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Geographical variations in the comparative effectiveness and safety of abbreviated or standard antiplatelet therapy after PCI in patients at high bleeding risk

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Abstracts

Background: The treatment effects of abbreviated or standard antiplatelet therapy (APT) across geographical regions after PCI is unknown.

Aims: to assess the consistency of the treatment effects of abbreviated or standard APT across geographical regions after drug-eluting stent implantation in patients at high bleeding risk (HBR).

Methods and Results: In the MASTER DAPT trial, which compared 1 month of dual-APT to treatment continuation for at least 2 additional months in HBR patients, 3838 patients (abbreviated APT, n=1927; standard APT, n=1911), 583 patients (abbreviated APT, n=286; standard APT, n=297) and 158 patients (abbreviated APT, n=82; standard APT n=76) were enrolled from Europe, Asia, and Argentina/Australia, respectively. At 1-year, net and major adverse cardiac and cerebral events did not differ across geographies, whereas major or clinically relevant nonmajor bleeding was lower in patients from Asia than Europe or Argentina/Australia. Net adverse clinical events and major adverse cardiac and cerebral events did not differ with abbreviated or standard APT among patients from Europe, Asia or Argentina/Australia, with negative treatment-by geography interaction testing (P-interaction=0.472 and 0.306, respectively). Major or clinically relevant nonmajor bleeding was consistently reduced with abbreviated compared with standard APT across regions (P-interaction=0.445), although the rates were significantly lower only in patients from Europe (6.9% versus 9.7%, HR 0.69, 95% CI 0.55 to 0.86, P=0.001).

Conclusions: The treatment effect of abbreviated or standard APT on the occurrence of net and major adverse clinical events as well as bleeding were consistent across geographies, suggesting generalizability of overall study findings across investigated ethnicities.

Keywords: Dual antiplatelet therapy; high bleeding risk; Percutaneous coronary intervention

Abbreviations and Acronyms

APT: antiplatelet therapy

BARC: Bleeding Academic Research Consortium

DAPT: dual antiplatelet therapy

HR: hazard ratios (HR)

CI: confidence intervals

PCI: percutaneous coronary intervention

OAC: Oral anticoagulation

HBR: high bleeding risk

MASTER DAPT: the management of high bleeding risk patients post bioresorbable polymer-coated stent implantation with an abbreviated versus standard DAPT regimen

Introduction

Several randomized clinical trials compared different antiplatelet strategies to guide treatment decisions after drug-eluting stent implantation.[1] However, a strategy evaluated in a certain geographical region may not be optimal for individuals of other geographical regions.[2] Recent global meta-analyses of coronary artery disease risk factors in percutaneous coronary intervention (PCI) clinical trials showed that patients enrolled in North American, European, and Asian PCI clinical trials have remarkable differences in baseline patient characteristics, suggesting caution when interpreting the generalizability of study findings.[3] In addition, the ischemic and bleeding risks, as well as treatment effect of various antiplatelet therapy (APT) treatment strategies may differ by ethnical or racial differences, according to geographical variations.[4-11]

The MASTER DAPT (The Management of High Bleeding Risk Patients Post Bioresorbable Polymer-Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) trial showed the non-inferiority of 1 month dual-APT to treatment continuation for at least 2 additional months, for the occurrence of net and major adverse clinical events with a significant reduction in bleeding in high-bleeding risk (HBR) Patients.[12,13] We assessed here the consistency of the treatment effects for effectiveness and safety of abbreviated or standard APT by geographical variations.

Methods

Study design

The MASTER DAPT trial (ClinicalTrials.gov number, NCT03023020), as previously reported,[12,13] enrolled largely unselected patients at HBR following implantation of a biodegradable-polymer-coated Ultimaster™ (Terumo Corporation, Tokyo, Japan) sirolimus-eluting stent. Ethics approval was obtained in each country and center. All patients gave written informed consent. An independent data safety monitoring board regularly reviewed the conduct of the trial and the safety of the patients.[12,13]

Study patients

Patients at HBR who underwent treatment of all planned coronary artery stenoses with Ultimaster stent implantation for acute or chronic coronary syndromes were eligible if they remained uneventful until the time of randomization. HBR was defined if at least one of the following criteria applied: oral anticoagulant (OAC) therapy for at least 12 months, recent (<12 months) non-access site bleeding episode(s) that required medical attention, previous bleeding episode(s) that required hospitalization if the underlying cause had not been definitively treated, age ≥75 years, systemic conditions associated with an increased bleeding risk (e.g. haematological disorders or any known coagulation disorder associated with increased bleeding risk), documented anaemia (defined as repeated haemoglobin levels <11 g/dL or transfusion within 4 weeks before randomization), need for chronic treatment with steroids or non-steroidal anti-inflammatory drugs, diagnosed malignancy (other than skin), stroke at any time or transient ischaemic attack in the previous 6 months, and PRECISE-DAPT score ≥25.

Of a total of 4579 patients who underwent randomization in the MASTER DAPT trial, 3838 patients were enrolled from 19 European countries (Austria, Belgium, Bulgaria, Czech, Denmark, Estonia, France, Germany, Hungary, Italy, Macedonia, Netherlands, Poland, Portugal, Serbia, Spain, Sweden, Switzerland, United Kingdom), 583 patients from 9 Asian countries (Bangladesh, India, Israel, Japan, Kingdom of Bahrain, Saudi Arabia, Singapore, South Korea, Vietnam), and 158 patients in Argentina or Australia. In this study, all comparisons were performed among the three groups; patients from Europe, those from Asia, and those from Argentina/Australia.

Randomization and follow-up

Patients were centrally randomized with a 1:1 ratio to an open-label abbreviated APT group or standard APT group 30 – 44 days after the index procedure. Randomization was

concealed using a web-based system; randomization sequences were computer generated, blocked, with randomly selected block sizes of 2, 4, or 6, and were stratified by site, history of acute myocardial infarction within the past 12 months, and clinical indication for at least 12 months of OAC therapy. Follow-up visits occurred at 60 and 150 days after randomization, preferably as on-site visits, and at 335 days after randomization, exclusively as an on-site visit. Three independent clinical research organizations (CERC, Massy, France; Cardialysis, Rotterdam, the Netherlands; and CVQuest, Tokyo, Japan) performed on-site and remote monitoring visits, verified the source documents, and collected source material for event adjudication. All events were adjudicated by an independent adjudication committee that was unaware of the treatment allocations. All data were stored at a central database (CTU, Bern, Switzerland).

Randomized treatment

Patients randomly assigned to the abbreviated APT group immediately discontinued dual-APT and continued single-APT until study completion, except for those receiving OAC, who continued single-APT up to 6 months after the index procedure. Patients allocated to the standard APT group continued dual-APT for at least 5 additional months (6 months after the index procedure) or, for those receiving OAC, for at least 2 additional months (3 months after the index procedure) and continued thereafter on single-APT. Antiplatelet and anticoagulant treatments were dosed according to authorizations for use and locally approved regimens; detailed descriptions of the two treatment regimens are provided in the Supplementary Appendix.

Outcomes

The three co-primary outcomes were net adverse clinical events (a composite of death from any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (a composite of death from any cause, myocardial infarction, or stroke), and

major or clinically relevant non-major bleeding [composite of types 2, 3, or 5 Bleeding Academic Research Consortium (BARC) bleeding events]; cumulative incidences were assessed at 335 days. The secondary outcomes included the individual components of the three co-primary outcomes. All outcomes were pre-specified. All analyses evaluated the occurrence of the adjudicated outcomes between randomization and 335 days.

Statistical analysis

The data were analysed according to the intention-to-treat principle. Outcomes were assessed separately for the patients enrolled from Europe, Asia, and Argentina/Australia by calculating hazard ratios (HR) with 95% confidence intervals (CI). We report cause-specific estimates. Time-to-event was calculated as the difference between the date of occurrence of the outcome event and the date of randomization plus 1. For patients with incomplete clinical follow-up, time to censoring was defined as the difference between the dates of last known clinical status and randomization plus 1. For patients with an outcome event and complete follow-up until the end of day 335, time to censoring was calculated as 335 days. For patients with incomplete clinical follow-up, time to censoring was defined as the difference between the dates of last known clinical status and randomization plus 1. For the third coprimary outcome, the occurrence of death was defined as a competing risk event, and follow-up was censored at the time of the occurrence of death. Kaplan-Meier curves were created for the first 2 (time-to-event) coprimary outcomes, and cause-specific Kaplan-Meier curves for the third coprimary outcome (with censoring at the time of the competing risk event of unrelated death). Kaplan–Meier calculations included all (first) adjudicated outcome events that occurred between randomization and 335 days thereafter according to the randomized treatment assignment. P-values for testing homogeneity of the HR in subgroups of patients were derived in Cox proportional hazards models with the interaction term for the treatment group (abbreviated APT vs. standard APT) and the three geographical regions tested using two degrees of freedom. The 95% CI and P-values for interaction were not

adjusted for multiplicity and should not be used to infer definitive treatment effects.

Results

In the MASTER DAPT trial, 3838 patients (abbreviated APT, n=1927; standard APT, n=1911), 583 patients (abbreviated APT, n=286; standard APT, n=297) and 158 patients (abbreviated APT, n=82; standard APT n=76) were enrolled from Europe, Asia, and Argentina/Australia, respectively. Clinical characteristics across geographic regions were well balanced in the two randomized APT groups (**Table 1**). Clinical characteristics stratified by geography are presented in **Supplementary Table 1**. Patients from Asia were younger (73±11 years) and had lower body mass index (25±4 kg/m^2) than those from Europe (76±8 years and 28±5 kg/m^2, respectively) or from Argentina/Australia (76±8 years and 29±5 kg/m^2, respectively). Patients from Asia had lower proportion of hypertension (68%) but more frequently diabetes (49%) than those from other regions (Europe, 79% and 31%; Argentina/Australia, 75% and 32%, respectively). The proportion of atrial fibrillation (13%) and treatment with OAC (19%) were lower in patients from Asia than those from Europe (36% and 39%, respectively) or from Argentina/Australia (32% and 32%, respectively). Procedural characteristics across the three regions were well balanced in the two randomized APT groups (**Table 2**). Procedural characteristics stratified by region are shown in **Supplementary Table 2**. Patients with myocardial infarction or unstable angina were most frequent in Argentina/Australia (72%), followed by Asia (59%) and Europe (46%). The radial artery was the most frequent access site in Europe (87%). The number of treated vessels and lesions were lower in patients from Asia than from Europe or Argentina/Australia. Total number of stents per lesion, total stent length per lesion and the proportion of post-dilation also differed by geography (**Supplementary Table 3)**. Medications are shown in **Supplementary Tables 4 and 5**).

Clinical outcomes were comparable across geographical regions with the exception for major or clinically relevant nonmajor bleeding, which occurred less frequently in patients

from Asia than Europe (4.5% versus 8.3%, HR 0.53, 95% CI 0.36 to 0.80, P=0.002), or Argentina/Australia (9.7%; HR 0.36, 95% CI 0.20 to 0.65, P=0.001) **Supplementary Table 6)**.

Net adverse clinical events and major adverse cardiac and cerebral events did not differ with abbreviated or standard APT among patients from Europe (7.8% versus 8.0%, HR 0.98, 95% CI 0.78 to 1.22, P=0.831; and 6.3% versus 5.9%, HR 1.06, 95% CI 0.82 to 1.38, P=0.635, respectively), Asia (5.6% versus 6.8%, HR 0.82, 95% CI 0.42 to 1.58, P=0.552; and 4.9% versus 6.1%, HR 0.80, 95% CI 0.40 to 1.60, P=0.521, respectively), or Argentina/Australia (7.3% versus 13.2%, HR 0.53, 95% CI 0.19 to 1.45, P=0.217; 4.9% versus 10.5%, HR 0.45, 95% CI 0.14 to 1.49, P=0.191), with negative treatment-by geography interaction testing (P-interaction=0.472 and 0.306, respectively) (**Central illustration, Table 3**, **Figures 1** and **2**). Major or clinically relevant nonmajor bleeding was consistently reduced with abbreviated compared with standard APT across regions (P-interaction=0.445), although the rates were significantly reduced in the largest subset of patients from Europe (6.9% versus 9.7%, HR 0.69, 95% CI 0.55 to 0.86, P=0.001) but not in Asia (4.2% versus 4.8%, HR 0.87, 95% CI 0.40 to 1.89) or Argentina/Australia (7.3% versus 17.5%, HR 0.39, 95% CI 0.15 to 1.04) (**Central illustration, Table 3, Figure 1C** and **Figure 2**). Treatment-by-region interaction testing was negative for all individual components of the primary endpoints or other secondary endpoints (**Table 3** and **Figure 2**). The consistency of the treatment effects was further confirmed in patients with and without OAC, when separately appraised (**Supplementary Figures 1** and **2**).

Discussion

In this prespecified sub-analysis from the MASTER DAPT trial, in spite of notable differences across regions in clinical or procedural features, the treatment effectiveness and safety of abbreviated APT versus standard APT were consistent across geographies in HBR patients after use of biodegradable-polymer-coated sirolimus-eluting stents. There was no

heterogeneity across the three geographies with regard to the three co-primary outcomes, nor for secondary endpoints, suggesting consistent treatment effects of abbreviated compared with standard APT. The rates of net and major adverse clinical events were similar with the two APT regimens, and major or clinically relevant non-major bleeding lower with abbreviated APT, although differed significantly only in the larger cohort of patients from Europe. These findings were further corroborated in the analyses which separately appraised patients with and without OAC.

The optimal antiplatelet strategies after drug-eluting stent implantation have been evaluated from the several randomized clinical trials.[1] However, clinical trials with limited or no geographical variations have raised concerns about trial result generalizability.[2] In this study, we observed a significant heterogeneity of baseline clinical features among HBR patients who underwent PCI according to the geographical variations, consistent with previous analyses.[3] Patients from Asia were more likely to be younger, had less hypertension, atrial fibrillation, and the need for OAC, but more frequently affected by diabetes mellitus than patients from other regions. These findings may be partly due to the ethnic or racial differences in the risk factors of coronary artery disease and also potentially attributable to the geographical variations in the diagnostic or treatment strategies for coronary artery disease.[14-18] Clinical outcomes were also different according to the geographical regions. Major or clinically relevant nonmajor bleeding occurred significantly less frequently in patients from Asia, which may be at least explained by the differences in baseline clinical characteristics, including the use of OAC.

In spite of baseline differences, the treatment effect of abbreviated versus standard APT was consistent across the geographical regions, supporting the generalizability of study regions across at least Europe and Asia, which largely contributed to patient inclusion. These findings carry clinical relevance in view of previous data suggesting that East Asian patients have unique racial features distinct from those of Westerners, leading to higher propensity towards bleeding and concomitant lower likelihood of ischemic events and

clopidogrel responsiveness, known as the Asian paradox.[7,21] The higher frequency of clopidogrel hypo-responsiveness in East Asian than in Western patients is mainly attributable due to a higher prevalence of loss of function CYP2C19 alleles. High on-clopidogrel platelet reactivity has been associated with higher ischemic risk of mortality and stent thrombosis.[22,23] Yet, in MASTER DAPT the rate of major adverse clinical events was not higher in Asian versus European patients, irrespective of APT duration, which is a reassuring finding considering that both in Asia and Europe, clopidogrel monotherapy was the most frequently single antiplatelet agent after DAPT discontinuation.

There are several imitations in our study. First, the number of patients from Asia or Argentina/Australia was relatively small, limiting the evaluation of outcomes with small events numbers or individual outcomes. Second, because of the relatively small number of patients enrolled from the Asian region, the differential treatment effect within the Asian region (i.e., East Asian versus South Asian) was not further analysed. Third, our trial exclusively included patients at HBR who underwent biodegradable polymer sirolimus-eluting stent implantation. Our results may not be applicable to patients who are not at HBR or received other stent types. Fourth, randomization was not stratified by the geographical regions though it was stratified by the enrolling sites.

In conclusion, among the HBR patients undergoing biodegradable polymer sirolimus-eluting stent implantation, in spite of heterogeneities in clinical and procedural features by the geographical variations, the treatment effects of abbreviated versus standard APT on the occurrence of net and major adverse clinical events as well as bleeding were consistent across geographies, suggesting generalizability of overall study findings across investigated ethnicities.

Impact on daily practice

One-month duration of dual antiplatelet therapy is associated with similar treatment effects among different geographic regions, including Europe and Asia, consisting of similar risk of fatal or non-fatal ischaemic events and lower bleeding compared with a more prolonged treatment duration after PCI in patients at high bleeding risk.

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Table 1. Clinical characteristics according to the APT groups across geographical regions

	Europe		Asia		Argentina/Australia	
	Abbreviated APT N=1927	**Standard APT N=1911**	**Abbreviated APT N=286**	**Standard APT N=297**	**Abbreviated APT N=82**	**Standard APT N=76**
Age, years	76±8	76±8	74±11	73±11	77±9	76±7
Male sex	1324 (69)	1314 (69)	208 (73)	218 (73)	58 (71)	49 (65)
Body mass index, kg/m²	28±5	28±5	25±4	25±4	29±5	29±5
Family history of CAD	509 (26)	503 (26)	22 (8)	30 (10)	25 (31)	20 (26)
Arterial hypertension	1517 (79)	1519 (80)	187 (65)	212 (71)	62 (76)	56 (74)
Uncontrolled hypertension	99 (5)	104 (5)	16 (6)	11 (4)	4 (5)	2 (3)
Diabetes mellitus	598 (31)	606 (32)	135 (47)	149 (50)	21 (26)	29 (38)
Hyperlipidemia	1311 (68)	1302 (68)	166 (58)	191 (64)	65 (79)	62 (82)
Current smoker	200 (10)	158 (8)	23 (8)	21 (7)	7 (9)	5 (7)
Peripheral/Vascular disease	222 (12)	224 (12)	13 (5)	12 (4)	8 (10)	6 (8)
Carotid artery disease	90 (5)	111 (6)	27 (9)	28 (9)	3 (4)	5 (7)
History of heart failure	365 (19)	367 (19)	56 (20)	59 (20)	8 (10)	12 (16)
Left ventricular ejection fraction, %	53±11	53±12	54±12	54±12	54±11	53±13
Prior myocardial infarction	365 (19)	368 (19)	53 (19)	53 (18)	16 (20)	9 (12)
Prior PCI	514 (27)	507 (27)	58 (20)	72 (24)	22 (27)	15 (20)
Prior cerebrovascular event	222 (12)	245 (13)	37 (13)	49 (17)	9 (11)	8 (11)
History of arterial thromboembolism	28 (2)	22(1)	3 (1)	1 (<1)	0	1 (1)
History of venous thromboembolism	114 (6)	101 (5)	2 (1)	6 (2)	8 (10)	8 (11)
Prior CABG	157 (8)	147 (8)	10 (4)	19 (6)	3 (4)	5 (7)
Prior prosthetic mechanical heart valve	40 (2)	50 (3)	3 (1)	6 (2)	0	2 (3)
Known aortic valve stenosis	79 (5)	92 (6)	9 (3)	6 (2)	3 (4)	6 (8)
Prior bleeding	155 (8)	141 (7)	22 (8)	22 (7)	7 (9)	12 (16)
Chronic pulmonary disease	225 (12)	250 (13)	18 (6)	20 (7)	12 (15)	13 (17)
Chronic Renal Failure	348 (18)	384 (20)	59 (21)	60(20)	11 (13)	14 (18)
Liver disease	25 (1)	25 (1)	4 (1)	6 (2)	0	1 (1)
Atrial fibrillation	704 (37)	663 (35)	42 (15)	31 (10)	24 (29)	26 (34)
History of cancer	296 (15)	310 (16)	40 (14)	32 (11)	12 (15)	9 (12)
Active cancer	101 (5)	110 (6)	5 (2)	14 (5)	4 (5)	2 (3)
Hematological/coagulation disorders	228 (12)	215 (11)	55 (19)	60 (20)	7 (9)	13 (17)
Chronic use of steroids or NSAIDS	174 (9)	194 (10)	20 (7)	23 (8)	8 (10)	22 (29)

Prior VKA	302 (16)	270 (14)	17 (6)	25 (8)	8 (10)	4 (5)
Need for current treatment with OAC	771 (40)	740 (39)	53 (19)	55 (19)	25 (31)	25 (33)
Clinical indication for 12 months OAC	769 (40)	738 (39)	53 (19)	55 (19)	26 (32)	25 (33)
OAC treatment at randomization	764 (99)	734 (>99)	53 (100)	55 (100)	25 (96)	25 (100)
PRECISE DAPT score	27±11	27±11	28±12	27±12	25±9	29±11
Prior bleeding	135 (7)	121 (6)	24 (8)	25 (8)	6 (7)	9 (12)
Hemoglobin, g/L	13.3±1.7	13.3±1.8	12.6±1.9	12.7± 2.0	13.6±1.8	13.4±1.7
White blood cell count WBC, 10^9/L	8.3±12.3	8.0±3.5	8.6±5.6	8.3±3.0	7.7±2.5	8.4±3.2
Creatinine clearance, ml/min/1.73 m²	70±23	71±24	72±31	73±27	73±23	67±22

Data on smoking status was obtained in 3826 patients in Europe. Left ventricular ejection fraction was obtained in 3591 patients in Europe and 569 patients in Asia. Known aortic valve stenosis was obtained in 3392 patients in Europe, and in 572 patients in Asia. White blood cell count was obtained in 3837 patients in Europe.

CABG = coronary artery bypass graft; CAD = coronary artery disease; APT = antiplatelet therapy; NSAIDs; non-steroidal anti-inflammatory drugs; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; PRECISE DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy; WBC = white blood cell.

Table 2. Procedural characteristics according to the APT groups across geographical regions

	Europe		Asia		Argentina/Australia	
	Abbreviated APT	**Standard APT**	**Abbreviated APT**	**Standard APT**	**Abbreviated APT**	**Standard APT**
	N = 2295	N = 2284	N = 286	N = 297	N = 82	N = 76
Indication* (n [%])	n = 2295,	n = 2284,	N = 286	N = 297	N = 82	N = 76
Stable angina	922 (40.2%)	927 (40.6%)	92 (32.2%)	92 (31.0%)	12 (14.6%)	15 (19.7%)
Silent ischemia	245 (10.7%)	274 (12.0%)	27 (9.4%)	31 (10.4%)	11 (13.4%)	7 (9.2%)
NSTEMI	595 (25.9%)	558 (24.4%)	64 (22.4%)	70 (23.6%)	32 (39.0%)	34 (44.7%)
STEMI	273 (11.9%)	265 (11.6%)	65 (22.7%)	62 (20.9%)	9 (11.0%)	5 (6.6%)
Unstable angina	260 (11.3%)	260 (11.4%)	38 (13.3%)	42 (14.1%)	18 (22.0%)	15 (19.7%)
Clinical status*						
Killip II, III or IV	252 (11.0%)	254 (11.1%)	252 (11.0%)	254 (11.1%)	252 (11.0%)	254 (11.1%)
Cardiac arrest	26 (1.1%)	32 (1.4%)	26 (1.1%)	32 (1.4%)	26 (1.1%)	32 (1.4%)
Heart rate, beats/min (mean ± SD)	n = 2294, 73.53 ± 16.46	n = 2280, 73.78 ± 16.50	n = 2294, 73.53 ± 16.46	n = 2280, 73.78 ± 16.50	n = 2294, 73.53 ± 16.46	n = 2280, 73.78 ± 1
Systolic blood pressure, mmHg (mean ± SD)	n = 2289, 137.40 ± 25.84	n = 2278, 136.88 ± 25.14	n = 2289, 137.40 ± 25.84	n = 2278, 136.88 ± 25.14	n = 2289, 137.40 ± 25.84	n = 2278, 136.88 ± 2
Procedural specifications*						
Arterial access site (n [%])	n = 2295,	n = 2284,	n = 2295,	n = 2284,	n = 2295,	n = 2284,
femoral	360 (15.7%)	293 (12.8%)	360 (15.7%)	293 (12.8%)	360 (15.7%)	293 (12.8%)
radial	1930 (84.1%)	1984 (86.9%)	1930 (84.1%)	1984 (86.9%)	1930 (84.1%)	1984 (86.9%)
brachial	5 (0.2%)	7 (0.3%)	5 (0.2%)	7 (0.3%)	5 (0.2%)	7 (0.3%)
IABP (n [%])	24 (1.0%)	30 (1.3%)	24 (1.0%)	30 (1.3%)	24 (1.0%)	30 (1.3%)
LVAD (n [%])	2 (0.1%)	6 (0.3%)	2 (0.1%)	6 (0.3%)	2 (0.1%)	6 (0.3%)
Total amount of contrast, cc (mean ± SD)	n = 2275, 168.16 ± 80.42	n = 2262, 166.81 ± 79.41	n = 2275, 168.16 ± 80.42	n = 2262, 166.81 ± 79.41	n = 2275, 168.16 ± 80.42	n = 2262, 166.81 ± 7
Medications during the procedure* (n [%])						

Unfractioned heparin	n = 2295, 2184 (95.2%)	n = 2283, 2172 (95.1%)	n = 2295, 2184 (95.2%)	n = 2283, 2172 (95.1%)	n = 2295, 2184 (95.2%)	n = 2283, 2172 (95.
Bivalirudin	n = 2295, 5 (0.2%)	n = 2283, 2 (0.1%)	n = 2295, 5 (0.2%)	n = 2283, 2 (0.1%)	n = 2295, 5 (0.2%)	n = 2283, 2 (0.1%
Low molecular weight heparin	n = 2295, 63 (2.7%)	n = 2283, 64 (2.8%)	n = 2295, 63 (2.7%)	n = 2283, 64 (2.8%)	n = 2295, 63 (2.7%)	n = 2283, 64 (2.8
Cangrelor	n = 2295, 8 (0.3%)	n = 2283, 3 (0.1%)	n = 2295, 8 (0.3%)	n = 2283, 3 (0.1%)	n = 2295, 8 (0.3%)	n = 2283, 3 (0.1%
Glycoprotein II/IIIa inhibitors	n = 2295, 86 (3.7%)	n = 2283, 76 (3.3%)	n = 2295, 86 (3.7%)	n = 2283, 76 (3.3%)	n = 2295, 86 (3.7%)	n = 2283, 76 (3.3
Total number of PCIs¶ (n [%])	n = 2295,	n = 2284,	n = 2295,	n = 2284,	n = 2295,	n = 2284,
one	2093 (91.2%)	2066 (90.5%)	2093 (91.2%)	2066 (90.5%)	2093 (91.2%)	2066 (90.5%)
two	191 (8.3%)	214 (9.4%)	191 (8.3%)	214 (9.4%)	191 (8.3%)	214 (9.4%)
three	11 (0.5%)	4 (0.2%)	11 (0.5%)	4 (0.2%)	11 (0.5%)	4 (0.2%)
Total nr of vessels treated per patient¥ (n [%])	n = 2295,	n = 2284,	n = 2295,	n = 2284,	n = 2295,	n = 2284,
one	1716 (74.8%)	1649 (72.2%)	1716 (74.8%)	1649 (72.2%)	1716 (74.8%)	1649 (72.2%)
two	483 (21.0%)	541 (23.7%)	483 (21.0%)	541 (23.7%)	483 (21.0%)	541 (23.7%)
three	96 (4.2%)	94 (4.1%)	96 (4.2%)	94 (4.1%)	96 (4.2%)	94 (4.1%)
Treated vessel(s) per patient (n [%])	n = 2295	n = 2284	n = 2295	n = 2284	n = 2295	n = 2284
Left main	126 (5.5%)	134 (5.9%)	126 (5.5%)	134 (5.9%)	126 (5.5%)	134 (5.9%)
Left arterial descending artery	1240 (54.0%)	1271 (55.6%)	1240 (54.0%)	1271 (55.6%)	1240 (54.0%)	1271 (55.6%)
Left circumflex artery	652 (28.4%)	689 (30.2%)	652 (28.4%)	, 689 (30.2%)	652 (28.4%)	689 (30.2%)
Right coronary artery	854 (37.2%)	806 (35.3%)	854 (37.2%)	806 (35.3%)	854 (37.2%)	806 (35.3%)
Bypass graft	38 (1.7%)	38 (1.7%)	38 (1.7%)	38 (1.7%)	38 (1.7%)	38 (1.7%)
Total nr of treated lesions per patient	n = 2295,	n = 2284,	n = 2295,	n = 2284,	n = 2295,	n = 2284,
one	1579 (68.8%)	1536 (67.3%)	1579 (68.8%)	1536 (67.3%)	1579 (68.8%)	1536 (67.3%)
two	503 (21.9%)	522 (22.9%)	503 (21.9%)	522 (22.9%)	503 (21.9%)	522 (22.9%)
three or more	213 (9.3%)	226 (9.9%)	213 (9.3%)	226 (9.9%)	213 (9.3%)	226 (9.9%)
Total stented lesions per patient	n = 2295,	n = 2284,	n = 2295,	n = 2284,	n = 2295,	n = 2284,

one	1611 (70.2%)	1565 (68.5%)	1611 (70.2%)	1565 (68.5%)	1611 (70.2%)	1565 (68.5%)
two	486 (21.2%)	507 (22.2%)	486 (21.2%)	507 (22.2%)	486 (21.2%)	507 (22.2%)
three	198 (8.6%)	212 (9.3%)	198 (8.6%)	212 (9.3%)	198 (8.6%)	212 (9.3%)
At least one complex lesion B2 or C (n [%])	1562 (68.1%)	1579 (69.1%)	1562 (68.1%)	1579 (69.1%)	1562 (68.1%)	1579 (69.1%)
Number of stents per patient (mean ± SD)	1.74 ± 1.13	1.76 ± 1.11	1.74 ± 1.13	1.76 ± 1.11	1.74 ± 1.13	1.76 ± 1.11
Total stent length per patient (mean ± SD)	39.29 ± 29.24	39.73 ± 28.40	39.29 ± 29.24	39.73 ± 28.40	39.29 ± 29.24	39.73 ± 28.40
Any overlapping stenting (n [%])	488 (21.3%)	450 (19.7%)	488 (21.3%)	450 (19.7%)	488 (21.3%)	450 (19.7%)
Any Bifurcation or trifurcation stenting§ (n [%])	83 (3.6%)	101 (4.4%)	83 (3.6%)	101 (4.4%)	83 (3.6%)	101 (4.4%)

PCI: percutaneous coronary intervention; IABP: intra-aortic balloon pump used; LVAD: left-ventricular assist device used; DAPT and SAPT: Dual and Single antiplatelet treatment.

*Data from first PCI only.

¶one PCI and up to two staged PCIs - the last PCI was the qualifying PCI one month before the randomisation.

§into both main- and side-branch, MADS classes 3, 4, 5, 9, 10, 11, 12, 15, 16, 17, 21, 22, 23, 24

¥Left main counted as two vessels; LIMA/RIMA/Radial grafts counted as one vessel; SVG grafts counted with the vessel as follows: LCX = 1MO, 2M0, PL(Cx) AL branch, or DG; LAD = LAD; RCA = RCA or Posterior descending RC.

p-values comparing the three regions (chisquare tests for counts or ANOVAs for continuous parameters)

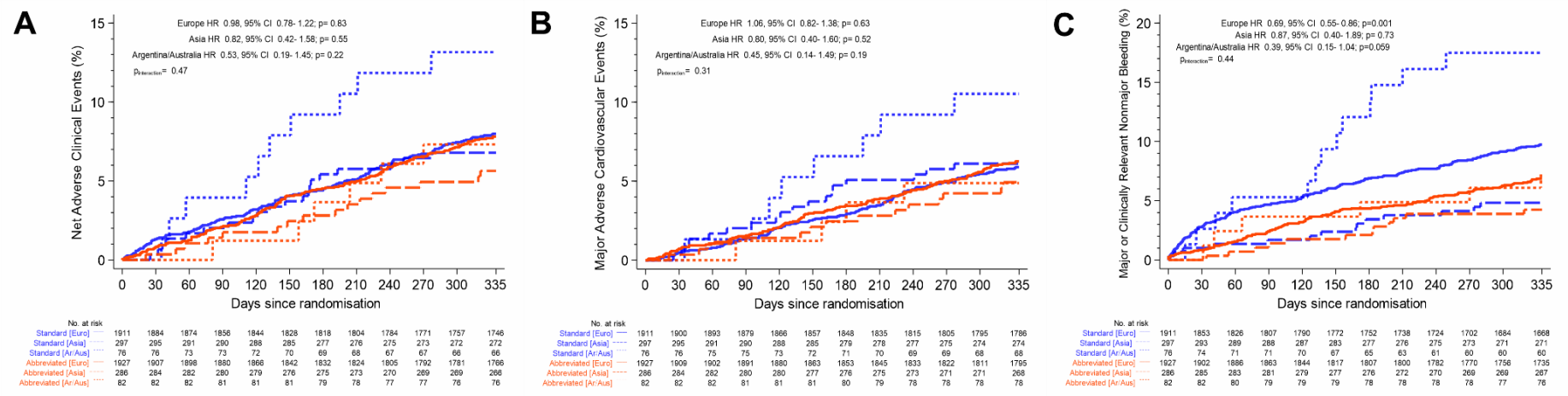
Table 3. Clinical outcomes according to the APT groups across geographical regions

	Europe				Asia				Argentina/Australia				P-int
	Abbreviated APT N=1927	Standard APT N=1911	Hazard ratio (95% CI)	p-value	Abbreviated APT N=286	Standard APT N=297	Hazard ratio (95% CI)	p-value	Abbreviated APT N=82	Standard APT N=76	Hazard ratio (95% CI)	p-value	
Net adverse clinical events	150 (7.8)	152 (8.0)	0.98 (0.78-1.22)	0.831	16 (5.6)	20 (6.8)	0.82 (0.42-1.58)	0.552	6 (7.3)	10 (13.2)	0.53 (0.19-1.45)	0.217	0.472
Major adverse cardiac or cerebral events	120 (6.3)	112 (5.9)	1.06 (0.82-1.38)	0.635	14 (4.9)	18 (6.1)	0.80 (0.40-1.60)	0.521	4 (4.9)	8 (10.5)	0.45 (0.14-1.49)	0.191	0.306
Major or clinically relevant nonmajor bleeding	130 (6.9)	184 (9.7)	0.69 (0.55-0.86)	0.001	12 (4.2)	14 (4.8)	0.87 (0.40-1.89)	0.729	6 (7.3)	13 (17.5)	0.39 (0.15-1.04)	0.059	0.445
Death	66 (3.4)	67 (3.5)	0.98 (0.70-1.37)	0.894	7 (2.5)	10 (3.4)	0.71 (0.27-1.88)	0.494	2 (2.4)	4 (5.3)	0.45 (0.08-2.48)	0.362	0.589
Cardiovascular death	31 (1.6)	34 (1.8)	0.90 (0.56-1.47)	0.686	6 (2.1)	7 (2.4)	0.87 (0.29-2.60)	0.809	0	3 (4.0)	0.13 (0.01-2.48)	0.109	0.954
Non-cardiovascular death	27 (1.4)	25 (1.3)	1.07 (0.62-1.85)	0.804	1 (0.4)	2 (0.7)	0.51 (0.05-5.62)	0.582	1 (1.2)	1 (1.3)	0.90 (0.06-14.43)	0.942	0.835
Undetermined death	8 (0.4)	8 (0.4)	0.99 (0.37-2.64)	0.986	0	1 (0.4)	0.35 (0.01-8.56)	1.000	1 (1.2)	0	2.78 (0.11-67.22)	1.000	
Cardiovascular or undetermined death	39 (2.1)	42 (2.2)	0.92 (0.60-1.42)	0.711	6 (2.1)	8 (2.7)	0.76 (0.27-2.20)	0.620	1 (1.2)	3 (4.0)	0.30 (0.03-2.92)	0.302	0.618
Cerebrovascular Accident	15 (0.8)	26 (1.4)	0.57 (0.30-1.08)	0.084	2 (0.7)	4 (1.4)	0.50 (0.09-2.76)	0.430	0	2 (2.7)	0.19 (0.01-3.89)	0.230	0.992
Stroke	11 (0.6)	17 (0.9)	0.64 (0.30-1.37)	0.252	1 (0.4)	4 (1.4)	0.25 (0.03-2.26)	0.218	0	2 (2.7)	0.19 (0.01-3.89)	0.230	0.432
Ischemic stroke	11 (0.6)	14 (0.8)	0.78 (0.35-1.72)	0.537	0	3 (1.1)	0.15 (0.01-2.89)	0.249	0	1 (1.3)	0.31 (0.01-7.50)	0.481	1.000
Hemorhagic stroke	0	2 (0.1)	0.20 (0.01-4.16)	0.248	1 (0.4)	2 (0.7)	0.51 (0.05-5.60)	0.580	0	1 (1.4)	0.31 (0.01-7.50)	0.481	
Transient ischemic attack	4 (0.2)	9 (0.5)	0.44 (0.14-1.43)	0.172	1 (0.4)	0	3.12 (0.13-76.27)	0.491	0	0			
Myocardial infarction	47 (2.5)	41 (2.2)	1.14 (0.75-1.73)	0.542	10 (3.5)	5 (1.8)	2.05 (0.70-6.01)	0.189	3 (3.7)	3 (4.1)	0.90 (0.18-4.47)	0.899	0.565
Definite or probable sent thrombosis	9 (0.5)	9 (0.5)	0.99 (0.39-2.50)	0.988	4 (1.4)	0	9.35 (0.51-172.88)	0.057	1 (1.3)	0	2.78 (0.11-67.22)	1.000	
Definite stent thrombosis	8 (0.4)	7 (0.4)	1.13 (0.41-3.13)	0.807	2 (0.7)	0	5.19 (0.25-107.64)	0.240	1 (1.3)	0	2.78 (0.11-67.22)	1.000	
Probable stent thrombosis	1 (0.1)	2 (0.1)	0.50 (0.05-5.48)	0.567	2 (0.7)	0	5.19 (0.25-107.64)	0.240	0	0			1.000
Bleeding BARC classification													
Type 1	64 (3.4)	100 (5.3)	0.63 (0.46-0.86)	0.004	1 (0.4)	6 (2.1)	0.17 (0.02-1.40)	0.100	0	3 (4.0)	0.13 (0.01-2.48)	0.109	0.486
Type 2	90 (4.8)	134 (7.1)	0.66 (0.50-0.86)	0.002	8 (2.8)	9 (3.1)	0.91 (0.35-2.35)	0.842	4 (4.9)	9 (12.2)	0.39 (0.12-1.27)	0.118	0.552
Type 3	45 (2.4)	52 (2.8)	0.85 (0.57-1.27)	0.442	4 (1.4)	4 (1.4)	1.02 (0.25-4.06)	0.982	4 (4.9)	3 (4.0)	1.17 (0.26-5.24)	0.834	0.898
Type 3a	23 (1.2)	24 (1.3)	0.95 (0.54-1.68)	0.857	2 (0.7)	3 (1.1)	0.68 (0.11-4.07)	0.673	1 (1.2)	3 (4.0)	0.30 (0.03-2.84)	0.291	0.595
Type 3b	18 (1.0)	20 (1.1)	0.89 (0.47-1.69)	0.725	1 (0.4)	0	3.12 (0.13-76.27)	0.491	2 (2.5)	0	4.64 (0.23-95.12)	0.498	
Type 3c	5 (0.3)	8 (0.4)	0.62 (0.20-1.90)	0.402	1 (0.4)	1 (0.4)	1.02 (0.06-16.25)	0.991	1 (1.3)	0	2.78 (0.11-67.22)	1.000	0.743
Type 4	0	0			0	0			0	0			
Type 5	1 (0.1)	6 (0.3)	0.17 (0.02-1.37)	0.096	1 (0.4)	1 (0.4)	1.02 (0.06-16.25)	0.991	0	1 (1.4)	0.31 (0.01-7.50)	0.481	0.594
Type 5a		2 (0.1)	0.20 (0.01-4.16)	0.248	0	0			0	0			1.000
Type 5b	1 (0.1)	4 (0.2)	0.25 (0.03-2.22)	0.212	1 (0.4)	1 (0.4)	1.02 (0.06-16.25)	0.991	0	1 (1.4)	0.31 (0.01-7.50)	0.481	0.434
Type 3 or 5	46 (2.4)	58 (3.1)	0.78 (0.53-1.15)	0.217	5 (1.8)	5 (1.8)	1.02 (0.29-3.51)	0.980	4 (4.9)	4 (5.4)	0.88 (0.22-3.51)	0.854	0.914

BARC = Bleeding Academic Research Consortium; CI = confidence interval; APT = antiplatelet therapy.

Figure Legends

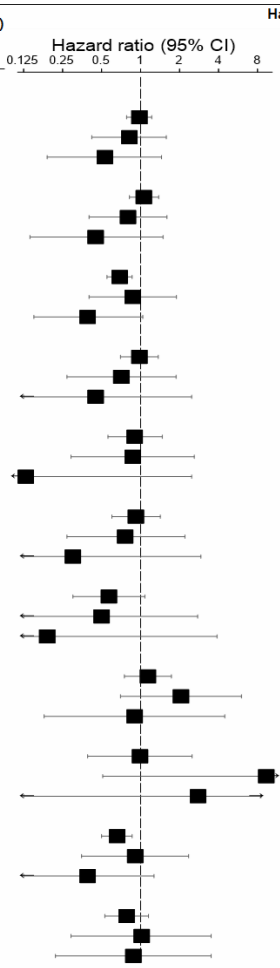
Figure 1. Kaplan-Meier curves of the primary outcomes



NACE (A), MACCE (B), and Major or clinically relevant nonmajor bleeding (C) according to the three geographical regions and APT groups. NACE = net adverse clinical events; MACCE = major adverse cardiac and cerebral event; APT = antiplatelet therapy.

Figure 2. Forest plot of clinical endpoints

	Abbreviated DAPT	Standard DAPT	Hazard ratio (95% CI)	Hazard ratio p-value	interaction p-value
Net Adverse Clinical Events					0.47
Europe	150 (7.81)	152 (7.99)	0.98 (0.78-1.22)	0.831	
Asia	16 (5.64)	20 (6.79)	0.82 (0.42-1.58)	0.552	
Argentina/Australia	6 (7.32)	10 (13.16)	0.53 (0.19-1.45)	0.217	
Major Adverse Cardiovascular Events					0.31
Europe	120 (6.25)	112 (5.89)	1.06 (0.82-1.38)	0.635	
Asia	14 (4.94)	18 (6.11)	0.80 (0.40-1.60)	0.521	
Argentina/Australia	4 (4.88)	8 (10.53)	0.45 (0.14-1.49)	0.191	
Major or Clinically Relevant Nonmajor Bleeding					0.44
Europe	130 (6.85)	184 (9.74)	0.69 (0.55-0.86)	0.001	
Asia	12 (4.24)	14 (4.83)	0.87 (0.40-1.89)	0.729	
Argentina/Australia	6 (7.32)	13 (17.50)	0.39 (0.15-1.04)	0.059	
Death					0.59
Europe	66 (3.44)	67 (3.52)	0.98 (0.70-1.37)	0.894	
Asia	7 (2.47)	10 (3.39)	0.71 (0.27-1.88)	0.494	
Argentina/Australia	2 (2.44)	4 (5.26)	0.45 (0.08-2.48)	0.362	
Cardiovascular death					0.95
Europe	31 (1.63)	34 (1.80)	0.90 (0.56-1.47)	0.686	
Asia	6 (2.12)	7 (2.38)	0.87 (0.29-2.60)	0.809	
Argentina/Australia	0 (0.00)	3 (3.98)	0.13 (0.01-2.48)	0.109	
Cardiovascular or Undetermined death					0.62
Europe	39 (2.05)	42 (2.22)	0.92 (0.60-1.42)	0.711	
Asia	6 (2.12)	8 (2.72)	0.76 (0.27-2.20)	0.620	
Argentina/Australia	1 (1.23)	3 (3.98)	0.30 (0.03-2.92)	0.302	
Cerebrovascular Accident					0.99
Europe	15 (0.79)	26 (1.39)	0.57 (0.30-1.08)	0.084	
Asia	2 (0.72)	4 (1.40)	0.50 (0.09-2.76)	0.430	
Argentina/Australia	0 (0.00)	2 (2.68)	0.19 (0.01-3.89)	0.230	
Myocardial infarction					0.57
Europe	47 (2.49)	41 (2.18)	1.14 (0.75-1.73)	0.542	
Asia	10 (3.54)	5 (1.75)	2.05 (0.70-6.01)	0.189	
Argentina/Australia	3 (3.67)	3 (4.11)	0.90 (0.18-4.47)	0.899	
Definite or Probable Stent Thrombosis					
Europe	9 (0.48)	9 (0.48)	0.99 (0.39-2.50)	0.988	
Asia	4 (1.42)	0 (0.00)	9.35 (0.51-172.88)	0.057	
Argentina/Australia	1 (1.25)	0 (0.00)	2.78 (0.11-67.22)	1.000	
BARC Type 2					0.55
Europe	90 (4.75)	134 (7.11)	0.66 (0.50-0.86)	0.002	
Asia	8 (2.82)	9 (3.09)	0.91 (0.35-2.35)	0.842	
Argentina/Australia	4 (4.89)	9 (12.22)	0.39 (0.12-1.27)	0.118	
BARC Type 3 or 5					0.91
Europe	46 (2.43)	58 (3.07)	0.78 (0.53-1.15)	0.217	
Asia	5 (1.77)	5 (1.76)	1.02 (0.29-3.51)	0.980	
Argentina/Australia	4 (4.88)	4 (5.37)	0.88 (0.22-3.51)	0.854	



BARC = Bleeding Academic Research Consortium; CI = confidence interval; APT = antiplatelet therapy.