Long versus short dual antiplatelet therapy in acute coronary syndrome patients treated with prasugrel or ticagrelor and coronary revascularization: insights from the RENAMI

Long vs. short dual antiplatelet therapy in ACS patients treated with prasugrel or ticagrelor and coronary revascularization: a propensity score analysis from the RENAMI registry.

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Abbreviations: ACS =Acute Coronary Syndrome; BARC =Bleeding Academic Research Consortium; DAPT =Dual AntiPlatelet Therapy; MACE =Major Adverse Clinical Events; MI =Myocardial Infarction; NACE = Net Adverse Clinical Events; PCI = Percutaneous Coronary Intervention

ABSTRACT.

Introduction. The benefits of short *vs.* long term dual antiplatelet therapy (DAPT) based on the 3rd generation P2Y12 antagonists prasugrel or ticagrelor, in patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI), remain to be clearly defined, due to current evidences limited to patients treated with clopidogrel.

Methods. All ACS patients from the registry RENAMI (REgistry of New Antiplatelets in patients with Myocardial Infarction) undergoing PCI and treated with aspirin prasugrel or ticagrelor were stratified according to the of DAPT time duration, i.e. shorter than 12 months (D1-group), 12 months (D2-group) and longer than 12 months (D3-group). The three groups were compared before and after propensity score matching. Net adverse clinical events (NACE), defined as a combination of major adverse clinical events (MACE) plus major bleeding complications (including all cause death, myocardial infarction (MI) and BARC 3-5 bleeding) were the primary end point, MACE (including all cause death and MI) the secondary one. Single components of NACE and MACE were defined co-secondary end points, along with BARC 2-5 bleeding and stent thrombosis.

Results. A total of 4'424 patients from the RENAMI registry with data about length of DAPT available were included in the model. 985 received DAPT less than 12 months, 2'216 DAPT for 12 months, and 1'223 DAPT longer than 12 months. After propensity score matching, 628 patients from each group were selected**.** At 20 months of follow up, DAPT for 12 months and DAPT for longer than 12 months significantly reduced the risk of NACE compared to DAPT for less than 12 months (D1 11.6% vs. D2 6.7% vs. D3 7.2%, p = 0.003), and of MACE (10% vs. 6.2% vs. 2.4%, p <0.001), mainly driven by a reduced risk of all cause death (7.8% vs. 1.3% vs. 1.6%, p<0.001), CV death (5.1% vs 1.0% vs. 1.2%,p <0.0001) and

recurrent MI (8.3% vs. 5.2% vs. 3.5%, p = 0.002) despite higher risk of BARC 2-5 bleeding (4.6% vs. 5.7% vs. 6.2%, p = 0.04) and a trend towards BARC 3-5 bleedings (2.4% vs. 3.3% vs. 3.9% p = 0.06).

In particular, DAPT beyond 12 months reduced the risk of MACE compared to DAPT for 12 months (6.2% vs, 2.4%, p<0.001), due to a reduced risk of MI (5.2% vs. 3.5% p = 0.016), despite a higher risk of BARC 3-5 and 2-5 bleedings (respectively 3.3% vs. 3.9% and 5.7% vs. 6.2%, all p <0.05) resulting in a not significant trend for higher NACE (6.7% vs. 7.2%, p = 0.74).

Conclusion. In unselected real world ACS patients treated with PCI, DAPT with prasugrel or ticagrelor prolonged beyond 12 months markedly reduces fatal and non-fatal ischemic events, offsetting the increased risk deriving from bleedings.

INTRODUCTION

Acute coronary syndromes (ACS) remain a pivotal problem in global health (1). Registry data shows that ACS incidence is more than 3 cases/1000/year, with in-hospital mortality ranging from 2.4% to 14% and first-year mortality up to 30% [1-2], as a consequence of the burden of comorbidities.

Percutaneous coronary intervention (PCI) and dual antiplatelet therapy (DAPT) markedly improve ACS management and prognosis [4]. PCI has led to a decreasing trend in mortality rates, thanks to the reduced symptom-to-revascularization delay, paralleled by the technological improvement of PCI, and despite the increased clinical and angiographic complexity of the enrolled patients [5-10].

In this scenario, the optimal DAPT time duration still represents a relevant area of uncertainty for clinicians, with conflicting data emerging from literature. It was observed that short DAPT time duration reduces bleeding risks, but increases the occurrence of recurrent ischemic events, while evidence in real world ACS settings on optimal DAPT time duration after ACS is still limited [2-16]. The ACS population, known to be at high risk of both ischemic and bleeding events, is typically underrepresented in randomized controlled trials (RCTs) on the topic, where less than 50% of patients with myocardial infarction, and without pre-specified analysis, was enrolled [2]. To complete the picture, clopidogrel, not prasugrel nor ticagrelor, was the drug of choice in most of these studies [16,17], against the evidence that DAPT delivery with P2Y12 antagonists such as prasugrel and ticagrelor significantly reduced recurrent ischemic events, compared to clopidogrel-based DAPT (despite the increased risk of bleeding in RCTs [11,12] as well as in real world registries [13]).

The depicted scenario suggests making binding the exploration of data reflecting real life daily practice in ACS population. [17]

Due to lack of data in unselected ACS patients treated with different DAPT strategies after PCI, in this study a propensity score sub-analysis of the registry RENAMI, (REgistry of New Antiplatelets in patients with Myocardial Infarction) is carried out. The aim is the evaluation of the impact of DAPT with different time duration in real life-ACS patients treated with either prasugrel or ticagrelor. In particular, attention is focused on the evaluation of the benefit-to-risk ratio of different DAPT time durations in ACS patients undergoing PCI and stent implantation.

METHODS.

Study population.

The study population was selected from the registry RENAMI, which extends from 2012 to 2016, and includes 12 European centers. The institutional review board of each center approved participation in RENAMI registry.

Inclusion criteria for RENAMI were: patients with final diagnosis of non ST-segment elevation myocardial infarction (NSTEMI)-ACS and ST-segment elevation myocardial infarction (STEMI)-ACS, aged ≥ 18 years with an obtained informed consent (according to the Declaration of Helsinki). No exclusion criteria were used. All patients underwent coronary angiography for ACS and were treated with DAPT using aspirin and either ticagrelor or prasugrel.

Clinical variables.

Clinical (i.e., burden of cardiovascular risk factors, clinical presentation) and interventional data (i.e., access, kind of coronary disease and treatment) were collected and supervised by a trained study coordinator in each participant center, along with outcome data. In particular, DAPT time duration was assessed through regular clinical evaluation, and, if the latter was missing, according to formal query to primary care physicians or to dedicated clinical evaluation.

Cohorts of interests.

All patients were stratified according to the effective DAPT time duration after the ACS event, as follows: DAPT shorter than 12 months (D1-group); DAPT of 12 months (D2-group); DAPT longer than 12 months (D3-group). Patients who discontinued DAPT before 6 months were excluded from analysis.

End-point and follow-up.

Clinical assessments, ECG recordings and further instrumental evaluation (when required) were performed periodically in every patient.

Net adverse clinical events (NACE), defined as a combination of major adverse clinical events (MACE) plus major bleeding complications (including all cause death, myocardial infarction (MI) and BARC 3-5 bleeding) were the primary end point. MACE (including all cause death and MI) the secondary end point. Single components of NACE and MACE were defined co-secondary end points, along with Bleeding Academic Research Consortium (BARC) 2-5 bleeding and stent thrombosis [18].Subgroup analyses for NACE and MACE were performed for gender, age older than 75 years, levels of creatinine higher than 1.5 mg/dl, and STEMI presentation. Subgroup analyses for NACE and MACE and their single components were performed also for ticagrelor and prasugrel. In order to allow for comparison among the three different DAPT groups, follow up was censored at 20 months.

Statistical analysis.

The statistical analysis was performed by applying SPSS 24.0, R 3.2.2, and STATA 13.0 softwares. Continuous variables were compared applying the*t* test. Categorical data were tested applying the chi-square test.

Triplets of propensity matched patients were obtained by a three steps procedure, as reported elsewhere (19). Due to the lack of randomization, a three-steps procedure was applied: (1) for each patient, a propensity score (PS) was generated from a multivariable logistic regression model based on (*i*) pre-treatment covariates as independent variables and (*ii*) 12 months *vs.* shorter than 12 months (D2- *vs.* D1-group) DAPT as binary dependent variable; (2) a second PS was generated for each patient from a multivariable logistic regression model based on (*i*) pre-treatment covariates as independent variables and (*ii*) 12 months vs. longer than 12 months (D2- *vs.* D3-group) DAPT as binary dependent variable; (3) a a filtering strategy was applied to include into the analysis only those patients with 12 months DAPT who were successfully matched into both a shorter than (D3-group), and longer than 12 months (D3-group) DAPT, thus resulting in a matched triplets.

The quality of the matching was assessed by comparing the selected pre-treatment variables in PS–matched cohort of patients in terms of standardized mean difference (SMD), where an absolute standardized difference greater than 20% is considered as representative of covariate imbalance.

Multivariable linear regression was used to model each outcome within the PS-matched cohort of patients. Any of the aforementioned covariables, that were considered univariate significant at the 0.05 significance level, were included in the multivariable models. A sensitivity analysis was carried out to assess the robustness of the proposed primary analysis method. This was done by applying the Cox proportional hazards regression, in

order to assess the effect that long *vs.* short DAPT on NACE with variables significantly different at univariate analysis. In the Cox regression, odd (OR) ratios and 95% confidence intervals (CI) were calculated to ascertain the significance of the differences.

RESULTS.

Overall population.

A total of 4'424 patients from RENAMI with available data on DAPT time duration were included in the model. Of them, 985 patients were discharged with a DAPT regimen shorter than 12 months, 2'216 with a DAPT of 12 months, and 1'223 with a DAPT longer than 12 months. At baseline, cardiovascular risk factors were more relevant in patients discharged with 12 months or longer DAPT time duration of, STEMI being the most frequent clinical presentation. Patients discharged with DAPT time duration longer than 12 months presented with a more complex coronary artery disease (more frequent involvement of the left main coronary artery and multivessel disease), without difference in treatment. Exhaustive details depicting the situation at baseline can be found in the Appendix (web only Table 1). After 18.2±3.4 months of follow up, NACE and MACE were more frequent in patients discharged with shorter DAPT, being mainly driven by a reduction in all cause death and recurrent myocardial infarction as well as with a higher risk of BARC 3-5 and BARC 2-5 bleeding (see appendix, web only table 2).

Propensity score

After propensity score with matching, 628 patients of each group were selected. **(Figure 1).** Median time of DAPT was 6.2 months (5.8-6.4) in the first group and 18.1 (14.3-20.2) in the last group. Cardiovascular risk factors did not differ. Diabetes mellitus was reported in 20.4% vs. 23.4% vs. 28.0% respectively in patients with DAPT<12 months, of 12 and > 12 months. (p = 0.69). In the three groups, 62.4%, 61.0% and 58.0% of the patients, respectively had been admitted with STEMI (p = 0.89; **Table 1**). About half of them presented with multivessel disease which was managed with complete revascularization in 43.0%, 46.2% and 41.1%, respectively (p = 0.26; **Table 1).** All patients were discharged with aspirin,

while in the three DAPT duration groups 41.3%, 45.7% and 51.4% received prasugrel and 58.7%, 54.3% and 48.6% ticagrelor (p = 0.87 and p = 0.91, respectively).

After 20 months (range: 18-24 months), DAPT for 12 months and DAPT longer than 12 months significantly reduced the risk of NACE compared to DAPT of less than 12 months (D1 11.6%, D2 6.7% and D3 7.2%, p = 0.003), and of MACE (10%, 6.2% and 2.4%, p <0.001), mainly driven by a reduced risk of death (7.8%, 1.3% and 1.6%, p<0.001), of CV death (5.1%, 1.0% and 1.2%, p <0.0001) and of recurrent MI (8.3%, 5.2% and 3.5%, p = 0.002). BARC 2-5 bleedings were increased (4.6%, 5.7% and 6.2%, p = 0.04) with a trend towards an increase of BARC 3-5 bleeding (2.4%, 3.3% and 3.9%, p = 0.06). Moreover, longer DAPT reduced the risk of stent thrombosis (2.7%, 0.6% and 1.4%, p = 0.01; **Figure 2**).

DAPT beyond 12 months reduced the risk of MACE compared to DAPT for 12 months (6.2% vs, 2.4%, p<0.001), due to a reduced risk of MI (5.2% vs. 3.5%, p = 0.016), albeit with a higher risk of BARC 3-5 and 2-5 bleedings (3.3%, 3.9% and 5.7% vs. 6.2%, respectively; all p<0.05) resulting in a non significant trend for higher NACE (6.7% vs. 7.2%, p = 0.74).

Subgroup Analysis

Subgroup analysis confirmed similar trends in STEMI and NSTEMI-ACS patients, and in those with reduced or preserved renal function (i.e. with creatinine concentration lower or higher than 2.5 mg/dl, respectively). The observed clinical benefit on patients administered with DAPT time duration longer than 12 months was found to be attenuated in females and in patients older than 75 years **(Figures 3** and **4).** Regarding use of prasugrel and ticagrelor, the trend for benefit of longer DAPT time duration was confirmed for both these drugs, as extensively proved in the appendix **(web only Figures 1 and 2).**

Cox multivariate analysis revealed that DAPT for 12 months and beyond 12 months reduced the risk of NACE compared to a shorter DAPT duration (OR 0.59, 95%CI 0.39-0.91, p <0.001 and OR 0.23, 95%CI 0.15-0.33, p <0.001 , respectively), independently of clinical and procedural features **(see appendix, Table 4).**

DISCUSSION.

This study does represent the first attempt to explore the impact of different DAPT time duration procedures on ACS patients treated with prasugrel or ticagrelor and coronary revascularization . In detail, shorter than, equal to, and longer than 12 months time duration for therapy were investigated using the RENAMI dataset.

The main findings of the study are: (1) DAPT time duration longer than 12 months, with aspirin and either the new P2Y12 antagonist prasugrel or ticagrelor, reduces the incidence of MACE with a slight increase in bleedings, resulting in (*i*) an overall significant reduction of NACE when compared to DAPT time duration shorter than 12, and (*ii*) a not statistically significant increase of NACE compared to DAPT time duration equal to 12 months; (2) the main part of the observed benefits in the D3-group can be explained in terms of a reduction in recurrent acute MI; (3) the observed favorable effect in terms of reduced MACE associated with longer DAFT time duration appears to be less evident in females and older patients.

Based on our findings, a DAPT time duration shorter than 12 months does not appear to be appropriate in the setting of a real life ACS population treated with novel P2Y12 inhibitors. The ESC guidelines on stable coronary artery disease recommend at least 6 months of DAPT time duration after PCI and even suggests to consider a shorter duration of 3 months in patients at high bleeding risk [20,21]. However, only few data are available on appropriate DAPT time duration in the higher risk ACS population, especially in relation to the newest generation of drug-eluting stents (DES) and to use of ticagrelor or prasugrel. In the LEADERS FREE trial [22], patients at very high bleeding risk with an indication for PCI were safely treated with only one month of DAPT time duration after polymer-free DES implantation. However ACS patients, particularly those admitted for STEMI, as well as those with complex coronary lesions, were poorly represented in that study [22]. In a network meta

analysis, Palmerini et al. reported that in patients admitted for ACS a DAPT time duration shorter than 3 months favors ischemic events (such as acute MI or stent thrombosis) [23]. However, in the population enrolled in the study by Palmerini et al. [23], derived from randomized controlled trials, unstable angina (UA) was the prevalent diagnosis and clopidogrel was the second antiplatelet agent of choice. The findings of the present study suggest that and in a higher risk real world population with ACS, even with newer P2Y12 inhibitors, a longer DAPT time duration of at least 12 months is considerably more appropriate than a shorter one in terms of NACE, with a clear reduction of MACE (i.e. death, recurrent MI and stent thrombosis), without a significant concomitant increase in major bleeding.

Of note, patients presenting with ACS have an increased risk of ischemic events, including stent thrombosis as well as MI not related to the stented segment, that lasts beyond the first year from the index event [16,24]. Indeed, a large body of literature suggests that prolonged DAPT beyond the first year after an ACS results in a reduced incidence of MACE [16, 24-27]. In particular, Bonaca et. al [25] recently demonstrated reduced ischemic events, extending DAPT with ticagrelor, in patients with recent acute myocardial infaction (AMI) and high ischemic risk profile. A concomitant, inevitable slight increase in major bleedings was also observed, even if without fatal or intracranial risk increments [25]. On the other hand, only TRILOGY-ACS trial [26] tested DAPT procedures longer than 12 months using prasugrel *vs.* clopidogrel, including patients with a NSTE-ACS not treated with percutaneous revascularization. Even if the primary outcome was reported to be independent of the drug administrated, a diverging trend favoring prasugrel emerged after the first 12 months of DAPT. In this study we confirm such a protective effect of prolonged DAPT time duration in a real world population using new P2Y12 inhibitors. Indeed, we observed a significant reduction in ischemic events, predominantly in terms of recurrent MI. On the other hand, such a benefit

should be balanced against a concomitant increase in bleeding events, particularly major ones which inevitably are associated with a higher morbidity and mortality [27,28]. However, in this study only a marginal increase in the incidence of major bleedings was observed, with a DAPT duration prolonged beyond 12 months (3.9% for the D3-group, against 3.3% for the D2-group, in terms of BARC 3-5 bleeding), suggesting that when clinically and technically indicated, a strategy of prolonged DAPT time duration can be selected for this patient population.

In this context, different risk scores have been proposed to identify patients at increased risk of ischemic events with an acceptable bleeding risk. The American College of Cardiology/American Heart Association guidelines suggest using the "*DAPT Score*" for decision making [29,30]. Among the proposed indicators, presentation with an acute MI, as well as a history of MI are considered as risk factor for recurrent ischemic events. Those patients with a score equal or higher than 2 are considered candidates for prolonged DAPT time duration, without a risk for increased major bleedings events. However, this score has not yet been convincingly validated in ACS patients with use of newer generation DES and with newer antiplatelet agents such as prasugrel or ticagrelor [12]. Alternatively, Costa and colleagues [30] have proposed the "PRECISE-DAPT" score. It is a simple 5-items tool to select the optimal DAPT duration after PCI. Using this tool, low score patients present a net clinical advantage from prolonged DAPT time duration, while with high score patients seem to benefit more from a shorter DAPT time duration. The authors conjecture that by integrating tools proposed in refs [29,30], and by considering individual clinical and procedural data, a a more clear assessment of the risk-benefit ratio of a prolonged DAPT time duration is feasible.

Finally, here a reduced benefit of prolonged DAPT beyond 12 months in patients older than 75 years and in females was observed. With ageing of general population, more

complex, poly-comorbid and frail patients present with an ACS. An important extra-cardiovascular burden of disease is probably the main determinant for the worse prognosis of these sub-populations [3,19]. Furthermore, older patients are more likely to present with impaired renal function and a general predisposition for peri-procedural and post-procedural bleedings [31]. For these reasons, the possible ischemic benefit of a longer DAPT time duration is in this setting overruled by the harm, in term of major bleeding leading to an increased mortality. Importantly, women are often underrepresented in RCTs [32] and they tend to be less frequently treated with novel P2Y12 Inhibitors in real life registries [33], so that no solid data are available on this sub-population. Although there are conflicting data, some studies suggest a higher platelet reactivity in women [34,35], considering that no clear clinical implication has yet been demonstrated for this pharmacokinetic observation [36]. However, in a recently published meta-analysis of RCTs on new antiplatelet therapies no significant difference in terms of MACE was observed between males and females with CAD [37]. On the other hand, some reports suggest that compared to males, females are at increased risk of bleeding after ACS when treated with potent P2Y12 Inhibitors [38]. A possible explanation for this is the higher drug exposure, due to females BMI and creatinine clearance, lower than males. Therefore, prolonged DAPT in females seems to be associated with increased NACE, but larger sample size is required to confirm this hypothesis.

Here the trend for benefit of longer DAPT time duration was confirmed for both prasugrel and ticagrelor, despite a higher rate of events with the latter. This is probably due to the fact that prasugrel is not administered to older patients, in patients with extreme low weight and in patients with a history of stroke. In RENAMI, ticagrelor-administered patients are more numerous than prasugrel-administered patients in sub-groups (1) older than 75 years (12.2% *vs.* 6.4%; p 0.001),, (2) with weight inferior to 60 kg (6.0% *vs.* 3.3%; p 0.008),

and (3) with a history of stroke (2.4% *vs.* 1.9%; p 0.45). All these factors, increasing the risk of bleeding and of ischemic events, arethe reason of the augmented rate of events in the ticagrelor group.

LIMITATIONS.

Several limitations could weaken the findings of this study. First of all, this is not a randomized controlled trial. As a consequence, and despite proper propensity score matching (AUC 0.78) and discrimination (p = 0.67, Hosmer-Lermeshow test) bias by indication cannot be truly excluded. Another possible limitation lies in the fact that this study is built on differences observed in follow ups in 12 participating centers, in the absence of a central adjudication. **Moreover, there is paucity, in provided data, of information related to interruptions and disruptions, which accounted for 3% and 2% of patients, respectively, uniformly distributed among the three groups.** Lastly, being this study based on effective DAPT time duration, it might suffer from biases related to events occurring after discharge.

CONCLUSION.

In a real-life registry of ACS patients treated with percutaneous coronary revascularization and matched with propensity, DAPT with prasugrel or ticagrelor longer than 12 months was beneficial in terms of reduction of ischemic events with a concomitant increased risk of bleeding, albeit predominantly minor ones. These findings should be confirmed in randomized controlled trials.

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Bibliography

1. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M2. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016 Nov 7;37(42):3232-3245. https://doi.org/10.1093/eurheartj/ehi002
2. Widimsky, P., Zelizko, M., Jansky, P., Tousek, F., Holm, F., & Aschermann, M. (2007). The incidence, treatment strategies and outcomes of acute coronary syndromes in the "reperfusion network" of different hospital types in the Czech Republic: Results of the Czech evaluation of acute coronary syndromes in hospitalized patients (CZECH) registry. *International Journal of Cardiology*, *119*(2), 212–219. https://doi.org/10.1016/j.ijcard.2007.02.036
3. Moretti, C., Iqbal, J., Murray, S., Bertaina, M., Parviz, Y., Fenning, S., … Denvir, M. (2016). Prospective assessment of a palliative care tool to predict one-year mortality in patients with acute coronary syndrome. *European Heart Journal: Acute Cardiovascular Care*, *6*(3), 272–279. https://doi.org/10.1177/2048872616633841
4. Collet JP, Roffi M, Byrne RA, Costa F, Valgimigli M; Task Force for the Management of Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC); ESC Scientific Document Group; Task Force for the Management of Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC). Case-based implementation of the 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease: The Task Force for the Management of Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2017 Aug 26. doi: 10.1093/eurheartj/ehx503. [Epub ahead of print]
5. Roffi, M., Patrono, C., Collet, J.-P., Mueller, C., Valgimigli, M., Andreotti, F., … Windecker, S. (2015). 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal*, *37*(3), 267–315. https://doi.org/10.1093/eurheartj/ehv320
6. D'Ascenzo, F., Iannaccone, M., De Filippo, O., Leone, A. M., Niccoli, G., Zilio, F., … Picchi, A. (2017). Optical coherence tomography compared with fractional flow reserve guided approach in acute coronary syndromes: A propensity matched analysis. *International Journal of Cardiology*, *244*, 54–58. https://doi.org/10.1016/j.ijcard.2017.05.108
7. Hoedemaker, N. P. G., Damman, P., Woudstra, P., Hirsch, A., Windhausen, F., Tijssen, J. G. P., & de Winter, R. J. (2017). Early Invasive Versus Selective Strategy for Non-ST-Segment Elevation Acute Coronary Syndrome: The ICTUS Trial. *Journal of the American College of Cardiology*, *69*(15), 1883–1893. https://doi.org/10.1016/j.jacc.2017.02.023
8. Quadri, G., D'Ascenzo, F., Moretti, C., D'Amico, M., Raposeiras-Roubín, S., Abu-Assi, E., … Gaita, F. (2017). Complete or incomplete coronary revascularisation in patients with myocardial infarction and multivessel disease: a propensity score analysis from the "real-life" BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) registry. *EuroIntervention*, *13*(4), 407–414. https://doi.org/10.4244/eij-d-16-00350
9. Montone, R. A., Niccoli, G., De Marco, F., Minelli, S., D'Ascenzo, F., Testa, L., … Crea, F. (2017). Temporal Trends in Adverse Events After Everolimus-Eluting Bioresorbable

Vascular Scaffold Versus Everolimus-Eluting Metallic Stent ImplantationClinical Perspective. *Circulation*, *135*(22), 2145–2154. https://doi.org/10.1161/circulationaha.117.028479

10. D'Ascenzo F, Iannaccone M, Saint-Hilary G, Bertaina M, Schulz-Schüpke S, Wahn Lee C, Chieffo A, Helft G, Gili S1, Barbero U, Biondi Zoccai G, Moretti C, Ugo F, D'Amico M, Garbo R, Stone G, Rettegno S, Omedè P, Conrotto F, Templin C, Colombo A, Park SJ, Kastrati , Hildick-Smith D, Gasparini M, Gaita F. Impact of design of coronary stents and length of dual antiplatelet therapies on ischaemic and bleeding events: a network meta-analysis of 64 randomized controlled trials and 102 735 patients. Eur Heart J. 2017 Nov 7;38(42):3160-3172.
11. Wiviott, S. D., Braunwald, E., McCabe, C. H., Montalescot, G., Ruzyllo, W., Gottlieb, S., … Antman, E. M. (2007). Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *New England Journal of Medicine*, *357*(20), 2001–2015. https://doi.org/10.1056/nejmoa0706482
12. Wallentin, L., Becker, R. C., Budaj, A., Cannon, C. P., Emanuelsson, H., Held, C., … Harrington, R. A. (2009). Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *New England Journal of Medicine*, *361*(11), 1045–1057. https://doi.org/10.1056/nejmoa0904327
13. Sahlén A, Varenhorst , Lagerqvist B, Renlund H, Omerovic E, Erlinge D, Wallentin L, James SK, Jernberg T7. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. Eur Heart J. 2016 Nov 21;37(44):3335-3342.
14. D'Ascenzo, F., Colombo, F., Barbero, U., Moretti, C., Omedè, P., Reed, M. J., … Gaita, F. (2014). Discontinuation of Dual Antiplatelet Therapy Over 12 Months after Acute Coronary Syndromes Increases Risk for Adverse Events in Patients Treated with Percutaneous Coronary Intervention: Systematic Review and Meta-Analysis. *Journal of Interventional Cardiology*, *27*(3), 233–241. https://doi.org/10.1111/joic.12107
15. Piccolo, R., Gargiulo, G., Franzone, A., Santucci, A., Ariotti, S., Baldo, A., … Valgimigli, M. (2017). Use of the Dual-Antiplatelet Therapy Score to Guide Treatment Duration After Percutaneous Coronary Intervention. *Annals of Internal Medicine*, *167*(1), 17. https://doi.org/10.7326/m16-2389
16. D'Ascenzo, F., Moretti, C., Bianco, M., Bernardi, A., Taha, S., Cerrato, E., … Stone, G. W. (2016). Meta-Analysis of the Duration of Dual Antiplatelet Therapy in Patients Treated With Second-Generation Drug-Eluting Stents. *The American Journal of Cardiology*, *117*(11), 1714–1723. https://doi.org/10.1016/j.amjcard.2016.03.005
17. Costa, F., Vranckx, P., Leonardi, S., Moscarella, E., Ando, G., Calabro, P., … Valgimigli, M. (2015). Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial. *European Heart Journal*, *36*(20), 1242–1251. https://doi.org/10.1093/eurheartj/ehv038
18. Mehran, R., Rao, S. V., Bhatt, D. L., Gibson, C. M., Caixeta, A., Eikelboom, J., … White, H. (2011). Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium. *Circulation*, *123*(23), 2736–2747. https://doi.org/10.1161/circulationaha.110.009449

19. Kopyeva T, Sessler DI, Weiss S, Dalton JE, Mascha EJ, Lee JH, Kiran RP, Udeh B, Kurz A. Effects of volatile anesthetic choice on hospital length-of-stay: a retrospective study and a prospective trial. Anesthesiology. 2013 Jul;119(1):61-70.
20. Kang, S.-H., Chae, I.-H., Park, J.-J., Lee, H. S., Kang, D.-Y., Hwang, S.-S., … Kim, H.-S. (2016). Stent Thrombosis With Drug-Eluting Stents and Bioresorbable Scaffolds: Evidence From a Network Meta-Analysis of 147 Trials. *JACC. Cardiovascular Interventions*, *9*(12), 1203–1212. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. (2016). *Circulation*, *134*(10), e156–e178. https://doi.org/10.1161/cir.0000000000000405
21. 2014 ESC/EACTS Guidelines on myocardial revascularization. (2014). *European Heart Journal*, *35*(37), 2541–2619. https://doi.org/10.1093/eurheartj/ehu278
22. Urban, P., Meredith, I. T., Abizaid, A., Pocock, S. J., Carrié, D., Naber, C., … Morice, M.-C. (2015). Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *New England Journal of Medicine*, *373*(21), 2038–2047. https://doi.org/10.1056/nejmoa1503943
23. Palmerini, T., Della Riva, D., Benedetto, U., Bacchi Reggiani, L., Feres, F., Abizaid, A., … Stone, G. W. (2017). Three, six, or twelve months of dual antiplatelet therapy after DES implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *European Heart Journal*, ehw627. https://doi.org/10.1093/eurheartj/ehw627
24. Jernberg, T., Hasvold, P., Henriksson, M., Hjelm, H., Thuresson, M., & Janzon, M. (2015). Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *European Heart Journal*, *36*(19), 1163–1170. https://doi.org/10.1093/eurheartj/ehu505
25. Bonaca, M. P., Bhatt, D. L., Cohen, M., Steg, P. G., Storey, R. F., Jensen, E. C., … Sabatine, M. S. (2015). Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. *New England Journal of Medicine*, *372*(19), 1791–1800. https://doi.org/10.1056/nejmoa1500857
26. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD, Merkely B, Gasparovic V, Corbalan R, Cinteză M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM; TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med. 2012 Oct 4;367(14):1297-309.
27. Udell, J. A., Bonaca, M. P., Collet, J.-P., Lincoff, A. M., Kereiakes, D. J., Costa, F., … Bhatt, D. L. (2015). Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *European Heart Journal*, ehv443. https://doi.org/10.1093/eurheartj/ehv443
28. Mauri, L., Kereiakes, D. J., Yeh, R. W., Driscoll-Shempp, P., Cutlip, D. E., Steg, P. G., … Massaro, J. M. (2014). Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-

Eluting Stents. *New England Journal of Medicine*, *371*(23), 2155–2166. https://doi.org/10.1056/nejmoa1409312

29. Levine, G. N., Bates, E. R., Bittl, J. A., Brindis, R. G., Fihn, S. D., Fleisher, L. A., … Smith, S. C. (2016). 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*, *134*(10), e123–e155. https://doi.org/10.1161/cir.0000000000000404
30. Costa, F., van Klaveren, D., James, S., Heg, D., Räber, L., Feres, F., … Valgimigli, M. (2017). Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *The Lancet*, *389*(10073), 1025–1034. https://doi.org/10.1016/s0140-6736(17)30397-5
31. Rao, S. V., Dai, D., Subherwal, S., Weintraub, W. S., Brindis, R. S., Messenger, J. C., … Peterson, E. D. (2012). Association Between Periprocedural Bleeding and Long-Term Outcomes Following Percutaneous Coronary Intervention in Older Patients. *JACC: Cardiovascular Interventions*, *5*(9), 958–965. https://doi.org/10.1016/j.jcin.2012.05.010
32. Kim, E. S. H., Carrigan, T. P., & Menon, V. (2008). Enrollment of Women in National Heart, Lung, and Blood Institute-Funded Cardiovascular Randomized Controlled Trials Fails to Meet Current Federal Mandates for Inclusion. *Journal of the American College of Cardiology*, *52*(8), 672–673. https://doi.org/10.1016/j.jacc.2008.05.025
33. Sherwood, M. W., Wiviott, S. D., Peng, S. A., Roe, M. T., DeLemos, J., Peterson, E. D., & Wang, T. Y. (2014). Early Clopidogrel Versus Prasugrel Use Among Contemporary STEMI and NSTEMI Patients in the US: Insights From the National Cardiovascular Data Registry. *Journal of the American Heart Association*, *3*(2), e000849–e000849. https://doi.org/10.1161/jaha.114.000849
34. Breet, N. J., Sluman, M. A., van Berkel, M. A. J. P. J., van Werkum, J. W., Bouman, H. J., Harmsze, A. M., … ten Berg, J. M. (2011). Effect of gender difference on platelet reactivity. *Netherlands Heart Journal*, *19*(11), 451–457. https://doi.org/10.1007/s12471-011-0189-y
35. D'Ascenzo, F., Barbero, U., Bisi, M., Moretti, C., Omedè, P., Cerrato, E., … Gaita, F. (2014). The Prognostic Impact of High On-Treatment Platelet Reactivity with Aspirin or ADP Receptor Antagonists: Systematic Review and Meta-Analysis. *BioMed Research International*, *2014*, 1–13. https://doi.org/10.1155/2014/610296
36. Lau, E. S., Braunwald, E., Murphy, S. A., Wiviott, S. D., Bonaca, M. P., Husted, S., … O'Donoghue, M. L. (2017). Potent P2Y 12 Inhibitors in Men Versus Women. *Journal of the American College of Cardiology*, *69*(12), 1549–1559.https://doi.org/10.1016/j.jacc.2017.01.028

37. Daugherty, S. L., Thompson, L. E., Kim, S., Rao, S. V., Subherwal, S., Tsai, T. T., … Masoudi, F. A. (2013). Patterns of Use and Comparative Effectiveness of Bleeding Avoidance Strategies in Men and Women Following Percutaneous Coronary Interventions. *Journal of the American College of Cardiology*, *61*(20), 2070–2078. https://doi.org/10.1016/j.jacc.2013.02.030
38. Yu, J., Mehran, R., Grinfeld, L., Xu, K., Nikolsky, E., Brodie, B. R., … Stone, G. W. (2014). Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: Three year results from the HORIZONS-AMI trial. *Catheterization and Cardiovascular Interventions*, *85*(3), 359–368. https://doi.org/10.1002/ccd.25630

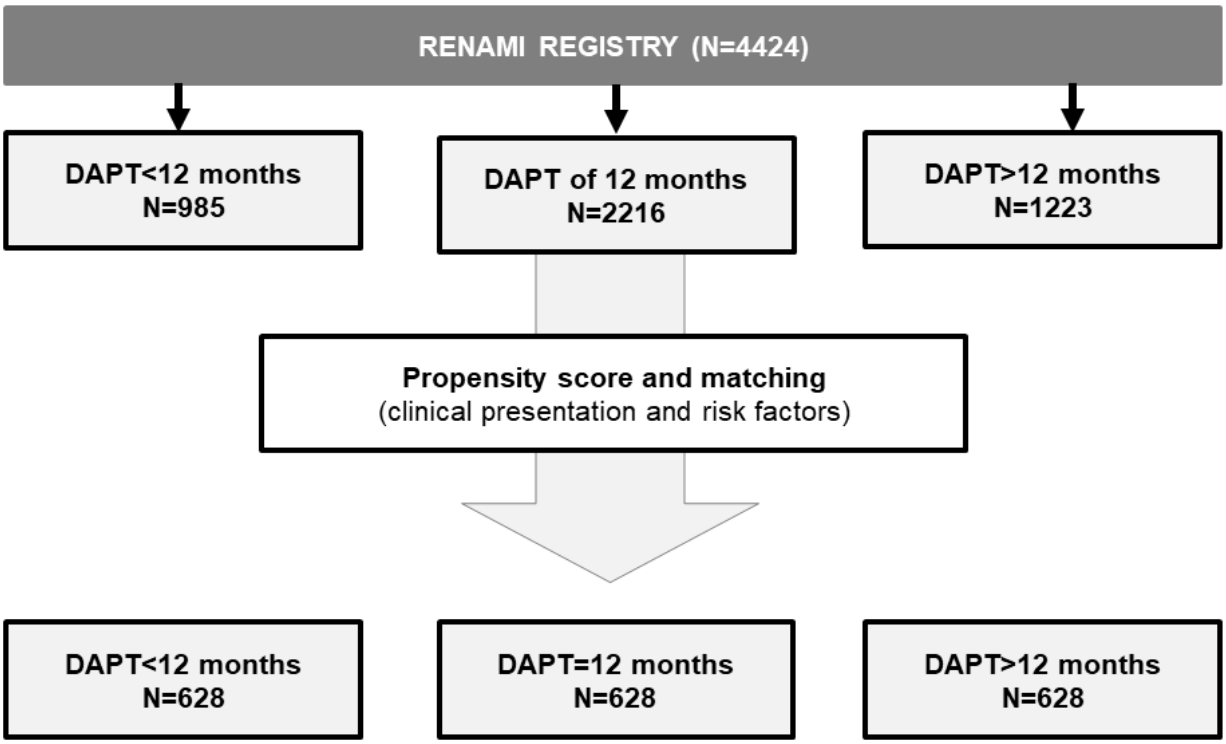


Figure 1. Design of the study

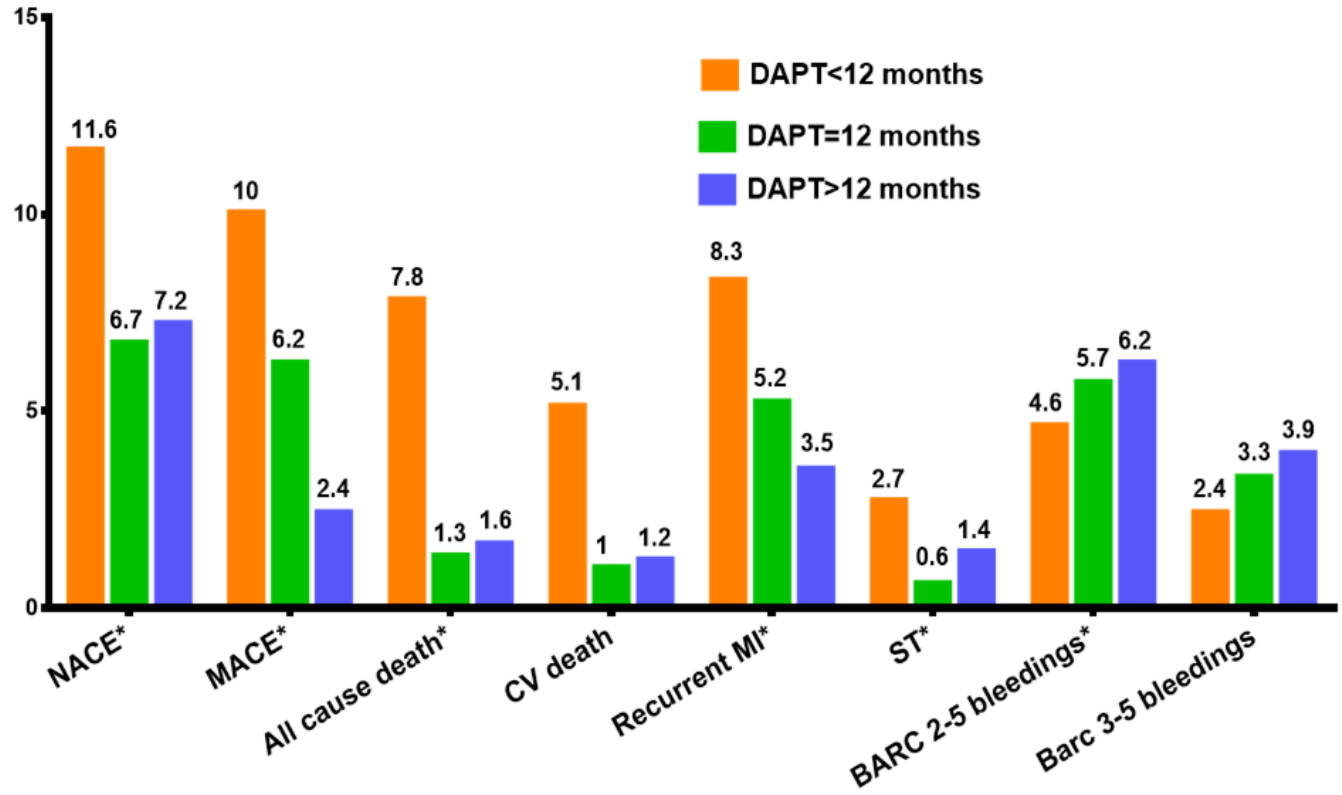
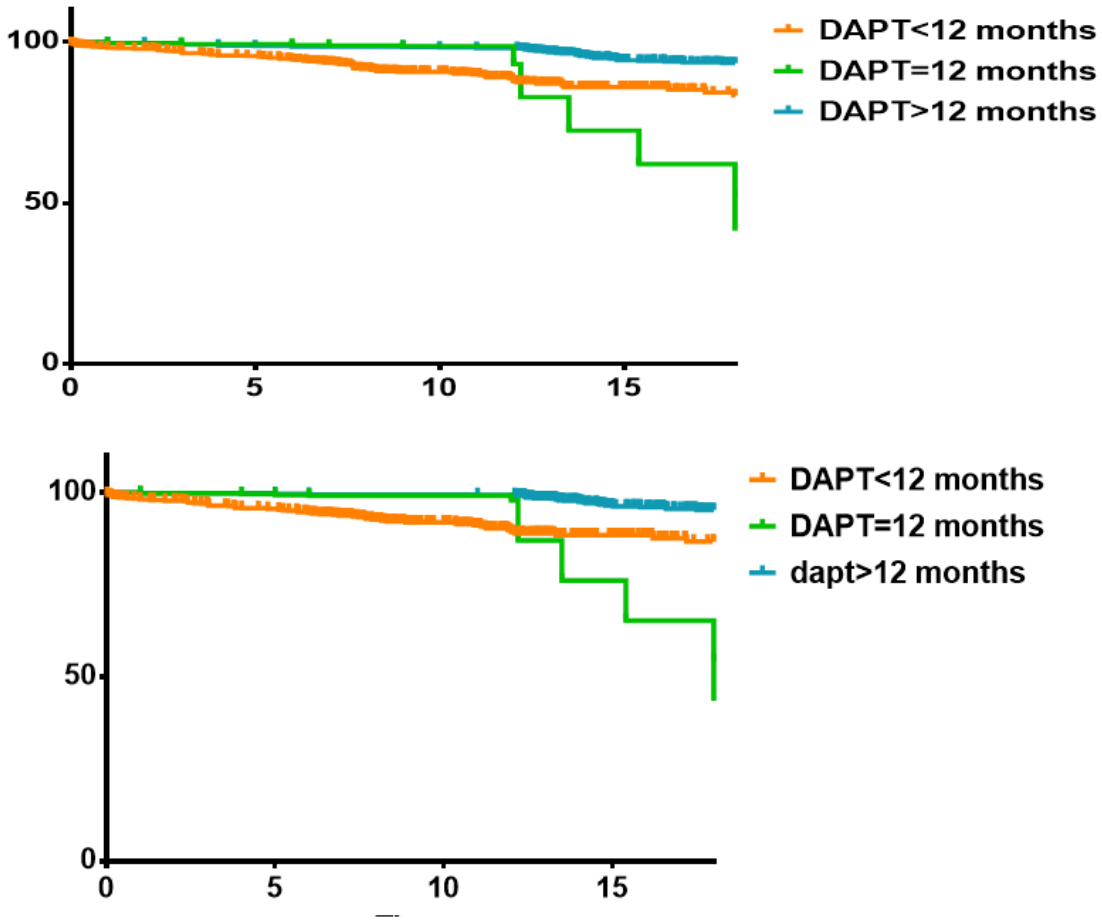


Figure 2. Long term outcome.* with significant difference overall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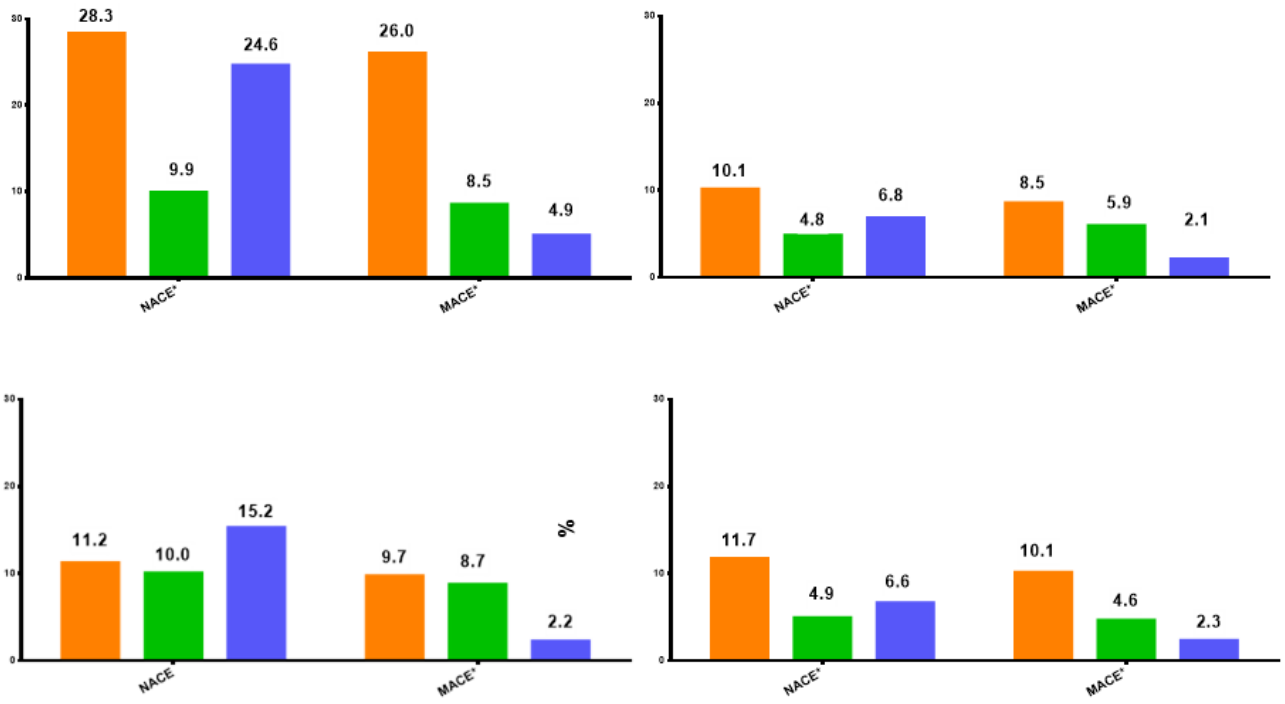

Figure 3. Long term composite outcome for:
-above: patients older (left) and younger (right) than 75 years old
-below: female (left) and male (right)

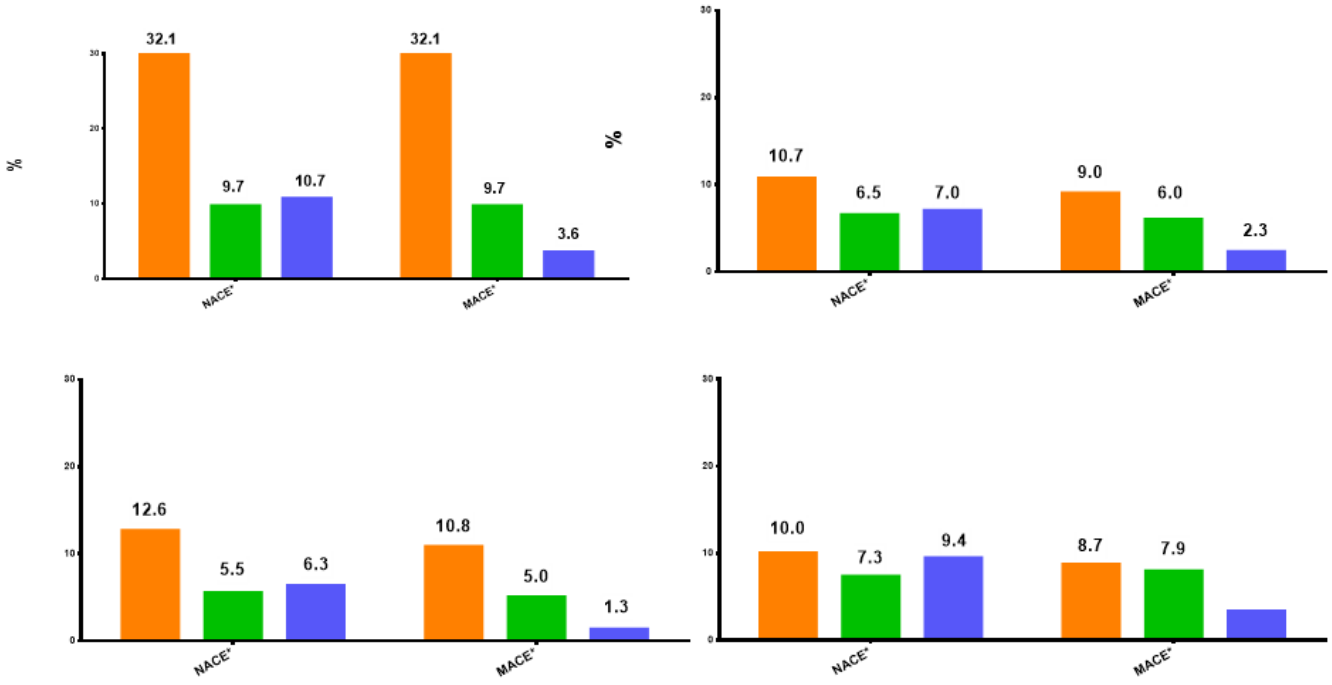

Figure 4. Long term composite outcome for:
-above: patients with creatinine >1.5 mg/dl (left) and lower (right)
-below: patients with STEMI (left) vs. NSTEMI-ACS (right)