# Efficacy and safety of Clopidogrel, Prasugrel and Ticagrelor in ACS patients treated with PCI: a propensity score analysis of the RENAMI and BleeMACS registries

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# Efficacy and Safety of Clopidogrel, Prasugrel and Ticagrelor in ACS Patients Treated with PCI: A Propensity Score Analysis of the RENAMI and BleeMACS Registries

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**Abstract.**

**Introduction** Real life data comparing clopidogrel, prasugrel and ticagrelor for unselected patients undergoing PCI (Percutaneous Coronary Intervention) for ACS (Acute Coronary Syndrome) are lacking, as well as temporal distribution of ischemic and bleeding risks.

**Methods.** Consecutive ACS patients treated with PCI enrolled in Bleemacs and Renami registries were enrolled. One-year Net Adverse Clinical Events (NACE - a composite and mutual exclusive end point of all cause death, myocardial infarction and BARC 3-5 bleeding) was the primary end-point, while Major Adverse Cardiovascular Events (MACE - a composite and mutual exclusive end point of death and MI) was the secondary one along with their single components. Patients were stratified into three groups: clopidogrel, prasugrel and ticagrelor and three comparisons were performed with propensity score with matching. Instantaneous daily bleeding and ischemic rates were calculated for each group.

**Results.** A total of 14105 patients (71.2%) were treated with clopidogrel, 2364 patients (11.9%) with prasugrel and 3356 patients (16.9%) with ticagrelor. After the first comparison, 1479 (67.2%) patients were treated with clopidogrel and 721 (32.8%) with prasugrel. Then 1831 (69.7%) patients were treated with clopidogrel and 798 (30.3%) with ticagrelor, and finally 529 patients each for ticagrelor and prasugrel with similar baseline and interventional features were considered. At one year, prasugrel reduced incidence of NACE (4.2% *vs.* 7.6%, p 0.002) and of MACE compared to clopidogrel (2.6% *vs.* 5.2%, p 0.007). Ticagrelor decreased rates of MACE compared to clopidogrel (2.7% *vs*. 6.2%, p<0.001), but not of NACE (6.6% vs. 8.7%, p 0.07). Ticagrelor presented similar performance in terms of MACE compared to prasugrel (2.8% *vs.* 2.4%, p 0.56), with a trend towards reduction of MI (0.2% *vs.* 0.4%, p 0.56) but with higher risk of BARC 3-5 bleedings (3.8% *vs.* 1.7%, p 0.04). At daily risk analysis, (1) clopidogrel presented a binomial distribution with a peak of ischemic risk at 3 months which decreased towards

bleedings, (2) prasugrel a constant equivalence between opposite risks, and (3) ticagrelor constantly reduced recurrent MIs despite higher risk of BARC 3-5 events.

**Conclusion.** In real life, ticagrelor is more effective in reducing ischemic events during the first year after ACS despite an increased risk of major bleedings, while prasugrel assures a better balance between ischemic and bleeding recurrent events.

## INTRODUCTION

ACSs (Acute Coronary Syndromes) represent the leading cause for mortality and morbidity in Western Countries. In last years, PCI (Percutaneous Coronary Intervention) and DAPT (Dual Antiplatelet Therapy) have dramatically improved outcomes, decreasing incidence of recurrent events (1-8)

Regarding DAPT, prasugrel and ticagrelor have emerged as convincing alternatives to clopidogrel, due to a decrease in ischemic events, despite an augmented risk of bleedings (9,10). Physicians, both in acute setting and in ambulatory management of these patients, have to select (i) the most appropriate time duration of DAPT for ACS patients, and (ii) the P2Y12 inhibitor drug to be administered. While an individualized approach represents the most convincing solution to the first issue, less data have been provided for the second issue (11-14). The PRAGUE-18 (15,16), till now the only RCT (Randomized Controlled Trial) comparing prasugrel and ticagrelor, enrolled 1230 patients demonstrating both at 30 days and at one year follow up similar results in terms of recurrent MI and bleedings. This study was underpowered for single events (it was finished prematurely after an interim analysis) and excluded high risk patients like those older than 75 years and those with contraindication to prasugrel. A recent large multicenter study demonstrated similar outcomes after propensity score with matching between prasugrel and ticagrelor, although this analysis was limited at 30 days. (17)

Moreover, the recent published TOPIC trial suggested the safety of an antiplatelet strategy based on de-escalation from ticagrelor to clopidogrel after one month of PCI for ACS (18), stressing even more the need of understanding the true daily risk of ischemic *vs.* bleeding events in ACS patients according to different antiplatelet regimen (19).

Aiming at bridging this gap of knowledge, here we present the results of a propensity score analysis of the Bleemacs and the Renami registries (20,21) where one-

year outcomes and daily risk of ACS patients treated with clopidogrel, prasugrel and ticagrelor (22) are compared and discussed.

## METHODS

### Study population.

The study population was selected from the RENAMI and BleeMACS registry. The first extended from 2012 to 2016, including 4425 patients, from 12 European centers, while the second including 15,401 consecutive patients, between 2003 and 2014, from 15 tertiary hospitals in Europe, Asia, and North and South America (Germany, Netherlands, Poland, Spain, Italy, Greece, Japan, China, Canada and Brazil).

Inclusion criteria for the RENAMI registry 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.

Inclusion criteria for the BleeMACS registry were: all consecutive patients discharged alive after admission for ACS, including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) diagnosed according to European Society of Cardiology (ESC) guidelines. All patients underwent coronary angiography for ACS and were treated with DAPT using aspirin and either clopidogrel, ticagrelor, or prasugrel. Patients who died during hospitalization or those who did not undergo in-hospital PCI were not considered in BleeMACS.

### Clinical variables.

Clinical (burden of cardiovascular risk factors, clinical presentation) and interventional data (access, kind of coronary disease and treatment, in particular pharmacological therapy) were collected and supervised by a trained study coordinator in

each center along with outcome data. The institutional review board of each center approved participation in RENAMI and BleeMACS registry.

**Cohorts of interests.**

All patients were stratified according to the P2Y12 antagonists used at discharge, as follows:

- Clopidogrel - group 1;
- Prasugrel - group 2;
- Ticagrelor - group 3.

Patients without DAPT or those shifting between various groups were excluded from the present analysis.

**End-point and follow-up.**

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

Net adverse clinical events (NACE - a composite and mutual exclusive end point of all cause death, myocardial infarction and BARC 3-5 bleeding) were the primary end-point, while Major adverse cardiovascular events (MACE - a composite and mutual exclusive end point of death and MI) were the secondary one. Single components of NACE and MACE and in-hospital outcomes were co-secondary end points, along with stent thrombosis, and Bleeding Academic Research Consortium (BARC) 2-5 bleedings (23).

Subgroup analysis for NACE and MACE were performed for gender, age more than 75 years old and clinical presentation (STEMI, NSTEMI and ACS).

Follow up was stopped after 12 months from the index event.

**Statistical analysis.**

Continuous and categorical variables were reported as mean (standard deviation), or median (interquartile ranges) and percentage, respectively. One-way Analysis of Variance (ANOVA) was used to assess differences in baseline, procedural and clinical variables between the three treatment groups (clopidogrel, prasugrel, ticagrelor) for continuous variables. Fisher's exact test was adopted in case of categorical variables. A nearest neighbor propensity score matching accounting for baseline, procedural and clinical covariates was adopted for the following comparisons:

· Prasugrel *vs.* clopidogrel - 1-to-4 match, no calipers adopted;

· Ticagrelor *vs.* clopidogrel - 1-to-4 match, no calipers adopted;

· Ticagrelor *vs.* prasugrel - 1-to-1 match, with specified propensity score calipers (0.05).

Considering primary and secondary endpoints as time-to-event outcomes (survival outcomes), Cox regression analysis was used to estimate risk ratio (hazard ratio) between different treatments.

Instantaneous daily bleeding and ischemic rates were calculated dividing the number of events occurred in a specific day post PCI for ACS by the number of exposed people on the same day. As the registries we analyzed took in consideration only single events, patients who had an event were excluded from the population at risk thereafter. The average risk was defined as the total number of events in that interval divided by the total number of patient-days of follow-up (i.e. the total number minus loss at follow-up,

deaths and people who already had an event). After calculation of daily risks, paired t test was utilized to verify if there was a significant difference in term of ischemia/bleeding during the various time frame and subgroups. P values < 0.05 were considered statistically significant. Statistical analysis was performed using STATA 12.0 (StataCorp, 2011).

## RESULTS

19825 patients from RENAMI e BleeMACS registry, with available data about type of DAPT, were included in the analysis. A total of 14105 patients (71.2%) were treated with clopidogrel, 2364 patients (11.9%) with prasugrel and 3356 patients (16.9%) with ticagrelor (**see figure 1 and appendix, web only tables 1**).

### Baseline, clinical, procedural and pharmacological features

*Before propensity score matching.*

Before matching, patients treated with prasugrel were younger, less frequently females, with a lower burden of cardiovascular risk factor, STEMI being the most frequent clinical presentation, radial access was the preferred approach. Patients treated with clopidogrel were older, more frequently females, better ejection fraction. Patients treated with ticagrelor presented more often with a multivessel disease (**see appendix, web only tables 1 and 2).**

Both study groups treated with P2Y12 antagonists (prasugrel and ticagrelor) had a high rate of receiving optimal medical therapies. On the contrary, in clopidogrel group a significantly lower percentage of patients received adequate medical therapy, in particular as regards beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers **(see appendix, web only table 3).**

*After propensity score matching.*

In the first comparison, which includes 1479 (67.2%) patients treated with clopidogrel and 721 (32.8%) treated with prasugrel, baseline, clinical, procedural and

pharmacological features did not differ after propensity score with matching, with the exclusion of proton pump inhibitor (PPI). Median age in these 2 groups was 64.1 and 58.4 years, respectively (P value 0.298). Diabetes mellitus was the 26.3% in group 1 and 20.4% in group 2 (P value 0.85), 58.4% and 70.1% being admitted with STEMI, respectively (P value 0.943). Just under half of patients presented with multivessel disease (49.5% and 43%, respectively, P value 0.642) and around two thirds of them were managed with complete revascularization (61.1% and 67.4%,respectively, P value 0.366) **(for further details see table 1 and appendix, web only)**.

Also in the second propensity match comparison, similar features between clopidogrel group (1831 patients, 69.7%) and ticagrelor group (798 patients, 30.3%) were observed, with a mean age of 64.1 and 60.5 years, respectively, and with comparable profile of cardiovascular risk factors and clinical presentation (58.4% *vs.* 52.3% were admitted for STEMI, P value 0.483). Furthermore, no differences in term of multivessel disease (49.5% *vs.* 44.9%) and complete revascularization (61.2% *vs.* 68,4%) were reported. **(for further details see table 2 and appendix, web only).**

Finally, in the third comparison after propensity score with matching, 529 patients of each group were selected (ticagrelor and prasugrel). All the baseline and clinical features were balanced between the two groups. In particular, STEMI was the admission reason in 69.9% and 63.9%, respectively, and less than 50% had a multivessel disease (44.4% *vs.* 44.2%) and of these patients, the 65% underwent complete revascularization (65.2% *vs.* 65.8%). Also, regarding pharmacological therapy, no differences emerged **(for further details see table 3 and appendix, web only).**

**Outcomes**

*Before propensity score matching.*

At one year, prasugrel and ticagrelor significantly reduced incidence of NACE (clopidogrel 8.7%, prasugrel 4.6% and ticagrelor 5.3%, P value < 0.0001) and MACE (clopidogrel 6.2%, prasugrel 2.5% and ticagrelor 2.4%, P value < 0.0001), compared to clopidogrel. The same trend of risk reduction was observed for the single components of NACE and MACE. In particular, the observed difference was driven by rate of long-term myocardial infarction (clopidogrel 4,2%, prasugrel 1.6% and ticagrelor 1.6%, P value < 0.0001) and by rate of major bleeding (clopidogrel 3.2%, prasugrel 1.7% and ticagrelor 2.4%, P value < 0.0001). Exhaustive details can be found in the appendix, table 4.

Regarding direct comparisons, prasugrel and ticagrelor reduced the risk of NACE with respect to clopidogrel (P value < 0.0001 for both comparisons) and MACE (P value < 0.0001 for both comparisons), as detailed in the appendix, Table 5. No difference emerged in terms of primary and secondary outcomes comparing ticagrelor and prasugrel, except for a statistically significant increase in the risk of bleeding in the ticagrelor group (P value 0.035).

*After propensity score matching.*

After propensity score matching, at one year prasugrel reduced incidence of NACE (4.2% *vs*. 7.6%, p 0.002) and of MACE (2.6% *vs.* 5.2%, p 0.007), compared to clopidogrel. Ticagrelor decreased rates of MACE (2.7% *vs.* 6.2%, p<0.001), compared to clopidogrel, but not of NACE (6.6% *vs.* 8.7%, p 0.07). Ticagrelor performed similar to prasugrel, in terms of MACE (2.8% *vs.* 2.4%, p 0.56), with a trend towards reduction of MI (0.2% *vs.* 0.4%, p 0.56), but with higher risk of BARC 3-5 bleedings (3.8% *vs.* 1.7%, p 0.04). Subgroup analysis confirmed the positive trend for prasugrel in STEMI and ACS/NSTEMI

patients, while net clinical benefit was higher in patients younger than 75 years old. Furthermore, the statistically significant benefit of ticagrelor was confirmed in particular for ACS/NSTEMI patients. It should be noted that ticagrelor have a significant increase in the risk of major bleeding in elderly patients (**for further details see figures 2-6 and appendix, tables 9-12).**

**Daily risk analysis.**

Daily risk analysis highlighted an overall low average daily rate of events (MI risk 0.006%, bleeding risk 0.008%) in the analyzed population. Elderly patients (≥75 years) presented the highest average daily risk of MI and bleeding (0.01% and 0.022%, respectively) in the first year, but bleeding risk was significantly higher (average daily MI minus bleeding: -0.012%, p value 0.003) throughout the whole year, with an evident excess of bleeding in the 1$^{st}$ month (**for further details see figure 7 and appendix, figures 6-9 and appendix, tables 14,15**). Patients on Ticagrelor presented the absolute lowest average daily risk of MI (0.001%), lower than patients on Prasugrel (0.002%) and Clopidogrel (0.008%). Moreover, patients on Ticagrelor had a significantly higher daily risk of bleeding than MI throughout the year (daily MI minus bleeding -0.011%, p <0,001), but this is due to a very low risk of MI, with an acceptable average daily bleeding risk (0.012%). In patients on Clopidogrel and Prasugrel, there is no significant association between daily ischemic and bleeding risk (p values of 0.422 and 0.245, respectively). Patients who had a NSTEMI had a higher risk of subsequent MI (0.007% and 0.009%) and bleeding (0.005% and 0.008%), compared with STEMI ones *vs*.. Daily risk of MI was the highest in the first month, remaining high until the third month, and then progressively decreasing. Bleeding risk was characterized by a declining trend from the first month on. This resulted in a slightly higher MI risk compared to bleeding at around the third month, with a subsequent stabilization.

## DISCUSSION

To the best of our knowledge, this is the largest observational study aiming to compare the safety and efficacy of P2Y12 inhibitors each other. The main findings are:

1) prasugrel reduces incidence of MACE and major bleedings, resulting in an overall significant decrease of NACE compared to clopidogrel;

2) ticagrelor leads to a reduction in the long-term risk of of death and myocardial infarction, associated with a slight trend towards increased risk of major bleeding, resulting in a significant decrease of MACE rates, but only a trend for NACE;

3) prasugrel reduces NACE compared to ticagrelor due to decrease in risk of major bleeding, while ticagrelor appear more effective to reduce MI;

4) the favorable effect of use of prasugrel in terms of reduced NACE events seems to be less evident in old patients with ACS/NSTEMI at high risk of bleeding;

5) results at points 1 to 4 are confirmed at daily risk analysis, where the impact of clopidogrel is expressed by a binomial risk distribution with a peak of ischemic risk at 3 months which decreased towards bleedings, prasugrel leads to an equivalence between the two opposite risks, while ticagrelor constantly reduces recurrent MIs despite the higher risk of BARC 3-5 events.

Our results show that prasugrel emerged in a significant reduction (~50%), compared to clopidogrel, in the risk of the primary end point (all-cause death, nonfatal myocardial infarction and major bleeding). The superior antiplatelet effects compared with clopidogrel were concordant with those of TRITON-TIMI 38 (9) and with other studies (24-26). Moreover, when prasugrel was not prescribed to those patients who showed a peculiar high risk of bleeding in TRITON-TIMI (i.e., patients with extreme low body weight,

with previous stroke or older than 75 years old), it appeared even more efficacious than clopidogrel to reduce bleedings.

The benefits of ticagrelor over clopidogrel in patients with ACS in term of long term all-cause of death and MI have already been described in the PLATO (10). More interestingly, these results were reached without a significant increase in major bleedings, which can be justified in terms of its nature of reversible inhibitor (27). In previous sub analyses in PLATO study (28, 29), no interactions were observed for the treatment effect of ticagrelor versus clopidogrel on the composite end point of cardiovascular death, myocardial infarction or stroke. Nevertheless, the present study enrolled a large subset of STEMI patients with important ischemic risk, due to relevant rates of female hypertensive patients with previous MI, which can justify the aforementioned observations.

Concerning the comparison between ticagrelor and prasugrel, they both proved to be effective in reducing mortality and myocardial infarction as described in other previously published studies (30-35). In another registry, the lower incidence of major bleeding amongst patients treated with prasugrel was ascribed to the prescription to patients with a lower risk (30), although in our work the reduction remains significant after propensity score analysis. The reduced risk of major bleeding observed in prasugrel patients is consistent to that observed in previous studies (30, 31), and together with a trend towards a decrease in MI with ticagrelor may offer physicians interesting insights for personalization of drugs. Ticagrelor may offer more benefit in a high thrombotic risk setting, while prasugrel seems to be more efficacious when bleeding risk offsets ischemic risk.

At the subgroup analysis, prasugrel was superior to clopidogrel, regardless of clinical presentation, as reported in previous studies (36. 37). This superiority in terms of reduction of the primary outcome is more relevant in patients younger than 75 years, while

due to the increased risk of major bleeding in patients older than 75 years, this benefit is lost. This may be more evident analyzing the huge difference in terms of average age between the 2 subgroups (56.5 years against 80.9 years) and it is consistent with a previous RCT (38). Moreover, as demonstrated by a recent RCT (39), in patients over 75 years, prasugrel should be used at a reduced dose (5mg), because was superior to standard dose clopidogrel in these ACS population undergoing PCI. The benefit of ticagrelor on clopidogrel is more evident in patients discharged with the diagnosis of ACS/NSTEMI, due to the significant advantage in term of MACE without a significant increase in major bleeding. The observation of similar efficacy and safety endpoints between ticagrelor and prasugrel, also in subgroup analyzes. was in accord with a recent randomized trial (15).

The daily risk analysis showed an average low daily risk of MI and bleeding (0.006% and 0.008% respectively). As expected, older patients (≥75 years) had the greatest risk of both ischemia and bleeding, with the latter significantly prevailing (0.01% and 0.022%, p 0.003). The augmented ischemic risk can be easily explained by more complex coronary disease, the presence of prothrombotic state (cancer, chronic inflammation), reduced drug compliance; the augmented bleeding risk by the presence of comorbidities predisposing to it (e.g. gastrointestinal ulcer disease, cancer, predisposition to trauma and falls). Concerning antiplatelet drugs, clopidogrel has, as expected, the highest ischemic daily risk and elevated bleeding, with a balance between the two risks (0.008% and 0.009%, p 0.422). Prasugrel has shown a balanced low risk of MI and bleeding (0.002% and 0.004%, p 0.245). Ticagrelor is associated with the lowest daily risk of recurrent MI, with a slightly augmented risk of bleeding, resulting in a significantly excess of bleeding risk throughout all year (0.001% and 0.012%, respectively, p<0.001).

The temporal analysis shows, similar to reported in a recent study (22), a high ischemic risk in the first three months then declining, and a bleeding risk declining from the first month on, resulting in a relative peak of MI around the third month for all the subgroups analyzed. This confirms, on one side, that thrombotic risk decreases steeply from the third month. On the other side, it is reasonable to think that patients who are prone to bleeding would do that in the first months after beginning of DAPT (e.g. unknown malignancies, cerebral amyloid angiopathy, and gastric diseases). This implies that DAPT prolongation could be relatively safe but could provide only a modest benefit, and on the other side that shortening DAPT could increase MI risk by little but avoiding relatively few cases of bleeding. These findings enforce the concept of DAPT personalization, in order to identify those patients who present a disproportionate bleeding/ischemic risk, a disproportion who cannot be observed in our general analysis of daily risks.

## LIMITATIONS

The present paper shares some limitations. First of all, this is not a randomized controlled trial: drugs use are at the discretion of the physician, and so the comparisons should be interpreted with carefulness due to the possible interplay of unmeasured confounding variables; although, using a correction using a propensity score greatly reduces the risk of misinterpretations. Second, being an observational study, these results can only be interpreted as descriptive and hypothesis-generating for subsequent scientific studies (clinical trials or meta-analyses). Third, there may be some degree of selection bias, which can partly justify the reduced bleeding risk of patients being treated with prasugrel or ticagrelor.

## CONCLUSIONS

In real life comparison, ticagrelor seemed more effective to reduce ischemic events during first year after ACS despite an increased risk of major bleedings, while prasugrel seemed to offer a better balance between ischemic and bleeding recurrent events.

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## Tables

## Table 1. Baseline, Clinical and procedural characteristics and in-hospital outcomes (post propensity score analysis)

| | Clopidogrel (1479 -67.23%) | Prasugrel (721 – 32.8 %) | P value |
|---|---|---|---|
| Age (years) | 64.05 | 58.37 | 0.298 |
| Female n. (%) | 21.7 | 15.6 | 0.687 |
| DM n. (%) | 26.3 | 20.4 | 0.85 |
| HTN n. (%) | 57.4 | 47.2 | 0.845 |
| DLP n. (%) | 49.8 | 43.6 | 0.354 |
| PAD (%) | 8.1 | 3.1 | 0.765 |
| Mean Creatinin | 0.96 | 0.93 | 0.831 |
| Prior AMI (%) | 11.9 | 13.8 | 0.806 |
| Prior PCI (%) | 9.8 | 13.7 | 0.705 |
| Prior CABG (%) | 3.4 | 1.3 | 0.587 |
| Prior Stroke (%) | 6.5 | 0.8 | 0.819 |
| Prior Bleeding (%) | 3.8 | 3.4 | 0.830 |
| Malignancy (%) | 6.1 | 1.3 | 0.762 |
| STEMI (%) | 58.4 | 70.1 | 0.943 |
| Hb (SD) | 14.0 | 14.1 | 0.933 |
| LVEF (SD) | 53.5 | 48.2 | 0.055 |
| Radial Access (%) | 39.5 | 62.7 | 0.828 |
| Thrombolysis (%) | 2,4 | 7.6 | 0.921 |
| Multivessels disease (%) | 49.5 | 43.0 | 0.642 |
| DES (%) | 48.4 | 24.9 | 0.702 |
| Complete revascularization (%) | 61.1 | 67.4 | 0.366 |
| In-hospital MI (%) | 2.1 | 0.1 | 0.850 |
| In-hospital Bleeding (%) | 5.9 | 2.6 | 0.577 |
| NACE (%) | 7.6 | 4.2 | 0.002 |
| MACE (%) | 5.1 | 2.6 | 0.007 |
| Death (%) | 5.1 | 2.1 | 0.001 |
| Long-term MI (%) | 3.0 | 0.8 | 0.003 |
| Major bleeding (%) | 3.0 | 1.5 | 0.034 |

DM: Diabetes Mellitus; HTN: Hypertension; DLP: Dyslipidemia, PAD: peripheral artery disease; CKD: Chronic Kidney Disease, SD: standard deviation; PriorAMI: Prior Acute Myocardial Infarction; PriorPCI: percutaneous coronary intervention, Prior CABG: coronary artery bypass grafts; STEMI: ST elevation myocardial infarction; Hb: Haemoglobin; LVEF: left ventricle ejection fraction; DES: drug eluting stent; MI: myocardial infarction; MACE: major adverse cardiac events; NACE: net adverse clinical event.

## Table 2. Baseline, Clinical and procedural characteristics and in-hospital outcomes (post propensity score analysis)

| | Clopidogrel (1831 – 69.7%) | Ticagrelor (798 – 30.3%) | P value |
|---|---|---|---|
| Age (years) | 64.05 | 60.51 | 0.611 |
| Female n. (%) | 21.7 | 17.8 | 0.805 |
| DM n. (%) | 26.3 | 24.2 | 0.919 |
| HTN n. (%) | 57.4 | 55.8 | 0.801 |
| DLP n. (%) | 49.8 | 42,4 | 0.879 |
| PAD (%) | 8.1 | 1.9 | 0.928 |
| Mean Creatinin (SD) | 0.97 | 0.99 | 0.583 |
| Prior AMI (%) | 11.9 | 8.1 | 0.799 |
| Prior PCI (%) | 9.8 | 10.2 | 0.755 |
| Prior CABG (%) | 3.4 | 1.7 | 0.922 |
| Prior Stroke (%) | 6.5 | 4.1 | 0.799 |
| Prior Bleeding (%) | 3.8 | 6.6 | 0.291 |
| Malignancy (%) | 6.1 | 1.9 | 0.291 |
| STEMI (%) | 58.4 | 52.3 | 0.483 |
| Hb (SD) | 14.0 | 13.99 | 0.957 |
| LVEF (SD) | 53.5 | 50.9 | 0.669 |
| Radial Access (%) | 39.5 | 42.2 | 0.284 |
| Thrombolysis (%) | 2.4 | 4.9 | 0.313 |
| Multivessels disease (%) | 49.5 | 44.9 | 0.802 |
| DES (%) | 48.3 | 23.2 | 0.724 |
| Complete revascularization (%) | 61.1 | 68.4 | 0.678 |
| In-hospital MI (%) | 2.1 | 1.1 | 0.808 |
| In-hospital Bleeding (%) | 5.9 | 4.5 | 0.758 |
| NACE (%) | 8.7 | 6.6 | 0.070 |
| MACE (%) | 6.2 | 2.8 | <0.001 |
| Death (%) | 6.2 | 2.6 | <0.001 |
| Long-term MI (%) | 3.3 | 0.4 | <0.001 |
| Major bleeding (%) | 3.3 | 4.3 | 0.212 |

DM: Diabetes Mellitus; HTN: Hypertension; DLP: Dyslipidemia, PAD: peripheral artery disease; CKD: Chronic Kidney Disease, SD: standard deviation; PriorAMI: Prior Acute Myocardial Infarction; PriorPCI: percutaneous coronary intervention, Prior CABG: coronary artery bypass grafts; STEMI: ST elevation myocardial infarction; Hb: Haemoglobin; LVEF: left ventricle ejection fraction; DES: drug eluting stent; MI: myocardial infarction;MACE: major adverse cardiac events; NACE: net adverse clinical event.

## Table 3. Baseline, Clinical and procedural characteristics and in-hospital outcomes (post propensity score analysis)

| | Ticagrelor (529 – 50%) | Prasugrel (529 – 50%) | P value |
|---|---|---|---|
| Age (years) | 57.7 | 58.6 | 0.597 |
| Female n. (%) | 14.8 | 15.1 | 0.664 |
| DM n. (%) | 20.8 | 21.6 | 0.881 |
| HTN n. (%) | 48.4 | 50.7 | 0.623 |
| DLP n. (%) | 46.1 | 46.7 | 0.579 |
| PAD (%) | 3.3 | 2.7 | 0.692 |
| Mean Creatinin (SD) | 0.92 | 0.94 | 0.759 |
| Prior AMI (%) | 14.3 | 9.5 | 0.835 |
| Prior PCI (%) | 14.4 | 10.9 | 0.546 |
| Prior CABG (%) | 1.6 | 1.3 | 0.795 |
| Prior Stroke (%) | 0.7 | 1.0 | 0.102 |
| Prior Bleeding (%) | 3.6 | 4.5 | 0.772 |
| Malignancy (%) | 1.1 | 1.3 | 1.000 |
| STEMI (%) | 69.9 | 63.9 | 0.479 |
| Hb (SD) | 14.1 | 14. 1 | 0.523 |
| LVEF (SD) | 49.2 | 49.7 | 0.685 |
| Radial Access (%) | 62.1 | 54.1 | 0.293 |
| Thrombolysis (%) | 7.8 | 8.3 | 1.000 |
| Multivessels disease (%) | 44.2 | 44.9 | 0.853 |
| DES (%) | 23.9 | 17.8 | 0.412 |
| Complete revascularization (%) | 65.2 | 65.8 | 0.948 |
| In-hospital MI (%) | 0.1 | 0.2 | 0.318 |
| In-hospital Bleeding (%) | 3.1 | 3.4 | 0.520 |
| NACE (%) | 6.4 | 4.0 | 0.072 |
| MACE (%) | 2.8 | 2.3 | 0.559 |
| Death (%) | 2.8 | 2.1 | 0.427 |
| Long-term MI (%) | 0.2 | 0.4 | 0.561 |
| Major bleeding (%) | 3.8 | 1.7 | 0.038 |

DM: Diabetes Mellitus; HTN: Hypertension; DLP: Dyslipidemia, PAD: peripheral artery disease; CKD: Chronic Kidney Disease, SD: standard deviation; PriorAMI: Prior Acute Myocardial Infarction; PriorPCI: percutaneous coronary intervention, Prior CABG: coronary artery bypass grafts; STEMI: ST elevation myocardial infarction; Hb: Haemoglobin; LVEF: left ventricle ejection fraction; DES: drug eluting stent; MI: myocardial infarction; MACE: major adverse cardiac events; NACE: net adverse clinical event.

## Table 4. Multivariate Cox regression analysis.

| | HR (prasugrel vs clopidogrel) | P value | HR (ticagrelor vs clopidogrel) | P value | HR (ticagrelor vs prasugrel) | P value |
|---|---|---|---|---|---|---|
| NACE | 0.535 | 0.002 | 0.744 | 0.062 | 1.631 | 0.078 |
| MACE | 0.511 | 0.009 | 0.436 | <0.001 | 1.249 | 0.566 |
| Death | 0.403 | 0.001 | 0.418 | <0.001 | 1.365 | 0.433 |
| MI | 0.277 | 0.003 | 0.112 | <0.001 | 0.496 | 0.568 |
| Major Bleeding | 0.496 | 0.037 | 1.299 | 0.223 | 2.247 | 0.044 |

HR: Hazard ration; MI: myocardial infarction; MACE: major adverse cardiac events; NACE: net adverse clinical event;

**FIGURES**

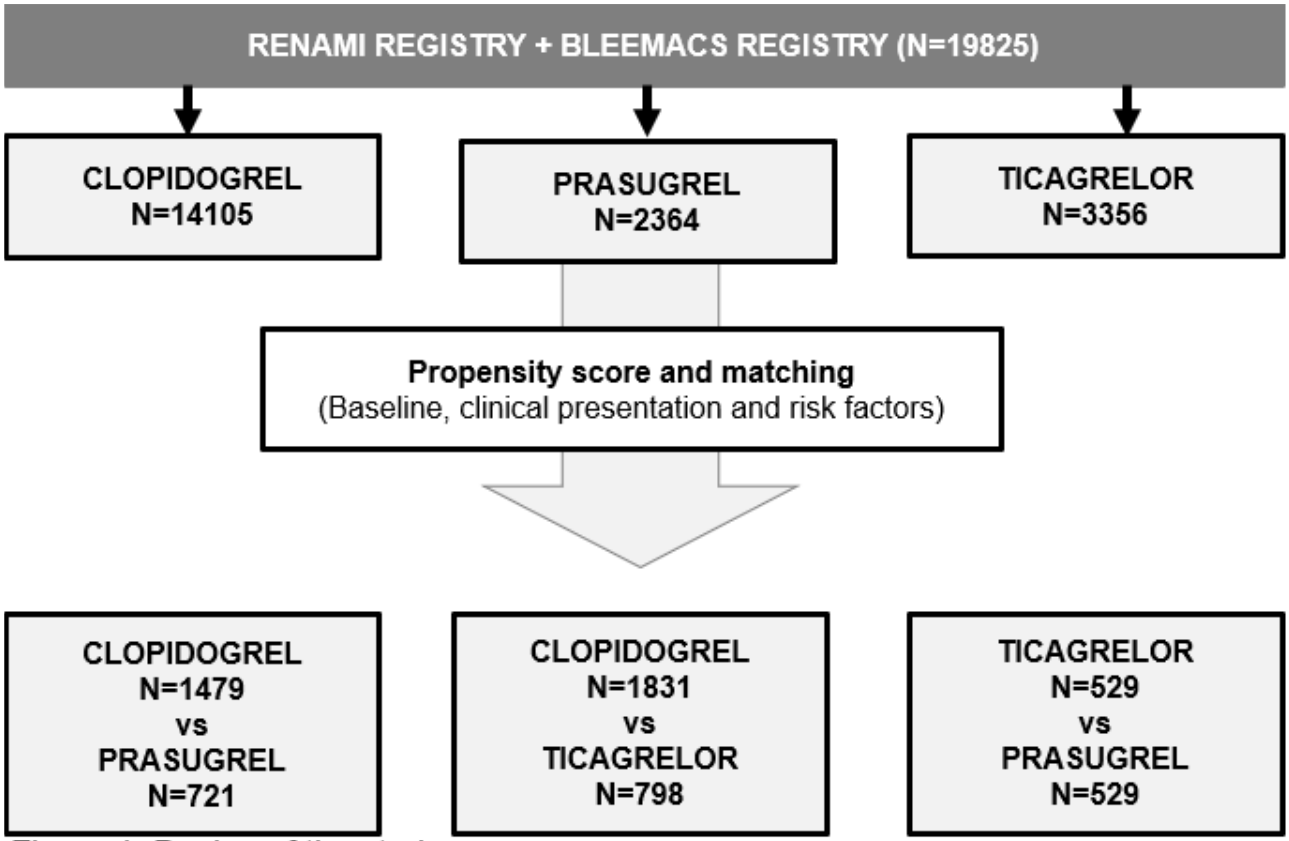



Figure 1. Design of the study

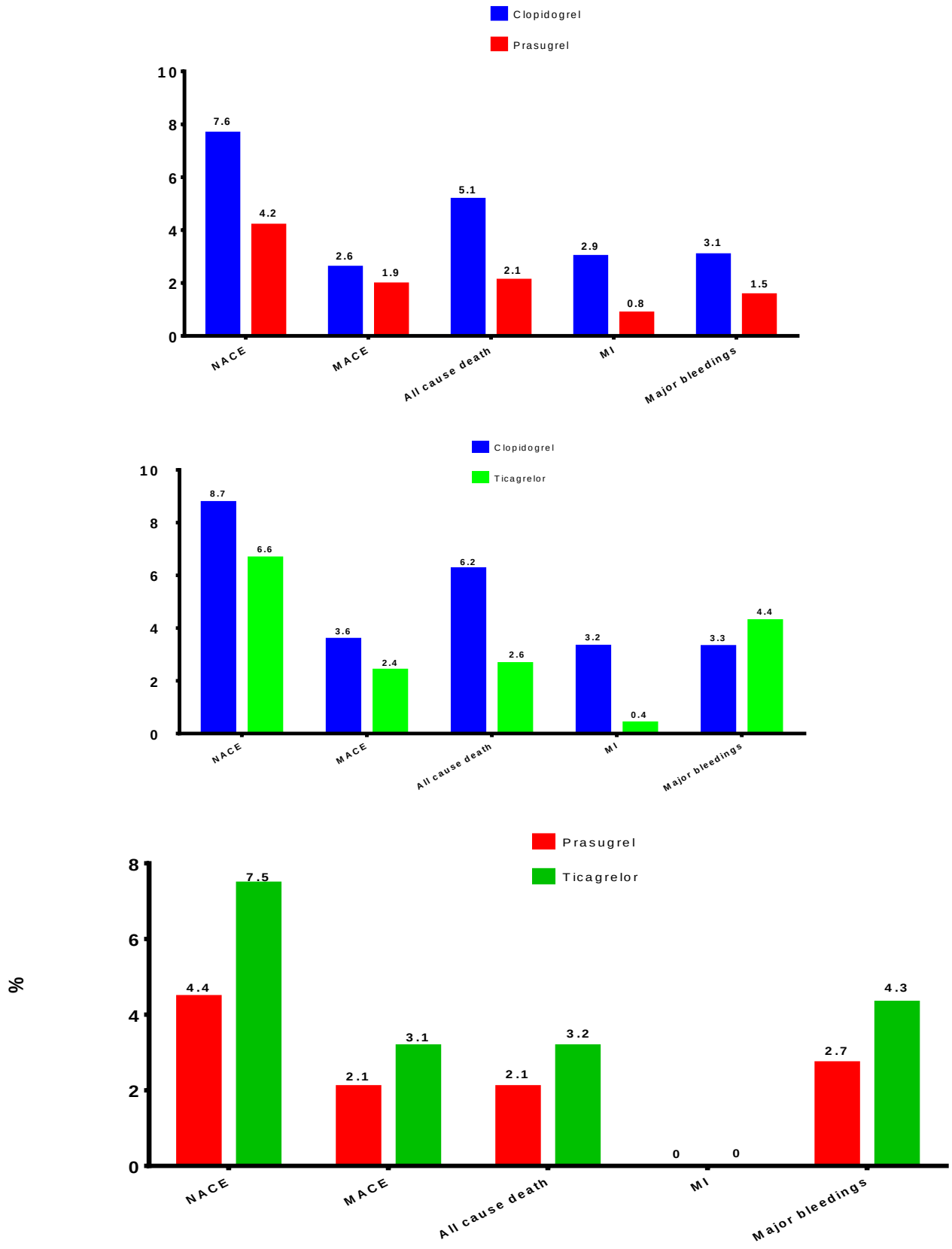



Figure 2. Incidence (%) of adverse outcomes after propensity score.

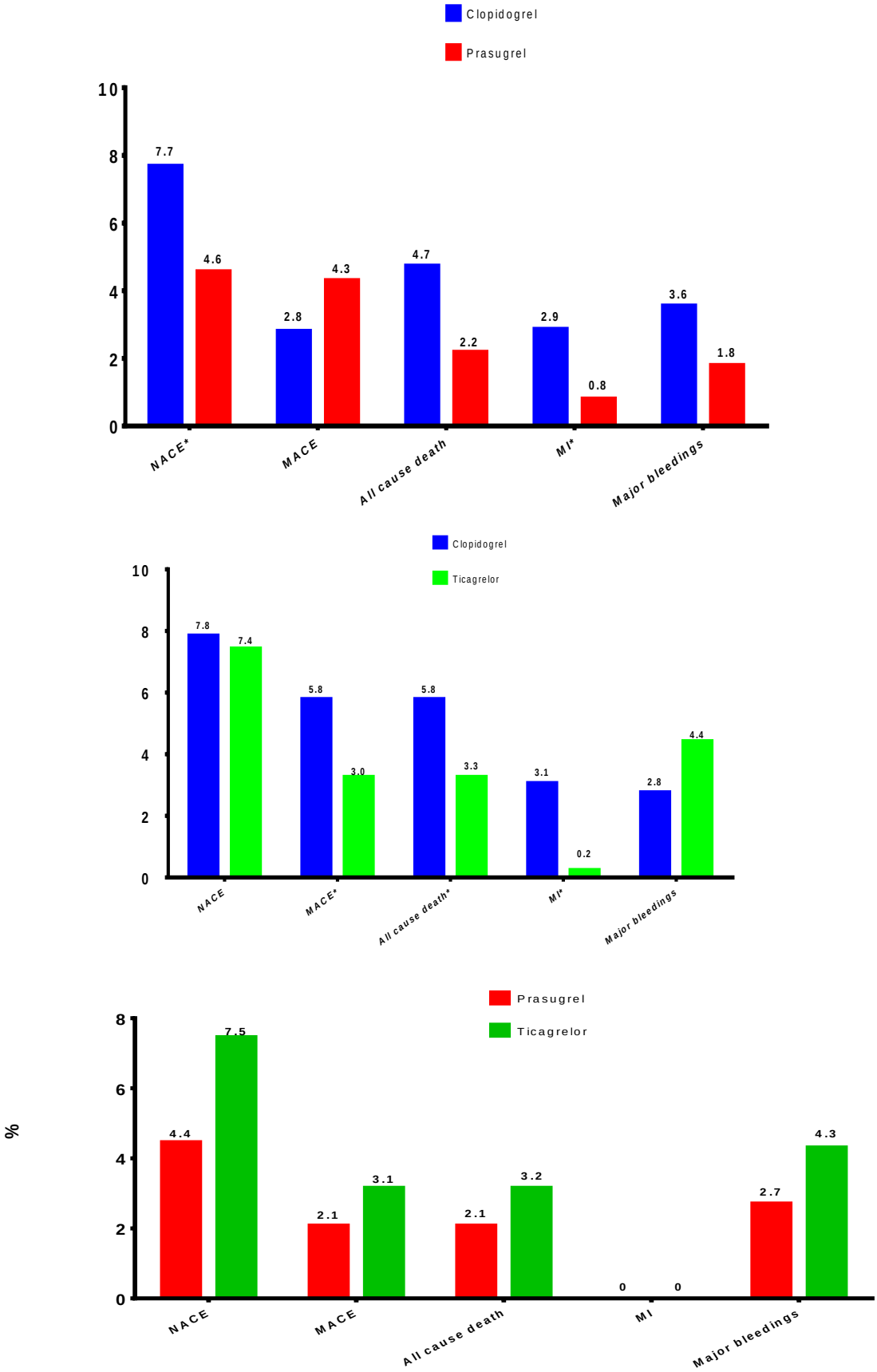



Figure 3. Incidence (%) of adverse outcomes for STEMI patients.

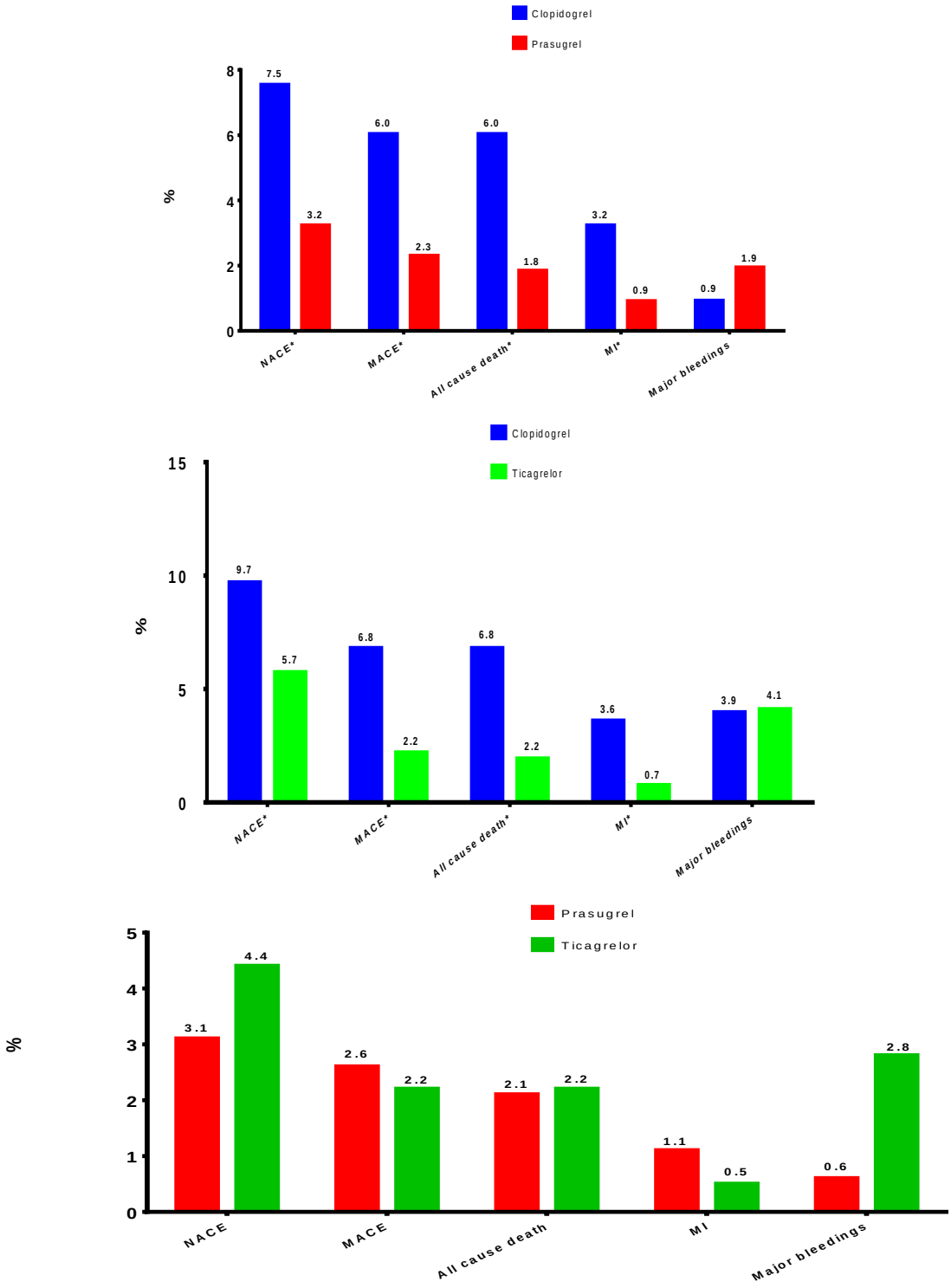



Figure 4. Incidence (%) of adverse outcomes for NSTEMI-ACS patients

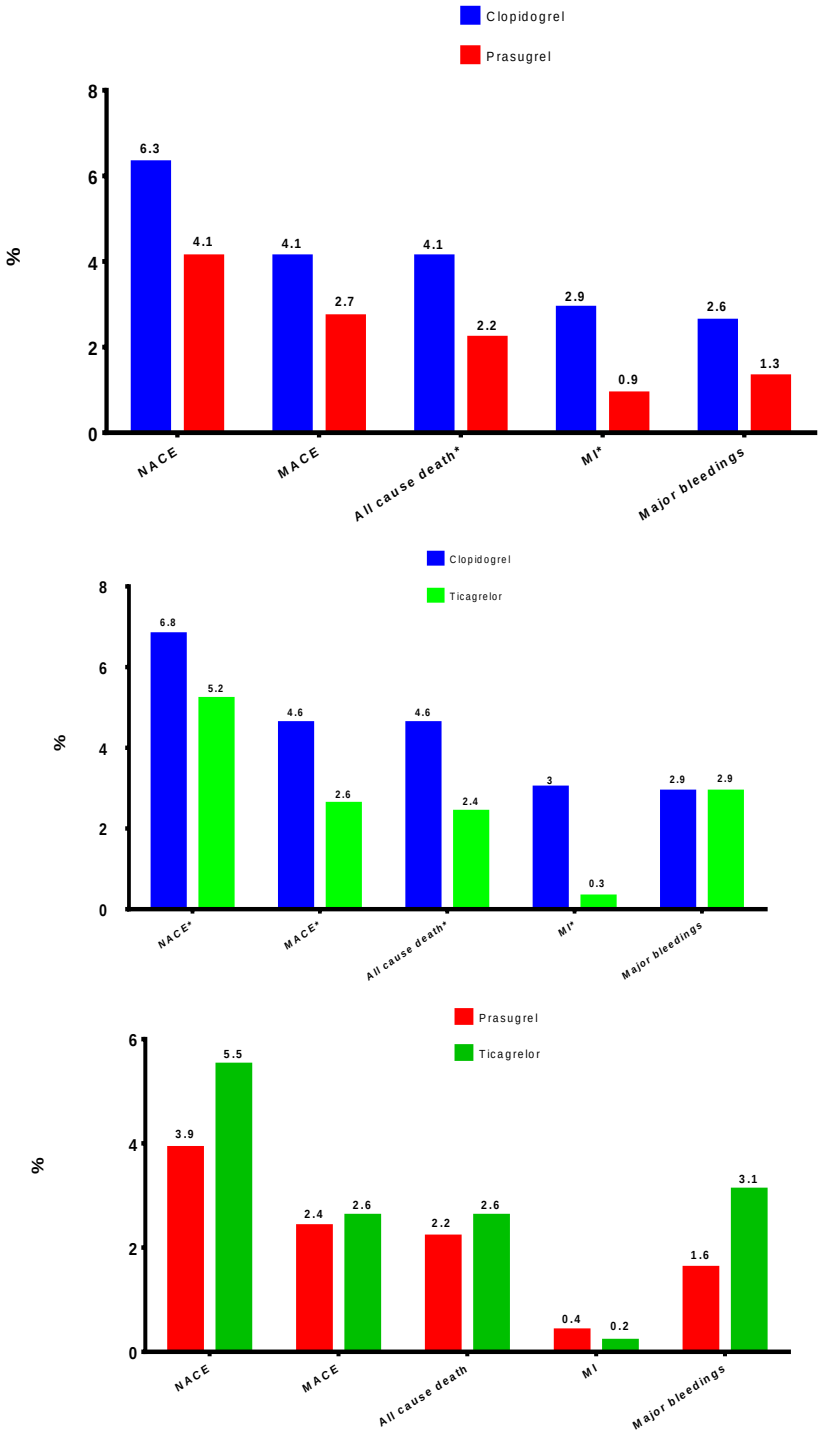



Figure 5. Incidence (%) of adverse outcomes for patients younger than 75 years old

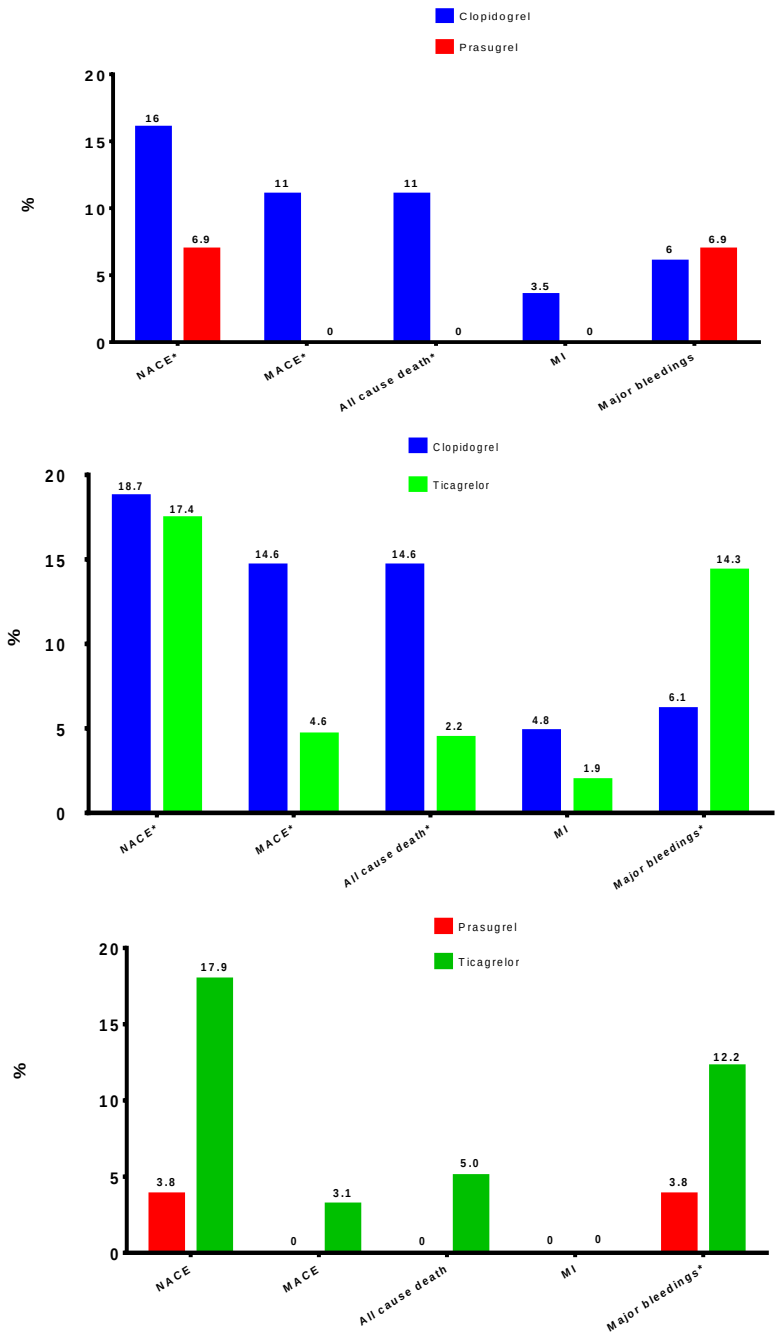
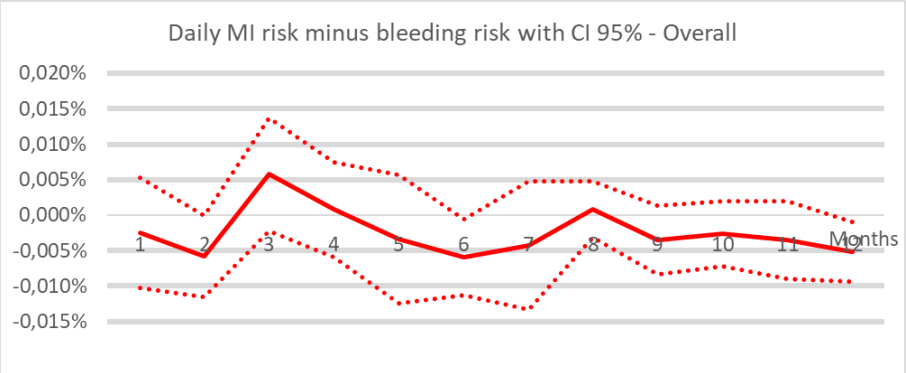
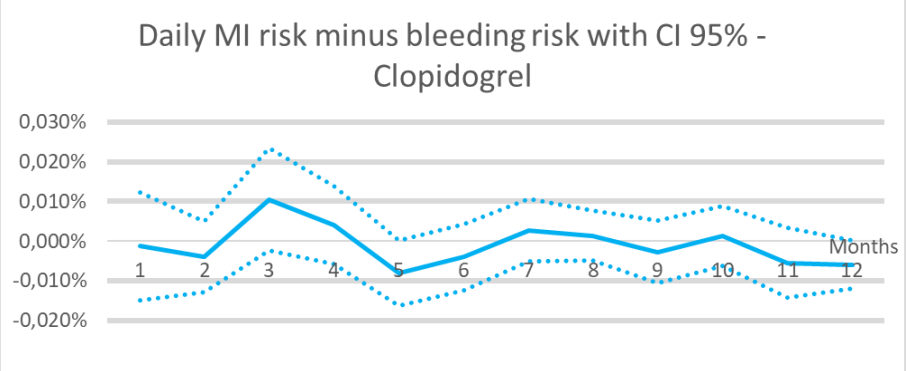



Figure 6. Incidence (%) of adverse outcomes for patients older than 75 years old

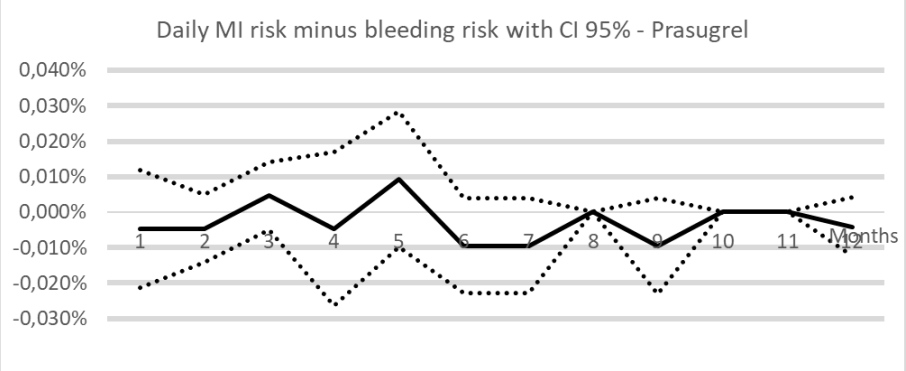
**A) Overall**




**B) Clopidogrel**




**C) Prasugrel**




**D) Ticagrelor**

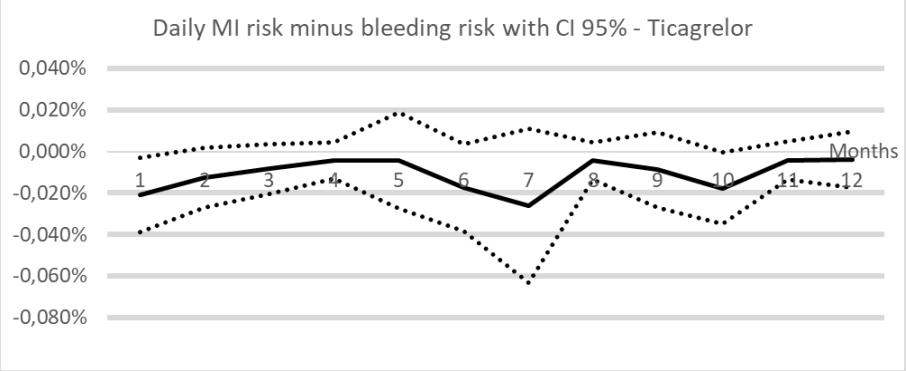



Figure 7. Daily MI risk minus bleeding risk with CI 95% per month in the first year