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

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ARTICLE INFO

Keywords:
Dual antiplatelet therapy (DAPT)
Dual antithrombotic therapy
Ticagrelor
Rivaroxaban
Acute coronary syndrome (ACS)
Chronic coronary syndrome (CCS)

ABSTRACT

Aim: To analyze the prevalence and clinical implications of the eligibility criteria for prolonged dual antithrombotic therapy with ticagrelor 60 mg twice daily and/or rivaroxaban 2.5 mg twice daily in a contemporary real-world ACS registry.

Methods: Patients from the START-ANTIPLATELET registry (NCT02219984) were stratified according to the eligibility criteria of the PEGASUS and COMPASS studies to investigate the proportion of patients eligible for prolonged dual antithrombotic therapy at discharge and after 1-year of DAPT. Net adverse clinical events (NACE), defined as all-cause death, myocardial infarction, stroke, and major bleeding, at 1 year were also evaluated and compared among groups.

Results: 1844 were considered for the analysis at baseline. Out of 849 event-free patients continually receiving dual antiplatelet therapy for at least 1 year, 577 (68%) and 583 (68.7%) met at least one eligibility criterion for ticagrelor and rivaroxaban, respectively. In the PEGASUS-like patients, age was the most common criterion (71% of cases). The presence $\geq$2 cardiovascular risk factors was the most common eligibility criterion in the COMPASS-like patients (80.8%). At 1-year follow-up, 211 (11.4%) and 119 (6.5%) patients experienced NACE and MACE, respectively. The incidence of NACEs was higher in the PEGASUS-only group (15.4% vs. 8.4%; $p = 0.008$) and numerically higher in the COMPASS-only group (10.9% vs. 8.4%; $p = 0.299$).

Conclusions: In a contemporary real-world ACS cohort, approximately two-thirds of patients that complete 1-year DAPT met the eligibility criteria for ticagrelor 60 mg twice daily or rivaroxaban 2.5 mg twice daily, showing a higher risk of NACEs.

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1. Introduction

Dual antiplatelet therapy (DAPT) is effective in reducing the incidence of atherothrombotic complications in patients with acute coronary events [1–3]. Based on this evidence, the European Society of Cardiology (ESC) [1] and the American College of Cardiology/American Heart Association (ACC/AHA) [2] guidelines recommend the use of DAPT with aspirin and a potent P2Y12 receptor inhibitor for 12 months after acute coronary syndrome (ACS), unless a high risk of bleeding. Furthermore, the European Guidelines on the management of chronic coronary syndromes [4] suggest that patients with high (class IIa) or moderate risk (class IIb) for ischemic risk who have well-tolerated DAPT within the first year after myocardial infarction (MI) may benefit of more intense (dual) antithrombotic therapy beyond 12 months from the acute event. Hence, in addition to aspirin 75–100 mg, ticagrelor 60 mg twice daily, clopidogrel 75 mg/day, prasugrel 10 mg/day (or 5 mg/day.; if bodyweight $<$ 60 kg or age $>$ 75 years) or rivaroxaban 2.5 mg twice daily, which is an alternative strategy, may be administered. These guidelines recommendations are mainly based on the results of: (i) The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial [5] and (ii) the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial [6]. The PEGASUS-TIMI 54 study [5] showed that in patients with prior MI - from 1 to 3 years earlier - and additional ischemic risk factors, the use of low-dose ticagrelor twice daily reduced the risk of cardiovascular events compared with placebo, showing a better safety profile than the ticagrelor 90 mg twice daily [5]. The COMPASS study [6] showed that the combination of rivaroxaban at the dose of 2.5 mg twice daily with aspirin in a population with stable vascular disease has significantly reduced the incidence of cardiovascular events compared to the standard regimen of aspirin alone or alternative regimen of rivaroxaban 5 mg twice daily [6]. In recent years, there has been a widespread discussion about the optimal duration of DAPT and the best combination of drugs. A recent international crowdsourcing survey on the treatment of ACS patients at high-bleeding risk undergoing percutaneous coronary intervention showed a high degree of variation with respect to duration of DAPT, antiplatelet monotherapy following DAPT, and thrombotic and bleeding risk assessment [7]. After 1 year of DAPT for ACS, clinicians face the dilemma of choosing between prolonged DAPT with aspirin and ticagrelor 60 mg twice daily (PEGASUS strategy) or aspirin and rivaroxaban 2.5 mg twice daily (COMPASS strategy).

In this study, we aimed at investigating the eligibility criteria for prolonged dual antithrombotic therapy with ticagrelor 60 mg twice daily and/or rivaroxaban 2.5 mg twice daily in the real-world ACS patients.

2. Methods

2.1. Study design and population

The START-ANTIPLATELET is a prospective, real-world registry including consecutive patients admitted for ACS in seven Italian cardiology high-volume centers. The current study was performed in accordance with the guidelines of the Declaration of Helsinki, and it was approved by the ethics committee of each participating institution. Moreover, it is a branch of the investigator-driven, non-sponsored START registry (NCT02219984) promoted by the Arianna Anticoagulazione Foundation, Bologna. The study design and main results have been previously reported [8–11].

START-ANTIPLATELET is an all-comer ACS registry. No explicit exclusion criteria were applied, and only patients who cannot or are not willing to provide written informed consent for longitudinal follow-up and those simultaneously participating in other research studies were excluded. Patients underwent clinical assessment at index event (baseline) during hospitalization and subsequently after 6 months and 1 year.

2.2. Study population

Study participants were stratified and categorized according to the eligibility criteria of the PEGASUS and COMPASS studies to identify those eligible to (i) PEGASUS-only strategy, (ii) COMPASS-only strategy, (iii) both strategies, and (iv) not eligible for any of the two drugs.

Eligibility was assessed at baseline as well as at the completion of 1 year of DAPT. Patients who experienced ischemic or bleeding events during follow-up and/or who did not complete 1-year DAPT for any clinical reasons were excluded from 1-year eligibility reassessment.

The eligibility analysis considers two time points: (i) at discharge, and (ii) at the completion of 1-year DAPT. When data are analyzed “at discharge”, all patients are included in the analysis as if they all would receive DAPT for 1 year. At variance, the “1-year eligibility analysis” includes only patients who effectively received DAPT for 1 year.

2.3. Eligibility criteria of the PEGASUS phenotype

Based on the enrolment criteria of the PEGASUS study [5], patients who had MI (within 2 years from the acute event and within 1 year from the discontinuation of previous treatment with a P2Y12 inhibitor), those aged $>$50 years, and those who had at least one cardiovascular risk factor (such as age $\geq$ 65 years, diabetes mellitus, chronic kidney disease [CKD, defined as estimated glomerular filtration rate (eGFR) of $<$60 mL/min/1.73 m^2], coronary artery stenosis of $\geq$50% in at least two coronary districts, and history of recurrent MI) were eligible for treatment with ticagrelor 60 mg twice daily. At baseline, we considered the age criterion as “age -1 year” in order to capture those who met the age requirement at 1-year follow-up. Patients at high risk of bleeding, who had a history of ischemic stroke and intracranial bleed at any time, gastrointestinal bleed within the last 6 months, or major surgery within 30 days, with planned coronary, cerebrovascular, or peripheral arterial revascularization, and who had coronary artery bypass within the last 5 years, unless spontaneous MI was experienced subsequent to the bypass surgery, were excluded. Patients were defined at high bleeding risk if they were on chronic oral anticoagulation or had a history of major or intracranial bleeding, severe thrombocytopenia (platelet count$<$50 $\times$ 10^9/L), or chronic bleeding diathesis.

2.4. Eligibility criteria of the COMPASS phenotype

Based on the enrolment criteria of the COMPASS study [6], participants with coronary artery disease (CAD), peripheral artery disease (PAD), or both and or both and at least one of the following: i) age $\geq$ 65 years; ii) age $<$ 65 and documented atherosclerosis in two vascular beds or at least 2 additional risk factors such as a) smoking; b) diabetes mellitus; c) CKD with eGFR $<$60 mL/min; d) heart failure e) non-lacunar ischemic stroke $\geq$1 month earlier can receive rivaroxaban 2.5 mg twice daily. Patients were not eligible if presenting a high risk of bleeding, those with severe heart failure (ejection fraction of $<$30% or New York Heart Association class III or IV symptoms), those with an eGFR of $<$15 mL/min, ongoing oral anticoagulant therapy, history stroke within 1 month and/or any history of hemorrhagic/lacunar stroke.

2.5. Study endpoints

The primary objective of the study was to investigate the proportion of patients who were eligible for treatment with ticagrelor 60 mg twice daily or rivaroxaban 2.5 mg twice daily in the study cohort, identifying the PEGASUS and COMPASS phenotypes. Moreover, an analysis of the prevalence of eligibility criteria and their clinical implications was conducted.

At 1-year, outcome descriptive analysis for patients in whom there

was a projection of eligibility at discharge for PEGASUS and/or COMPASS strategy was performed. Patients in the non-eligible group were considered as the reference.

The clinical endpoint was net adverse clinical event (NACE), which is defined as a composite of all-cause mortality, MI, stroke, and major bleeding within 1 year. Other clinical endpoints were major adverse cardiovascular events (MACE), defined as a composite of MI, stroke, and all-cause death; each individual component of NACE and MACE; and target vessel revascularization. MI and all-cause death were defined according to the Academic Research Consortium criteria [12]. 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 [13]. Major bleeding was classified as intracranial or overt bleeding, which is associated with low hemoglobin level (> 5 g/dL), according to the (Thrombolysis In Myocardial Infarction) TIMI scale [14].

2.6. 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 (with Mantel–Haenszel common odds ratio estimate) or the Fisher exact test when indicated, and continuous variables using the non-parametric Mann–Whitney *U* test or Kruskal–Wallis test, as appropriate. 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 25 (IBM ®, Armonk, New York) and R software (CRAN ® 3.3.4).

3. Results

3.1. Characteristics of the population

In the START-ANTIPLATELET registry, 2014 were enrolled between January 2014 and May 2020, of whom, 170 patients were excluded because they required long-term anticoagulant therapy, which is a contraindication for both low-dose ticagrelor and rivaroxaban treatments. The study population at discharge comprised 1844 patients who were classified into the following four groups: the PEGASUS-only group, including 208 (11.3%) patients who were eligible for ticagrelor 60 mg twice daily only; the COMPASS-only group, including 229 (12.4%) patients who were eligible for rivaroxaban 2.5 mg twice daily only; the PEGASUS/COMPASS group, including 992 (53.8%) patients who were eligible for both treatments; and the non-eligible group, including 415 (22.5%) patients who did not meet any eligibility criteria or who met at least one exclusion criterion (Fig. 1). The baseline characteristics of patients on admission are shown in Table 1. No patients were lost to follow-up. Patients have been stratified into 4 groups at discharge, but nevertheless, not all patients completed 1 year of DAPT and, therefore at reevaluation were no longer eligible for prolonged antithrombotic treatment. All patients were reassessed at 1 year, and only those who had received DAPT for at least 1 year and event-free were included in the final analysis of eligibility.

Overall, 849 patients were event-free, and they continually received DAPT for at least 12 months. Of these, 93 (11%) were in PEGASUS-only group, 99 (11.7%) were in COMPASS-only group, and 484 (57%) in PEGASUS/COMPASS group (Fig. 1).

Table S1 depicts data about the characteristics of procedures, revascularization strategy, and medical therapy at baseline.

3.2. Eligibility criteria

3.2.1. PEGASUS phenotype

At baseline, 1200 (65.1%) patients were potentially eligible for ticagrelor 60 mg twice daily, with consideration of those eligible for

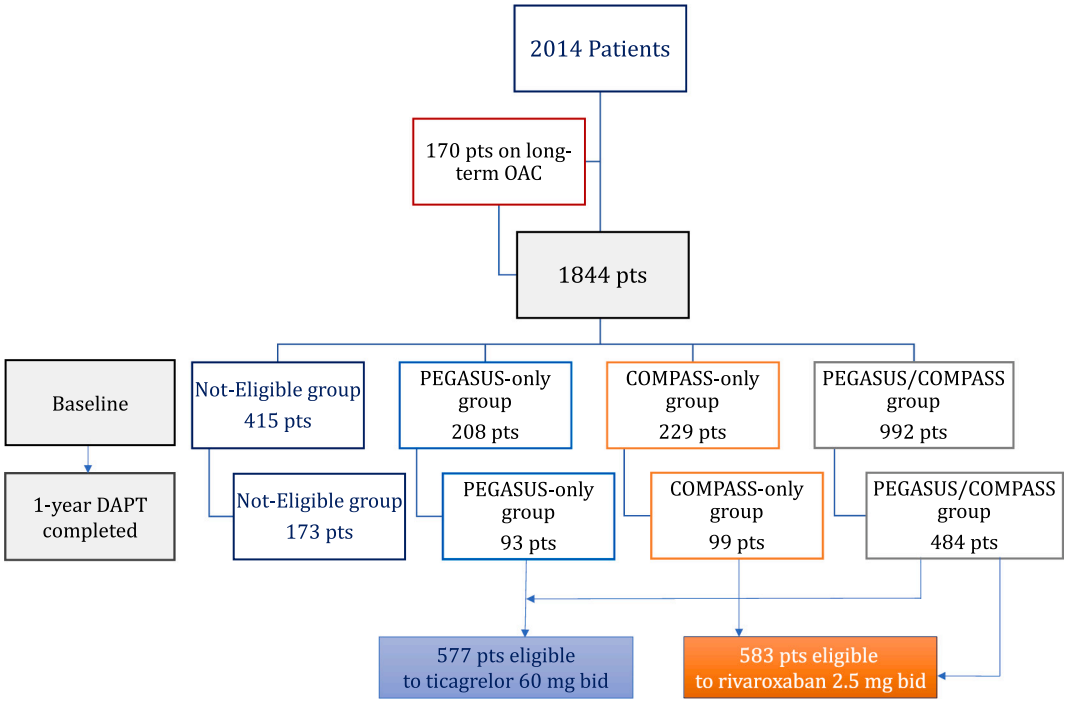

Fig. 1. Subgroups stratification according to PEGASUS and COMPASS eligibility criteria at discharge and after 1-year DAPT. COMPASS: Cardiovascular Outcomes for People Using Anticoagulation Strategies. PEGASUS: Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin. Pts: patients. OAC: Oral Anticoagulation.

Table 1
Baseline characteristics according to groups eligibility criteria.

	Not-eligible group (n = 415)	COMPASS-only group (n = 229)	PEGASUS-only group (n = 208)	PEGASUS/COMPASS group (n = 992)	p-Value
Age - yrs., mean (SD)	62 (13.4)	63.3 (14)	60.6 (9.46)	74.6 (8.90)	<0.001
Male sex, n (%)	317 (76.4)	187 (81.7)	171 (82.2)	688 (69.4)	<0.001
BMI [kg/m^2], mean (SD)	27.3 (4.47)	26.9 (3.93)	27.8 (4.81)	26.9 (4.18)	0.028
Hypertension, n (%)	268 (64.6)	146 (63.8)	133 (63.9)	733 (73.9)	<0.001
Current smoker, n (%)	225 (54.2)	126 (55)	158 (76)	405 (40.8)	<0.001
Hypercholesterolemia, n (%)	239 (57.6)	137 (59.8)	107 (51.4)	529 (53.3)	0.142
Diabetes, n (%)	72 (17.3)	34 (14.8)	81 (38.9)	306 (30.8)	<0.001
Familial history of CAD, n (%)	123 (29.6)	68 (29.7)	83 (39.9)	255 (25.7)	0.001
Previous MI, n (%)	45 (10.8)	82 (35.8)	35 (16.8)	188 (19)	<0.001
Previous PCI, n (%)	76 (18.3)	73 (31.9)	37 (17.8)	201 (20.3)	<0.001
Multivessel CAD, n (%)	13 (3.1)	16 (6.99)	32 (15.4)	123 (12.4)	<0.001
Prior TIA, n (%)	9 (2.2)	4 (1.7)	3 (1.4)	27 (2.7)	0.731
Prior ischemic stroke, n (%)	19 (4.6)	28 (12.2)	–	–	<0.001
Peripheral artery disease, n (%)	23 (5.5)	17 (7.4)	7 (3.4)	60 (6)	0.318
History of heart failure, n (%)	10 (2.4)	3 (1.31)	4 (1.92)	21 (2.1)	0.852
Clinical presentation, n (%)					<0.001
STEMI	184 (44.3)	90 (39.3)	138 (66.3)	548 (55.2)	
NSTEMI	72 (17.3)	79 (34.5)	70 (33.7)	444 (44.8)	
Unstable angina	159 (38.3)	60 (26.2)	-	-	
Hemoglobin - g/dL, mean (SD)	13.7 (2.03)	13.8 (2.06)	14 (1.74)	13.5 (1.88)	<0.001
Hematocrit - %, mean (SD)	40.6 (5.65)	41 (5.58)	41.9 (5.04)	40.3 (5.32)	<0.001
Platelets - 10^3, mean (SD)	230 (74.2)	222 (62.4)	238 (70.8)	225 (69.2)	0.034
Creatinine Clearance, mean (SD)	95.7 (43.2)	98.4 (38.9)	102 (37.9)	77 (29.5)	<0.001
PRECISE DAPT, mean (SD)	14.8 (16.6)	15.7 (18.3)	11 (13.7)	22.3 (12.8)	<0.001

BMI = Body Mass Index; CAD = Coronary artery disease; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; TIA = Transient Ischemic Attack; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; IQR = Interquartile Range.

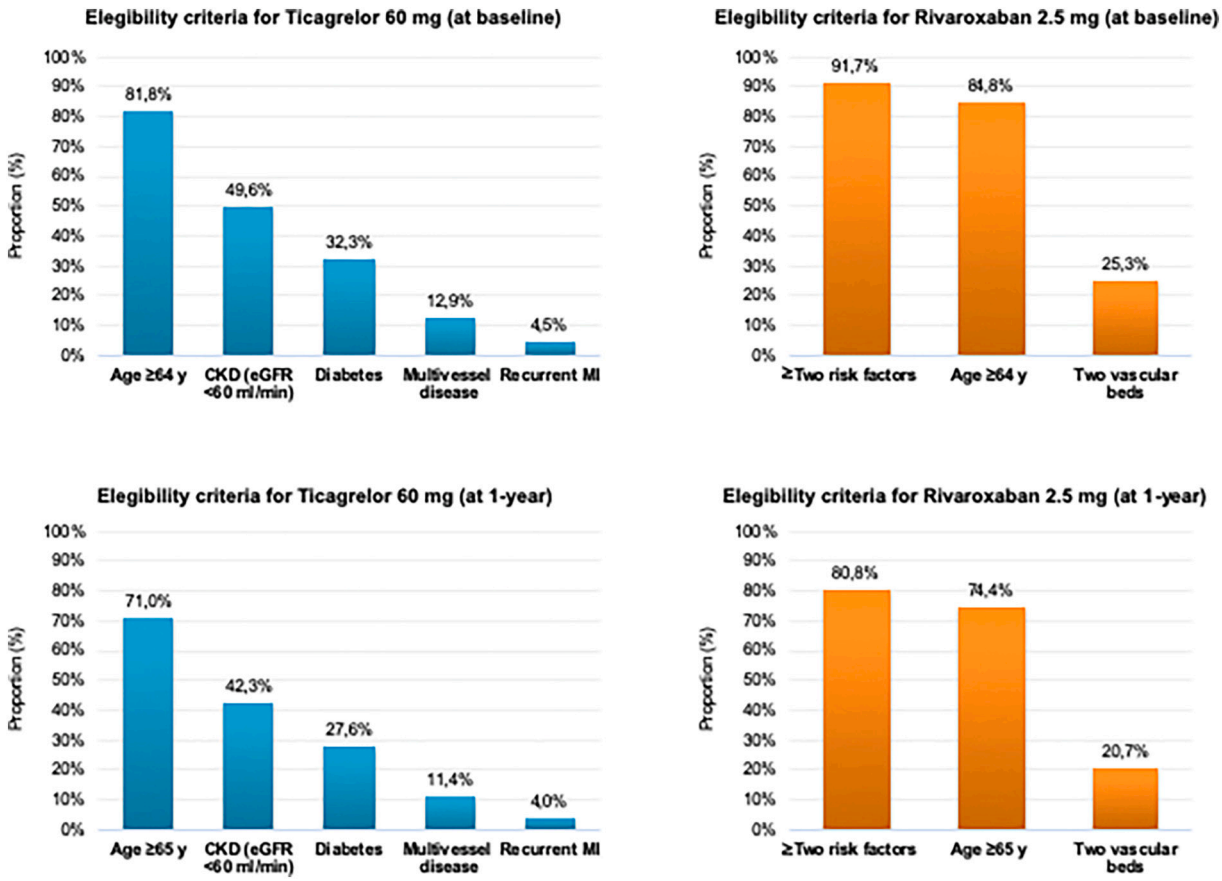

Fig. 2. Eligibility criteria for ticagrelor 60 mg twice daily and rivaroxaban 2.5 mg twice daily at discharge and after 1-year DAPT.
CKD: Chronic kidney disease; eGFR: Estimated Glomerular Filtration Rate; MI: myocardial infarction; y: years.

ticagrelor alone (208 patients – 11.3%) and those eligible for both treatments (992 patients – 53.8%). At 1-year follow-up, 577 (68%) of 849 patients with complete 1-year DAPT were eligible for prolonged DAPT with ticagrelor 60 mg twice daily and aspirin.

At baseline, among the five risk factors included in the eligibility criteria of the PEGASUS phenotype, age (81.8%) was the most common, followed by CKD (49.6%), while recurrent MI (4.5%) was the least common (Fig. 2). Diabetes mellitus and multivessel disease accounted for 32.3% and 12.9% of the study patients with PEGASUS phenotype, respectively. At 1-year follow-up, the ranking of criteria did not change, with a variation in the prevalence. After excluding patients who experienced NACE, age (71%) was still the most common criterion, and recurrent MI (4%) was the least common.

3.2.2. *COMPASS phenotype*

Considering the eligibility criteria of the COMPASS phenotype at baseline, 1221 (66.2%) patients were potentially eligible for rivaroxaban 2.5 mg twice daily, with consideration of those eligible for rivaroxaban alone (229 patients – 12.4%) and those for both treatments (992 patients – 53.8%). At 1-year follow-up, 583 (68.7%%) of 849 patients remained eligible for dual antithrombotic therapy with rivaroxaban 2.5 mg twice daily and aspirin.

At baseline, the presence of two or more risk factors (91.7%) was the most common eligibility criterion, followed by age (84.8%) and atherosclerosis in two vascular beds (25.3%).

At 1-year follow-up, similar to the PEGASUS-like patients, the ranking of criteria did not change, with a variation in the prevalence. In fact, the presence of at least 2 risk factors represented the criterion for 80.8% of patients, the age represented 74.4%, and polyvascular disease 20.7% (Fig. 2).

3.3. *Clinical outcomes*

Within 1-year follow-up, 211 (11.4%) and 119 (6.5%) patients experienced NACE and MACE, respectively (Fig. 3). After stratifying events according to group classification, NACEs occurred in 8.4% of patients in the non-eligible group vs. 15.4% of patients in the PEGASUS-only group ($p = 0.008$), 10.9% of patients in the COMPASS-only group ($p = 0.299$), and 12% of patients in PEGASUS/COMPASS group ($p = 0.051$). Also, the incidence of MACEs occurred in 4.6% of patients in the not-eligible group vs. 9.6% in the PEGASUS-only group (0.014), 4.8% of patients in the COMPASS-only group ($p = 0.897$), and 7% of patients in the PEGASUS/COMPASS group ($p = 0.093$) (Fig. 3 and Table S2). There was no difference in terms of major bleeding, stroke, MI, or revascularization.

4. Discussion

The main findings of the current analysis can be summarized as follows. First, at 1-year follow-up, approximately 60% of the patients in our study were potentially eligible for prolonged antithrombotic therapy with low-dose ticagrelor or low-dose rivaroxaban. In our cohort, more than 60% of patients met the eligibility criteria for ticagrelor 60 mg twice daily and rivaroxaban 2.5 mg twice daily after 1-year DAPT. Second, age and recurrent MI were the most and least common eligibility criteria for ticagrelor 60 mg twice daily, respectively. Moreover, the presence of two or more risk factors and polyvascular disease were the most and least frequent eligibility criteria, respectively, for rivaroxaban 2.5 mg twice daily. Third, on admission, the COMPASS and PEGASUS criteria might be used to identify upfront patients who are at higher risk of cardiovascular events at follow-up and worse outcomes. Our study reproduces a real-life scenario when the clinician is faced with a choice of whether to continue and how to continue antithrombotic therapy 1 year after DAPT.

The 2019 European guidelines on the management of chronic coronary syndromes [4] recommend adequate risk stratification among patients with coronary artery disease to implement appropriate secondary prevention strategies, including a long-term antithrombotic approach. In our cohort, after 1-year DAPT, as much as 68% of these patients met at least one eligibility criterion for ticagrelor 60 mg twice daily and rivaroxaban 2.5 mg twice daily. Several observational studies aimed to assess the study populations of the two trials in real-world clinical practice. Our study is the first assessing and comparing the prevalence of these two phenotypes in a real-world cohort of ACS patients. A French cohort study included 865 (55%) of 1585 PEGASUS-like patients (71% of the source population) who had a 1-year MI recurrence-free period [15]. Although the proportion of eligible patients may be consistent with our data, the eligible population in the French cohort is lower because only 89.2% of patients were on aspirin therapy.

The clinical feasibility of the COMPASS trial was assessed in the national and international registries [16–18]. After applying the inclusion/exclusion criteria of the COMPASS trial to the population ($n =$

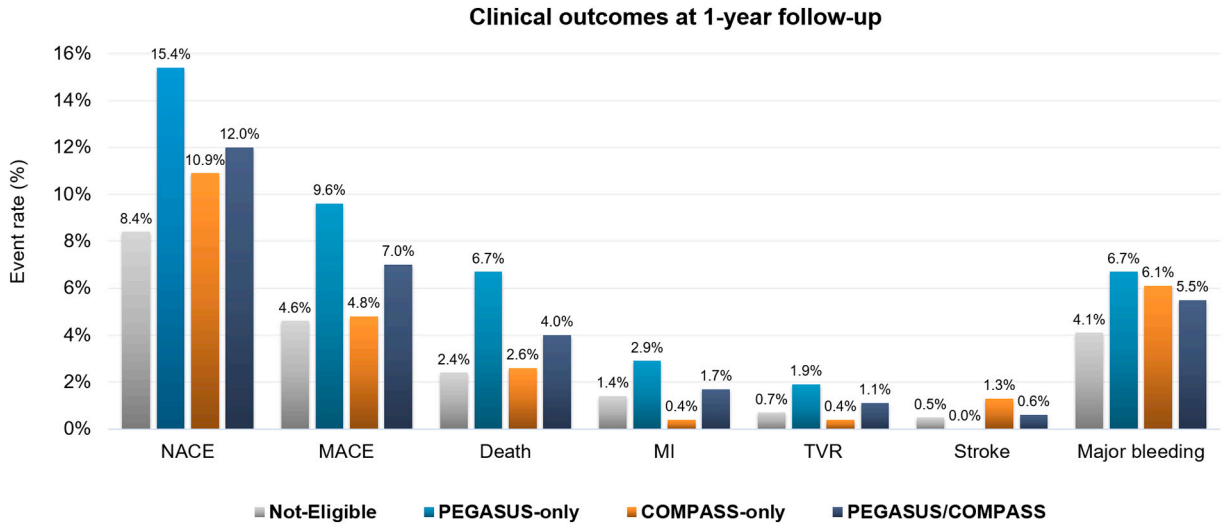

Fig. 3. Clinical outcomes at 1-year follow-up according to group stratification and eligibility criteria at discharge.
COMPASS: Cardiovascular Outcomes for People Using Anticoagulation Strategies. MACE: major adverse cardiac and cerebral events. MI: myocardial infarction. NACE: net adverse clinical events. PEGASUS: Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin. TVR: Target vessel revascularization.

31,873) of the large international REduction of Atherothrombosis for Continued Health (REACH) registry, 53% of patients were found to be eligible for the COMPASS strategy [18]. In a recent analysis of a nationwide cohort, 44.5% of 4068 patients were classified as COMPASS-like patients [19]. Compared to our results, in both cases, the proportion of potentially eligible patients appears to be lower.

Our study also investigated the distribution of criteria among different groups. In patients eligible for ticagrelor, age $\geq$ 65 was the most frequent criterion. These data highlight the importance of careful evaluation of patients aged more than 65 years who might be candidates for prolonged DAPT. Recent real-world data showed that multivessel coronary disease was the most common criterion for the prescription of ticagrelor 60 mg twice daily [20]. Meanwhile, CKD was the least common. This appears at odds with the findings in our analysis since in our cohort, the multivessel disease is the next-to-last criterion at 1-year follow-up, as observed in 11.4% of cases only. CKD is the second most common criterion, as observed in 42.3% of cases. Based on these contrasting results, the criterion of CKD is probably underestimated and under-considered for drug prescription in clinical practice, even though a large proportion of patients with ACS present with this condition in real-world.

More than 70% of patients eligible for rivaroxaban, similar to those eligible for ticagrelor, were aged $\geq$65 years. Yet, in this group of patients, the presence of at least two risk factors, which is a broad criterion based on its definition, is the most prevalent criterion. In clinical practice, the proportion of patients with multiple risk factors and previous cardiovascular events or CAD is extremely high, and these patients should be therefore carefully evaluated. Diabetes is a criterion that is well represented among study groups. In diabetics, particular attention should be paid in choosing antithrombotic therapy given their high ischemic risk and considering the greater benefit they derive from prolonged treatment compared with non-diabetics as showed in the PEGASUS and COMPASS studies [21,22].

In our analysis, patients with PEGASUS and COMPASS phenotypes at discharge appear to have a higher risk of cardiovascular events at follow-up. The RECLOSE 2-ACS study conducted a sub-analysis of 1789 patients with ACS, and results showed that the risk of cardiovascular events after 1 year increased with a greater number of PEGASUS risk factors [23].

In a sub-analysis of the COMPASS study, combined treatment with rivaroxaban and aspirin was more effective in patients with multiple risk factors [24]. In a recent study, patients in the COMPASS trial were stratified using the REACH risk score and the Classification and Regression Tree (CART) [25] analysis. Among patients with $\geq$1 risk factor, the combination of rivaroxaban and aspirin showed to prevent 33 severe vascular events per 1000 patients treated for 30 months. Moreover, Darmon et al. have applied key COMPASS selection criteria to identify a COMPASS-eligible population from the REACH Registry showing that patients with multiple enrichment criteria had a greater absolute increase in ischemic than in bleeding risk [26]. In a further analysis of the COMPASS study, the combination of rivaroxaban low-dose and aspirin compared with aspirin showed greater absolute mortality benefit with increasing baseline risk [27]. Rivaroxaban and aspirin combination reduced overall and cardiovascular mortality with consistent reduction in cardiovascular mortality in patients with CAD or PAD [27].

Based on these data and the prevalence of risk factors in our real-life population with COMPASS phenotype, we can speculate that the cardiovascular benefits observed in the trial could be amplified in real-world clinical scenarios. In a previous study by De Luca et al. [19], comparing patients meeting 1 with those meeting $\geq$3 COMPASS criteria, showed that patients with multiple criteria had a significantly high risk of MACE (from 1.0% to 3.3%, $p = 0.012$) and a modest absolute increase in the risk of major bleeding (from 0.2% to 0.4%, respectively; $p = 0.46$) [19].

Since the PEGASUS and COMPASS trials differed in terms of enrollment criteria and study population, the characteristics of participants in the two trials can be used to identify real-world patients who can be treated with either of the two antithrombotic drugs. However, a tailored approach for each patient is important for assessing the benefits of both treatment strategies as the two drugs can be used to prevent ischemic events in different patients.

5. Limitations

The current study had several limitations that must be considered. Our conclusions are limited by the observational design of the study. This is an observational real-life all-comers registry, and a proportion of patients who had discontinued DAPT before 1-year are included in baseline projection. For a limited proportion of patients (33 or 1.78%), the presence of CAD cannot be established (or excluded). Yet, to avoid possible selection bias, these patients were maintained in the analysis. The timing for eligibility to ticagrelor has been established. For rivaroxaban 2.5 mg twice daily, eligibility can be assessed even before reaching 1 year of therapy, when the clinician considers the acute phase concluded and stops DAPT. Therefore, some patients who might be eligible for rivaroxaban were not evaluated. However, it should be noted that although the ESC chronic coronary syndrome guidelines recommend the use of rivaroxaban 2.5 mg twice daily in post-MI patients >1 year or multivessel CAD, prescription of a COMPASS-like strategy after 1 year of DAPT has not been formally studied. In addition, an observational registry could have incomplete data or coding that can result in biases.

6. Conclusion

In a contemporary real-world cohort of patients with ACS, a substantial proportion of patients are potentially eligible at 1 year to prolong antithrombotic therapy with ticagrelor 60 mg twice daily or rivaroxaban 2.5 mg twice daily. The identification of PEGASUS and COMPASS phenotypes at baseline based on drug eligibility criteria may help to select patients at higher risk of ischemic events who may benefit of more intense treatment. The identification of post-ACS patients who may benefit more of a PEGASUS-like vs COMPASS-like treatment strategy in clinical practice remains difficult, and further studies addressing this point remain desirable.

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.

Authors' contributions

AC, FG, EM, PC and RM contributed to the concept and design of the article. FS, IC, FF and EA contributed to the attainment and analysis of data for the article. FP, PP, Pl.C, Giu.P, Gua.P, VP, PG and EB contributed to the data interpretation. AC, FG, EM and PC drafted the article

manuscript. A critically revision of the manuscript was done by FS, FF, Giu.P, Gua.P, IC, EA, Pl.C, PP, VP, FP, PG, EB and RM. All authors approved the final manuscript and agreed to be accountable for all parts of the work guaranteeing reliability and accuracy.

Declaration of Competing Interest

GP: speaker/consultant fees from Abbott, Astra Zeneca, Sanofi, Amgen, Bayer, Pfizer, BristolMyers Squibb, Daiichi Sankyo, PIAM, Malesci, Sigma Tau, Chiesi, Menarini, Merck Sharp Dohme, Boehringer Ingelheim. IC received honoraria from BMS-Pfizer and Boeringher Ingelheim.

Other Authors have no conflicts of interest to disclose.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Acknowledgements

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

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