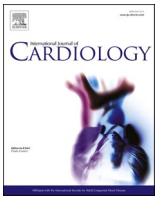
International Journal of Cardiology 423 (2025) 133028

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Eligibility for and practical implications of Semaglutide in overweight and obese patients with acute coronary syndrome

Vincenzo De Sio [a,b], Felice Gragnano [a,b], Antonio Capolongo [a,b], Natale Guarnaccia [a,b], Pasquale Maddaluna [a,b], Vincenzo Acerbo [a,b], Mattia Galli [c,d], Martina Berteotti [e], Simona Sperlongano [a,b], Arturo Cesaro [a,b], Elisabetta Moscarella [a,b], Francesco Pelliccia [f], Giuseppe Patti [g], Emilia Antonucci [h], Plinio Cirillo [i], Pasquale Pignatelli [j], Gualtiero Palareti [h], Vittorio Pengo [h,k], Paolo Gresele [l], Rossella Marcucci [e], Paolo Calabrò [a,b,*]

[a] Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Caserta, Italy
[b] Division of Clinical Cardiology, A.O.R.N. "Sant'Anna e San Sebastiano", Caserta, Italy
[c] Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy
[d] Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy
[e] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[f] Department of Cardiovascular Sciences, Sapienza University, Rome, Italy
[g] University Of Eastern Piedmont "Amedeo Avogadro", Novara, Italy
[h] Arianna Anticoagulation Foundation, Bologna, Italy
[i] Department of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy
[j] Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy
[k] Thrombosis Research Laboratory, University of Padua, Campus Biomedico "Pietro D'Abano", Padova, Italy
[l] Department of Medicine and Surgery, Section of Internal and Cardiovascular Medicine, University of Perugia, Perugia, Italy

ARTICLE INFO

Keywords:
Acute coronary syndromes
Obesity
Semaglutide
Residual risk
Secondary prevention

ABSTRACT

Aims: Semaglutide has been shown to reduce cardiovascular events in non-diabetic patients with preexisting cardiovascular disease and overweight/obesity in the SELECT trial. Data on the applicability of these results to clinical practice are limited. We evaluated the eligibility for and practical implications of semaglutide in overweight/obese non-diabetic patients with recent acute coronary syndrome (ACS) from a contemporary real-world registry.

Methods: Patients from the multicenter START-ANTIPLATELET registry (NCT02219984) were stratified to investigate the proportion of patients eligible for semaglutide >60 days after discharge for ACS (post-acute phase), according to the SELECT trial eligibility criteria: age ≥ 45 years; body mass index ≥27 kg/m^2; history of myocardial infarction (MI), stroke, or peripheral artery disease; no diabetes. Major adverse cardiovascular events (MACE), defined as a composite of all-cause death, MI, target vessel revascularization, or stroke, and net adverse clinical events (NACE), a composite of all-cause death, MI, stroke, or major bleeding, were assessed at 1-year follow-up.

Results: The study population comprised 2940 consecutive ACS patients. At 60 days after discharge, 807 patients (27.4 %) met the SELECT eligibility criteria (SELECT-like group) and 2133 patients were ineligible (not-eligible group). At 1 year, incidence of MACE (4.6 % vs. 8.2 %; $p = 0.004$) and NACE (3.6 % vs. 7.6 %; $p < 0.001$) was lower in the SELECT-like group compared to the not-eligible group.

Conclusions: In a contemporary real-world registry, a significant proportion of post-ACS patients were eligible for semaglutide according to the SELECT trial criteria. Future studies are needed to evaluate the potential implications of semaglutide for secondary prevention.

* Corresponding author at: Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Viale Abramo Lincoln 5, IT- 81100 Caserta, Italy.
E-mail address: paolo.calabro@unicampania.it (P. Calabrò).

https://doi.org/10.1016/j.ijcard.2025.133028
Received 10 December 2024; Received in revised form 18 January 2025; Accepted 28 January 2025
Available online 29 January 2025

1. Introduction

Obesity is a prevalent global health problem affecting populations across a range of socioeconomic backgrounds in both low- and high-income countries [1] A body mass index (BMI) greater than 27 kg/m^2 is associated to 4–6 million deaths worldwide per year, with the majority of which being attributed to cardiovascular causes [2]. Overweight (BMI ≥27 kg/m2) and obesity (BMI ≥30 kg/m2) are independent cardiovascular risk factors that adversely affect prognosis, even when other factors, such as hypertension, dyslipidaemia, and diabetes are effectively managed [3–9]. Weight loss of 5 % or more has been shown to exert multiple beneficial effects on both cardiovascular system lipid profile and glucose metabolism, and to improve prognosis [10,11]. The introduction of effective pharmacologic agents capable of reducing body weight and improving cardiovascular outcomes is therefore of significant clinical importance in current practice [12,13].

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist currently recommended for use in high-risk patients with type 2 diabetes mellitus and/or atherosclerotic cardiovascular disease (ASCVD) [14]. Recent evidence from the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial [15] indicates that semaglutide may reduce the incidence of cardiovascular events in non-diabetic patients with pre-existing ASCVD and who are overweight or obese, potentially expanding the application of semaglutide in this high-risk population [15]. In the 2024 European guidelines for the management of chronic coronary syndromes (CCS) [16], the use of semaglutide is recommended as a treatment option for non-diabetic patients with overweight/obesity (class of recommendation IIa, level of evidence B). To date, the epidemiologic significance and clinical implications for the use of semaglutide in contemporary ASCVD populations in real-world practice remain understudied. In this study, we aimed to investigate the eligibility for semaglutide according to the SELECT trial criteria and to appraise the potential implication of its use for secondary prevention in a contemporary real-world population of patients with recent acute coronary syndrome (ACS) [17,18].

2. Methods

2.1. Study design

This study is a prospective observational cohort analysis using data from the START-ANTIPLATELET registry, which includes consecutive patients admitted for ACS at seven Italian high-volume cardiology centers. The START-ANTIPLATELET is a branch of the investigator-driven, non-sponsored START registry (NCT02219984) promoted by the Arianna Anticoagulazione Foundation. Detailed information regarding study design, enrolment criteria and main results of the START registry have been previously published [1,19–23]. The study protocol was approved by the institutional ethics committees of participating institutions and the central regulatory body of each center. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice and all patients provided written informed consent.

2.2. Study population

All patients enrolled in the START-ANTIPLATELET registry until October 2023 were considered for inclusion. We excluded patients with incomplete information on BMI, diabetes, or previous cardiovascular events. Patients who were unable or unwilling to provide written informed consent for longitudinal follow-up or who retired it during the follow-up were also excluded. Study participants were evaluated based on data collected at the time of admission for ACS. Patients who met all the eligibility criteria of the SELECT trial [15] and who were free from recurrent cardiovascular events at 60 days after the index admission for ACS were included in the SELECT-like group. The timeframe of 60 days after hospital admission for ACS (e.g., post-acute phase) was selected in accordance with enrolment criteria of the SELECT trial that excluded patients with recent acute cardiovascular events (<60 days) [15]. All patients who did not fulfil the trial criteria formed the not-eligible group. A clinical assessment of the enrolled patients was conducted firstly during the hospitalization, and follow-up evaluations were scheduled at six-month and one-year intervals after discharge. All laboratory values reported in this study were extracted from electronic medical records at all centres and verified at the local laboratories by the investigators. The analysis of outcomes was conducted on patients who completed at least 6-months of follow-up.

2.3. Eligibility criteria of the SELECT-like group

According to the enrolment criteria of the SELECT trial [15], patients were included in the "SELECT-like" group if they presented the following characteristics: non-diabetic patients aged ≥45 years, BMI ≥27 kg/m^2, previous ASCVD (MI, stroke, or symptomatic peripheral arterial disease [PAD]) >60 days from the acute events. In the present analysis patients were included in the SELECT-like group only if they were free from cardiovascular events during the 60 days after index hospitalization for ACS (post-acute phase) to comply with the exclusion of acute patients from the SELECT trial. For patients included in the registry due to acute MI, this event qualified for inclusion in the SELECT-like group. In patients presenting unstable angina (UA), a history of previous acute MI, stroke, or PAD was needed for the inclusion in the SELECT-like group. Data on BMI, history of diabetes, stroke, or PAD were considered at the time of hospital admission. Age was considered at 60 days after discharge for index ACS.

2.4. Study endpoints

The primary objective of the study was to evaluate the proportion of patients eligible for treatment with semaglutide in the study cohort (e.g., SELECT-like patients). An analysis of the prevalence of eligibility criteria was conducted. A one-year descriptive analysis of clinical outcomes was also performed to compare the crude incidence of cardiovascular and bleeding events between the SELECT-like group and not-eligible group. The primary clinical endpoint was the incidence of major adverse cardiovascular events (MACE), defined as a composite of all-cause death, MI, stroke, and target vessel revascularization (TVR). As secondary clinical endpoints, the incidence of net adverse clinical events (NACE), defined as a composite of all-cause death, MI, stroke, and major bleeding at 1 year, and each individual component of NACE and MACE were evaluated. All-cause death and MI were defined according to the Academic Research Consortium criteria [21]. Coronary revascularization was defined as either percutaneous or surgical coronary revascularization. Stroke was defined as an abrupt onset of a focal neurologic deficit, generally distributed in the territory of a single brain artery, lasting more than 24 h [24]. Major bleeding was classified as intracranial or overt bleeding, which is associated with low haemoglobin level (>5 g/dL), according to the Thrombolysis In Myocardial Infarction (TIMI) scale [21].

2.5. Statistical analysis

Continuous variables were presented as mean and standard deviation or median and interquartile range and categorical variables as number and percentage. The normal distribution was first assessed using the Kolmogorov–Smirnov Goodness-of-Fit test. Categorical data were compared using either the Pearson chi-square test or the Fisher exact test when indicated, and continuous variables using the non-parametric Mann–Whitney *U* test. In case of a percentage of either row or column <5 events, the Yates correction of continuity was applied. A *p*-value of <0.05 was considered statistically significant. All analyses were performed with the Statistical Package for the Social Sciences software

version 27 (IBM ®, Armonk, New York) and R software (CRAN ® 3.3.4).

3. Results

Among the 3087 patients enrolled in the START-ANTIPLATELET registry between January 2014 and October 2023, 147 (4.7 %) patients were excluded because of incomplete information on BMI (n = 141) or because they had a cardiovascular event within 60 days after hospital discharge (n = 6). Among those patients experiencing an acute adverse event, 3 had a MI, 2 underwent TVR, and 1 had a stroke (Fig. 1). At 60 days after discharge, the study cohort comprised 2940 patients with complete information for the SELECT criteria, of whom 807 (27.4 %) patients fulfilled all eligibility criteria and were included in the SELECT-like group and 2133 (72.6 %) patients did not meet the eligibility criteria and were included in the not-eligible group.

Patients in the SELECT-like group were younger (mean age 63.8±10.7 vs 66.3±12.7; $p < 0.001$) and presented with higher BMI (30.7±3.5 vs 26.1±4.1; $p < 0.001$) than not-eligible patients. At baseline, previous percutaneous coronary intervention (PCI) was less frequent in the SELECT-like group than in the not-eligible group (17.3 % vs 22.7 %, $p = 0.001$), whereas there was no significant difference in terms of previous MI between groups. Patients in the SELECT-like group exhibited higher mean values of haemoglobin, hematocrit, and creatinine clearance than those observed in the group of non-eligible patients. In terms of clinical presentation at the time of inclusion in the registry, 58.1 % of patients in the SELECT-like cohort were admitted with a diagnosis of STEMI (vs. 49.4 % in the not-eligible cohort; $p < 0.001$), 36.1 % with NSTEMI (vs. 34.3 %; $p = 0.405$) and 5.8 % with a diagnosis of UA (vs. 16.3 %, $p < 0.001$). The demographic and clinical characteristics of the study population are presented in Table 1.

3.1. The prevalence of SELECT trial inclusion criteria

At 60 days after admission for ACS, among 807 (27.4 %) patients included in the SELECT-like group, 797 (98.7 %) patients met the MI criterion, of whom 363 (44.9 %) patients were obese and 434 (53.8 %) overweight. In the SELECT-like group, prior stroke and symptomatic PAD were observed in 2.6 % and 4.7 %, respectively. Most patients within the SELECT-like group (n = 760, 94.2 %) met a single criterion for previous cardiovascular disease (history of MI, stroke, or PAD), whereas the remaining 5.8 % had at least two of those criteria (Fig. 2).

3.2. Clinical outcomes

One-year follow-up information was available for 2143 patients. The crude incidence of MACE (4.6 % vs. 8.2 %; $p = 0.004$) and NACE (3.6 % vs. 7.6 %; $p \leq 0.001$) was significantly lower in the SELECT-like group compared to the not-eligible group. Among individual endpoints, all-cause death (2.7 % vs. 5.1 %; $p = 0.016$) was observed less frequently less frequently in the SELECT-like group. There were no differences in terms of recurrent MI, stroke, major and minor bleeding, or coronary revascularization between the two groups (Fig. 3).

4. Discussion

In the present study, we assessed in an all-comer population of

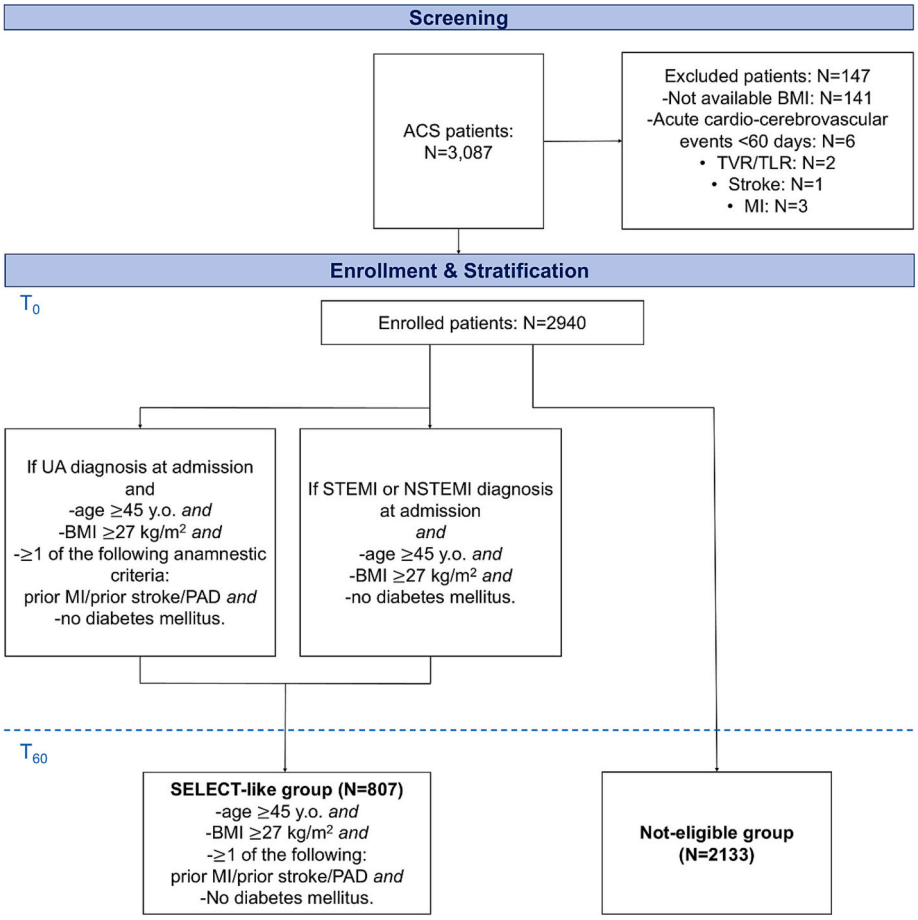


Fig. 1. Study flow-chart.
ACS = acute coronary syndrome; BMI = body mass index; MI = myocardial infarction; PAD = peripheral artery disease; TLR = target lesion revascularization; TVR = target vessel revascularization.

Table 1
Baseline characteristics.

Characteristics	SELECT-like cohort ($N = 807$)	Non-eligible cohort ($N = 2133$)	p-value
Age, mean (SD)	63.81 (10.75)	66.31 (12.67)	<0.001
Male, n (%)	640 (79.3)	1555 (72.9)	<0.001
BMI, mean (SD)	30.65 (3.47)	26.08 (4.11)	<0.001
Hypertension, n (%)	587 (72.7)	1533 (71.9)	0.640
Diabetes mellitus, n (%)	0 (−)	814 (38.2)	<0.001
Current smokers, n (%)	437 (54.2)	987 (46.3)	<0.001
Familiar history of CAD, n (%)	239 (29.6)	520 (24.4)	0.004
Previous MI, n (%)	147 (18.2)	426 (20.0)	0.283
Previous PCI, n (%)	140 (17.3)	485 (22.7)	0.001
Prior TIA, n (%)	11 (1.4)	56 (2.6)	0.041
Prior stroke, n (%)	21 (2.6)	75 (3.5)	0.213
PAD, n (%)	38 (4.7)	119 (5.6)	0.348
NVAF, n (%)	53 (6.6)	165 (7.7)	0.281
Valvular AF, n (%)	7 (0.9)	39 (1.8)	0.061
Hypercholesterolemia, n (%)	472 (58.5)	1252 (58.7)	0.918
Clinical presentation			
STEMI, n (%)	469 (58.1)	1054 (49.4)	<0.001
NSTEMI, n (%)	291 (36.1)	731 (34.3)	0.405
UA, n (%)	47 (5.8)	348 (16.3)	<0.001
Laboratoristic values			
Haemoglobin - g/dL, mean (SD)	14.00 (4.86)	13.27 (2.08)	<0.001
Hematocrit - %, mean (SD)	41.39 (6.48)	39.74 (9.45)	<0.001
Platelets count - 10^3 mean (SD)	224.5 (69.60)	226.38 (74.26)	0.533
Creatinine clearance, mean (SD)	124.18 (46.00)	100.32 (45.10)	<0.001
Cardiovascular medications - n (%)			
ACE inhibitors/ARBs	616 (76.3)	1501 (70.4)	0.001
Beta-blocker	621 (77.0)	1578 (74.0)	0.098
Statin	780 (96.7)	2054 (96.3)	0.642
PCSK9 inhibitors	21 (2.6)	29 (1.4)	0.020
PUFA n-3	14 (1.7)	51 (2.4)	0.280
PPI	788 (97.6)	2074 (97.2)	0.535
Aspirin	796 (98.6)	2090 (98.0)	0.239
Clopidogrel	164 (20.3)	563 (26.4)	<0.001
Ticagrelor	549 (68.0)	1303 (61.1)	<0.001
Prasugrel	68 (8.4)	146 (6.8)	0.141

ACE inhibitors/ARBs = angiotensin-converting–enzyme inhibitors/angiotensin-receptor blockers; BMI = body mass index; CAD = coronary artery disease; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; NVAF = non-valvular atrial fibrillation; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/kexin type 9; PPI = proton pump inhibitors; PUFA n-3 = poly-unsatured fatty acids omega-3; STEMI=ST-segment elevation myocardial infarction; TIA = transient ischemic attack; UA = unstable angina.

patients with ACS, the prevalence of SELECT trial eligibility criteria in real-world practice and the 1-year incidence of ischemic and bleeding events of SELECT-like and not-eligible patients. The main findings can be summarized as follows. First, among patients with ACS, at 2 months of follow-up, 27.4 % were potentially eligible for subcutaneous therapy with semaglutide up to 2.4 mg once-weekly, as they fulfilled all the entry criteria of the SELECT trial and were free from cardiovascular events. Second, in post-ACS patients, a SELECT-like strategy was mostly for post-MI secondary prevention (98.7 %), whereas only a minority of patients could be eligible to treatment because of previous stroke or symptomatic PAD. A history of a single cardiovascular disease was frequently reported in the SELECT-like cohort (94.2 %), whereas 2 criteria or more were found only in 5.8 % of cases. Third, the SELECT-like cohort included patients with a lower rate of 1-year MACE and NACE. Fourth, in a real-world ACS population, up to 55 % of patients may potentially benefit from semaglutide to reduce the risk of future cardiovascular events.

Overweight and obesity are serious public health concern due to an increased risk of developing both cardiovascular and non-cardiovascular complications [25]. ASCVD currently affect approximately 5–8 % of Western populations, with many of them having overweight or obesity [26]. Despite the presence of well-controlled risk factors (e.g., dyslipidemia, hypertension, diabetes), residual CV risk in patients with established ASCVD and excess body weight remains high and additional secondary prevention strategies are needed to improve outcomes in this population [13,27–29]. Over the past decade, GLP1 RAs (e.g., liraglutide and semaglutide) have demonstrated considerable efficacy in reducing body weight in non-diabetic patients, offering a promising option for the treatment of overweight and obesity [13,30–33]. Recently, the SELECT trial [15] investigated the efficacy and safety of semaglutide in patients with pre-existing cardiovascular disease and BMI of 27 or greater, but without diabetes. The trial demonstrated that the use of semaglutide up to 2.4 mg weekly was associated with a 20 % relative reduction in the rate of major adverse cardiovascular events for secondary prevention [13]. The findings of the SELECT trial underline the key role of body weight management to complement the standard-of-care medical treatment for the secondary prevention of cardiovascular disease.

In our cohort of contemporary patients with ACS, as much as 27.4 % of the patients were eligible for SELECT-like treatment strategy in the post-acute phase (at 60 days discharge), according to the eligibility criteria of the trial. Our study is the first to assesses the prevalence of the SELECT phenotype in a real-world ACS cohort and to evaluate the crude incidence of adverse events at 1 year in patients who are eligible or ineligible to the SELECT-like strategy.

In a recent analysis [34] applying the inclusion criteria of the SELECT trial in a large population of the Western Denmark Heart Registry, including 34,405 patients with first-time MI and coronary artery disease, 31 % of patients were found to be eligible for semaglutide in secondary prevention [34]. Our study confirms the results of this previous study, indicating that a relevant proportion of ACS patients may be candidates for a SELECT-like strategy, and provides novel evidence compared to this previous report. Indeed, the Western Denmark Heart Registry enrolled only patients experiencing first MI, and therefore excluded patients with recurrent MI or with UA plus a history of stroke or PAD, who may be eligible to receive semaglutide according the SELECT trial [34].

A comparison of the baseline characteristics between the SELECT trial participants and those of our real-world ACS cohort revealed several differences. In the SELECT study [15], more than two-third of patients were obese, with the minority of participants being overweight (28.55 %). A similar rate of the overweight condition was found in the START-ANTIPLATLET registry ($n = 734$; 24.95 %), 675 (22.95 %) patients were obese, and one in two patients ($n = 1573$; 53.5 %) had a BMI <27 kg/m^2. Among the eligible cohort, a total of 436 (54.02 %) patients were overweight, and 371 (45.97 %) patients were obese. When comparing the SELECT trial population with the SELECT-like cohort of our ACS registry, the mean BMI was higher (33.3 vs. 30.6 kg/m^2), the mean age was lower (61.6 vs. 63.8 years), the prevalence of smokers was one third (17 % vs. 54.2 %), and proportion of participants with hypertension was greater (81.9 % vs. 72.7 %). In our ACS cohort, as much as 98 % of patients were included in the SELECT-like group because of previous MI, whereas less than 10 % of patients had prior stroke or PAD. At odds with our findings, in the SELECT trial approximately 67 % of patients met the criteria for MI, roughly 18 % had a history of stroke, and 4–5 % had PAD. Of note, in accordance to the SELECT trial criteria, the eligible group of patients in our study did not include patients with diabetes. In the not-eligible group, 814 (38.2 %) patients had diabetes at admission, and these patients may also be potentially eligible to semaglutide prescription given its efficacy in high-risk patients with diabetes, suggesting that more than 55 % of patients admitted with ACS may be candidates to semaglutide for secondary prevention irrespective of diabetic status.

The current study also offers a descriptive analysis of one-year outcomes for 2143 patients, showing that the incidence of MACE and NACE was lower in SELECT-like patients than in not-eligible patients. The

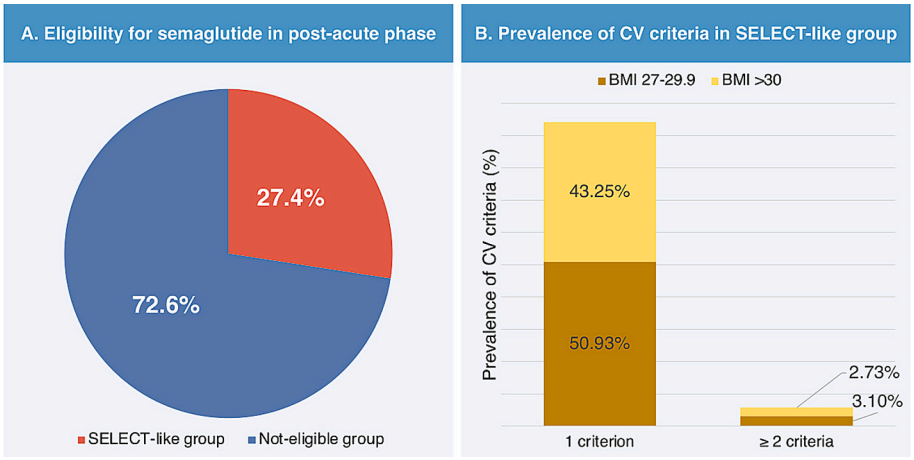


Fig. 2. Eligibility for semaglutide in the study population. Eligibility for semaglutide in the total population (A). Prevalence of cardiovascular criteria in the SELECT-like group (B).
BMI = body mass index; CV = cardiovascular.

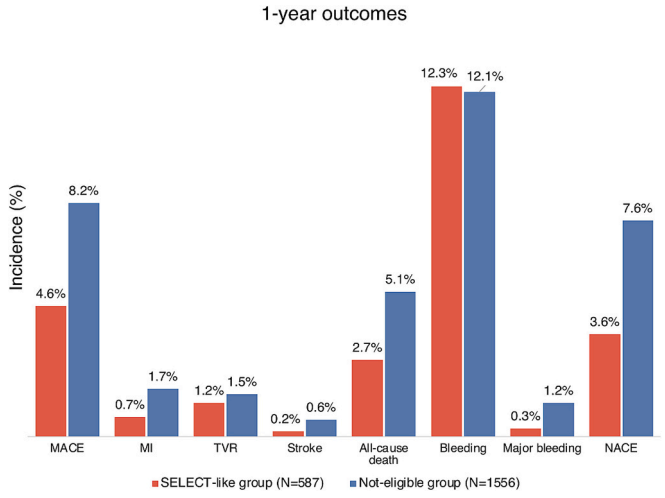


Fig. 3. One-year outcomes in the SELECT-like group vs. the not-eligible group.
MACE = major adverse clinical events; MI = myocardial infarction; NACE = net adverse clinical events.TVR = target vessel revascularization.

lower incidence of adverse events may be due in part to the fact that the SELECT-like cohort was younger, had a lower prevalence of comorbidities, and did not have diabetes. These factors are important determinants of cardiovascular outcomes and may have contributed to this observation. We also acknowledge the potential relevance of the "obesity paradox" in our study, as all SELECT-like patients were overweight/obese [35]. However, the "obesity paradox" in patients with atherosclerotic cardiovascular disease remains controversial and may be influenced by several confounders; therefore, its impact on the results is uncertain and other factors may also be at play. SELECT-like patients may be more engaged in healthcare, more adherent to preventive therapies, or have less advanced complications of comorbid conditions and thus be inherently predisposed to better outcomes. Further research is needed to disentangle the relative contributions of obesity, comorbidities, and other risk factors to the prognosis in SELECT-like patients. In addition, future randomized trials and observational studies should evaluate whether semaglutide has a protective effect in the specific setting of post-ACS cohorts and help refine clinical guidelines for patients with obesity and established cardiovascular disease. Mechanistic analyses may also help to elucidate how GLP-1 RAs influence inflammatory pathways, endothelial function, and plaque stabilization in the overweight/obese ACS population, thereby providing insight into potential mediators of improved prognosis.

5. Limitations

Our results should be interpreted in view of some limitations. The observational design of the START-ANTIPLATELET registry may include incomplete data or coding resulting in biases. Eligibility criteria, such as BMI or diabetic status, were assessed on admission for ACS but these data were used to define eligible patients at 2-month follow-up. This time difference in assessment may have affected our results. A direct comparison with the results of the SELECT trial is not possible due to the one-year follow-up and the observational design of this study which include only patients who could potentially benefit from semaglutide. Some patients had incomplete information on BMI and were therefore excluded from the study. Our results apply to the post-ACS setting and the application to other secondary prevention settings is not possible.

6. Conclusions

In a contemporary real-world population of patients with ACS, a substantial proportion of patients are potentially eligible for treatment with semaglutide after the acute phase (>60 days) according to the SELECT trial criteria. Identification of these patients may help to identify those who could potentially benefit from semaglutide for secondary prevention of cardiovascular disease.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committees of all participating centers.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Funding

None declared.

CRediT authorship contribution statement

Vincenzo De Sio: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Felice Gragnano:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Antonio Capolongo:** Writing – review & editing, Visualization, Conceptualization. **Natale Guarnaccia:** Writing – review & editing, Visualization, Data curation. **Pasquale Maddaluna:** Writing – review & editing, Data curation. **Vincenzo Acerbo:** Writing – review & editing, Data curation. **Mattia Galli:** Writing – review & editing. **Martina Berteotti:** Writing – review & editing. **Simona Sperlongano:** Writing – review & editing. **Arturo Cesaro:** Writing – review & editing. **Elisabetta Moscarella:** Writing – review & editing. **Francesco Pelliccia:** Writing – review & editing, Supervision, Formal analysis. **Giuseppe Patti:** Writing – review & editing, Visualization, Data curation. **Emilia Antonucci:** Writing – review & editing, Data curation. **Plinio Cirillo:** Writing – review & editing, Data curation. **Pasquale Pignatelli:** Writing – review & editing, Data curation. **Gualtiero Palareti:** Writing – review & editing, Data curation. **Vittorio Pengo:** Writing – review & editing, Data curation. **Paolo Gresele:** Writing – review & editing, Data curation. **Rossella Marcucci:** Writing – review & editing, Data curation. **Paolo Calabrò:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

None.

Acknowledgements

The Arianna Anticoagulation Foundation supported the START Register and the START Antiplatelet sub-registry.

References

[1] P. Calabrò, E. Moscarella, F. Gragnano, A. Cesaro, P.C. Pafundi, G. Patti, et al., START-ANTIPLATELET collaborators, effect of body mass index on ischemic and bleeding events in patients presenting with acute coronary syndromes (from the START-ANTIPLATELET registry), Am. J. Cardiol. 124 (2019) 1662–1668, https://doi.org/10.1016/j.amjcard.2019.08.030.

[2] A. Afshin, M.H. Forouzanfar, M.B. Reitsma, P. Sur, K. Estep, A. Lee, et al., GBD 2015 obesity collaborators, health effects of overweight and obesity in 195 countries over 25 years, N. Engl. J. Med. 377 (2017) 13–27, https://doi.org/10.1056/NEJMoa1614362.

[3] H.B. Hubert, M. Feinleib, P.M. McNamara, W.P. Castelli, Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham heart study, Circulation 67 (1983) 968–977, https://doi.org/10.1161/01.cir.67.5.968.

[4] Y. Lu, K. Hajifathalian, M. Ezzati, M. Woodward, E.B. Rimm, G. Danaei, Global burden of metabolic risk factors for chronic diseases collaboration (BMI mediated effects), metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants, Lancet 383 (2014) 970–983, https://doi.org/10.1016/S0140-6736(13)61836-X.

[5] P.W.F. Wilson, S.R. Bozeman, T.M. Burton, D.C. Hoaglin, R. Ben-Joseph, C. L. Pashos, Prediction of first events of coronary heart disease and stroke with consideration of adiposity, Circulation 118 (2008) 124–130, https://doi.org/10.1161/CIRCULATIONAHA.108.772962.

[6] C. Baigent, L. Blackwell, J. Emberson, L.E. Holland, C. Reith, N. Bhala, et al., Cholesterol treatment Trialists' (CTT) collaboration, efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, Lancet 376 (2010) 1670–1681, https://doi.org/10.1016/S0140-6736(10)61350-5.

[7] J.T. Wright, J.D. Williamson, P.K. Whelton, J.K. Snyder, K.M. Sink, M.V. Rocco, et al., SPRINT research group, a randomized trial of intensive versus standard blood-pressure control, N. Engl. J. Med. 373 (2015) 2103–2116, https://doi.org/10.1056/NEJMoa1511939.

[8] D.K. McGuire, W.J. Shih, F. Cosentino, B. Charbonnel, D.Z.I. Cherney, S. Dagogo-Jack, et al., Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a Meta-analysis, JAMA Cardiol. 6 (2021) 148–158, https://doi.org/10.1001/jamacardio.2020.4511.

[9] N. Sattar, M.M.Y. Lee, S.L. Kristensen, K.R.H. Branch, S. Del Prato, N.S. Khurmi, et al., Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials, Lancet Diabetes Endocrinol. 9 (2021) 653–662, https://doi.org/10.1016/S2213-8587(21)00203-5.

[10] M.J. Franz, J.L. Boucher, S. Rutten-Ramos, J.J. VanWormer, Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials, J. Acad. Nutr. Diet. 115 (2015) 1447–1463, https://doi.org/10.1016/j.jand.2015.02.031.

[11] K.I. Galaviz, M.B. Weber, A. Straus, J.S. Haw, K.M.V. Narayan, M.K. Ali, Global diabetes prevention interventions: a systematic review and network Meta-analysis of the real-world impact on incidence, weight, and glucose, Diabetes Care 41 (2018) 1526–1534, https://doi.org/10.2337/dc17-2222.

[12] A. Cesaro, G. De Michele, F. Fimiani, V. Acerbo, G. Scherillo, G. Signore, et al., Visceral adipose tissue and residual cardiovascular risk: a pathological link and new therapeutic options, Front. Cardiovasc. Med. 10 (2023) 1187735, https://doi.org/10.3389/fcvm.2023.1187735.

[13] F. Gragnano, V. De Sio, P. Calabrò, FLOW trial stopped early due to evidence of renal protection with semaglutide, Eur. Heart J. Cardiovasc. Pharmacother. 10 (2024) 7–9, https://doi.org/10.1093/ehjcvp/pvad080.

[14] N. Marx, M. Federici, K. Schütt, D. Müller-Wieland, R.A. Ajjan, M.J. Antunes, et al., ESC scientific document group, 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes, Eur. Heart J. 44 (2023) 4043–4140, https://doi.org/10.1093/eurheartj/ehad192.

[15] A.M. Lincoff, K. Brown-Frandsen, H.M. Colhoun, J. Deanfield, S.S. Emerson, S. Esbjerg, et al., SELECT trial investigators, Semaglutide and cardiovascular outcomes in obesity without diabetes, N. Engl. J. Med. 389 (2023) 2221–2232, https://doi.org/10.1056/NEJMoa2307563.

[16] C. Vrints, F. Andreotti, K.C. Koskinas, X. Rossello, M. Adamo, J. Ainslie, et al., ESC guidelines for the management of chronic coronary syndromes, Eur. Heart J. 45 (2024) (2024) 3415–3537, https://doi.org/10.1093/eurheartj/ehae177.

[17] A. Mitsis, F. Gragnano, Myocardial infarction with and without ST-segment elevation: a contemporary reappraisal of similarities and differences, Curr. Cardiol. Rev. 17 (2021) e230421189013, https://doi.org/10.2174/1573403X16999201210195702.

[18] F. Gragnano, D. van Klaveren, D. Heg, L. Räber, M.W. Krucoff, S. Raposeiras-Roubin, et al., Derivation and validation of the PRECISE-HBR score to predict bleeding after percutaneous coronary intervention, Circulation (2024), https://doi.org/10.1161/CIRCULATIONAHA.124.072009.

[19] A. Cesaro, F. Gragnano, P. Calabrò, E. Moscarella, F. Santelli, F. Fimiani, et al., START-ANTIPLATELET collaborators, prevalence and clinical implications of eligibility criteria for prolonged dual antithrombotic therapy in patients with PEGASUS and COMPASS phenotypes: insights from the START-ANTIPLATELET registry, Int. J. Cardiol. 345 (2021) 7–13, https://doi.org/10.1016/j.ijcard.2021.10.138.

[20] F. Gragnano, E. Moscarella, P. Calabrò, A. Cesaro, P.C. Pafundi, A. Ielasi, et al., START-ANTIPLATELET collaborators, Clopidogrel versus ticagrelor in high-bleeding risk patients presenting with acute coronary syndromes: insights from the multicenter START-ANTIPLATELET registry, Intern. Emerg. Med. 16 (2021) 379–387, https://doi.org/10.1007/s11739-020-02404-1.

[21] P. Calabrò, F. Gragnano, M. Di Maio, G. Patti, E. Antonucci, P. Cirillo, et al., For EYESHOT study and START Antiplatelet register, epidemiology and Management of Patients with Acute Coronary Syndromes in contemporary real-world practice: evolving trends from the EYESHOT study to the START-ANTIPLATELET registry, Angiology 69 (2018) 795–802, https://doi.org/10.1177/0003319718760917.

[22] P. Gresele, G. Guglielmini, M. Del Pinto, P. Calabrò, P. Pignatelli, G. Patti, et al., START Antiplatelet registry group, peripheral arterial disease has a strong impact on cardiovascular outcome in patients with acute coronary syndromes: from the START Antiplatelet registry, Int. J. Cardiol. 327 (2021) 176–182, https://doi.org/10.1016/j.ijcard.2020.10.079.

[23] I. Cavallari, E. Maddaloni, F. Gragnano, G. Patti, E. Antonucci, P. Calabrò, et al., START-ANTIPLATELET collaborators, ischemic and bleeding risk by type 2 diabetes clusters in patients with acute coronary syndrome, Intern. Emerg. Med. 16 (2021) 1583–1591, https://doi.org/10.1007/s11739-021-02640-z.

[24] R.L. Sacco, S.E. Kasner, J.P. Broderick, L.R. Caplan, J.J.B. Connors, A. Culebras, C. on C.S. and A. American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, P.A. and M. Council on Nutrition, et al., An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 44 (2013) 2064–2089, https://doi.org/10.1161/STR.0b013e318296aeca.

[25] T.M. Powell-Wiley, P. Poirier, L.E. Burke, J.-P. Després, P. Gordon-Larsen, C. J. Lavie, et al., American Heart Association Council on lifestyle and Cardiometabolic health; council on cardiovascular and stroke nursing; council on clinical cardiology; council on epidemiology and prevention; and stroke council, obesity and cardiovascular disease: a scientific statement from the American Heart Association, Circulation 143 (2021) e984–e1010, https://doi.org/10.1161/CIR.0000000000000973.

[26] M. Blüher, Obesity: global epidemiology and pathogenesis, Nat. Rev. Endocrinol. 15 (2019) 288–298, https://doi.org/10.1038/s41574-019-0176-8.

[27] A. Spirito, F. Gragnano, N. Corpataux, L. Vaisnora, R. Galea, S. Svab, et al., Sex-based differences in bleeding risk after percutaneous coronary intervention and implications for the academic research consortium high bleeding risk criteria, J. Am. Heart Assoc. 10 (2021) e021965, https://doi.org/10.1161/JAHA.121.021965.

[28] M. Valgimigli, F. Gragnano, M. Branca, A. Franzone, B.R. da Costa, U. Baber, et al., Single versus dual Antiplatelet therapy (Sidney-3) collaboration, Ticagrelor or

Clopidogrel monotherapy vs dual Antiplatelet therapy after percutaneous coronary intervention: a systematic review and patient-level Meta-analysis, JAMA Cardiol. 9 (2024) 437–448, https://doi.org/10.1001/jamacardio.2024.0133.
[29] A. Cesaro, V. Acerbo, F. Scialla, G. Scherillo, G. De Michele, D. Panico, et al., Role of LipoprotEin(a) in CardiovascuLar Diseases and Premature Acute Coronary Syndromes (RELACS Study): impact of Lipoprotein(a) levels on the premature coronary event and the severity of coronary artery disease, Nutr. Metab. Cardiovasc. Dis. (2024) 103843, https://doi.org/10.1016/j.numecd.2024.103843.
[30] T. Vilsbøll, M. Christensen, A.E. Junker, F.K. Knop, L.L. Gluud, Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials, BMJ 344 (2012) d7771, https://doi.org/10.1136/bmj.d7771.
[31] H.C. Tan, O.A. Dampil, M.M. Marquez, Efficacy and safety of Semaglutide for weight loss in obesity without diabetes: a systematic review and Meta-analysis, J. ASEAN Fed. Endocr. Soc. 37 (2022) 65–72, https://doi.org/10.15605/jafes.037.02.14.
[32] N. Arastu, O. Cummins, W. Uribe, E.C. Nemec, Efficacy of subcutaneous semaglutide compared to placebo for weight loss in obese, non-diabetic adults: a systematic review & meta-analysis, Int. J. Clin. Pharmacol. Ther. 44 (2022) 852–859, https://doi.org/10.1007/s11096-022-01428-1.
[33] Z. Xie, S. Yang, W. Deng, J. Li, J. Chen, Efficacy and safety of Liraglutide and Semaglutide on weight loss in people with obesity or overweight: a systematic review, Clin. Epidemiol. 14 (2022) 1463–1476, https://doi.org/10.2147/CLEP.S391819.
[34] M.K. Hansen, K.K.W. Olesen, C. Gyldenkerne, P.G. Thrane, N. Stødkilde-Jørgensen, M.B. Mortensen, et al., Eligibility for and preventive potential of Semaglutide in overweight and obese patients with myocardial infarction, J. Am. Coll. Cardiol. 83 (2024) 956–958, https://doi.org/10.1016/j.jacc.2023.12.029.
[35] S.H. Kim, J.-P. Després, K.K. Koh, Obesity and cardiovascular disease: friend or foe? Eur. Heart J. 37 (2016) 3560–3568, https://doi.org/10.1093/eurheartj/ehv509.