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

"Real world data of Prasugrel vs Ticagrelor in acute myocardial infarction: results from the RENAMI registry"

Ovidio De Fillippo MD [a], Martina Cortese MD [a], Fabrizio D´Ascenzo MD [a*], Sergio Raposeiras-Roubin MD [b*], Emad Abu-Assi MD [b], Tim Kinnaird MD [c], Albert Ariza-Solé MD [d], Sergio Manzano-Fernández MD [e], Christian Templin Prof [f], Lazar Velicki MD [g], Ioanna Xanthopoulou MD [h], Enrico Cerrato MD [i], Andrea Rognoni MD [j], Giacomo Boccuzzi MD [k], Antonio Montefusco MD [a], Andrea Montabone MD [k], Salma Taha MD [l], Alessandro Durante MD [m], Sebastiano Gili MD [f], Giulia Magnani MD [f], Michele Autelli MD [a], Alberto Grosso MD [a], Pedro Flores Blanco MD [e], Alberto Garay MD [d], Giorgio Quadri MD[i], Ferdinando Varbella MD [i], Berenice Caneiro Queija MD [b], Rafael Cobas Paz MD [b], María Cespón Fernández MD [b], Isabel Muñoz Pousa MD [b], Diego Gallo MD [n], Umberto Morbiducci Prof [n], Alberto Dominguez-Rodriguez MD [o], Mariano Valdés MD [e], Angel Cequier MD [d], Dimitrios Alexopoulos MD [h], Andrés Iñiguez-Romo Prof [b], Mauro Rinaldi Prod.[a]

[a]Department of Cardiology, Department of Medical Sciences, University of Torino, Italy.
[b]Department of Cardiology, University Hospital Álvaro Cunqueiro, Vigo, Spain.
[c]Cardiology Department, University Hospital of Wales, Cardiff, United Kingdom.
[d]Department of Cardiology, University Hospital de Bellvitge, Barcelona, Spain.
[e]Department of Cardiology, University Hospital Virgen Arrixaca, Murcia, Spain.
[f] Department of Cardiology, University Heart Center, University Hospital Zurich, Switzerland.
[g] Institute of cardiovascular Diseases, Vojvodina, Serbia.
[h]University Patras Hospital, Athens, Greece.
[i]Interventional Unit, San Luigi Gonzaga University Hospital, Orbassano and Infermi Hospital, Rivoli (Torino), Italy.
[j] Catheterization Laboratory, Maggiore della Carità Hospital, Novara, Italy.
[k] Department of Cardiology, S.G. Bosco Hospital, Torino, Italy.
[l] Department of Cardiology, Faculty of Medicine, Assiut University.
[m]U.O. Cardiologia, Ospedale Valduce, Como, Italy.
[n]PolitoBIOMed Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino.
[o]Department of Cardiology, University Hospital from Canarias, Tenerife, Spain.
*both the authors gave the same contribute

Key words: Acute coronary syndromes, PCI; double antiplatelet therapy

Corresponding author: Dr Martina Cortese,
martin89ibero.it,+39 3335493975

ABSTRACT.

Limited data are available concerning differences in clinical outcomes of real-life patients treated with Ticagrelor and Prasugrel after PCI.

Objective: To determine and compare efficacy and safety of Ticagrelor and Prasugrel in a real-word population.

Design: RENAMI is a retrospective, observational registry. Data and outcomes of patients with acute coronary syndrome who underwent PCI and discharged with DAPT between January 2012 and January 2016 were included. The mean follow-up period was of 17±9 months.

Setting: 11 university hospitals from 6 European countries participated.

Participants: Consecutive patients with ACS discharged with DAPT after primary PCI were enrolled. After propensity-score matching there were no substantial differences in the baseline clinical and interventional features.

Exposures: All patients were treated with acetylsalicylic acid plus prasugrel (10 mg o.d.) or plus ticagrelor (90 mg b.d.). Mean duration of DAPT was 12.04±3.4 for patients treated with prasugrel and 11.90±4.1 months for ticagrelor (p 0.47).

Main outcomes and measures: Long-term NACE was the primary end-point, while MACEs the secondary ones, along with their single components. Subgroup analysis for freedom from NACE and MACE were performed according to length of DAPT and to clinical presentation (STEMI-ACS) vs (NSTEMI-ACS).

Results: 4244 patients (1699 in ticagrelor and 2275 in prasugrel group) were enrolled. After propensity-score matching 1290 patients of each cohort were included in the analysis. At 12 months, the incidence of NACE was lower in prasugrel patients (5.3% vs. 8.5%, p 0.0001), as that of MACE (6.05% vs. 8.1%, p 0.001), mainly driven by a reduction

in recurrent MI (2.4% vs. 4.0%, p 0.029) and a lower rate of BARC 3-5 bleeding (1.5% vs. 2.9%, p 0.011). The benefit of prasugrel was confirmed for NSTEMI patients and for those discharged with a DAPT regimen of 12 months or less. Only a trend in reduction for of NACE and MACE was noted for STEMI or for those treated with longer DAPT.

Conclusions and relevance: The comparison between the drugs suggests better efficacy and safety of prasugrel versus ticagrelor used in combination with aspirin after NSTEMI, while not in STEMI patients. No differences were found for events occurring after 12 months. **Due to the non-randomized design of the present research, further studies are warranted to support these findings**.

KEY MESSAGES

- **Dual antiplatelet therapy is a cornerstone of the treatment of acute coronary syndromes but evidences comparing ticagrelor vs prasugrel in the real life setting are missing**
- **According to the results of this observational study, prasugrel is safer and more effective than ticagrelor in NSTEMI patients with a reduction of re-infarction and major bleeding after a follow up of 12 months.**
- **In STEMI patients and in the subgroup of patients treated with a long DAPT regimen (>12 months) benefit of prasugrel as compared to ticagrelor was not significant.**

1. Introduction

Acute Coronary Syndromes (ACS) represent the most common clinical presentation for patients with CAD (Coronary Artery Disease) leading to a high risk of mortality and morbidity (1-4).

From an interventional point of view, PCI (Percutaneous Coronary Intervention) improved the prognosis of these patients, thanks to technological improvement also in high risk anatomic settings (5-7). Regarding Dual AntiPlatelet Therapy (DAPT), the most debated questions are related to its length (8-11) and to the choice of the new antiplatelet agents (prasugrel and ticagrelor) which in randomized controlled trials (RCTs) offered a reduction of recurrent ischemic events despite a higher risk of bleeding (12,13).

Both ticagrelor and prasugrel were found to be superior to clopidogrel for the treatment of ACS after PCI, showing some differences in their effect that may be related to the study design, but potentially also to the different drug formulation (14). Actually, from a pharmacodinamic point of view, level of antiaggregation did not differ in most of the reported studies (15). From a clinical point of view, randomized controlled trial on this topic did not show any difference, although underpowered especially due to low rate of events in a selected population (16). In most of the observational reports, prasugrel and ticagrelor have been compared to clopidogrel, showing a better efficacy and safety profile, while direct comparisons are limited by 30 days follow up or mostly focused on economic point of views (17,18). Another RCT designed to directly compare the two drugs in terms of clinical outcome is ongoing, but partial results have not been anticipated (19).

Consequently we performed the RENAMI, (REgistry of New Antiplatelets in patients with Myocardial Infarction) to allow a real life comparison between these such diffused new antiplatelet medicaments.

2. Methods

2.1 Study population.

RENAMI (REgistry of New Antiplatelet therapy in patients with acute Myocardial Infarction) is a retrospective, observational, multicenter, and international registry, in which 11 centers from 6 European countries (Spain, Italy, Switzerland, Greece, Serbia, United Kingdom) have voluntarily participated. RENAMI is an unfunded registry whose aim was to expand the knowledge about the long-term ischemic and hemorrhagic outcomes of patients discharged with DAPT with prasugrel or ticagrelor. All participating centers were university hospitals that had 24-hour catheterization laboratory, with internal clinical databases for ACS patients. Patients with ACS who underwent PCI and were discharged with DAPT with acetylsalicylic acid plus prasugrel (10 mg o.d.) or plus ticagrelor (90 mg b.d.) between January 2012 and January 2016 were consecutively included in the registry by the different participating centers.

ACS were classified as acute myocardial infarction (AMI) with persistent ST-segment elevation (STEMI), AMI without persistent ST segment elevation (NSTEMI) and unstable angina, based on the definitions from clinical practice guidelines (20-21). The diagnoses of AMI were based on the universal definition of AMI (22). The diagnosis of unstable angina was established in the presence of suggestive symptoms or objective evidence of myocardial ischemia in the stress test, together with the detection of a significant stenosis

in the coronary angiography (≥ 70%, except for left main coronary artery, where the cut-off is ≥ 50%).

Given the retrospective nature of the RENAMI registry, the diagnostic and therapeutic procedures were performed according to the protocols and preferences of each center and each physician.

For the purpose of RENAMI, a database was specifically designed and sent to each of the 11 participating centers. This database included information about clinical, analytical, echocardiographic, and angiographic variables, as well as follow-up data in terms of mortality, ischemic events and hemorrhagic events. The completed databases from each center were sent in an encrypted way to the coordination centers, University Hospital from Turin and University Hospital Álvaro Cunqueiro from Vigo, where they were merged into a single registry. The analysis of this registry for this study was carried out by 3 investigators from University Hospital from Turin. All of these steps were performed in accordance with the rules of Helsinki Declaration. The registry was approved by the local ethics committees of each center.

2.2 End points.

Long term NACE (Net Adverse Clinical Events, a composite end point of all cause death, mi and barc 3-5 bleedings) was the primary end point, while MACE (Major Adverse Clinical Events, a composite end point of all cause death, MI and ST) the secondary ones, along with their single components, and all cause bleeding. Subgroup analysis for freedom from NACE and MACE were performed according to length of DAPT and to clinical presentation (STEMI-ACS) vs. (NSTEMI-ACS). All events were right censored at 12

months, while a sub group analysis was performed for events occurring after 12 months only for patients with prolonged DAPT.

2.3 Statistical analysis.

Continuous variables are presented as means ± standard deviation or median with the interquartile range (IQR) and categorical variable are presented as frequency (%). Categorical variables were compared with the Fisher's exact test. Parametric distribution of continuous variables was tested graphically and with Kolmorogov Smirnov, and the appropriate analyses were used in accordance with the results. For propensity score, first logistic regression analysis was done for all baseline features that differed between aspirin and DAT and matching was computed after division into quintiles and methods of nearest neighbor on the estimated propensity score (23). Calibration was tested with Hosmer-Lermeshow, and accuracy was assessed with Area Under the Curve. Standardized differences were evaluated before and after matching to evaluate performance of the model. The cumulative incidences of NACE and MACE were calculated using the Kaplan-Meier method using length of DAPT as median follow up analysis and differences among groups were analyzed using a stratified log-rank test. **Cox multivariate analysis on data before propensity score were performed with NACE and MACE as dependent variables.** All statistical analyses were performed with SPSS 21 and differences were considered significant at $\alpha=0.05$.

3. Results

3.1 Baseline features and outcomes before propensity score with matching

A total of 1699 patients were enrolled in the Prasugrel group and 2725 in the Ticagrelor group (**see Figure number 1).** The two populations significantly differed for the prevalence of some cardiovascular risk factors since patients in the Ticagrelor group were more frequently smokers (31% vs 19.3%, p<0.001), more often had arterial hypertension (56.4% vs 50.3%, p<0.001), diabetes (31.6% vs 27.2%, p=0.002) and dyslipidaemia (55.3% vs 51.4%, p=0.012) compared with Prasugrel group. Moreover a higher number of female (24.1% vs 15.7%, p<0.0001), patients older than 75 years old (17.8% vs 5.7%, p <0.0001) and with an impaired LVEF (10.9% vs 7.8%, p=0.007) could be notice in the Ticagrelor group. Clinical presentation was slightly different with a lower prevalence of STEMI (72.9% vs 48.8%, p<0.0001) in patients committed to Ticagrelor, although this group had more frequently a multivessel disease (47.1% vs 41.7, p=0.002) and a known history of CAD (25.4% vs 17.4%, p<0.0001, **see Appendix, web only, Tables S1 and S2**). A complete revascularization was achieved in 82.9% of patients in the ticagrelor group, whereas in the prasugrel group in the 76.8% of the cases (p<0.0001). DES were significantly more used in the ticagrelor group (68.9% vs 60.6%, p<0.0001) compared with the prasugrel group. However, patients enrolled in the latest, received more frequently a pre-treatment with GP IIB-IIIa inhibitors (28.6% vs 16.2%, p>0.0001) and thrombus aspiration (38.1% vs 20.3% p<0.0001). At discharge, length of DAPT was slightly longer in prasugrel (12.89±3.6 for patients treated with prasugrel and 11.33±3.5, p<0.001).

A comparison between standardized difference for baseline and interventional features of patients before and after propensity score with matching is provided in table S1a and S2a respectively (see appendix, web only).

A lower incidence of in-hospital adverse events was recorded among patients enrolled in Prasugrel group. In particular rates of IH-Re-AMI (0.8% vs 1.7%, p =0.012), IH-Stroke (0% vs 0.6%, p=0.002) and IH bleeding (2.3% vs 3.7%, p=0.008) were significantly inferior, although this had no impact on MACEs (4.8% vs 4.4%, p=0.47) or all-cause death (2.6% vs 2.1%, p=0.32, **see Appendix, web only Table S3**). Indeed, after a mean follow up of 17±9 months, no difference of statistical meaning was observed in the frequency of the main outcomes investigated between the two enrolled populations.

3.2 Baseline features and outcomes after propensity score with matching

After propensity score with matching 1290 patients of each cohort were included in the analysis (**see Figure n 1**). There were no substantial differences in the baseline clinical and interventional features, most of patients being men, with a relevant burden of CV risk factors and presenting most frequently with STEMI (**see Tables 1 and 2)**. Length of DAPT was 12.04 ± 3.4 for patients treated with prasugrel and 11.90 ± 4.1 months for ticagrelor (p 0.47). After propensity score with matching **(see Table 3a)** at 12 months, incidence of NACE was lower in prasugrel patients (5.3% vs. 8.5%, p 0.0001), as that of MACE (6.05% vs. 8.1%, p 0.001), mainly driven by recurrent MI (2.4% vs. 4.0%, p 0.029) and BARC 3-5 bleedings (1.5% vs. 2.9%, p 0.011, **see fig n 2)**. No differences were found for events occurring after 12 months for patients with prolonged DAPT **(see Table 3b and Figure 3).** Kaplan-Meier analysis was performed for NACE and MACE **(see figure 4),** confirming the overall trend in favor of prasugrel.

Benefit of prasugrel for NACE and MACE was confirmed for patients treated with a DAPT of 12 months or less (median 12, 11-13 I and III IQR), while only a trend was noted for those treated with longer DAPT (median 16, 13-18 I and III IQR) **(see figure 5).** Regarding clinical presentation, STEMI patients did not show significant difference at survival analysis, while those presenting with NSTEMI derived more benefit from prasugrel **(see figure 6).** **The same results were confirmed at multivariate analysis for NACE and MACE as dependent variable (see appendix, web only tables 1 and 2).**

4. Discussion.

The present observational study provides a real-word head-to-head comparison of the efficacy and safety of ticagrelor versus prasugrel in a contemporary European cohort of patients with ACS undergoing PCI. After propensity score matching, we have found that DAPT with prasugrel was associated with significantly less incidence of ischemic and bleeding events, during a follow-up period of 17 ± 9 months. Interestingly, this reported benefit was concentrated in NSTEMI patients, without differences in ischemic or bleeding outcomes in STEMI patients.

Although the present study was not a randomized trial, the importance of its results lies in the limited scientific evidence currently available that directly compares DAPT with ticagrelor and prasugrel. Physicians are increasingly being confronted with the need to select a P2Y12 antagonist as part of the daily care of ACS patients. ESC guidelines recommended DAPT with ticagrelor or prasugrel instead of DAPT with clopidogrel, in absence of contraindications (9). DAPT with clopidogrel has been relegated to those ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC. In their pivotal clinical trials (PLATO and TRITON-TIMI 38), both ticagrelor and prasugrel have been shown to reduce

ischemic events against clopidogrel, with consequent increased hemorrhagic risk (12,13) These data, together with the recommendations of clinical practice guidelines (9,22), could suggest that ticagrelor and prasugrel could be interchangeable. Even with the more marked bleeding risk reported with prasugrel in TRITON-TIMI 38, specially in high risk patients (prior stroke, <60 kg,> 75 years) (12), the routine clinical practice could tend to favor the use of ticagrelor. However, very few studies have directly compared the efficacy and safety of ticagrelor versus prasugrel in patients with ACS (16, 18, 25-27). Our study provides more evidence in this issue, and our results must be faced with data from the few studies published to date about this topic.

There is only one randomized clinical trial that compared prasugrel and ticagrelor in ACS patients, which is the PRAGUE-18 trial, that has not found significant differences in adverse outcomes between DAPT with ticagrelor and DAPT with prasugrel (16). This is a randomized, multicenter study designed to compare the efficacy and safety of prasugrel and ticagrelor in patients with AMI treated with primary or immediate PCI. The PRAGUE-18 trial included 1,230 STEMI and very-high risk NSTEMI patients (634 with prasugrel, 596 with ticagrelor). At 30 days, there was no difference in all-cause mortality, non-fatal AMI, stroke and stent thrombosis. There were also no differences in bleeding rates based on the TIMI definition or on the BARC definition. **Despite the potential limitations regarding the non-randomized design of the present analysis,** our results are **somewhat** in line with those of the PRAGUE-18 clinical trial, since we have not found differences in adverse events for patients with STEMI, and in PRAGUE-18 trial, most of patients (90%) had STEMI. The benefit of DAPT with prasugrel versus DAPT with ticagrelor that we found was focused on patients with NSTEMI, who were only 5% in the PRAGUE-18 trial and were not specifically analyzed for low-size samples (n < 100). A possible explanation of this finding

could also lie in the different physiopathology of the two different ACS syndromes. STEMI, from an epidemiological point of view, is in fact more often a monovessel disease whereas NSTEMI patients frequently report a multivessel pathology (28). This could have resulted in a low number of vessels treated and stent implanted in STEMI patients, probably not enough to bring out differences of statistical meaning.

In addition to the PRAGUE-18 trial data, there is also a retrospective observational study that performed a "real-world" comparison of prasugrel and ticagrelor in ACS patients. This is the study of Larmore et al. (18), that has shown net benefit at 3 months of DAPT with prasugrel versus DAPT with ticagrelor. It is an observational study, using a payer database from United States, with 16,098 ACS patients (<40% STEMI) undergone PCI (13,134 with prasugrel, 2,964 with ticagrelor). After propensity score matching, 90-days net adverse clinical events (NACE) was 22% lower in prasugrel-treated than in ticagrelor-treated patients (RR 0.78; 95% CI, 0.64–0.94), with less mortality, myocardial infarction and severe bleeding (defined as ≥ 3 or 4 transfusions, intracranial bleeding or bleeding leading to death within 72 hours). Therefore, in a population in which NSTEMI predominates, the results of a lower rate of NACE with DAPT with prasugrel versus DAPT with ticagrelor are consistent with those of our study. Moreover, using another US-database (ProMetis-Lx) with approximately 60% of NSTEMI, Simeone JC et al. (25) have found a higher 1-year healthcare resource utilization (HRU) with ticagrelor than with prasugrel, primarily driven by cardiovascular causes (all over congestive heart failure), although with no significant difference in bleeding HRU.

Considering the presented studies and our data, it seems reasonable to hypothesize that DAPT with prasugrel may be superior in terms of safety and efficacy to DAPT with ticagrelor in patients with NSTEMI, with no differences between the two drugs in patients

with STEMI. It is difficult to give an explanation to these unexpected findings, although consistent with current scientific evidence. With the current approved maintenance dosing for both drugs, adequate levels of platelet inhibition are achieved in over 90% of patients (29-31). However, the finding of significantly lower rates of ischemic events associated with prasugrel in NSTEMI patients, common with the results of Larmore et al. (18), is also directionally in line with two meta-analyses (26-27). In them, using PLATO and TRITON-TIMI 38 data, making indirect comparisons between ticagrelor and prasugrel, it was shown a greater ischemic protection with DAPT with prasugrel versus DAPT with ticagrelor, especially in the reduction of stent thrombosis, with no difference in non-CABG bleeding rates (26-27). The more extended explanation is based on the ticagrelor-induced non-platelet side effects, in particular the onset of dyspnea, and of a twice-daily dosing regimen on medication adherence and discontinuation, factors that may confer an increased risk for subsequent cardiac events, especially given the more rapid offset of the antiplatelet effect of ticagrelor (14). However, the finding of lower bleeding rates in NSTEMI patients treated with Prasugrel results more difficult to explain. Larmore at al. (18), who in their study found the same data, suggested that the different dosages of ASA used in the different countries, not recorded in their database, could have contributed to the final outcome. Higher doses could have obviously conferred an higher bleeding risk on one hand, but, on the other, PLATO study demonstrated reduced efficacy of ticagrelor with high-dose aspirin thus increasing the thrombotic risk as well. Finally it can not be excluded that differences in prescribility of the two drugs could have influenced the results obtained, since both Prasugrel and Ticagrelor are contraindicated in patients with active bleeding, but the former is to be avoided in patients with previous TIA or stroke, thus probably contributing to select a population with a lower hemorrhagic and thrombotic risk.

4.1 Limitations

While an important strength of this study is the use of a multicentric database that capture patients from 6 European countries, several limitations need to be considered when interpreting the data. First, those that are inherent to retrospective studies. Second, **this is not a RCT;** although propensity-score matching was used to adjust baseline differences, residual confounding may remain due to the potential imbalance of unknown and unmeasured known confounders (e.g., socioeconomic status, access to care, provider characteristics, therapy adherence…) between treatments groups, **consequently results have to be interpreted with caution**. D**espite all the patients enrolled were managed according the most recent available ESC guidelines for clinical practice, we acknowledge the lack of a specific analysis aimed to investigate differences in diagnostic and therapeutic approaches among participating centers. Finally, missing about baseline and procedural features were less than 5%, while less than 10% for outcomes, supporting our results.** In the context of these limitations, our finding should be considered as hypothesis-generating, and should encourage to conduct further head-to-head randomized trials.

5. Conclusions

Results of the present retrospective, observational, propensity-adjusted study suggest a better efficacy and safety profile of prasugrel as compared to ticagrelor in real-life ACS patients treated with primary PCI and DAPT. At subgroup analysis according the clinical presentation and DAPT duration, the benefit of prasugrel was confirmed in NSTEMI patients and in those treated with a 12 months or shorter DAPT, but not in STEMI patients or in those treated with long DAPT regimen. Further RCT are warranted to support these results.

Compliance with ethical standards

Funding

No external funding was used in the preparation of this manuscript.

Conflict of interest: Ovidio De Fillippo, Martina Cortese, Fabrizio D´Ascenzo, Sergio Raposeiras-Roubin, Emad Abu-Assi, Tim Kinnaird, Albert Ariza-Solé, Sergio Manzano-Fernández, Christian Templin Prof, Lazar Velicki, Ioanna Xanthopoulou, Enrico Cerrato, Andrea Rognoni, Giacomo Boccuzzi, Antonio Montefusco, Andrea Montabone, Salma Taha, Alessandro Durante, Sebastiano Gili, Giulia Magnani, Michele Autelli, Alberto Grosso, Pedro Flores Blanco, Alberto Garay, Giorgio Quadri, Ferdinando Varbella, Berenice Caneiro Queija, Rafael Cobas Paz, María Cespón Fernández, Isabel Muñoz Pousa, Diego Gallo, Umberto Morbiducci, Alberto Dominguez-Rodriguez, Mariano Valdés, Angel Cequier, Dimitrios Alexopoulos, Andrés Iñiguez-Romo, Fiorenzo Gaita Prof **have no potential conflicts of interest that might be relevant to the contents of this manuscript.**

REFERENCES.

1- Abu-Assi E, Raposeiras-Roubín S, García-Acuña JM, González-Juanatey JR. Bleeding risk stratification in an era of aggressive management of acute coronary syndromes. World J Cardiol. 2014; 6(11):1140-8.

2- Gong IY, Goodman SG, Brieger D, Gale CP, Chew DP, Welsh RC, Huynh T, DeYoung JP, Baer C, Gyenes GT, Udell JA, Fox KAA, Yan AT. Canadian GRACE/GRACE-2 and CANRACE Investigators. GRACE risk score: Sex-based validity of in-hospital mortality prediction in Canadian patients with acute coronary syndrome. Int J Cardiol. 2017; 244:24-29.

3- Cordeiro F, Mateus PS, Ferreira A, Leao S, Moz M, Moreira JI; investigators of the Portuguese Registry of Acute Coronary Syndromes (ProACS). Short-term prognostic effect of prior cerebrovascular and peripheral artery disease in patients with acute coronary syndrome: Can we do better? Eur Heart J Acute Cardiovasc Care. 2017; 1:2048872617716388

4- Moretti C, Quadri G, D'Ascenzo F, Bertaina M, Giusto F, Marra S, Moiraghi C, Scaglione L, Torchio M, Montrucchio G, Bo M, Porta M, Cavallo Perin P, Marinone C, Riccardini F, Iqbal J, Omedè P, Bergerone S, Veglio F, Gaita F. THE STORM (acute coronary Syndrome in paTients end Of life and Risk assesMent) study. Emerg Med J. 2016; 33(1):10-6.

5- D'Ascenzo F, Iannaccone M, De Filippo O, Leone AM, Niccoli G, Zilio F, Ugo F, Cerrato E, Fineschi M, Mancone M, Rigattieri S, Amabile N, Ferlini M, Sardella G, Cresti A, Barbero U, Motreff P, Colombo F, Colangelo S, Garbo R, Biondi-Zoccai G, Tamburino C, Montefusco A, Omedè P, Moretti C, D'amico M, Souteyrand G, Gaita F, Limbruno U, Picchi A. Optical coherence tomography compared with fractional flow reserve guided approach in acute coronary syndromes: A propensity matched analysis. Int J Cardiol. 2017; 244:54-58

6- Hoedemaker NPG1, Damman P1, Woudstra P1, Hirsch A1, Windhausen F1, Tijssen JGP1, de Winter RJ2; ICTUS Investigators1. Early Invasive Versus Selective Strategy for Non-ST-Segment Elevation Acute Coronary Syndrome: The ICTUS Trial. J Am Coll Cardiol. 2017; 69(15):1883-1893.

7- Quadri G, D Ascenzo F, Moretti C, D'Amico M, Raposeiras-Roubín S, Abu-Assi E, Henriques JP, Saucedo J, González-Juanatey JR, Wilton SB, Kikkert WJ, Nuñez-Gil I, Ariza-Sole A, Song X, Alexopoulos D, Liebetrau C, Kawaji T, Huczek Z, Nie SP, Fujii T, Correia L, Kawashiri MA, García-Acuña JM, Southern D, Alfonso E, Terol B, Garay A, Zhang D, Chen Y, Xanthopoulou I, Osman N, Möllmann H, Shiomi H, Omedè P, Montefusco A, Giordana F, Scarano S, Kowara M, Filipiak K, Wang X, Yan Y, Fan JY, Ikari Y, Nakahashi T, Sakata K, Yamagishi M, Kalpak O, Kedev S, Varbella F, Gaita F. Complete or incomplete coronary revascularization 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. 2017; 13(4):407-414

8- D'Ascenzo F, Colombo F, Barbero U, Moretti C, Omedè P, Reed MJ, Tarantini G, Frati G, Di Nicolantonio JJ, Biondi Zoccai G, Gaita F. 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. J Interv Cardiol. 2014; 27(3):233-41.

9- Piccolo R, Gargiulo G, Franzone A, Santucci A, Ariotti S, Baldo A, Tumscitz C, Moschovitis A, Windecker S, Valgimigli M. Use of the Dual-Antiplatelet Therapy Score to Guide Treatment Duration After Percutaneous Coronary Intervention. Ann Intern Med. 2017; 167(1):17-25.

10- D'Ascenzo F, Moretti C, Bianco M, Bernardi A, Taha S, Cerrato E, Omedè P, Montefusco A, Frangieh AH, Lee CW, Campo G, Chieffo A, Quadri G, Pavani M, Zoccai GB, Gaita F, Park SJ, Colombo A, Templin C, Lüscher TF, Stone GW. Meta-Analysis of the Duration of Dual Antiplatelet Therapy in Patients Treated With Second-Generation Drug-Eluting Stents. Am J Cardiol. 2016; 117(11):1714-23.

11- Costa F, Vranckx P, Leonardi S, Moscarella E, Ando G, Calabro P, Oreto G, Zijlstra F, Valgimigli M. 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. Eur Heart J. 2015; 36(20):1242-51.

12- Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357(20):2001-15.

13- Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes.N Engl J Med. 2009; 361(11):1045-57.

14- Bonaca MP, Wiviott SD. Prasugrel Versus Ticagrelor: Uncertainty Remains. Circulation. 2016; 134(21):1613-1616.

15- Lee YS, Jin CD, Kim MH, Guo LZ, Cho YR, Park K, Park JS, Park TH, Kim YD. Comparison of Prasugrel and Ticagrelor Antiplatelet Effects in Korean Patients Presenting With ST-Segment Elevation Myocardial Infarction. Circ J. 2015; 79(6):1248-54.

16- Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, Knot J, Jarkovsky J, Kala P, Rokyta R, Tousek F, Kramarikova P, Majtan B, Simek S, Branny M, Mrozek J, Cervinka P, Ostransky J, Widimsky P; PRAGUE-18 Study Group. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. Circulation. 2016; 134(21):1603-1612.

17- Yudi MB, Clark DJ, Farouque O, Eccleston D, Andrianopoulos N, Duffy SJ, Brennan A, Lefkovits J, Ramchand J, Yip T, Oqueli E, Reid CM, Ajani AE; Melbourne Interventional Group. Clopidogrel, prasugrel or ticagrelor in patients with acute coronary syndromes undergoing percutaneous coronary intervention. Intern Med J. 2016; 46(5):559-65.

18- Larmore C, Effron MB, Molife C, DeKoven M, Zhu Y, Lu J, Karkare S, Lieu HD, Lee WC, Vetrovec GW. "Real-World" Comparison of Prasugrel With Ticagrelor in Patients With Acute Coronary Syndrome Treated With Percutaneous Coronary Intervention in the United States. Catheter Cardiovasc Interv. 2016; 88(4):535-544.

19- Schulz S, Angiolillo DJ, Antoniucci D, Bernlochner I, Hamm C, Jaitner J, Laugwitz KL, Mayer K, von Merzljak B, Morath T, Neumann FJ, Richardt G, Ruf J, Schömig G, Schühlen H, Schunkert H, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 Trial Investigators. Randomized comparisonof ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy – design and rationale of intracoronary stenting and Antithrombotic regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 Trial. J Cardiovasc Transl Res. 2014; 7(1):91-100.

20- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute

myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018 Jan 7;39(2):119–77.

21- Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14;37(3):267–315.

22- Thygesen K, Alpert JS, Jaffe AS, Simoons ML; Chaitman BR; White HD et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012; 60:1581-1598.

23- D'Ascenzo F, Cavallero E, Biondi-Zoccai G, Moretti C, Omede P, Bollati M, Castagno D, Modena MG, Gaita F, Sheiban I. Use and misuse of multivariable approaches in interventional cardiology studies on drug-eluting stents: a systematic review. J Interv Cardiol. 2012; 25(6):611-2

24- Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 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. 2016; 134(10):e123-55.

25- Simeone JC, Molife C, Marrett E, Frech-Tamas F, Effron MB, Nordstrom BL1, Zhu YE4, Keller S, Murphy BR, Nair KV, Vetrovec GW, Page RL 2nd, McCollam PL. One-year post-discharge resource utilization and treatment patterns of patients with acute coronary syndrome managed with percutaneous coronary intervention and treated with ticagrelor or prasugrel. Am J Cardiovasc Drugs. 2015; 15(5):337-50.

26- Biondi-Zoccai G, Lotrionte M, Agostoni P, Abbate A, Romagnoli E, Sangiorgi G, Angiolillo DJ, Valgimigli M, Testa L, Gaita F, Sheiban I. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. Int J Cardiol. 2011; 150(3):325-31.

27- Chatterjee S, Ghose A, Sharma A, Guha G, Mukherjee D, Frankel R. Comparing newer oral anti-platelets prasugrel and ticagrelor in reduction of ischemic events-evidence from a network meta-analysis. J Thromb Thrombolysis. 2013; 36(3):223-32.

28- Ferrara LA, Russo BF, Gente R, Esposito G, Rapacciuolo A, de Simone G-, STEMI and NSTEMI: a mono versus a multivessel disease? Int J Cardiol. 2013; 168(3):2905-6).

29- Li YG, Ni L, Brandt JT, Small DS, Payne CD, Ernest CS 2nd, Rohatagi S, Farid NA, Jakubowski JA, Winters KJ. Inhibition of platelet aggregation with prasugrel and clopidogrel: an integrated analysis in 846 subjects. Platelets. 2009; 20(5):316-27..

30- Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, Wickens M, Emanuelsson H, Gurbel P, Grande P, Cannon CP. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes J Am Coll Cardiol. 2007; 50(19):1852-6

31- Storey RF, Angiolillo DJ, Patil SB, Desai B, Ecob R, Husted S, Emanuelsson H, Cannon CP, Becker RC, Wallentin L. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATelet inhibition and patient Outcomes) PLATELET substudy. J Am Coll Cardiol. 2010; 56(18):1456-62.

Figures caption and legends

Figure 1 caption: design of the study.

Figure 2 caption: 12 months outcomes after propensity score with matching.

Legend: BARC = Bleeding Academic Research Consortium; MACE = Major adverse cardiovascular events; MI= Myocardial infarction; NACE = net adverse clinical events; ST= stent thrombosis

Figure 3 caption: Outcomes after 12 months (median 19:13-22) for patients with DAPT longer than 12 months after propensity score with matching.

Legend: BARC = Bleeding Academic Research Consortium; MACE = Major adverse cardiovascular events; MI= Myocardial infarction; NACE = net adverse clinical events;; ST= stent thrombosis

Figure 4 caption: Kaplan Meier for survival from NACE (above) and MACE (below)

Figure 5 caption: Kaplan Meier for survival from NACE (right) and MACE (left) for patients with with DAPT of 12 months (above) and longer (below).

Figure 6 caption: Kaplan Meier for survival from NACE (right) and MACE (left) for STEMI (above) and NSTEMI-ACS (below).