, Korhonen MJ, Gisev N. Prevalence and incidence of prescription opioid analgesic use in Australia. Br J Clin Pharmacol. 2019;85:202–15.