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Review

Paradoxical real-life underuse of GLP-1 receptor agonists in type 2 diabetes patients with atherosclerotic cardiovascular disease
Underuse of GLP-1RAs in patients with ASCVD

André J. Scheen[a,b,*]

[a] Division of Diabetes, Nutrition and Metabolic Disorders, CHU Liège, Liège, Belgium
[b] Division of Clinical Pharmacology, Centre for Interdisciplinary Research on Medicines (CIRM), Liège University, Liège, Belgium

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ABSTRACT

Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce the risk of cardiovascular (CV) complications in patients with type 2 diabetes (T2DM) and atherosclerotic cardiovascular disease (ASCVD) in placebo-controlled CV outcome trials, yet the use of these cardioprotective agents remains rather low in clinical practice.
Methods: Analysis of the proportion of T2DM patients treated with GLP-1RAs in retrospective observational studies by comparing patients with versus without established ASCVD.
Results: Nine cohorts from seven studies were collected in the international literature between 2019 and 2022. Overall, the percentages of patients treated with GLP-1RAs were low (< 10 %) in most studies, yet a progressive increase was noticed over time. The use of GLP-1RAs in patients with ASCVD was slightly lower in 7 out of 9 cohorts not higher when compared to the use in patients without ASCVD (odds ratio 0.80, 95 % CI 0.79–0.81).
Conclusion: Despite a positive trend over the last decade, the real-world use of GLP-1RAs remains limited, especially in patients with established ASCVD. Bridging the gap between clinical evidence of cardioprotective effects of GLP-1RAs and their underuse in clinical practice in T2DM patients at high/very high CV risk should be considered as a key objective for health care providers, especially cardiologists.

Introduction

Patients with type 2 diabetes mellitus (T2DM) are at high risk of atherosclerotic cardiovascular disease (ASCVD) [1]. Two antihyperglycaemic pharmacological classes have demonstrated a cardiovascular (CV) protection in patients with T2DM: sodium-glucose cotransporter 2 inhibitors (SGLT2is) [2] and glucagon-like peptide-1 receptor agonists (GLP-1RAs) [3,4]. Despite this demonstration in placebo-controlled CV outcome trials [5,6] and the recommendations published by different international scientific societies [7–9], the use of these agents remains rather limited in clinical practice. More importantly, the underuse of GLP-1RAs appears also present in T2DM patients at high/very high CV risk, including in those with antecedents of ASCVD [10,11]. We already discussed in this journal the underuse of SGLT2is, another class associated with cardiorenal protection in at-risk patients with T2DM [12].

The present comprehensive concise review aims at comparing the use of GLP-1RAs in T2DM patients with ASCVD versus without ASCVD in patients with T2DM in real-life conditions corresponding to clinical practice. We hypothesize that GLP-1RAs should be more often prescribed in T2DM patients with versus without ASCVD.

Methods

We screened the literature to detect real-life observational studies that compared the use of GLP-1RAs in T2DM patients with versus without ASCVD. We searched PubMed, EMBASE and the Cochrane Database of Systematic Reviews to identify English-language studies published between 1 January 2015 and December 2023. The terms used for the research were “GLP-1 receptor agonists” (including each individual compound of this pharmacological family), combined with “real-life” OR “real-world” OR “clinical practice” The reference lists of previously published systematic reviews, meta-analyses and observational studies on a similar topic were also scrutinized to identify any further reports of potential interest.

Most studies reported a positive trend in the use of GLP-1RAs over the last decade in both subgroups with and without ASCVD. When different levels of use were published, the results corresponding to

* Correspondence to.
E-mail address: andre.scheen@chu.ulg.ac.be

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Table 1
Percentages of T2DM patients with or without atherosclerotic cardiovascular disease treated with GLP-1RAs in real-life studies.

Reference	Country	Year	Patients with ASCVD		Patients without ASCVD	
			N total patients	% on GLP-1RAs	N total patients	% on GLP-1RAs
Studies included in the meta-analysis						
Weng et al. 2019 [13]	US	2014–15	543 938	5.0	659 498	6.2
Farmer et al. 2021 [14]	UK	2019–20	44,808	4.3	100,565	4.9
Shin et al. 2021 [15]	US (Medicare)	2015–17	43,142	0.98	55,925	0.73
Shin et al. 2021 [15]	US (Clinformatics)	2018–19	19,001	2.52	67,184	2.57
Shin et al. 2021 [15]	US (MarketScan)	2018	5482	3.11	38,896	3.28
Nargesi et al. 2021 [16]	US	2017–18	265	1.6	191	0.7
Eberly et al. 2021 [17]	US	2019	815,319	9.4	364,941	11.6
Mosenzon et al. 2021 [18]	13 countries	2018–19	3582	8.3	6241	8.7
Limonte et al. 2022 [19]	US	2017–20	316	3.5	1059	4.7
Other studies not included in the meta-analysis						
Hao et al. 2022 [20]	Canada	2018–19	680 (*)	4.6	6488 (**)	11.0
Khera et al. 2023 [21]	US (MDCR)	2019–21	NA	15.7	NA	22.3
Khera et al. 2023 [21]	US (CUIMC)	2019–21	NA	21.0	NA	38.0
Khera et al. 2023 [21]	US (CCAE)	2019–21	NA	28.0	NA	29.0
Khera et al. 2023 [21]	France	2019–21	NA	13.4	NA	10.7

ASCVD : atherosclerotic cardiovascular disease.
CCAE = IBM MarketScan Commercial Claims and Encounters Data.
CUIMC = Columbia University Irving Medical Centre.
MDCR = IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database.
NA : not available.
* Patients with ASCVD or heart failure.
** Patients without ASCVD or heart failure.

the last years were used for the analysis. In each study, the following parameters were considered: year of interest, total number of patients with and without ASCVD, the percentage of patients treated with GLP-1RAs in each subgroup.

A meta-analysis comparing the use of GLP-1RAs in patients with versus without ASCVD was performed using Review Manager (RevMan) 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). To construct this meta-analysis, the percentages mentioned in Table 1 were converted in numbers of patients treated with GLP-1RAs ("events"). Interstudy heterogeneity was assessed using the Higgins and Thompson I^2 index; if the latter value was > 50 %, this indicated a substantial degree of heterogeneity.

Results

Seven observational retrospective studies with dedicated comparison of the use of GLP-1RAs in T2DM patients with versus without ASCVD were collected in the literature [13–19] (Table 1). Most studies were performed in the US. One of these US studies included three different cohorts depending on the insurance system [15]. Thus, overall, nine different cohorts were considered for final examination. The evaluations were performed between 2014–2015 [13] and 2017–2020 [19]. The size of these studies varied considerably from a few hundreds of patients to above 500,000 patients. The percentages of patients with ASCVD who were treated with GLP-1RAs varied between 0.98 and 9.4 % whereas the corresponding percentages of T2DM patients without ASCVD treated with GLP-1Ras varied between 0.73 and 11.6 %. The percentages of GLP-1RA-treated T2DM patients were slightly lower in people with versus without ASCVD in 7 out of 9 cohorts (Table 1). The corresponding data are summarized in Fig. 1 depicting the results of the meta-analysis. The odds ratio (OR) of using GLP-1Ras was significantly lower in patients with ASCVD than n those without ASCVD (OR 0.80, 95 % confidence interval 0.79, 0.81), although with a high degree of heterogeneity and a marked influence of two large cohorts [13,17].

Another study could not be included in the meta-analysis because it compared the use of GLP-1RAs among T2DM patients with versus without ASCVD and/or heart failure. This study reported a much lower use of GLP-1RAs in patients with ASCVD/heart failure in comparison with those without these CV complications (4.6 % versus 11.0 %) [20]. In the pharmaco-epidemiological LEGEND-T2DM study, which evaluated ten US and seven non-US electronic health record and administrative claim databases from 2011 to the end of 2021, the use of GLP-1 was also lower in patients with ASCVD than in those

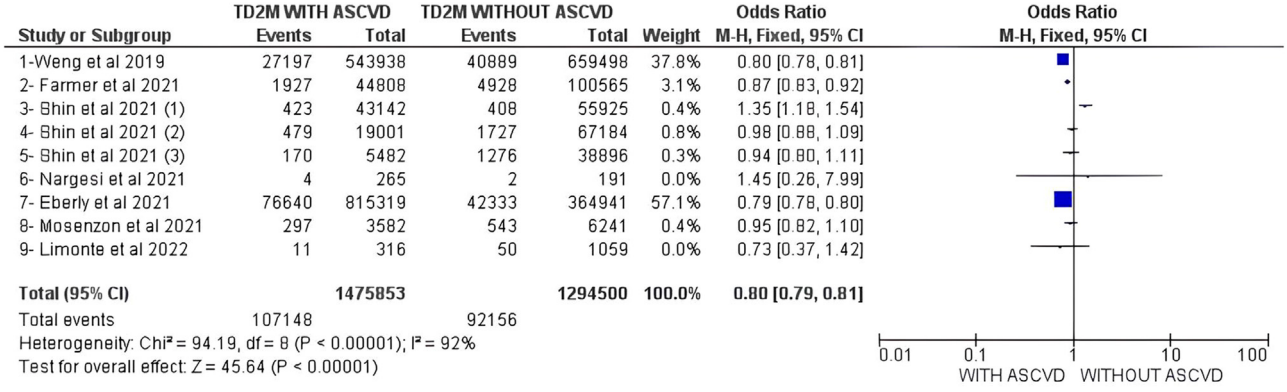

Fig. 1. Meta-analysis of studies comparing the proportion of patients treated with GLP-1RAs in type 2 diabetes people with versus without atherosclerotic cardiovascular disease. ASCVD : atherosclerotic cardiovascular disease. M-H : Mantel–Haenszel method. CI : confidence interval. Events: patients treated with GLP-1RAs.

without ASCVD (yet the number of patients in each subgroup was not available in the publication, thus not allowing to include these results in the meta-analysis) [21] (Table 1). In the France Longitudinal Patient Database, a computerized network of physicians including general practitioners who contribute to a centralized database of anonymized patient electronic medical records from 2012 to present, the use of GLP-1RAs was higher in patients with versus without ASCVD (13.4 % versus 10.7 %). However, the annualized change in the age- and sex-standardized incident use of GLP-1RAs was lower for patients with established ASCVD (0.35 %, 95 % CI 0.06 to 0.64) than for patients without established ASVCD (1.07 %, 95 % CI 0.28 to 1.86; p = 0.045) (cited in [21]). In another US study among older adults with T2DM, patients with a history of myocardial infarction, who would benefit from GLP-1RA therapy, were equally likely to start GLP-1RA treatment as were those without such history (OR 0.96; 95 % CI 0.90−1.03). Even more surprising, patients with cerebrovascular disease, who would also benefit from GLP-1RA therapy whose protective effect against stroke was reported in CV outcome trials [22], were less likely to start such treatment compared with patients without cerebrovascular disease (OR 0.92; 95 % CI 0.87−0.98) [23]. In a retrospective US analysis of claims of adults with T2DM, patients with prior myocardial infarction or cerebrovascular disease were less likely to start GLP-1RAs rather than dipeptidyl peptidase-4 inhibitors (DPP-4is) compared with patients without these conditions (relative risk ratio [RRR] 0.83, 95 % CI 0.78−0.88 for myocardial infarction and RRR 0.77, 0.74−0.81 for cerebrovascular disease) [24].

Discussion

The present analysis showed that the clinical use of GLP-1RAs remains low for the treatment of T2DM (< 10 %), despite a trend for a progressive increase over the last decade as shown in several retrospective observational studies [14,17,25,26]. More surprisingly, the use of GLP-1 is lower rather than higher in patients with ASCVD compared to patients without ASCVD. However, caution is required before drawing a definite conclusion and more dedicated studies are probably required. What so ever, these findings contrast with robust and mounting evidence demonstrating the efficacy of GLP-1RAs in reducing the progression of CV complications [3,4], and the recommendations of major professional organizations [7−9]. In contrast, medications without equivalent evidence for cardiorenal protection, such as sulphonylureas, DPP-4is and basal insulin, continue to be more frequently prescribed in these high-risk patients. In a cohort of 435,000 patients with T2DM identified from the “Swedish National Diabetes Register”, among patients recommended a GLP-1RA according to the 2019 ADA (American Diabetes Association) / EASD (European Association for the Study of Diabetes) consensus report, only 20.0 % had received this treatment [27].

The reasons for the low penetrance of GLP-1RAs in the management of T2DM are diverse and have been extensively discussed elsewhere [11,28]. Clinical inertia of prescribers, reluctance (fear of needle injection) and low treatment persistence among T2DM patients, knowledge of medication-associated gastrointestinal intolerance, the relative high price imposed by pharmaceutical companies and barriers of healthcare system for economic reasons, all these factors may contribute to the underuse of GLP-1RAs in clinical practice. Why the use of GLP-1RAs is generally somewhat lower in patients with established ASCVD is more astonishing and more difficult to be explained. Bridging the gap between clinical evidence demonstrated in cardiovascular outcome trials [3,4] and the underuse of GLP-1RAs in clinical practice remains a challenge [10,11]. Coordinated and multilevel interventions engaging clinicians, patients, payers, pharmaceutical companies, professional societies, and health care systems must be implemented to incentivize the adoption of GLP-1RAs as part of routine CV care in clinical practice, especially among T2DM patients with established ASCVD [11,29]. Indeed, if education remains fundamental to increasing adoption of therapeutic guidelines, a large body of evidence suggests it is not enough on its own to induce sustainable clinician behavior change [29]. A recently published cluster randomized clinical trial with 43 US cardiology clinics demonstrated that a coordinated, multifaceted intervention increased prescription of three groups of evidence-based cardioprotective therapies in adults with T2DM and ASCVD, including the use of GLP-1RAs and SGLT2is [30]. A US study reported that patients with T2DM were two times more likely to see a cardiologist than an endocrinologist in clinic, and patients were four times more likely to see a cardiologist than an endocrinologist if they had T2DM plus ASCVD [31]. Thus, cardiologists are uniquely positioned to participate in integration of this evidence-based but underutilized class of GLP-1RAs to advance comprehensive CV care [32−34].

Finally, as recently emphasized [35], socioeconomic disparities in the uptake of GLP-1RAs may constrain the collective advantages offered by these medications to a broader population. Advocating for a reduction in the price of GLP-1 RAs is a pivotal initial step to enhance their affordability among lower socioeconomic groups [17] and further improve their value-for-money from a societal perspective [35].

Conclusion

Despite a progression in the prescriptions in recent years, the use of GLP-1RAs for treating patients with T2DM remains rather low worldwide, generally below 10 %. The reasons are probably diverse, including the need of subcutaneous injections, the fear of gastrointestinal adverse events and the higher price. However, and surprisingly, the use of GLP-1RAs appears to be even lower in patients with a history of ASCVD compared with those without ASCVD, in contrast with our initial hypothesis. This finding sounds astonishing considering the demonstration of the CV protection with GLP-1RAs reported in many outcome trials and the clear-cut recommendations of international scientific societies. The reason for this paradoxical finding remains unclear. What so ever, efforts should be made to offer the best protective drugs in T2DM patients at high/very high CV risk.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

André J. Scheen: Writing – original draft, Writing – review & editing.

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