European Heart Journal Supplements (2025) **27** (Supplement 5), v247-v255
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suaf071

ESC
European Society
of Cardiology

ANMCO statement: semaglutide in the cardio-nephro-metabolic continuum

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KEYWORDS
Cardio-metabolic syndrome;
Chronic kidney disease;
Diabetes mellitus;
Inflammation;
Obesity;
Semaglutide

Semaglutide, a glucagon-like peptide-1 receptor agonist, has emerged as a pivotal therapeutic agent in the management of the cardio-renal-metabolic continuum. Initially developed for glycaemic control in Type 2 diabetes mellitus, its benefits extend far beyond glucose regulation. Clinical trials have demonstrated semaglutide's potential to reduce major adverse cardiovascular events, particularly in overweight/obese patients with high cardiovascular risk, as well as improving functional capacity in patients suffering from heart failure with preserved left ventricular function. Additionally, it has shown promise in improving renal outcomes, such as slowing the progression of albuminuria and reducing the risk of chronic kidney disease in diabetic populations. These effects are likely due to its multifaceted mechanisms, including anti-inflammatory properties, weight reduction, blood pressure lowering, and direct renal protection. This review synthesizes current evidence on semaglutide's role in the interrelated domains of cardiovascular, renal, and metabolic health.

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Introduction

The main goals of cardiovascular (CV) disease prevention are to prolong life expectancy, reduce morbidity, and improve quality of life. The treatment of major traditional risk factors serves as an indispensable foundation for CV risk reduction, which, despite the unprecedented progress in recent decades, still remains high.[1,2] Cardiovascular diseases rarely occur in isolation, but rather share the same risk factors that increase the multi-morbidity and severity of CV events.[3] In this sense, the cardio-nephro-metabolic syndrome reflects the interaction between metabolic risk factors, particularly diabetes and obesity, chronic kidney disease (CKD), and CV diseases.[4]

It is estimated that around 537 and 810 million people worldwide live with diabetes and obesity, respectively; the prevalence of the two diseases is dramatically increasing, and it is predicted that a 1.5 billion people will live with obesity in 2035 and 783 million people with diabetes in 2045.[5] About one in three patients with Type 2 diabetes has at least one CV disease, and in 9 out of 10 cases, it is atherosclerotic CV disease (ASCVD).[6] Cardiovascular disease accounts for about half of the causes of death in patients with Type 2 diabetes and is the cause of death in about 70% of those living with overweight and obesity.[7,8] Insulin resistance and chronic systemic inflammation represent two conditions that feed off each other and constitute the lowest common denominator between diabetes, obesity, and ASCVD. Insulin resistance refers to the reduced tissue response to insulin, which cannot fully exert its biological activity to facilitate the glucose entry, used as the primary energy substrate in cells. The result is hyperglycaemia and an adaptation of tissues that change their metabolic pathways in response to inadequate energy intake, which results in oxidative stress, inflammation, and lipotoxicity that inevitably leads to structural and functional alterations.[9] The adipocyte is endowed with extraordinary plasticity and in the presence of the aforementioned metabolic diseases, becomes dysfunctional, and changes its cell morphology becoming hypertrophic at both visceral level and ectopic deposit level. A change in the secretory profile then occurs, resulting in increased production and release of pro-inflammatory cytokines, such as tumour necrosis factor-α, interleukin-6, and interleukin-1β, along with a reduction in anti-inflammatory adipokines, such as adiponectin.[10] Among ectopic fat depots, the epicardial adipose tissue in both diabetes and obesity becomes dysfunctional with an abnormal expression of pro-inflammatory mediators and local lipotoxicity, which promotes coronary atherosclerosis, atrial fibrillation, and heart failure.[11] The perivascular adipose tissue is another ectopic depot, which becomes dysfunctional and spills its altered paracrine onto the vessels, increasing atherothrombotic risk, as well as exacerbating insulin resistance.[12]

Chronic kidney disease affects about 10% of the world's population and is the fifth leading cause of death worldwide.[13] Hyperglycaemia leads to altered renal cell metabolism, increased glomerular and tubulointerstitial inflammation, and increases the processes of apoptosis and tissue fibrosis.[14] Obesity produces haemodynamic modifications at renal level, increased tubular sodium reabsorption, increased activation of the renin-angiotensin-aldosterone system mediated by adiposopathy, and plasma volume overload that promotes the development of hypertension, which in turn contributes to glomerular hyperfiltration and renal microvascular damage.[15]

In recent years, the paradigm of managing the treatment of patients with Type 2 diabetes and overweight-obese patients has been revolutionized by the development of a class of innovative drugs, namely glucagon-like peptide-1 (GLP-1) analogues. Within this class, semaglutide is currently the most studied receptor agonist (GLP-1 RA) for the management of cardio-nephro-metabolic syndrome, but it is also more manageable due to the availability of both an oral formulation in diabetes and an injection formulation in obesity.

Semaglutide in the cardio-nephro-metabolic continuum

Semaglutide is a GLP-1 analogue, with a 94% sequence homology to human GLP-1, capable of selectively binding the GLP-1 receptor (GLP-1R), and activating it.[16]

Glucagon-like peptide-1 is a physiological hormone produced mainly by intestinal enteroendocrine L cells, is a member of the incretin family, and performs multiple actions in glucose and appetite regulation, as well as on the cardio-nephro-vascular system[17] (*Figure 1*).

The effects on glucose levels and appetite are mediated specifically by GLP-1Rs present in the pancreas and brain. On the one hand, semaglutide reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and reducing glucagon secretion when blood glucose is elevated;[18] on the other hand, it reduces appetite by acting on the arcuate nucleus at the hypothalamic level resulting in reduced caloric intake and consequently reduced body weight and fat mass.[19] In addition, semaglutide reduces the preference for palatable foods both sweet and salty and foods high in fat.[20-23] In clinical trials, semaglutide showed improvement in plasma lipids and reduction in systolic and diastolic blood pressure.[24,25] The mechanism of the action of semaglutide, and thus multi-organ protection, is independent of the administration route and related to the direct and indirect GLP-1R effects, which also impacts heart, vascular system, immune system, and kidneys.[26-29] Semaglutide exhibits an antiatherosclerotic action, determining an attenuation effect of atherosclerotic plaque development observed to be correlated with its anti-inflammatory mechanism and modulation of gene expression of the atherosclerosis mediators.[30] Reduction in systemic inflammation, only partly attributable to reduction in body weight and adiposity and to improved insulin resistance, would appear to be mediated by direct effects and potentially serve as the lowest common denominator to cardio-renal protection (*Figure 2*).

Two main pathways through which semaglutide would exert its anti-inflammatory effects consist of: (1) reduction of pro-inflammatory cytokine levels and (2) modulation of immune system activity. The damaged endothelium produces cytokines and chemokines that promote a chronic inflammatory state characteristic of atherosclerosis which lead to plaque progression, instability, and rupture. In this context, GLP-1 RAs reduce the production and secretion of inflammatory cytokines and chemokines, monocyte recruitment and infiltration, foam cell formation, and differentiation of vascular smooth muscle cells and intimal

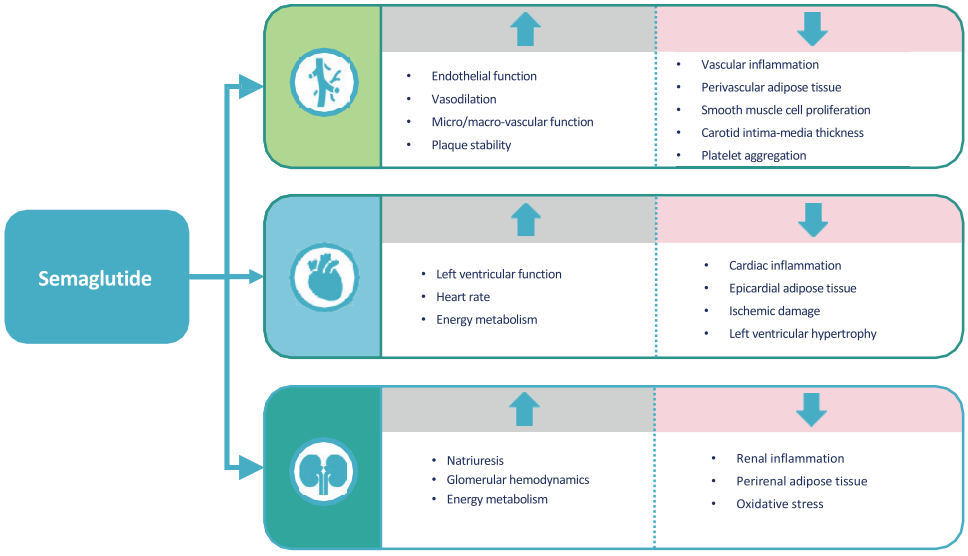

Figure 1 The direct effects of semaglutide on the cardio-nephro-vascular system.

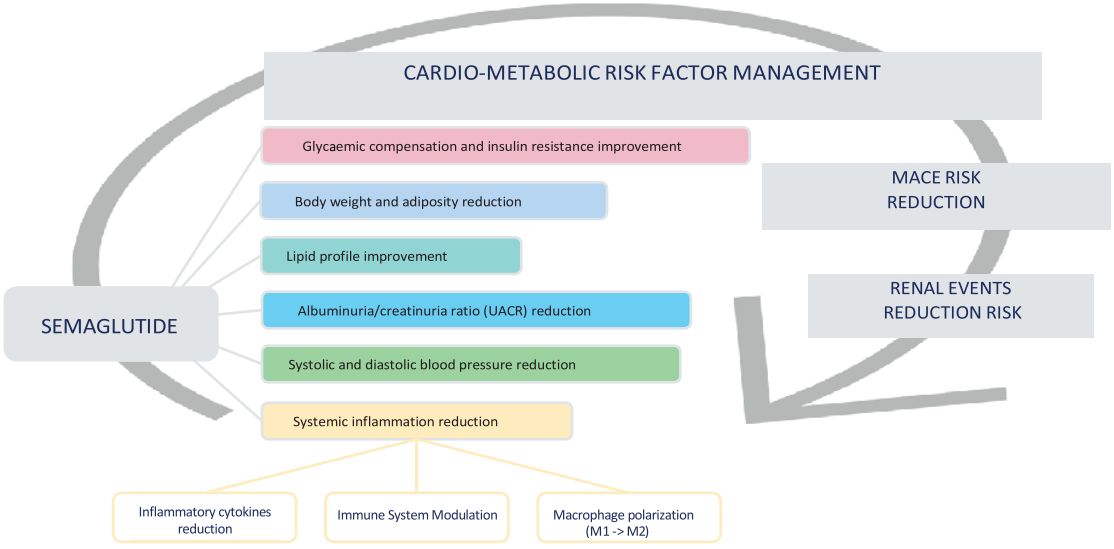

Figure 2 Major actions of semaglutide in the cardio-nephro-metabolic continuum. MACE, major adverse cardiovascular events.

thickening, acting against plaque progression and promoting plaque stabilization.[31] A meta-analysis that examined the effects of semaglutide on high-sensitivity C-reactive protein (hs-PCR) showed a significant reduction in its levels both in the population with Type 2 diabetes and in the overweight or obese population without diabetes.[32,33] In addition, the promotion of GLP-1 RA of angiogenesis (and improvement of arterial stiffness and dysfunction), the reduction of NADPH oxidase activity and oxidative stress, and the increase of endothelial nitric oxide synthase function with nitric oxide production prevent endothelial damage, which is the key factor in the initiation and progression of atherosclerosis.[31]

Enteroendocrine L cells within the mucosa of the small and large intestines serve as pathogen sensors, secreting GLP-1 in response to infection or tissue damage.[34] Glucagon-like peptide-1 in turn acutely reduces intestinal and systemic inflammation both in animals and humans. Cell sites in the immune system where GLP-1R expression is predominant are the intestinal intra-epithelial lymphocytes (IELs) and some T cells.[35,36] The GLP-1R IEL is required to transduce the local and systemic anti-inflammatory actions of GLP-1 when inflammation is induced through T-cell activation, for example, using antibodies that target the CD3 T-cell co-receptor.[37] The systemic anti-inflammatory action of GLP-1, which mitigates toll-like receptor-activated inflammation, surprisingly requires GLP-1R neuronal signalling. Such neuronal activation has proved necessary to mitigate systemic inflammation in the lungs and myeloid cells of mice with polymicrobial sepsis.[38] In addition, GLP-1R appears to regulate the polarization of macrophages from M1 (pro-inflammatory) to M2

(anti-inflammatory), and this could be an additional mechanism by which semaglutide exerts a protective role in the progression of ASCVD.[39] Semaglutide also shows nephroprotective effects, such as attenuating the rate of decline of the estimated glomerular filtrate (eGFR) and reducing albuminuria over time, especially in patients with more impaired renal function. This occurs through both indirect and direct effects mediated by renal GLP-1Rs localized in proximal convoluted tubule cells and vascular smooth muscle cells of afferent arterioles, arcuate and interlobular arteries, resulting in a natriuretic, and again anti-inflammatory and antioxidant action.[40]

Semaglutide in patients with Type 2 diabetes

Patients with Type 2 diabetes have an increased risk of developing CV disease, which has an important impact on prognosis and treatment strategies. Given the high prevalence of undiagnosed diabetes, the 2023 European Society of Cardiology (ESC) guidelines on the management of Type 2 diabetes recommend that all patients with CV disease be screened for the presence of diabetes using fasting blood glucose and glycosylated haemoglobin (HbA1c) dosage. Conversely, the guidelines also recommend that all patients with diabetes be evaluated for the presence of ASCVD by assessing history and the presence of suggestive symptoms.[41] To reduce CV events, the same guidelines report the classes of GLP-1 RAs and sodium-glucose co-transporter Type 2 (SGLT2) inhibitors with proven CV benefit in Class I recommendation on a type A level of evidence in patients with diabetes and ASCVD regardless of baseline glycaemia or HbA1c target and regardless of concomitant use of other antidiabetic drugs.[41] In addition, the recent 2024 ESC guidelines on the management of chronic coronary syndrome recognize the CV benefit exerted by reducing the risk of ASCVD and confirm the I A use recommendation, regardless of glycaemic control, for the GLP-1 RA class in the coronary artery disease patient with Type 2 diabetes.[42]

The safety of GLP-1 RAs in Type 2 diabetes has been studied in eight studies with CV outcomes, revealing reduced rates of heart attack, stroke, and CV death.[41] These results were accompanied by a 12% reduction in all-cause mortality and a 11% reduction in heart failure hospitalizations.[43] Data from observational studies also suggest that GLP-1 RAs exert an additional CV benefit when used concomitantly with SGLT2 inhibitors in patients with Type 2 diabetes.[44]

Semaglutide is the most potent GLP-1 analogue and has been shown to be more effective than other antidiabetic treatments in terms of improving blood glucose and other cardiometabolic risk factors.[45-48] In this regard, analysis of the aggregated data from the SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) and PIONEER 6 (Peptide Innovation for Early Diabetes Treatment) studies demonstrated a significant reduction in major adverse CV events (MACE) by 24% compared with placebo.[49] The SOUL trial (ClinicalTrials. gov: NCT03914326), a double-blind randomized controlled event-driven trial designed with a primary endpoint of superiority, which evaluated oral semaglutide in a population of 9650 patients with Type 2 diabetes and established ASCVD and/or CKD,[50] has recently been published. The primary-outcome event (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) rate was significantly reduced in the oral semaglutide group by 16%, as compared to placebo. The results for the confirmatory secondary outcomes that included major kidney disease events did not differ significantly between the two groups.

Another cornerstone of the cardio-nephro-metabolic benefits of semaglutide is represented by the recent FLOW (Evaluate Renal Function with Semaglutide Once Weekly) study, which evaluated the drug in a population of 3533 patients with Type 2 diabetes and CKD. The study discontinued early due to manifested renal protection, in which semaglutide significantly reduced the primary composite endpoint of renal events and CV death by 24%. In addition, the superiority of semaglutide was also confirmed for the secondary endpoints, i.e. annual change in eGFR, MACE, and death from all causes.[51]

Recent and growing evidence on cardio-nephro-metabolic outcomes and the availability of an oral formulation are all

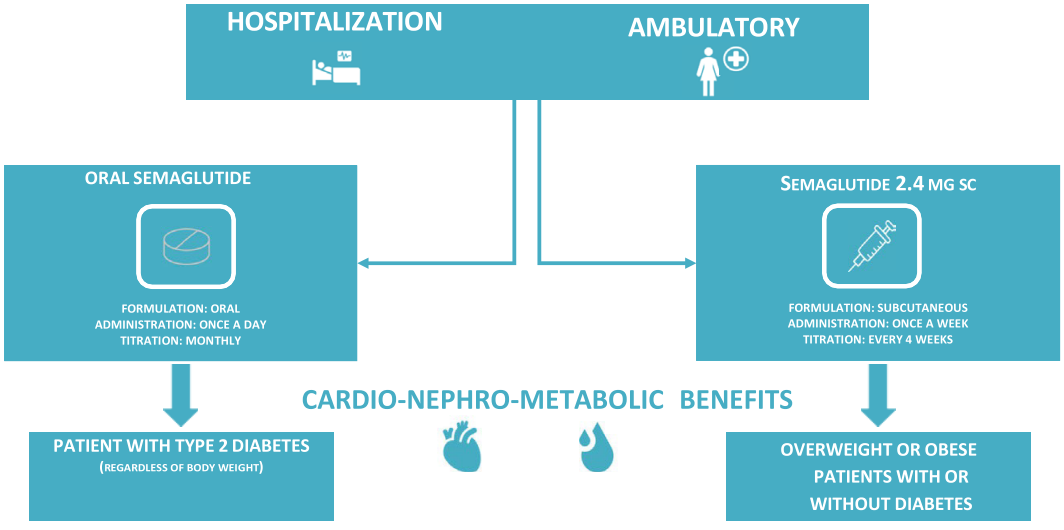

Figure 3 Scheme of semaglutide use in subjects with Type 2 diabetes or overweight-obesity. sc, subcutaneously.

components that advocate an early treatment strategy, immediately after metformin, on the population with Type 2 diabetes[52] (*Figure 3*). In addition, with the introduction in Italy of the Italian Medicines Agency's Note 100 (https://www.aifa.gov.it/nota-100), as is already the case for the management of other risk factors, the cardiologist plays a primary role with respect to the management of Type 2 diabetes and the prevention of CV complications.

Semaglutide in overweight and obese patients

The 2024 ESC guidelines on the management of chronic coronary syndrome report for the first time semaglutide specifically, making a Class IIa and level of evidence B recommendation in the overweight or obese coronary artery disease patient without diabetes, in order to reduce the risk of CV death, myocardial infarction, and stroke.[42] This new development represents an improvement on the 2021 ESC Guidelines on CV Disease Prevention in Clinical Practice, which places emphasis on the importance of an effective diagnosis and treatment of obesity in the prevention of CV disease. The same guidelines recommend a full assessment, using body mass index (BMI) calculation and waist circumference measurement, for overweight/obese subjects in order to examine the risk of adiposity-related comorbidities, including hypertension, dyslipidaemia, insulin resistance, systemic inflammation, and decline in renal function. In addition, maintaining even modest weight loss of 5–10% has salutary effects on risk factors such as blood pressure, plasma lipids, and blood glucose.[53] The scenario of the therapeutic armamentarium for the treatment of excess weight has evolved considerably in recent years.

The efficacy of semaglutide 2.4 mg once-weekly subcutaneous (s.c.) has been demonstrated in the STEP (Semaglutide Treatment Effect in People with Obesity) programme in a wide range of populations, where semaglutide was found to be associated with up to ∼18% weight loss compared with placebo in subjects without Type 2 diabetes.[54] The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) study recently evaluated the efficacy and safety of semaglutide 2.4 mg s.c. in 17 604 patients with BMI ≥27 kg/m^2 and documented history of ASCVD but without known Type 2 diabetes. The CV benefits of semaglutide appeared rather early in the treatment and did not appear to be closely related to the amount of weight loss.[55]

To date, semaglutide is the most potent GLP-1 analogue for body weight management and is also the only treatment with proven CV benefit in the population with overweight or obesity (BMI ≥27 kg/m2) and associated ASCVD (*Figure 3*).

Semaglutide in heart failure with preserved ejection fraction

More than 80% of heart failure patients with preserved ejection fraction (HFpEF) are overweight or obese, and growing evidence suggests the existence of a strong correlation between increased BMI and the development of HFpEF.[56,57]

Semaglutide showed clinically significant benefits in the obesity phenotype with HFpEF (with or without diabetes), mediated by indirect and direct effects (*Figure 4*). Semaglutide has showed a wide range of favourable

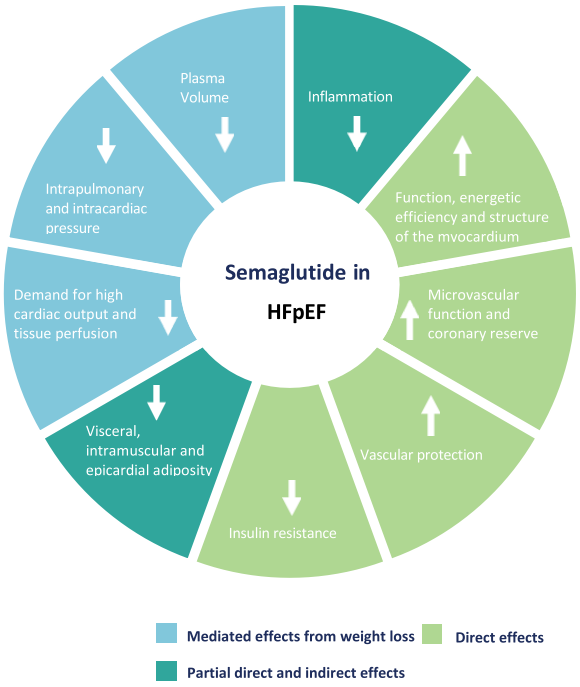

Figure 4 Potential action mechanisms of semaglutide in the phenotype of heart failure with preserved ejection fraction with obesity. HFpEF, heart failure with preserved ejection fraction.

cardiometabolic effects that go far beyond those dependent on weight loss obtained in a pair-feeding animal model. Indeed, it improves cardiac structure and function, left ventricular cytoskeleton function, and endothelial function and restores protective immune responses in visceral adipose tissue.[58]

In the studies 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, and Type 2 Diabetes) that evaluated the effects of semaglutide 2.4 mg s.c. with HFpEF and obesity (BMI ≥30 kg/m2), without ($n = 529$) and with Type 2 diabetes mellitus ($n = 616$), respectively, semaglutide was found to be associated with improved symptoms and function upon exercise and greater weight loss than placebo.[59,60] Analysis of aggregate data from the STEP-HFpEF and STEP-HFpEF DM studies examined the effects of semaglutide in a total of 1145 obese patients. The analysis confirmed that semaglutide leads to a substantial improvement in heart failure symptoms as measured by the Kansas City Cardiomyopathy Questionnaire and a significant reduction in body weight compared with the placebo group. In addition, the semaglutide-treated group experienced significant improvements in physical limitations, particularly on the 6-min walk test, as well as a significant reduction in levels of systemic inflammation as measured by hs-PCR and the *n*-terminal fragment of B-type natriuretic propeptide (NT-proBNP).[61] Note that although participants with Type 2 diabetes lost less weight, ∼40% less than those without diabetes, symptom improvements were similar to those in the STEP-HFpEF and STEP-HFpEF

DM trials.[59,60] Surprisingly, the reduction in both hs-PCR and NT-proBNP levels was similar in the two studies and about 40 and 20% from baseline, respectively. Such effects of semaglutide suggest a specific anti-inflammatory, decongestant, and natriuretic action regardless of the presence or absence of diabetes. This could explain the substantially lower numbers of both events [hazard ratio (HR) 0.27, 95% confidence interval (CI) 0. 12–0.56; $P=$ 0.0004], consisting of urgent visits and hospitalizations for heart failure, and of the composite outcome of heart failure events and CV death (HR 0.31, 95% CI 0.15–0.62; $P=0.0008$) in the semaglutide-treated group.[61] In the STEP-HFpEF programme, semaglutide also revealed its effects on cardiac remodelling, significantly reducing the progression of the left atrial enlargement, improving the left ventricular diastolic function, the right ventricular size, and the E-wave velocity in comparison with placebo.[62] These benefits suggest a possible mechanism of decongestion consistent with reduced NT-proBNP and diuretic use.[63,64]

In a recent SELECT prespecified analysis that examined the impact of semaglutide on CV events in overweight or obese patients, with or without a diagnosis of heart failure at baseline, in subjects with heart failure, 4286 patients or 24.3% of the overall population, the drug showed a reduction in MACEs, composite endpoint of heart failure, CV death, and death from all causes with similar data when compared with the subgroup without heart failure ($P>$ 0.19).

Semaglutide treatment also showed CV benefit regardless of heart failure type, with improved outcomes in both subjects with HFpEF and those with reduced ejection fraction heart failure (HFrEF), even though subjects with HFrEF had a higher incidence of events than those with HFpEF.[65] In addition, a meta-analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM studies evaluated the effects of semaglutide with respect to heart failure events in a subgroup of 3743 subjects with a history of HFpEF. Semaglutide showed a significant 31% risk reduction in the composite endpoint of CV death or worsening in heart failure compared with placebo. Specifically, semaglutide reduced the risk of worsening heart failure by 41%, while no significant effect was observed on CV mortality alone (HR 0.82, 95% CI 0.57–1.16; $P=0.25$). In addition, fewer patients treated with semaglutide reported serious adverse events than those treated with placebo (29.9 vs. 38.7%).[66]

Semaglutide safety profile and recommendations for use

A recent meta-analysis that included a total of 23 randomized controlled trials evaluating the safety of semaglutide vs. placebo, with an overall sample size of 57 911 patients, showed the favourable safety profile of semaglutide. Rare cases of acute kidney damage or cholelithiasis likely caused by excessive dehydration have been reported and, as already known for the class of GLP-1 analogues, that the most frequent adverse event is gastrointestinal in nature (nausea, vomiting, constipation, and diarrhoea).[67] These are usually transient events, beginning during the dose escalation phase and resolving shortly after the maintenance dose is reached and, in most cases, are of mild-to-moderate severity. However, it is essential that patients and caregivers are aware of some useful precautions to be taken to prevent the occurrence of gastrointestinal adverse events or, if they occur, mitigate their effects and thus improve adherence and persistence to treatment[68] (*Table 1*). If gastrointestinal adverse events appear during the dose escalation phase, it may be helpful to implement one of the following actions:

- prolong the duration of the dose escalation phase (2–4 weeks longer with the previous dose);
- avoid increasing the dose while the gastrointestinal adverse event persists;
- if a gastrointestinal adverse event occurs and persists when switching to the higher dose, return to the lower dose and remain there until the symptom diminishes or disappears;
- in the case of persistent tolerability limitations, set a lower dose than the maximum dose recommended in the data sheet as the maintenance dose;
- in the case of persistence of the gastrointestinal adverse event even at the lower doses, temporarily suspend treatment until the adverse events are resolved and then resume treatment.

Delayed gastric emptying is already reported as an undesirable effect in the product information for the different GLP-1 RAs, and therefore, an increased risk of pulmonary aspiration and subsequent pulmonary complications are possible during procedures requiring anaesthesia or deep sedation in patients treated with GLP-1 RA.[69] In a prospective study of overweight or obese patients treated with semaglutide evaluated by ultrasound, it was found that 70% of patients treated with semaglutide compared with 10% of control patients had solid material in

Table 1 Recommendations for reducing the occurrence and severity of gastrointestinal adverse events when initiating therapy with glucagon-like peptide-1 receptor agonists

Improve eating habits:
• Eat slowly
• Eat smaller portions
• Increase the frequency of meals
• Eat only if you are really hungry
• Recognize the feeling of fullness and stop eating
• Avoid drinking using a straw
• Eat without distractions and savour the food
• Try not to be too active after eating
• Avoid lying down after eating
• Avoid going straight to bed at night after eating
Adjust food composition:
• Choose easy-to-digest foods and low-fat diets
• Prefer healthy foods that contain water (soups, liquid yogurt, gelatin, and others)
• Increase fluid intake, especially cool drinks (in small sips), but not so much that you feel too full
• Avoid sweet meals
• Avoid condiments, spicy foods, canned foods, and sauces that are not home cooked
• Use cooking methods such as baking, grilling, or boiling
Get some fresh air and do some light exercise
Keep a food diary, as it may be helpful in identifying foods or meal times that worsen the situation

Figure 5 Main outcome trials on the cardio-nephro-metabolic benefits of semaglutide. CV, cardiovascular; HR, hazard ratio; CI, confidence interval; AMI, acute myocardial infarction; RR, relative risk.

the stomach after at least 10 h of overnight fasting.[70] A causal relationship could not be established; however, it seems reasonable to assess the risk of the presence of residual gastric contents due to delayed gastric emptying, and possibly consider discontinuing treatment, with the appropriate timing, before subjecting patients to elective procedures requiring general anaesthesia.

Dosage of semaglutide does not require adjustment when used in elderly patients, in patients with impaired renal function, with impaired liver function, or with upper gastrointestinal tract disease, as no effects on pharmacokinetics have been found.[71-75] It is specified, however, that the 2023 ESC guidelines on the management of Type 2 diabetes recommend the use of GLP-1 analogues in Class I recommendation on a type A level of evidence in patients with eGFR >15 mL/min/1.73 m^2. This is to achieve adequate glycaemic control, given the low risk of hypoglycaemia and beneficial effects on weight, CV risk, and albuminuria.[41]

Conclusions

Semaglutide is a GLP-1 RA that has demonstrated clinical benefits in patients with (i) Type 2 diabetes mellitus at high CV risk, with or without CKD; (ii) overweight or obesity without diabetes mellitus; and (iii) HFpEF and obesity, with or without diabetes mellitus (*Figure 5*). While waiting for new drugs targeting GLP-1R currently under evaluation, semaglutide appears to date to be the ideal drug in the management of the cardio-nephro-metabolic continuum, easy for the cardiologist to manage due to its normoglycaemic effect and associated with a low rate of side effects.

Funding

This paper was published as part of a supplement financially supported by Centro Servizi ANMCO SrL - Società Benefit.

Conflict of interest: none declared.

Disclaimer

This Position Paper was originally published in the Italian language as 'Statement ANMCO: la semaglutide nel continuum cardio-nefro-metabolico', in the official journal of the Italian Federation of Cardiology (IFC) 'Giornale Italiano di Cardiologia', published by Il Pensiero Scientifico Editore. This paper was translated by a representative of the Italian Association of Hospital Cardiologists (ANMCO) and reprinted with permission of IFC and Il Pensiero Scientifico Editore.

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