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Safety and effectiveness of the new P2Y12r inhibitor agents vs clopidogrel in ACS patients according to the geographic area: East Asia vs Europe

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ABSTRACT

Background: In the setting of the Acute Coronary Syndrome (ACS), differences in response to prasugrel and ticagrelor between East Asian and European patients have not been investigated yet.
Methods: This is a sub-analysis of the "BleeMACS registry". Patients admitted for ACS and underwent PCI from between 2012 and 2014 were stratified first according to their provenance, Europe vs. East Asia (China and Japan), and then by country. The adjusted rate of 1-year serious bleeding -safety end-point- and 1-year death/re-infarction -effectiveness endpoint- of the new P2Y12r inhibitors were compared.
Results: Data of 10004 patients in Europe and 2332 patients in East Asia were collected. At baseline prior stroke (6% vs 9%, $p < 0.001$, respectively) and type of ACS (59% vs 71% STEMI, 11% vs 21% Unstable Angina) were significantly different among the groups. At 1 year follow-up no difference in bleeding (3% vs 3%, $p = 0.84$) was found, while the between group incidence of death/re-infarction was significantly higher in the European centers (9% vs 5%, $p < 0.001$). At the multivariate analysis, ticagrelor decreases the risk of MACE (Europe: HR 0.5, CI 0.3–0.9; East Asia: HR 0.5, CI 0.2–0.9), despite of a higher risk of bleeding in Caucasians (HR 1.7, CI 1.1–2.6). Prasugrel reduces death/re-infarction (HR 0.4, CI 0.2–0.6), without increasing bleeding (HR 0.9, CI 0.5–1.3).
Conclusions: In the setting of the ACS, the new anti-platelets drugs appear to be safe and efficacious at mid-term

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follow-up independently from the geographic area. Prasugrel seems to have the best risk–benefit, while ticagrelor appears safer in East Asians.

1. Introduction

In the last years, two new molecules - prasugrel and ticagrelor- have been introduced into clinical practice for the treatment of patients affected by Acute Coronary Syndrome (ACS).

TRITON-TIMI 38 has shown that prasugrel, at a loading dose of 60 mg followed by 10 mg daily, reduces the risk of ischemic events at follow-up compared to clopidogrel, although at the expense of increased major bleeding [1].

Similarly, in the PLATO trial, ticagrelor, at doses of 180 mg loading and 90 mg twice a day, significantly reduces the rate of death from vascular causes, heart attack or stroke, and death from any cause compared with clopidogrel, without a significant increase in the rate of major bleeding, at a price of a higher incidence of dyspnoea and atrium-ventricular blocks [2]. According to these studies, in the 2012, prasugrel and ticagrelor have been validated by European guidelines as well as by the ACC/AHA guidelines (2014, class IB), for the treatment of acute myocardial infarction with and without ST-segment elevation, as second antiplatelet drug in addition to aspirin (class IB) [3,4].

This evidence is limited in scope because of strict inclusion criteria. In particular, differences in response to these new anti-platelets agents according to ethnicity have not been largely investigated [5,6]. For example, an increasing body of data suggests that East Asian patients have different risk profiles for both thrombotic events and bleeding compared to Caucasian patients. In particular, the so-called "East Asian paradox" has been recognized, that is a lower rate of ischemic events after PCI in East Asian patients compared to Caucasian ones, despite a higher level of platelet reactivity during PCI [7]. Despite this, few East Asian patients have been included in the trials to assess the use of these newer agents, prasugrel (<1% in the TIMI-TRITON 38) and ticagrelor (3.5% in the PLATO trial), and the World Heart Federation had then produced an expert consensus statement to determine the best treatment strategies for these patients [8].

The "Bleeding complications in a Multicenter international registry of patients discharged after an Acute Coronary Syndrome (BleeMACS)" project, an international observational database of outcomes for patients who underwent Percutaneous Coronary Intervention (PCI) and are discharged with diagnosis of ACS, has been built to characterize patients at high risk of bleeding and to develop a risk score to accurately predict the risk of major bleeding within the first year after discharge from the hospital for an ACS.

In this scenario, this sub-analysis of the BleeMACS registry aims to appraise potential differences in response to different antiplatelet drugs according to ethnicity, in terms of bleedings and ischemic events.

2. Methods

This is a sub-analysis of the international multicenter BleeMACS registry.

The analysis has included the patients consecutively admitted to the Cardiology Departments of the European (Spain, Holland, Greece, Germany, Italy, Poland) and East Asian (China, Japan) Centers involved in the BleeMACS registry, from January 2012 to December 2014, that complied with the following criteria: age above 18, admission to hospital for ACS and PCI treatment. ACS included ST-elevation myocardial infarction (STEMI), non ST-elevation myocardial infarction (NSTEMI) and Unstable Angina (UA), diagnosed as per standard definition [9]. Both drug eluting stents (DES) and bare metal stents (BMS) were implanted, according to the coronary anatomy and to the patients co-morbidities. Exclusion criteria were: age under 18 or admission for stable angina with indication to double anti-platelets therapy.

Clinical and laboratory data, as well as procedural features, were collected at admission. History of bleeding included prior bleeding and in-hospital bleeding. Prior bleeding included any episode of serious bleeding, defined as intracranial bleeding or any other bleeding leading to hospitalization and/or red blood transfusion, occurred before the qualifying ACS hospitalization. In-hospital bleeding was defined as follows:

- TIMI (Thrombolysis In Myocardial Infarction) major or TIMI minor bleeding, or
- GUSTO (Streptokinase and t-PA for Occluded Coronary Arteries) severe or moderate bleeding, or
- BARC (Bleeding Academic Research Consortium) type 3 bleeding [10–12]

Vascular disease was defined as prior stroke/transient ischemic attack or peripheral arterial disease (PAD). Malignancy was defined as any active cancer or any non-active cancer diagnosed in the last 5 years.

Apart from aspirin, the choice of the second anti-platelets drug (clopidogrel, ticagrelor or prasugrel) was driven by the physician preference, according to the international guidelines, and by the internal protocol of the single Centre involved in the study.

Patients were divided on the basis of the location of the Centres, according to a classification which distinguishes, at higher level, the two macro-regions Europe and Asia, and, at lower level, the interested countries of each region, i.e. China and Japan for Asia, and Spain, Holland, Greece, Germany, Italy and Poland, for Europe. It was assumed that, for most patients, ethnicity and region of the Centre did correspond.

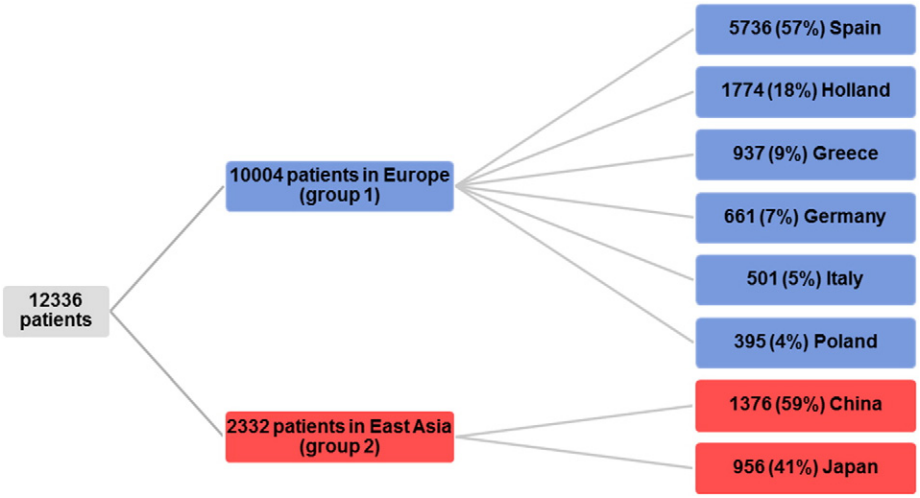


Fig. 1. Patient's sub-groups, according to the belonging country.

3. Endpoints

The primary end-point was the safety (one-year serious bleeding) of the new P2Y12r inhibitors in the different Countries involved in the BleeMACS registry (Europe and East Asia)[xi].

The secondary end-point was the efficacy (one-year FU composite of death and re-infarction) of the new P2Y12r inhibitors in the different Countries involved in the BleeMACS registry (Europe and Asia).

Data on the vital status (alive vs. dead) and information about bleeding were obtained from hospital or national records, by contacting the patients or their relatives by phone, and/or by contacting the primary care physicians, as necessary, for additional information. At least two physicians involved in the study (FDA; SRS) adjudicated each event.

3.1. Statistical analysis

Through statistical analysis, the two groups were compared with each other, in relation to the end-points measured. Comparing the various approaches of dual anti-platelets treatments of the Centres, subgroups of patients were identified according to the level of benefit derived from the different treatments.

Categorical variables were compared by chi-square test and Fisher's exact test for 2 × 2 tables. Parametric distribution of continuous variables (presented as mean ± SD) was tested graphically and with Kolmorogov Smirnov, and appropriate analysis was used according to the results [13]: the t-test was used to assess differences between parametric continuous variables, Man-Whitney U test for non parametric variables.

Relative Risk (RR) to assess clinical factor relevance on outcome. Furthermore, significant variables were compared with Cox regression analysis to assess bleeding, death and re-infarction predictors in general population and independent impact of geographic area. The Kaplan-Maier survival analysis, to compare categorical variables tested by log-rank test, and sensitivity analysis, for the prescribed anti-platelet therapy at discharge, were performed.

For constructing the multivariate models, all the variables significant at univariate analysis were included: type of anti-platelets therapy, female gender, diabetes mellitus, malignancy and STEMI. A two-sided P value < 0.05 was considered statistically significant; all analyses were performed with SPSS 21.0 (IBM, Armonk, NY, USA).

4. Results

12,336 consecutive patients have been included, 10004 in Europe (group 1) and 2332 in East Asia (group 2). Among Caucasian patients, 5736 (57%) came from Spain, 1774 (18%) from Holland, 937 (9%) from Greece, 661 (7%) from Germany, 501 (5%) from Italy and 395 (4%) from Poland. Among the East Asian group, 1376 (59%) were Chinese, the other 956 (41%) Japanese (Fig. 1).

At baseline, a significant difference between groups was found in prior stroke (6% vs 9%, p < 0.001, respectively), malignancy (7% vs 5%, p = 0.03) and type of SCA (59% vs 71% STEMI, 11% vs 21% Unstable Angina). 460 (5%) Caucasian patients vs 85 (4%) East Asian patients have experienced previous bleeding (p = 0.04) and 156 (2%) vs 11 (0%) have an history of ulcus. Drug eluting stent were implanted in the majority of patients (87%) of the group 2, while only 37% of the group 1 received a DES (p < 0.001) (Table 1).

Apart from 1% of Caucasian patients, everybody was discharged with Aspirin. A significant difference between groups was registered in the use of clopidogrel (86% vs 91%, p < 0.001), ticagrelor (5% vs 6%, p = 0.01) and prasugrel (7% vs 0%, p < 0.001), while no difference in the use of double or triple anti-platelets therapy was found (Table 2).

4.1. Safety end-point

At 1 year FU, no differences were found between Caucasians and East Asians (3% vs 3%, p = 0.84), also comparing the rate of bleeding according to the anti-platelets received (Clopidogrel 2.9% vs 2.6%, p = 0.51,

Table 1
Baseline characteristics. ACE, Angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; CABG, coronary artery by-pass grafting; DES, drug eluting stent implantation; Hb, haemoglobin; LVEF, left ventricular ejection fraction; NSTEMI, non ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation acute myocardial infarction; UA, unstable angina.

	European patients, n = 10,004, *n* (%) or *mean* ± *DS*	East Asian patients, n = 2334, *n* (%) or *mean* ± *DS*	P value
Age, *yo*	64.5 ± 12.8	62.2 ± 12.7	<0.001
Female	2342 (23)	508 (22)	ns
Diabetes mellitus	2425 (24)	675 (29)	<0.001
Artery hypertension	5668 (57)	1449 (62)	<0.001
Dyslipidemia	4653 (47)	1198 (51)	<0.001
Periferal artery disease	784 (8)	55 (2)	<0.001
Prior AMI	1317 (13)	199 (9)	<0.001
Prior PCI	1228 (12)	267 (11)	ns
Prior CABG	407 (4)	27 (1)	<0.001
Previous stroke	575 (6)	205 (9)	<0.001
History of chronic heart failure	262 (3)	36 (2)	0.002
Currently malignancy	672 (7)	128 (5)	0.03
History of Bleeding	460 (5)	85 (4)	0.04
Previous ulcus	156 (2)	11 (0)	<0.001
Clinical presentation			
. STEMI	5859 (59)	1667 (71)	<0.001
. UA	1093 (11)	492 (21)	<0.001
. NSTEMI	3052 (31)	173 (7)	<0.001
Killip classification 2[a]	1196 (12)	436 (19)	<0.001
LVEF, %	53,1 ± 11.4	56.5 ± 11.5	<0.001
Hb at admission, *mg/dl*	13.9 ± 1.7	13.6 ± 2	<0.001
Hb at discharge, *mg/dl*	13 ± 2.3	13 ± 2.8	0.72
Creatinine at admission, *mg/dl*	0.9 ± 0.5	0.9 ± 0.5	<0.001
Femoral access	4636 (46)	1705 (73)	<0.001
Multivessel disease	4232 (42)	1031 (44)	ns
DES implantation	3645 (36)	2023 (87)	<0.001
PCI whithout stenting	463 (5)	39 (2)	<0.001
Trombolysis	193 (2)	39 (2)	ns
Complete revascularization	6003 (60)	1046 (45)	<0.001
Therapy at discharge			
. Oral anti-coagulant	594 (6)	132 (6)	ns
. Beta-blockers	8540 (85)	1593 (68)	<0.001
. ACE-i or ARB	7668 (77)	1650 (71)	<0.001
. Statin	9468 (95)	1997 (86)	<0.001
. Proton pump-inhibitor	4808 (48)	944 (40)	<0.001

[a] *Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol. 1967 Oct.;20(4):457–64.*

Table 2
Differences in anti-platelets therapy between European and East Asian patients at discharge. DAPT, double anti-platelet therapy, SAPT, single anti-platelet therapy, TAPT, triple anti-platelet therapy.

	European patients, n = 10,004, *n* (%) or *mean* ± *DS*	East Asian patients, n = 2334, *n* (%) or *mean* ± *DS*	P value
Aspirin	9859 (99)	2324 (100)	Ns
Clopidogrel	8612 (86)	2132 (91)	<0.001
Ticagrelor	464 (5)	136 (6)	0.01
Prasugrel	665 (7)	0	<0.001
SAPT	241 (2)	36 (2)	0.01
DAPT	9629 (96)	2263 (97)	Ns
TAPT	460 (5)	99 (4)	Ns
Anti-coagulation only	34 (0)	3 (0)	Ns

Table 3
Primary and Secondary end-point. AMI, acute myocardial infarction; FU, follow-up.

	European patients, n = 10,004, *n* (%) or *mean* ± *DS*	East Asian patients, n = 2334, *n* (%) or *mean* ± *DS*	P value
1 year-FU bleeding	349 (3)	68 (3)	0.18
Transfusion	108 (1)	29 (1)	ns
Time_bleeding	349.4 ± 62.7	348.9 ± 65.7	0.12
1 year-FU death or re-AMI	866 (9)	105 (5)	<0.001
1 year FU death	452 (5)	73 (3)	0.003
Time to death	354.8 ± 51.3	356.7 ± 49.1	0.126
1 year FU re-AMI	414 (4)	32 (1)	<0.001

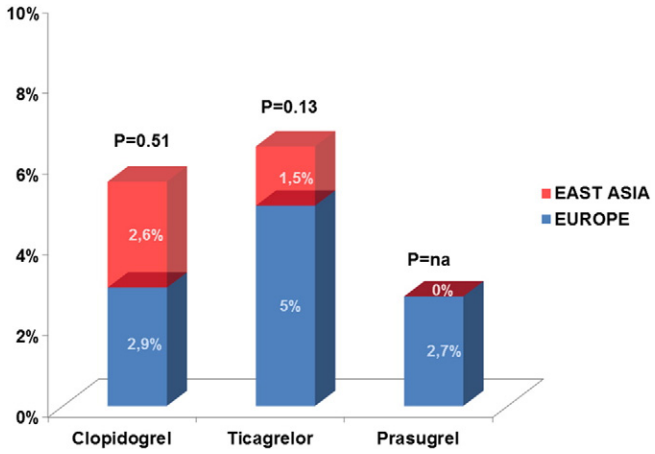


Fig. 2. Comparison of 1-year follow-up bleeding In European and East Asian patients, stratifying the population according to the anti-platelets received. A, aspirin; C, clopidogrel; FU, follow-up; P, prasugrel; T, ticagrelor.

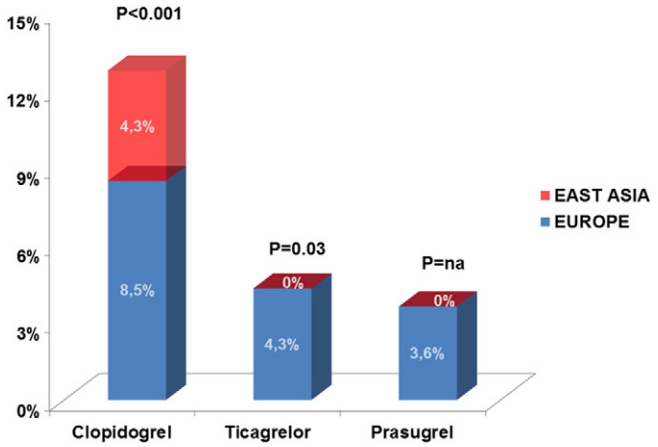


Fig. 4. Comparison of 1-year follow-up death and re-infarction in European and East Asian patients, stratifying the population according to the anti-platelets received.

Ticagrelor 4.9% vs 1.5%, p = 0.13, Prasugrel 2.7% vs 0%, p = na, respectively) (Table 3). Considering the different P2Y12r inhibitors used in each group, the results are superimposable (Caucasians: 2.9% vs 5% vs 2.7%, p = 0.05; East Asians 2.6% vs 5% vs 0%, p = 0.59, respectively) (Fig. 2). At the multivariate analysis, ticagrelor increases the risk of bleeding in the overall population (HR 1.5, CI 1.1–2.3), which is driven by the Caucasian population (HR 1.7, CI 1.1–2.60), while prasugrel is neutral (HR 0.9, CI 0.5–1.3). Moreover, in the overall population and in Caucasians, current malignancy increases bleeding (HR 2.2, CI 1.6–3.2 and HR 2.1, CI 1.5–3.2 respectively) too (Fig. 3).

Among patients treated with single anti-platelets therapy, in the Caucasian patients 10 bleeding occurred, 1 in clopidogrel and 9 in aspirin, compared to the 3 bleeding in aspirin (p = 0.70) in the East Asian group.

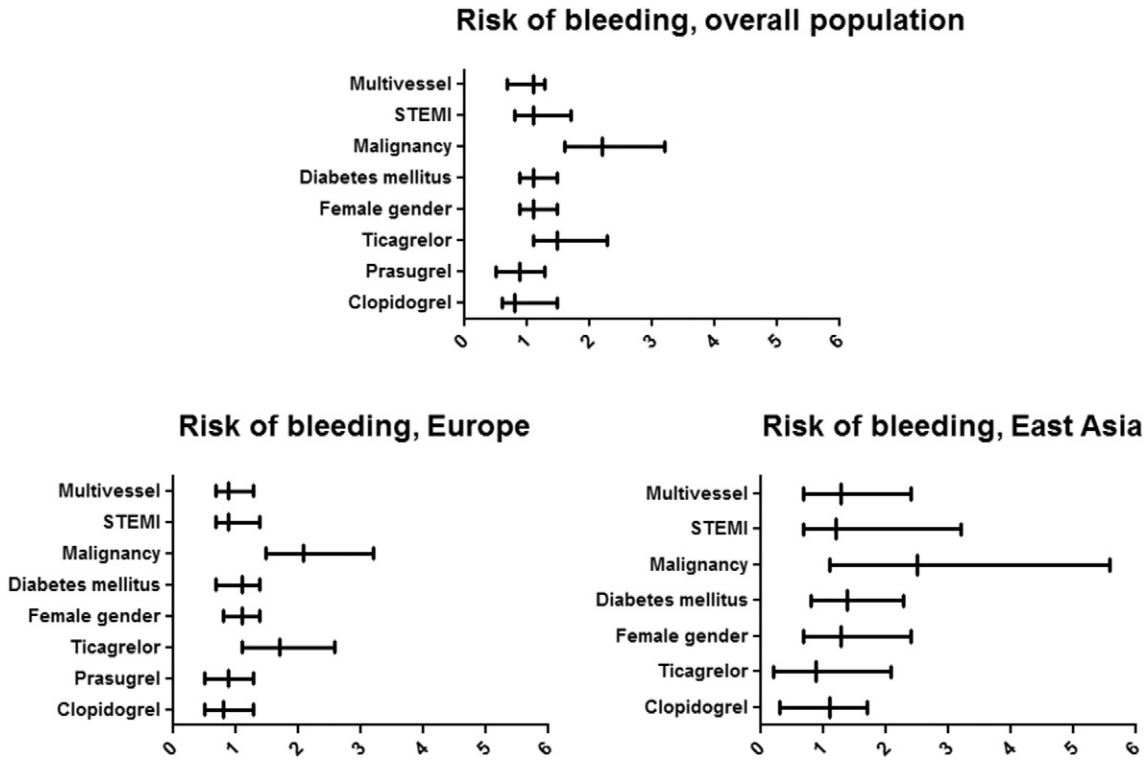


Fig. 3. Independent predictors of bleeding.

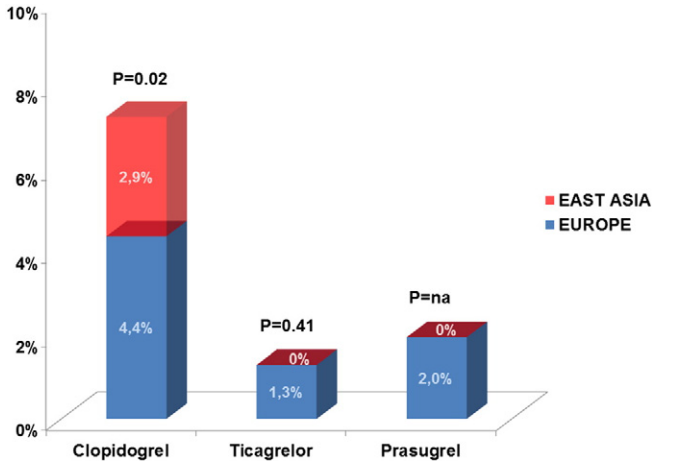


Fig. 5. Comparison of 1-year follow-up death in European and East Asian patients, stratifying the population according to the anti-platelets received. A, aspirin; C, clopidogrel; FU, follow-up; P, prasugrel; T, ticagrelor.

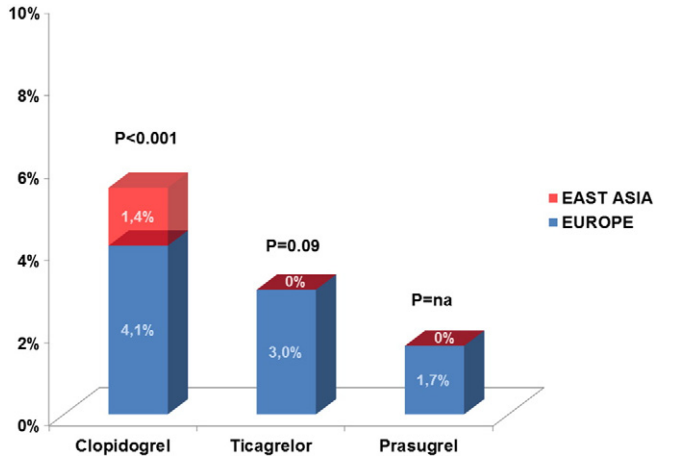


Fig. 6. Comparison of 1-year follow-up re-infarction in European and East Asian patients, stratifying the population according to the anti-platelets received.

4.2. Efficacy end-point

At 1-year FU the Caucasian population had a major incidence of death and re-AMI (9% vs 5%, $p < 0.001$), which is maintained even if the end-points are considered separately (5% vs 3%, $p = 0.003$ and 4% vs 1%, $p = 0.003$, respectively) (Table 3). Stratifying the population according to the anti-platelets received, the difference is mostly preserved: Caucasian patients treated with clopidogrel had a major incidence of MACE compared to those in ticagrelor and prasugrel (8.5% vs 4.3% vs 3.6%, $p < 0.001$). Similarly, in East Asian patients the rate of death and re-AMI in clopidogrel was higher compared to ticagrelor (4.3% vs 0%, $p = 0.03$) (Figs. 4, 5 and 6). These results are confirmed at multivariate analysis, both in overall population (HR 2, CI 1.4–2.7 vs HR 0.2, CI 0.1–0.5 vs HR 0.5, CI 0.3–0.9) and in the sub-groups (Europe: HR 2, CI 1.4–1.7 vs HR 0.5, CI 0.3–0.9 vs HR 0.4, CI 0.2–0.6; East Asia: HR 1.4, CI 1.3–2.2 vs HR 0.5, CI 0.2–0.9) (Fig. 7a–c).

Among patients in single anti-platelets therapy, a significant major incidence of death and re-infarction occurred in Caucasian patients treated with aspirin alone, compared to East Asian patients (1.8% vs 0.2%, $p < 0.001$).

5. Discussion

The main findings of this study are: 1. The new P2Y12-inhibitors seem to be safe and efficacious independently from the ethnicity 2. Among the P2Y12i available, prasugrel seems to have the best risk–benefit; on the other hand, ticagrelor appears safer in Asian patients 3. The lower incidence in the East Asian population of death and re-infarction at 1-year FU could be explained by a different risk profile of this population, for both thrombophilia and bleeding, compared to Europeans.

The Bleemacs registry will indicate predictors of bleeding in patients undergoing PCI for an acute coronary syndrome [14] (NCT02466854). While waiting for the results of this study, from our side we found a good safety profile of prasugrel and ticagrelor in the overall population, as the incidence of bleeding at 1-year follow-up showed to be at 3% lower than what is reported in the milestone trials [1,2]. In literature, two recent meta-analysis published by Gan et al. and Singh et al., showed controversial results, assessing, the first one, a comparable rate of bleeding among different P2Y12i, whereas the second one an higher bleeding complications for the new-molecules treated cohorts [15,16]. In our population, ticagrelor doesn't increase bleeding in East Asian patients, despite of a reduction of incidence of death and myocardial infarction. This could be explained by a different risk profile compared to Caucasians, as hypothesized by the "East Asian Paradox". This phenomenon was observed in the clinical experience with warfarin, showing an higher risk of intracranial haemorrhages for Asian patients compared to Westerns [17,18]. Likewise, the use of clopidogrel is associated with a higher risk of bleeding for Asian patients [19–21] but with the same or even a lower rate of post-PCI ischemic events compared to Westerns [22–26].

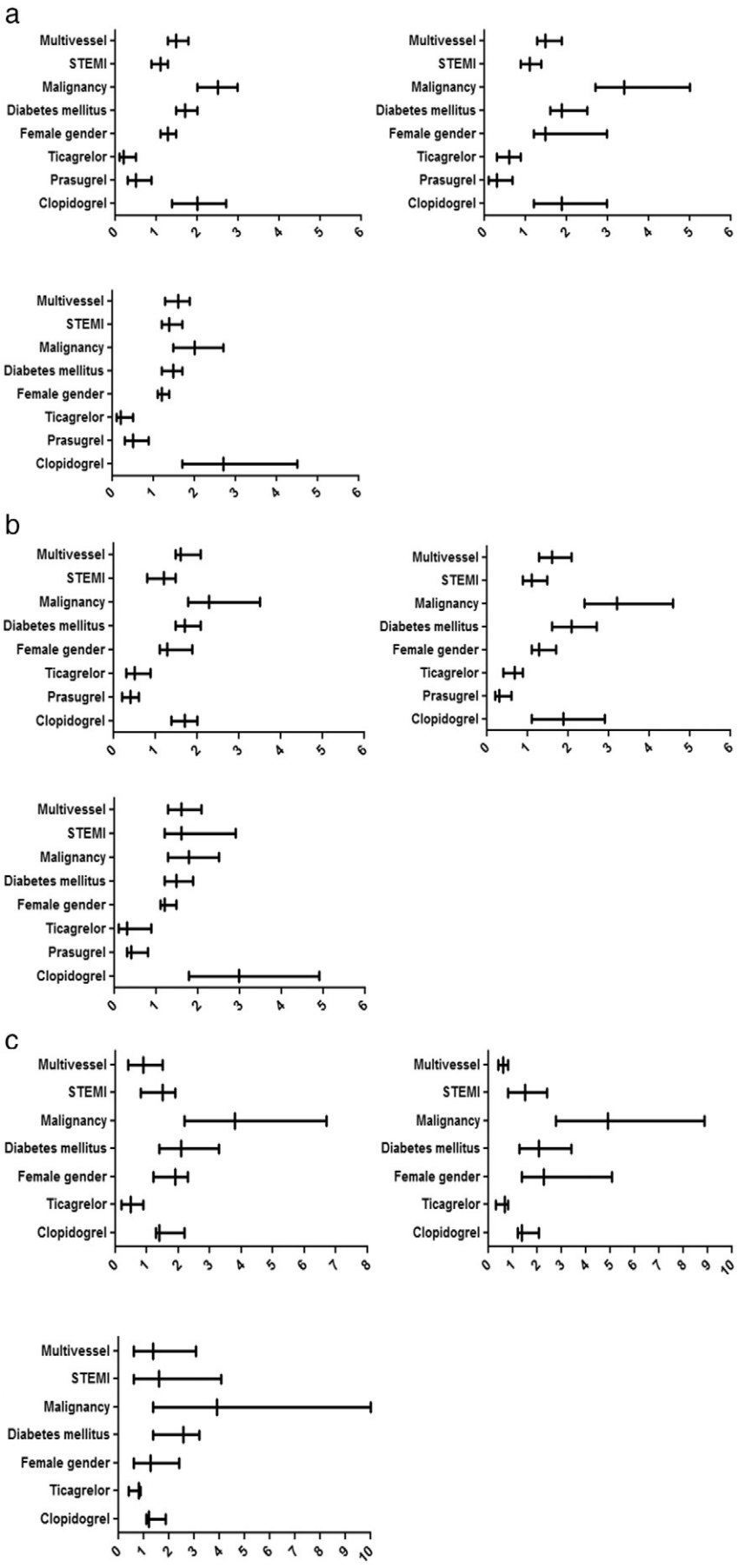
Current plausible explanations for this phenomenon includes differences in gene expression and polymorphisms of genes involved in pharmacokinetic and pharmacodynamics [27–33], platelets activity, hypercoagulability factors (inflammation, coagulation, fibrinolysis markers), environmental factors (obesity, important risk factor associated with pro-thrombotic state). These factors may be the reason why the new $P2Y_{12}$ inhibitors find hard to get consideration from physicians operating in East Asia: their singular platelets reactivity may in fact induce to extreme caution in introducing these new potent antiplatelet drugs, despite dedicated trials have shown their efficacy[xxviii,XXIX,XXX]. In our East Asian cohort, ticagrelor has shown a good safety profile, encouraging the use of this drug also in this corner of the world. However, looking now at the other population, the higher incidence of MACE in Europeans could be explained by this phenomenon, too, considering that, as previously demonstrated, clopidogrel was found to increase the incidence of MACE at one year FU, compared with the other two drugs, independently from the ethnicity. However, beside these encouraging results, the use of ticargrelor is still limited, and prasugrel is not used in East Asian population yet. The PRASFIT-ACS study promotes the spread of these P2Y12i in the Eastern: in the setting of ACS, they compared prasugrel 20/3.75 mg vs. clopidogrel 300/75 mg [5,34,35], finding a lower incidence of MACE in the first group (RRR 23%), without a significant increase in spontaneous bleeding events (HR 1.09, CI 0.83–1.42) [5].

In view of the above, there is still need of a tailored anti-platelets therapy with appropriate dosage, not only according to the patient's comorbidities-based risk profile, but also to the different ethnicity.

Limits

The study has the constraints and limits of any observational and retrospective study, and therefore the findings should be interpreted with caution and need to be confirmed in prospective analysis. On the

Fig 7. a. From above to below, from right to left: independent predictors of MACE, death and myocardial infarction in overall population. b. From above to below, from right to left: independent predictors of MACE, death and myocardial infarction in European patients. c. From above to below, from right to left: independent predictors of MACE, death and myocardial infarction in East Asian patients.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Clopidogrel
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Multivessel
STEMI
Malignancy
Diabetes mellitus
Female gender
Ticagrelor
Clopidogrel
0 1 2 3 4 5 6 7 8 9 10

other hand, it shares the advantage to be very close to current routine clinical practice.

Conflict of interest

None.

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