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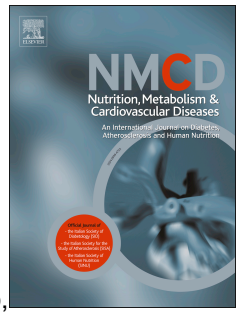

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Beneficial Effects of Glucagon-Like Peptide 1 Receptor Agonists on Glucose Control, Cardiovascular Risk Profile, and Non-Alcoholic Fatty Liver Disease. An Expert Opinion of the Italian Diabetes Society

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Abstract

Patients with type 2 diabetes mellitus (T2DM) show an increased risk of cardiovascular diseases (CVD) and mortality. Many factors are implicated in the pathogenesis of CVD in patients with T2DM. Among the factors involved, chronic hyperglycemia and the cluster of CVD risk factors, such as dyslipidemia, hypertension, and obesity, appear to play a major role. For many years, the control of hyperglycemia has been complicated by the fact that the use of many available drugs was associated with an increased risk of hypoglycemia. Paradoxically, hypoglycemia per se represents a risk factor for CVD. Recently, new drugs for the control of hyperglycemia have become available: many of them can determine a good control of hyperglycemia with minor risks of hypoglycemia. Among these new classes of drugs, glucagon-like peptide-1 receptor agonists (GLP-1RAs) offer many advantages. In addition to a strong anti-hyperglycemic action, they possess the ability to act on body weight and other relevant risk factors for CVD. Consistently, some of the GLP-1RAs have demonstrated, in RCT designed to assess their safety, to reduce the risk of major adverse cardiovascular events. Furthermore, GLP-1RAs possess properties useful to treat additional conditions, as the capability of improving liver damage in patients with NAFLD or NASH, highly prevalent conditions in people with T2DM.

In this document, written by some experts of the Italian diabetes society (SID), we will focus our attention on the therapy with GLP-1RAs in patients with T2DM, focusing on the effects on hyperglycemia, cardiovascular disease risk factors, NAFLD/NASH and CVD prevention.

Introduction

The treatment strategy for type 2 diabetes mellitus (T2DM) aims primarily to restore glucose homeostasis [1]. Some pioneering studies, such as the UKPDS (United Kingdom Prospective Diabetes Study) and ADOPT (A Diabetes Outcome Progression Trial) strongly emphasized the important role played by good glycemic control for the prevention of microvascular complications of diabetes [2, 3]. However, these studies did not completely clarify the role that the correction of hyperglycemia may exert in the prevention of macrovascular complications. In light of this evidence, the major scientific societies recommended a "tight glycemic control", supporting the target of keeping blood glucose levels as near as possible to the normal range by using the anti-hyperglycemic agents available at that time (sulfonylureas, metformin, and insulin).

In light of these considerations, the haemoglobin A1c (HbA1c) became the ideal parameter to follow to pursue good metabolic control in diabetic patients.

In the following years, the results of two independent clinical trials, the ADVANCE [4] and ACCORD studies [5], evaluating the effect of intensive glucose control in people with T2DM, obtained by using sulfonylureas, metformin, and/or insulin, did not support the hypothesis that a more stringent glucose control improves the risk of macrovascular complications. Moreover, in the ACCORD trial, the more intensive treatment was associated with an increased risk of all-cause mortality. Further analysis of the data of these trials suggested that the lack of beneficial effect of intensive glucose control on the development of macrovascular complications might be partly due to an increased occurrence of hypoglycaemic episodes [6]. Nevertheless, targeting a "good glycaemic control" became an integral part of diabetes treatment. Today, thanks to the introduction on the market of new classes of anti-hyperglycemic drugs that are effective but less dangerous for severe hypoglicemic episodes, rather than a treat-to-target approach aimed at reaching simply a good glycemic control, the concept of treat-to-benefit has arisen. With this approach, cardiovascular diseases (CVD) prevention, beta-cell preservation, the protection of the vessels, kidneys, and brain represent new targets of the disease treatment.

Among the new drugs that emerged in the last few years, the glucagon-like peptide 1 receptor agonists (GLP-1RAs) have profoundly modified the strategy for the treatment of T2DM. GLP-1RAs, in addition to their ability to control blood glucose concentration, possess multiple beneficial pleiotropic activities [7]. The results of a series of Cardio-Vascular Outcome Trials (CVOTs) with GLP-1RAs have demonstrated beneficial effects of these drugs, independent from the blood glucose control, on the risk of macrovascular complications.

Management of hyperglycemia by GLP-1RAs

The proper management of hyperglycaemia in T2DM must rely on a correct lifestyle and a balanced diet. This strategy should be integrated with a modern pharmacological approach targeting the pathophysiological mechanisms of the disease. Impaired insulin secretion, hyperglucagonemia, insulin resistance, lipid overload involving many tissues (including also liver, muscle, and heart) represent important treatment targets to provide the best therapy to any diabetic patient. Taking into account this new strategy, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guideline/recommendations recommend "a patient-centered" approach in the choice of the pharmacological agents to be used [8, 9].

According to such a "patient-centered" strategy", the clinical characteristics of the single patient should inspire and guide the choice of the best therapeutic options for T2DM treatment. In particular, physicians should consider the coexistence of Atherosclerotic cardiovascular disease (ASCVD) and/or chronic kidney disease (CKD). In this setting, the GLP-1RAs can be considered an attractive therapeutic strategy for the treatment of T2DM. GLP-1 RAs belongs to a growing class of glucose-lowering drugs that improve glucose homeostasis through several mechanisms,

including the enhancement of insulin secretion induced by the meal ingestion, the inhibition of glucagon secretion, and the slowing of gastric emptying. This class of drugs is effective at lowering HbA1c levels and also induces body weight loss with a low risk of hypoglycemia. Furthermore, they exert potentially protective benefits on the heart, liver, and kidney. Exenatide, the first GLP-1 RA to be approved for the treatment of T2DM, is the synthetic exendin-4, a peptide from the saliva of a lizard (*Heloderma suspectum suspectum* lizard), which was purified without any intention to be in search of diabetes medication [10]. In the last ten years, the GLP-1 RAs class has grown with several new agents, while several more are in development. To date, we have different GLP-1RAs with different peptide sequences, structure, and kinetics. From exenatide with an half-life of approximately 2.5 hour [11, 12] to new formulations designed for once-weekly injections with a long and persistent action on the GLP-1R. Recently, an oral preparation of semaglutide has been developed. This new formulation, prevents GLP-1 RA gastric degradation, and facilitates absorption, most likely through the gastric mucosa [13]. To date, there are many GLP-1RAs available on the market and this makes the drug selection difficult because of the need to evaluate the real effectiveness and the extra-glycemic benefits of the chosen compound to make the most appropriate choice, besides the patient's preferences. Therefore, the most important scientific societies recommend taking into account the overall patient clinical status, the presence of comorbidity, and also the availability of solid and reliable clinical research data. The results available from the CVOTs allow us to select the most appropriate drug for a better personalization of the therapeutic choices.

Effects of GLP-1Ras on glycaemic control

After a decade of clinical studies, head-to-head trials, CVOTs, and meta-analysis on the GLP-1 RAs class, we can state that this class of drugs is safe and very effective in the control of glycemia. So far, the data show that GLP-1 RAs induce more than one percentage point reduction in HbA1c, with a sustained and long-lasting effect (Table 1). Moreover, large randomized controlled trials (RCTs) have clearly demonstrated that GLP-1RAs, achieving and sustaining optimal glycemic control, may prevent or delay the development of microvascular and macrovascular complications of diabetes [14]. These data, consistent in all available trials, confirm that this class of drugs may represent a new effective therapeutic strategy to achieve a more stringent glycemic control in most patients with T2DM. However, some points need to be discussed when analyzing these data: to what extent can the data on HbA1c obtained under RCT's conditions be fully extrapolated to the real life? In a study published in 2017, Edelman and Polonsky [15] report that there is a gap between clinical trial and real-world setting, and this difference could represent about the 50% of benefit demonstrated by RCTs. We don't know whether all patients with T2DM respond equally to treatment with GLP-1RAs, irrespective of diabetes duration, baseline treatment for diabetes or some specific clinical features, race, etc. It is the general opinion that early treatment with these pharmacological compounds might represent an advantage in terms of benefits [16]. However, the most relevant CVOTs often include very compromised T2DM patients with a long duration of diabetes and a history of previous CVD. Thus, the clinical heterogeneity makes data interpretation very difficult, in particular in terms of glycemic control and HbA1c response to treatment.

Both short and long-acting GLP-1RAs significantly reduce HbA1c in patients on oral antidiabetic therapies (OAD); they also improve both fasting or postprandial hyperglycemia and increase the proportion of patients reaching the target HbA1c $\leq$7%. Data from a systematic review and meta-analysis [17] evaluated the pooled effects of incretin-based therapies, such as GLP-1RAs and dipeptidyl peptidase 4 inhibitors [DDP-4i], on HbA1c reduction and weight loss, stratifying by comparator therapy (placebo, mono-therapy, etc.) and also estimating the comparative efficacy on glycemic control between GLP-1RAs and DDP-4i. This meta-analysis showed that these new agents decreased HbA1c by − 0.28% (95% CI − 0.19, − 0.09) compared to sulfonylureas, metformin, pioglitazone or insulin. In contrast, GLP-1RAs lowered HbA1c by 1.02% compared to

placebo. Within-class GLP-1 RAs, this comparative meta-analysis also showed that the four long-acting agents (liraglutide, dulaglutide, taspsoglutide, and exentaide QW) lowered HbA1c by 0.35% vs. exenatide 10 μg BID, with small, non-statistically significant differences. However, it should be noted that the reduction of the HbA1c levels was achieved in a context of safety, without any additional risk of hypoglycemia. Furthermore, treatment with GLP-1RAs also showed a longer durability effect, which suggests its potential protective action on pancreatic beta cells. As highlighted by Edelman and Polonsky, independent of the exact percentage drop in HbA1c, the important aspect of the treatment with GLP-1 RAs is that the these drugs target euglycaemia mostly acting on the pathophysiological mechanisms underlying T2DM.

Extra-glycemic effects of GLP-1RAs

After the identification of the beneficial effects of GLP-1 on hyperglycemia, other relevant actions of this hormone in the regulation of several metabolic functions in humans have been demonstrated [18]. GLP-1 acts through receptors that are widely expressed and distributed in many human tissues and organs, such as pancreas, central nervous system, gut, kidneys, lungs, liver, heart, muscle, fat cells, peripheral nervous system, etc. [19]. Combining the activity on the different tissues and cells by using multiple mechanisms, GLP-1 can modulate many important body functions capable of affecting prognosis and risks of macro- or micro-vascular complications in people with T2DM. Due to the very short half-life of the endogenous GLP-1, under physiological circumstances GLP-1 plasma concentration and secretion may change rapidly in response to different stimuli. To take advantage of the beneficial effects of GLP-1 on human metabolism in the treatment of T2DM, several different approaches have been proposed and implemented by the industry to prolong GLP-1 action. One of these approaches has been the synthesis of modified GLP-1 molecules, used per se or differently combined with other macromolecules, to extend its half-life. As a result, we cannot exclude that many effects that we observe during the treatment with GLP-1RAs might be due to the chronic, constant rather than pulsatile, elevation of plasma GLP-1 levels that we do not find in nature, and that are specific, if not exclusive, of the pharmacological treatment and not present under physiological circumstances. On the other hand, the different GLP-1RAs commercially available have different half-lives, from few hours to many days or weeks, resulting in actions sometimes substantially different among them. Therefore, when we look at the extra-glycemic effects of the GLP-1RAs, we must keep in mind that the entity and quality of such effects might differ in response to the different agonists we consider [18].

In addition, to control blood glucose concentration, treatment with GLP-1RAs has shown, in humans or in experimental conditions, to be able to affect body weight, gastric emptying, diet and satiety, thermogenesis, neurogenesis, retinal repair, energy homeostasis, arterial blood pressure, lipid metabolism, heart rate, natriuresis, albuminuria, endothelial function, microvascular recruitment in muscle and heart, myocardial protection from injury, myocardial contractility, liver function and metabolism, etc. (as reviewed in [7]). Among the numerous effects of GLP-1RAs, some of them might be particularly relevant for the treatment of people with T2DM, to prolong their survival and improve the risk of chronic vascular complications. We know that controlling hyperglycemia, dyslipidemia, arterial blood pressure or body weight can reduce the risk of cardiovascular events or mortality in T2DM patients [20-22]. Therefore, we will focus our attention on the effects of treatment with GLP-1RAs on body weight, arterial blood pressure, and dyslipidemia.

The recent ADA standard of medical care in diabetes suggests that GLP-1RAs should be used for the treatment when ‘compelling need to minimize weight gain or promote weight loss’ is present, because the action of GLP-1 RAs on body weight reduction is supposed to be the most effective among the drugs used for the treatment of T2DM [23]. Although the long-term treatment with GLP-1RAs is associated with body weight reduction, the entity of this reduction varies with the different molecules used and their dosage. In addition, the effect on body weight seems to be

independent, and sometimes divergent, from the effect of the drugs on hyperglycemia, i.e. albiglutide possesses a meaningful effect on blood glucose concentration, but it is very weak in the control of body weight [24]. The ability of the drug to affect body weight, even in absence of an anti-hyperglycemic effect, allow its use also in obese non-diabetic people to induce weight loss [25, 26]. The mechanisms behind the effect of GLP-1RAs on body weight reduction can be multiple: inhibition of gastric emptying and feeling of gastric fulness and/or reduction of appetite through the direct action on the central nervous system, involving direct interaction with specific regions of the central nervous system [27]. GLP-1 RA action affects meal initiation and energy intake, rather than energy expenditure [28]. The entity of the body weight reduction varies among subjects and with the type of GLP-1RAs used. It is currently unclear why some subjects respond to the treatment with GLP-1RAs with a marked reduction in body weight, whereas others show only minimal body weight changes. This inconsistent response might involve some differences in the GLP-1RA action on central nervous system in certain individuals [29], or the interaction with the person's lifestyle behavior [30], or both.

Recently, a large network meta-analysis, including 746 trials evaluating the efficacy of GLP-1RAs and sodium-glucose cotransporter-2 (SGLT2) inhibitors on several parameters, also included a comparative analysis of their effects on body weight loss [31]. Somehow surprisingly, GLP-1RAs were reported to reduce body weight, on average, of only 1.42 kg, 0.47 kg less than SGLT2 inhibitors. A previously published meta-analysis [32] on the same topic, selecting data from 64 different trials, showed that the mean reduction in body weight induced by 24 weeks of treatment with short-acting GLP-1RAs was 1.32 kg while was 1.77 kg with the long-acting. At 52 weeks of treatment, therapy with long-acting GLP-1RAs was associated with the reduction of 1.18 kg compared to placebo. This was also associated with a reduction of waist circumference (-1.59 cm, on average). However, as a further support to the notion that there is a wide variability even among drugs of the same family, semaglutide reported a much larger body weight reduction (~3.4 kg at 24 weeks and 5.0 kg at 52 weeks). In general, short-acting GLP-1RAs appear to have a lower ability to reduce body weight than long-acting GLP-1RAs [33].

If we exclude the HARMONY-7 trial [34] using albiglutide, i.e. a drug not commercially available, there are currently 14 trials that can be used to evaluate the relative impact of different GLP-1RAs on body weight when directly compared among themselves [35-48]. In the LEAD-6 trial [35] liraglutide 1.8 mg/day was compared to exenatide 10 ug twice a day in T2DM patients already treated with metformin and sulfonylureas. The two treatment arms resulted in a similar weight reduction (3.2 vs. 2.9 kg, respectively). In both the DURATION-1 and DURATION-5 [36, 37] studies, exenatide once weekly was compared with exenatide twice daily in patients treated with one or two anti-hyperglycemic drugs. The effects of these two treatments on body weight were very similar. In the DURATION-6 trial [38], patients on oral hypoglycemic agents were treated with either liraglutide or exenatide once weekly and treatment with liraglutide resulted in a larger decrease in body weight (3.6 vs 2.7 kg, respectively, p=0.0005). When lixisenatide once a day was compared with exenatide twice daily in the GetGoal-X trial [39], a difference in favor of exenatide of 1 kg in body weight reduction was observed between the two treatment regimens. When lixisenatide, a short-acting analog, was compared with liraglutide, a long-acting compound, on the background of the metformin treatment, no difference in the reduction in body weight could be detected [40]. In the AWARD-1 [41] trial two doses of dulaglutide were compared with exenatide twice daily: no significant differences were found between exenatide and dulaglutide on body weight reduction. In contrast, in the AWARD-6 trial [42], liraglutide achieved a greater body weight reduction compared to dulaglutide 1.5 mg weekly (p=0.01). All the trials involving semaglutide, given either subcutaneously or orally, were associated with a greater body weight reduction vs the comparators. In the SUSTAIN-3 [43], SUSTAIN-7 [44], and in the SUSTAIN-10 [45] trials, semaglutide at the subcutaneous dose of 1 mg once weekly was able to induce a greater loss in body weight compared to exenatide once weekly, dulaglutide 0.75 or 1.5 mg once weekly or liraglutide 1.2 mg once daily. In the SUSTAIN-7 trial [44] semaglutide even at the dose of 0.5

weekly was able to induce a greater loss in body weight compared to dulaglutide 0.75 mg weekly. Oral semaglutide (dose escalated to 14 mg daily) was compared to liraglutide (dose escalated to 1.8 mg s.c.) in the PIONEER-4 trial [46]. Oral semaglutide induced a larger weight loss than liraglutide (4.4 vs 3.1 kg, respectively, $p<0.0001$). Finally, in the PIONEER-9 [47], and 10 [48] trials, oral semaglutide, when compared with the maximum doses of either liraglutide (0.9 mg s.c. daily) or dulaglutide (0.75 mg s.c. weekly) allowed in Japan, resulted in a greater body weight reduction.

GLP-1RAs are also capable of acting beneficially at several levels on the vessel wall. Multiple mechanisms can be invoked to explain the observed effects that GLP-1RAs exert on arterial blood pressure. In a recent meta-analysis, both short- and long-acting GLP-1RAs have been shown to significantly reduce systolic blood pressure (SBP) compared to placebo (-2.22 and -2.72 mmHg, respectively) [32]. In the same meta-analysis, short-acting, but not long-acting, have shown to reduce diastolic blood pressure (DBP) (-1.01 mmHg vs placebo). Another systematic review and meta-analysis [49] showed that GLP-1RAs reduced SBP by 1.8-4.6 mmHg compared to placebo, insulin or sulfonylureas. Among the GLP-1RAs, liraglutide and semaglutide appear to be more effective in reducing SBP. Regarding the DBP, only exenatide twice daily reduced diastolic blood pressure by 1.1 mmHg.

In the RCT used to register new anti-hyperglycemic products, the comparison between the drug tested and the comparator(s) is done without minimizing the effect of the agents on blood glucose concentration or HbA1c, since the purpose of the trial is the evaluate all the effects. In this context, the evaluation of the effects of GLP-1RAs on body weight loss or SBP might be influenced by the difference in blood glucose control. In CVOT, to maintain the equipoise, the difference in blood glucose concentration is minimized on purpose and the data on body weight loss or SBP might be better evaluated. In Fig. 1 we summarized the differences in body weight or SBP *vs* placebo registered during the CVOT [24, 50-55]. Although direct statistical comparisons cannot be made, semaglutide, either given oral daily or subcutaneously once weekly, appears to be the most powerful in the control of body weight or SBP.

Even plasma lipid profile may be improved by the treatment with GLP-1RAs [32]. Long-acting GLP-1RAs reduce the circulating levels of total cholesterol by 0.18 mmol/L and LDL-cholesterol by 0.10 mmol/L, while they do not affect plasma triglycerides.

In conclusion, GLP-1RAs, in addition to their marked effects on glucose control, can exert other beneficial actions in people with T2DM by reducing body weight and improving the levels of known CVD risk factors. Although some of these beneficial effects, i.e. reduction of blood pressure or decrease in plasma LDL-cholesterol levels, appear to be modest, it is reasonable to hypothesize that their combination might play an additive or synergistic role in improving the overall CVD risk profile.

Effects of GLP-1RAs on non-alcoholic fatty liver disease.

Non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions and occurs in up to ~30% of adults in the general population in Western countries. The prevalence of NAFLD is even greater in people with T2DM (occurring in up to ~70% of these patients) [56, 57].

Strong evidence indicates that T2DM is one of the most important clinical risk factors for the faster progression of NAFLD to non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma [57-59]. In the past decade, growing evidence also indicates that the global health burden of NAFLD is not only confined to liver-related complications, but also includes important extra-hepatic conditions, such as cardiovascular disease (i.e., the predominant cause of mortality in patients with NAFLD) and other cardiac complications (mostly left ventricular diastolic dysfunction or hypertrophy and permanent atrial fibrillation), as well as CKD, which are the most important chronic vascular complications of diabetes [60-62].

Presently, there are no approved pharmacological treatments for NAFLD or NASH, although several drugs are in advanced stages of development [63-65]. Lifestyle changes and weight reduction remain the cornerstone of management for NAFLD and NASH [63-65]. A network meta-analysis of RCTs and non-randomized intervention studies of patients with biopsy-confirmed NASH recently showed that long-term use of pioglitazone and bariatric surgery were the two most effective treatment options for NASH, thereby further supporting that weight loss and improvements in systemic/hepatic insulin resistance and other related metabolic disorders are key approaches for the treatment of this common and burdensome liver disease [66]. However, it is important to underline that although long-term use of pioglitazone may induce histological resolution of NASH in both type 2 diabetic and nondiabetic adults with biopsy-proven NASH, this drug may also have some side-effects, such as moderate weight gain, peripheral oedema, and risk of distal bone fractures (especially in post-menopausal women) [64, 67].

The strong association of NASH with obesity and T2DM led to preclinical investigations into the effects of GLP1-RAs in hepatocytes and murine models of NASH. In these experimental studies, GLP-1RAs reduced liver enzymes and oxidative stress, decreased expression of genes associated with fatty acid synthesis and improved liver histology (as reviewd in [68]). The potential role of GLP-1RAs in the treatment of NAFLD and NASH has since been investigated in an ever-increasing number of phase-2 RCTs that enrolled both individuals with and without pre-existing T2DM. Many of these studies have been also included in an updated meta-analysis that incorporated a total of eleven RCTs (6 placebo-controlled and 5 active-controlled trials published until December 2020) testing the efficacy of liraglutide (n=6 RCTs), exenatide (n=3 RCTs), dulaglutide (n=1 RCT) or semaglutide (n=1 RCT) to specifically treat NAFLD or NASH [69]. These RCTs were conducted for a median period of 26 weeks and provided aggregate data on 935 overweight or obese individuals (~70% with T2DM), in whom the diagnosis of NAFLD or NASH was based on either liver biopsy or imaging techniques (mostly magnetic resonance-based techniques, i.e., magnetic resonance imaging-Proton Density Fat Fraction or magnetic resonance spectroscopy) [69]. This meta-analysis showed that compared to placebo/reference therapy, treatment with GLP-1RAs was significantly associated with an improvement in the absolute percentage of liver fat content, as assessed by magnetic resonance-based techniques (pooled weighted mean difference: -3.92%, 95% CI -6.3 to -1.6%; $p<0.0001$), as well as in serum alanine aminotransferase and gamma-glutamyltransferase concentrations. Notably, this meta-analysis also showed that among patients with biopsy-confirmed NASH, a significantly higher percentage of patients had histological resolution of NASH with no worsening of fibrosis with once-daily subcutaneous treatment with either liraglutide or semaglutide compared with placebo (n=2 RCTs included; pooled random-effects odds ratio 4.06, 95% CI 2.5-6.6; $p<0.0001$) [69]. Conversely, there were no significant between-group differences in the percentage of patients with an improvement in fibrosis stage without worsening of NASH (pooled random-effects odds ratio 1.50, 95% CI 0.98-2.3; $p=0.06$). This meta-analysis confirmed that treatment with GLP-1RAs was also associated with significant reductions of body weight (~4 kg) and HbA1c levels (~0.5%) [69]. In all eligible RCTs, treatment with GLP-1RAs was usually well tolerated with a rate of adverse events not exceeding that of either placebo or reference therapy, except for a higher frequency of mild-to-moderate and transient gastrointestinal disorders [69]. Similar results were also reported by another recent meta-analysis [70].

It is well known that magnetic resonance-based techniques accurately quantify temporal changes in liver fat content, but their accuracy for diagnosing NASH and assessing the severity of liver fibrosis is somewhat limited [71-73]. So, looking at the RCTs included in the aforementioned meta-analysis, there is now a paucity of large, high-quality RCTs with sufficiently long follow-ups and primary histological endpoints assessed by liver biopsy, which is the “gold standard” modality for assessing and staging NAFLD [67, 69].

To our knowledge, there are only two placebo-controlled phase 2 RCTs that examined the effects of GLP1-RAs on the histological resolution of NASH or improvement in fibrosis stage [74,

75], which are the two key prognostic factors for adverse clinical outcomes in people with NAFLD [59, 76-79]. One of these studies, the Liraglutide Efficacy and Action in NASH (LEAN) phase 2 trial assessed the efficacy and safety of once-daily liraglutide 1.8 mg daily compared with placebo after 48 weeks in 52 UK obese patients with biopsy-confirmed NASH. 33% of these patients had pre-existing T2DM [74]. Treatment with liraglutide resulted in a significantly higher percentage of patients with histological resolution of NASH than placebo (39% of patients who received liraglutide vs. 9% of patients in the placebo group; relative risk 4.3, 95% CI 1.0-17.7; p=0.019). Liraglutide was not associated with a significant improvement of at least one fibrosis stage with no worsening of NASH (26% vs. 14%; p=0.46). However, 9% of patients in the liraglutide group vs. 36% of patients in the placebo group had progression of liver fibrosis after treatment with liragluitide (p=0.04) [74]. As expected, liraglutide was significantly associated with greater weight loss compared with placebo (-5.3 kg vs. -0.6 kg) [74]. Most adverse events were mild to moderate in severity, transient, and similar in the two treatment groups, with the exception of gastrointestinal disorders (e.g., nausea, diarrhoea, abdominal pain, vomiting or constipation). A recent larger phase 2 RCT appeared to show an improvement on results reported for liraglutide In fact, Newsome et al. compared once-daily (rather than once weekly) subcutaneous semalutide at doses of 0.1, 0.2 or 0.4 mg and placebo in 320 obese patients with biopsy-proven NASH and liver fibrosis (of whom 230 had stage F2 or F3 fibrosis, and 199 had pre-existing T2DM) [75]. The percentage of patients in whom NASH resolution was achieved with no worsening of fibrosis (i.e. the primary endpoint) was 40% with semaglutide 0.1 mg, 36% with semaglutide 0.2 mg, 59% with with semaglutide 0.4 mg and 17% with placebo after 72 weeks (p<0.001 for semaglutide 0.4 mg vs. placebo). There was no significant difference in the percentage of patients with improvement in fibrosis stage without worsening of NASH (i.e., the secondary endpoint; 43% with semaglutide 0.4 mg and 33% with placebo; p=0.48). Treatment with semaglutide also resulted in significant, dose-dependent reductions in body weight (−13% with semaglutide 0.4 mg and −1% with placebo), serum aminotransferase levels, non-invasive fibrosis biomarkers and liver stiffness (assessed by transient elastography). Semaglutide was safe and well tolerated, irrespective of the severity of underlying disease [75]. It should be noted that this phase 2 RCT with semaglutide did not include patients with cirrhosis and thus the efficacy and safety in these patients is unknown. However, phase 2 studies are planned or ongoing to assess semaglutide monotheraphy and combination regimens with cilofexor and/or firsocostat in patients with compensated cirrhosis due to NASH.

The precise mechanisms by which GLP-1RAs exert their potential hepatoprotective effects are not fully understood. It is reasonable to hypothesize that the potential mechanisms of action of GLP-1RAs in NAFLD/NASH are multifactorial and a consequence of their combined effects on glycaemic control, insulin resistance, weight loss and a direct beneficial effect on the liver (beyond weight reduction and related metabolic improvements) [69]. Experimental studies have shown that GLP-1RAs may improve NAFLD by reducing hepatic de novo lipogenesis, enhancing fatty acid oxidation and improving multiple insulin signaling pathways [80-83]. In addition, preclinical studies in animals have also suggested that GLP-1RAs improve hepatic inflammation, possibly through mechanisms that are at least in part independent of weight loss [84].

Taken together, these aforementioned findings mostly derived from phase 2 RCTs indicate that GLP-1RAs, especially liraglutide and semaglutide, may have favorable effects on NAFLD and NASH (as schematically shown in Fig. 2). Phase 3 trials of GLP-1RAs in NASH are now needed to answer further questions regarding their long-term effects on fibrosis and NASH resolution, and to confirm safety. A phase 3 trial in approximately 1,200 patients with biopsy-proven NASH is ongoing, to investigate the efficacy and safety of once-weekkly semaglutide versus placebo over 240 weeks (NCT04822181). That said, if these promising results will be confirmed in phase-3 RCTs, it is reasonable that GLP-1RAs will become a suitable treatment option for NAFLD or NASH (alone or more likely in combination with other drugs), especially in people with coexisting T2DM or obesity.

Effects of GLP-1RAs on CVD risk reduction

CVD is the leading cause of morbidity and mortality in patients with T2DM, although in the last few years new therapeutic approaches have been developed to improve outcomes [85-87]. An optimal control of diabetes during the 1st year after diagnosis may confer prolonged risk reduction for diabetic complications and mortality. Therefore, treating patients with T2DM earlier in the course of the disease and more intensively, avoiding weight gain and hypoglycemic episodes, has the potential to provide substantial, long-term improvements [88]. T2DM subjects are at "high risk" for CVD even when they are in primary prevention and the control of CVD complications, as well as the cardiovascular safety of anti-hyperglycemic drugs, should be a primary objective in the treatment selection [88]. GLP-1RAs have demonstrated to significantly reduce the risk of major adverse cardiovascular events (MACE) [89]. As discussed extensively above, this could be the result of a direct action of these drugs on vasculature, but also to their effectiveness on glycemic control in the absence of significant side effects, such as the risk of hypoglycemia or weight gain, which are typically associated with the use of "old" glucose-lowering drugs [90].

Data showing that GLP-1RAs reduce MACEs in patients with T2DM and previous CVD triggered a major paradigm shift beyond glucose control to a broader strategy of comprehensive CVD risk reduction [85, 86, 89, 91-93]. Therefore, in this section, we will briefly discuss data related to CVD risk reduction in T2DM of GLP-1RAs currently available in clinical setting . To date, liraglutide, semaglutide, and dulaglutide have demonstrated benefits for MACE prevention, particularly among those with established ASCVD. Among them dulaglutide is the only agent also approved for CVD disease reduction in T2DM patients without established ASCVD [94]. Exenatide once weekly and oral semaglutide showed numerically favourable but not statistically significant results for 3-point MACE [53, 55]. Lixisenatide did not significantly reduce risk for CVD events in patients studied after a recent episode of acute coronary syndrome [50] (Fig. 3). However, the results obtained in the different CVOTs could be influenced by the heterogeneity in patient selection criteria, percentage of subjects with established CVD, baseline HbA1c levels, as well as different study design and therapeutic exposure duration [95] (Fig 3).

Lixisenatide

The evaluation of lixisenatide in acute coronary syndrome (ELIXA) [50] was designed as a non-inferiority trial. A total of 6068 patients were included, randomised to treatment with lixisenatide (10 μg titrated to a maximum dose of 20 μg daily) or placebo. All subjects enrolled in this trial were affected by T2DM with a history of myocardial infarction or hospitalization for unstable angina within the previous 180 days (secondary prevention). Average baseline HbA1c was 7.7% and the median follow-up was 25 months in each group. The primary endpoint was the first occurrence of one of the following: CVD death, non-fatal stroke or myocardial infarction or hospitalisation for unstable angina. No statistical difference was observed regarding the occurrence of the primary endpoint (13.4% in the treatment group vs. 13.2% in the placebo group) or in the percentage change in the urinary albumin-to-creatinine ratio between groups. The study characteristics were a short follow-up period of 2 years and a high percentage of participants on statin therapy, providing further CVD benefit. The study demonstrated that the addition of lixisenatide to usual care did not significantly alter the rate of MACE in patients with T2DM and a recent acute coronary syndrome.

Liraglutide

Liraglutide and cardiovascular outcomes in type 2 diabetes (LEADER) trial [51] demonstrated for the first time that treatment with a GLP-1RAs could be beneficial in the prevention of CVD events in T2DM. Participants were older than 50 years with pre-existing CVD disease, chronic heart failure or CKD or older than 60 years with at least one CVD risk factor. The subjects were randomly assigned to 1.8 mg liraglutide (or maximum tolerated dose) or placebo injection. The primary outcome was the first occurrence of a 3-point MACE (CVD death, non-fatal myocardial

infarction or stroke). A total of 9340 participants were enrolled with a baseline HbA1c of 8.7%, 80% of them had established CVD disease (secondary prevention) and 20% were on primary prevention. During the median follow-up of 3.5 years, the primary composite outcome was reduced by 13% (hazard ratio: 0.87; 95% CI: 0.78-0.97) in the liraglutide group vs placebo. All components of the composite contributed significantly to a reduction in 3-point MACE, while all-cause death was reduced by 15% (hazard ratio: 0.85; 95% CI: 0.74-0.97). No significant reduction in heart failure events was noted. Incidence of diabetic nephropathy was lower in liraglutide group compared with placebo (1.5 vs 1.9 events per 100 patient-years, p=0.003), while non-significant differences in diabetic retinopathy events were detected between groups (0.6 liraglutide vs 0.5 placebo events per 100 patient-years). Characteristics of the study population enrolled in the LEADER trial were an elevated number of T2DM patients with CVD disease and high baseline HbA1c values, thus representing a very high-risk population. Therefore, the benefit observed in this trial may not be extended *sic-et-simpliciter* to a lower risk population or to subjects without established CVD.

Semaglutide

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes' (SUSTAIN-6) was a non-inferiority trial that compared once-weekly semaglutide with placebo [52]. Using the same inclusion criteria of the LEADER [51], a total 3232 T2DM patients completed the trial (out of 3297 patients enrolled), with a median observation time of 2.1 years. Overall, 83% of these patients had established CVD (including CKD stage 3), 59% of patients had established CVD not including CKD, and their mean HbA1c level at baseline was 8.7%. Participants were randomised to receive 0.5 or 1.0 mg of semaglutide once weekly or placebo. The primary composite outcome was a 3-point MACE as previously described. The primary endpoint occurred in 6.6% of patients in the semaglutide group compared with 8.9% in the placebo group. Although the study was not specifically designed to test superiority, semaglutide significantly reduced the primary endpoint by 26% (hazard ratio: 0.74; 95% CI: 0.58-0.95). This reduction was mostly driven by a significant decrease in the rate of non-fatal stroke (by 39%, p=0.04) and a non-significant decrease in non-fatal MI (by 26%), with a lack of any significant effect on CVD mortality or hospitalization for heart failure.

Once-weekly exenatide

The 'Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes'-EXSCEL trial [53] enrolled 14 752 participants with T2DM presenting a HbA1c between 6.5% and 10.0% (median 8%), and a wide range of CVD risk (73.1% had a previous history of CVD). They were assigned to either 2 mg of extended release exenatide or placebo once weekly. The primary study outcome was a 3-point MACE during a median duration of 3.2 years. The 3-point MACE occurred in 11.4% of patients in the exenatide group compared with 12.2% in the placebo group, which did not reach significance for superiority (hazard ratio: 0.91, 95% CI: 0.83-1.00, p<0.001 for non-inferiority, p=0.06 for superiority). However, the EXSCEL met the goal of CVD safety. The findings for secondary study outcomes (i.e. rates of CVD death, fatal or nonfatal MI, fatal or nonfatal stroke and hospitalisation for heart failure) did not differ significantly between the two treatment groups [53]. This trial was the largest CVOT conducted, with about 30% of T2DM patients in primary prevention for CVD. It did not have a run-in period and had one of the highest discontinuation rates of the medication compared with the other CVOTs.

Dulaglutide

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) [54], was the first trial designed to show superiority of the drug compared to placebo. The 9901 T2DM participants were older than 50 years. 32% of them had a history of CVD events, 68% were in primary prevention and presented with multiple CVD risk factors. Average baseline HbA1c was 7.2% and median follow-

up was 5.4 years. Dulaglutide significantly reduced the primary outcome (any of the following: non-fatal myocardial infarction, non-fatal stroke, or death from CVD causes or unknown causes) by the 12% (hazard ratio: 0.88; 95% CI: 0.79-0.99). These results were consistent across subgroups of patients with and without known ASCVD and were driven by a 24% reduction in the risk of stroke (hazard ratio: 0.76; 95% CI: 0.62-0.94). Significantly fewer adverse renal outcomes were found with dulaglutide vs placebo (17.1% vs. 19.6%, p=0.0004).
This study was the longest trial with the lowest risk population (only 32% of T2DM participants were affected by established CVD) and the lowest baseline HbA1c.

Oral semaglutide
The most recent CVOT is 'Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes' –PIONEER-6 [55]. Participants were older than 50 years of age with established CVD disease or CKD, or older than 60 years of age with CVD risk factors. They were randomly assigned to either to placebo or 14 mg once daily oral semaglutide . A total of 3183 T2DM patients with average baseline HbA1c of 8.2% were enrolled and followed for a median of 15.9 months. 84.7% of them had established CVD or CKD. The PIONEER-6 was a non-inferiority trial. The primary outcome (3-point MACE) occurred in 3.8% of patients receiving oral semaglutide compared with 4.8% receiving placebo (hazard ratio: 0.79 95% CI: 0.57-1.11, p=0.17). This trial had the shortest duration and had the lowest CVD event rates compared with other CVOTs. It is important to note that although oral semaglutide did not show any significant CVD benefit, the hazard ratio for oral semaglutide was similar to that previously reported for injectable semaglutide (HR 0.79 vs 0.74).

Meta-analysis and 'real world' evidence
Data are emerging from meta-analytic studies indicating that the GLP-1RAs CVD benefit regards patients affected by T2DM, regardless of the presence of ASCVD.
In a meta-analysis including four CVOTs studies comparing GLP-1RAs to placebo in 33 457 patients with T2DM [96], Bethel and coll. reported a significant reduction of 3-point MACE (by 10%), CVD mortality (13%) and all-cause mortality (12%) with a favourable trend (not statistically significant) on risk reduction of nonfatal stroke, MI, and hospitalization for heart failure.
Two recent meta-analysis have been carried out on placebo-controlled trials with aim of assessing whether CVD risk reductions of GLP-1RAs were similar in T2DM patients with or without established CVD. Among the 56 004 patients included in the analysis, 14 008 were in primary prevention. The results demonstrated that GLP1-RAs induced significant reductions in 3-point MACE, CVD death, all-cause mortality, fatal or non-fatal MI, fatal or non-fatal stroke, as well as in hospital admission for heart failure and in a broad composite kidney outcome (mainly driven by effects on albuminuria) [97, 98]. Consistently, a study based on a 20-year follow-up data from the Danish National Patient Registry, showed that T2DM people on regimens including GLP-1RAs had the highest reductions for MACE. The lowest risk was, in general, seen for people on GLP-1RAs *plus* SGLT2 inhibitors [99].

GLP-1RAs-SGLT2i combination therapy

No CVOTs have been conducted on the effects on major CVD outcome of concomitant use of both SGLT2 inhibitors and GLP-1RAs, although combination therapy is included in current management guidelines for T2DM [8, 92]. In randomized, placebo-controlled trials, treatment with dulaglutide, liraglutide, and semaglutide have shown an additive glucose-lowering benefit over placebo in patients treated with background SGLT2 inhibitors, indicating that the mechanisms regulating their efficacy on blood glucose control are independent [100-102]. Therefore, if clinically indicated, it appears reasonable to use both a GLP-1RA and an SGLT2 inhibitor with demonstrated CVD benefit concomitantly, even though such combination therapy has not been studied for CVD risk reduction in large clinical trials. In conclusion, based on the available results, in T2DM patients with

established ASCVD or at high risk of ASCVD and/or heart failure, the initiation of a GLP-1RA with demonstrated cardiovascular benefit should be considered, irrespective of HbA1c levels [93].

Conclusions

We know from solid literature that good glycemic control is capable of preventing microvascular complications and, in the long term, even macrovascular complications. The main obstacle to obtaining a good glycemic control with the traditional glucose-lowering drugs used in the past was the increased risk of hypoglycemia, associated with short- and long-time risks of serious complications, including an increased risk of CVD. Roughly a little more than a decade ago, the introduction on the market of new drugs to treat hyperglycemia in T2DM patients profoundly changed our approach to the treatment of diabetes. In particular, GLP-1RAs, which are the focus of this narrative review, have shown that blood glucose control can be easily ad safely obtained with a negligible risk of hypoglycaemia. In addition, treatment with GLP-1RAs may beneficially affect many CVD risk factors and further contribute to reducing the overall risk of CVD complications in people with T2DM. Indeed, we know from the CVOT results that GLP-1RAs can reduce the risk of 3-point MACE in patients with T2DM, regardless of the presence or absence of pre-existing CVD. Interestingly, in the last few years, further and unexpected beneficial effects of GLP1RAs have been revealed, i.e. the capability of improving liver damage in patients with NAFLD or NASH that is a highly prevalent condition in people with T2DM.

In conclusion, as suggested by some recent guidelines, treatment with GLP-1RAs should be considered mandatory in T2DM patients with ACVD and strongly encouraged in all the other patients for the potential benefits in the prevention of CVD.

Competing interests.
The authors have nothing to disclose.

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Table I. HbA1c level modification in available CVOTs using GLP-1RAs. Length of the follow-up is expressed in weeks, months or years, according to the original study.

Study name	Duration (median)	HbA1c (%) at begin of the study	HbA1c (%) at the end of the study	Delta of reduction (%)	Reference
ELIXA	25 months	7.7±1.3	7.4	-0.6 at 12 weeks	50
LEADER	3.8 years	8.7	7.6	-1.1 at 54 weeks	51
SUSTAIN-6	104 weeks	8.7±1.4	7.6 (0.5 mg) 7.4 (1.0 mg)	-1.0 at 104 weeks	52
EXSCEL	3.2 years	8.0	7.6	-0.7 at 6 months; -0.5 at 5 years	53
PIONEER 6	15.9 months	8.2±1.6	7.2	-1.0 at 62 weeks	55
HARMONY	1.5 years	8.76±1.5	7.8	-0.9 at 16 months	24
REWIND	5.4 years	7.3	7.0	-0.7 at 3 years -0.2 at 5 years	54

FIGURE LEGENDS

Figure 1.
Differences in body weight loss and systolic blood pressure *vs* placebo in the CVOT with GLP-1 RAs (24, 50-55)

Figure 2.
Schematic overview of the possible beneficial effects of treatment with GLP-1RAs on NAFLD or NASH. Data are derived from a recent systematic review and meta-analysis of randomized controlled trials (69).

Figure 3.
Graphical representation of the main results (panel A-D) and the proportion of patients with established atherosclerotic cardiovascular disease (panel E) in the GLP-1RAs cardiovascular (CV) safety trials. MACE: composite CV outcome consisting in death from CV causes, non-fatal myocardial infarction or non-fatal stroke;
* statistically significant for noninferiority, but not for superioriority; ** statistically significant for both noninferiority and superioriority; # not statistically significant

Fig. 1

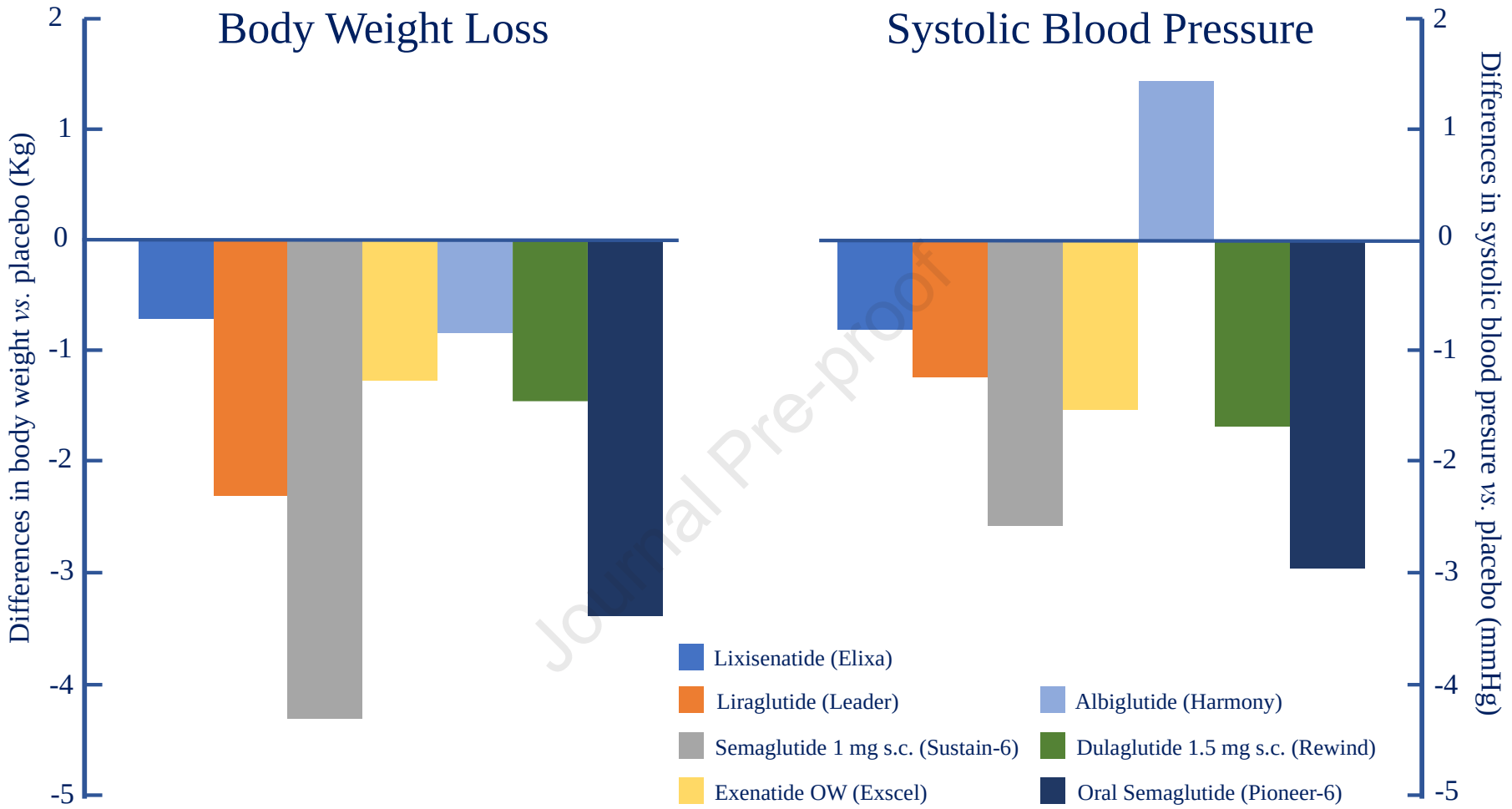


Fig. 2

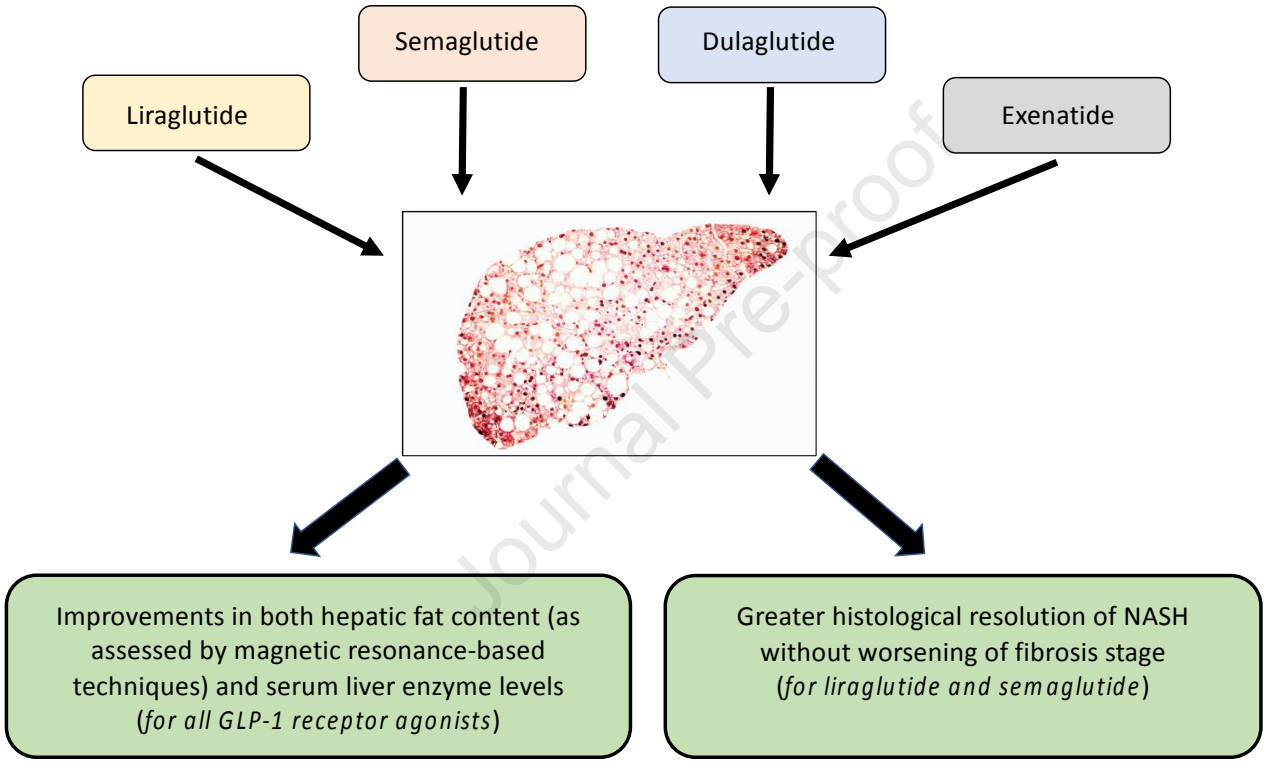
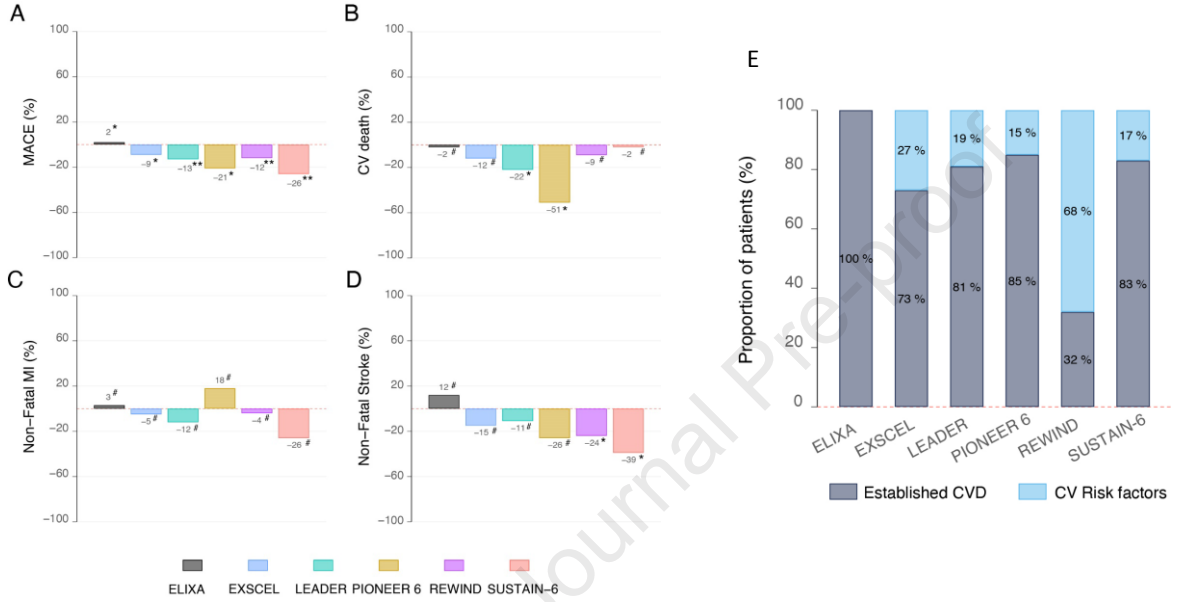


Fig. 3



Highlights

- Experts opinion of the Italian diabetes society (SID) on the therapy with GLP-1RAs in patients with T2DM, focusing on the effects on hyperglycemia, cardiovascular disease risk factors, NAFLD/NASH and CVD prevention.
- New drugs for the control of hyperglycemia in type 2 diabetes mellitus (T2DM) can maintain a good control of hyperglycemia without or with minor risks of hypoglycemia. Glucagon-like peptide-1 receptor agonists (GLP-1RA), in addition to a strong anti-hyperglycemic action, act on body weight and other relevant risk factors for CVD.
- Some of the GLP-1RAs have demonstrated to reduce the risk of major adverse cardiovascular events.
- GLP-1RAs possess properties useful to treat conditions other than T2DM, as NAFLD or NASH
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