International Journal of Cardiology 155 (2012) 424–429

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Safety and efficacy of prasugrel compared with clopidogrel in different regions of the world

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ARTICLE INFO

*Article history:*
Received 9 June 2010
Received in revised form 8 October 2010
Accepted 23 October 2010
Available online 19 November 2010

*Keywords:*
Prasugrel
Clopidogrel
TRITON-TIMI 38
Regional differences
HDI

ABSTRACT

*Background:* Among patients with acute coronary syndrome (ACS), demographics, procedural characteristics and adjunctive medications differ globally. We examined whether there were differential effects of prasugrel compared with clopidogrel in the multinational TRITON-TIMI 38 study.
*Methods:* We divided the enrollment into 5 pre-specified geographic regions. Patients were randomized to prasugrel or clopidogrel without regard to country of enrollment. End points are expressed as Kaplan–Meier failure estimates through 15 months. Heterogeneity was evaluated using Cox proportional hazards model. Additional sensitivity analyses were performed by dividing countries into categories based on the Human Development Index (HDI), which is a composite measure of social and economic development.
*Results:* 13,608 patients were enrolled. Clinical characteristics including age, comorbidities, ACS presentation, stent types, and adjunctive medications differed broadly among regions. Despite these differences, no regional heterogeneity was observed with prasugrel compared to clopidogrel in the reduction of ischemic events (HR range: 0.76–0.87, $p_{interaction}>0.10$ for each) and stent thrombosis (HR range: 0.34–0.72, $p_{interaction}>0.10$ for each) or in the increased rate of non-CABG TIMI major bleeding (HR range: 1.16–1.76, $p_{interaction}>0.10$ for each). There was a consistent trend in net clinical benefit (all cause death/MI/stroke/non-CABG TIMI major bleeding) favoring prasugrel (HR range: 0.81–0.97, $p_{interaction}>0.10$ for each). Consistent results were also observed regarding the safety and efficacy of prasugrel compared with clopidogrel in both developed and developing countries.
*Conclusions:* Despite differences in patient demographics, procedural techniques and adjunctive medications, consistent reduction in ischemic events and increased bleeding were seen with prasugrel compared with clopidogrel throughout the world.



## 1. Introduction

Disparities exist in cardiovascular outcomes across geographical regions [1,2]. A number of acute coronary syndrome (ACS) trials have demonstrated significant regional variation in clinical outcomes and treatment effects [3–12]. There is controversy over the reasons responsible for these differences; they have been attributed to variable baseline risk of subjects, regional differences in care processes and statistical chance due to post hoc subgroup analyses [3,12–14].

With the increasing globalization of clinical trials, resulting in substantial international participation, it is now possible to investigate whether regional differences in baseline patient characteristics and management impact clinical outcomes in patients with cardiovascular disease.

Dual antiplatelet therapy with aspirin and a thienopyridine is a cornerstone of treatment to prevent thrombotic complications of ACS and percutaneous coronary intervention (PCI) [15–21]. In the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), more intensive and consistent antiplatelet therapy with the third-generation thienopyridine prasugrel resulted in a reduction in ischemic events, increase in bleeding and, on balance, an

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doi:10.1016/j.ijcard.2010.10.040

improved net clinical outcome [22]. The present analysis compares the effects of prasugrel compared with clopidogrel in the multinational TRITON-TIMI 38 trial based on regional differences in patient characteristics and therapies.

Analyzing outcomes by geographical regions is not without limitations as countries, and even hospitals, within a given region may be quite disparate with respect to socioeconomic conditions that likely impact patient populations and medical practices. Individual countries may in fact have much more similar social, economic and medical structures with nations geographically remote from them compared with their neighboring countries.

Therefore, we performed a sensitivity analyses based on the Human Development Index (HDI). The HDI is a comparative measure of life expectancy, literacy, education and standards of living for countries worldwide that creates a single statistic to serve as a reference for both social and economic development. The index was developed in 1990 by the economists Mahbub ul Haq and Amartya Sen [23]. Countries can be divided into four broad categories based on their HDI: very high, high, medium and low human development. The countries in the first category (very high) are considered "developed" and the others are categorized as "developing". For our analysis we divided the countries into these groups using the United Nations Development Program's Human Development Report released on October 5, 2009, compiled on the basis of data from 2007 [24].

## 2. Methods

### 2.1. Patients

This analysis includes all 13,608 subjects randomized in the TRITON-TIMI 38 trial. Inclusion and exclusion criteria for the main trial have been reported previously [22,25]. Briefly, individuals could be enrolled with moderate- to high-risk unstable angina, non-ST-elevation myocardial infarction (UA/NSTEMI), or ST-segment elevation myocardial infarction (STEMI) after medical therapy with coronary anatomy known to be suitable for percutaneous coronary intervention (PCI), or on first contact in patients with planned primary PCI for STEMI. Key exclusion criteria included active bleeding, increased risk of bleeding or any thienopyridine use within 5 days prior to enrollment. Patients were randomized in a 1 to 1 fashion to double-blinded prasugrel or clopidogrel. Treatment was to be continued for the total duration of the patient's participation in the trial, a minimum of 6 months and a maximum of 15 months.

### 2.2. End points

End point definitions for TRITON-TIMI 38 have been previously reported and were used for these analyses [22,25]. All components of the end points were adjudicated by a clinical events committee unaware of treatment assignment. The primary end point of the TRITON-TIMI 38 trial and these analyses was the composite of cardiovascular death, non-fatal MI, or non-fatal stroke. The additional efficacy end point of stent thrombosis was examined using the definite/probable Academic Research Consortium definition [26,27]. The key safety end point was non-coronary artery bypass grafting (CABG)-related TIMI major bleeding. Net clinical outcome was evaluated as the composite of all-cause mortality, MI, stroke, or non-CABG-related TIMI major bleeding. Efficacy event rates were calculated from intention-to-treat analyses, and safety analyses were based on the safety cohort which consisted of patients who received at least one dose of the study drug.

### 2.3. Statistical analysis

Subjects were divided into 5 pre-specified geographic regions: North America (NA), South America (SA), Western Europe (WE), Eastern Europe (EE), and Africa/Asia Pacific/Middle East (AAM). An exploratory analysis divided subjects into those enrolled in developed countries and those enrolled in developing countries based on their HDI rankings. Baseline characteristics of subjects in the different regions and HDI development categories were compared using the $\chi^2$ test for categorical variables and Wilcoxon rank for continuous variables. Survival analysis methods were used to compare outcomes by treatment assignment (prasugrel versus clopidogrel) stratified by region and HDI development categories. Event rates are reported as Kaplan–Meier failure estimates at 450 days and were compared using the log-rank test. Comparisons between prasugrel and clopidogrel by region and HDI development categories are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs) including the entire duration of follow-up. Testing for heterogeneity between the efficacy of prasugrel compared with clopidogrel and region of enrollment (North America as the referent) and HDI development categories was performed using a Cox proportional hazards model. For all analyses, values of $P<0.05$ were considered to be significant. All analyses were performed with STATA/SE 9.2 (STATA Corp, College Station, TX).

The sponsors of TRITON-TIMI 38, Eli Lilly and Company and Daiichi Sankyo Ltd., supported the design and implementation of the main trial from which these results are obtained. All analyses were performed by the TIMI Study Group using an independent copy of the complete clinical trial database. The authors wrote all drafts of the article and take responsibility for its content.

## 3. Results

A total of 13,608 patients were randomized in 30 countries (Table 1) across 5 continents between November 2004 and January 2007. Enrollment was divided into 5 pre-specified geographic regions: 4310 (32%) subjects were enrolled in North America (NA), 534 (4%) subjects in South America (SA), 3553 (26%) in Western Europe (WE), 3322 (24%) in Eastern Europe (EE), and 1889 (14%) in Africa/Asia Pacific/Middle East (AAM). When divided by HDI category there were 9688 (71%) subjects enrolled in developed countries and 3920 (29%) in developing countries. Though randomization was not stratified by region or HDI category, there were essentially equal number of subjects randomized to clopidogrel and prasugrel within each region and HDI group.

Baseline characteristics stratified by region of enrollment and HDI category are shown in Table 2. Clinical characteristics including age, comorbidities, ACS presentation, stent types, and adjunctive medications differed broadly, as expected. There were particularly marked differences in the use of drug-eluting stents across the regions with much more common use in NA (88%) compared with the other regions (SA 8%, WE 49%, EE 7%, and AAM 39%). Drug-eluting stent use was also much more extensive in the developed HDI group (60%) compared with the developing HDI group (14%). These differences were also seen with the selection of adjunctive medications. Glycoprotein IIb/IIIa-receptor antagonists were used widely in NA

**Table 1**
Participating countries.

| Country | Randomized | HDI category |
|---|---|---|
| North America | 4310 (32%) | |
| Canada | 251 | Developed |
| United States of America | 4059 | Developed |
| South America | 534 (4%) | |
| Argentina | 195 | Developing |
| Brazil | 225 | Developing |
| Chile | 114 | Developing |
| Western Europe | 3553 (26%) | |
| Austria | 182 | Developed |
| Belgium | 287 | Developed |
| Denmark | 33 | Developed |
| Finland | 116 | Developed |
| France | 146 | Developed |
| Germany | 999 | Developed |
| Iceland | 10 | Developed |
| Italy | 782 | Developed |
| Netherlands | 390 | Developed |
| Portugal | 67 | Developed |
| Spain | 178 | Developed |
| Sweden | 154 | Developed |
| Switzerland | 136 | Developed |
| United Kingdom | 73 | Developed |
| Eastern Europe | 3322 (24%) | |
| Czech Republic | 340 | Developed |
| Hungary | 695 | Developing |
| Estonia | 134 | Developing |
| Latvia | 21 | Developing |
| Lithuania | 54 | Developing |
| Poland | 1938 | Developing |
| Slovakia | 140 | Developing |
| Africa/Asia Pacific/Middle East | 1889 (14%) | |
| Australia | 217 | Developed |
| Israel | 1219 | Developed |
| New Zealand | 49 | Developed |
| South Africa | 404 | Developing |

**Table 2**
Baseline characteristics by region.

| Characteristics | North America (N = 4310) | South America (N = 534) | Western Europe (N = 3553) | Eastern Europe (N = 3322) | Africa/Asia Pacific/ Middle East (N = 1889) | Developed HDI (N = 9688) | Developing HDI (N = 3920) |
|---|---|---|---|---|---|---|---|
| Unstable angina or NSTEMI (%) | 82 | 100**,* | 71* | 69* | 62* | 75 | 72* |
| STEMI (%) | 18 | 0**,* | 29* | 31* | 38* | 25 | 28* |
| Age (yr) | | | | | | | |
| Median | 59 | 61* | 63* | 60* | 58* | 61 | 60* |
| 25th percentile, 75th percentile | 52, 68 | 53, 70 | 55, 71 | 53, 69 | 51, 68 | 53, 70 | 53, 68 |
| Female sex (%) | 27 | 31 | 23* | 31* | 19* | 24 | 30* |
| BMI | | | | | | | |
| Median | 29 | 27* | 27* | 28* | 28* | 28 | 28* |
| 25th percentile, 75th percentile | 26, 33 | 25, 30 | 25, 30 | 25, 31 | 25, 31 | 25, 31 | 25, 31 |
| Medical history (%) | | | | | | | |
| Hypertension | 69 | 76* | 59* | 68 | 54* | 63 | 67* |
| Hypercholesterolemia | 66 | 60* | 54* | 42* | 59* | 59 | 45* |
| Diabetes mellitus | 26 | 29 | 20* | 20* | 27 | 24 | 20* |
| Tobacco use | 38 | 28* | 37 | 38 | 44* | 39 | 37 |
| Previous MI | 20 | 23 | 15* | 17* | 18 | 18 | 18 |
| Previous CABG | 12 | 11 | 6* | 3* | 9* | 9 | 5* |
| Creatinine clearance <60 mL/min | 9 | 19* | 13* | 11* | 10 | 11 | 12 |
| TIMI risk score | | | | | | | |
| Unstable angina/NSTEMI | | * | | * | * | | * |
| 0–2 | 13 | 9 | 13 | 9 | 16 | 13 | 10 |
| 3–4 | 59 | 61 | 62 | 68 | 56 | 60 | 66 |
| 5–7 | 28 | 31 | 25 | 23 | 28 | 27 | 24 |
| STEMI | | * | * | | | | * |
| 0–2 | 52 | 0** | 45 | 56 | 57 | 50 | 56 |
| 3–4 | 29 | 0** | 33 | 28 | 26 | 30 | 27 |
| ≥5 | 19 | 0** | 22 | 16 | 17 | 20 | 17 |
| Index procedure (%) | | | | | | | |
| CABG | 1.2 | 0.6 | 0.6* | 0.4* | 1.0 | 0.9 | 0.5* |
| PCI | 98 | 99 | 98 | 99* | 98 | 98 | 99* |
| Stent | 97 | 94* | 97 | 94* | 95* | 96 | 94* |
| Bare-metal stent only | 12 | 86* | 46* | 86* | 55* | 35 | 80* |
| ≥1 drug-eluting stent | 84 | 8* | 49* | 7* | 39* | 60 | 14* |
| Multivessel PCI | 16 | 14 | 14* | 9* | 19* | 16 | 10* |
| Antithrombin use to support PCI (%) | | * | * | * | * | | * |
| Heparin | 65 | 79 | 63 | 65 | 68 | 66 | 66 |
| LMWH | 8 | 3 | 12 | 7 | 9 | 9 | 7 |
| Bivalirudin | 9 | 0 | 0.3 | 0.03 | 1.9 | 5 | 0.03 |
| Other or multiple therapies | 18 | 18 | 24 | 28 | 22 | 21 | 28 |
| Glycoprotein IIb/IIIa-receptor antagonist use during index hospitalization | 75 | 22* | 56* | 29* | 60* | 63 | 34* |
| Timing of study-drug administration (%) | | | | | | | |
| Before PCI | 14 | 48* | 19* | 45* | 21* | 19 | 42* |
| During PCI | 84 | 51* | 80* | 54* | 78* | 80 | 58* |
| After PCI | 1.5 | 0.6* | 0.8* | 0.4* | 1.3* | 1.2 | 0.5* |
| Pharmacotherapy during index hospitalization (%) | | | | | | | |
| ACE inhibitor or ARB | 69 | 72 | 75* | 87* | 73* | 73 | 81* |
| Beta-blocker | 91 | 88 | 89 | 90 | 78* | 89 | 87* |
| HMG-CoA reductase inhibitor | 90 | 93* | 91* | 96* | 92* | 91 | 94* |
| Calcium-channel blocker | 21 | 12* | 15* | 13* | 24* | 20 | 13* |
| Aspirin | 99 | 99 | 99 | 99* | 99 | 99 | 99 |

Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; HDI = Human Development Index; N = number of subject in each region; LMWH = low molecular weight heparin; MI = myocardial infarction; mL = milliliter; min = minute; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
**Enrollment in SA began after a protocol amendment prohibiting further enrollment of patients with STEMI.
*p-value<0.05 (NA and developed HDI as referents).

(75%) and the developed HDI group (63%), but to a more limited extent in other regions (SA 22%, WE 56%, EE 29%, and AAM 60%) and the developing HDI group (34%). The proportion of patients presenting with STEMI demonstrated considerable regional variability (NA 18%, SA 0% [enrollment in SA began after a protocol amendment prohibiting further enrollment of patients with STEMI], WE 29%, EE 31%, and AAM 38%) but was similar with respect to HDI groups (developed 25%, developing 28%).

Despite these differences there was consistency in the efficacy of prasugrel in reducing ischemic events compared with clopidogrel. Across the regions there were reductions in the primary composite end point of CV death, non-fatal MI and non-fatal stroke (NA: HR 0.76; SA: HR 0.87; WE: HR 0.86; EE: HR 0.84; AAM: HR 0.79; $p_{interaction}>0.10$ for each) (Fig. 1) and in the occurrence of stent thrombosis (NA: HR 0.42; SA: HR 0.49; WE: HR 0.72; EE: HR 0.41; AAM: HR 0.34; $p_{interaction}>0.10$ for each) (Fig. 2). Consistency in the efficacy of prasugrel compared with clopidogrel was also seen in developed countries compared with developing countries with respect to the primary composite end point (developed HDI: HR 0.82; developing HDI: HR 0.79; $p_{interaction}>0.10$) (Fig. 1) and the occurrence of stent thrombosis (developed HDI: HR 0.58; developing HDI: HR 0.28; $p_{interaction}=0.033$) (Fig. 2).

This reduction in ischemic events was accompanied by an increase in non-CABG TIMI major bleeding that was seen in all regions (NA: HR 1.16; SA: HR 1.35; WE: HR 1.25; EE: HR 1.76; AAM: HR 1.16;

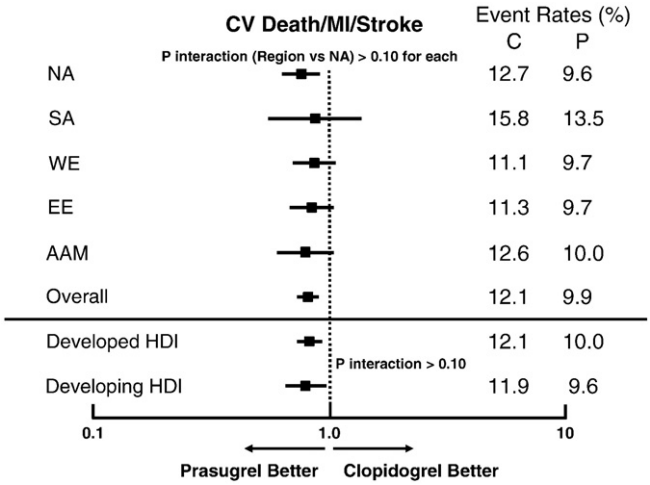


**Fig. 1.** Effect of prasugrel versus clopidogrel on CV death/MI/stroke stratified by region and HDI category. Point estimate and 95% CI for the relative risk of CV death/MI/stroke in patients assigned prasugrel compared with those assigned clopidogrel. Abbreviations: AAM = Africa/Asia Pacific/Middle East; C = clopidogrel; EE = Eastern Europe; HDI = Human Development Index; NA = North America; P = prasugrel; SA = South America; WE = Western Europe. Enrolled subjects by region: NA = 4310; SA = 534; WE = 3553; EE = 3322; AAM = 1889; and overall = 13,608. Enrolled subjects by HDI category: developed HDI = 9688; developing HDI = 3920.

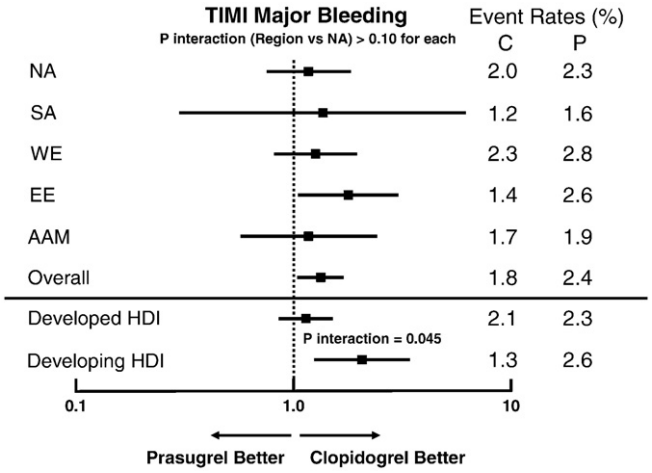


**Fig. 3.** Effect of prasugrel versus clopidogrel on non-CABG TIMI major bleeding stratified by region and HDI category. Point estimate and 95% CI for the relative risk of major bleeding in patients assigned prasugrel compared with those assigned clopidogrel. Abbreviations: see Fig. 1 legend.

$p_{interaction}$>0.10 for each) and in both developed and developing countries (developed HDI: HR 1.13; developing HDI: HR 2.03; $p_{interaction}$ = 0.045) (Fig. 3).

In aggregate there remained a favorable net clinical outcome with prasugrel in the composite end point of death/MI/stroke and non-CABG TIMI major bleeding seen in both the regional analysis (NA: HR 0.81; SA: HR 0.97; WE: HR 0.90; EE: HR 0.93; AAM: HR 0.82; $p_{interaction}$>0.10 for each) and HDI development categories (developed HDI: HR 0.85; developing HDI: HR 0.91; $p_{interaction}$>0.10) (Fig. 4).

## 4. Discussion

Consistent reduction in ischemic events, increased bleeding and a favorable net clinical outcome were seen with prasugrel compared with clopidogrel throughout the regions of the world and in both developed and developing countries, despite differences in patient demographics, procedural techniques, medical device use, and adjunctive medications.

Understanding the impact of regional variation on clinical trial results has become increasingly more relevant as worldwide "mega-trials" become the norm. Because of the pharmacological and procedural advancements in the treatment of ACS, event rates have become progressively lower and trials now require ever larger sample sizes to reliably detect a treatment effect. Large clinical trials are now truly a global effort that allows researchers an opportunity to evaluate the impact of regional and international differences in baseline characteristics and clinical care processes [28].

It has been well established that disparities exist in cardiovascular outcomes across geographical regions [1,2]. Data from the Global Registry of Acute Coronary Events (GRACE) indicates significant geographic and practice variations in the use of antithrombotic and antiplatelet therapies which may partially explain these differences [29].

There are numerous clinical trials in patients with ACS that have confirmed regional heterogeneity of outcomes and treatment effects [3–12]. Significant regional variations were observed in the PURSUIT trial, which compared the platelet glycoprotein IIb/IIIa inhibitor

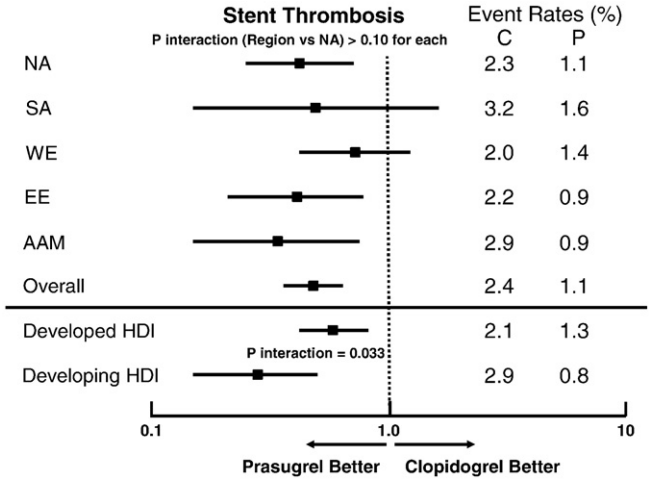


**Fig. 2.** Effect of prasugrel versus clopidogrel on Academic Research Consortium definite or probable stent thrombosis stratified by region and HDI category. Point estimate and 95% CI for the relative risk of stent thrombosis in patients assigned prasugrel compared with those assigned clopidogrel. Abbreviations: see Fig. 1 legend.

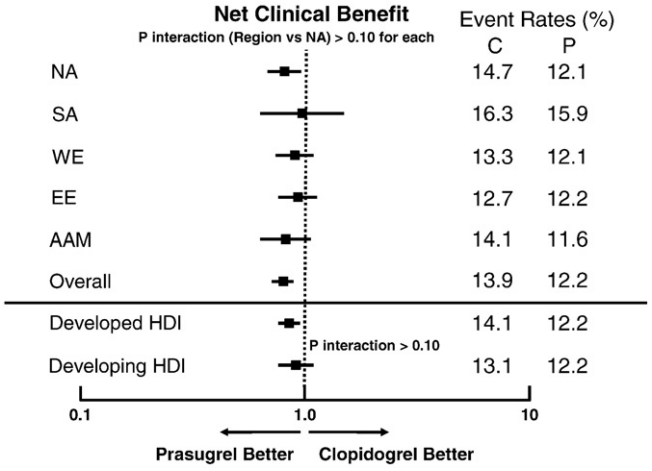


**Fig. 4.** Effect of prasugrel versus clopidogrel on net clinical benefit (death/MI/stroke/non-CABG TIMI major bleeding) stratified by region and HDI category. Point estimate and 95% CI for the relative risk of net clinical benefit in patients assigned prasugrel compared with those assigned clopidogrel.

eptifibatide with placebo, given in addition to standard therapy, in patients with non-ST-segment elevation ACS [30]. Patients in North America had the greatest treatment benefit whereas there was no apparent benefit in patients in Latin America and Eastern Europe. Explanations have focused on the interaction between the use of early PCI and eptifibatide treatment and significant regional variation in practice patterns suggesting that the timing of coronary interventions could explain most of the regional differences [12].

Regional heterogeneity was also observed in the GUSTO-1 trial which investigated mortality rates of 4 fibrinolytic strategies [31]. A significant treatment by country interaction was found for the combination of streptokinase with tPA and intravenous heparin, which performed as well as accelerated tPA and intravenous heparin in the non-United States (US) patients but was associated with worse outcomes in US patients [12,32]. This was attributed to excess of hemorrhagic stroke in US patients receiving the combination therapy that was not seen outside the US. Closer analysis suggested that a possible explanation was a larger bolus and total tPA dose given to US patients due to their greater weight. There were also significant geographic variations in practice and adjusted mortality seen in the InTIME-II trial which compared the fibrinolytics alteplase and lanoteplase in patients presenting with acute myocardial infarction [33]. Mortality differences persisted despite consideration of baseline clinical and hospital characteristics, and stratification for baseline risk using known predictors of mortality.

The ESSENCE trial demonstrated that enoxaparin was more effective than unfractionated heparin in reducing the incidence of ischemic events in ACS [34]. The overall treatment effect was maintained across all participating countries but the absolute incidence rates of ischemic events differed substantially in the participating countries. Analyses revealed that the observed regional heterogeneity could be explained by differences in baseline characteristics and clinical management [9]. In fact, it was noted that the inter-country difference in ischemic event rates were larger than the difference between enoxaparin and unfractionated heparin [14].

More recently, the PLATO trial demonstrated the superiority of ticagrelor over clopidogrel for the prevention of death from vascular causes, MI and stroke in patients presenting with ACS. The direction and magnitude of benefit was consistent in all regions except for NA, where there was a trend towards harm [11].

It is reassuring that our results demonstrate that more potent platelet inhibition with prasugrel resulted in a consistent reduction in ischemic events across all regions despite significant differences in age, comorbidities, ACS presentation, stent types and use of adjunctive medications, specifically glycoprotein IIb/IIIa-receptor antagonists. This benefit was seen not only for the primary outcome of cardiovascular death, non-fatal MI and non-fatal stroke but also a consistent and significant reduction was observed for the clinically important end point of stent thrombosis. This consistent reduction in ischemic events may not only be due to the greater platelet inhibition with prasugrel but also the increasing recognition of the importance and prevalence of reduced-function genetic variants in *CYP2C19* that have been associated with reduced concentrations of active drug metabolite and higher rates of adverse cardiovascular events with clopidogrel treatment, but not prasugrel [35–38]. As was seen in the overall trial results, the reduction in ischemic events was accompanied by an increase in major bleeding across all regions. However, there remained a net clinical benefit of treatment with prasugrel compared with clopidogrel in all regions.

Additional analyses comparing developed and developing countries demonstrated consistent results with traditional regional groupings. Interaction tests were non-significant for most comparisons but there were significant interactions of HDI development category with non-CABG TIMI major bleeding (developed HDI: HR 1.13, 95% CI 0.85–1.50; developing HDI: HR 2.03, 95% CI 1.23–3.35; $p_{interaction} = 0.045$) and stent thrombosis (developed HDI: HR 0.58, 95% CI 0.42–0.82; developing HDI: HR 0.28, 95% CI 0.15–0.50; $p_{interaction} = 0.033$). The apparent increase in the relative bleeding risk with prasugrel compared to clopidogrel in developing countries is not readily explained by the distribution of clinical risk factors such as age and body weight. Additionally, this interaction indicates that there are quantitative differences in the magnitude of the effect but the directionality of the effect was the same in each comparison. These statistical differences could be accounted for by chance, given the multiple comparisons. It may be more important to look at the consistency or directionality of a benefit or harm rather than focus on a statistical threshold for significance as diseases are usually similar in their effects among various groups and it is the magnitude of the treatment effect that differs. Although international differences in the selection and management of patients would be expected to produce differences in absolute event rates, differing event rates would not be expected to produce differences in the direction of the treatment effect. If the directionality of a treatment effect is found for a region or specific group it is important to determine if a difference in baseline risk profile or practice pattern is responsible for that difference.

In light of previous studies suggesting marked regional differences in outcomes with antithrombins and antiplatelet agents, why was there general consistency seen in TRITON-TIMI 38? One potential explanation is that despite differences in some demographic features and concomitant medications, TRITON-TIMI 38 was a trial that by design had a relatively homogenous treatment strategy. Specifically all patients enrolled were undergoing planned PCI. In many previous trials, region may have served as a surrogate for type of hospital (referral versus community) or treatment strategy (invasive versus conservative) rather than true differences in care related to geography [9,12,30,34,39]. In TRITON-TIMI 38, in order to enroll patients, hospitals had to be PCI-capable. Treatment and outcomes in these hospitals across the world may be more alike than in different types of hospitals within a region. In addition, compared with previous trials, the globalization and cooperation of cardiac societies have created consistent guidelines and treatment standards, leading to less heterogeneity in clinical practice.

There are limitations to our analyses. Patients were randomized to prasugrel or clopidogrel without regard to region of enrollment or HDI development category, so unmeasured confounders may exist. The study was not powered to look at outcomes by individual regions or HDI groups and certain populations (such as South East Asians) were not well represented in the trial. Additionally, any regional categorization by necessity combines countries (or centers within countries) that are not uniform. This makes it challenging to interpret heterogeneity in clinical trials (or the lack thereof) and conclusions must be made cautiously, as is the case with any subgroup analysis.

## 5. Conclusions

There are important differences in patient characteristics, use of medications and procedural care processes across the world. These differences could affect the outcomes of patients and the potential benefit of new therapies. The globalization of clinical trials provides an important opportunity to understand how regional differences may impact patient care. Despite differences in patient demographics, procedural techniques and adjunctive medications, consistent reduction in ischemic events and increased bleeding were seen with prasugrel compared with clopidogrel throughout the world in patients with ACS undergoing PCI.

## Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [40].

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