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Letter to the Editor

Protective activity of Ticagrelor against bacterial infection in acute myocardial infarction patients

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Dear Editor,

Recent investigations have suggested some antimicrobial properties of Ticagrelor [1,2], a reversible inhibitor of platelet adenosine diphosphate P2Y12 receptor, helpful to prevent cardiovascular events in ischemic heart disease but also used in patients undergoing primary percutaneous intervention (PCI) in acute myocardial infarction [3]. Moreover, a recent an animal study has described a bactericidal activity of ticagrelor against antibiotic-resistant gram -positive bacteria [4]. We questioned whether Ticagrelor could protect against unspecified staphylococcus aureus infection after primary PCI in those patients subsequently hospitalized in Intensive Cardiac Care Unit (ICCU) [5].

We retrospectively analysed the clinical and instrumental records of consecutive patients referred to our tertiary center for primary PCI in ST- segment elevation acute myocardial infarction (STEMI) between 1st January 2012 and 1st January 2019. Patients were included in the study if: 1) they have at least 3 positive haemocultures after 48 h from the PCI, for methicillin- sensible staphylococcus aureus (MSSA, ATCC 25,904 and ATCC 6538) or methicillin-resistant staphylococcus aureus (MRSA, ATCC BAA 1556); 2) they received, as antiplatelet regimen before the PCI:

-Ticagrelor 180 mg loading dose followed by 90 mg twice a day plus Aspirin 100 mg daily

or

- Clopidogrel 600 mg loading dose followed by 75 mg daily plus aspirin 100 mg daily.

3) they received the same antibacterial treatment for the MSSA or MRSA and specifically Piperacillin/Tazobactan for the former and Vancomycin for the latter, accordingly to the antibiogram results and optimized for renal function.

Patients treated with other antibiotic drugs and/or antiplatelet regimens or oral anticoagulants were excluded from the analysis.

STEMI and septic shock waswere defined and diagnosed as per current guidelines [3,6].

MIC of anti-MRSA drugs was evaluated by the E-test (SYSMEX bioMerieux Co. Ltd) and the micro-dilutional test using Microscan® (SIEMENS, CA, USA).

The study outcomes were cardiovascular and all-causes 30-day mortalities. The local Ethics Board approved the study.

Continues and categorical variables were expressed as mean ± standard deviation (SD) or percentage and were compared by Student' *t*-test or Wilcoxon-Mann-Whitney U test and Pearson's $\chi 2$ test. To estimate 30-mortality, the Kaplan–Meier method and the log-rank test were applied. Statistical significance was defined as $p < 0.05$.

Over the study period, 284 patients met the inclusion criteria and were retrospectively analysed (Table 1). Demographic, clinical and procedural characteristics were observed among MSSA and MRSA groups and different antiplatelet regimens. Ticagrelor and Clopidogrel were administered in 104 (55.3%) and 84 (46.8%) subjects among MSSA patients and in 52 patients (54.1%) and 44 (45.8%) among MRSA patients, respectively.

A significant difference for all-cause mortality was observed among patients treated with Ticagrelor and Clopidogrel in both MSSA (2.8% vs 14.2%, $p = 0.004$). and MRSA groups (3.8% vs 15.9%, $p = 0.04$), respectively. On the contrary, no significant differences were observed considering the 30-cardiovascular mortality among Ticagrelor and Clopidogrel patients in MSSA (1.9% VS 1.1%, $p = 0.65$) and MRSA group (3.8% vs 4.5%, $p = 0.86$), respectively (Fig.1).

Our study suggested a potential antibacterial benefit, in terms of all-cause mortality, in patients treated with Ticagrelor and having a MSSA or MRSA infection after a STEMI. STEMI is certainly a very delicate setting and with the increasing use of supporting devices and complex percutaneous recanalization procedures, the risk of dangerous infections is consistent configuring an ideal field where to test an eventual antibacterial protection offered by Ticagrelor.

Although the study is a retrospective small sample and not powered for addressing the real contribution of a potential antibacterial activity of Ticagrelor against different bacterial infections\, the significant difference in all causes-mortality between Ticagrelor and Clopidogrel treated groups of patients fits particularly well with the initial hypothesis raised by the early phases studies [1,2] and recently confirmed in the animals [4] of a certain antibacterial protection of Ticagrelor.

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Table 1
Demographics and clinical characteristics of the study population.

	MSSA N = 188 Ticagrelor N = 104	Clopidogrel N = 84	*P*	MRSA N = 96 Ticagrelor N = 52	Clopidogrel N = 44	*p*
Mean age (year)	69.4 ± 14.2	72.6 ± 13.6	0.11	69.9 ± 14.1	73.2 ± 11.6	0.21
Males n(%)	45 (40.3)	40 (47.6)	0.31	26 (50.0)	20 (45.4)	0.65
STEMI localization						
-anterior	34 (32.6)	31 (36.9)	0.53	21 (40.3)	15 (34.0)	0.52
-inferior	28 (26.9)	24 (28.5)	0.80	13 (25.0)	13 (29.5)	0.62
-lateral	39 (37.5)	32 (38.0)	0.94	18 (34.6)	17 (38.6)	0.68
Septic shock	4 (3.8)	27 (32.1)	<0.001	4 (7.6)	16 (36.3)	<0.001
DB time (minutes)	45.1 ± 14.6	41.3 ± 13.2	0.66	45.3 ± 10.2	49.6 ± 14.3	0.90
IABP	27 (25.9)	25 (29.7)	0.56	17 (32.6)	12 (27.2)	0.56
Final TIMI 3	96 (92.3)	76 (90.4)	0.64	46 (88.4)	38 (86.3)	0.75
Cardiogenic shock	21 (20.1)	17 (16.6)	0.54	7 (13.4)	5 (11.3)	0.75
MV	26 (25.0)	22 (26.1)	0.86	18 (34.6)	19 (43.1)	0.39
VT	8 (7.6)	4 (4.7)	0.42	4 (7.6)	5 (11.3)	0.55
Prosthetic valve	28 (26.9)	24 (28.5)	0.80	16 (30.7)	15 (34.0)	0.97
Vegetations	18 (17.3)	17 (20.2)	0.61	11 (21.1)	9 (20.4)	0.93

DR: door to balloon time; IABP: intraaortic balloon pump; MV: mechanical ventilation; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction count; VT: ventricular arrhythmias.

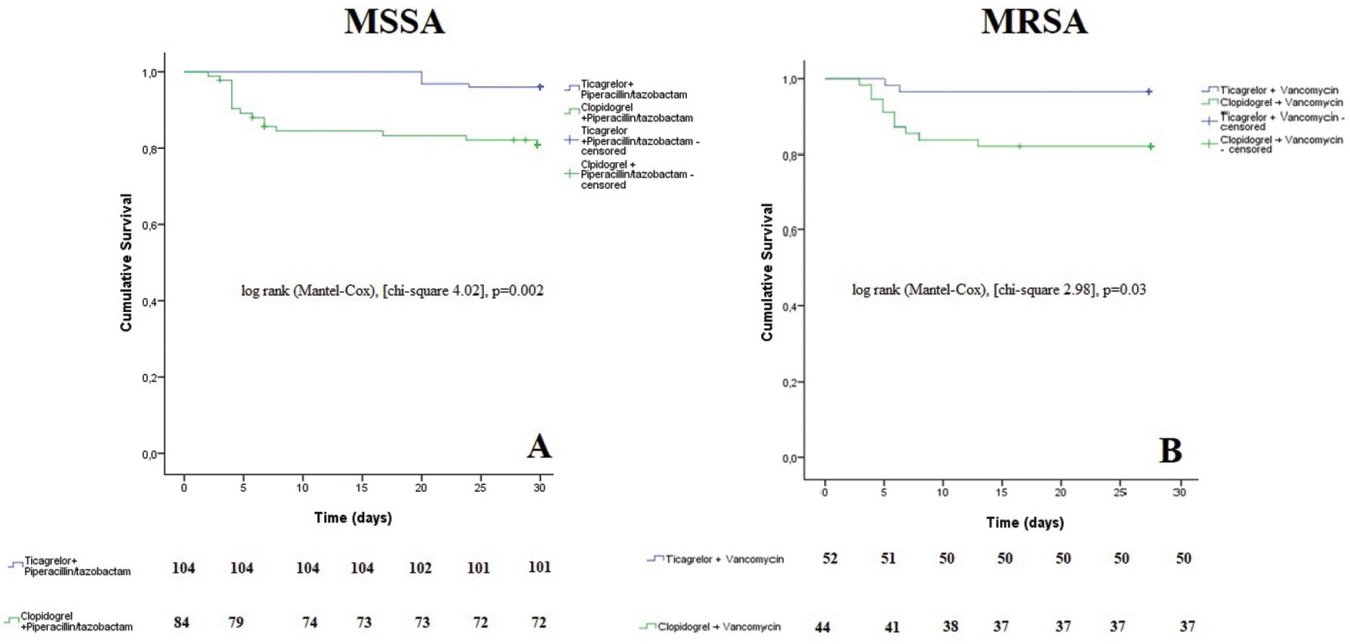

Fig. 1. Kaplan-Meir analysis of 30-day mortality in patients with Ticagrelor and clopidogrel in MSSA (A) and MRSA (B) patients.

Our results, if confirmed by larger and properly powered studies, would be important in understanding the contribution of Ticagrelor to lower short-term mortality in STEMI patients.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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