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Obesity update: cardiovascular risk and therapeutic innovations (focus on semaglutide and tirzepatide)

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Excess or dysfunctional adipose tissue is a key pathophysiological factor in cardiovascular–kidney–metabolic syndrome. However, until very recently, there was no evidence that pharmacological treatments for obesity could significantly impact major cardiovascular outcomes. Recently, the SELECT study represented the first, and to date the only, cardiovascular outcome trial conducted in the context of pharmacological treatment for obesity, and subcutaneous (s.c.) semaglutide 2.4 mg is the first molecule capable of leading to a statistically significant reduction in the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke in obese, non-diabetic patients with pre-existing cardiovascular disease. Furthermore, in the context of heart failure with preserved ejection fraction with obesity-related phenotype, s.c. semaglutide 2.4 mg and tirzepatide have been shown to improve prognosis, functional capacity, and quality of life. The main limiting factors for the implementation of semaglutide and tirzepatide are represented by the suboptimal adherence to treatment due to gastrointestinal intolerance, as well as by the reduced accessibility and economic sustainability. It is therefore necessary to wait to see how the drug regulatory agencies and international guidelines will implement the evidence of semaglutide and tirzepatide in the specific setting of the cardiovascular risk of obese patients.

Obesity and cardiovascular risk

In recent years, a growing body of evidence has demonstrated a close link between obesity [body mass index (BMI) $\geq$ 30 kg/m^2] and cardiovascular risk. The concept of 'cardiovascular–kidney–metabolic syndrome' (CKM) has emerged, defined as a pathological condition resulting from interactions between obesity, Type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and cardiovascular disease [CVD; including heart failure (HF), atrial fibrillation, coronary atherosclerotic artery disease, stroke, and peripheral arterial disease], including both patients at risk of CVD and those with established CVD. Recently, the American Heart Association has proposed a 'physiopathological' staging of CKM, identifying the initial stage (Stage 1) as the presence of either excess adipose tissue or 'adiposity' (i.e. BMI $\geq$ 25 kg/m^2 or visceral obesity) or dysfunctional adiposity (i.e. impaired glucose tolerance or pre-diabetes). This adiposity progressively leads to the onset of metabolic risk factors such as dyslipidaemia, arterial hypertension, diabetes, and/or CKD (Stage 2), subclinical CVD or the presence of risk equivalents (Stage 3), and up to clinically established CVD (Stage 4).[1] Excess or dysfunctional adiposity is the key pathophysiological factor in the systemic consequences of CKM, which has cardiovascular events and cardiovascular mortality as its most significant clinical outcome. It must therefore be treated in order to

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prevent progression to more advanced stages of CKM and potentially promote its regression.

Obesity and therapeutic innovations

Pharmacological treatment of obesity

Pharmacological treatment of obesity is recommended for BMI ≥30 or ≥27 kg/m^2 in the presence of one or more related comorbidities. To date, six drugs are approved for the long-term management of non-syndromic obesity: orlistat, phentermine/topiramate, naltrexone/bupropion, the subcutaneous (s.c.) glucagon-like peptide-1 receptor agonists (GLP-1 RAs) liraglutide 3 mg and semaglutide 2.4 mg, and the dual agonist of the glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor tirzepatide 5–15 mg. These molecules lead to weight loss and improved metabolic parameters with variable potency and effect, and s.c. semaglutide and s.c. tirzepatide have demonstrated higher efficacy.[2]

Semaglutide's mechanism of action is expressed centrally by reducing appetite and peripherally by increasing insulin secretion, reducing intestinal motility, and delaying gastric emptying. Semaglutide was studied at a dose of 2.4 mg s.c. per week in the randomized controlled trial (RCT) STEP (Semaglutide Treatment Effect in People with Obesity),[1] where it demonstrated a reduction in body weight of 14.9% (−15.3 kg) at 68 weeks of treatment compared to placebo.[2] These data were confirmed by a pooled analysis from three RCTs in which s.c. semaglutide 2.4 mg showed a mean difference of 12.6% at 68 weeks compared to placebo. Moreover, when compared to s.c. liraglutide 3 mg in the STEP 8 study, it demonstrated a significantly higher weight loss, with a mean difference of 9.4% at 68 weeks, as well as less discontinuation due to adverse events (3.5 vs. 12.6%).[2]

Tirzepatide is a dual agonist that acts on the gastric inhibitory polypeptide (GIP) and GLP-1 receptors, exploiting the complementary action of the two incretins. GIP facilitates insulin secretion, especially after a meal, increases the effects of GLP-1, and improves the therapeutic efficacy of the drug. Similar to GLP-1 RAs, tirzepatide acts centrally by reducing appetite and peripherally by delaying gastric emptying. In the pivotal study SURMOUNT-1 (Efficacy and Safety of Tirzepatide Once Weekly in Participants Without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities), weekly s.c. administration of tirzepatide at the doses of 5, 10, and 15 mg was compared to placebo in 2539 obese non-diabetic patients, demonstrating a respective mean weight reduction of 15, 19.5, and 20.9 at 72 weeks, respectively. Additionally, 50 and 57% of patients receiving the 10 and 15 mg doses, respectively, achieved a ≥20% reduction in body weight.[3] When compared to s.c. semaglutide 1 mg in the SURPASS-2 [A Study of Tirzepatide (LY3298176) vs. Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants with Type 2 Diabetes] trial, tirzepatide at the doses of 5, 10, and 15 mg demonstrated a more significant reduction in body weight (−1.9, −3.6, and −5.5 kg, respectively; $P <$ 0.001), despite a numerically higher occurrence of serious adverse events (5–7 vs. 3%).[4]

Therapeutic innovations in obesity and cardiovascular risk

Until very recently, the only class of drugs that have demonstrated a significant impact on metabolic risk factors and cardiovascular and renal outcomes of CKM was that of sodium-glucose cotransporter-2 inhibitors (SGLT2-i). In parallel, the class of GLP-1 RAs had demonstrated a significant impact on the so-called major adverse cardiovascular events (MACE) [cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke] in cardiovascular outcome studies (CVOTs) in the setting of T2DM.[5] However, there was no evidence available on the impact of pharmacological treatments for obesity in reducing the cardiovascular risk related to it independently of the presence of T2DM, and therefore it remained a significant 'unmet need' in clinical practice.

It is within this framework that the results of the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) study should be placed and interpreted. This is a randomized, multicentre, controlled, double-blind trial conducted on 17 604 non-diabetic patients aged ≥45 years, with BMI ≥ 27 kg/m^2 that were randomized to s.c. semaglutide titrated up to a dose of 2.4 mg once a week vs. placebo, on top of the remaining medical therapy.[6] The trial showed a statistically significant 20% reduction of the composite primary outcome of MACE at a mean follow-up of 39.8 months [6.5 vs. 8.0%; hazard ratio (HR) 0.80; 95% confidence interval (CI), 0.72–0.90; $P < 0.001$]. Regarding confirmatory secondary endpoints, an HR of 0.82 (95% CI, 0.71–0.96) was reported for the composite outcome of cardiovascular death or HF event, and an HR of 0.81 (95% CI, 0.71–0.93) was reported for all-cause death, although a superiority test for these endpoints was not performed. The difference in the effect of semaglutide vs. placebo emerged early after the treatment initiation, suggesting that at least part of the cardiovascular benefit could be mediated by different and more rapid mechanisms than the extent of weight loss.[6]

The SELECT study extended to a different patient population the results already observed in a *post hoc* analysis of pooled data from two CVOTs on semaglutide, namely, SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) and PIONEER 6 (Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes), in which semaglutide was shown to reduce the risk of MACE in diabetic patients at high risk of cardiovascular events (HR 0.76; 95% CI, 0.62–0.92).[7] A similar finding was also reported in the oral semaglutide CVOT SOUL (Semaglutide cardiOvascular oUtcomes triaL), with a significant 14% reduction in MACE in diabetic patients with established CVD.

Therefore, SELECT represents the first and to date the only dedicated CVOT in the field of pharmacological treatment of obesity, and s.c. semaglutide 2.4 mg is the first and to date, to our knowledge, the only drug approved for obesity to have demonstrated a significant impact on MACE in a secondary cardiovascular prevention setting. Furthermore, differently from other

Table 1 Selection of randomized controlled trials of semaglutide and tirzepatide in obese patients

Study	Year	Population	Design	Primary endpoint	Main results/adverse events
STEP-1[2]	2021	$n = 1961$ Non-diabetic BMI ≥30 or ≥27 kg/m^2 + 1 obesity-related condition	2:1 randomization s.c. semaglutide 2.4 mg vs. placebo for 68 weeks	Composite: % weight loss + ≥5% weight loss	% weight loss: 14.9% semaglutide vs. 2.4% placebo ≥5% weight loss: 86.4% semaglutide vs. 31.5% placebo Adverse events (semaglutide vs. placebo): 89.7 vs. 86.4% With treatment discontinuation: 7 vs. 3.1%
SURMOUNT-1[3]	2022	$n = 2539$ Non-diabetic BMI ≥30 or ≥27 kg/m^2 + 1 obesity-related condition	1:1:1:1 randomization s.c. tirzepatide 5, 10, and 15 mg vs. placebo for 72 weeks (20-week titration period)	Composite: % weight loss + ≥5% weight loss	% weight loss (tirzepatide 5 vs. 10 vs. 15 mg vs. placebo): 15 vs. 19.5 vs. 20.9 vs. 3.1% ≥5% weight loss (tirzepatide 5 vs. 10 vs. 15 mg vs. placebo): 85 vs. 89 vs. 91 vs. 35% Adverse events (tirzepatide vs. placebo): 78.9–81 vs. 72% With treatment discontinuation: 4.3–7.1 vs. 2.6%
SELECT[6]	2023	$n = 17\,604$ Non-diabetic, ≥45 years BMI ≥ 27 kg/m^2 + established CV disease	1:1 randomization s.c. semaglutide 2.4 mg vs. placebo Event-driven	Composite (time-to-event): CV death, non-fatal MI, non-fatal stroke	Primary endpoint: 6.5% semaglutide vs. 8.0% placebo CV death: 2.5% semaglutide vs. 3.0% placebo Adverse events (semaglutide vs. placebo): 33.4 vs. 36.4% With treatment discontinuation: 16.6 vs. 36.4%
SUMMIT[13]	2024	$n = 731$ HFpEF (EF ≥ 50%) + BMI ≥ 30 kg/m^2	1:1 randomization s.c. tirzepatide up to 15 mg vs. placebo for 52 weeks	Dual primary endpoints: (1) Composite of CV death or WHF event (2) Δ-KCCQ-CSS	CV death or WHF: 9.9% tirzepatide vs. 15.3% placebo (greater impact on the risk of hospitalization for WHF; non-significant increase in all-cause mortality) Δ-change in KCCQ-CSS score: +6.9 points vs. placebo Adverse events (tirzepatide vs. placebo): 26.4 vs. 25.6% With treatment discontinuation: 6.3 vs. 1.4%
STEP-HFpEF	2023	$n = 529$ Non-diabetic HFpEF (EF ≥ 45%, NYHA II-IV) + BMI ≥ 30 kg/m^2	1:1 randomization s.c. semaglutide 2.4 mg vs. placebo for 52 weeks	Dual primary endpoints: Δ-KCCQ + weight loss	Δ-KCCQ: +7.8 points (4.8–10.9) vs. placebo Weight loss: −10.7% (9.4–11.4%) vs. placebo Adverse events (semaglutide vs. placebo): 13.3 vs. 26.7% With treatment discontinuation: 13.3 vs. 5.3%
STEP-HFpEF DM	2024	$n = 616$ T2DM HFpEF (EF ≥ 45%, NYHA II-IV) + BMI ≥ 30 kg/m^2	1:1 randomization s.c. semaglutide 2.4 mg vs. placebo for 52 weeks	Dual primary endpoints: Δ-KCCQ + weight loss	Δ-KCCQ: +7.3 points (4.1–10.4) vs. placebo Weight loss: −6.4% (5.2–7.6%) vs. placebo Adverse events (semaglutide vs. placebo): 17.7 vs. 28.8% With treatment discontinuation: 10.6 vs. 8.2%

BMI, body mass index (kg/m^2); CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; s.c., subcutaneous; T2DM, Type 2 diabetes mellitus; WHF, worsening heart failure; Δ, delta; 6MWD, 6 min walking distance.

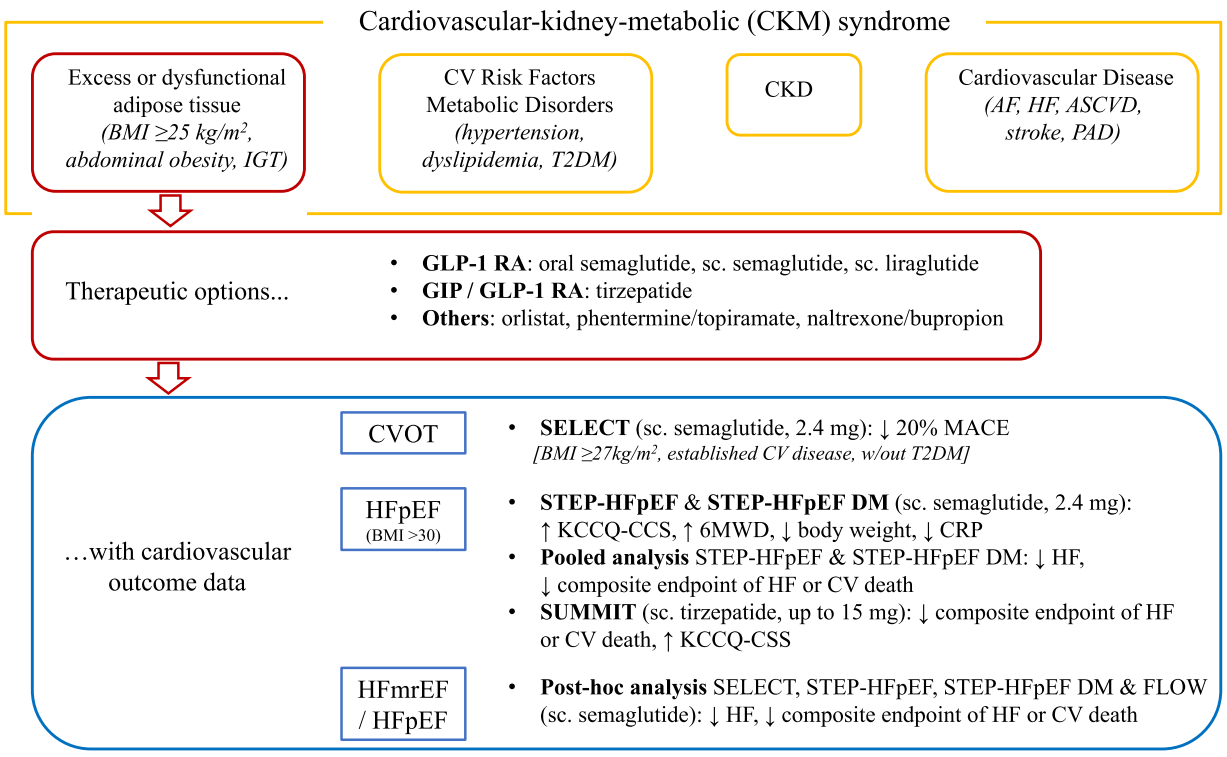

Figure 1 Randomized clinical trials with cardiovascular outcomes of semaglutide and tirzepatide in obese patients.

cardiovascular drugs, it is not possible to speak of a 'class effect' for GLP-1 RAs, given the clear difference in cardiovascular effects in favour of semaglutide compared to other GLP-1 RAs.

In conclusion, a recent meta-analysis of 16 studies (3 with liraglutide, 10 with semaglutide, and 3 with tirzepatide) and 28 168 overweight or obese patients without a history of diabetes showed a significant reduction in MACE [odds ratio (OR) 0.79; 95% CI, 0.71-0.89], all-cause death (OR 0.80; 95% CI, 0.70-0.92), and non-fatal MI (OR 0.72; 95% CI, 0.61-0.85), as well as a trend in the reduction of cardiovascular death (OR 0.84; 95% CI, 0.71-1.01; $P = 0.06$).[8]

Although cardiovascular outcome data for tirzepatide in the obese patient setting are still lacking, two RCTs are currently underway: the SURPASS-CVOT (A Study of Tirzepatide Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes) trial, which compared tirzepatide 15 mg vs. s.c. dulaglutide 1.5 mg in terms of MACE in diabetic patients with BMI $\geq$ 25 kg/m^2 and documented atherosclerotic CVD (ClinicalTrials.gov ID: NCT04255433), and the SURMOUNT-MMO (A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Effect of Tirzepatide on the Reduction of Morbidity and Mortality in Adults with Obesity) trial, which evaluated tirzepatide vs. placebo in non-diabetic patients aged $\geq$40 years, with BMI $\geq$ 27 kg/m^2 and either established CVD or cardiovascular risk factors (i.e. primary prevention), with a primary composite endpoint of all-cause death, non-fatal MI, non-fatal stroke, coronary revascularization, or HF events (ClinicalTrials.gov ID: NCT05556512).

Therapeutic innovations in obesity and heart failure with preserved ejection fraction

The impact on the risk of cardiovascular events has also been studied in the context of HF with preserved ejection fraction (HFpEF), where there is evidence in favour of semaglutide and tirzepatide. A pre-specified subgroup analysis of SELECT showed that in the subgroup of patients with HF at baseline, semaglutide was able to reduce not only the primary combined outcome of MACE (HR 0.72; 95% CI, 0.60-0.87) but also the composite outcome of hospitalizations for HF and cardiovascular death (HR 0.79; 95% CI, 0.64-0.98), in the absence of significant interaction between HFrEF and HFpEF.[9] In a pre-specified exploratory analysis of pooled data from the STEP-HFpEF (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-Related Heart Failure with Preserved Ejection Fraction) and STEP-HFpEF DM (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-Related Heart Failure with Preserved Ejection Fraction) studies, focusing on obese patients (BMI $\geq$ 30 kg/m^2) with HFpEF [EF $\geq$ 45%, New York Heart Association (NYHA) II-IV], s.c. semaglutide 2.4 mg demonstrated a reduction in HF-related events (hospitalizations or urgent visits for HF) with an HR of 0.27 (95% CI, 0.12-0.56) and in the composite outcome of HF-related events or cardiovascular death (HR 0.31; 95% CI, 0.15-0.62).[10] Furthermore, in a recent *post hoc* analysis of pooled data on 3743 patients with a history of HFmrEF or HFpEF at baseline from the SELECT, STEP-HFpEF, STEP-HFpEF DM, and FLOW (Evaluate Renal Function with

Table 2 GLP-1 RA: practical considerations

Oral semaglutide

Initial dose: 3 mg o.d. for 1 month. Then, titrate to the therapeutic maintenance dose of 7 mg o.d. and, if tolerated for at least another month, to the target dose of 14 mg o.d.

How to take: once a day on an empty stomach, with half a glass of water. Wait at least 30 min before taking other medicines, food, or drinks.

Do not split, crush, or chew the tablets. Do not take more than one tablet per day. If you miss a dose, take the next dose the following day at the indicated time.

Practical suggestions to reduce the occurrence and severity of gastrointestinal adverse events of GLP-1 RAs and increase their tolerability

- Acquire regular eating habits:
- Eat slowly, take in calories from small and divided meals, recognize the feeling of fullness, limit activities and avoid lying down immediately after the meal, and avoid exposure to strong odours and flavours after taking GLP-1 RA.
- Prefer low-fat diets and foods that contain water; increase fluid intake in small sips; avoid sweet meals, condiments, and hot spices; and use baking, grilling, or boiling.

Occasional use of prokinetics is possible.

Consider that nausea is felt especially in the first 4–5 weeks of treatment and tends to resolve. Emesis tends to appear less frequently (in case of persistent vomiting, maintain adequate hydration).

- If gastrointestinal adverse events occur during the dose-escalation phase:
- Continue taking the previous dosage before titration for 2–4 weeks, and remain at that dosage until the symptom decreases or disappears.
- Do not increase the dose while the symptom persists.
- If limited tolerability persists, use a lower-than-target dose as the maintenance dose; if symptoms persist even at the lowest doses, temporarily suspend until the symptom resolves.

Semaglutide Once Weekly; the latter conducted on diabetic patients with CKD), semaglutide confirmed to reduce both the composite endpoint of cardiovascular death or worsening HF events (5.4 vs. 7.5%; HR, 0.69; 95% CI, 0.53–0.89) and the worsening HF risk *per se*.[11] Furthermore, from a physiopathological point of view, the results of an imaging substudy of the STEP-HFpEF programme have led to the hypothesis that semaglutide may constitute a 'disease-modifying' treatment, due to the observed impact on adverse remodelling mediated by an attenuation of the progression of left atrial remodelling and right ventricular dilation and by an improvement in diastolic function parameters (E wave velocity, E/A ratio, and E/e' ratio).[12]

Similarly, tirzepatide was evaluated in the recently published SUMMIT (A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Comparing the Efficacy and Safety of Tirzepatide Versus Placebo in Patients with Heart Failure with Preserved Ejection Fraction and Obesity) study. In this trial, tirzepatide was studied on 731 obese patients (BMI $\geq$ 30 kg/m^2) affected by HFpEF (EF $\geq$ 50%) and was shown to significantly reduce the primary composite outcome of death from cardiovascular causes or worsening HF (HR 0.62; 95% CI, 0.41–0.95), mainly due to an effect on the latter (HR 0.54; 95% CI, 0.34–0.85), despite a higher number of adverse events (6.3 vs. 1.4%), mainly gastrointestinal in nature, which led to the drug discontinuation.[13] Exploratory subgroup analyses showed that the effect of tirzepatide on the primary outcome was homogeneous (e.g. for BMI >5 vs. <35 kg/m^2 or for NT-proBNP >200 vs. <200 pg/mL). In the SUMMIT cardiac magnetic resonance imaging substudy, tirzepatide was shown to reduce left ventricular mass and pericardiac adipose tissue compared to placebo,[14] while in a secondary analysis, tirzepatide was shown to reduce systolic blood pressure (estimated difference vs. placebo: −5 mmHg), blood volume (−0.58 L), C-reactive protein (−37.2%), albuminuria-creatinine ratio (25.0%), NT-proBNP (−10.5%), and troponin T (−10.4%) and to increase estimated glomerular filtration rate (eGFR) (2.9 mL/min/1.73 m^2), thereby mitigating cardiovascular and kidney organ damage and providing new hypotheses underlying the benefit of tirzepatide.[15]

Table 1 and *Figure 1* summarize the main findings for semaglutide and tirzepatide.

Practical considerations and potential limitations

To date, semaglutide is reported in the European Society of Cardiology (ESC) guidelines on chronic coronary syndromes, with a class of recommendation IIa and level of evidence B, for the reduction of MACE in overweight or obese non-diabetic patients affected by chronic coronary syndrome.

Semaglutide can be used in CKD with eGFR values up to 15 mL/min/1.73 m^2 without the need for dose adjustment, has a low risk of hypoglycaemia even when used in combination with other oral hypoglycaemic agents (except sulfonylureas), and can also be used in elderly patients and in the presence of liver failure. A recent meta-analysis of 23 studies and 57 911 patients confirmed the favourable safety profile of semaglutide in different patient populations and treatment durations, with a low incidence of adverse events, mainly gastrointestinal in nature (nausea and vomiting).[16] However, GLP-1 RA adherence still constitutes one of the main limiting factors in their implementation. In the SELECT study, for example, adverse events leading to permanent treatment discontinuation occurred in 16.6% (vs. 8.2% of placebo), even if there was a

low incidence of serious gastrointestinal adverse events, which was not different from placebo (3.9 vs. 3.7%).[6] In contrast, in the pooled analysis of the STEP-HFpEF and STEP-HFpEF DM studies, semaglutide showed a lower incidence of serious adverse events than placebo (29.9 vs. 38.7%).[10] For guidance on how to take the oral formulation of semaglutide and for practical advices to improve tolerability and reduce the occurrence and severity of the gastrointestinal adverse events of GLP-1 RAs, see *Table 2*.[17]

Conclusions

Semaglutide is the most effective GLP-1 RA in reducing body weight, as well as the only molecule to have demonstrated a significant reduction in cardiovascular risk in obese, non-diabetic patients with pre-existing CVD. The results of the SELECT study have the potential to represent a turning point in clinical practice and to impact cardiovascular morbidity and mortality in the context of secondary prevention. Furthermore, together with tirzepatide, it can have a potential role in patients with the phenotype of HFpEF related to obesity, given the shown reduction in the risk of worsening HF in a context where there has always been a paucity of effective treatments. Undoubtedly, the impact on cardiovascular–kidney–metabolic outcomes of a therapy with both GLP-1 RA and SGLT2-i will need to be evaluated in the future. In the meantime, we have to wait to see how the drug regulatory agencies and international guidelines will receive the available evidence for semaglutide and tirzepatide in the specific setting of obesity and cardiovascular risk.

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Data availability

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