Use of incretin-based medications: What do current international recommendations suggest with respect to GLP-1 receptor agonists and DPP-4 inhibitors?

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Abstract

In recent years guidelines for the treatment of type 2 diabetes (T2DM) have evolved substantially. Initially limited to a few glucose lowering agents, early guidelines predicated strict glycemic control as a main goal in the attempt to reduce the risk of long-term diabetic complications. Nowadays, guidelines are not limited to such a goal but include cardiovascular (and renal) protection. This rapid evolution was made possible by the introduction of new glucose lowering agents, which have been extensively tested in randomized clinical studies including large cardiovascular outcome trials (CVOTs). In this review we will specifically consider the use of incretin-based medications in T2DM as recommended in the recent ADA/EASD consensus, and other international guidelines, with special consideration of their glucose-lowering efficacy, their cardiovascular (and renal) benefit, their effect on body weight and risk of hypoglycemia, as well as the economic implications for their use.

Introduction

In the past decade the number of guidelines, recommendations, positions and consensus statements for the management of T2DM have increased considerably [1-5]. Nonetheless, advances in care, including increased availability of new classes of glucose-lowering agents, have not necessarily been associated with improved patient outcomes [6]. This may reflect the requirement for a much more holistic management approach and a failure to acknowledge the complex factors that need to be addressed to improve patient outcomes, including complex pathophysiology, therapeutic inertia, poor adherence and persistence to treatment and failure to provide effective self-management support, as well as access to new glucose lowering agents [1,2].

The recent ADA/EASD consensus for the management of hyperglycemia in T2DM [1,2] represented a paradigm shift in the management of the disease. The decision cycle was intended to encapsulate those critical factors that need to be addressed in order to optimise an individual person's outcomes (Figure 1). The decision cycle starts with assessing key patient characteristics and suggests that the existence of co-morbidities such as atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD) or heart failure (HF) should precipitate preferential use of certain classes of glucose-lowering agents. The second step is to consider specific factors which impact on choice of treatment, including side effects of medications, and highlighting the importance of choosing treatment regimens to optimise adherence and persistence. Shared decision making is pivotal to success and in modern diabetes management there is an ethical imperative to support patient autonomy [1,2].

In the ADA/EASD consensus, metformin is still considered the first-line treatment medication of choice, but the recommendation is to escalate treatment if the HbA1c target has not been achieved after 3-6 months of therapy with metformin. The choice of escalating strategy is based on the individual's needs such as reducing the risk of cardiovascular and

renal disease, reducing the risk of hypoglycemia, avoiding body weight gain, and considering the cost of therapy.

In recent times, incretin-based therapy has gained a greater role in the guidelines for clinical management of T2DM. Whilst these agents were initially considered a second-tier option, in the recent update of the ADA/EASD consensus on treatment of hyperglycemia [7] they have become more relevant with the increase in the number of clinical studies completed. Incretin therapies include glucagon-like peptide-1 receptor agonists (GLP-1RAs), referred to as incretin mimetics and dipeptidyl peptidase-4 inhibitors (DPP4is), referred to as incretin enhancers.

GLP-1RAs trigger GLP-1 effects, which include glucose-mediated stimulation of insulin secretion and reduction of glucagon release, reduced hepatic glucose output, delayed gastric emptying, and increased satiety [8]. GLP-1RAs can be categorised on the basis of their homology to human GLP-1 or duration of action (Figure 2). Agents that are currently licensed and available include dulaglutide, exenatide, either twice daily or once weekly, liraglutide, lixisenatide, and semaglutide. An oral formulation of the latter has been recently approved by the Food and Drug Administration and the European Medicines Agency.

DPP4is are oral agents which potentiate the effects of endogenously secreted GLP-1 [8] by preventing its inactivation by aminopeptidase, resulting in its persistence at higher concentration in the circulation [9]. The increase of GLP-1 levels is less than that achieved with GLP-1RAs and not sufficient to elicit satiety, to slow gastric emptying, or to cause nausea. Nonetheless, the increased availability of GLP-1 is sufficient to enhance nutrient-induced insulin release and suppress glucagon secretion [8]. Current available agents include alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin, the latter not being available in the United States.

In this article we will specifically consider the use of incretin-based medications in T2DM with respect to the individualization strategies recommended in the recent ADA/EASD consensus as well as in other international guidelines. To this purpose we searched Medline and Google Scholar for diabetes guidelines and randomized controlled trials evaluating the efficacy and safety of GLP-1RAs and DPP4is. The following terms were used in the search: alogliptin, diabetes, dulaglutide, exenatide, guidelines, linagliptin, liraglutide, lixisenatide, saxagliptin, semaglutide, sitagliptin, and vildagliptin. Articles up to December 2019 were included. Studies were excluded if they were not published in English, were not prospective randomized trials, or did not enroll patients with T2DM.

Glucose-lowering efficacy

In spite of different pharmacokinetics and pharmacodynamics (Table 1), DPP4is have similar anti-hyperglycemic properties. DPP4i monotherapy generally results in smaller HbA1c

reductions than metformin, but overall they are equivalent to sulfonylureas and thiazolidinediones (TZDs) as an add-on therapy to metformin [10]. The combination of metformin and DPP4is is associated with lower incidence of gastrointestinal side effects as compared to metformin monotherapy [10,11]. Because of the greater efficacy, a DPP4i and metformin may be considered as initial combination therapy in patients with elevated HbA1c levels at diagnosis, though this combination could be also considered in patients with lower HbA1c at presentation, as recently suggested by the VERIFY (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes) study [12,13]. This randomized, double-blind trial showed that, in subjects newly diagnosed with T2DM (n=2001) and an average HbA1c at baseline of 6.5%, an early intervention with a combination therapy of the DPP4i vildagliptin and metformin provides greater and more durable glucose benefits compared with current standard-of-care initial metformin monotherapy followed by addition of vildagliptin [12,13].
The sulfonylurea/DPP4i combination has also been shown to provide additional glycemic efficacy but at the expense of increased risk of hypoglycemia. Thus, the sulfonylurea dose should be reduced when a DPP4i is added [14]. The pioglitazone/DPP4i combination reduces HbA1c more than with either agent alone [15] due to complementary mechanisms of action. Combination therapy with sodium-glucose cotransporter type 2 inhibitors (SGLT2is) and DPP4is is both efficacious and safe [16]. Adding a DPP4i to insulin can improve glycemic control with no increase in hypoglycemia [17] while providing some concomitant insulin-sparing [18]. DPP4is have a good safety profile often indistinguishable from that of placebo [19,20]. In particular, the risk of hypoglycemia is trivial, unless they are co-administered with sulfonylureas or insulin. Also, they have a neutral effect on body weight. DPP4is can be safely and effectively used even in end-stage renal disease with appropriate dose reduction, the only exception being linagliptin, which can be freely used because of its non-renal clearance [21].

Treatment with GLP-1RAs lowers HbA1c by 1-2% [22]. These medications, either as monotherapy or in combination with oral glucose-lowering medications or insulin, improve glycemic control and increase the odds of achieving HbA1c targets [23]. They are more efficacious in terms of HbA1c reduction and weight loss than metformin and sulfonylureas. Compared to DPP4is, GLP-1RAs yield greater mean reductions in HbA1c (-0.41%, 95% CI -0.53 to -0.30) and weight (-2.15 kg; -3.04 to -1.27), with more gastrointestinal symptoms but a similar risk of hypoglycemia [24]. Replacing a DPP4i with a GLP-1RA provides additional benefits in glycemic control and weight loss [24]. As adjunctive therapy to insulin, GLP-1RAs show the greatest HbA1c-lowering effect (-0.84%; 95% CI, -1.00% to -0.69%), compared to other glucose lowering agents [25]. Two recent meta-analyses showed that slightly better glycemic control can be achieved by adding GLP-1RAs to oral glucose-lowering medications as compared to insulin treatment, with the added benefit of less weight gain and lower risk of hypoglycemia [26,27]. Once-weekly, but not once-daily, GLP-1RAs are superior to basal insulin with respect to HbA1c reduction [27].

Structural differences between various GLP-1RAs result in unique clinical profiles; therefore, individual GLP-1RAs differ one from the other with respect to glycemic control, effects on weight, safety, and tolerability. Once-weekly semaglutide is believed to exert the greatest HbA1c reduction, followed by dulaglutide and liraglutide, closely followed by exenatide once weekly, and then exenatide twice daily and lixisenatide [23, 28-30]. The short-acting GLP-1RAs, exenatide twice daily and lixisenatide, have greater postprandial glucose control particularly after the meal immediately following their administration.
Exenatide and lixisenatide are not recommended in patients with a eGFR <30 mL/minx1.73m^2 while liraglutide, dulaglutide and semaglutide can be used in patients with severe renal impairment (eGFR ≥ 15 to < 30 mL/min) with no need for dose adjustment [31].

In the ADA/EASD consensus, DPP4is and GLP-1RAs are recommended as second line therapy, after metformin , while the AACE guidelines [3] consider them, as well as SGLT2is and TZDs as acceptable alternatives to metformin as initial therapy,) in select patient groups. Both guidelines acknowledge the greater glucose-lowering efficacy of GLP-1RAs as compared to DPP4is, though they underline how the choice between the two classes of incretin-based therapies should take into account other characteristics including cardiovascular protection and effect on body weight, as well as ease of use and drug tolerability. The distinction between oral and injectable administration is a matter for discussion with the person with diabetes to whom the benefits and risks of alternative treatment options should be presented and discussed.

Cardiovascular benefits

All DPP4is currently available in Europe have been evaluated in *ad hoc* CVOTs with the exception of vildagliptin. This accounts for a total of five large CVOTs, four of which (SAVOR-TIMI 53 [32], EXAMINE [33], TECOS [34], CARMELINA [35]) evaluated the effect of saxagliptin, alogliptin, sitagliptin, and linagliptin respectively, as compared to placebo when added to standard of care. More recently, in the CAROLINA [36] trial the effect of linagliptin was compared to the sulphonylurea glimepiride. All trials consistently showed non-inferiority for three-point major adverse cardiovascular events (MACE; cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke; Figure 3).
In contrast, a number of CVOTs with GLP-1RAs have demonstrated cardiovascular benefit (i.e. reduction to the first MACE event). A total of seven trials have been so far reported: ELIXA (lixisenatide) [37], LEADER (liraglutide) [38], SUSTAIN-6 (semaglutide) [39], EXSCEL (exenatide) [40], Harmony Outcomes (albiglutide) [41], REWIND (dulaglutide) [42], and PIONEER 6 (oral semaglutide) [43]. The results of these trials are somewhat discordant, with two studies missing statistical significance for superiority [40, 43] and one being neutral [37]. There has been much discussion about the potential explanation for these differences including the design of the studies, study populations and potential pharmacologic/biologic differences between exendin-4 vs GLP-1-based agonists. However, as pointed out in a recent review, the CV protection of GLP-1RAs is likely to be a class effect with the

differences among trials potentially explained by time of drug exposure [44]. A recent meta-analysis including all CV outcomes trials, showed that the treatment with GLP-1RAs, as compared to placebo, added on top of standard of care, reduced MACE by 12% (HR 0·88, 95%CI 0.82–0.94; p<0·0001), cardiovascular mortality by 12% (HRs 0.88, 0.81–0.96; p=0003), fatal or non-fatal stroke by 16% (0.84, 0.76–0.93; p<0·0001), and fatal or non-fatal myocardial infarction by 9% (0.91, 0.84–1.00; p=0.043) [45]. Moreover, GLP-1RAs reduced all-cause mortality by 12% (0.88, 0.83–0.95; p=0·001) and hospital admission for heart failure by 9% (0.91, 0.83–0.99; p=0.028) [44].

On the basis of these results, current guidelines (ADA, ADA/EASD, Canadian, AACE) [1-4] recommend both GLP-1RAs and SGLT2is in patients with T2DM with established cardiovascular disease. The recent update to the ADA/EASD Consensus suggested that GLP-1RAs should be considered to reduce the risk of MACE in high-risk T2DM individuals even without established CV disease [46]. In recent guidelines on diabetes, prediabetes and cardiovascular disease from the European Society of Cardiology, GLP-1RAs and SGLT2is were recommended as an add-on therapy to metformin and even as a first line therapy in people with T2DM and ASCVD or at high/very high CV risk [5].

The ADA/EASD consensus [1-2, 46], as well as the ADA, Canadian, and AACE guidelines, makes a distinction between people with diabetes with prevalent ASCVD and those with prevalent HF. For the latter, a common condition not necessarily secondary to ischemic heart disease, SGLT2is are preferred over GLP-1RAs because of more robust evidence of reduction in the risk of HF hospitalization and/or death. In keeping with this recommendation, a recent meta-analysis of the available CVOTs has reported a 9% relative risk reduction (HR 0.91, 095%CI 0.83 – 0.99) with GLP-1RAs [45] as compared to a 31% relative risk reduction (0.69; 0.61 – 0.79) with SGLT2is [47].

Similarly, the ADA/EASD consensus recommends the use of SGLT2is for those patients with apparent CKD [1-2]. These agents, indeed, seem to exert a favourable renal protection irrespective of the baseline kidney function [47]. A favourable effect has been reported with GLP-1RAs as well, although their overall impact is mainly driven by an effect on macroalbuminuria. A recent meta-analysis of GLP-1RA CVOTs, reported a 17% relative risk reduction (HR0.83, 0.78–0.89; p<0.0001) for composite kidney outcome (development of new-onset macroalbuminuria, decline in estimated glomerular filtration rate, progression to end-stage kidney disease, or death attributable to renal causes. This effect was mainly due to a reduction in urinary albumin excretion as a non-significant 13% reduction was apparent when just worsening of kidney function was considered (HR 0.87, 0.73-1.03) [47].

As far as DPP4is are concerned, after the initial concern generated by an unexpected increase in the risk for HF hospitalization in SAVOR-TIMI 53 [32] and a trend for a similar increase in EXAMINE [33], all other CVOTs found no negative effect on the risk of HF [34-36]. A potential nephroprotective effect of these agents was initially postulated [48] but the results of these clinical trials do not support a beneficial effect on the progression of renal impairment (MARLINA, CARMELINA) [35,49]. The same trials, however, have provided

support to their safe use even in subjects with advanced kidney failure [35,49], in whom glucose-lowering efficacy is retained along with a reduced risk of hypoglycemia.

Positioning of incretin-based medications based on body weight

Obesity increases the risk of T2DM and other important concomitant conditions such as hypertension, stroke, osteoarthritis, and gallbladder disease [50] and, ultimately, CV risk [51]. As such, the ADA/EASD consensus identifies the need to minimize weight gain, if not promote weight loss, as compelling for some of the subjects with T2DM [1-2]. In such patients, preference is given to GLP-1RAs and SGLT2is, both of which are associated with significant weight loss [1-2], whereas DPP4is are weight neutral.

Recent publications have reviewed the literature across the GLP-1RA class and their impact on HbA1c and weight reduction is summarised in figures 4 and 5 [28-30, 52,53]. In brief, there is marked heterogeneity across the GLP-1RA class in terms of weight loss, with the most modest reduction of body weight observed with albiglutide, lixisenatide and exenatide (twice daily) and the most significant weight loss occurring with the use of subcutaneous semaglutide [28-30, 52,53]. This apparent greater efficacy of semagutide is reflected in a statement in the ADA/EASD consensus report [1-2].

Much less is available in terms of how the SGLT2i class and the GLP-1RA class directly compare with respect to weight loss. In the DURATION 8 trial [56], there was no statistical comparison between those on exenatide 2mg once weekly and those on dapagliflozin 10mg once daily, though a numerically greater weight loss with the SGLT2i dapagliflozin (2.3kg) was apparent as compared to exenatide once weekly (1.5kg) from a baseline weight of 91kg. In the PIONEER 2 trial [55], a head-to-head comparison of oral semaglutide 14mg versus empagliflozin 25mg was performed, showing significantly greater weight loss with semaglutide (4.7kg) than with empagliflozin (3.8kg) from an average baseline body weight of 92kg. The SUSTAIN 8 study [56] is the only other head-to-head comparison of a GLP-1RA (subcutaneous semaglutide 1mg) compared to canagliflozin 300mg; this study showed that once-weekly semaglutide 1mg was superior to daily canagliflozin 300 mg in reducing body weight. A recent systematic literature review and network meta-analysis [57] reported that the mean difference in change from baseline in HbA1c of once-weekly semaglutide 1.0 mg versus SGLT-2is ranged from -0.56% compared to canagliflozin 300 mg and -0.95% compared to dapagliflozin 5 mg. The mean difference in change from baseline in weight of once-weekly semaglutide 1.0 mg versus SGLT-2is ranged from -1.35 kg compared to canagliflozin 300 mg and -2.48 kg compared to dapagliflozin 5 mg.

Of potential interest is the impact on weight of the combination of the GLP-1RAs and the SGLT2isThis approach has been examined in three RCTs: DURATION 8 [54], AWARD 10 [58], SUSTAIN 9 [59]. A combination of dapagliflozin and exenatide once-weekly was tested, while the effect of 0.75 and 1.5 mg dulaglutide added to a background of various SGLT2is was assessed in AWARD 10 [58]. In SUSTAIN 9 semaglutide (1mg) was added on top of various

SGLT2is [61]. More recently, the effect of liraglutide as add-on to SGLT2i±metformin has been reported [60]. All studies showed benefit in terms of both HbA1c-lowering as well as weight loss reduction with the greatest advantage being achieved with semaglutide providing an incremental weight loss of 3.8kg compared to 1kg with the maximum dose of dulaglutide 1.5mg weekly [54, 58-60].

Positioning of incretin-based medications and risk of hypoglycemia

Hypoglycemia is often the limiting factor for intensive glucose control in diabetes management [61] and is associated with cardiovascular events and death [62]. Thus, preventing hypoglycemia has become a major focus of T2DM management, especially in older and/or at-risk T2DM populations [63]. In the same token, the recent ADA/EASD consensus appreciates how minimising the risk of hypoglycemia can be a compelling need for some of the population with diabetes and no prior cardiovascular events [1-2]. There is a clear differentiation among glucose-lowering agents with respect to their risk of causing hypoglycemia, with sulphonylureas and insulin being the main cause of iatrogenic hypoglycemia. Of interest, all agents that have been associated with potential cardiovascular risk reduction are typically free of intrinsic risk of hypoglycemia. Due to their glucose-dependent mechanism of enhancement of insulin secretion, both DPP4is and GLP-1RAs represent valid options to improving glycemic control, minimizing the risk of hypoglycemia [8].

In a meta-analysis by Karagiannis *et al*., only a minimal number of hypoglycemic events were observed in any treatment arm in trials comparing a DPP4i with metformin as monotherapy or with pioglitazone as second-line treatment [10]. In most trials comparing a DPP4i with sulfonylureas combined with metformin, the risk for hypoglycemia was higher in the group treated with a sulfonylurea [10, 64]. The clear difference in term of hypoglycemia has been recently provided by the results of the CAROLINA trial [36]. After 6.3-year follow-up the trial showed no difference in CV risk (MACE; HR 0.98, 95. %CI 0.84-1.14; $p<0.001$ for non-inferiority) but the proportion of participants experiencing at least one episode of hypoglycemia was significantly lower in those randomized to treatment with linagliptin (10.6%) than in those receiving glimepiride (37.7%; HR 0.23, 0.21-0.26). These figures translate in a Number Needed to Treat of 18 per year to avoid one event of any form of hypoglycemia and 36 to avoid one episode of hypoglycemia ≤54 mg/dl or severe hypoglycemia. The results obtained in the clinical trials have been also confirmed in the clinical setting [65] and real-world studies [66].

Similarly, the risk of hypoglycemia with GLP-1RAs is low. Overall, all GLP-1RAs, except for albiglutide, were found to increase the risk of hypoglycemia when compared to placebo [67] but incidence of hypoglycemia is >30% lower compared to insulin [68] and sulphonylureas [67]. The greatest proportion of patients reporting minor hypoglycemic events occurred when adding treatments to a sulfonylurea background [22,69]. Assessment of the rate of hypoglycemia within the CVOTs suggests a non-significant 10% relative risk reduction of

severe hypoglycemia (HR 0.90, 95%CI 0.73 – 1.12) [44] but it must be kept in mind that GLP1-RAs were used on top of other glucose-lowering agents. In the LEADER trial a total of 267 patients experienced severe hypoglycemia (liraglutide n = 114, placebo n = 153; rate ratio 0.69; 95% CI 0.51, 0.93) [70] but the impact of liraglutide on the risk of MACE was similar in patients with (HR 0.85, 0.52 – 1.39) and without severe hypoglycemia (HR 0.88, 0.78 – 0.98; P-interaction= 0.90).
Because of these properties, the ADA/EASD recommend DPP4is and GLP-1RAs (along with SGLT2is and TZDs) for those subjects in whom minimising hypoglycemia is the clinical priority.

Costs (cost-effectiveness)

Incretin-based therapies are more expensive and still less accessible than more traditional agents such as metformin, sulphonylureas, and TZDs. The ADA/EASD consensus recommend that access, treatment cost and insurance coverage should be taken into account when selecting glucose-lowering medications and treatment escalation. In many regions of the world, including Europe, cost and access to newer pharmacologic agents remain a barrier to their use and in less advanced countries metformin, sulphonylureas and insulin still represent the only therapeutic options.
T2DM and its related complications impose a very high economic burden to both patients and society globally [71], making financial equilibrium a growing challenge for health systems. People with diabetes have medical costs approximately 2.3-fold higher than people without diabetes. More than half of the cost of the diseases are accounted for by hospitalization due to diabetes-related complications or side effects of treatment, including iatrogenic hypoglycemia. Since GLP-1RAs and DPP4is are associated with lower risk of hypoglycemia and the former could also reduce the risk of CV complication, a cost-effectiveness analysis should be taken into account.
Hypoglycemia can represent a significant source of costs. In an Italian study the direct cost of insulin-related hypoglycemia was estimated at €144.7 million per year, with €65 million attributable to severe episodes and €79.6 million due to non-severe episodes [72]. Hypoglycemia in T2DM accounts for >60% of these costs. A reduction in the rate of hypoglycemia could result in substantial cost savings: a 20% reduction in severe and non-severe hypoglycemia could result in a saving of €47,769 per general population of 100,000 people [72]. Cardiovascular comorbidities in patients with T2DM are one of the main contributors of this excess cost. According to Einarson *et al.* [73] at a population level, CVD costs contributed between 20% and 49% of the total direct costs of treating T2DM. The median annual costs per patient for CVD, coronary artery disease, heart failure, and stroke were, respectively, 112%, 107%, 59%, and 322% higher compared with those of patients with diabetes without CVD. On average, treating patients with CVD and T2DM resulted in a cost increase ranging from $3418 to $9705 compared with treating patients with diabetes alone. Therefore, higher drug costs related particularly to GLP-1RAs could be offset by the

reduction of other diabetes management costs (i.e. lower use of devices for blood glucose self-monitoring, lower incidence of hypoglycemia and MACE, and less requirement for insulin therapy (delayed initiation and lower insulin dose required)). Reducing the rate of hypoglycemia and other side effects may also offer additional opportunity to ensure better and more effective treatment. Lack of persistence with glucose-lowering agents is frequently found in primary care patients. DPP-4is, because of their lower risk of hypoglycemia and excellent tolerability, have been shown to be associated with a lower risk of discontinuation compared to sulphonylureas [74]. Continuous patient benefit has been observed for up to three years with GLP-1RAs. Four-year comparative data demonstrated a longer time to treatment failure for exenatide BID than for sulfonylurea [75], and three-year comparative extension data demonstrated greater HbA1c reductions and weight loss with exenatide QW than with insulin glargine [76]. Finally, the study DURATION-1 showed continuous HbA1c reductions and weight loss in patients continuing treatment with exenatide QW with no unexpected adverse events [77]. Nonetheless, differences in persistence to treatment exist between drug classes. DPP4is retain greater persistence as compared to SGLT2is and GLP-1RAs [78]. Improvement of treatment adherence is therefore a major need, which can be approached by sharing decision making with the person with T2DM, implementing a monitoring plan based not only on glucose control, but also focusing on the individual's emotional well-being, tolerability of medications and lifestyle (Fig. 1).

Conclusions

Guidelines for the treatment of hyperglycemia of people with T2DM have undergone significant changes in recent years, partly as a result of the availability of newer glucose-lowering agents. Up until the turn of the past century, treatment of hyperglycemia was limited to insulin, metformin and sulfonylureas and major emphasis was put on achieving satisfactory metabolic control. This was informed by early intervention trials such as the United Kingdom Prospective Diabetes study (UKPDS). This trial was largely based on those early glucose-lowering agents and showed that achievement of a HbA1c ≤ 7.0% was associated with a reduction of the risk of developing microvascular complications with an uncertain effect on macrovascular outcomes [79,80]. This goal was initially incorporated in almost all diabetes guidelines, including the first version of the ADA/EASD consensus [81]. More recently, agents with more targeted mechanisms of action have been made available, including DPP4is and GLP-1RAs. The second version of the ADA/EASD consensus [7] suggested them as second tier agents. More evidence has been generated with more clinical trials being performed and greater daily life experience built up in the diabetes clinics. In the meantime, intervention studies exploring the effect of intensive glycemic control resulted in the recommendation for personalization of the treatment of T2DM with respect to target HbA1c and selection of the pharmacologic agents to better match the patient's individual needs and the characteristics (glucose-lowering efficacy, effect on body weight, risk of hypoglycemia and costs) of glucose-lowering agents. GLP-1RAs were found to be more potent than the neutral effect of DPP4is [1-4] in causing body weight loss, while both were

suggested for reduction of the risk of hypoglycemia and both being more expensive than traditional drugs.

The next step in the evolution of diabetes guidelines has occurred recently after several CVOTs have shown that at least two classes of glucose-lowering agents, GLP-1RAs and SGLT2is, confer, a significant benefit in reducing CV risk and renal protection in those with prior CV events or elevated cardiovascular risk, while overall safety of DPP4is have been documented. Therefore, guidelines have incorporated, along with the recommendation of achieving appropriate glycemic control to reduce the risk of microvascular complication, the preferential use of drugs with proven CV (and renal) benefits. With respect to this, GLP-1RAs and SGLT2is are considered a preferred option in T2DM patients with ASCVD as well as agents in those with no prior CV events but with high CV profile. Moreover, these drugs may exert a favorable effect on body weight and reduce the risk of hypoglycemia [1,2,46].

By the same token, in current guidelines, DPP4is are listed as a therapeutic option after failure of metformin in those with no prior CV events and no HF in whom a low risk of hypoglycemia and maintenance of body weight is deemed necessary.

These considerations and recommendations need to be adapted to the specific needs of the person with diabetes with an ultimate goal to avoid long-term organ damage or reduce the risk of high-burden complications.

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Authors contribution

C. Bianchi performed literature research and drafted the paper. MJ Davies and S. Del Prato critically reviewed the draft and finalized the paper.

Duality of interest

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Legend to the figures

Figure 1 Decision cycle for patients-centred glycemic management in Type 2 diabetes as proposed by the ADA/EASD consensus [1]

Figure 2 Main characteristics of approved GLP-1 receptor agonists

Figure 3 Effect of DPP4 inhibitors on MACE

Figure 4 Glucose-lowering efficacy of GLP-1 Receptor Agonists in randomized clinical trials

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