Received: 27 September 2021 | Revised: 21 October 2021 | Accepted: 31 October 2021

DOI: 10.1111/dom.14603

REVIEW ARTICLE

WILEY

Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: A systematic literature review

Marc Evans MD[1] | Susanne Engberg MD[2] | Mads Faurby MSc[2] | João Diogo Da Rocha Fernandes MSc[2] | Pollyanna Hudson MSc[3] | William Polonsky PhD[4,5]

[1]Department of Diabetes and Endocrinology, University Hospital Llandough, Penarth, UK

[2]Novo Nordisk A/S, Søborg, Denmark

[3]Mtech Access, Bicester, UK

[4]Behavioral Diabetes Institute, San Diego, California, USA

[5]Department of Medicine, University of California, San Diego, California, USA

Correspondence
Marc Evans, MD, Department of Diabetes and Endocrinology, University Hospital, Llandough, Penarth, Cardiff, Wales, UK.
Email: marclyndon1@hotmail.com

Present address
João Diogo Da Rocha Fernandes, Current address: Ferring Pharmaceuticals A/S, Copenhagen, Denmark

Funding information
Novo Nordisk A/S

Abstract

We designed a systematic literature review to identify available evidence on adherence to and persistence with antidiabetic medication in people with type 2 diabetes (T2D). Electronic screening and congress searches identified real-world noninterventional studies (published between 2010 and October 2020) reporting estimates of adherence to and persistence with antidiabetic medication in adults with T2D, and associations with glycaemic control, microvascular and/or macrovascular complications, hospitalizations and healthcare costs. Ninety-two relevant studies were identified, the majority of which were retrospective and reported US data. The proportions of patients considered adherent (median [range] 51.2% [9.4%-84.3%]) or persistent (median [range] 47.7% [16.9%-94.0%]) varied widely across studies. Multiple studies reported an association between greater adherence/persistence and greater reductions in glycated haemoglobin levels. Better adherence/persistence was associated with fewer microvascular and/or macrovascular outcomes, although there was little consistency across studies in terms of which outcomes were improved. More adherent and more persistent patients were typically less likely to be hospitalized or to have emergency department visits/admissions and spent fewer days in hospital annually than less adherent/persistent patients. Greater adherence and persistence were generally associated with lower hospitalization costs, higher pharmacy costs and lower or budget-neutral total healthcare costs compared with lower adherence/persistence. In conclusion, better adherence and persistence in people with T2D is associated with lower rates of microvascular and/or macrovascular outcomes and inpatient hospitalization, and lower or budget-neutral total healthcare expenditure. Education and treatment

strategies to address suboptimal adherence and persistence are needed to improve clinical and economic outcomes.

KEYWORDS
adherence, GLP-1RAs, healthcare costs, insulin, oral antidiabetic medications, persistence, resource utilization, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (T2D) is a chronic, progressive disease that has a substantial clinical impact on patients as well as imposing an economic burden on healthcare systems.[1] T2D is associated with cardiovascular, renal, retinal and neurological complications, and it has been estimated that 50% of people with T2D have early signs of these conditions at diagnosis.[2] Complications account for a considerable proportion of the lifetime costs of treating diabetes,[3] and are also linked to reduced health-related quality of life[4] and increased indirect costs from lost workplace productivity.[5] The risk of T2D complications is higher in patients with poor glycaemic control.[6-12] Various demographic, social, and patient- and physician-related factors contribute to the likelihood of people with T2D achieving glycaemic control,[13,14] including the extent to which patients are adherent to and persistent with antidiabetic medication.[15,16] Although there is evidence that adherence and persistence are associated with improved outcomes, medication-taking behaviour is not usually considered by decision-makers and payers alongside clinical benefits and health utility gains when evaluating T2D treatments.

Patients are closely monitored in clinical trials, therefore adherence and persistence during these trials is not representative of medication-taking behaviour in real-world settings.[17] Observational studies must thus be used to estimate adherence and persistence rates and to evaluate the link between medication-taking behaviour and clinical or economic outcomes. As there is a considerable volume of real-world evidence in T2D, a systematic review of the literature is a robust way to identify such studies and collate their results. An earlier systematic literature review (SLR) of articles published from 2007 to 2014 found that higher rates of adherence to antidiabetic medication were associated with not only better glycaemic control and fewer hospitalizations but also lower healthcare costs.[18] During the past few years, however, the use of newer drug classes such as dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors has increased.[19] Consequently, a new review of the literature is warranted to examine medication-taking behaviour and its link to outcomes across the current spectrum of available antidiabetic medications.

The present SLR was designed to identify relevant evidence on the patterns of adherence to and persistence with antidiabetic medication in people with T2D, as well as clinical and economic outcomes linked to adherence and persistence, over the period of 2010 to 2020.

2 | MATERIALS AND METHODS

2.1 | Systematic literature review

Electronic searches were designed to identify real-world non-interventional studies reporting estimates of adherence to and persistence with antidiabetic medications in people with T2D and associations with clinical and economic outcomes. Journal publications from January 2010 to October 2020 were included in electronic searches, and relevant congress publications from January 2018 to October 2020 were also identified. Systematic searches were conducted in October 2020 in the Medical Literature Analysis and Retrieval System Online (MEDLINE), Embase, Evidence-Based Medicine Reviews and EconLit. Any databases that were not up to date were also searched via the University of York Centres for Reviews and Dissemination website. The search strategy for MEDLINE is shown in Table S1. The congresses searched are listed in Table S2.

Titles and abstracts were screened in a double-blind manner by two independent reviewers to determine whether they met the eligibility criteria for inclusion (Table 1). Any disagreements between reviewers were referred to a third reviewer and resolved by consensus. The reference lists of included studies and relevant reviews/editorials were reviewed to identify any further eligible publications that had not been detected in the database searches. All publications meeting the criteria were obtained as full articles and reassessed, and relevant data from publications included after full-text review were entered into a data extraction table. Quality assessment was carried out on the studies using the critical appraisal tools from the Joanna Briggs Institute.[20]

2.2 | Outcomes

Relevant outcomes in the SLR were estimates of adherence to and persistence with antidiabetic medications and their associations with glycaemic control, microvascular and macrovascular outcomes, hospitalizations and healthcare costs. We defined adherence as the extent to which a person's antidiabetic medication-taking behaviour corresponds with recommendations from their healthcare provider. In the studies identified, it was most often measured as proportion of days covered (PDC) by medication, or medication possession ratio (MPR) as detailed below. Persistence, the duration of antidiabetic medication use by a patient, was usually measured as the proportion of patients who remained on treatment for a specified period or as the mean number of days to treatment discontinuation within the observation period.

TABLE 1 Eligibility criteria

Criteria	Include	Exclude
Population	People with T2D, regardless of age or disease severity	• Animal/in vitro studies
		• T1D
		• Gestational diabetes
		• Mixed populations where results for T2D are not reported separately
Intervention	Pharmacological antidiabetic medications	Nonpharmacological interventions (eg, diet-based interventions, lifestyle changes, guidelines, digital apps)
Outcomes	• Estimates of persistency and adherence to antidiabetic medications (including definition of adherence, persistence, discontinuations)	Outcomes not listed in "include" column
	• Links between persistency and adherence to clinical and economic outcomes, specifically: ○ Healthcare costs (eg, total costs of care) ○ Hospitalizations ○ HbA1c (glycaemic control) ○ Macrovascular/microvascular short-term and long-term outcomes	
	• Drivers of persistence and adherence (eg, mode of treatment administration, dosing regimen, patient characteristics)	
	• Statistical/analytical methods	
	• Data sources	
Study design	Studies which have utilized real-world data to investigate outcomes of interest, including:	• Reviews/editorials
	• Cohort studies (prospective/retrospective)	• RCTs
	• Case-control studies	• Nonrandomized experimental studies
	• Before-and-after studies (observational)	• Cross-sectional studies
	• Correlation studies	• Case reports/case series
	• Longitudinal studies	• Animal/in vitro studies
Geography	No restriction	-
Publication date	Full publications: 2010 onwards (last 10 years) Conference abstracts: 2017 onwards (last 3 years)	Full publications: pre-2010 Conference abstracts: pre-2017
Language	English-language publications or non-English-language publications with an English abstract	Non-English-language publications without an English abstract

Abbreviations: HbA1c, glycated haemoglobin; RCT, randomized controlled trial; T1D, type 1 diabetes; T2D, type 2 diabetes.

3 | RESULTS

3.1 | Search results

In total, 3227 references were included for screening, of which 508 were determined to be relevant for full-text review (see Figure S1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] diagram). In total, 255 publications met the inclusion criteria at full-text review, and an additional eight publications were identified by hand searches.

Only full publications reporting data on the associations between adherence/persistence and the clinical/economic outcomes of interest were prioritized for data extraction and are the focus of this manuscript (n = 92).[21-112] The remaining 171 publications (conference abstracts [n = 47] and full publications reporting estimates of adherence/persistence but not associations with clinical/economic outcomes [n = 124]) were excluded.

3.2 | Study characteristics

Of the 92 full publications included,[21-112] 39 studies were published from 2010 to 2015 and 53 from 2016 to 2020. Most of the studies were retrospective observational cohort studies or database analyses; only 13 of the 92 studies (14%) were prospective.[21,23,33,45,59,67,70,87,92,93,97,102,111] Sixty of the 92 studies (65%) were from the United States. The remaining studies were from Europe (Germany,[24,93] Italy,[35,81] Spain,[47] Sweden[112] and Switzerland[57]; 7% of studies in total), Asia (China,[29] India,[97] Iran,[45] Israel,[74,75] Pakistan[92] and Taiwan[1,33]; 9% of studies in total), Canada (2%)[49,111] and Australia (1%).[64] Three studies were multinational

(3%).[70,102,106] Some studies had additional patient inclusion criteria such as a focus on older[28,77,85,96] or younger patients[27] or US veterans.[41-43,62,78] Table S3 shows the number of studies reporting each outcome.

3.3 | Estimates of adherence

In total, 71 studies included estimates of adherence (cited in Table S3). There was variation in how adherence was defined: 30 studies used PDC[22,28-31,34,36-39,48,50,56,57,60,63,71,75,76,78-80,82,83,85,86,88,98,100,110] and 26 studies used the MPR.[23,29,32,33,35,41,42,44,49,51,53-55,64,68,73,77,90,91,95,101,103,104,106,108,109] MPR is calculated as the total days' supply of treatment in the defined period, divided by the total number of days in the defined period. It is easy to estimate but can lead to overestimation of adherence if patients refill prescriptions early.[113] PDC is the most commonly used indirect measure of adherence for chronic diseases.[113] It is a more conservative measure than MPR as it accounts for overlapping days between prescriptions, so it cannot exceed 100% and therefore avoids falsely inflating mean population adherence. A PDC or MPR >80% was the threshold most frequently used to define adherence. Sixteen studies used other methods to define adherence, including self-reported measures and pill counts.[21,26,45-47,59,65,67,70,84,87,92-94,97,111]

Study follow-up duration ranged from 3 months to 10 years; 22 of the 71 studies had a 12-month follow-up period. Overall, 28 studies examined adherence to oral antidiabetic medications (OADs),[23,29,33,44,45,48,49,51,53-57,59,60,63,71,78,82,84-86,90-92,94,98,110] eight studies examined insulin,[26,32,39,70,77,88,104,109] seven studies examined injectable GLP-1RAs[30,37,38,79,80,83,106] and one study examined combination therapies.[75] Twenty studies reported adherence estimates for multiple classes (OADs, insulins and/or GLP-1RAs).[22,28,31,34-36,41,42,50,64,68,73,76,95,101,103,108] Seven studies did not report which antidiabetic medication(s) were included.[21,46,67,87,93,97,100]

Estimates of adherence varied considerably across studies, from 9.4% to 84.3%, across all medication classes. In general, reported rates of adherence to antidiabetic medications were relatively low: the median adherence across all studies was 51.2%. There was no clear consensus across studies regarding which medication classes were associated with higher adherence.

3.4 | Estimates of persistence

Estimates of persistence were reported in 31 studies (Table S3). In most studies, persistence was estimated based on the fill time between prescriptions or medication insurance claims. A gap in medication of ≥90 days was used to define discontinuation of medication (non-persistence) in nine studies,[24,29,30,40,58,69,96,106,109] whereas thresholds of ≥30,[25,31,52,89] 45,[79,80] 60[60,61,90,107] or 120 days[74] were used in other studies. Thirteen studies used other definitions for treatment gaps indicating discontinuation, such as a gap exceeding the 90th percentile of the mean duration of prescription fills.[77,104]

All 31 studies were retrospective. Study duration ranged from 6 months[75,107] to 3 years,[94] and was 12 months in 17 studies.[24,25,29-31,40,52,58,60,62,69,77,80,90,96,104] Overall, six studies examined persistence with OADs,[29,58,60,62,90,94] 11 studies with insulin,[24,25,40,52,61,77,89,96,104,107,109] seven studies with injectable GLP-1RAs[30,38,74,79-81,106] and four studies with combination therapies.[69,75,105,112] Three studies reported persistence estimates for multiple classes of antidiabetic medication.[27,31,66]

As was the case for adherence, persistence estimates varied widely among studies. The proportion of persistent patients ranged from 16.9% to 94.0% (median: 47.7%) in the studies reporting persistence with the most frequently studied classes of antidiabetic medication (OADs, insulins and GLP-1RAs).

3.5 | Associations between adherence/persistence and clinical and economic outcomes

3.5.1 | Glycaemic control

The specific glycaemic outcomes assessed in the studies examining adherence and persistence were overall change in glycated haemoglobin (HbA1c) level, expressed as a percentage, the proportion of patients achieving a target HbA1c or the incidence of hypoglycaemia.

An association between medication adherence and glycaemic control was reported in 42 studies (Table S3), 30 of which investigated OADs or multiple classes of antidiabetic medications. Better adherence to antidiabetic medication was generally associated with improved glycaemic control. A significantly greater decrease in HbA1c, or a lower HbA1c at follow-up, in more adherent versus less adherent patients was reported by most studies investigating this outcome.[22,29,30,44,47,73,79,85] In the remaining studies, the HbA1c reduction was nonsignificantly lower in the more adherent patients[94] or similar in the two groups.[78] The studies also consistently reported a significantly higher likelihood of more adherent patients achieving specific HbA1c targets, such as a ≥1.0% reduction[29] or reduction to <7%,[45] than less adherent patients.[29,45,56,78,82,84,85,90,94]

Four studies investigated the association between adherence to antidiabetic medication and risk of hypoglycaemia. Two of these studies investigated OADs (including sulphonylureas) and found no significant association,[78,91] and two studies investigating multiple antidiabetic medication classes found significantly lower rates of acute complications, including hypoglycaemia, in more versus less adherent patients.[28,34]

Fewer studies (n = 20) investigated the association between persistence and glycaemic control, including six studies examining injectable GLP-1RAs,[30,38,74,79,81,106] six examining combination therapies[27,66,69,75,105,112] and four each examining insulin[40,96,107,109] and OADs.[58,60,62,94] Persistence with medication was also generally associated with better glycaemic control. All but one[106] of the 14 studies examining GLP-1RAs, insulin or OADs reported a greater reduction in HbA1c, a greater proportion of patients achieving a target HbA1c

or a trend for better outcomes in persistent than in nonpersistent patients.[30,38,40,58,60,62,74,79,81,94,96,107,109] However, the results were more heterogeneous in the studies investigating combination therapies,[27,66,69,75,105,112] with only two studies clearly demonstrating superior glycaemic control in persistent compared with nonpersistent patients.[69,112] Lin et al,[69] in a study of patients receiving GLP-1RAs and basal insulin, also reported that medication persistence was linked to lower rates of hypoglycaemia. Figure 1 summarizes the findings from studies investigating the association between adherence or persistence and change in HbA1c.

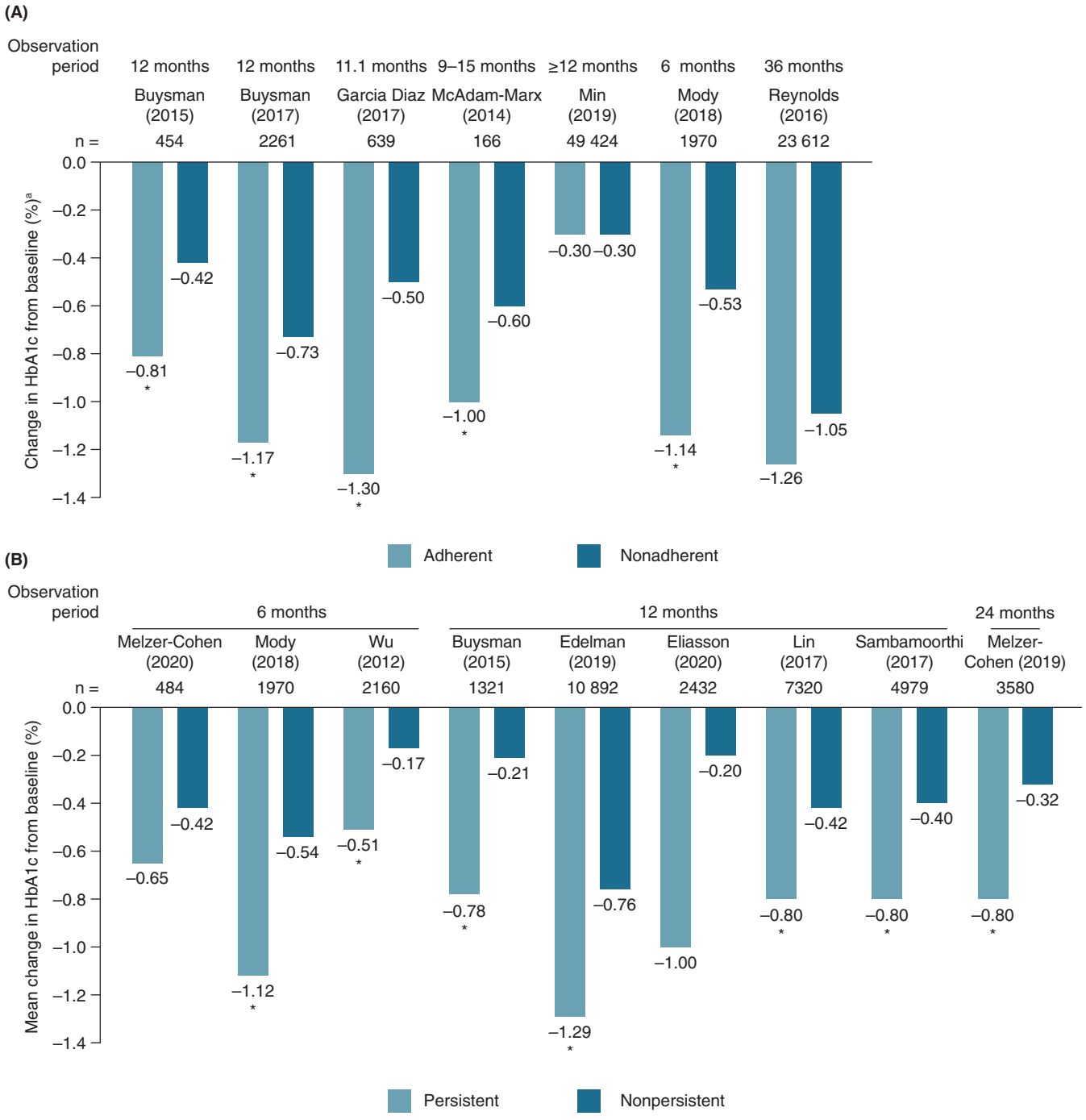

FIGURE 1 Change in HbA1c level from baseline by **A**, adherence to and **B**, persistence with antidiabetic medication in studies reporting this outcome. Bars with an asterisk indicate statistically significant results for adherent/persistent versus nonadherent/nonpersistent patients ($P < 0.05$). Min et al[78] and Reynolds et al[94] did not report *P* values for adherent versus nonadherent patients. Eliasson et al[112] and Melzer-Cohen et al[75] did not report *P* values for persistent versus nonpersistent patients. For adherence, studies were included if they reported change in HbA1c (follow-up times varied, as indicated for each study); for persistence, studies were included if they reported change in HbA1c over 6, 12 or 24 months. [a]Data shown are means, except for Min et al[78] which are median. HbA1c, glycated haemoglobin

TABLE 2 Findings from studies reporting associations between adherence or persistence and microvascular and/or macrovascular outcomes[a]

Study	Country, design	Treatment	Number of patients	Follow-up	Statistically significant associations		No significant associations found	
					Microvascular outcomes	Macrovascular outcomes	Microvascular outcomes	Macrovascular outcomes
Adherence								
An and Nichol[22]	United States, retrospective	OADs (biguanides, SUs, TZDs and/or insulin-sensitizing agents) and hypertension medication	2334	33 months	Any microvascular outcome (from renal failure and diabetic retinopathy)	Any macrovascular outcome (from MI and stroke)		
Fukuda and Mizobe[46]	Japan, retrospective	NR	11 331	96 months	Retinopathy Nephropathy Neuropathy			IHD Cerebrovascular disease Chronic arterial occlusion
Gatwood et al[48]	United States, retrospective	OADs (not specified)	159 032	5 years	Retinopathy	Stroke MI	Neuropathy	TIA Angina
Gibson et al[50]	United States, retrospective	SUs, meglitinides, biguanides, TZDs or AGIs	55 356 (OADs only)	18 months	Amputations/ulcers Renal events Neuropathy Retinopathy	MI	PVD	Cerebrovascular disease
		SUs, meglitinides, biguanides, TZDs or AGIs ± insulin	96 734 (OADs ± insulin)		Amputations/ulcers Renal events Neuropathy Retinopathy	MI Cerebrovascular disease	PVD	
Kim et al[63]	Korea, retrospective	Biguanide, SUs and others	65 067	10 years	NR	Cerebrovascular disease	NR	MI
Samu et al[97]	India, prospective	NR	86	3 months	Neuropathy (diabetic foot)	NR		
Sattler et al[98]	United States, prospective	OADs (not specified)	243	12 months	Rate of "no (microvascular or macrovascular) complication" was higher in adherent than nonadherent patients		PVD Nephropathy Neuropathy	Cerebrovascular complications Cardiovascular complications
Simpson et al[99]	United States, retrospective	OADs (not specified)	54 505	2.3 years (mean)		Any macrovascular outcome (from MI, stroke, heart failure, angina, CABG and angioplasty)	Any microvascular outcome (nephropathy, neuropathy, PVD or retinopathy)	
Yu et al[108]	United States, retrospective	Insulin and/or OADs	4708	12-90 months	Any microvascular outcome (from diabetic foot, neuropathy, retinopathy and nephropathy)	NR	NR	NR

TABLE 2 (Continued)

Study	Country, design	Treatment	Number of patients	Follow-up	Statistically significant associations		No significant associations found	
					Microvascular outcomes	Macrovascular outcomes	Microvascular outcomes	Macrovascular outcomes
Persistence								
Iglay et al[58]	United States, retrospective	SUs (first, second and third generation)	104 082	12 months	PVD	Stroke TIA CHF MI IHD		
Kalirai et al[61]	United States, retrospective	Insulin detemir or insulin glargine	23 645	24 months	Nephropathy Neuropathy		Retinopathy	CVD Cerebrovascular disease

Abbreviations: AGI, alpha glucosidase inhibitor; CABG, coronary artery bypass graft; CHF, chronic heart failure; CVD, cardiovascular disease; IHD, ischaemic heart disease; MI, myocardial infarction; NR, not reported; OAD, oral antidiabetic drug; PVD, peripheral vascular disease; SU, sulphonylurea; TIA, transient ischaemic attack; TZD, thiazolidinedione.

[a]Where there are discrepancies reported int results in the same article depending on the statistical model, the key findings as reported by authors in the article abstract are shown.

3.5.2 | Microvascular and macrovascular outcomes

Nine studies investigated the associations between adherence to antidiabetic medications and microvascular and/or macrovascular outcomes.[22,46,48,50,63,97-99,108] Five of these examined OADs[48,50,63,98,99]; medication class was mixed or not specified in the remaining studies.[22,46,97,108] Most studies were retrospective, and four of these studies had >54 000 participants.[48,50,63,99] The two prospective studies were small, with <250 patients each.[97,98] Follow-up ranged from 3 months[97] to 10 years,[63] and was ≥5 years in four studies.[46,48,63,108]

The microvascular outcomes examined included peripheral vascular disease, retinopathy, nephropathy, renal events, neuropathy and amputations/ulcers. The macrovascular outcomes included cerebrovascular disease, stroke, transient ischaemic attack, ischaemic heart disease, myocardial infarction and angina (Table 2). Six studies examined both microvascular and macrovascular outcomes.[22,46,48,50,98,99]

In general, adherence to antidiabetic medication was associated with lower rates of both microvascular and macrovascular complications compared with nonadherence, but there was substantial heterogeneity across the study results (Table 2). For example, the four largest studies, all of which assessed adherence to OADs, found that adherent patients have significantly lower rates of some outcomes but not others, with no consensus on which outcome category (microvascular or macrovascular) was significantly linked to adherence.[48,50,63,99] The medications that patients received were not fully reported in each study, and therefore no inferences between outcomes and medication class can be made using these data.

Two large US studies that examined the association between persistence and microvascular and macrovascular outcomes were identified (Table 2). Iglay et al[58] included 104 082 patients followed up for 1 year and found lower rates in persistent versus nonpersistent patients for all cardiovascular, cerebrovascular and peripheral vascular outcomes examined. Kalirai et al[61] studied 23 645 patients and reported significantly lower rates of nephropathy and neuropathy after insulin initiation in persistent versus nonpersistent patients, but no significant difference in the rates of retinopathy, cardiovascular disease (CVD) or cerebrovascular disease.[61]

3.5.3 | Hospitalizations

The association between medication adherence and rates of hospitalization was reported in 18 studies, for patients receiving insulin,[26,88] OADs,[33,48,54,55,57,71,94] injectable GLP-1RAs[83] or multiple treatment classes,[28,34,36,47,50,101] or with treatment not specified.[93,100] The specific outcomes investigated included hospital inpatient admissions, emergency department (ED) visits and admissions, and outpatient visits. Follow-up duration ranged from 6 months to 7 years, with a median of 3 years. Most studies included >5000 patients; six studies had >90 000 patients (Table S4).[28,34,48,50,100,101]

Patients who were more adherent to antidiabetic medications were generally less likely to be hospitalized (and/or were less likely to

have ED visits or admissions, or spent fewer days in hospital annually) than less adherent patients in the majority of studies across all treatment classes (Table S4).[26,28,33,34,48,50,54,57,71,83,88,94,100,101] The association between adherence and outpatient visits was more complex. Some studies found no significant association between adherence and outpatient visits,[47,93] whereas others found that adherence

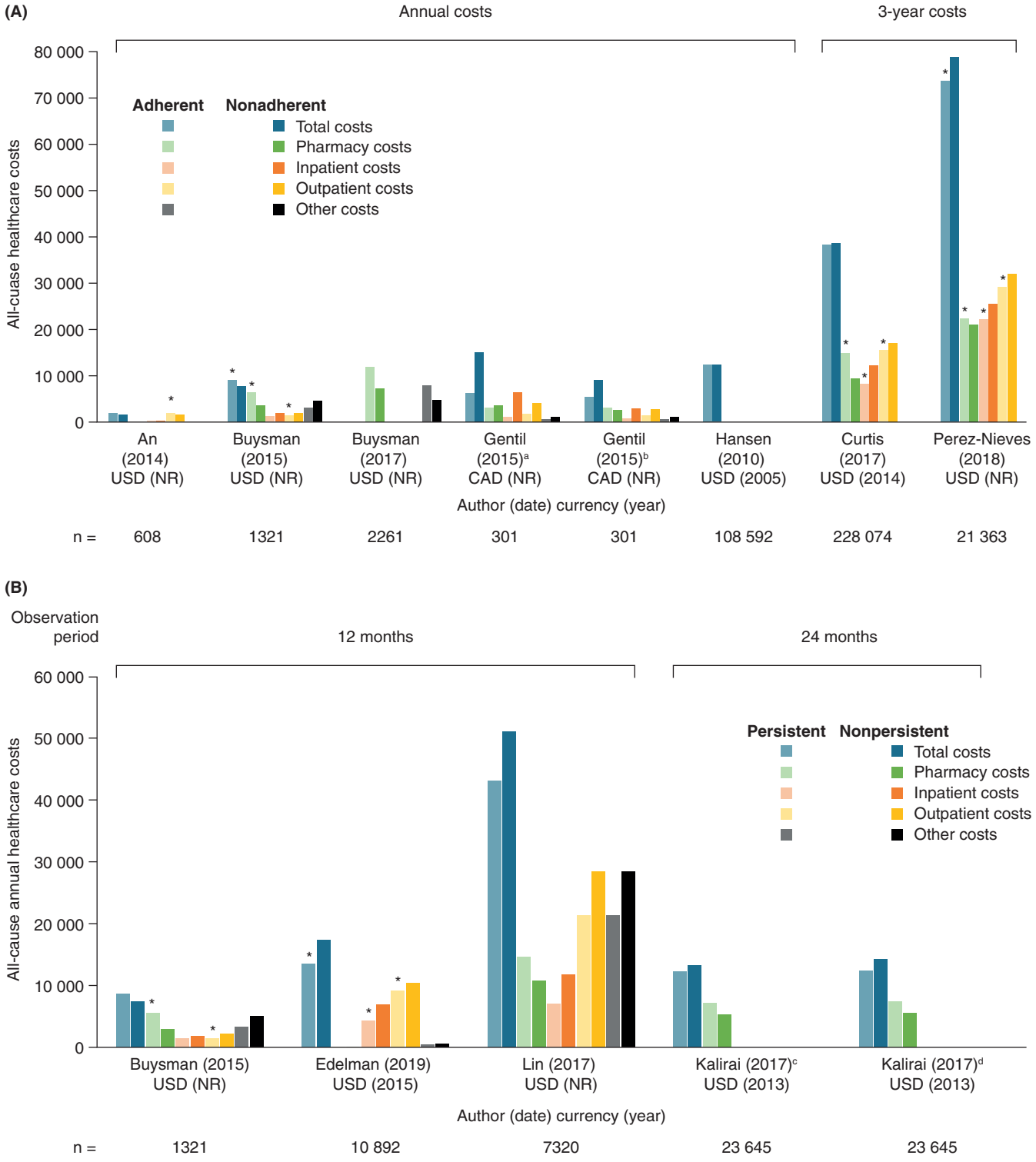

FIGURE 2 Healthcare costs by **A**, adherence to and **B**, persistence with antidiabetic medication in selected relevant studies. Bars with an asterisk indicate statistically significant results for adherent/persistent versus nonadherent/nonpersistent patients ($P < 0.05$). Buysman et al,[29] Gentil et al[49] and Hansen et al[53] did not report *P* values for adherent versus nonadherent patients. Kalirai et al[61] and Lin et al[69] did not report *P* values for persistent versus nonpersistent patients. [a]Data from the subset of patients with depression/anxiety. [b]Data from the subset of patients without depression/anxiety. [c]Data from the first year of treatment. [d]Data from the second year of treatment. CAD, Canadian dollar; ED, emergency department; FU, follow-up; NR, not reported; USD, United States dollars

was linked to having more outpatient visits (Table S4).[36,50,55] Among the latter studies, two were designed to investigate whether the rate of outpatient visits influenced adherence, and concluded that more frequent outpatient visits led to better adherence to antidiabetic medication; however, these studies did not report rates of hospitalization or other interactions with the healthcare system.[36,55] The third study reported that greater adherence was linked to more outpatient visits, but fewer ED visits and hospitalizations.[50]

Eleven studies reported data on the association between persistence and the rate of hospitalization (including ED visits and/or ED admissions) in patients receiving insulin,[40,52,61,77,89,104,107] injectable GLP-1RAs,[74,106] OADs[94] or combination therapy.[69] Follow-up duration ranged from 6 months to 3 years, and sample sizes ranged from 534 to 23 645 patients (Table S5). Interruption or discontinuation of therapy was associated with an increased rate of hospitalization and longer hospital stays in most studies,[40,52,69,77,89,94,104,107] but not in all studies.[74,106] However, four[52,61,69,77] of the five studies that reported data on outpatient visits found no significant association with persistence (Table S5).

3.5.4 | Healthcare costs

Associations between adherence and healthcare costs in people with T2D were reported in 20 studies that investigated OADs,[23,29,33,49,53,54] insulin,[26,32,39,88] injectable GLP-1RAs[30] or multiple treatment classes,[28,34,35,41,50,68,72,76] or that did not specify the treatment.[46] Thirteen studies were from the United States, with the remaining studies from Canada,[49] Italy,[35] Japan,[46] Korea[23,54] and Taiwan.[33,68] Seven studies had a follow-up duration of ≤1 year and nine studies had ≥3 years' follow-up. Sample size varied widely, from 301 to 0.74 million patients, with a median of 17 982 patients.

Despite substantial heterogeneity across studies, greater adherence was generally associated with lower inpatient admission costs but higher pharmacy costs.[26,28-30,33,34,39,41,49,72,76,88] Most studies found that total healthcare expenditure in adherent patients was lower than[28,32,39,49,53,54,72,88] or similar to[23,26,34,76] that in nonadherent patients (Figure 2), but in two studies adherence was associated with higher total costs than nonadherence.[30,33]

In total, 11 studies reported data on healthcare costs associated with persistence on insulin,[24,25,40,52,61,77,89,96,107] injectable GLP-1RAs[30] and/or combination therapies.[69] The study duration was relatively short for studying persistence: 6 months[107] or 12 months[24,25,30,40,52,69,77,96] in most studies and 24 months[61,89] in two studies. Persistence was typically associated with higher pharmacy costs[24,25,29,30,40,52,61,69,77,89,107] but lower healthcare costs, including acute care costs, inpatient and outpatient visits and ED visits.[24,25,52,61,69,89] Overall, total healthcare expenditure for persistent patients across studies was typically lower than or similar to that for nonpersistent patients (Figure 2).

4 | DISCUSSION

Observational studies are recognized by payers and other stakeholders as an important means of obtaining data on medication-taking behaviour, which cannot be assessed in clinical trials.[17] We reviewed the available evidence from observational studies on adherence to and persistence with antidiabetic medication in people with T2D, and how these relate to clinical and economic outcomes. Despite heterogeneity across studies in terms of antidiabetic medications used, length of follow-up, geography, patients' clinical and demographic characteristics and the specific outcomes examined, some findings were consistent. Overall rates of adherence and persistence in people with T2D are suboptimal, as previously reported,[114] but better adherence and persistence are associated with clinical benefits, including improved glycaemic control, fewer hospitalizations and ED visits, and lower incidences of microvascular and macrovascular complications. Adherence and persistence were linked to lower rates of some microvascular and/or macrovascular outcomes but not others, which may be attributable in part to disparities in medications used, study setting and design. Overall, several outcomes that predict disability and absenteeism in people with T2D, including myocardial infarction, stroke, peripheral neuropathy, retinopathy and diabetic foot,[115] were associated with worse adherence and/or persistence in at least some of the studies identified in this review, highlighting the relevance of these outcomes in treatment decision-making.

As a chronic condition affecting multiple organ systems, T2D is associated with substantial and rising healthcare costs. The International Diabetes Federation estimates that the worldwide health expenditure due to diabetes in adults has increased threefold in the past 15 years, from $232 billion in 2007 to $760 billion in 2019, of which 50% is attributable to managing diabetes complications[115]; therefore, the influence of adherence and persistence on healthcare costs in T2D is a pertinent area for study. In the present SLR, we found an association between better adherence and persistence and either lower or similar total healthcare costs, compared with worse adherence and persistence. Cost estimates varied widely across the studies identified, which was likely to be owing to disparities in study variables and location. Generally, both adherence and persistence were associated with higher pharmacy costs that were offset by lower hospitalization costs, resulting in lower or budget-neutral total healthcare expenditure for adherent/persistent patients. An association between adherence and reduced total health expenditure has been reported for several other chronic conditions.[116] Notably, more than two-thirds of the studies reporting cost data were from North America, and most of the remainder were from Asia, with only one study from a European country (Italy). Further evidence is therefore needed, in particular from Europe, on the associations between adherence and persistence and healthcare costs.

This was a large SLR, including studies from all geographical regions and examining a broad range of outcomes. Although the outcomes examined are not independent from each other—for example, reduced rates of complications result in lower healthcare costs—this is

nonetheless a comprehensive overview of the impact of adherence and persistence. Further SLRs could be used to capture additional outcomes linked to suboptimal adherence and persistence: previous studies have reported increased absenteeism,[117] more days of short-term disability[117] and greater mortality.[63,118] Although most studies reported the antidiabetic medication class used, discrepancies across studies in patient characteristics, study methodology and duration did not enable direct comparisons to be made between medication classes for any of the outcomes. Approximately half of the studies identified in the SLR were published between 2010 and 2015, meaning that more recently approved antidiabetic medications were not included in most of these studies. Further good-quality observational studies are needed to systematically compare adherence and persistence across different drug classes and drugs with different modes and frequency of administration and different treatment benefits for complications such as CVD.

Several limitations of the studies identified in this review should be noted, particularly the fact that many were retrospective analyses using healthcare and claims databases. Such studies are inherently vulnerable to the effects of confounding, whereby certain factors, such as education, lifestyle and other sociodemographic variables, could influence both adherence to medication and health outcomes. Inertia in treatment decision-making may also confound the relationship between medication-taking behaviour and outcomes: adherence to or persistence with antidiabetic medication that has not been optimized is unlikely to be reflected in clinical benefit. Furthermore, PDC and MPR are useful proxies for adherence, but may not always accurately reflect actual medication-taking behaviour. Finally, although comparing different antidiabetic medication classes is of great clinical interest, the substantial inter-study heterogeneity in patient characteristics and methods used to estimate adherence/persistence in this SLR did not enable meaningful comparisons across drug classes.

The present SLR highlights the benefits that can be achieved by using therapeutic approaches that improve adherence and persistence as well as clinical outcomes. Across various diseases, higher compliance, a close correlate of adherence, has been reported for dosing regimens that require less frequent administration.[119] To illustrate, a study included in this SLR examining two populations receiving GLP-1RAs in Germany and the United Kingdom found that twice-daily exenatide was associated with a 30% to 40% greater likelihood of treatment discontinuation than once-daily liraglutide.[106] Furthermore, a recent meta-analysis of seven studies investigating 75 159 people with T2D reported an 11% lower risk of nonadherence with once-weekly versus once-daily injectable GLP-1RAs.[120] Persistence is also favourably influenced by less frequent dosing regimens: in a real-world, United States-based study, the use of once-weekly injectable GLP-1RAs was associated with better persistence and adherence than daily regimens in propensity score-matched cohorts.[121] Evidence from populations with other chronic diseases such as osteoporosis[122] and CVD[123] also indicates that lower dosing frequency predicts better adherence and/or persistence. The use of medications early in the treatment pathway that are linked to symptomatic benefit in addition to adherence and persistence may provide an ongoing positive effect on health outcomes; however, to achieve sustained improvements, the use of treatment regimens that enhance adherence and persistence should also be considered as part of wider, holistic treatment strategies for people with T2D. As indicated by the studies identified in this review, many of which were carried out in primary care databases, routine management of patients with T2D is increasingly delivered in a primary care setting.[124] Consequently, it is vital that primary care physicians receive education in strategies to maximize adherence and persistence, in communicating the benefits of this to patients, and in understanding and addressing reasons for poor adherence or persistence. Other approaches to maximizing the likelihood of adherence and persistence that may be applicable in primary care include the use of personalized digital technologies.[125]

In this SLR of studies published between 2010 and 2020, greater adherence to and persistence with antidiabetic medication in adults with T2D was typically associated with better clinical and economic outcomes. These findings suggest that the clinical benefits of adherence and persistence for patients are likely to be reflected in positive impacts for payers, healthcare systems and society. Further investigation of the factors that determine medication-taking behaviour should be used to identify barriers to optimal adherence and persistence in people with T2D.

ACKNOWLEDGMENTS

The development of this SLR was carried out by Mtech Access, Bicester, UK, funded by Novo Nordisk A/S. The authors acknowledge the medical writing support of Oxford PharmaGenesis, Oxford, UK, funded by Novo Nordisk A/S.

CONFLICT OF INTEREST

M.E. has received honoraria from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. S.E. and M.F. are employees of Novo Nordisk A/S. J.F. was an employee of Novo Nordisk A/S at the time of the review, and is now an employee of Ferring Pharmaceuticals A/S. P.H. is an employee of Mtech Access, funded by Novo Nordisk A/S to carry out the SLR. W.P. has served as a consultant for Eli Lilly, Novo Nordisk and Sanofi.

AUTHOR CONTRIBUTIONS

Mads Faurby, João Diogo Da Rocha Fernandes and Pollyanna Hudson: designed the SLR. All authors contributed to the interpretation of data and critical review of the manuscript and approved the final version for submission.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14603.

DATA AVAILABILITY STATEMENT

'All data analyzed during this systematic literature review are published elsewhere, and relevant collated data are included in this article

[and/or] its supplementary material files. Further enquiries can be directed to the corresponding author'

ORCID

Marc Evans https://orcid.org/0000-0003-0671-0778

REFERENCES

1. Alzaid A, Ladron de Guevara P, Beillat M, Lehner Martin V, Atanasov P. Burden of disease and costs associated with type 2 diabetes in emerging and established markets: systematic review analyses. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21(4):785-798.
2. Diabetes.co.uk. Type 2 Diabetes. 15 January 2019. https://www.diabetes.co.uk/type2-diabetes.html. Accessed August 5, 2021.
3. Zhuo X, Zhang P, Hoerger TJ. Lifetime direct medical costs of treating type 2 diabetes and diabetic complications. *Am J Prev Med*. 2013;45(3):253-261.
4. Shao H, Yang S, Fonseca V, Stoecker C, Shi L. Estimating quality of life decrements due to diabetes complications in the United States: the health utility index (HUI) diabetes complication equation. *Pharmacoeconomics*. 2019;37(7):921-929.
5. Andersson E, Persson S, Hallen N, et al. Costs of diabetes complications: hospital-based care and absence from work for 392,200 people with type 2 diabetes and matched control participants in Sweden. *Diabetologia*. 2020;63(12):2582-2594.
6. Kontopantelis E, Springate DA, Reeves D, et al. Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study. *Diabetologia*. 2015;58(3):505-518.
7. Rawshani A, Svensson AM, Gudbjörnsdottir S. Glycaemic control and incidence of dementia in 363,573 patients with type 2 diabetes: an observational study. *Diabetologia*. 2015;58(1):S5.
8. Svensson E, Baggesen LM, Johnsen SP, et al. Early glycemic control and magnitude of HbA1c reduction predict cardiovascular events and mortality: population-based cohort study of 24,752 metformin initiators. *Diabetes Care*. 2017;40(6):800-807.
9. Tijera FHDL, Servin-Caamano A, Navarro-Estrada A, Soto-Martinez K, Alexanderson-Rosas EG, Cruz-Estrada A. Uncontrolled glycaemia is the strongest predictive factor for liver-related and cardiovascular death, in cirrhotic patients with type 2 diabetes. *Gastroenterology*. 2019;156(6):S-1367.
10. Turgeon RD, Koshman SL, Youngson E, Pearson GJ. Association between hemoglobin A1c and major adverse coronary events in patients with diabetes following coronary artery bypass surgery. *Pharmacotherapy*. 2020;40(2):116-124.
11. van Wijngaarden RPT, Overbeek JA, Heintjes EM, et al. Relation between different measures of glycemic exposure and microvascular and macrovascular complications in patients with type 2 diabetes mellitus: an observational cohort study. *Diabetes Ther*. 2017;8(5):1097-1109.
12. Mitsios JP, Ekinci EI, Mitsios GP, Churilov L, Thijs V. Relationship between glycated hemoglobin and stroke risk: a systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7(11):e007858.
13. Cheng LJ, Wang W, Lim ST, Wu VX. Factors associated with glycaemic control in patients with diabetes mellitus: a systematic literature review. *J Clin Nurs*. 2019;28(9-10):1433-1450.
14. de Pablos-Velasco P, Parhofer KG, Bradley C, et al. Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: data from the PANORAMA study. *Clin Endocrinol (Oxf)*. 2014;80(1):47-56.
15. Rhee MK, Slocum W, Ziemer DC, et al. Patient adherence improves glycemic control. *Diabetes Educ*. 2005;31(2):240-250.
16. Guerci B, Chanan N, Kaur S, Jasso-Mosqueda JG, Lew E. Lack of treatment persistence and treatment nonadherence as barriers to glycaemic control in patients with type 2 diabetes. *Diabetes Ther*. 2019;10(2):437-449.
17. Roberts MH, Ferguson GT. Real-world evidence: bridging gaps in evidence to guide payer decisions. *Pharmacoecon Open*. 2021;5(1):3-11.
18. Capoccia K, Odegard PS, Letassy N. Medication adherence with diabetes medication: a systematic review of the literature. *Diabetes Educ*. 2016;42(1):34-71.
19. Engler C, Leo M, Pfeifer B, et al. Long-term trends in the prescription of antidiabetic drugs: real-world evidence from the Diabetes Registry Tyrol 2012-2018. *BMJ Open Diabetes Res Care*. 2020;8(1):e001279.
20. Joanna Briggs Institute (JBI). Critical Appraisal Tools [online]. https://joannabriggs.org/critical-appraisal-tools. Accessed September 9, 2021.
21. Aikens JE, Piette JD. Longitudinal association between medication adherence and glycaemic control in type 2 diabetes. *Diabet Med*. 2013;30(3):338-344.
22. An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care*. 2013;51(10):879-887.
23. An SY, Kim HJ, Chun KH, et al. Clinical and economic outcomes in medication-adherent and -nonadherent patients with type 2 diabetes mellitus in the Republic of Korea. *Clin Ther*. 2014;36(2):245-254.
24. Anderten H, Dippel FW, Kostev K. Early discontinuation and related treatment costs after initiation of basal insulin in type 2 diabetes patients: a German primary care database analysis. *J Diabetes Sci Technol*. 2015;9(3):644-650.
25. Ascher-Svanum H, Lage MJ, Perez-Nieves M, et al. Early discontinuation and restart of insulin in the treatment of type 2 diabetes mellitus. *Diabetes Ther*. 2014;5(1):225-242.
26. Ayyagari R, Wei W, Cheng D, Pan C, Signorovitch J, Wu EQ. Effect of adherence and insulin delivery system on clinical and economic outcomes among patients with type 2 diabetes initiating insulin treatment. *Value Health*. 2015;18(2):198-205.
27. Barnes NS, White PC, Hutchison MR. Time to failure of oral therapy in children with type 2 diabetes: a single center retrospective chart review. *Pediatr Diabetes*. 2012;13(7):578-582.
28. Boye KS, Curtis SE, Lage MJ, Garcia-Perez LE. Associations between adherence and outcomes among older, type 2 diabetes patients: evidence from a medicare supplemental database. *Patient Prefer Adherence*. 2016;10:1573-1581.
29. Buysman EK, Anderson A, Bacchus S, Ingham M. Retrospective study on the impact of adherence in achieving glycemic goals in type 2 diabetes mellitus patients receiving canagliflozin. *Adv Ther*. 2017;34(4):937-953.
30. Buysman EK, Liu F, Hammer M, Langer J. Impact of medication adherence and persistence on clinical and economic outcomes in patients with type 2 diabetes treated with liraglutide: a retrospective cohort study. *Adv Ther*. 2015;02(32):341-355.
31. Carls GS, Tuttle E, Tan RD, 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(11):1469-1478.
32. Chandran A, Bonafede MK, Nigam S, Saltiel-Berzin R, Hirsch LJ, Lahue BJ. Adherence to insulin pen therapy is associated with reduction in healthcare costs among patients with type 2 diabetes mellitus. *Am Health Drug Benefits*. 2015;8(3):148-158.
33. Cheng SH, Chen CC, Tseng CH. Does medication adherence lead to lower healthcare expenses for patients with diabetes? *Am J Manag Care*. 2013;19(8):662-670.
34. Curtis SE, Boye KS, Lage MJ, Garcia-Perez LE. Medication adherence and improved outcomes among patients with type 2 diabetes. *Am J Manag Care*. 2017;23(7):e208-e214.

35. Degli Esposti L, Saragoni S, Buda S, Sturani A, Degli EE. Glycemic control and diabetes-related health care costs in type 2 diabetes; retrospective analysis based on clinical and administrative databases. *Clinicoecon Outcomes Res*. 2013;5(1):193-201.
36. Dobbins JM, Elliott SW, Cordier T, et al. Primary care provider encounter cadence and hba1c control in older patients with diabetes. *Am J Prev Med*. 2019;57(4):e95-e101.
37. Durden E, Lenhart G, Lopez-Gonzalez L, Hammer M, Langer J. Predictors of glycemic control and diabetes-related costs among type 2 diabetes patients initiating therapy with liraglutide in the United States. *J Med Econ*. 2016;19(4):403-413.
38. Durden E, Liang M, Fowler R, Panton UH, Mocevic E. The effect of early response to GLP-1 RA therapy on long-term adherence and persistence among type 2 diabetes patients in the United States. *J Manag Care Spec Pharm*. 2019;25(6):669-676.
39. Eby EL, Bajpai S, Faries DE, Haynes VS, Lage MJ. The association between adherence to insulin therapy and health care costs for adults with type 2 diabetes: evidence from a U.S. retrospective claims database. *J Manag Care Spec Pharm*. 2020;26(9):1081-1089.
40. Edelman SV, Ermakova A, Xiong Y, Sieradzan R, Taylor SD. Persistence with basal-bolus insulin therapy in patients with type 2 diabetes mellitus and effect on clinical and economic outcomes: a retrospective claims database study. *J Manag Care Spec Pharm*. 2019;25(12):1420-1431.
41. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. *Diabetes Care*. 2012;35(12):2533-2539.
42. Egede LE, Gebregziabher M, Echols C, Lynch CP. Longitudinal effects of medication nonadherence on glycemic control. *Ann Pharmacother*. 2014;48(5):562-570.
43. Egede LE, Gebregziabher M, Hunt KJ, et al. Regional, geographic, and racial/ethnic variation in glycemic control in a national sample of veterans with diabetes. *Diabetes Care*. 2011;34(4):938-943.
44. Farmer AJ, Rodgers LR, Lonergan M, et al. Adherence to oral glucose-lowering therapies and associations with 1-year HbA1c: a retrospective cohort analysis in a large primary care database. *Diabetes Care*. 2016;39(2):258-263.
45. Farsaei S, Sabzghabaee AM, Zargarzadeh AH, Amini M. Adherence to glyburide and metformin and associated factors in type 2 diabetes in Isfahan, Iran. *Iran J Pharm Sci*. 2011;10(4):933-939.
46. Fukuda H, Mizobe M. Impact of nonadherence on complication risks and healthcare costs in patients newly-diagnosed with diabetes. *Diabetes Res Clin Pract*. 2017;123:55-62.
47. García Díaz E, Ramírez Medina D, García López A, Morera Porras ÓM. Determinants of adherence to hypoglycemic agents and medical visits in patients with type 2 diabetes mellitus. *Endocrinol Diabetes Nutr*. 2017;64(10):531-538.
48. Gatwood JD, Chisholm-Burns M, Davis R, et al. Differences in health outcomes associated with initial adherence to oral antidiabetes medications among veterans with uncomplicated type 2 diabetes: a 5-year survival analysis. *Diabet Med*. 2018;35(11):1571-1579.
49. Gentil L, Vasiliadis HM, Préville M, Berbiche D. Adherence to oral antihyperglycemic agents among older adults with mental disorders and its effect on health care costs, Quebec, Canada, 2005-2008. *Prev Chronic Dis*. 2015;12:E230.
50. Gibson TB, Song X, Alemayehu B, et al. Cost sharing, adherence, and health outcomes in patients with diabetes. *Am J Manag Care*. 2010;16(8):589-600.
51. Gordon J, McEwan P, Idris I, Evans M, Puelles J. Treatment choice, medication adherence and glycemic efficacy in people with type 2 diabetes: a UK clinical practice database study. *BMJ Open Diabetes Res Care*. 2018;6:e000512.
52. Hadjiyianni I, Desai U, Suzuki S, et al. Basal insulin persistence, associated factors, and outcomes after treatment initiation: a retrospective database study among people with type 2 diabetes mellitus in Japan. *Diabetes Ther*. 2017;8(1):149-166.
53. Hansen RA, Farley JF, Droege M, Maciejewski ML. A retrospective cohort study of economic outcomes and adherence to monotherapy with metformin, pioglitazone, or a sulfonylurea among patients with type 2 diabetes mellitus in the United States from 2003 to 2005. *Clin Ther*. 2010;32(7):1308-1319.
54. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. *Med Care*. 2011;49(4):378-384.
55. Hong JS, Kang HC. Relationship between continuity of ambulatory care and medication adherence in adult patients with type 2 diabetes in Korea: a longitudinal analysis. *Med Care*. 2014;52(5):446-453.
56. Horii T, Momo K, Yasu T, Kabeya Y, Atsuda K. Determination of factors affecting medication adherence in type 2 diabetes mellitus patients using a nationwide claim-based database in Japan. *PLoS One*. 2019;14:e0223431.
57. Huber CA, Rapold R, Brüngger B, Reich O, Rosemann T. One-year adherence to oral antihyperglycemic medication and risk prediction of patient outcomes for adults with diabetes mellitus: an observational study. *Medicine*. 2016;95(26):e3994.
58. Iglay K, Qiu Y, Steve Fan CP, Li Z, Tang J, Laires P. Risk factors associated with treatment discontinuation and down-titration in type 2 diabetes patients treated with sulfonylureas. *Curr Med Res Opin*. 2016;32(9):1567-1575.
59. Ito H, Ando S, Tsugami E, et al. Changes in medication adherence and unused drugs after switching from daily dipeptidyl peptidase-4 inhibitors to once-weekly trelagliptin in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2019;153:41-48.
60. Jude EB, O'Leary C, Myland M, et al. Evaluating glycaemic control in patients poorly controlled on oral antidiabetic drugs in real-world setting: results from assessing the Appropriate Timing of Type 2 diAbetes INtensification (ATTAIN). *Endocrinol Diabetes Metab*. 2020;3:e00094.
61. Kalirai S, Duan R, Liu D, Reed BL. Economic impact of treatment duration and persistence with basal insulin in previously insulin-naive users. *J Manag Care Spec Pharm*. 2017;23(3):327-336.
62. Kim N, Agostini JV, Justice AC. Refill adherence to oral hypoglycemic agents and glycemic control in veterans. *Ann Pharmacother*. 2010;44(5):800-808.
63. Kim YY, Lee JS, Kang HJ, Park SM. Effect of medication adherence on long-term all-cause-mortality and hospitalization for cardiovascular disease in 65,067 newly diagnosed type 2 diabetes patients. *Sci Rep*. 2018;8(1):12190.
64. Krass I, Hebing R, Mitchell B, et al. Diabetes management in an Australian primary care population. *J Clin Pharm Ther*. 2011;36(6):664-672.
65. Kreyenbuhl J, Leith J, Medoff DR, et al. A comparison of adherence to hypoglycemic medications between type 2 diabetes patients with and without serious mental illness. *Psychiatry Res*. 2011;188(1):109-114.
66. Levin PA, Wei W, Zhou S, Xie L, Baser O. Outcomes and treatment patterns of adding a third agent to 2 OADS in patients with type 2 diabetes. *J Manag Care Spec Pharm*. 2014;20(5):501-512.
67. Li X, Gao M, Zhang S, et al. Medication adherence mediates the association between type d personality and high HbA1c level in Chinese patients with type 2 diabetes mellitus: a six-month follow-up study. *J Diabetes Res*. 2017;2017:7589184.
68. Lin CS, Khan H, Chang RY, et al. A study on the impact of poor medication adherence on health status and medical expense for diabetes mellitus patients in Taiwan: a longitudinal panel data analysis. *Medicine (Baltimore)*. 2020;99(26):e20800.
69. Lin J, Lingohr-Smith M, Fan T. Real-world medication persistence and outcomes associated with basal insulin and glucagon-like peptide

1 receptor agonist free-dose combination therapy in patients with type 2 diabetes in the US. *Clinicoecon Outcomes Res*. 2017;9:19-29.
70. Linetzky B, Jiang D, Funnell MM, Curtis BH, Polonsky WH. Exploring the role of the patient-physician relationship on insulin adherence and clinical outcomes in type 2 diabetes: insights from the MOSAIc study. *J Diabetes*. 2017;9(6):596-605.
71. Lo-Ciganic WH, Donohue JM, Thorpe JM, et al. Using machine learning to examine medication adherence thresholds and risk of hospitalization. *Med Care*. 2015;53(8):720-728.
72. MacEwan JP, Sheehan JJ, Yin W, et al. The relationship between adherence and total spending among medicare beneficiaries with type 2 diabetes. *Am J Manag Care*. 2017;23(4):248-252.
73. McAdam-Marx C, Bellows BK, Unni S, et al. Impact of adherence and weight loss on glycemic control in patients with type 2 diabetes: cohort analyses of integrated medical record, pharmacy claims, and patient-reported data. *J Manag Care Spec Pharm*. 2014;20(7):691-700.
74. Melzer-Cohen C, Chodick G, Husemoen LLN, Rhee N, Shalev V, Karasik A. A retrospective database study of liraglutide persistence associated with glycemic and body weight control in patients with type 2 diabetes. *Diabetes Ther*. 2019;10(2):683-696.
75. Melzer-Cohen C, Chodick G, Naftelberg S, Shehadeh N, Karasik A. Metabolic control and adherence to therapy in type 2 diabetes mellitus patients using IDegLira in a real-world setting. *Diabetes Ther*. 2020;11(1):185-196.
76. Meng J, Casciano R, Lee YC, et al. Effect of diabetes treatment-related attributes on costs to type 2 diabetes patients in a real-world population. *J Manag Care Spec Pharm*. 2017;23(4):446-452.
77. Miao R, Wei W, Lin J, Xie L, Baser O. Does device make any difference? A real-world retrospective study of insulin treatment among elderly patients with type 2 diabetes. *J Diabetes Sci Technol*. 2014;8(1):150-158.
78. Min JY, Griffin MR, Chipman J, et al. Recent metformin adherence and the risk of hypoglycaemia in the year following intensification with a sulfonylurea. *Diabet Med*. 2019;36(4):482-490.
79. Mody R, Grabner M, Yu M, et al. Real-world effectiveness, adherence and persistence among patients with type 2 diabetes mellitus initiating dulaglutide treatment. *Curr Med Res Opin*. 2018;34(6):995-1003.
80. Mody R, Huang Q, Yu M, et al. Adherence, persistence, glycaemic control and costs among patients with type 2 diabetes initiating dulaglutide compared with liraglutide or exenatide once weekly at 12-month follow-up in a real-world setting in the United States. *Diabetes Obes Metab*. 2019;21(4):920-929.
81. Morieri ML, Frison V, Rigato M, et al. Effectiveness of dulaglutide in the real world and in special populations of type 2 diabetic patients. *J Clin Endocrinol Metab*. 2020;105(7):dgaa204.
82. Mosen DM, Glauber H, Stoneburner AB, Feldstein AC. Assessing the association between medication adherence and glycemic control. *Am J Pharm Benefits*. 2017;9(3):82-88.
83. Nguyen H, Dufour R, Caldwell-Tarr A. Glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy adherence for patients with type 2 diabetes in a Medicare population. *Adv Ther*. 2017;34(3):658-673.
84. Nichols GA, Conner C, Brown JB. Initial nonadherence, primary failure and therapeutic success of metformin monotherapy in clinical practice. *Curr Med Res Opin*. 2010;26(9):2127-2135.
85. Nichols GA, Raebel MA, Dyer W, Schmittdiel JA. The effect of age and comorbidities on the association between the medicare STAR oral antihyperglycemic adherence metric and glycemic control. *J Manag Care Spec Pharm*. 2018;24(9):856-861.
86. Nichols GA, Rosales AG, Kimes TM, Tunceli K, Kurtyka K, Mavros P. The change in HbA1c associated with initial adherence and subsequent change in adherence among diabetes patients newly initiating metformin therapy. *J Diabetes Res*. 2016;2016(9687815):1-5.
87. Parchman ML, Zeber JE, Palmer RF. Participatory decision making, patient activation, medication adherence, and intermediate clinical outcomes in type 2 diabetes: a STARNet study. *Ann Fam Med*. 2010;8(5):410-417.
88. Perez-Nieves M, Boye KS, Kiljanski J, Cao D, Lage MJ. Adherence to basal insulin therapy among people with type 2 diabetes: a retrospective cohort study of costs and patient outcomes. *Diabetes Ther*. 2018;9(3):1099-1111.
89. Perez-Nieves M, Kabul S, Desai U, et al. Basal insulin persistence, associated factors, and outcomes after treatment initiation among people with type 2 diabetes mellitus in the US. *Curr Med Res Opin*. 2016;32(4):669-680.
90. Pollack M, Chastek B, Williams SA, Moran J. Impact of treatment complexity on adherence and glycemic control: an analysis of oral antidiabetic agents. *J Clin Outcomes Manag*. 2010;17(6):20-30.
91. Quilliam BJ, Ozbay AB, Sill BE, Kogut SJ. The association between adherence to oral anti-diabetic drugs and hypoglycaemia in persons with type 2 diabetes. *Diabet Med*. 2013;30(11):1305-1313.
92. Rana B, Bukhsh A, Khan TM, Sarwar A, Omer MO, Jamshed SQ. Evaluation of therapeutic effectiveness of prescribed medications in patients with type 2 diabetes mellitus: findings from a tertiary care hospital, Lahore, Pakistan. *J Pharm Bioallied Sci*. 2017;9(2):121-125.
93. Raum E, Krämer HU, Rüter G, et al. Medication non-adherence and poor glycaemic control in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2012;97(3):377-384.
94. Reynolds K, An J, Wu J, et al. Treatment discontinuation of oral hypoglycemic agents and healthcare utilization among patients with diabetes. *J Diabetes Complications*. 2016;30(8):1443-1451.
95. Rodgers LR, Weedon MN, Henley WE, Hattersley AT, Shields BM. Cohort profile for the MASTERMIND study: using the clinical practice research Datalink (CPRD) to investigate stratification of response to treatment in patients with type 2 diabetes. *BMJ Open*. 2017;7:e017989.
96. Sambamoorthi U, Garg R, Deb A, Fan T, Boss A. Persistence with rapid-acting insulin and its association with A1C level and severe hypoglycemia among elderly patients with type 2 diabetes. *Curr Med Res Opin*. 2017;33(7):1309-1316.
97. Samu AM, Amirthalingam PS, Mohammed OS. Assessment of patient medication adherence among the type 2 diabetes mellitus population with peripheral diabetic neuropathy in South India. *J Taibah Univ Med Sci*. 2017;12(2):164-168.
98. Sattler EL, Lee JS, Bhargava V. Food insecurity and medication adherence in low-income older Medicare beneficiaries with type 2 diabetes. *J Nutr Gerontol Geriatr*. 2014;33(4):401-417.
99. Simpson SH, Lin M, Eurich DT. Medication adherence affects risk of new diabetes complications: a cohort study. *Ann Pharmacother*. 2016;50(9):741-746.
100. Snider JT, Seabury S, Lopez J, McKenzie S, Wu Y, Goldman DP. Impact of type 2 diabetes medication cost sharing on patient outcomes and health plan costs. *Am J Manag Care*. 2016;22(6):433-440.
101. Sun P, Lian J. Treatment adherence in newly diagnosed type 2 diabetes: patient characteristics and long-term impact of adherence on inpatient care utilization. *Postgrad Med*. 2016;128(4):338-345.
102. Vichayanrat A, Matawaran BJ, Wibudi A, et al. Assessment of baseline characteristics, glycemic control and oral antidiabetic treatment in Asian patients with diabetes: the registry for assessing OAD usage in diabetes management (REASON) Asia study. *J Diabetes*. 2013;5(3):309-318.
103. Virdi N, Daskiran M, Nigam S, Kozma C, Raja P. The association of self-monitoring of blood glucose use with medication adherence and glycemic control in patients with type 2 diabetes initiating non-insulin treatment. *Diabetes Technol Ther*. 2012;14(9):790-798.
104. Wang L, Wei W, Miao R, Xie L, Baser O. Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: a comparative retrospective database study. *BMJ Open*. 2013;3:e002348.

105. Wilding J, Godec T, Khunti K, et al. Changes in HbA1c and weight, and treatment persistence, over the 18 months following initiation of second-line therapy in patients with type 2 diabetes: results from the United Kingdom clinical practice research Datalink. *BMC Med*. 2018;16(116):116.
106. Wilke T, Mueller S, Groth A, et al. Non-persistence and non-adherence of patients with type 2 diabetes mellitus in therapy with glp-1 receptor agonists: a retrospective analysis. *Diabetes Ther*. 2016;7(1):105-124.
107. Wu EQ, Zhou S, Yu A, et al. Outcomes associated with insulin therapy disruption after hospital discharge among patients with type 2 diabetes mellitus who had used insulin before and during hospitalization. *Endocr Pract*. 2012;18(5):651-659.
108. Yu AP, Yu YF, Nichol MB. Estimating the effect of medication adherence on health outcomes among patients with type 2 diabetes—an application of marginal structural models. *Value Health*. 2010;13(8):1038-1045.
109. Zhou FL, Xie L, Pan C, et al. Relationship between treatment persistence and A1C trends among patients with type 2 diabetes newly initiating basal insulin. *Diabetes Obes Metab*. 2018;20(5):1298-1301.
110. Zhu VJ, Tu W, Rosenman MB, Overhage JM. Nonadherence to oral antihyperglycemic agents: subsequent hospitalization and mortality among patients with type 2 diabetes in clinical practice. *Stud Health Technol Inform*. 2015;216:60-63.
111. Zongo A, Guénette L, Moisan J, Grégoire JP. Predictive validity of self-reported measures of adherence to noninsulin antidiabetes medication against control of glycated hemoglobin levels. *Can J Diabetes*. 2016;40(1):58-65.
112. Eliasson B, Ekelund J, Miftaraj M, et al. Persistence with ideglira in patients in clinical practice: a nationwide observational study in Sweden. *Diabetes Ther*. 2020;11(8):1807-1820.
113. Forbes CA, Deshpande S, Sorio-Vilela F, et al. A systematic literature review comparing methods for the measurement of patient persistence and adherence. *Curr Med Res Opin*. 2018;34(9):1613-1625.
114. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307.
115. International Diabetes Federation. IDF Diabetes Atlas, 9th Edition 2019. https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf#page=62&zoom=auto. Accessed August 3, 2021.
116. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Aff (Millwood)*. 2011;30(1):91-99.
117. Carls GS, Roebuck MC, Brennan TA, Slezak JA, Matlin OS, Gibson TB. Impact of medication adherence on absenteeism and short-term disability for five chronic diseases. *J Occup Environ Med*. 2012;54(7):792-805.
118. Yen FS, Wei JC, Liu JS, Hsu CC, Hwu CM. Persons with type 2 diabetes and high insulin persistence were associated with a lower risk of mortality: a nationwide retrospective cohort study. *J Diabetes Investig*. 2021;12(2):146-154.
119. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001;23(8):1296-1310.
120. Weeda ER, Muraoka AK, Brock MD, Cannon JM. Medication adherence to injectable glucagon-like peptide-1 (GLP-1) receptor agonists dosed once weekly vs once daily in patients with type 2 diabetes: a meta-analysis. *Int J Clin Pract*. 2021;75(9):e14060.
121. Liebl A, Arora R, Fernandes J, Polonsky W. Adherence and persistence in patients with type 2 diabetes initiating once-weekly versus daily injectable GLP-1 RAs in US clinical practice (STAY study). American Diabetes Association 81st Scientific Session 2021; 83-LB. https://eventpilot.us/web/page.php?page=IntHtml&project=ADA21&id=1397. Accessed August 16, 2021.
122. Fatoye F, Smith P, Gebrye T, Yeowell G. Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review. *BMJ Open*. 2019;9(4):e027049.
123. Weeda ER, Coleman CI, McHorney CA, Crivera C, Schein JR, Sobieraj DM. Impact of once- or twice-daily dosing frequency on adherence to chronic cardiovascular disease medications: a meta-regression analysis. *Int J Cardiol*. 2016;216:104-109.
124. Riordan F, McHugh SM, O'Donovan C, Mtshede MN, Kearney PM. The role of physician and practice characteristics in the quality of diabetes management in primary care: systematic review and meta-analysis. *J Gen Intern Med*. 2020;35(6):1836-1848.
125. Wu IXY, Kee JCY, Threapleton DE, et al. Effectiveness of smartphone technologies on glycaemic control in patients with type 2 diabetes: systematic review with meta-analysis of 17 trials. *Obes Rev*. 2018;19(6):825-838.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Evans M, Engberg S, Faurby M, Fernandes JDDR, Hudson P, Polonsky W. Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: A systematic literature review. *Diabetes Obes Metab*. 2022;24(3):377-390. doi:10.1111/dom.14603