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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.

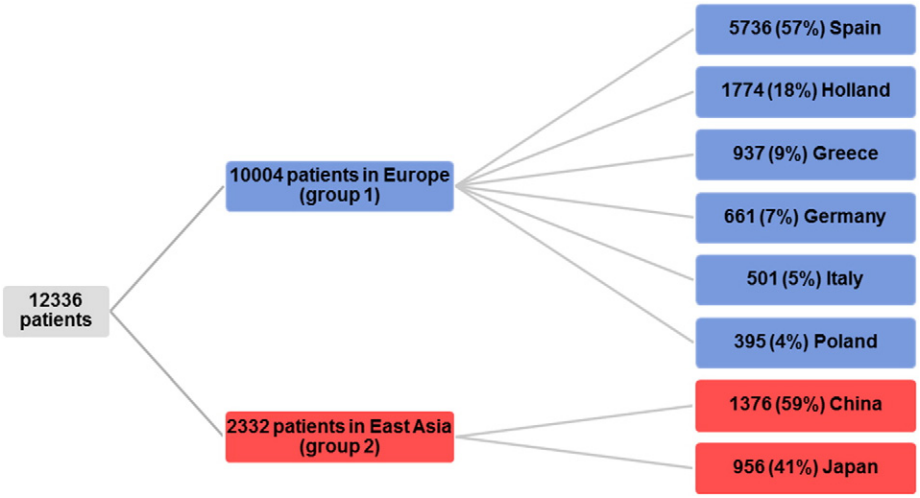

Fig. 1. Patient's sub-groups, according to the belonging country.