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REVIEW

Adherence and Persistence to Basal Insulin Among People with Type 2 Diabetes in Europe: A Systematic Literature Review and Meta-analysis

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ABSTRACT

***Introduction*:** Diabetes is associated with a number of complications, particularly if glycaemic targets are not achieved. Glycaemic control is highly linked to treatment persistence and adherence. To understand the burden of poor persistence and adherence, this systematic literature review identified existing evidence regarding basal insulin adherence/non-adherence and persistence/non-persistence among people with diabetes in Western Europe (defined as the UK, France, Spain, Switzerland, the Netherlands, Ireland, Austria, Portugal, Denmark, Norway, Sweden, Finland, Italy, Germany, Iceland and Belgium).

***Methods*:** Eligible studies were systematically identified from two databases, Medline and Embase (published between 2012 and June 2022). Conference abstracts from ISPOR and EASD were manually included. Identified studies were screened by two independent reviewers in a two-step blinded process. The eligibility of studies was decided on the basis of pre-established criteria. A proportional meta-analysis and comparative narrative analyses were conducted to analyse the included studies.

***Results*:** Twelve studies were identified. Proportions of adherence/non-adherence and persistence/non-persistence varied across studies. Pooled rates of non-persistence at 6, 12 and 18 months were 20.3% (95% CI 13.8; 27.8), 33.8% (95% CI 24.1; 44.3) and 36.5% (95% CI 33.6; 39.4), respectively. In the literature, the proportion of adherent people ranged from 41% to 64% (using the outcome measure medication possession ratio (MPR) > 80%), with a pooled rate of 55.6% (95% CI 45.3; 65.6), suggesting that approximately 44% of people with type 2 diabetes (T2D) are non-adherent.

***Conclusion*:** The results highlight that almost half of patients with T2D in Western Europe have poor adherence to insulin therapy and, at 18 months, one in three patients do not persist on treatment. These findings call for new basal

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insulin therapies and diabetes management strategies that can improve treatment persistence and adherence among people with T2D.

Keywords: Basal insulin; Adherence; Persistence; Systematic literature review; Type 2 diabetes; Western Europe

Key Summary Points

If glycaemic targets are not achieved, diabetes is associated with a high number of health complications, which are burdensome for both the individual and society.

Lack of adherence and persistence to basal insulin treatment is one cause of poor glycaemic control. In order to support people with diabetes achieving adherence and persistence, it is important first to understand the scope of the problem.

Twelve eligible studies presenting estimates of basal insulin adherence/non-adherence and/or persistence/non-persistence in people with type 2 diabetes (T2D) in Western European countries were identified.

The findings suggest that approximately 20%, 34% and 37% of people with T2D are non-persistent to basal insulin within 6, 12 and 18 months of initiation of treatment, respectively. Additionally, 44% are non-adherent to basal insulin treatment within 12 months.

The findings of the present systematic literature review highlight a huge unmet need in the care for people with T2D and indicate that there is a clear opportunity to improve adherence and persistence.

INTRODUCTION

The prevalence of diabetes is increasing and the number of adults with diabetes in Europe is expected to increase from 61 million in 2021 to 69 million in 2045 [1]. Type 2 diabetes (T2D) accounts for around 90% of diabetes cases [2]. As a result of the gradual onset of T2D, the condition can remain undiagnosed for many years, while health complications might develop and progress [3].

It is well known that diabetes is associated with a high number of health complications (renal, cardiovascular, neurological and retinal) as well as increased mortality, especially if glycaemic targets are not achieved [4–9]. According to the World Health Organization (WHO), adults with diabetes have more than a twofold risk of vascular outcomes, including both coronary heart disease and stroke [4], and cardiovascular disease is the most common cause of death among people with diabetes [10]. Additionally, a registry study including 32,725 people with diabetes found a statistically significant association between glycaemic burden and micro- and macrovascular complications such as diabetes foot, disease of the arteries and cerebrovascular disease [6]. Diabetes complications are burdensome for both the individual and society, as they are associated with a reduced health-related quality of life among people with diabetes and increased costs due to healthcare utilisation and absence from work [11, 12]. This emphasises the need for correct and sufficient treatment of diabetes.

Several factors impact whether people with T2D achieve glycaemic control [13, 14]. Long-acting insulin, also called basal insulin, has a longer duration and a lower peak of action, which allows for more flexible treatment. The mechanism of basal insulins contributes to an improved glycaemic control among people with T2D who cannot maintain adequate glycaemic control by other glucose-lowering drugs alone as well as a reduction in the risk of hypoglycaemia [15–18]. Thus, basal insulin is associated with clinical benefits and potentially a reduced fear of hypoglycaemia among people with T2D and clinicians [17]. However, earlier research has shown that one in three people with T2D are unwilling to start insulin treatment [19, 20]. Furthermore, some people have difficulties managing the insulin treatment, which may result in discontinuation of the treatment [16], and evidence has shown that one cause of poor glycaemic control is the lack of adherence (defined as complying with the prescribed medicine in terms of drug schedules

and dosages) and persistence (defined as continuing to take medication throughout the prescribed period) to antidiabetic medication, i.e. basal insulin treatment [21–23]. A previously published systematic literature review has found that improved adherence to antidiabetic medication in people with T2D is associated with improved glycaemic control and fewer hospitalisations and emergency department visits [24]. Hence, adherence and persistence are essential determinants of improved diabetes control.

In order to support people with diabetes in achieving adherence and persistence to insulin treatment and thus disease control, it is important first to understand the scope of the problem in a real-world setting. Evidence regarding insulin adherence/non-adherence and persistence/non-persistence among people with diabetes is broad. However, hardly any publications compare and pool evidence focusing particularly on adherence/non-adherence and persistence/non-persistence to basal insulin in Western Europe [24–26]. Newly published reviews by Evans et al. [24] and Lee et al. [26] investigated adherence and persistence to major antidiabetic medication classes, including basal insulin, among people with T2D. However, both studies had no eligibility criteria regarding geography, thus including data from all over the world. Another review by Azharuddin et al. [27] also investigated adherence to antidiabetic medication among all people living with diabetes, but only with evidence from low- and middle-income countries. Inclusion of countries with differences in the organisation and financing of healthcare systems makes direct comparisons across studies and pooled analyses problematic. Therefore, to make more direct comparisons possible, the objective of this systematic literature review was to identify and collate existing evidence on basal insulin adherence/non-adherence and persistence/non-persistence among people with diabetes in Western Europe.

METHODS

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [28]. The following research question was addressed in the systematic literature review: What is the persistence/non-persistence and adherence/non-adherence among adults with diabetes using basal insulin in Western Europe? The two electronic databases MEDLINE (via the PubMed platform) and Embase were searched in June 2022. The details of the search strings applied in this systematic literature review are presented in Table 1. In addition to the systematic search, EASD and ISPOR were manually searched for relevant peer-reviewed conference abstracts. These conferences are some of the leading societies for health economics and outcome research as well as diabetes research, and they are known to publish relevant abstracts on adherence or persistence in diabetes care.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria

The PICO (population, intervention, comparator and outcomes) reporting system was used to define a relevant review question and to help formulate the search strategy. The eligibility criteria are presented in Table 2. The systematic literature review included studies in which there was a population of adults from Western Europe (including the UK, France, Spain, Switzerland, Netherlands, Ireland, Austria, Portugal, Denmark, Norway, Sweden, Finland, Italy, Germany, Iceland and Belgium) with diabetes treated with basal insulin. In addition, studies had to present original data and analyses. The predefined outcomes of interest were all findings related to adherence/non-adherence or persistence/non-persistence to basal insulin treatment reported as proportions of patients. Treatment persistence is defined as continuing to take medication throughout the prescribed period, and treatment adherence is defined as complying with the prescribed medicine in terms of drug schedules and dosages [21]. The included studies were English-language studies published between 2012 and 2022.

Table 1 Search strings

Database	Search string				
	Diabetes	AND	Outcomes	AND	Insulin
Medline	"Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR diabetes[Title/Abstract] OR diabetic[Title/Abstract] OR diabetics[Title/Abstract] NOT "pre-diabetes" OR "pre diabetes" OR "pregnancy induced diabetes" OR "gestational diabetes" OR "diabetes insipidus"		"Adherance" OR "adhere" OR "adhered" OR "adherence" OR "adherences" OR "adherent" OR "adherents" OR "adherer" OR "adherers" OR "adheres" OR "adhering" OR "persist" OR "persistance" OR "persistant" OR "persisted" OR "persistence" OR "persistences" OR "persistencies" OR "persistency" OR "persistent" OR "persistently" OR "persistents" OR "persister" OR "persisters" OR "persisting" OR "persists"		Insulin[Title/Abstract] AND "Insulin glargine" OR Lantus OR Toujeo OR Basaglar OR Semglee OR "Insulin detemir" OR Levemir OR "Insulin degludec" OR Tresiba OR "Basal insulin" OR "background insulin" OR "Intermediate-acting insulin" OR "Long-acting insulin" OR "Ultra-long acting insulin" OR NPH OR "neutral protamine Hagedorn"
Embase	Exp diabetes mellitus/OR exp insulin dependent diabetes mellitus/OR exp non insulin dependent diabetes mellitus/ AND diabetes.ti,ab. OR diabetic.ti,ab. OR diabetics.ti,ab NOT pre-diabetes.mp. OR pre diabetes.mp. OR pregnancy induced diabetes.mp. OR gestational diabetes.mp. OR diabetes insipidus.mp		(Adherance OR adhere OR adhered OR adherence OR adherences OR adherent OR adherents OR adherer OR adherers OR adheres OR adhering OR persist OR persistance OR persistant OR persisted OR persistence OR persistences OR persistencies OR persistency OR persistent OR persistently OR persistents OR persister OR persisters OR persisting OR persists).mp		Insulin.ti,ab AND (Insulin glargine OR Lantus OR Toujeo OR Basaglar OR Semglee OR Insulin detemir OR Levemir OR Insulin degludec OR Tresiba OR Basal insulin OR background insulin OR Intermediate-acting insulin OR Long-acting insulin OR Ultra-long acting insulin OR NPH OR neutral protamine hagedorn).mp

Study Selection and Data Collection

All studies were reviewed in a blinded two-step process by two independent reviewers. The first step was screening of title and abstract. In the second step, eligible studies were screened at full-text level. The studies were included in accordance with the predefined eligibility criteria and any case of disagreement about the eligibility of a study was resolved through discussion between the two reviewers or by referral to the project manager. Each study could only be included once, meaning that a publication would be excluded if it presented a study already included through another publication. However, background information such as study characteristics could be combined from both publications if complete information was not available in one of the publications. Silvi was used to ensure a structured review process [29].

Table 2 Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Adults with diabetes	Pre-diabetes, gestational diabetes, diabetes insipidus Children and adolescents Not diabetes Not humans
Intervention	Basal insulin such as insulin glargine, Lantus, Toujeo, Basaglar, Semglee, insulin detemir, Levemir, insulin degludec, Tresiba, NPH, neutral protamine Hagedorn, background insulin, intermediate-acting insulin, long-acting insulin and ultra-long-acting insulin	Bolus insulin such as insulin lispro, insulin glulisine, insulin aspart, Humulin, Novolin, Novolog, Humalog mix, rapid-acting and short-acting. Pre-mix insulin
Comparator	Not relevant	Not relevant
Outcomes	Proportions related to adherence or persistence to basal insulin treatment	Adherence of devices to support insulin usage (such as an app, patient education programmes etc.) or treatments other than basal insulin
Study type	Original data sources/analyses (such as observational studies, questionnaires, clinical trials) Aggregated population data	Reviews, systematic reviews, meta-analysis Commentaries, editorial letters, case studies, case series, case report, abstracts and conference posters Individual patient data In vivo or in vitro
Language	English	Other languages
Time limit	Published within the last 10 years	Published prior to 2012
Countries	Results should be presented on country level. Including countries from Western Europe, including the UK, France, Spain, Switzerland, Netherlands, Ireland, Austria, Portugal, Denmark, Norway, Sweden, Finland, Italy, Germany, Iceland and Belgium	All other countries

Any measures of adherence/non-adherence and persistence/non-persistence available from the literature were considered relevant regardless of the follow-up period or methodology. Adherence/non-adherence was often measured by medication possession ratio (MPR) which is calculated as the proportion (or percentage) of days covered by the medication dispensed during a specified time period or over a period of refill intervals (using a threshold of 80%). Other measures of adherence/non-adherence included missed doses, mistimed doses and reduced doses. Persistence/non-persistence was measured as uninterrupted treatment administration.

Identified Studies

The systematic literature search of Medline and Embase resulted in 11 eligible studies. Additionally, we identified two relevant poster abstracts from EASD and ISPOR, yielding a total of 13 eligible studies [9, 15, 16, 25, 30–38]. The flow of studies through the two-step study selection process is presented in a flowchart in Fig. 1. This manuscript presents results from the studies regarding insulin adherence/non-adherence and persistence/non-persistence among people with T2D. By

further excluding studies that do not present any subgroup results stratified by T2D, this manuscript includes 12 eligible studies. From the 12 studies, a total of 30 relevant subgroup results were identified. It should be noted that one subgroup could present results on multiple outcome measures.

Of the 12 studies included in this manuscript, four presented results on adherence/non-adherence [15, 30, 32, 37] and nine presented results on persistence/non-persistence [9, 16, 25, 31, 33–37], one of which presented results on both adherence/non-adherence and persistence/non-persistence [37]. This last-mentioned study included people treated with all kinds of insulin, which is why it was not possible to extract results for basal insulin only. Therefore, the insulin type in the study will be categorised as basal-bolus insulin throughout this manuscript.

Data Extraction and Statistical Analyses

A comprehensive data extraction was conducted from all eligible studies following the PRISMA checklist [28] and using a pre-specified data

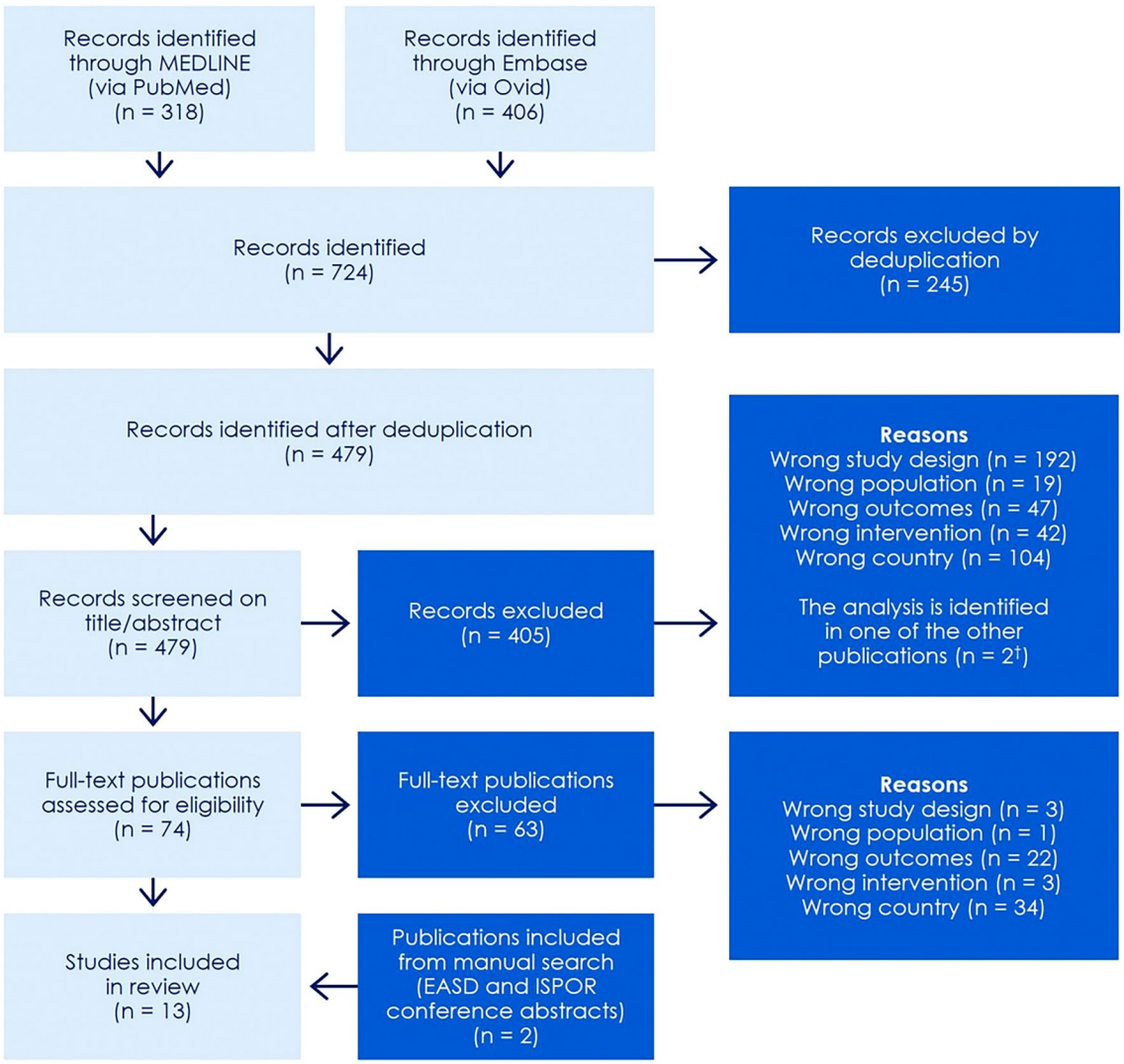

Fig. 1 Flowchart. †Although the studies were excluded, they contributed with background information about the subpopulations

extraction form in Microsoft Excel. Separate data points were extracted for each population and subpopulation with individual findings, i.e. subgroups by country, insulin type or background therapy. Data extraction included information on study characteristics, i.e. author, year of publication and information about the study population (size, country, mean age, background therapy, diabetes status, insulin status and diabetes-associated complications), methodology, i.e. data source and follow-up time, and findings from all outcomes deemed relevant for the research question.

When appropriate, a proportional meta-analysis calculating pooled rates was performed to assess insulin adherence/non-adherence and persistence/non-persistence among people with T2D in Western Europe. As recommended in the literature, the pooled rates were based on a random-effects model and Freeman–Tukey transformation using the software JBI SUMARI [39, 40]. Heterogeneity between the included studies was assessed through tau squared, chi squared and I^2 statistics. As a result of high variance in the outcome definitions applied in the included studies, comparative narrative analyses were performed, when proportional meta-analysis was inappropriate. In studies not reporting non-persistence or non-adherence rates, these were calculated as 1 minus the reported persistence or adherence rate.

To investigate the identified data further, a number of sensitivity analyses were conducted, including an analysis of persistence rates when results on NPH were excluded, and analyses of both persistence and adherence findings when data not differentiating between basal and bolus insulin were excluded.

RESULTS

Identified Outcome Measures

Among the 12 eligible studies, insulin persistence/non-persistence and adherence/non-adherence were evaluated using 19 different outcome measures (persistence, 5; adherence, 14). Table 3 provides an overview of the identified outcome measures for both persistence and adherence, together with the number of subgroup results for the respective outcome measures.

Results on Insulin Persistence

Persistence to basal insulin was measured after either 3, 6, 12, 18 or 24 months in the nine studies reporting results on insulin persistence. The most frequent measure was persistence after

Table 3 Outcome measures identified from the eligible studies

Identified outcome measures	No.
Persistence	
Persistence after 24 months (%)	8
Persistence after 18 months (%)	2
Persistence after 12 months (%)	8
Persistence after 6 months (%)	7[†]
Persistence after 3 months (%)	1
Adherence	
MPR after 12 months	1
Share with MPR > 80% (%)	4
Share with MPR 50–79% (%)	1
Share with MPR < 50% (%)	1
Share with missed doses (%)	3
Mean number of missed doses	3
Share with 5+ missed doses within 30 days (%)	3
Share with mistimed doses (%)	3
Mean number of mistimed doses	3
Share with 5+ mistimed doses within 30 days (%)	3
Share with reduced doses (%)	3
Mean number of reduced doses	3
Share with 5+ reduced doses within 30 days (%)	3
Share that are adherent all 7 days within a week (%)	1

[†]Includes four studies that reported persistence as treatment discontinuation within 6 months

12 months, which was used in five of the nine studies [31, 34–37]. Persistence after 6 months was measured in four of the studies [9, 31, 36, 37], and persistence after 3 and 18 months was measured in one study each [25, 37]. Persistence after 24 months was measured in two studies [16, 33]. The majority of the included studies were based on registry data [16, 25, 31, 33–37]; however, one study used self-reported questionnaire data [9]. The size of study populations varied from 549 included people [9] to 680,131 included people [16]. An overview of the studies, study characteristics and respective results regarding persistence to basal insulin among people with T2D is presented in Table 4.

On the basis of results from the studies reporting 6- and 12-month persistence rates, we calculated non-persistence rates (equal to 1 minus persistence rates). These are shown by different types of basal insulin in Fig. 2. Within the first 6 months of treatment, non-persistence ranged between 6% and 33% in the included studies. The lowest non-persistence was reported for degludec (6%) [31], while the highest non-persistence was reported for the group of non-specified basal insulin therapies (33%) [9]. It should be noted that the majority of the studies reporting results on persistence at 6 months did not specify the insulin type [9, 36, 37]. Non-persistence rates within the first 12 months of treatment ranged from 14% to 52%. The lowest non-persistence rate within the first 12 months of treatment was reported for insulin glargine-300 (14%) and insulin degludec (16%) [31, 35]. The highest non-persistence rate was reported for neutral protamine Hagedorn (NPH) insulin (52%) [34].

On the basis of the studies, pooled non-persistence rates among people with T2D were calculated for 6, 12 and 18 months. The pooled non-persistence rate within 6 months of initiation of basal insulin was 20.3% (95% CI 13.8; 27.8) (Fig. S1). It should be noted that four of the seven estimates of non-persistence within 6 months were based on self-reported data, whereas the remaining three were based on registry data. The pooled non-persistence rate was 14.6% (95% CI 6.3; 25.5) if only registry-based data were included and 25.9% (95% CI 20.5; 21.8) if only self-reported data were included (Figs. S2 and S3). The pooled rate of non-persistence further increased from 6 to 12 months to 33.8% (95% CI 24.1; 44.3) (Fig. S4). In a sensitivity analysis, data on NPH were excluded from this analysis, which resulted in a pooled non-persistence rate within 12 months of 31.3% (95% CI 21.7; 41.8) (Fig. S5). Finally, the pooled rate of non-persistence within 18 months of initiating basal insulin was 36.5% (95% CI 33.6; 39.4) (Fig. S6). Figures S7 and S8 show the results of sensitivity analyses in which the study by Sicras et al. 2013 was excluded [37].

Results on Insulin Adherence

Adherence/non-adherence to basal insulin was measured with several methods in the four included studies reporting results on insulin adherence. The most frequently used measure was MPR > 80%, which was used in two of the four studies [32, 37]. MPR > 80% was the only measure that was used by more than one of the included studies. Among the included studies, half of them were based on registry data [32, 37], whereas the other half were based on self-reported questionnaire data [15, 30]. The size of study populations varied from 162 included people [15] to 2413 included people [32]. An overview of all included studies reporting results on insulin adherence/non-adherence is presented in Table 5.

Figure 3 illustrates the proportion of people with T2D who were adherent to basal insulin treatment (defined as MPR > 80%) within the first 12 months of treatment, stratified by different types of basal insulin. The share of people with MPR > 80% ranged from 41% to 64% [32, 37]. The pooled rate of people with MPR > 80% across the relevant studies was 55.6% (95% CI 45.3; 65.6). The results reported by Esposti et al. 2019 differed across different types of background therapies (included as separate subgroup results) [32]. Figure S10 presents the results of a sensitivity analysis of the pooled rate of people with MPR > 80% when the study by Sicras et al. was excluded [37].

One of the four included studies assessed insulin non-adherence by measuring the share of people with T2D who missed insulin doses

Table 4 Overview of studies reporting results on insulin persistence

Author and year	Country	Study type and data source	Follow-up	Type of basal insulin	Population size	Age, mean (SD)	Background therapy (%)		Diabetes duration	Complications associated with diabetics	Outcome measure
Eliasson et al. 2020 [31]	Sweden	Cohort study with registry data	12 months	Degludec	*N* = 2432	61.3 (11.8)	Liraglutide		12.7 (7.6) years	Microalbuminuria: 30.51% Macroalbuminuria: 9.04% Retinopathy: 41.85%	Persistence after 6 months: 94% Persistence after 12 months: 84%
Perez-Nieves et al. 2017 [9]	UK, Germany, France, Spain	Cross-sectional study with questionnaire data	24 months	Glargine, detemir or degludec	*N* = 549 UK: *n* = 131 Germany: *n* = 131 France: *n* = 137 Spain: *n* = 150	Total: 40.6 (14.1)[†]	Antihyperglycaemic medication: 65.5 (Oral: 57.7, Injectable: 24.1)		Total: 6.8 (7.0) years[†]	NR	Persistence after 6 months UK: 24% Germany: 20% France: 27% Spain: 33.3%
Pscherer et al. 2014 [33]	Germany	Cohort study with registry data	24 months	Glargine, detemir or NPH	*N* = 5736 Glargine[‡]: *n* = 1398 Detemir[‡]: *n* = 292 NPH[‡]: *n* = 874 Glargine[§]: *n* = 866 Detemir[§]: *n* = 512 NPH[§]: *n* = 1794	Total: NR Glargine[‡]: 67.7 (11.3) Detemir[‡]: 66 .4 (11.4) NPH[‡]: 65 (11.1) Glargine[§]: 63.8 (12.8) Detemir[§]: 60.4 (12.9) NPH[§]: 63.9 (11.9)	Antihypertensive drugs Glargine[‡]: 80.3 Detemir[‡]: 81.5 NPH[‡]: 73.8 Glargine[§]: 65.6 Detemir[§]: 57.8 NPH[§]: 64.9	Lipid-lowering drugs Glargine[‡]: 44.6 Detemir[‡]: 48.6 NPH[‡]: 45.5 Glargine[§]: 37.6 Detemir[§]: 40.4 NPH[§]: 38.9	> 5 years Glargine[‡]: 44.0% Detemir[‡]: 48.6% NPH[‡]: 35.6% Glargine[§]: 32.3% Detemir[§]: 26.6% NPH[§]: 30.2%	Diagnosed comorbidity (% for glargine, detemir, NPH) Coronary heart disease: 26.8, 25.7, 24.9 Myocardial infarction: 4.7, 4.5, 4.5 Stroke: 8.8, 7.2, 6.8 Peripheral vascular disease: 12.5, 17.8, 13.4 Heart failure: 18.8, 14.7, 14.0 Hypertension: 75.3, 80.8, 72.4 Hyperlipidemia: 51.8, 52.7, 53.4 Retinopathy: 5.4, 7.9, 5.6 Nephropathy: 13.9, 11.0, 12.0 Neuropathy: 14.5, 16.8, 19.7	Persistence after 24 months Glargine[‡]: 64.5% Detemir[‡]: 52.7% NPH[‡]: 59.2% Glargine[§]: 84.3% Detemir[§]: 85.4% NPH[§]: 86.6%
Quinzler et al. 2012 [34]	Germany	Cohort study with registry data	12 months	Glargine or NPH	*N* = 97,998 Glargine: *n* = 61,070 NPH: *n* = 36,928	NR	Metformin + OAD Glargine: 65.6 NPH: 66.6 Metformin only Glargine: 8.0 NPH: 12.2	Sulfonylurea Glargine: 16.8 NPH: 13.1 Other OAD Glargine: 9.7 NPH: 8.1	NR	NR	Persistence after 12 months Glargine: 42.4% NPH: 36.8%

Table 4 continued

Author and year	Country	Study type and data source	Follow-up	Type of basal insulin	Population size	Age, mean (SD)	Background therapy (%)		Diabetes duration	Complications associated with diabetics	Outcome measure
Rathmann et al. 2017 [16]	Germany	Cohort with registry data	24 months	NPH, glargine or detemir	*N* = 680,131 NPH: *n* = 226,064 Glargine/detemir: *n* = 454,067	Total: NR NPH: 68.1 (11.3) Glargine/detemir: 67.7 (12.2)	Antidepressants NPH: 17.2 Glargine/detemir: 19.5 Antihypertensives NPH: 83.3 Glargine/detemir: 82.5	Antiepileptics NPH: 12.0 Glargine/detemir: 13.1 Lipid-lowering drugs NPH: 49.2 Glargine/detemir: 49.0	NR	NR	Persistence after 24 months NPH: 79% Glargine/detemir: 92.6%
Roussel et al. 2016 [36]	France	Cohort study with registry data	24 months	NR	*N* = 1199	67.5 (14.2)	Insulin + 1 OAD: 23.0 Insulin + 2 OAD: 31.6 Insulin + 3 OAD: 24.9 Insulin ≥ 4 OAD: 1.6 Metformin: 59.6	Sulfonylurea: 44.6 Glinides: 17.9 Alpha-glucosidase inhibitor: 3.5 GLP-1 receptor agonists: 10.6 DPP4 inhibitor: 31.4	NR	NR	Persistence after 6 months: 80.9% Persistence after 12 months: 71.3%
Roussel et al. 2020 [35]	France	Cohort study with registry data	24 months	Glargine-300, glargine-100 or detemir	*N* = 181,263 Glargine-100: *n* = 134,127 Glargine-300: *n* = 21,306 Detemir: *n* = 25,830	All: NR Glargine-100: 67.5 (15.6) Glargine-300: 64.8 (14.3) Detemir: 67 (16.9)	OAD Glargine-100: 57.9 Glargine-300: 60.9 Detemir: 53.8 GLP-1 RA + OAD Glargine-100: 7.1 Glargine-300: 14.2 Detemir: 13.8	Other insulins + OAD Glargine-100: 33.1 Glargine-300: 21.8 Detemir: 30.1 Other insulin + GLP-1 RA + OAD Glargine-100: 1.9 Glargine-300: 3.1 Detemir: 2.4	All: NR Glargine-100: 8.5 (7.2) years Glargine-300: 8.4 (6.7) years Detemir: 9 (7.2) years	Charlson Comorbidity index (% for glargine-100, glargine-300, detemir) 0: 39.78, 32.88, 29.87 1: 21.48, 18.24, 20.07 2: 14.01. 14.16, 14.50 3: 8.86, 10.65, 10.94 4: 5.76, 7.76, 7.81 5: 3.70. 5.49, 5.52 6: 2.18, 3.28, 3.41 7 or more: 4.23, 7.54, 7.88	Persistence after 12 months: 72% Glargine-100: 66% Glargine-300: 86% Detemir: 63%

Table 4 continued

Author and year	Country	Study type and data source	Follow-up	Type of basal insulin	Population size	Age, mean (SD)	Background therapy (%)	Diabetes duration	Complications associated with diabetics	Outcome measure
Sicras et al. 2013 [37]	Spain	Cohort study with registry data	12 months	NR	$N = 935$	67.6	NR	NR	NR	Persistence after 3 months: 90.3% Persistence after 6 months: 79.4% Persistence after 12 months: 55.9%
Westerbacka et al. 2015 [25]	Finland	Cohort study with registry data	18 months	Glargine or detemir	$N = 14,462$ Glargine: $n = 8594$ Detemir: $n = 5868$	NR	NR	NR	NR	Persistence after 18 months Glargine: 65% Detemir: 62%

NR not reported, *OAD* oral antidiabetic drug, *GLP* glucagon-like peptide, *RA* receptor agonists, *DPP4* dipeptidyl peptidase 4

[†]Includes data from the USA, Brazil and Japan

[‡]BOT: Basal supported oral therapy

[§]ICT: Intensified conventional therapy

during a 30-day period [30]. The outcome was measured through an online survey sent to people with T2D and healthcare professionals (primary care practitioners, specialists and nurses). The study found that, on average, 16% of people with T2D had one or more missed doses during a 30-day treatment period, while 1.3% had missed five or more doses in that same period. In addition, the study reported that people with T2D on average missed 1.8 doses of basal insulin within a 30-day treatment period.

Wieringa et al. measured adherence using a questionnaire in the Netherlands by asking their study respondents (physicians involved in the management of T2D in primary and secondary care and people with T2D) how many of the last 7 days they took the recommended basal insulin as prescribed. They found that 84% of people with T2D were adherent all 7 days of the last week [15].

DISCUSSION

This systematic literature review identified 12 studies that reported findings of persistence/non-persistence or adherence/non-adherence to basal insulin in people with T2D from Western European countries. The findings highlight an important problem with both persistence (defined as continuing to take medication throughout the prescribed period [21]) and adherence (defined as complying with the prescribed medicine in terms of drug schedules and dosages [21]) in T2D.

This systematic literature review found pooled non-persistence rates at 6 and 12 months of approximately 20% and 34%, respectively. At 18 months, the pooled non-persistence rate increased to approximately 37%. In the pooled non-persistence rate at 12 months, results for insulin NPH have been included. Insulin NPH might be given more than once per day, and it is therefore likely that a higher non-persistence rate is found among people receiving insulin NPH compared to other types of basal insulin. Information about daily doses of insulin NPH was not available. However, a sensitivity analysis showed that the

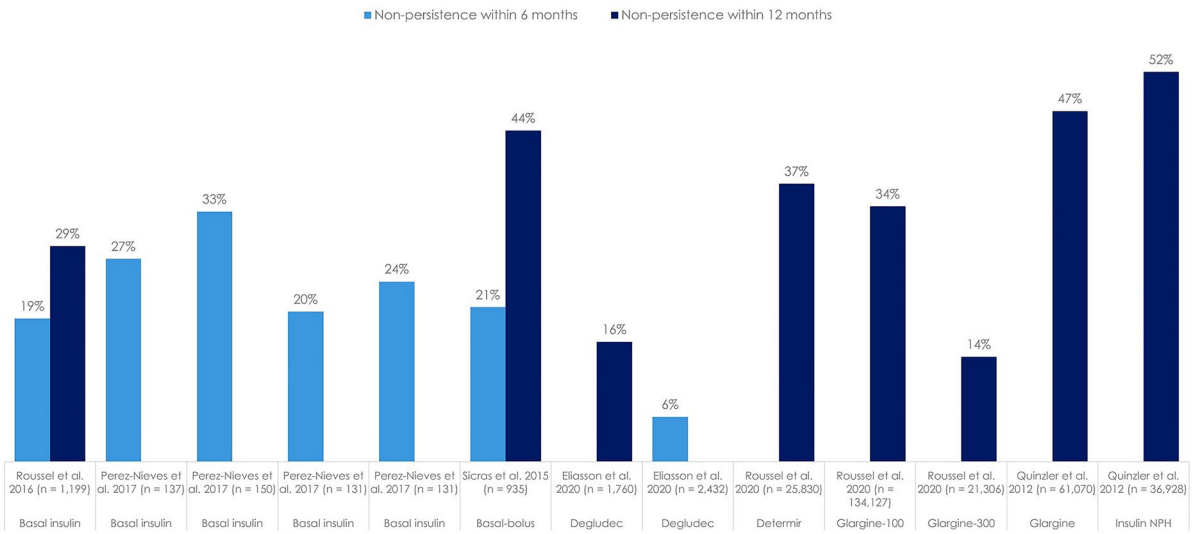

Fig. 2 Non-persistence within 6 and 12 months of initiation of basal insulin treatment by type of basal insulin, %. The figure present rates of non-persistence from the eligible studies and lists population size and insulin type for each subgroup. Not all included studies reported results for persistence within both 6 and 12 months. Neither did all studies specify the specific type of basal insulin assessed. Estimates of persistence reported by Perez-Nieves et al. [9] differ across different countries and are reported in the following countries listed from left to right: France, Spain, Germany and the UK

pooled non-persistence rate within 12 months only changes by three percentage points (from 34% to 31%) when excluding insulin NPH from the analysis. Although direct comparisons across the studies should be made with caution, taking into account different study characteristics, the numbers for persistence over time could suggest that non-persistence among people with T2D is present already within the first 6 months and that it increases over time but at a diminishing rate. Considering that non-persistence could possibly be related to an unpreferable safety profile or dosing scheme, it seems fair to expect that people not experiencing issues with a treatment within the first 6 months do not experience issues after 6 months. Thus, it seems likely that non-persistence will stall over time. Furthermore, this systematic review found that estimates of adherence in the eligible studies were most often measured as MPR > 80%, which is the adherence rate needed for optimal treatment effect [41]. Using MPR > 80%, this review found a pooled adherence rate to basal insulin treatment over a 12-month period of approximately 56%. This suggests that 44% of people with T2D are non-adherent to basal insulin treatment within 12 months. It should be noted that one study, which was included in both the persistence and adherence analyses, did not differentiate between basal and bolus insulin. However, neither persistence nor adherence findings changed significantly when the study was excluded in a sensitivity analysis.

It is well established that non-persistence with and non-adherence to prescribed diabetes therapy, including basal insulin, can have profound consequences for people with diabetes, including poor glycaemic control [21]. Medication non-adherence has been shown to be a key reason why antidiabetic medication is less effective in a real-world setting than in clinical studies. For example, a study by Carls et al. from 2017 found significantly smaller reductions in glycaemic level among people with T2D 1 year after initiation of antidiabetic medication than what had been observed in the randomised control trial setting for the same period. The authors concluded that approximately 75% of the gap was due to lack of patient adherence [42].

Table 5 Overview of studies reporting results on insulin adherence

Author and year	Country	Study type and data source	Follow-up	Type of basal insulin	Population size	Age, mean (SD)	Background therapy (%)	Diabetes duration	Complications associated with diabetics	Outcome measure
Brod et al. 2012 [30]	UK, Germany, Denmark	Cross-sectional study with questionnaire data	1 month	NR	*N* = 681 UK: *n* = 322 Germany: *n* = 302 Denmark: *n* = 57	All: NR UK: 60 (8.63) Germany: 57 (7.75) Denmark: 62 (8.27)	NR	All: NR UK: 11 years (6.45) Germany: 9 years (5.94) Denmark: 11.7 years (6.47)	Number of diabetes complications (median (range)) UK: 3 (0–10) Germany: 3 (0–9) Denmark: 3 (0–8)	% of people with missed, mistimed and reduced doses UK: 16%, 20%, 18% Germany: 19%, 25%, 15% Denmark: 12%, 20%, 12% % of people with 5+ missed, mistimed and reduced doses UK: 1.6%, 4.3%, 3.5% Germany: 2.2%, 6.3%, 5% Denmark: 0%, 6%, 0% Mean number of missed, mistimed and reduced doses UK: 2.1, 3.7, 3.8 Germany: 2.3, 3.9, 5.3 Denmark: 1.1, 3.7, 1.3

Table 5 continued

Author and year	Country	Study type and data source	Follow-up	Type of basal insulin	Population size	Age, mean (SD)	Background therapy (%)	Diabetes duration	Complications associated with diabetics	Outcome measure
Esposti et al. 2019 [32]	Italy	Cohort study with registry data	12 months	Glargine-100	*N* = 2413 Insulin only: *n* = 466 OGLD: *n* = 1590 DPP4 inhibitor: *n* = 357	All: NR Insulin only: 71.7 (14.6) OGLD: 71.8 (11.9) DPP4 inhibitor: 67.7 (10)	OGLD or DPP4 inhibitor	NR	% reported for insulin only, OGLD, DPP4 inhibitor Hypertension: 65.0, 75.6, 77.0 Dyslipidemia: 32.8, 50.6, 60.2 Anti-inflammatory agents: 14.4, 18.1, 17.4 Asthma/COPD: 10.3, 9.7, 6.2 Kidney disease: 8.6, 3.4, 3.4 Hypoglycaemia: 0.6, 0.7, 1.4 Previous CV events: 28.3, 14.6, 10.9 Hypertensive disease: 14.4, 9.2, 7.0 Acute myocardial infarction: 2.4, 1.1, 0.8	% of people with MPR > 80% Insulin only: 41% OGLD: 61.9% DPP4 inhibitor: 64.4%

Table 5 continued

Author and year	Country	Study type and data source	Follow-up	Type of basal insulin	Population size	Age, mean (SD)	Background therapy (%)	Diabetes duration	Complications associated with diabetics	Outcome measure
									Coronary disease: 8.2, 4.0, 6.4 Heart failure: 7.7, 3.5, 2.2 Stroke and other cerebral circulatory dysfunction: 11.4, 5.0, 1.7 Arteriosclerosis of the main arteries and aneurysm: 1.7, 1.8, 1.4	
Sicras et al. 2013 [37]	Spain	Cohort study with registry data	12 months	NR	*N* = 935	67.6	NR	NR	NR	MPR after 12 months: 82.7% % of people with MPR > 80%: 54.7% % of people with MPR 50–79%: 39.9% % of people with < 50%: 5.5%

Table 5 continued

Author and year	Country	Study type and data source	Follow-up	Type of basal insulin	Population size	Age, mean (SD)	Background therapy (%)	Diabetes duration	Complications associated with diabetics	Outcome measure
Wieringa et al. 2018 [15]	Netherlands	Cohort study with questionnaire data	6 months	Glargine-300	$N = 162$	65.54 (9.05)	NR	15.14 years (6.65)	Ongoing complications and/or comorbidities at baseline 0: 34.2% 1: 28.4% 2: 23.9% 3 or more: 13.5%	% of patients adherent all 7 days within a week: 84.4%

NR not reported, *OGLD* oral glucose-lowering drugs, *DPP4* dipeptidyl peptidase 4

The findings in this systematic review indicate that non-persistence and non-adherence have a great impact in Western Europe. It should be noted that there can be several reasons for interrupting insulin therapy. For instance, insulin therapy might be initiated temporarily, or it might be substituted with other medicines. In addition, insulin persistence and adherence might be impacted by diabetes-related complications, which could complicate the treatment regimen. According to the literature identified as part of this review, studies investigating adherence/non-adherence and persistence/non-persistence among people with type 1 diabetes are sparse. This calls for further investigation before any conclusions can be made about adherence/non-adherence and persistence/non-persistence in this population. However, it should be noted that, according to findings by Elek et al. T2D constitutes 90% of the overall population of people with diabetes [43].

While achievement of glycaemic targets is associated with a reduction in diabetes complications, improper diabetes care, e.g. poor glycaemic control, entails a great risk of long-term complications [21, 44]. A systematic literature review from 2019 that investigated the lack of treatment persistence and treatment adherence in people with T2D found that an increase in diabetes complications as a result of poor adherence and persistence is linked to poorer health status and an increase in healthcare resource use and costs [9]. Additionally, a large study from the UK found a strong association between non-adherence and increased all-cause mortality [45]. Although a vast number of studies have investigated the cost associated with poor adherence or persistence to insulin treatment among people with T2D, many of these studies have been USA-based; hence, patients' adherence and persistence are likely to be greatly affected by the high out-of-pocket payments known to be part of the US healthcare system. Thus, in order to understand the complete economic consequences of improper insulin treatment in the Western Europe, where healthcare systems are organised differently from the USA, additional evidence is needed.

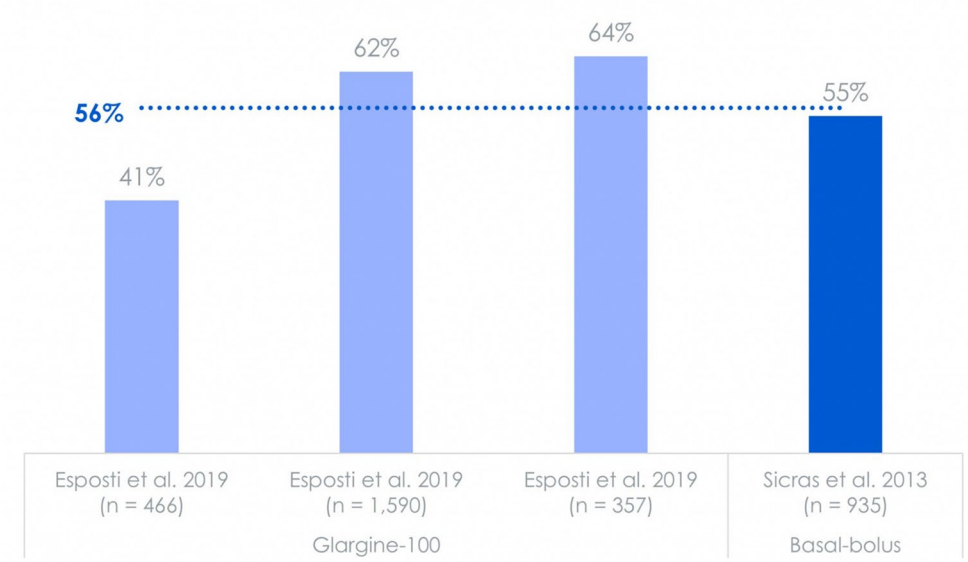

Fig. 3 Share of people with T2D and MPR > 80% by different types of basal insulin, %. The figure presents proportions of MPR > 80% from the eligible studies and lists population size and insulin type for each subgroup. Estimates of adherence reported by Esposti et al. [32] differed across different types of background therapies, including the following background therapies listed from left to right: No background therapies, other oral glucose-lowering drugs and DPP4 inhibitors

Strength and Limitations

As is best practice, this systematic literature review includes a search of two databases, namely Medline (via PubMed) and Embase. For a systematic review literature search, Embase and MEDLINE are key databases. MEDLINE contains more than 22 million records from 5600 journals, whereas Embase has over 29 million records from 8500 journals. Additionally, the systematic literature review complies with the PRISMA guidelines. Inclusion and exclusion criteria used in this study were defined prior to the literature search, and the review process was conducted by two independent reviewers.

The number of studies identified in this systematic literature review was small in light of the seriousness of the challenge with poor control in diabetes. Additionally, they were heterogeneous. The methodological differences, particularly the use of differing outcome measures, problematise the direct comparisons of results across the different studies, countries, insulin products and time. As a result of the lack of a unified criterion for defining adherence and persistence in the identified studies, only a few studies could be meaningfully pooled, thus narrowing the data that went into the calculated pooled rates on persistence/non-persistence and adherence/non-adherence. This constitutes a limitation for the final pooled rates. Furthermore, the statistical tests of heterogeneity in the proportional meta-analyses showed high heterogeneity in the included estimates. It should be noted that the results of the heterogeneity tests should be interpreted with caution, since heterogeneity is expected in prevalence estimates. Therefore, high heterogeneity does not necessarily indicate inconsistent data [40]. To understand the factors that affect persistence and adherence and thus be able to provide people with T2D with treatment strategies that can improve persistence and adherence in the future, it would be relevant to have a standard practice for the measurement of persistence and adherence. Standardisation of the measurement of persistence and adherence in diabetes care will provide scientists with a

guideline for what data should be included in future studies and enable the comparison of results across studies, products etc. Differing data sources in the included studies also poses a challenge in the comparisons. Finally, the inclusion of abstracts of conference papers may be a limitation as they do not include the same information as an article published in a scientific journal. However, the number of studies included from this source was small and it was ensured that they were studies of interest for the systematic review.

Given the clinical and economic consequences associated with non-adherence and non-persistence in T2D, an unmet need remains. These findings call for new basal insulin therapies and diabetes management strategies that can improve treatment persistence and adherence among people with T2D and thus positively affect clinical and economic outcomes. It was outside the scope of this study to investigate reasons for non-persistence and non-adherence. However, several approaches to improve persistence and adherence have been recommended in previous literature, including reduced treatment complexity (fixed-dose combinations and decreased dosing schemes), improved safety profiles, increased knowledge through better educational programmes and improved communication [21, 45]. Additionally, knowledge about how other factors, e.g. sociodemographic factors or the presence of diabetes-related complications, influence persistence and adherence should be considered in future research.

CONCLUSION

This systematic literature review described real-world evidence on basal insulin adherence/non-adherence and persistence/non-persistence among people with T2D from Western Europe. The study identified 12 eligible studies in which non-persistence and non-adherence were evaluated using different outcome measures. Data on non-persistence among people with T2D suggest that non-persistence stagnates over time, with non-persistence rates of 21%, 34% and 37% at 6 months, 12 months and 18 months, respectively. By defining non-adherence as MPR < 20%, this systematic literature review found that 44% of people with T2D are non-adherent within 12 months. These numbers highlight a huge unmet need in the care for people with T2D and indicate that there is a clear opportunity to improve adherence and persistence, while also decreasing the risk of diabetes complications and the healthcare resource utilisation, by providing new diabetes management strategies with reduced treatment complexity, reduced dosing frequency, improved safety profile and better patient education and communication.

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Declarations

Conflict of Interest. Hongye Ren and Sara Larsen are employees of Novo Nordisk. Mette Bøgelund, Signe Baattrup Reitzel and Anna Okkels are employees of EY, which is a paid vendor of Novo Nordisk. After completion of the manuscript, Signe Baattrup Reitzel has changed affiliation to Medical Science, Novo Nordisk Foundation. Esteban Jodar reports consultancy services and speaker fees from Audium, Amgen, AstraZeneca, Boehringer, FAES, Eli Lilly, MSD, Novo Nordisk, UCB and ZP pharmaceutica. Domingo Orozco-Beltrán has provided consultancy services to MSD and Novartis and has

lectured for Novartis, Mundipharma, Novo Nordisk, Sanofi Aventis and Eli Lilly.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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