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# Prehospital Ticagrelor in Patients with ST-Segment Elevation Myocardial Infarction with Long Transport Time to Primary PCI Facility

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## ABSTRACT

**BACKGROUND:** Pre-hospital ticagrelor, given less than 1 hour before coronary intervention (PCI), failed to improve coronary reperfusion in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary PCI. It is unknown whether a longer interval from ticagrelor administration to primary PCI might reveal any improvement of coronary reperfusion.

**METHODS:** we retrospectively compared 143 patients, pre-treated in spoke centres or ambulance with ticagrelor at least 1.5 hours before PCI (Pre-treatment Group), with 143 propensity score-matched controls treated with ticagrelor in the hub before primary PCI (Control Group) extracted from RENOVAMI, a large observational Italian registry of more than 1400 STEMI patients enrolled from Jan 2012 to Oct 2015 (ClinicalTrials.gov id: NCT01347580). The median time from ticagrelor administration and PCI was 2.08 hours (95% CI 1.66-2.84) in the Pre-treatment Group and 0.56 hours (95% CI 0.33-0.76) in the Control Group. TIMI flow grade before primary PCI in the infarct related artery was the primary end point.

**RESULTS:** The primary end point, baseline TIMI flow grade, was significantly higher in Pre-treatment Group (0.88 ± 1.14 vs 0.53 ± 0.86, P = 0.02). However in hospital mortality, in hospital stent thrombosis, bleeding rates and other clinical and angiographic outcomes were similar in the two groups.

**CONCLUSIONS:** In a real world STEMI network, pre-treatment with ticagrelor in spoke hospitals or in ambulance loading at least 1.5 hours before primary PCI is safe and might improve pre-PCI coronary reperfusion, in comparison with ticagrelor administration immediately before PCI.

## INTRODUCTION

Dual antiplatelet therapy inhibiting both thromboxane A2-dependent platelet aggregation and P2Y12 receptors has a capital role in ST-segment elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI) and this particular patient population needs more aggressive antiplatelet drugs to improve clinical outcomes (1-5). To maximize this benefit, an earlier administration of P2Y12- receptor inhibitors has been advocated according to theoretical pharmacological issues (6). However the translation into clinical practice of such theories was not so straightforward, with conflicting results in registries (7), randomized studies (8-10) and meta-analyses (11,12). In fact an early treatment with clopidogrel before primary PCI had been previously suggested to reduce the rate of ischemic events without bleeding excess (9,11,12), but these benefits might be limited by a variability in the individual response to the drugs (13) and the time needed for absorption and active metabolites production (14). Conversely prasugrel and ticagrelor could become active in a time range compatible with the majority of transfers for primary PCI (10,15), even if a full antiplatelet efficacy may manifest only after several hours (16-18). Recently the Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) study, a multicentre, randomized, double-blind clinical trial involving 1862 STEMI patients, compared pre-hospital (in ambulance) versus in-hospital treatment with ticagrelor (8). In this study pre-hospital ticagrelor administration did not improve pre-PCI coronary reperfusion, even if a trend for better ST-segment elevation resolution after primary PCI and a reduction of definite stent thrombosis at 30 days were reported. As the ATLANTIC median time from randomization to angiography was 48 minutes, time for ticagrelor absorption and platelet inhibition might have been insufficient in many cases to affect the primary endpoint, especially in large MIs with reduced cardiac output or after treatment with opioids (18), both causes of delayed intestinal absorption. Thus, at the moment, it is unknown if prehospital treatment with ticagrelor might improve pre-PCI reperfusion in real world STEMI

patients with expected longer transport times and consequently more time for the novel antiplatelet agent to function.

## METHODS

*Population*

The RENOVAMI ("REgister of Myocardial Infarction Patients Treated by the NOVAra STE-MI Network ", ClinicalTrials.gov Identifier: NCT01760382) is a prospective, ongoing, observational, cohort study focusing on STE-ACS patient treated with primary PCI conducted in a single, tertiary, large-volume centre which serves as Hub centre for a local primary PCI network. RENOVAMI has been organized by the Hospital Cardiology Department of the "Maggiore della Carità" Hospital of Novara and is endorsed by the Italian Council of Cardiology Practice.

We analysed data from a cohort of consecutive acute coronary syndrome presenting with ST segment elevation (STE-ACS) patients undergoing primary PCI in our centre, treated between January 2012 (date of first availability for clinical use of ticagrelor in our network) and December 2015. We applied standard criteria for STE-ACS diagnosis, taking into account clinical presentation, electrocardiographic findings and the results of serum biochemical markers of necrosis (19). Patients were treated according to usual clinical practice and PCI was performed using standard techniques (6). We excluded patients younger than 18 years, patients presenting more than 12 hours after symptoms onset, patients treated with thrombolysis, patients with failure of primary PCI to mechanically restore the patency of the culprit coronary vessel and patients unable to give informed consent.

A team of research nurses collected and entered in a dedicated database the information on patient demographic characteristics, medical history, pre-and in-hospital therapy, timing of care delivery, angiographic and interventional details, laboratory tests and in-hospital patient outcomes. In particular, a detailed recording of the administered antithrombotic treatment was made. The antithrombotic strategy and the initial P2Y12 inhibitor choice, along with the subsequent

confirmation or change of hospital and pre-discharge antiplatelet therapy, were done at discretion of the treating physicians. Data on in hospital major adverse cardiovascular events (MACE) including death, myocardial infarction, definite or probable stent thrombosis, urgent revascularization, stroke, and bleeding events according to Bleeding Academic Research Consortium (BARC) criteria (21) were prospectively collected. Outcome adjudication were performed by a local adjudicator committee formed by the Cardiology Department director, the Coronary Care Unit director and the Catheterization Laboratory director, who reviewed the respective medical records (clinical charts, coronary angiography reports, laboratory values, discharge summaries). In controversial cases divergence was resolved by consensus.

*Study endpoints and statistical analysis*

The primary focus of this retrospective analysis was the intention-to-treat comparison of patients pre-treated (in spoke centres or in ambulance) with a 180mg ticagrelor load at least 1.5 hours before PCI (Group 1) with a population of propensity score matched controls treated with ticagrelor load only at the time of primary PCI in the hub hospital (Group 2). To account for the effect over reperfusion indexes of the duration of ischemia, patients were also matched according to time from symptoms onset to mechanical reperfusion.

Thrombolysis In Myocardial Infarction (TIMI) flow grade (20) in the infarct related coronary artery (IRCA) immediately before primary PCI was the primary end point of the study.

Other secondary end points included the clinical and angiographic pre- and post-procedural outcomes and the rates of in-hospital major adverse cardiovascular events and definite stent thrombosis. In particular, we assessed the rate of patency of the IRCA (TIMI flow grade >0) before primary PCI, the TIMI thrombotic burden (0-5) before primary PCI (20), the rates of >70% reduction from baseline of ST-segment elevation 90min after PCI, the rates of post-procedural TIMI 3 flow grade (0-3), the rates of post-procedural TIMI perfusion grade (0-3) (20), the postprocedural TIMI 3-2 vs 1-0 blood flow grade, the postprocedural corrected TIMI frame count (cTFC) (20). New myocardial infarction was defined according to the “universal definition of myocardial

infarction" (19). Coronary stenosis were described according to the AHA-ACC classification and thrombus burden was graded according to the TIMI grade I-V classification as recommended (20). Finally TIMI coronary blood flow grade and cTFC were assessed according to current recommendations (20). Angiograms were analysed on site by 2 independent experienced interventional cardiologists, discrepancies were resolved by consensus.

As in hospital outcomes we considered the rates of in-hospital mortality, in-hospital definite stent thrombosis, in-hospital nonfatal reinfarction, in-hospital stroke and in-hospital bleedings, classified according to BARC (21).

Categorical data are presented as counts and percentages. Continuous data with normal and skewed distribution are presented as means ± SD and medians (interquartiles) respectively. The Kolmogorov-Smirnov test was used to examine data distribution normality. Unpaired T test was employed for comparisons of continuous variables with normal distribution, whereas Mann Whitney U-test was used for continuous variables with non-normal distribution, and $Chi^2$ test was used for categorical clinical and angiographic characteristics and for outcome rates.

In total, 15 clinical variables with a potential influence over the baseline TIMI flow grade were used to calculate propensity scores (age, male sex, body mass index, admission from a spoke hospital, symptoms to reperfusion time, hypertension or hypotensive drugs use, type 2 diabetes or antidiabetic drugs use, dyslipidemia or lipid-lowering drugs use, tobacco use, peripheral vascular disease, impaired renal function with glomerular filtration rate≤ 30mL/min, ST elevation in the anterior precordial leads, baseline left ventricular ejection fraction, previous MI, PCI or coronary artery bypass graft, clopidogrel preprocedural load). Greedy, Mahalanobis distance 1:10 within propensity score calipers (width of 0.20 of the standard deviation of the logit of the propensity score) matching was used. Standardized differences of the mean <10% were taken to indicate good balance in the matched sample.

Variables independently correlated with pre-intervention TIMI blood flow in the infarct related artery were identified with multiple regression analysis. The covariates tested for in this model were

age, diabetes, estimated glomerular filtration rate (eGFR) <30mL/min, anterior location of the ST elevation, pretreatment with Ticagrelor 180mg loading dose and time interval from symptoms to balloon. Covariates with an exploratory P<0.1 were entered into a multiple regression analysis model. Potential interactions between covariates were tested; variables with a significance that was explained by multicollinearity were excluded. Finally, covariates significantly associated with the outcome of interest at a significance level of P<0.05 were included in the final model. .

In hospital mortality, stent thrombosis, BARC 3 bleeding and net clinical effect rates were calculated and plotted according to the Kaplan Meier method, and comparisons between groups were performed using the Log-rank test. The relation of ticagrelor pretreatment and the risk for each study end-point was assessed with Cox proportional hazards models. The covariates tested for in this model were male sex, age, hypertension, diabetes, dyslipidemia, body mass index (BMI) > 30kg/$m^2$ of body surface area (BSA), estimated glomerular filtration rate (eGFR) <30mL/min, cigarette smoking (active or quitted <2years), previous MI and/or PCI, previous CABG, peripheral artery disease, left ventricular ejection fraction (LVEF), pretreatment with Ticagrelor 180mg loading dose, intraprocedural use of GP2b3a inhibitors, multivessel CAD, left main, type B2/C lesion, multivessel PCI, direct stenting, high pressure postdilation, number of implanted stents, drug eluting stents (DES) use, total stent length (mm). Univariate associations with clinical outcomes were estimated for all clinical and procedural variables and included with a P level <0.10). Covariates were considered independently associated with the outcome of interest at a significance level of P<0.05 in the final model.

All tests were 2-tailed and statistical significance was considered for P<0.05. Statistical analyses were performed using SPSS for Windows (version 16.0; SPSS, Inc., Chicago, IL), NCSS (version 8.0 NCSS, Kaysville, UT, USA) and PASS (version 11.0, Kaysville, UT, USA).

*Ethical issues*

The present study is a retrospective propensity score-matched analysis and was conducted according to the local Institutional Review Board guidelines. All patients signed a written informed consent for personal data treatment when enrolled in the RENOVAMI registry.

## RESULTS

*Study population, propensity score matching and baseline clinical characteristics*

Patient treatment flow-chart is summarized in Figure 1. From Jan 2012 to Dec 2015, 1405 consecutive STEMI patients were admitted to our STE-ACS network and treated with primary PCI and 929 were treated with an oral 180mg loading dose of ticagrelor. In 143 of them, treated in spoke hospitals or in ambulance, a 180mg oral ticagrelor load was administered at least 1.5 hours before mechanical reperfusion (Pre-treatment Group). This group was compared with a cohort of 143 propensity score matched controls (Control Group) selected from the 448 patients who received a ticagrelor 180mg loading dose immediately before or after primary PCI in the Hub hospital.

Clinical and angiographic baseline characteristics of the 2 groups were similar, as shown in table 1 and table 2, except for the median time from ticagrelor administration and reperfusion that was 2.08 hours (95% CI 1.66-3.84) in the Pre-treatment Group and 0.56 (95% CI 0.33-0.76) in the Control Group ($p<0.0001$).

The primary end point, IRCA TIMI flow grade immediately before primary PCI was significantly higher in the Pre-treatment Group (0.88 ± 1.14 vs 0.53 ± 0.86, P = 0.02, figure 2) with a significantly higher rate of TIMI 3 flow in ticagrelor pre-treated patients (14.0 vs 4.9%, P = 0.01). Also IRCA thrombus burden was lower in the Pre-treatment Group (3.91 ± 1.33 vs 4.30 ± 0.99, P = 0.03), but IRCA patency rates before PCI showed only a nonsignificant trend in favour of the Pre-treatment Group (44.8 vs 37.8%, P = 0.23). The maximum ST-segment elevation at admission was not significantly different in ticagrelor pre-treated patients (3.9 ± 2.3 vs 4.4 ± 2.9mm, P=0.21), while admission cTnI showed a nonsignificant trend to be higher in the Pre-treatment Group (1.52, 95% CI 0.36-5.33 vs 0.29, 95% CI 0.08-2.25ng/mL, P=0.13).

*Post-procedural ECG, laboratory and angiographic characteristics*

Post-procedural ECG, laboratory and angiographic outcomes are summarized in table 3. Post-procedural maximum ST elevation was similar in the 2 groups (1.4 ± 1.9 vs 1.7 ± 1.8mm, P=0.33) as well as the rates of post-procedural ST recovery >70% at 1hour from PCI (62.9% vs 53.2%, P=0.19). Peak cTnI was also similar in the 2 Groups (77.47, 95% CI 27.54-208.73 vs 73.01, 95% CI 30.01-197.43 ng/mL, P=1.00). Also post-procedural angiographic outcomes were similar between the 2 Groups (TIMI flow grade 2.78 ±0.5 vs 2.67 ± 0.73, P = 0.14; corrected TIMI frame count 15.0 ± 6.9 vs 16.2 ± 10.0 frames, P=0.26; TIMI perfusion grade 2.53 ± 0.71 vs 2.49 ± 0.88, P=0.69, slow flow or no reflow 18.2 vs 21.0%, P=0.55). Multiple regression analysis showed that ticagrelor pre-treatment was an independent predictor of pre-PCI TIMI coronary flow grade (, r = 0.35, P = 0.004, table 4).

*Post-procedural clinical outcomes*

Clinical outcomes following primary PCI are summarized in table 3. A borderline significant trend for lower in-hospital mortality in the Pre-treatment Group was observed (3.5 vs 9.1%, P = 0.088), while in-hospital stent thrombosis and nonfatal myocardial infarction rates, as well as the rates of bleeding events classified according to BARC, were similar in the two Groups (table 3). Cox proportional hazard analysis failed to demonstrate any independent effect over clinical outcomes of a ticagrelor pre-treatment administered at least 1.5 hours before primary PCI.

## DISCUSSION

In the present study patients with STEMI and a long (median 2.1 hours) time interval between ticagrelor load administration and primary PCI showed a better baseline coronary flow profile in the IRCA, in comparison with propensity score matched controls treated with ticagrelor immediately before PCI. Even if a nonsignificant trend for in hospital mortality reduction was observed in ticagrelor pre-treated patients, the other in-hospital clinical outcomes were similar in the 2 groups.

*Comparison with previous studies*

The potential advantages of pre-hospital administration of antiplatelet agents in primary PCI was first investigated with the intravenous glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor abciximab, which improved TIMI flow grade before primary PCI, in comparison with placebo (22). Further studies confirmed some benefit of earlier GP IIb/IIIa administration, especially in STEMI patients treated very soon after symptom onset (23-27). Various studies and meta-analyses suggested that also oral pre-treatment with clopidogrel could reduce the rate of ischemic events without bleeding excess in STEMI patients (9,11,12), but the effectiveness of this drug may be limited by a slow onset of action and a genetically determined variable response (13,14). Conversely, the novel oral P2Y12-receptor inhibitors prasugrel and ticagrelor seem to tackle platelet function much sooner than clopidogrel and maybe after less than 1 hour from administration, a reasonable time interval to benefit most primary PCIs (10,15).

Ticagrelor is a direct-acting inhibitor of the platelet P2Y12 receptor with a rapid antiplatelet effect (10,15-18,28) and higher clinical efficacy over major cardiovascular events in patients with acute coronary syndromes, as compared with clopidogrel (29,30). The drug showed a potential to improve coronary reperfusion and prognosis in STEMI patients treated with primary PCI (30) and this aspect was recently tested in ATLANTIC randomized controlled trial (8). This study evaluated whether early, in-ambulance administration of ticagrelor could improve coronary reperfusion in STEMI patients transferred to hub hospitals for primary PCI but failed to demonstrate effects over the primary endpoint (reperfusion of the culprit artery before PCI). The main reason for this negative result was probably the short time interval between ticagrelor administration and primary PCI, with a median time from randomization to angiography of 48 minutes. However, ticagrelor use might have reduced the post-procedural acute stent thrombosis rate and this benefit is also consistent with previous data suggesting that ticagrelor full antiplatelet effect may manifest only after several hours (16-18), well after the end of the PCI. Thus pre-hospital ticagrelor might be efficacious to improve pre-PCI reperfusion in cases with an expected longer time interval from drug administration to procedure, even if this issue was not formally tested by the ATLANTIC study. This perspective is

not in contrast with a recent landmark analysis focused on the first 24 hours of the ATLANTIC trial, which showed a benefit over pre-PCI coronary reperfusion rates in pre-hospital ticagrelor-treated patients (31).

Our retrospective analysis, based upon data from a large high quality Italian clinical registry, showed that patients pre-treated with ticagrelor with a median time interval from drug administration to primary PCI of about 2 hours might gain benefit in terms of pre-PCI TIMI flow grade in the IRCA. This benefit was not merely related to patency of the IRCA, which showed only a nonsignificant trend for higher rates in pre-treated patients, but rather to a better IRCA flow profile in patients presenting before PCI with a patent IRCA. In fact we observed a baseline TIMI 3 flow more frequently in the IRCA of ticagrelor pre-treated patients, in comparison with controls. The finding that prehospital ticagrelor, given with a reasonable time interval for drug adsorption, improved TIMI flow grade profile without a parallel increase in IRCA patency rate suggests a patho-physiologic explanation. We hypothesize that prehospital ticagrelor probably do not affect the frequency of spontaneous IRCA reperfusion, a well-known patho-physiologic phenomenon (32), but might improve coronary flow once reperfusion occurred, blunting platelet reactivity in the reperfusion blood, favouring haemorheolytic thrombus disruption, avoiding platelet plug formation in the microcirculation and finally leading to a better pre-PCI TIMI flow grade. This hypothesis is corroborated by the observed lower thrombus burden in the IRCA of patients pre-treated with ticagrelor in our analysis.

The present study confirmed the safety of ticagrelor pre-hospital administration observed in the ATLANTIC study, without demonstrable increase of bleedings. Conversely, we did not appreciate the reduction of stent thrombosis rates previously described in ATLANTIC, probably due to the small number of patients with long time interval from ticagrelor administration to PCI obtainable from the RENOVAMI cohort (143 patients from a total of over 1400). Also other hard clinical endpoints like nonfatal in-hospital re-infarction and MACEs rates were not affected by ticagrelor pre-treatment in our study, even if we observed a nonsignificant trend for in-hospital mortality

reduction in ticagrelor pre-treated patients. However, the number of clinical hard events in our report was small and almost all the observed deaths were due to cardiogenic shock, cardiac arrest, or cardiac rupture rather than to bleeding or ischemic events, thus no definitive clinical deduction can be drawn from these data. To our knowledge the present study is the first real world report about the effect of ticagrelor pre-treatment over coronary blood flow before primary PCI when a reasonable time interval separates the drug administration and coronary revascularization.

*Limitations of the study*

First, our study is a retrospective propensity-matched comparison of non-randomized patients included in a real world registry. Thus, even if propensity matching should have mitigated selection bias for known covariates, this statistical technique cannot exclude interference from any unknown covariates linked to outcomes but not included in propensity scores calculation.

Second, even if our registry enrolled in 3 years more than 1400 patients, only a small sample of about 10% fulfilled the inclusion criteria of a time interval ≥ 1.5 hours between ticagrelor loading dose administration and PCI, thus the statistical power of our study was anticipated to be insufficient to draw conclusions about hard end points like in hospital mortality and stent thrombosis rates.

Third, data about platelet inhibition was not available and the hypothesis that a ≥1.5 hours' time interval between the drug administration and PCI could be enough to obtain significant platelet inhibition before coronary revascularization is based upon theoretical pharmacokinetic and pharmacodynamic assumptions rather than upon empirical data.

Finally, another potential limitation is related to the delayed absorption of orally administered P2Y12-receptor antagonists (16-18), due to morphine administration in a significant proportion of the study population (18,33). In our study the proportion of patients who did and did not receive morphine was similar between the 2 groups, and opioid administration before PCI was not an independent predictor of baseline TIMI flow. Thus the extent to which the described interaction of opioids and antiplatelet drug efficacy (18,34) may have affected our results remains unknown at this

stage. The administration of ticagrelor loading dose in crushed form has been proposed to facilitate the antiplatelet drug absorption process (35). However, in our study population, this particular treatment was not used systematically, with the exception of a few patients needing intubation. Thus it seems very unlikely that the administration of ticagrelor according to the MOJITO study protocol could have biased our results.

*Conclusions*

In conclusion, prehospital administration of ticagrelor with a median time of 2 hours before primary PCI appeared to be safe and improved angiographic pre-procedural coronary reperfusion. Further studies are warranted to assess whether such improvement might affect harder endpoints such in-hospital mortality and acute stent thrombosis.

## REFERENCES


1. Montalescot G, Wiviott SD, Braunwald E et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723-31.
2. Steg PG, James S, Harrington RA et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131-41.
3. Bellemain-Appaix A, Brieger D, Beygui F et al. New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention: a meta-analysis. J Am Coll Cardiol 2010;56:1542-51.
4. Bhatt DL, Stone GW, Mahaffey KW et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013;368:1303-13.
5. Bhatt DL, Lincoff AM, Gibson CM et al. Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 2009;361:2330-41.
6. Zimarino M, Sacchetta D, Renda G, De Caterina R. Facilitated PCI: rationale, current evidence, open questions, and future directions. J Cardiovasc Pharmacol 2008;51:3-10.
7. Clemmensen P, Grieco N, Ince H et al. MULTInational non-interventional study of patients with ST-segment elevation myocardial infarction treated with PRimary Angioplasty and Concomitant use of upstream antiplatelet therapy with prasugrel or clopidogrel--the European MULTIPRAC Registry. Eur Heart J Acute Cardiovasc Care 2015;4:220-9.
8. Montalescot G, van 't Hof AW, Lapostolle F et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016-27.
9. Zeymer U, Arntz HR, Mark B et al. Efficacy and safety of a high loading dose of clopidogrel administered prehospitally to improve primary percutaneous coronary intervention in acute myocardial infarction: the randomized CIPAMI trial. Clin Res Cardiol 2012;101:305-12.
10. Montalescot G, Bolognese L, Dudek D et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369:999-1010.

11. Bellemain-Appaix A, O'Connor SA, Silvain J et al. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. JAMA 2012;308:2507-16.
12. Sabatine MS, Cannon CP, Gibson CM et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA 2005;294:1224-32.
13. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908-13.
14. Ford NF. Clopidogrel resistance: pharmacokinetic or pharmacogenetic? J Clin Pharmacol 2009;49:506-12.
15. Storey RF, Angiolillo DJ, Patil SB et al. 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;56:1456-62.
16. Valgimigli M, Tebaldi M, Campo G et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. JACC Cardiovasc Interv 2012;5:268-77.
17. Alexopoulos D, Xanthopoulou I, Gkizas V et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2012;5:797-804.
18. Parodi G, Valenti R, Bellandi B et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013;61:1601-6.
19. Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581-98.
20. Cutlip DE, Windecker S, Mehran R et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
21. Mehran R, Pocock S, Nikolsky E et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. JACC Cardiovasc Interv 2011;4:654-64.
22. Montalescot G, Barragan P, Wittenberg O et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895-903.
23. Herrmann HC, Lu J, Brodie BR et al. Benefit of facilitated percutaneous coronary intervention in high-risk ST-segment elevation myocardial infarction patients presenting to nonpercutaneous coronary intervention hospitals. JACC Cardiovasc Interv 2009;2:917-24.
24. Van't Hof AW, Ten Berg J, Heestermans T et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-46.
25. ten Berg JM, van 't Hof AW, Dill T et al. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. J Am Coll Cardiol 2010;55:2446-55.
26. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. Eur Heart J 2009;30:2705-13.
27. Huber K, Holmes DR, Jr., van 't Hof AW et al. Use of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention: insights from the APEX-AMI trial. Eur Heart J 2010;31:1708-16.

28. Storey RF, Husted S, Harrington RA et al. 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;50:1852-6.
29. Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
30. Deeks ED. Ticagrelor: a review of its use in the management of acute coronary syndromes. Drugs 2011;71:909-33.
31. Montalescot G, van 't Hof AW, Bolognese L et al. Effect of Pre-Hospital Ticagrelor During the First 24 Hours After Primary PCI in Patients With ST-Segment Elevation Myocardial Infarction: The ATLANTIC-H Analysis. JACC Cardiovasc Interv 2016.
32. Hackworthy RA, Vogel MB, Harris PJ. Relationship between changes in ST segment elevation and patency of the infarct-related coronary artery in acute myocardial infarction. Am Heart J 1986;112:279-84.
33. Cohen MV, Downey JM. Combined cardioprotectant and antithrombotic actions of platelet P2Y12 receptor antagonists in acute coronary syndrome: just what the doctor ordered. J Cardiovasc Pharmacol Ther 2014;19:179-90.
34. Alexopoulos D, Xanthopoulou I, Goudevenos J. Effects of P2Y12 receptor inhibition in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2014;113:2064-9.
35. Parodi G, Xanthopoulou I, Bellandi B et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. J Am Coll Cardiol 2015;65:511-2.

**Table and figure legends:**

Table 1: Demographic and clinical characteristics of the propensity matched study population.

Table 2: Angiographic characteristics of the propensity matched study population.

Table 3: Post-PCI outcomes of the propensity matched study population.

Table 4: Independent predictors of TIMI blood flow grade in the infarct related artery before primary PCI, according to multiple regression analysis.

Figure 1: Flow chart of patient flow through the RENOVAMI network.

Figure 2: TIMI flow grade (primary endpoint) in ticagrelor pre-treated patients and in the control group.

Table 1: Demographic and clinical characteristics of the propensity matched study population

| | Control Group (143 pts) Mean ± SD / Count (%) / Median (95% CI) | Pre-treatment Group (143 pts) Mean ± SD / Count (%)/ Median (95% CI) | P level |
|---|---|---|---|
| Age (years) | 64.4±13.2 | 64.0±11.5 | 0.79 |
| Male sex | 108 (75.5%) | 109 (76.2%) | 0.89 |
| Directly admitted to hub hospital | 143 (100.0%) | 0 (0.0%) | <0.0001 |
| Transfer from spoke hospital | 0 (0.0%) | 130 (90.9%) | <0.0001 |
| Transport by ambulance | 0 (0.0%) | 13 (9.1%) | <0.0001 |
| Symptoms-first medical contact (hours) | 1.64 (1.10-2.16) | 2.20 (1.82-3.9) | 0.001 |
| Symptoms-hub admission interval (hours) | 3.50 (2.35-6.00) | 4.00 (2.55-5.88) | 0.73 |
| Symptoms to reperfusion interval (hours) | 4.00 (2.75-6.23) | 4.31 (3.00-6.00) | 0.87 |
| Hypertension | 94 (65.7%) | 93 (65.0%) | 0.90 |
| Type 2 diabetes | 34 (23.8)% | 24 (16.8%) | 0.14 |
| Tobacco (active / stopped < 2 years) | 59 (41.3%) | 55 (38.5%) | 0.63 |
| Dyslipidaemia | 46 (32.2%) | 44 (30.8%) | 0.80 |
| BMI > 30 kg/m$^2$ BSA | 34 (23.8%) | 29 (20.3%) | 0.48 |
| Peripheral artery disease | 24 (16.8%) | 19 (13.3%) | 0.41 |
| Previous MI and/or PCI | 30 (21.0%) | 26 (18.2%) | 0.55 |
| Previous CABG | 6 (4.2%) | 4 (2.8%) | 0.52 |
| eGFR < 30 cc/min | 6 (4.2%) | 8 (5.6%) | 0.59 |
| Anterior STEACS | 70 (49.0%) | 70 (49.0%) | 1.00 |
| Inferior STEACS | 59 (41.3%) | 59 (41.3%) | 1.00 |
| Lateral STEACS | 14 (9.7%) | 14 (9.7%) | 1.00 |
| Admission LVEF% | 46.6 ± 10.2 | 48.4±9.0 | 0.07 |
| TIMI risk score | 5.2 ± 2.7 | 4.3 ± 2.5 | 0.01 |
| Crusade score | 25.4 ± 15.7 | 24.7 ± 13.4 | 0.69 |
| Time from ticagrelor load to PCI (hours) | 0.56 (0.33-0.76) | 2.08 (1.66-2.84) | 0.0001 |
| Switch from prasugrel or ticagrelor to clopidogrel | 1 (0.7%) | 3 (2.0%) | 0.35 |
| Opioid administration before PCI | 92 (64.3%) | 94 (65.7%) | 0.94 |
| Angina at admission | 103 (73.0%) | 88 (64.2%) | 0.11 |
| Baseline maximum ST elevation (mm) | 4.4 ± 2.9 | 3.9 ± 2.3 | 0.21 |

(SD = standard deviation, BMI = body mass index, BSA = body surface area, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, e GFR = estimated glomerular filtration rate, STEACS = ST elevation acute coronary syndrome, LVEF= left ventricular ejection fraction).

Table 2: Angiographic characteristics of the propensity matched study population

| | Control Group, 143 pts Mean ± SD / Count (%) | Pre-treatment Group, 143 pts Mean ± SD / Count (%) | P level |
|---|---|---|---|
| Radial access | 73.4% | 76.9% | 0.43 |
| Fluoroscopy time (min) | 9.5 ± 5.2 | 11.0 ± 8.4 | 0.08 |
| Multivessel CAD | 80 (55.9%) | 76 (53.1%) | 0.64 |
| ACC/AHA type 2B or C plaque | 130 (90.9%) | 128 (89.5%) | 0.69 |
| Collaterals | 32 (24.4%) | 34 (24.3%) | 0.98 |
| Patent infarct related artery | 54 (37.8%) | 64 (44.8%) | 0.23 |
| Saphenous vein graft intervention | 4 (2.8%) | 2 (1.4%) | 0.41 |
| Baseline TIMI flow grade (0-3) in IRCA | 0.53 ± 0.86 | 0.88 ± 1.14 | 0.02 |
| Pts with baseline TIMI 3 in IRCA | 7 (4.9%) | 20 (14.0%) | 0.01 |
| Baseline TIMI thrombus grade (0-5) | 4.30 ± 0.99 | 3.91 ± 1.33 | 0.03 |
| TIMI collateral flow grade (0-3) | 0.37 ± 0.73 | 0.37 ± 0.75 | 0.98 |
| IIb / IIIa inhibitor use during PCI | 52 (34.4%) | 19 (13.3%) | <0.001 |
| Bivalirudin use during PCI | 56 (39.2%) | 80 (55.9%) | <0.001 |
| Manual thrombectomy | 37.1% | 30.8% | 0.26 |
| Direct stenting | 52.4% | 47.6% | 0.41 |
| Vessel treated / pt | 1.08 ± 0.32 | 1.17 ± 0.43 | 0.06 |
| Stent deployed / pt | 0.68 ± 0.67 | 1.52 ± 0.97 | 0.36 |
| DES used | 65 (45.5%) | 80 (55.9%) | 0.08 |
| POBA | 3 (2.1%) | 4 (2.8%) | 0.70 |
| Reference coronary diameter (mm) | 3.06 ± 0.50 | 3.06 ± 0.57 | 0.96 |
| Lesion length (mm) | 18.1 ± 8.2 | 18.3 ± 8.9 | 0.84 |
| Stent diameter (mm) | 3.12 ± 0.43 | 3.07 ± 0.46 | 0.35 |
| Stent length (mm) | 24.2 ± 10.2 | 23.5 ± 9.9 | 0.58 |
| IABP | 9 (6.3%) | 9 (6.3%) | 1.00 |

(SD = standard deviation, CAD = coronary artery disease, IRCA = infarct-related coronary artery, PCI = percutaneous coronary intervention, DES = drug eluting stent, POBA = plain old balloon angioplasty).

Table 3: Post-PCI outcomes of the propensity matched study population

| | Control Group (143 pts) Mean ± SD / Count (%) Median (95% CI) | Pre-treatment Group (143 pts) Mean ± SD / Count (%) Median (95% CI) | P level |
|---|---|---|---|
| *ECG* | | | |
| Post-procedural maximum ST elevation | 1.7 ± 1.8 | 1.4 ± 1.9 | 0.33 |
| Post-procedural ST recovery >70% at 90min | 76 (53.2%) | 90 (62.9%) | 0.19 |
| *Angiography* | | | |
| Post-procedural TIMI flow grade (0-3) | 2.67 ± 0.73 | 2.78 ±0.52 | 0.14 |
| Post-procedural corrected TIMI frame count | 16.2 ± 10.0 | 15.0 ± 6.9 | 0.26 |
| Post-procedural TIMI perfusion grade (0-3) | 2.49 ± 0.88 | 2.53 ± 0.71 | 0.69 |
| Post-procedural slow flow/no reflow (TIMI 0-2) | 30 (21.0%) | 26 (18.2%) | 0.55 |
| *Laboratory* | | | |
| Baseline cTnI (ng/mL) | 0.29 (0.08-2.25) | 1.52 (0.36-5.33) | 0.13 |
| Peak cTnI (ng/mL) | 73.01 (30.01-197.43) | 77.47 (27.54-208.73) | 1.00 |
| Platelets (count/mm3) | 233.6±71.7 | 238.0±68.9 | 0.60 |
| Baseline Hb (g/dL) | 14.3±1.6 | 13.8±1.5 | 0.01 |
| Minimum Hb (g/dL) | 12.6±1.7 | 12.6±1.8 | 0.99 |
| Maximum Hb loss (g/dL) | 1.7±1.2 | 1.3±1.6 | 0.03 |
| *Clinical outcomes* | | | |
| Persistent angina after PCI | 15 (10.7%) | 7 (5.1%) | 0.10 |
| In-hospital death | 13 (9.1%) | 5 (3.5%) | 0.09 |
| In-hospital MI | 2 (1.4%) | 3 (2.1%) | 0.65 |
| In-hospital stroke | 0 (0.0%) | 0 (0.0%) | na |
| In-hospital stent thrombosis (all in the first 48h) | 2 (1.4%) | 2 (1.4%) | 1.00 |
| Bleeding according to BARC | | | |
| BARC2 | 8 (5.6%) | 9 (6.3%) | 0.80 |
| BARC3 | 11 (7.7%) | 8 (5.6%) | 0.48 |
| BARC4 | 0 (0.0%) | 1 (0.7%) | 0.32 |
| BARC5 | 0 (0.0%) | 0 (0.0%) | na |
| Bleeding from arterial puncture site | 11 (7.7%) | 10 (7.0%) | 0.82 |
| CNS bleeding | 0 (0.0%) | 0 (0.0%) | na |
| Other bleedings | 10 (7.0%) | 9 (6.3%) | 0.81 |
| Need for transfusion | 3 (2.1%) | 5 (3.5%) | 0.47 |

(SD = standard deviation, cTnI = cardiac troponin I, Hb = haemoglobin, PCI= percutaneous coronary intervention, MI = myocardial infarction, BARC = bleeding academic research consortium, CNS = central nervous system).

Table 4: Variables independently associated with pre-procedural TIMI blood flow grade in the infarct related artery according to multiple regression analysis

| Independent variables | Coefficient | Std. Error | t | P | Coefficient | Std. Error | t | P |
|---|---|---|---|---|---|---|---|---|
| Age (years) | 0.0008 | 0.005 | 0.155 | 0.88 | | | | |
| Symptoms to balloon time (hours) | -0.062 | 0.02 | -3.05 | 0.003 | -0.062 | 0.02 | -3.1 | 0.002 |
| Type 2 diabetes | -0.032 | 0.015 | -0.22 | 0.83 | | | | |
| e GFR < 30cc/min | 0.32 | 0.28 | 1.16 | 0.25 | | | | |
| Anterior STE-ACS | 0.037 | 0.12 | 0.31 | 0.76 | | | | |
| Ticagrelor pre-treatment ≥ 1.5 hours before PCI | 0.34 | 0.12 | 2.87 | 0.004 | 0.35 | 0.12 | 2.95 | 0.004 |
| Overall model significance | | | | 0.004 | | | | 0.0002 |

(Std. = standard, e GFR = estimated glomerular filtration rate, STE-ACS = ST elevation acute coronary syndrome).

*Figure 1*

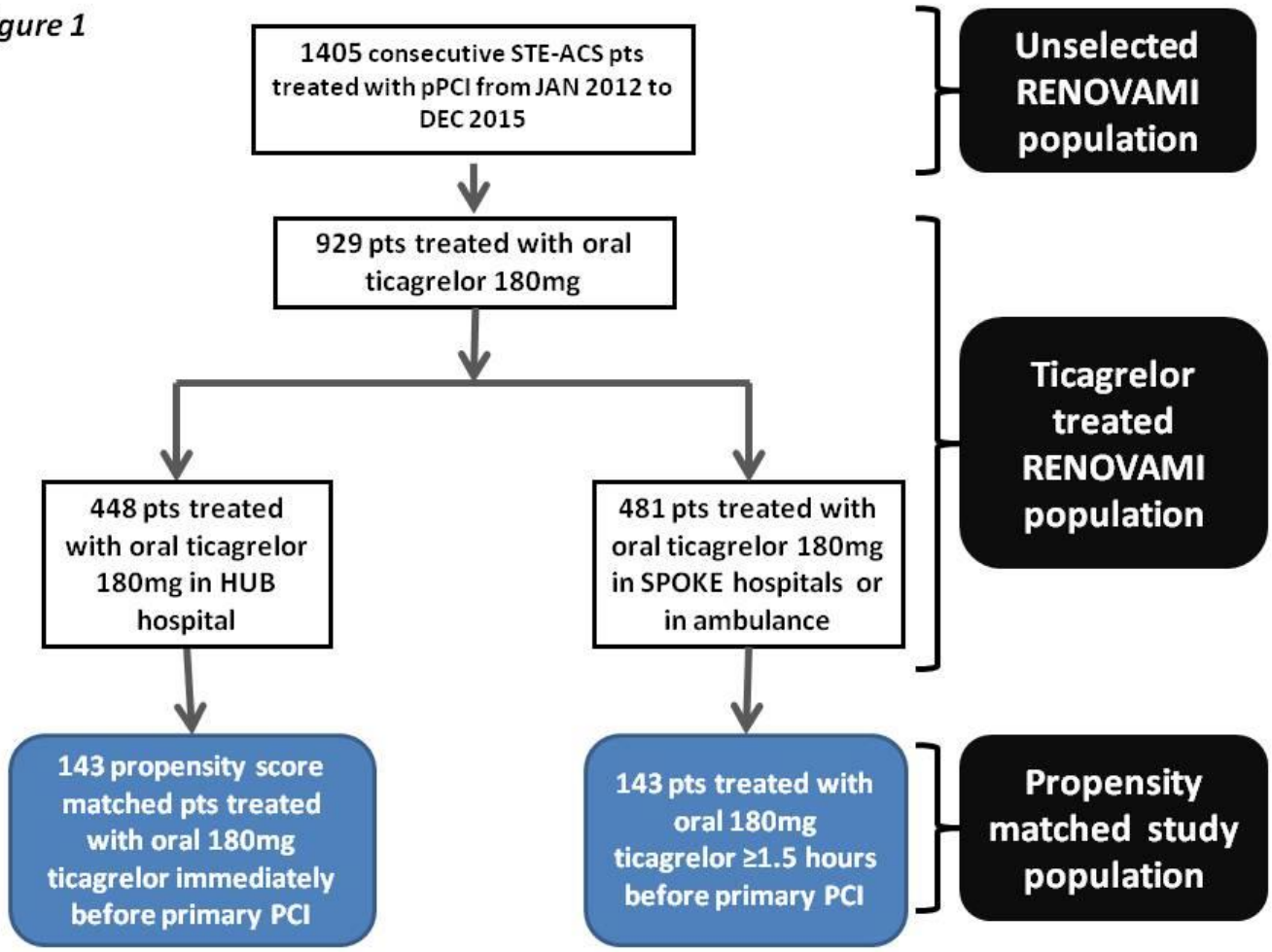
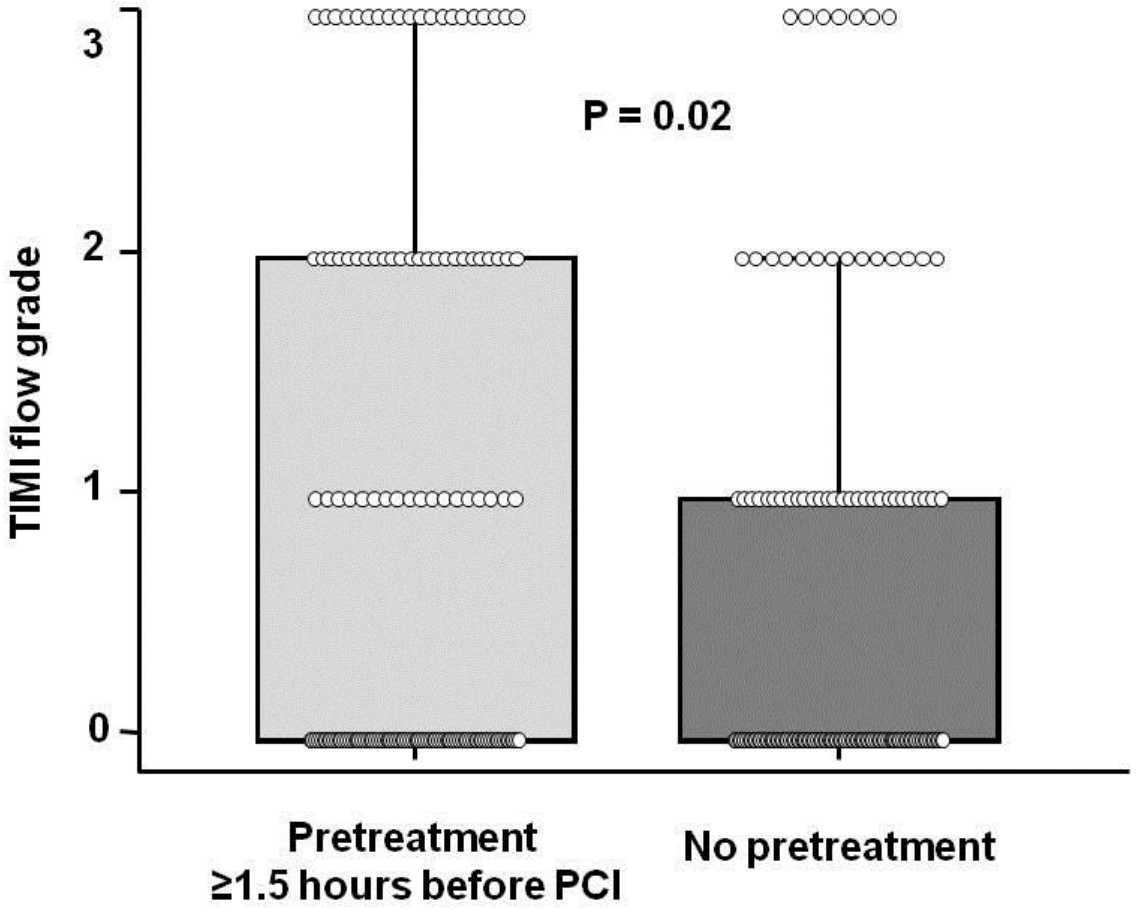


*Figure 2*



# Prehospital Ticagrelor in Patients with ST-Segment Elevation Myocardial Infarction with Long Transport Time to Primary PCI Facility

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## Highlights

- The ATLANTIC randomized study failed to demonstrate a superiority of ticagrelor pre-treatment before primary PCI, probably due to a too short interval between the drug administration and coronary angiography. Thus this treatment is not currently recommended before primary PCI.
- In many real world Hub & Spoke STEMI networks the time interval between ticagrelor administration and primary PCI may be much longer than those observed in the ATLANTIC study.
- In the large Italian STEMI registry RENOVAMI, ticagrelor pre-treatment at least 1.5 hours before primary PCI was safe and improved pre-PCI coronary reperfusion, in comparison with ticagrelor administration at the moment of primary PCI. These data support the hypothesis that, in selected patients with a long time from first medical contact and primary PCI, pre-treatment with ticagrelor may give some clinical benefit.