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Ticagrelor loading on ST-elevation myocardial infarction: interaction with pre-infarction angina on infarct size and clinical events

João Pedro Ferreira Faria

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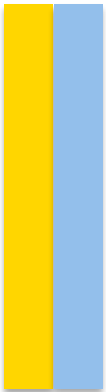

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Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

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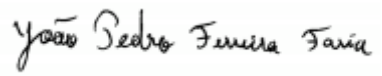
Estudante



(João Pedro Ferreira Faria)

Orientador

(Professor Doutor André Miguel Coimbra Luz)

Porto, junho de 2022

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Resumo

Introdução e Objetivos: O ticagrelor pode exercer um estímulo de condicionamento cardíaco. A angina pré-enfarte (PIA) é um estímulo de pré-condicionamento eficaz que reduz a lesão de isquemia-reperfusão. O objetivo deste estudo consiste em determinar se doentes com enfarte agudo do miocárdio com supradesnivelamento do segmento ST (EAMcST) tratados com ticagrelor tiveram melhores resultados clínicos e estudar a sua interação com a PIA.

Materiais e Métodos: De 1272 doentes com EAMcST submetidos a intervenção coronária percutânea primária e tratados com clopidogrel ou ticagrelor entre janeiro de 2008 e dezembro de 2018, 826 foram analisados após emparelhamento por score de propensão. O *endpoint* primário consistiu no tamanho de enfarte, estimado através do pico enzimático de creatinina quinase (CK) e troponina T (TnT). O *endpoint* secundário consistiu no somatório de eventos adversos cérebro-cardiovasculares major (MACCE) após 1 ano de seguimento. Foi também analisada a interação do ticagrelor com a PIA.

Resultados: Doentes tratados com ticagrelor tinham menor pico enzimático de CK [1405.50 (730.25-2491.00), $p<0.001$] e TnT [3.58 (1.73-6.59), $p<0.001$)], de forma independente da PIA. A PIA está associada a menor CK ($p=0.030$), mas não TnT ($p=0.097$). Não houve interação entre tratamento com ticagrelor e PIA ($p=0.788$ para TnT e $p=0.555$ for CK). Não houve diferenças na incidência de MACCE entre tratamento com clopidogrel ou ticagrelor ($p=0.129$). A sobrevivência cumulativa foi semelhante entre ticagrelor e clopidogrel, independentemente da PIA ($p=0.103$).

Conclusão: O ticagrelor reduziu tamanhos de enfarte de forma independente e sem efeito aditivo ou sinérgico com a PIA. Apesar de reduzir tamanhos de enfarte, os resultados clínicos foram semelhantes em ambos os grupos. O tratamento com ticagrelor pode influenciar o resultado de ensaios clínicos que estudam estratégias para reduzir o fenómeno isquemia-reperfusão.

Palavras-chave: ticagrelor; cardioproteção; condicionamento; EAMcST; angina pré-enfarte

Abstract

Introduction and Objectives: Ticagrelor might exert a potential conditioning stimulus. Pre-infarction angina (PIA) is an effective preconditioning stimulus that reduces ischemia-reperfusion injury. We sought to determine if patients presenting with ST-elevation myocardial infarction (STEMI) treated with ticagrelor had improved clinical outcomes and study its interaction with PIA.

Materials and Methods: From 1272 STEMI patients submitted to primary percutaneous coronary intervention and treated with clopidogrel or ticagrelor from January 2008 to December 2018, 826 were analyzed after propensity score matching. The primary endpoint was infarct size, estimated using peak creatinine kinase (CK) and troponin T (TnT). The secondary endpoint was cumulative major adverse cardiac and cerebrovascular events (MACCE) at 1-year follow-up. Matched patients and their interaction with PIA were analyzed.

Results: Patients loaded with ticagrelor had lower peak CK [1405.50 (730.25-2491.00), $p<0.001$] and TnT [3.58 (1.73-6.59), $p<0.001$)], regardless of PIA. The presence of PIA was associated with lower CK ($p=0.030$), but not TnT ($p=0.097$). There was no interaction between ticagrelor loading and PIA ($p=0.788$ for TnT and $p=0.555$ for CK). There was no difference in MACCE incidence between clopidogrel or ticagrelor loading ($p=0.129$). Cumulative survival was also similar between clopidogrel or ticagrelor, regardless of PIA ($p=0.103$).

Conclusion: Ticagrelor reduced infarct sizes independently and without an additive or synergic effect with PIA. Despite reducing infarct size, clinical outcomes were similar across both groups. Ticagrelor loading might influence the outcome of trials designed to overcome the reperfusion-injury phenomenon.

Keywords: ticagrelor; cardioprotection; conditioning; STEMI; pre-infarction angina

List of Abbreviations

ACE	Angiotensin-Converting Enzyme
ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CAD	Coronary Artery Disease
CK	Creatinine Kinase
eGFR	Estimated Glomerular Filtration Rate
ENT-1	Equilibrative Nucleoside Transporter-1
IABP	Intra-Aortic Balloon Pump
ICD	Implantable Cardioverter-Defibrillator
IR	Ischemia-Reperfusion
HF	Heart Failure
LAD	Left Anterior Descending artery
LCX	Left Circumflex Artery
LVEF	Left Ventricle Ejection Fraction
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MI	Myocardial Infarction
MPTP	Mitochondrial Permeability Transition Pore
PIA	Pre-Infarction Angina
PPCI	Primary Percutaneous Coronary Intervention
PS	Propensity Score
RCA	Right Coronary Artery
RISK	Reperfusion Injury Salvage Kinase
SAFE	Survival Activating Factor Enhancement
SD	Standard Deviation
STEMI	ST-Elevation Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target Lesion Revascularization
TnT	Troponin T

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Introduction

In patients presenting with ST-elevation myocardial infarction (STEMI), the best evidence-based approach in reducing infarct size and mortality is timely primary percutaneous coronary intervention (PPCI).[1] However, despite rescuing the ischemic cardiomyocytes from further infarction, reperfusion is also associated with an additional component of irreversible myocardial damage called the ischemia-reperfusion (IR) injury phenomenon.[2–4] While several cardioprotective strategies have consistently shown considerable promise in reducing the IR injury in preclinical studies, their translation to clinical practice has been unsatisfactory.[5–8]

Potent oral antiplatelet agents have been a mainstay of current PPCI to limit clot organization and to prevent stent thrombosis. Ticagrelor, a $P2Y_{12}$ inhibitor, has been used for this purpose in patients presenting with acute coronary syndrome (ACS).[1] It has been suggested that ticagrelor has pleiotropic effects, exerting a potential conditioning stimulus through the inhibition of the Equilibrative Nucleoside Transporter 1 (ENT-1), expressed on the surface of erythrocytes, which leads to reduced adenosine reuptake.[9–11] Adenosine would then act on cardiomyocytes, activating multiple pathways, including the Reperfusion Injury Salvage Kinase (RISK) and Survival Activating Factor Enhancement (SAFE) signaling pathways.[2,3] These are thought to promote the survival of the cardiomyocyte by inhibiting the mitochondrial permeability transition pore (MPTP) and stimulating the expression of cardioprotective genes.[2,3] However, there is inconsistent data regarding the potential cardioprotective effect of ticagrelor, with conflicting results.[12–17]

On the other hand, the presence of pre-infarction angina (PIA) has been most consistently shown to be an effective pre-conditioning stimulus in patients presenting with STEMI[2,18–20], protecting the cardiomyocyte from the IR injury. It is believed that, by reducing the IR injury, PIA may limit infarct size, reduce mortality, and improve left ventricle ejection fraction (LVEF).[15] PIA is a very potent preconditioning stimulus.[3] Therefore, it is possible that PIA may render additional cardioprotective agents irrelevant.

While several studies have researched the individual cardioprotective effect of ticagrelor and PIA, to the best of our knowledge, the potential synergism between PIA and ticagrelor has not yet been studied. Given the unmet need in identifying a strategy to limit the IR phenomenon, and postulating that ticagrelor loading in an already preconditioned patient might hamper any conditioning maneuver at reperfusion, our aim was to determine if ticagrelor loading in STEMI patients with or without preexisting PIA is related to improved outcomes.

Materials and Methods

Study population and definitions

We carried out a retrospective, observational, cohort study which included every consecutive patient with an admission for a STEMI who underwent PPCI, with a clearly identifiable culprit lesion, between January 1st 2008 and December 31st 2018, at a tertiary hospital. All patients were loaded with aspirin (500mg) and either clopidogrel (600mg) or ticagrelor (180mg) before PPCI. We excluded patients who were not treated with ticagrelor or clopidogrel at admission and those that switched the $P2Y_{12}$ inhibitor during hospital stay or at follow-up. We also excluded patients who presented with a culprit lesion at left main coronary artery or at a previous coronary bypass graft. For patients with multiple STEMI-related admissions, we only considered the first admission during the study period, with the remaining admissions being considered on follow-up. The diagnosis of STEMI was established according to the criteria defined by the European Society of Cardiology. [1] The clinical, demographic, laboratory and procedural data for these patients were retrospectively obtained by electronic medical chart review and included in an anonymized database.

PIA was diagnosed at admission when a patient presented arm, jaw, or chest pain, at rest or during exercise, lasting less than 20 minutes, in the week before the STEMI diagnosis. Total ischemic time is defined as the time between symptom onset and the passage of coronary guidewire with restoration of blood flow.

We calculated the Thrombolysis in Myocardial Infarction (TIMI) score, which gives an estimate of mortality in patients with STEMI[21], and the SYNTAX score, which estimates the complexity of multivessel coronary artery disease[22]. We stratified SYNTAX into 3 groups in order to have approximately a third of patients in each group: ≤16.00, 16.01-22.00 and ≥22.01. The estimated glomerular filtration rate (eGFR) was calculated according to the Cockcroft-Gault formula.

LVEF was calculated using 2D-echocardiography and stratified in four groups: good LVEF was considered for values equal to or higher than 55%; mild impairment was considered if LVEF was between 45-55%; moderate impairment if LVEF ranged from 35-45%; and severe impairment if LVEF lower than 35%.

The 1-year clinical follow-up data, regarding the occurrence of major cardiac and cerebrovascular events (MACCE) after the index STEMI, were obtained from electronic records by chart review. This study was approved by the ethics committee of Centro Hospitalar Universitário do Porto (2021.291[237-DEFI/245-CE]). Informed consents were waived due to the anonymization and retrospective nature of the study.

Definition of clinical outcomes

Our primary endpoint was infarct size, estimated using peak creatine kinase (CK) and peak troponin T (TnT) as surrogates. Our secondary endpoint was cumulative MACCE at 1 year follow-up. MACCE is a composite of death of any cause, stroke with imaging evidence, recurrent myocardial infarction (MI), and target lesion revascularization (TLR) (defined as angina or restenosis with ischemia, requiring reintervention, of a previous culprit lesion).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) when they followed a normal distribution or as median and interquartile range, between quartiles 25 (Q1) and 75 (Q3), when non-normally distributed. Categorical variables were represented as absolute values and percentages [n (%)]. The normality of distribution was assessed by Shapiro-Wilk and Kolmogorov-Smirnov tests.

To compare continuous variables between groups, we used an independent Student's *t* test or Mann-Whitney *U* test for non-normally distributed variables. To compare categorical values, we used χ^2 or Fisher exact tests, when appropriate.

The logarithmic transformation was applied to peak CK, peak TnT, total ischemic time and SYNTAX score in order to allow for parametric testing and adequate propensity score (PS) matching.

As the standard of antiplatelet therapy changed during the study period, with ticagrelor being favored over clopidogrel, we attempted to reduce the treatment assignment bias by using PS to match each patient treated with ticagrelor to a comparable patient treated with clopidogrel. To estimate the PS, we used seven baseline characteristics, namely sex (male/female), age (years), smoking habits (yes/no), diabetes mellitus (yes/no), dyslipidemia (yes/no), hypertension (yes/no), and eGFR (mL/min). We also used six variables related to procedural data, particularly TIMI and SYNTAX risk scores, anterior acute myocardial infarction (yes/no), LVEF at discharge (good/mild/moderate/severe), Killip class (≤2/≥3) and total ischemic time (minutes). The match tolerance was set at 0.01. We then performed all comparative analyses after PS matching.

To analyze the interaction between PIA and the use of ticagrelor or clopidogrel, a two-way factorial ANOVA was computed.

We estimated cumulative survival at follow-up with a Kaplan-Meier analysis, using the log-rank test for comparisons.

For all tests, a two-sided *p*-value less than 0.05 was considered statistically significant. We used SPSS version 27.0 (SPSS Inc., Chicago, Illinois, USA) for all comparative statistics and propensity score matching.

Results

Study population

A total of 1272 STEMI patients were treated by PPCI between January 1st 2008 and December 31st 2018. Of these, 1214 patients (95%) fulfilled the entry criteria and comprised our study sample. Supplementary tables SI and SII show the demographic and procedural characteristics and in-hospital outcomes, respectively, in accordance with ticagrelor vs clopidogrel loading, prior to PS matching. Patients who received ticagrelor were younger, had better renal function and were pre-treated more often with calcium channel blockers. Both groups presented similar procedural characteristics, except for door-to-balloon time, IIb/IIIa inhibitors and thrombectomy usage, and length of stay, which were lower on patients treated with ticagrelor. Furthermore, patients treated with clopidogrel had lower radial access and coronary disease complexity, as measured by the SYNTAX score. At discharge, patients treated with ticagrelor were less prescribed β-blockers and angiotensin-converting enzyme inhibitors. LVEF was not different at discharge from hospital.

By applying the PS matching as explained in the previous section, 413 patients loaded with ticagrelor were matched with 413 patients loaded with clopidogrel. Table I shows the baseline and procedural characteristics, and table II shows the in-hospital outcomes after PS matching. In patients treated with clopidogrel, although more patients [151 (36.7%)] presented PIA at admission, this difference was not statistically significant. The remaining baseline characteristics were identical between the studied groups. Regarding procedural characteristics, total ischemic time was comparable, whereas door-to-balloon time, IIb/IIIa inhibitors infusion, thrombectomy utilization and length of stay were lower in patients loaded with ticagrelor. Moreover, radial access and coronary artery disease complexity (SYNTAX score) were lower in patients treated with clopidogrel.

No follow-up data was available regarding MACCE in 3 patients (2%).

Outcomes

Patients treated with ticagrelor had a lower enzymatic activity for CK and TnT [1405.50 (730.25-2491.00) for CK, $p<0.001$, and 3.58 (1.73-6.59) for TnT, $p<0.001$)], regardless of PIA ($p<0.001$ for CK and TnT without PIA; $p=0.009$ for CK and $p=0.006$ for TnT in patients presenting with PIA) (Table III, fig.1). The presence of PIA was associated with lower CK values ($p=0.030$), but not TnT ($p=0.097$). No interaction was found between ticagrelor vs clopidogrel loading and PIA ($p=0.788$ for TnT and $p=0.555$ for CK).

Regarding MACCE at 1-year follow-up (table III, fig.2), while cumulative MACCE tended to be higher in patients treated with clopidogrel (13.3% vs 8.0% in patients loaded with ticagrelor), there

was no difference between clopidogrel or ticagrelor loading (p=0.129). Cumulative survival was also similar between clopidogrel or ticagrelor, regardless of PIA (p=0.103, fig. 3).

Discussion

In this study, we showed that ticagrelor reduced enzymatic activity when compared to clopidogrel and this effect is independent of PIA, which reduces peak CK, but not peak TnT. At discharge, there was no difference in LVEF between both groups. Also, there was no difference in MACCE at 1-year follow-up.

It has been consistently shown that the larger the infarct size, the higher the incidence of death, heart failure (HF) and an overall worse prognosis.[23] Our results show that, despite reducing peak CK and TnT, ticagrelor had no clinical impact in terms of MACCE reduction, despite tending to be lower in ticagrelor-loaded patients. The impact of ticagrelor as a cardioprotective strategy on MACCE or other hard endpoints has been controversial. The PLATO trial showed that ticagrelor reduced death from vascular causes, stroke, and MI in ACS patients.[24] Also, in a network meta-analysis comparing the efficacy and safety of $P2Y_{12}$ inhibitors in ACS, Navarese *et al* showed that ticagrelor reduced mortality when compared to clopidogrel and prasugrel.[16] However, in a STEMI population, Hjortbak *et al* demonstrated that, as compared to clopidogrel, ticagrelor led to lower hospitalization for HF at 1-year follow-up, while failing to show a difference in MACCE incidence.[25] While ticagrelor is related to smaller infarct sizes[26,27], its clinical impact may be blunted by other comorbidities or medications. It is also worth noting that many studies showing a reduction in mortality enrolled ACS patients, whether it referred to STEMI or not.[17,24,28] STEMI patients present with complete coronary occlusion[29], thus being more prone to IR injury that non-STEMI patients, and the confounding factor induced by non-STEMI patients could explain the disparities between studies.

Our results show that PIA reduces peak CK, but not TnT. This effect is independent of ticagrelor loading and, while not synergic, could potentially be additive. However, in our study, patients with PIA and loaded with ticagrelor had similar enzymatic activity to patients treated with ticagrelor who did not present PIA. It is not clear how PIA exerts cardioprotection, but it is thought to involve the activation of signaling pathways, among which the RISK and SAFE pathways, which ultimately target the MPTP.[3,30,31] As previously described, it is believed that ticagrelor exerts its cardioprotective effect through these pathways by enhancing local concentration of adenosine. In a preclinical trial in rabbits, Yang *et al* showed that when cangrelor, a $P2Y_{12}$ inhibitor, was combined with ischemic preconditioning, there was no additional cardioprotection when compared to cangrelor alone, suggesting they acted through a similar mechanism.[32] Therefore, this could explain the lack of additive effect in our study[33], as the cardioprotection provided by PIA might be superimposed by ticagrelor loading. However, there is still an advantage in ticagrelor loading, and this benefit, even if slight, is better than no benefit at all, especially among patients without PIA.

It is also possible that the current medical therapy for STEMI associated with PPCI, is optimized in such a way that cardioprotection is already at its possible maximum. This would possibly explain, in part, why most clinical trials testing other cardioprotective strategies show disappointing results.[34,35] However, these strategies have consistently been shown to reduce infarct sizes in a preclinical setting[2,3,33,36], and even in some clinical trials.[37,38] Therefore, a possible future direction would be to study the interaction of these strategies, with different cardioprotective mechanisms resembling current reperfusion modalities. It might be reasonable to say that PIA is the most powerful conditioning stimulus, which is the effect perconditioning maneuvers try to mirror at reperfusion. By sharing some of signaling cardioprotective pathways, our data suggests that ticagrelor loading might overtake the preconditioning effect afforded by PIA and might as well limit any postconditioning maneuver. Having those pathways already saturated after ticagrelor loading is a possible explanation. Of course, we cannot neglect the fact that its more potent antiplatelet effect might also have a role in limiting microvascular embolization and hence infarct size. Whichever the mechanism, we postulate that ticagrelor may limit the expected benefit of conditioning maneuvers, which should be taken into consideration in future trials.

At discharge, there was no difference in LVEF between groups. This could be partly explained by our stratification in 4 groups, according to a range of LVEF values. Regarding HF, by only evaluating LVEF, we are only identifying patients with HF with reduced ejection fraction, as we did not take HF signs and symptoms into consideration for this study. Another important aspect is that we may have overlooked an impact in cardiac remodeling that is not possible to identify from the evaluation of LVEF alone. The HEALING-AMI trial showed that, despite absolute LVEF being similar across the study sample, ticagrelor was associated with positive left ventricle remodeling.[15] This could explain the lower hospitalization for HF, as described in the referred studies above, and be the main endpoint to evaluate in further studies of cardioprotection.

Limitations

There are some limitations to our study. We did not evaluate hospitalization due to HF, which is an important clinical endpoint regarding the prognosis, mortality, and disease severity. We also did not take the value of NT-proBNP into consideration, as well as the variation in left ventricle diastolic or systolic volumes at 1 year follow-up, which could be better indicators of adverse cardiac remodeling.

Despite being a robust method and well correlated with imaging and clinical outcomes, we used CK and TnT as surrogates for infarct size instead of imaging techniques, such as cardiac magnetic resonance. These could be more rigorous in detecting true differences in infarct sizes and cardioprotective effects, as well as detecting the salvaged myocardia per the area at risk.[39]

We did not take into consideration which oral antidiabetic was used. Several studies have suggested that exenatide might have a putative cardioprotective effect[40,41], which we could have missed. We also did not consider whether hypertensive patients presented with left ventricle hypertrophy, which has been suggested to interfere with cardioprotection.[42]

Conclusions

In this propensity score-matched study of STEMI patients, we demonstrated that ticagrelor reduced infarct size. This effect is independent of PIA, and there was no additive or synergic effect between $P2Y_{12}$ inhibitor loading and PIA. The reduction of infarct size did not translate into better clinical outcomes, as the incidence of cumulative MACCE was not significantly different between groups. Since ticagrelor may significantly modulate infarct size as compared to clopidogrel, this should be taken into account in upcoming trials aiming to study cardioprotection in STEMI-patients.

Tables and Figures

Table I Baseline and procedural characteristics.

	Clopidogrel (n=413)	Ticagrelor (n=413)	*p*-value
Baseline characteristics			
Age (years) (mean ± SD)	61.82±13.37	61.96±12.34	0.877
Male [n (%)]	290 (70.2)	305 (73.8)	0.245
BMI (kg/m^2) (mean ± SD)	26.43±3.70	26.61±4.36	0.844
Diabetes mellitus [n (%)]	103 (24.9)	93 (22.5)	0.511
Hypertension [n (%)]	240 (58.1)	228 (55.2)	0.399
Dyslipidemia [n (%)]	230 (55.7)	214 (51.8)	0.264
Active smoker [n (%)]	233 (56.4)	221 (53.5)	0.401
Previous AMI [n (%)]	32 (7.8)	33 (8.0)	0.897
Peripheral artery disease [n (%)]	34 (8.3)	32 (7.7)	0.790
Family history of CAD [n (%)]	35 (13.4)	38 (9.2)	0.087
Pre-infarction angina [n (%)]	151 (36.7)	125 (30.3)	0.052
Creatinine (mg/dL) (Q1-Q3)	0.90 (0.74-1.08)	0.87 (0.73-1.03)	0.146
eGFR (ml/min/1.73 m^2) (Q1-Q3)	87.00 (63.00-111.00)	86.80 (63.00-112.39)	0.501
Hemoglobin at admission (g/dL) (mean ± SD)	14.09±1.79	14.06±1.70	0.799
Ongoing medications [n (%)]			
β-blocker	47 (11.4)	55 (13.4)	0.383
Statin	91 (22.0)	110 (26.8)	0.109
ACE inhibitor	71 (17.2)	59 (14.4)	0.264
Angiotensin receptor blocker	72 (17.5)	80 (19.5)	0.452
Calcium channel blocker	42 (10.2)	59 (14.4)	0.067
Aspirin	59 (14.3)	51 (12.4)	0.420
Clopidogrel	16 (3.9)	17 (4.1)	0.853
Insulin	17 (4.1)	20 (4.9)	0.614
Oral antidiabetics	72 (17.5)	62 (15.1)	0.345
Nitrates	22 (5.4)	14 (3.4)	0.173
Procedural characteristics			
Total ischemic time (minutes) (Q1-Q3)	240 (155.00-473.00)	240 (147.25-438.25)	0.482
Door-to-balloon time (minutes) (Q1-Q3)	80.00 (54.50-127.50)	72.50 (44.00-120.00)	0.023
Systolic BP (mmHg) (Q1-Q3)	121.00 (110.00-140.00)	120.00 (107.50-134.00)	0.108
Use of IIb/IIIa inhibitors [n (%)]	123 (29.9)	40 (9.7)	<0.001
Culprit artery [n (%)]			0.830
LAD	176 (42.8)	179 (44.0)	
LCX	58 (14.1)	61 (15.0)	
RCA	177 (43.1)	167 (41.0)	
Thrombectomy utilization [n (%)]	306 (74.1)	142 (34.4)	<0.001
Thrombectomy efficiency [n (%)]	272 (88.9)	122 (86.5)	0.472
No reflow [n (%)]	23 (5.6)	24 (5.8)	0.881
Radial access [n (%)]	184 (44.6)	385 (93.4)	<0.001

Killip class [n (%)]			0.816
≤2	371 (89.8)	373 (90.3)	
≥3	42 (10.2)	40 (9.7)	
TIMI score (Q1-Q3)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	0.706
Syntax score [n (%)]			0.002
≤16.00	178 (43.1)	182 (44.1)	
16.01-22.00	123 (29.8)	84 (20.3)	
≥22.01	112 (27.1)	147 (35.6)	
Length of stay (days) (Q1-Q3)	6 (5-9)	6 (5-8)	0.010
IABP [n (%)]	10 (2.4)	6 (1.5)	0.313

ACE – angiotensin converting enzyme; AMI - acute myocardial infarction; BMI - body mass index; BP – blood pressure; CAD - coronary artery disease; eGFR – estimated glomerular filtration rate; IABP – intra-aortic balloon pump; LAD -left anterior descending artery; LCX – left circumflex artery; RCA – right coronary artery; TIMI – thrombolysis in myocardial infarction.

Table II In-hospital outcomes.

	Clopidogrel (n=413)	Ticagrelor (n=413)	*p*-value
Intrahospital atrioventricular block [n (%)]	22 (5.3)	27 (6.6)	0.451
Intrahospital pacemaker or ICD [n (%)]	14 (3.4)	14 (3.4)	0.990
Medications at discharge [n (%)]			
β-blocker	381 (95.3)	328 (81.6)	<0.001
ACE inhibitor	316 (79.0)	208 (51.7)	<0.001
Statin	393 (98.3)	386 (96.0)	0.058
LVEF at discharge [n (%)]			0.202
Severe (<35%)	51 (12.3)	49 (11.9)	
Moderate (35-45%)	98 (23.7)	99 (24.0)	
Mild (45-55%)	84 (20.3)	108 (26.2)	
Good (>55%)	180 (43.6)	157 (38.0)	

ACE - angiotensin converting enzyme; ICD - implantable cardioverter defibrillator; LVEF - left ventricle ejection fraction

Table III Main outcomes.

	Clopidogrel (n=413)	Ticagrelor (n=413)	*p*-value
Peak CK (U/L) (Q1-Q3)	1726.50 (1044.75-3425.00)	1405.50 (730.25-2491.00)	<0.001[+]
Peak Troponin T (ng/mL) (Q1-Q3)	4.45 (2.56-7.88)	3.58 (1.73-6.59)	<0.001[+]
MACCE [n (%)]			0.129
Death	27 (6.6)	19 (4.6)	
Stroke	7 (1.7)	2 (0.5)	
Any MI	11 (2.7)	6 (1.5)	
TLR	10 (2.4)	6 (1.5)	
No event	357 (86.7)	378 (92.0)	

CK - Creatinine kinase; MACCE - major adverse cardiac and cerebrovascular events; MI – myocardial infarction; PIA - Pre-infarction angina; TLR – target leasion revascularization. [+]Compared by Student's t test after logarithmic transformation.

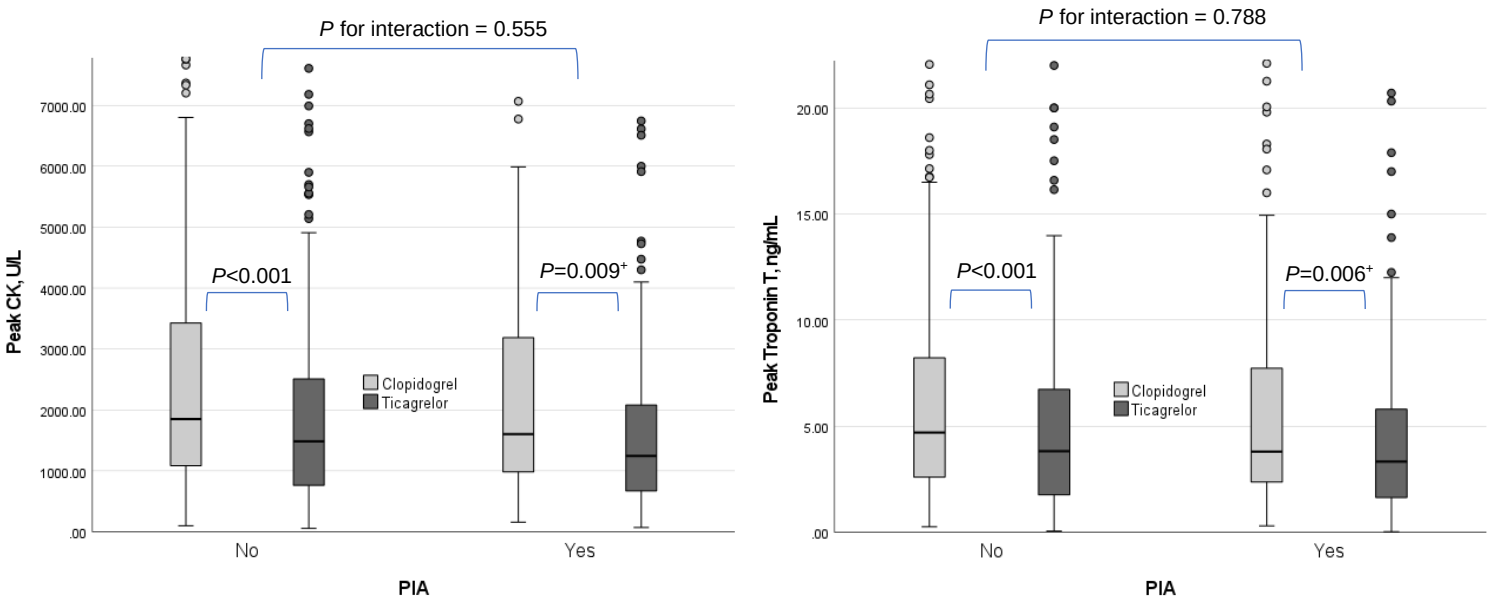

Fig. 1 Distribution of peak CK and peak troponin T according to PIA status. CK - creatinine kinase; PIA - pre-infarction angina. +Compared by Student's t test after logarithmic transformation.

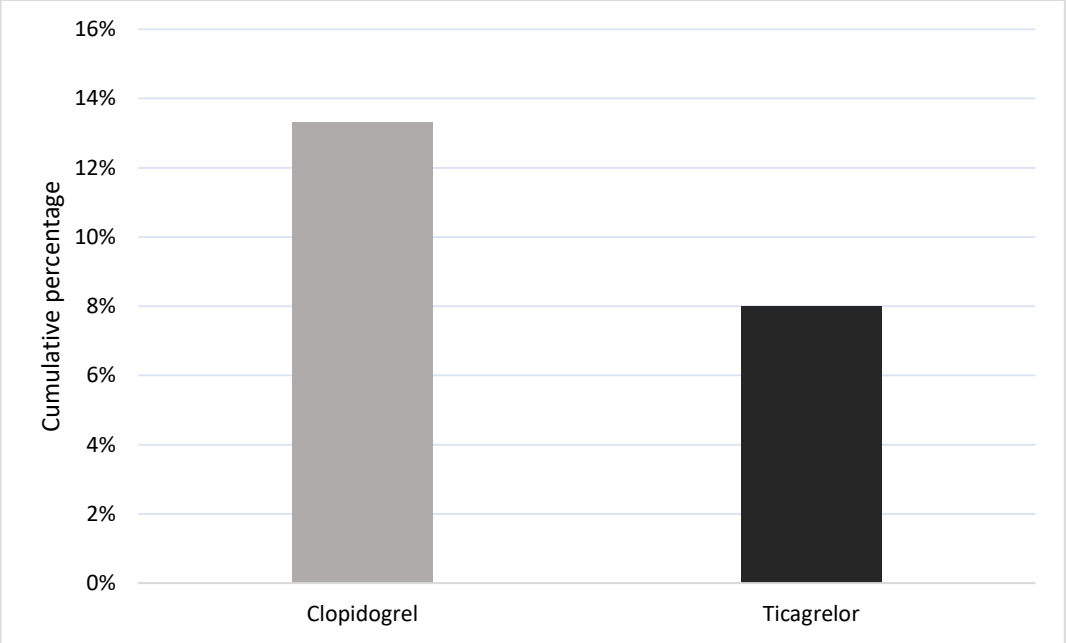

Fig. 2 Proportion of cumulative major cardiac and cerebrovascular events (MACCE) according to clopidogrel or ticagrelor loading.

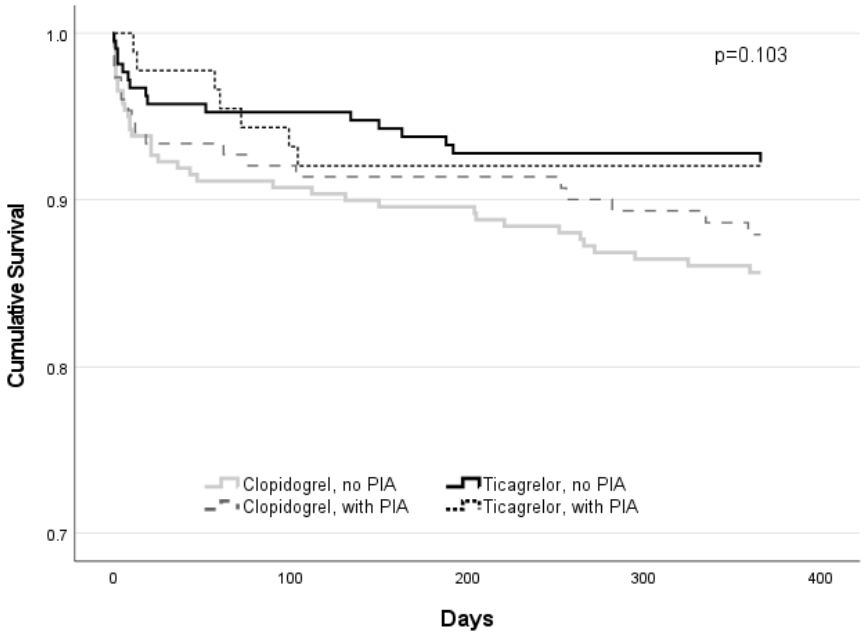

Fig. 3 Kaplan-Meier curves for cumulative survival. P-value represents the difference between groups. PIA - Pre-infarction angina

Supplementary tables

Table SI Baseline and procedural characteristics

	Clopidogrel (n=794)	Ticagrelor (n=452)	*p*-value
Baseline characteristics			
Age (years) (mean ± SD)	63.14±13.72	61.74±12.20	0.067
Male [n (%)]	590 (74.3)	328 (72.6)	0.502
BMI (kg/m^2) (mean ± SD)	26.41±3.79	26.58±4.34	0.487
Diabetes mellitus [n (%)]	199 (25.1)	104 (23.1)	0.415
Hypertension [n (%)]	452 (57.1)	251 (55.7)	0.611
Dyslipidemia [n (%)]	439 (55.4)	236 (52.4)	0.310
Active smoker [n (%)]	403 (50.9)	239 (52.9)	0.513
Previous AMI [n (%)]	67 (8.5)	37 (8.2)	0.869
Peripheral artery disease [n (%)]	71 (9.0)	36 (8.0)	0.532
Family history of CAD [n (%)]	67 (10.8)	40 (8.8)	0.283
Pre-infarction angina [n (%)]	255 (32.3)	141 (31.2)	0.693
Creatinine (mg/dL) (Q1-Q3)	0.91 (0.76-1.12)	0.87 (0.73-1.03)	0.002
eGFR (ml/min/1.73 m^2) (Q1-Q3)	83.60 (60.00-109.00)	87.60 (63.00-112.00)	0.023
Hemoglobin at admission (g/dL) (mean ± SD)	13.99±1.83	14.04±1.73	0.675
Ongoing medications [n (%)]			
β-blocker	97 (12.4)	62 (13.9)	0.461
Statin	182 (23.2)	121 (27.1)	0.134
ACE inhibitor	143 (18.3)	65 (14.5)	0.092
Angiotensin receptor blocker	134 (17.1)	89 (19.9)	0.225
Calcium channel blocker	78 (10.0)	66 (14.8)	0.012
Aspirin	116 (14.8)	58 (12.9)	0.361
Clopidogrel	37 (4.7)	18 (4.0)	0.560
Insulin	35 (4.5)	21 (4.7)	0.868
Oral antidiabetics	137 (17.5)	74 (16.5)	0.635
Nitrates	38 (4.9)	19 (4.2)	0.616
Procedural characteristics			
Total ischemic time (minutes) (Q1-Q3)	240 (155.00-480.00)	240 (146.50-457.50)	0.655
Door-to-balloon time (minutes) (Q1-Q3)	80.00 (55.00-130.00)	74.00 (44.00-120.00)	0.014
Systolic BP (mmHg) (Q1-Q3)	120.00 (105.00-139.00)	120.00 (106.00-133.00)	0.916
Use of IIb/IIIa inhibitors [n (%)]	200 (25.4)	47 (10.4)	<0.001
Culprit artery [n (%)]			0.455
LAD	330 (42.5)	200 (45.4)	
LCX	110 (14.2)	66 (15.0)	
RCA	337 (43.4)	175 (39.7)	
Thrombectomy utilization [n (%)]	492 (62.0)	153 (33.9)	<0.001
Thrombectomy efficiency [n (%)]	413 (84.1)	131 (86.8)	0.430
No reflow [n (%)]	65 (8.2)	26 (5.8)	0.112
Radial access [n (%)]	464 (58.7)	415 (92.0)	<0.001
Killip class [n (%)]			0.107
≤2	674 (85.4)	399 (88.7)	

≥3	115 (14.6)	51 (11.3)	
TIMI score (Q1-Q3)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	0.315
Syntax score [n (%)]			0.018
≤16.00	340 (43.0)	187 (42.1)	
16.01-22.00	210 (26.6)	92 (20.7)	
≥22.01	240 (30.4)	165 (37.2)	
Length of stay (days) (Q1-Q3)	6 (5-8)	6 (4-8)	0.023
IABP [n (%)]	20 (2.5)	8 (1.8)	0.384

ACE – angiotensin converting enzyme; AMI - acute myocardial infarction; BMI - body mass index; BP – blood pressure; CAD - coronary artery disease; eGFR – estimated glomerular filtration rate; IABP – intra-aortic balloon pump; LAD -left anterior descending artery; LCX – left circumflex artery; RCA – right coronary artery; TIMI – thrombolysis in myocardial infarction.

Table SII In-hospital outcomes

	Clopidogrel (n=413)	Ticagrelor (n=413)	*p*-value
Intrahospital atrioventricular block [n (%)]	39 (4.9)	29 (6.4)	0.262
Intrahospital pacemaker or ICD [n (%)]	31 (3.9)	15 (3.4)	0.600
Medications at discharge [n (%)]			
β-blocker	642 (89.4)	352 (81.9)	<0.001
ACE inhibitor	493 (68.7)	217 (50.6)	<0.001
Statin	693 (97.1)	412 (95.8)	0.261
LVEF at discharge [n (%)]			0.414
Severe (<35%)	110 (14.6)	56 (12.7)	
Moderate (35-45%)	170 (22.6)	103 (23.4)	
Mild (45-55%)	168 (22.4)	115 (26.1)	
Good (>55%)	303 (40.3)	167 (37.9)	

ACE - angiotensin converting enzyme; ICD - implantable cardioverter defibrillator; LVEF - left ventricle ejection fraction

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