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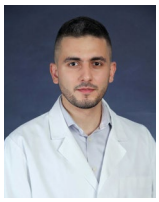
ORIGINAL RESEARCH

Performance of drug-coated balloons in East Asian and Caucasian patients: a *post hoc* analysis of the EASTBOURNE Registry



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ABSTRACT

BACKGROUND: The treatment of coronary artery disease (CAD) has evolved significantly over the years with the emergence of drug-coated balloons (DCBs). Research has shown that ethnicity can influence procedural approaches and clinical outcomes. Despite this, there are still limited data on DCB performance in different ethnic groups – particularly Caucasian and East Asian patients.

AIMS: In this *post hoc* analysis of the EASTBOURNE Registry, we aimed to assess differences in clinical outcomes between Caucasian and East Asian patients.

METHODS: EASTBOURNE was a prospective, investigator-driven, multicentre, international study investigating the safety and efficacy of a sirolimus-coated balloon (SCB). A propensity-matching analysis was performed to mitigate differences in variables. The primary endpoint was target lesion revascularisation (TLR) at 12 months.

RESULTS: From September 2016 to December 2020, EASTBOURNE enrolled 2,123 patients from 38 centres. This analysis includes 2,084 patients: 1,657 in the Caucasian group and 427 in the East Asian group. After propensity matching, we analysed 602 patients with no significant differences in clinical characteristics. In procedural terms, the Caucasian population had higher baseline percentage diameter stenosis and contrast media usage, but they had lower predilatation rates and used shorter SCBs at higher pressures; the rate of bailout stenting was also higher. Twelve-month follow-up showed higher rates of TLR (6.0% vs 1.5%; p<0.001), whereas major adverse cardiovascular events, all-cause death, and spontaneous myocardial infarction did not differ significantly. Bleeding Academic Research Consortium Type 2-5 bleedings were lower (0.0 vs 5.0%; p<0.001).

CONCLUSIONS: In this subgroup analysis of the EASTBOURNE Registry comparing patients of Caucasian versus East Asian origin treated with SCBs, there were higher incidences of TLR but less bleeding in the Caucasian population compared to East Asian patients.

KEYWORDS: Caucasian patients; drug-coated balloon; EASTBOURNE Registry; Eastern patients; sirolimus-coated balloon

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Drug-coated balloons (DCBs) represent an emerging technology in interventional cardiology which is gaining more indications in terms of lesion and patient subsets. If drug-eluting stents (DES) remain the preferred and most used technique for revascularisation worldwide[1], DCBs are now often considered the first option in indications such as in-stent restenosis (ISR) and *de novo* lesions in small vessel disease (SVD)[2]. Several studies have recently been published to test the efficacy and safety of this technology in other clinical and lesion settings[3], and the usage of DCBs, eluting either paclitaxel or sirolimus, is further expanding its indications all over the world[4]. According to the Japanese Association of Cardiovascular Intervention and Therapeutics, East Asian populations are culturally opposed to the long-term implantation of foreign materials, such as stents, into their bodies. This difference in cultural beliefs may result in higher use of the DCB technique compared to other techniques that require permanent implants, impacting clinical outcomes following DCB angioplasty when comparing the East Asian and Caucasian populations[5].

The performance of DCBs in various populations can be affected by several physiological and biological factors, which will influence how patients treated with DCBs respond to the treatment and, subsequently, their efficacy and safety outcomes. First, genetic variability can affect drug metabolism and response, and receptor variations can influence the pharmacokinetics and pharmacodynamics of the drugs used in DCBs. Notably, the East Asian population has been found to have a mutation in the CYP2C19 gene, which can affect the metabolism of drugs coated on balloons, such as paclitaxel and sirolimus[6]. Factors related to vessel physiology, e.g., endothelial function and vascular reactivity, can also vary between populations, leading to different outcomes[7]. Variations in plaque composition and distribution, and the occurrence of ISR, can also vary between East Asian and Caucasian populations. It is well known that East Asian and Caucasian populations have different diets, and dietary differences affecting lipid profiles and systemic inflammation may alter the local vascular environment and response to DCBs[8].

The focus of this study is to determine whether a sirolimus-coated balloon (SCB) is associated with meaningful clinical differences between geographical areas by comparing clinical outcomes between patients enrolled in East Asian and Caucasian centres participating in the EASTBOURNE prospective study.

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Impact on daily practice

Clinical and procedural differences between Caucasian and East Asian populations undergoing coronary angioplasty with drug-coated balloons can significantly impact their cardiovascular outcomes. It is important to understand these differences to address disparities. By studying and acknowledging these differences, physicians can develop more personalised and effective treatment plans for their patients, leading to better overall outcomes.

Methods

STUDY DESIGN AND POPULATION

The EASTBOURNE Registry (ClinicalTrials.gov: NCT03085823) is a prospective, multicentre, independent, investigator-driven study which enrolled an all-comer population treated with the MagicTouch SCB (Concept Medical) at 38 international centres in Europe and East Asia. The cases enrolled in this study were collected from different regions representing the East Asian and Caucasian populations. By including a diverse range of cases, this study aimed to provide more accurate and comprehensive results that can be applied to a larger population. Eligible patients had coronary artery disease (CAD) with a clinical indication for percutaneous coronary intervention (PCI) with DCBs. Investigators had to demonstrate proficiency by having performed at least 30 DCB angioplasties annually over the previous 5 years.

The inclusion criteria for this study were quite broad, allowing for all clinical indications for PCI with SCBs, as determined by the investigator. However, exclusion criteria were put in place to ensure the safety and effectiveness of the study. These included patients with known hypersensitivity or contraindications to certain medications, as well as target lesions or vessels with specific characteristics, such as severe calcification, high vessel tortuosity or visible thrombus. It is important to note that left main stem disease and ST-segment elevation myocardial infarction (STEMI) did not automatically disqualify a patient from participating in the study. The primary endpoint was target lesion revascularisation (TLR) at 12 months. The secondary endpoints were all-cause death and the occurrence of major adverse cardiovascular events (MACE) during follow-up, defined as a composite of TLR, myocardial infarction (MI), and cardiac death. Procedural success was defined as angiographic success without in-hospital complications. The occurrence of MI during follow-up was

Abbreviations

BARC	Bleeding Academic Research Consortium	**MI**	myocardial infarction
CABG	coronary artery bypass grafting	**MV-CAD**	multivessel coronary artery disease
CAD	coronary artery disease	**OCT**	optical coherence tomography
DCB	drug-coated balloon	**PCI**	percutaneous coronary intervention
DES	drug-eluting stent	**RVD**	reference vessel diameter
EES	everolimus-eluting stent	**SCB**	sirolimus-coated balloon
ISR	in-stent restenosis	**SVD**	small vessel disease
MACE	major adverse cardiovascular events	**TLR**	target lesion revascularisation

also analysed. Follow-up visits were programmed at 30 days, 6 months, and 12 months post-procedure via clinic visits and telephonic surveys. This article specifically reports 12-month outcomes based on ethnic origin.

MAIN STUDY RESULTS

The preliminary and main findings of the EASTBOURNE Registry have been detailed in other publications[9,10]. In summary, the study included a total cohort of 2,123 patients, addressing 2,440 lesions. Among the patients, 55% presented with *de novo* lesions, while 45% had ISR. At 12-month follow-up, which was available for 92.5% of the patients, TLR was observed in 5.9% of lesions, MACE occurred in 9.9% of patients, and the overall rate of all-cause death was 2.5%. Multivariate analysis identified ISR as the primary determinant for the occurrence of the primary endpoint, with an odds ratio of 5.5 (95% confidence interval [CI]: 3.38-8.88). All patients included in this study had clinical follow-ups at 30 days, 6 months and 12 months.

DEVICE DESCRIPTION AND PROCEDURE

The MagicTouch SCB features a nanocarrier technology with a dose of 1.27 micrograms of sirolimus/mm^2 of the balloon[11]. The device is offered in various dimensions, ranging from 10 mm to 40 mm in length and 1.5 mm to 4 mm in diameter, and its characteristics are described elsewhere[12].

Proximal and distal references were identified as locations with the largest lumen diameter within a 10 mm segment both proximal and distal to the plaque. The procedure was carried out according to international guidelines or consensus documents[13-16]. Heparin was administered following sheath insertion, along with loading doses of antiplatelets depending on the patient's clinical presentation and following investigator judgement. Aspirin was continued indefinitely, and the second antiplatelet drug was prescribed for up to 1 month post-procedure in the absence of additional stenting, or for 6-12 months in cases of DES implantation or presentation with acute coronary syndrome. The DCB was inflated to its nominal pressure and maintained for a minimum of 30 seconds. The DCB diameter was adjusted to the reference vessel diameter, maintaining a balloon-to-vessel ratio of 0.8-1.0/1.0, while the balloon length was selected to exceed both lesion ends by at least 3 mm. The decision to place a stent post-DCB angioplasty in a bailout fashion was at the discretion of the operator and was suggested in cases of coronary dissection of type >B or impaired coronary flow. The protocol also recommended against stenting small and uncomplicated dissections of type A or B.

STATISTICAL ANALYSIS

The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables are reported as means with standard deviations or medians with interquartile ranges (IQR) in case of Gaussian or non-Gaussian distribution, respectively. Comparisons between two groups used the Student's t-test or Mann-Whitney U test, as appropriate. Comparisons of continuous variables among more than two groups were performed using analysis of variance (ANOVA). Categorical variables are reported as frequencies and percentages and were compared by the chi-square test or Fisher's exact test, as appropriate. To control for the effect of potential confounding factors, one-to-one propensity score matching (PSM) was performed using the nearest-neighbour method without replacement, with a calliper width within 0.2 times the pooled standard deviation of the logit of the propensity scores. A Cox survival analysis was conducted for the endpoint all-cause death, with stratification by country, and reported as Kaplan-Meier curves. All p-values were based on two-sided tests. A p-value less than 0.05 was considered statistically significant for all the study analyses. The analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing), equipped with the packages "MatchIt", "survival", "survminer", and "Rcpp". The variables used for propensity score matching were selected based on their association with the probability of being in one group or the other, as well as their significant imbalance in the unadjusted population. These variables included age, diabetes, smoking status, dyslipidaemia, body mass index, family history of CAD, prior MI, peripheral artery disease, left ventricular ejection fraction, haemoglobin levels, angina, lesion length, right ventricular dysfunction, and whether the procedure was *de novo* or in-stent restenosis. For procedural characteristics, only selected variables were added to maintain a parsimonious model and avoid excessively reducing the number of matched pairs.

Results

Between September 2016 and December 2020, a total of 2,084 patients were included in the Caucasian versus East Asian ethnicity-based *post hoc* study of EASTBOURNE. Overall, a total of 1,657 patients were enrolled in the Caucasian subgroup and 427 patients in the East Asian subgroup.

BASELINE CHARACTERISTICS

Baseline characteristics are reported in **Supplementary Table 1**. The average age was 67 years, 81.2% were male, and 41.6% had diabetes. Multivessel coronary artery disease (MV-CAD) was present in 59.4% of the patients, previous MI in 42.9%, and previous PCI in 66.2%. The baseline characteristics were significantly different between groups. In the Caucasian group, patients were older with a lower incidence of diabetes (38.7% vs 52.9%; p<0.001) but more frequent family history of coronary disease (26% vs 11%; p<0.001), as well as higher rates of previous PCI (73.4% vs 38.4%; p<0.001) and previous coronary artery bypass grafting (CABG; 13.5% vs 4.7%; p<0.001). However, the lower diabetes incidence, which is not influenced by ethnicity, may not have significantly impacted the outcomes of the study. Stable angina pectoris was the most common disease type in both groups.

After propensity matching (n=602 patients), there were no significant differences in the baseline characteristics between the groups apart from greater STEMI rates in the Caucasian group compared to East Asian patients (8.7% vs 4.3%) **(Table 1)**. However, significant differences regarding antiplatelet regimens persisted after propensity matching **(Table 1)**.

PROCEDURAL CHARACTERISTICS

In terms of procedural characteristics of the 2,318 lesions treated, the reference vessel diameter was 2.5 (IQR 2.10,

Table 1. Baseline characteristics of patients after propensity matching.

Characteristic	Overall n=602	Caucasian n=301	East Asian n=301	*p*-value
Age, years	62.00 [55.00, 69.00]	62.00 [55.00, 70.00]	62.00 [55.00, 69.00]	0.560
Male sex	498 (82.7)	245 (81.4)	253 (84.1)	0.451
BMI, kg/m²	26.02 [23.54, 29.28]	26.12 [24.07, 28.93]	25.71 [23.39, 29.41]	0.392
Diabetes	306 (50.8)	161 (53.5)	145 (48.2)	0.221
Hypercholesterolaemia	443 (73.6)	222 (73.8)	221 (73.4)	1.000
Smoker	132 (21.9)	63 (20.9)	69 (22.9)	0.622
Renal insufficiency	60 (10.0)	31 (10.3)	29 (9.6)	0.892
Family history of CAD	90 (15.0)	47 (15.6)	43 (14.3)	0.732
Stroke	25 (4.2)	15 (5.0)	10 (3.3)	0.414
Congestive heart failure	43 (7.1)	17 (5.6)	26 (8.6)	0.205
Previous myocardial infarction	202 (33.6)	104 (34.6)	98 (32.6)	0.666
Previous CABG	41 (6.8)	25 (8.3)	16 (5.3)	0.195
Previous PCI	304 (50.5)	177 (58.8)	127 (42.2)	<0.001
Peripheral artery disease	306 (50.8)	161 (53.5)	145 (48.2)	0.221
MV-CAD	339 (56.3)	178 (59.1)	161 (53.5)	0.189
LVEF, %	55.00 [50.00, 60.00]	55.00 [50.00, 60.00]	55.00 [50.00, 60.00]	0.138
Creatinine, mg/dL	0.98 [0.84, 1.16]	0.98 [0.80, 1.19]	0.98 [0.85, 1.14]	0.805
Haemoglobin, g/dL	13.60 [12.43, 14.90]	13.50 [12.50, 14.80]	13.90 [12.30, 15.00]	0.408
Clinical indication for PCI				0.984
Non-STEMI	77 (12.8)	40 (13.3)	37 (12.3)	
Silent ischaemia	96 (15.9)	46 (15.3)	50 (16.6)	
Stable angina	265 (44.0)	133 (44.2)	132 (43.9)	
STEMI	54 (9.0)	26 (8.7)	13 (4.3)	
Unstable angina	110 (18.3)	56 (18.6)	54 (17.9)	

Data are presented as median [IQR] or n (%). BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; IQR: interquartile range; LVEF: left ventricular ejection fraction; MV-CAD: multivessel coronary artery disease; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

3.00) mm, and the length of the lesion was 16.66 (IQR 12.00, 23.00) mm. There was no difference in the number of lesions treated per patient. Specifically, over 80% of both groups had small CAD (<2.75 mm, 88.4% in Caucasians vs 91.3% in East Asians; p=0.061), and over 40% underwent multivessel PCI (41.9% vs 42.2%; p=0.956).

The procedural characteristics per lesion were significantly different between the two groups, as described in **Supplementary Table 2**. The rate of *de novo* lesions (87.2% vs 47.5%; p<0.001) was higher in East Asians. On the other hand, the rate of in-stent restenosis (52.5% vs 12.8%; p<0.001) was higher in the Caucasian population. Bailout stenting after DCB use occurred more frequently in the Caucasian population (9.2% vs 1.9%; p<0.001). In contrast, the rate of final dissections was higher in the East Asian population (6.6% vs 2.8%; p=0.001). Conversely, reference vessel diameter was similar in both groups (2.50 [IQR 2.25, 3.00] mm vs 2.50 [IQR 2.00, 2.75] mm; p<0.001). The lesion length was longer in East Asians compared to Caucasians (20.00 [IQR 13.59, 25.00] mm vs 18.59 [IQR 15.00, 25.00] mm; p=0.970). Procedural success was achieved in over 95% of both groups (97.9% vs 96.8%; p=0.169).

After adjustment of variables by propensity matching, out of 669 lesions treated with DCBs, in the Caucasian population, we found a lower predilatation rate and shorter DCBs used at higher pressures; Caucasian patients were also treated with a higher rate of bailout stenting. All other technical characteristics and in-hospital outcomes were not significantly different **(Table 2)**.

CLINICAL OUTCOMES

Clinical outcomes were available for 92.5% of the patients at a median follow-up of 366.5 (IQR 364, 388) days and showed significant differences among the groups **(Supplementary Table 3)**. After adjustment for confounding factors (n=602 patients), the incidence of the primary endpoint, TLR, was higher in Caucasians versus East Asians, (6.0% vs 1.5%; p<0.001), whereas neither all-cause death (including cardiac and non-cardiac death) nor spontaneous MI differed significantly. The rate of MACE (defined as the composite of TLR, MI and cardiac death) was significantly higher in the Caucasian population (10.6% vs 3.7%; p=0.001). Interestingly, the occurrence of Bleeding Academic Research Consortium (BARC) 2-5 bleeding was lower in Caucasians as compared to East Asians (0.0% vs 5.0%; p<0.001) **(Figure 1, Table 3)**. The difference in antiplatelet therapy, specifically aspirin and clopidogrel, between the East Asian and Caucasian populations may

Table 2. Procedural characteristics (after PSM).

Per patient	Overall n=602	Caucasian n=301	East Asian n=301	*p*-value
Vascular approach				0.285
Femoral	121 (20.1)	56 (18.6)	65 (21.6)	
Radial	479 (79.6)	243 (80.7)	236 (78.4)	
Multivessel PCI	241 (40.0)	121 (40.2)	120 (39.9)	1.000
Contrast media use, mL	160.00 [120.00, 200.00]	180.00 [120.00, 257.50]	150.00 [100.00, 180.00]	<0.001
Fluoroscopy time, minutes	19.00 [12.50, 34.00]	20.00 [13.00, 34.00]	18.00 [11.25, 32.75]	0.115
Per lesion	**Overall n=669**	**Caucasian n=336**	**East Asian n=333**	***p*-value**
Percentage diameter stenosis, %	80.00 [74.00, 90.00]	85.25 [80.00, 90.00]	80.00 [70.00, 90.00]	0.007
RVD, mm	2.50 [2.00, 2.75]	2.50 [2.00, 2.70]	2.50 [2.00, 2.75]	0.990
Lesion length, mm	20.00 [14.78, 25.00]	18.59 [15.00, 25.00]	20.00 [13.59, 25.00]	0.970
De novo lesions	536 (80.1)	263 (78.3)	273 (82.0)	0.246
ISR	132 (19.7)	74 (22.0)	58 (17.4)	0.146
Lesion type				0.291
A	126 (18.8)	55 (16.4)	71 (21.3)	
B1	243 (36.3)	121 (36.0)	122 (36.6)	
B2	157 (23.5)	81 (24.1)	76 (22.8)	
C	143 (21.4)	79 (23.5)	64 (19.2)	
Predilatation	621 (92.8)	294 (87.5)	327 (98.2)	<0.001
Predilatation balloon length, mm	15.00 [12.00, 20.00]	15.00 [12.00, 20.00]	15.00 [13.00, 15.00]	0.081
Predilatation balloon diameter, mm	2.00 [2.00, 2.50]	2.00 [2.00, 2.50]	2.25 [2.00, 2.50]	0.005
DCB length, mm	20.00 [20.00, 30.00]	20.00 [15.00, 30.00]	25.00 [20.00, 30.00]	<0.001
DCB diameter, mm	2.50 [2.00, 2.75]	2.50 [2.00, 2.75]	2.50 [2.00, 2.75]	0.319
DCB inflation pressure, atm	8.00 [6.00, 12.00]	10.00 [8.00, 12.00]	7.00 [6.00, 10.00]	<0.001
Procedural complications	13 (1.9)	7 (2.1)	6 (1.8)	1.000
Bailout stenting	55 (8.2)	46 (13.7)	9 (2.7)	<0.001
Final TIMI 3 flow	648 (96.8)	328 (97.6)	320 (96.1)	0.535
Postprocedural dissection remaining	95 (14.2)	45 (13.4)	50 (15)	0.293
Angiographic success	652 (97.5)	327 (97.3)	325 (97.6)	1.000
Procedural success	643 (96.1)	320 (95.2)	323 (97.0)	0.317

Data are presented as median [IQR] or n (%). DCB: drug-coated balloon; ISR: in-stent restenosis; PCI: percutaneous coronary intervention; PSM: propensity score matching; RVD: reference vessel diameter; TIMI: Thrombolysis in Myocardial Infarction

explain the higher incidence of bleeding events in the East Asian population even after matching. Aspirin usage was significantly higher in East Asians (94.7%) compared to Caucasians (70.8%; p<0.001), while clopidogrel usage was 42.9% in East Asians compared to 22.6% in Caucasians (p<0.001) **(Table 4)**.

Figure 2 shows the Kaplan-Meier curve of incidence of all-cause death. In addition, the statistical analysis shows that there is an adjusted hazard ratio for death of 2.77 before the use of propensity score matching, with a 95% CI of 0.15-53.05. After implementing PSM, the adjusted hazard ratio drops to 1.23 with a 95% CI of 0.16-9.53.

Our analysis also shows a similar outcome regarding the primary and secondary endpoints after stratification by treated lesion type, *de novo* vs ISR **(Figure 3)**.

According to the love plot, significant standardised mean differences were observed in the unadjusted cohort, but these differences were well balanced after PSM was applied **(Figure 4)**. The data were also balanced after PSM, as shown in **Figure 4**. This indicates that the matching process was successful in creating a more balanced and comparable cohort for analysis.

Discussion

In this large-scale prospective study, SCBs used in a diverse CAD population with a broad spectrum of clinical indications showed the following **(Central illustration)**:

- The clinical outcome after SCB PCI was worse in the Caucasian population in terms of TLR.
- BARC 2-5 bleeding was more frequent in the East Asian population.
- SCB performance seems to be reduced in ISR lesions as compared to *de novo* lesions in both populations, with a similar difference observed.

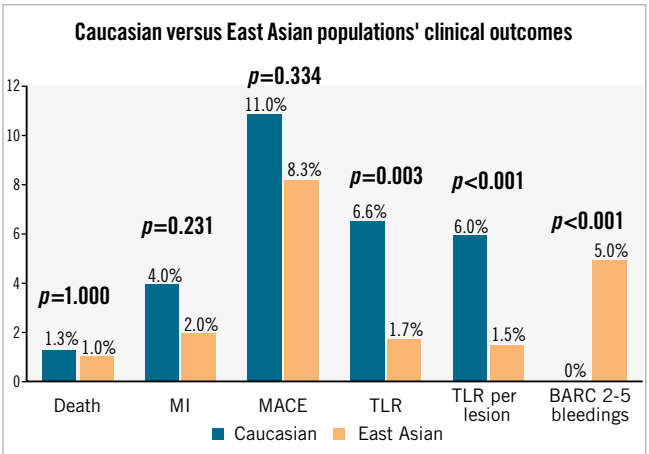


Figure 1. *Caucasian and East Asian clinical outcomes (PSM population). BARC: Bleeding Academic Research Consortium; MACE: major adverse cardiovascular events; MI: myocardial infarction; PSM: propensity score-matched; TLR: target lesion revascularisation*

Caucasians were found to have more severe disease, more in-stent restenosis, less predilatation, and required more bailout stenting. On the other hand, East Asians had higher rates of dual antiplatelet therapy and better lesion preparation. These important differences in factors could potentially explain the higher rates of TLR observed in the study.

At present, few studies have analysed the clinical and procedural differences between Caucasian and Asian populations with CAD or undergoing coronary angioplasty, and most of these studies investigated either Caucasian or Asian populations alone. In addition, no published study describes the outcomes between patients of different geographical areas treated with DCBs so far.

Geographical differences in patients with acute myocardial infarction were studied in the PARADISE-MI trial, which included 23% of patients from Eastern Europe, 18% of patients from Western Europe, 12% of patients from Southern Europe, 10% from Northern Europe, 12% from Latin America, 9% from North America, 10% from East and Southeast Asia, and 6% from South Asia. This study found that patients treated in Asia were younger compared to other geographical areas and had different comorbidities with higher rates of diabetes and atrial fibrillation. Patients from Asia had higher rates of STEMI and a lower rate of primary percutaneous coronary intervention[17]. Additionally, the usage of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers was lower in Asian patients compared to other patients from other global regions. In terms of outcome, the incidence of death or heart failure post-MI was lowest in South Asia, at a rate of 4.6%, and highest in Latin America, at a rate of 9.2%. In conclusion, PARADISE-MI confirmed that there were substantial differences between patients with MI from different regions regarding baseline characteristics, treatment approach, and outcomes, and it also gave us some insights to consider regional variations when treating patients with myocardial infarction using either drug-eluting stents, DCBs, or CABG but unfortunately did not go into the details of each category[17].

Another study that compared East Asians and Europeans, by Kwon et al[18], reported that intravascular ultrasound- or optical coherence tomography-guided interventions were more commonly used in East Asian patients due to specific reimbursement regulations, which might have contributed to better clinical outcomes despite the shorter duration of dual antiplatelet therapy[18].

The EPICOR and EPICOR ASIA trials[19] were two large studies comparing global geographical variations in STEMI management and post-discharge mortality that included

Table 3. Clinical outcomes after propensity score matching.

Outcome	Overall n=602	Caucasian n=301	East Asian n=301	*p*-value
All-cause death (including cardiac and non-cardiac death)	7 (1.2)	4 (1.3)	3 (1.0)	1.000
MI	18 (3.0)	12 (4.0)	6 (2.0)	0.231
MACE (composite of TLR, MI and cardiac death)	58 (9.6)	33 (11.0)	25 (8.3)	0.334
TLR (per lesion)	25 (4.2)	20 (6.0)	5 (1.5)	<0.001
BARC 2-5 bleeding	15 (2.5)	0 (0)	15 (5.0)	<0.001

Values are n (%). BARC: Bleeding Academic Research Consortium; MACE: major adverse cardiovascular events; MI: myocardial infarction; TLR: target lesion revascularisation

Table 4. Antiplatelet agents after propensity score matching.

Antiplatelet agent used at 1-year follow-up	Overall n=602	Caucasian n=301	East Asian n=301	*p*-value
Aspirin	498 (82.7)	213 (70.8)	285 (94.7)	<0.001
Clopidogrel	197 (32.7)	68 (22.6)	129 (42.9)	<0.001
Prasugrel	8 (1.3)	8 (2.7)	0 (0)	0.007
Ticagrelor	144 (23.9)	35 (11.6)	109 (36.2)	<0.001

Values are n (%).

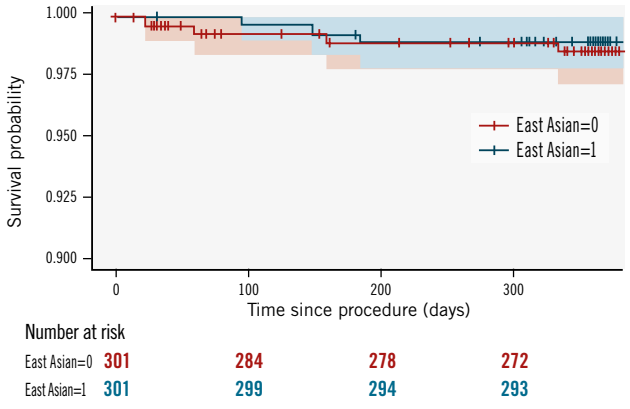


Figure 2. *Kaplan-Meier curves for the occurrence of all-cause death (propensity score-matched population).*

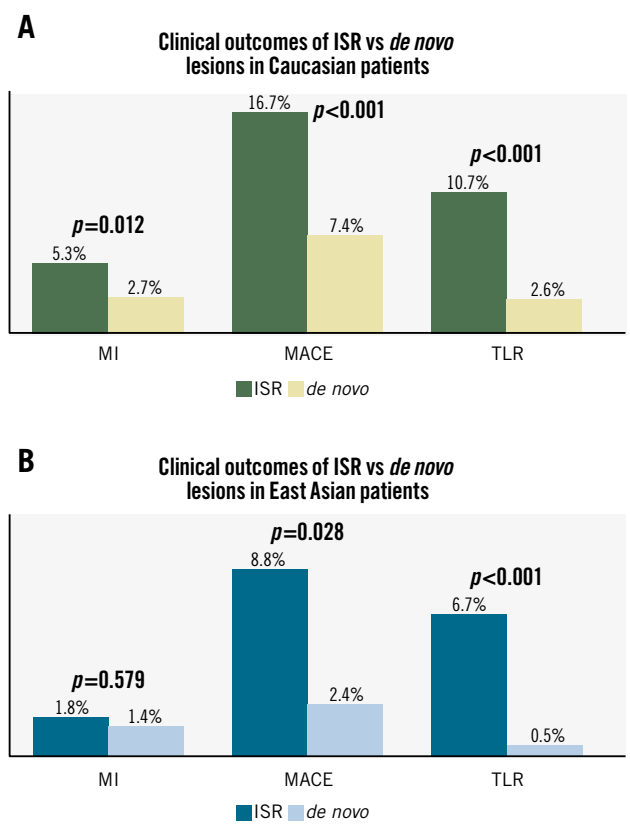


Figure 3. *Clinical outcomes based on lesion type (ISR and de novo). ISR: in-stent restenosis; MACE: major adverse cardiovascular events; MI: myocardial infarction; TLR: target lesion revascularisation*

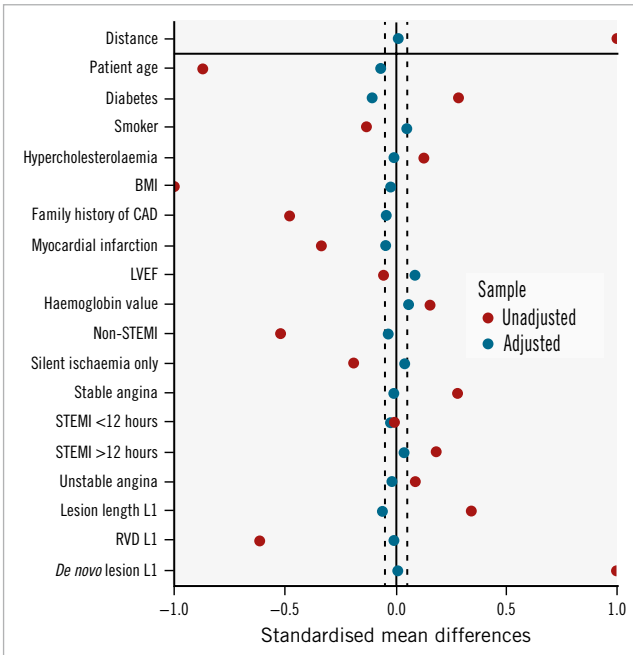


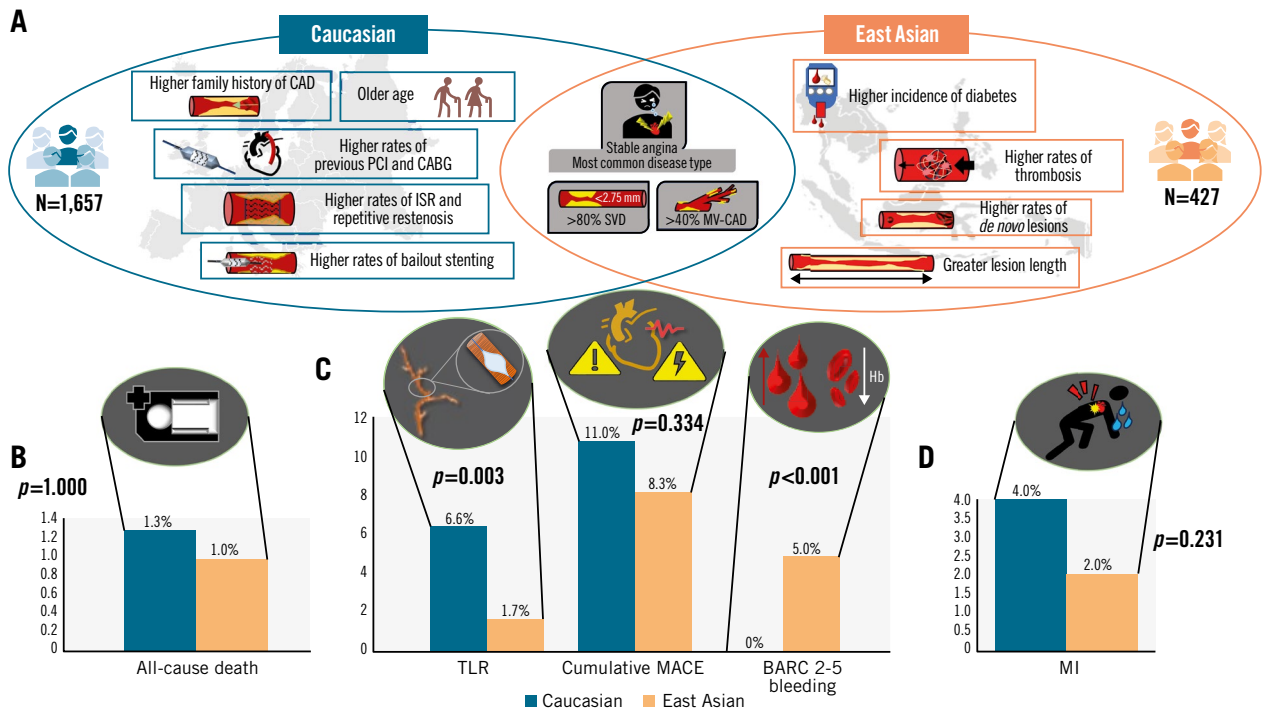
Figure 4. *Love plot showing covariate balance before and after propensity score matching. BMI: body mass index; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; RVD: reference vessel diameter; STEMI: ST-segment elevation myocardial infarction*

4,943 patients from Europe and Latin America and 6,616 from Asia. Use of reperfusion therapy was lowest in India, with a rate of 54%, and highest in Southern Europe, with a rate of 81%. Primary PCI was least used in India and most commonly used in Northern Europe as the primary therapeutic approach, with a rate of 65.6%. Fibrinolysis was less commonly used in China, with a rate of 8.1%, and most commonly used in Southeast Asia, with a rate of 34.2%. Time to primary PCI was lowest in Northern Europe, and mortality rates were lowest in Northern Europe up to two years after the MI event[19].

Several studies have analysed the performance of DCBs in European, Chinese, or Malaysian patients. The PICCOLETO II trial compared the performance of a paclitaxel DCB with an everolimus DES in European patients with *de novo* lesions in small coronary arteries and found that DCB performance was superior to the stent in terms of late lumen loss at 6 months[20]; an improved clinical outcome was also found after 3 years[21]. BASKET-SMALL2 enrolled patients with a reference vessel diameter <3 mm at 14 hospitals in Germany, Switzerland, and Austria. The 758 patients treated showed the non-inferiority of DCBs as compared to DES in terms of MACE up to 3 years[22]. The RESTORE SVD trial enrolled a Chinese population with SVD and showed similar angiographic performance between paclitaxel DCBs and DES at 9 months, along with a similar clinical outcome at 5 years[23,24]. Caucasian and East Asian patients with small vessel disease enrolled in these trials were treated with paclitaxel DCBs, which showed non-inferiority to DES at different follow-up durations.

The clinical differences depicted in this EASTBOURNE subanalysis can be attributed to several factors. The Caucasian population enrolled in EASTBOURNE had a higher initial percentage diameter stenosis and had lower rates of lesion predilatation (87% vs 98%; p<0.001), despite this being strongly recommended in the study protocol. Previous literature data show the importance of adequate lesion preparation before drug delivery via DCB, and any

Clinical differences between Caucasian and East Asian patient populations.



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A) Comparison of baseline characteristics; comparison of clinical outcomes for all-cause death (B); TLR, cumulative MACE, and BARC 2-5 bleeding (C); and MI (D). BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass grafting; CAD: coronary artery disease; Hb: haemoglobin; ISR: in-stent restenosis; MACE: major adverse cardiovascular events; MI: myocardial infarction; MV-CAD: multivessel coronary artery disease; PCI: percutaneous coronary intervention; SVD: small vessel disease; TLR: target lesion revascularisation

tool can be used to achieve this goal[25]; the clinical outcome of DCB therapy is in fact impaired when lesion predilatation is adequately performed or is ineffective[26]. Moreover, despite propensity matching adjustment, the Caucasian population underwent a higher rate of bailout stenting as compared to the East Asian one (13.7% vs 2.7%; p<0.001); stenting after treatment with DCBs has been associated with impaired outcomes and the need for TLR in other studies[22].

Racial differences may also play a role in terms of bleeding risk clinical outcomes and performance after DCB angioplasty. East Asian populations are prone to display higher rates of bleeding compared to their European counterpart[27], as previous literature has highlighted, a phenomenon known as the "East Asian Paradox"[28]. Genetic factors, such as polymorphisms in drug-metabolising enzymes like CYP2C19, are more common in East Asians and can affect drug response and bleeding risk[18]. Additionally, differences in platelet reactivity and endothelial function contribute to their unique risk profiles[29,30]. Even with advanced treatments like DCB therapy, these intrinsic factors continue to impact bleeding risk. Furthermore, variations in diet, lifestyle, and comorbid conditions like hypertension and diabetes may also play a role in this persistent tendency[31,32]. However, further studies are required to fully understand and confirm the impact of ethnic factors on clinical outcomes. While some research has shown a correlation between ethnicity and certain health conditions, more extensive and thorough studies are needed to establish a definitive relationship. The higher bleeding risk in East Asian patients in our study could also be partially attributed to the fact that these patients had more usage of the second antiplatelet drug (mostly ticagrelor) in their discharge medications and during clinical follow-up at 1 year compared to Caucasian patients (36.5% vs 9.7%; p<0.001) **(Table 4)**. Another important point to underline is that most of the literature data from DCB studies conducted in Asia or Europe involved patients treated with paclitaxel DCBs, whereas our study exclusively enrolled patients treated with sirolimus DCBs. Few studies have been performed that combined Caucasian and East Asian patients, and, to our knowledge, no study has assessed the difference between these two groups of patients. Understanding these factors can help improve treatment strategies for East Asian patients.

Limitations

This study included a large number of patients from different geographical areas and different hospitals, with varying

experience in DCB usage. Despite adjusting for measured confounding factors using propensity score matching, the different outcomes observed could be a consequence of varying expertise or local practice. Another limitation of this study is the absence of a core lab for assessing the different angiographic parameters during the index PCI. Finally, this is an observational study, and despite prospective patient enrolment, a direct comparison between devices was not performed, and the decision about treatment options was left to the physician's discretion.

Conclusions

DCB use is increasing in East Asian and Caucasian countries, for both ISR lesions and *de novo* coronary lesions. The current *post hoc* analysis of the EASTBOURNE Registry highlights some important clinical differences between Caucasian and East Asian patients treated with SCBs. Further *ad hoc* and adequately powered studies are needed to determine if the technical differences result in different outcomes.

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Conflict of interest statement

B. Cortese serves on the advisory board of Concept Medical. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Baseline characteristics of patients before propensity matching.

Supplementary Table 2. Procedural characteristics per lesion of Caucasians versus East Asians.

Supplementary Table 3. Caucasian and East Asian patients' clinical outcomes.

The supplementary data are published online at: https://AsiaIntervention.pcronline.com/doi/10.4244/AIJ-D-24-00044

Supplementary data

Supplementary Table 1. Baseline characteristics of patients before propensity matching.

Characteristics	Overall	Caucasian	East-Asian	p
n	2,084	1,657	427	
Patient Age (median [IQR])	67.00 [59.00, 75.00]	69.00 [61.00, 76.00]	59.00 [53.00, 67.00]	<0.001
Patient Gender = MALE (%)	1693 (81.2)	1338 (80.7)	355 (83.1)	0.267
BMI (median [IQR])	26.37 [24.22, 29.36]	26.56 [24.34, 29.38]	25.51 [23.39, 29.16]	<0.001
Diabetes (%)	867 (41.6)	641 (38.7)	226 (52.9)	<0.001
Hypercholesterolemia (%)	1501 (72.0)	1175 (70.9)	326 (76.3)	0.025
Smoker (%)	538 (25.8)	446 (26.9)	92 (21.5)	0.025
Renal Insufficiency (%)	218 (10.5)	177 (10.7)	41 (9.6)	0.595
Family History Coronary (%)	477 (22.9)	430 (26.0)	47 (11.0)	<0.001
Stroke (%)	93 (4.5)	81 (4.9)	12 (2.8)	0.066
Congestive Heart Failure (%)	170 (8.2)	132 (8.0)	38 (8.9)	0.552
Previous Myocardial Infarction (%)	894 (42.9)	763 (46.0)	131 (30.7)	<0.001
Previous CABG (%)	244 (11.7)	224 (13.5)	20 (4.7)	<0.001
Previous PCI (%)	1380 (66.2)	1216 (73.4)	164 (38.4)	<0.001
Peripheral artery Disease (%)	867 (41.6)	641 (38.7)	226 (52.9)	<0.001
MVD (%)	1237 (59.4)	998 (60.2)	239 (56.0)	0.122
LVEF (median [IQR])	55.00 [46.00, 60.00]	55.00 [48.00, 60.00]	55.00 [45.00, 60.00]	0.021
Creatinine Value (median [IQR])	1.00 [0.83, 1.20]	1.00 [0.82, 1.20]	0.98 [0.86, 1.17]	0.804
Hemoglobin Value (median [IQR])	13.60 [12.30, 14.80]	13.50 [12.22, 14.70]	14.00 [12.38, 15.00]	0.001
Clinical indication to PCI (%)				<0.001
Non STEMI	445 (21.4)	405 (24.4)	40 (9.4)	
Silent Ischemia	408 (19.6)	347 (20.9)	61 (14.3)	
Stable Angina	709 (34.0)	517 (31.2)	192 (45.0)	
STEMI<12 hours	91 (4.4)	73 (4.4)	18 (4.2)	
STEMI>12 hours	67 (3.2)	38 (2.3)	29 (6.8)	
Unstable Angina	364 (17.5)	277 (16.7)	87 (20.4)	

BMI= body mass index; IQR= Interquartile range; MVD= Multivessel coronary artery disease; LVEF= Left ventricular ejection fraction; CABG= Coronary artery bypass grafting; PCI= Percutaneous coronary intervention; STEMI=ST-elevation myocardial infarction.

Supplementary Table 2. Procedural characteristics per lesion of Caucasians versus East Asians.

Characteristics	Overall	Caucasian	East-Asian	p
n	2,318	1,851	467	
Stenosis L1 (median [IQR])	84.80 [75.00, 90.00]	85.00 [75.00, 90.00]	80.00 [70.00, 90.00]	0.360
RVD L1 (median [IQR])	2.50 [2.10, 3.00]	2.50 [2.25, 3.00]	2.50 [2.00, 2.75]	<0.001
Lesion Length L1 (median [IQR])	16.66 [12.00, 23.00]	15.24 [12.00, 20.00]	20.00 [15.00, 28.00]	<0.001
MLD L1 (median [IQR])	0.59 [0.25, 1.00]	0.50 [0.25, 1.00]	0.60 [0.30, 1.00]	0.378
De novo Lesion L1 = TRUE (%)	1287 (55.5)	880 (47.5)	407 (87.2)	<0.001
In stent RestenosisL1 = TRUE (%)	1031 (44.5)	971 (52.5)	60 (12.8)	<0.001
Repetitive ISR 1 = TRUE (%)	72 (3.1)	71 (3.8)	1 (0.2)	<0.001
Thrombus L1 = TRUE (%)	126 (5.4)	69 (3.7)	57 (12.2)	<0.001
Lesion Type Value L1 (%)				0.501
A	442 (19.1)	343 (18.5)	99 (21.2)	
B1	854 (36.8)	685 (37.0)	169 (36.2)	
B2	570 (24.6)	454 (24.5)	116 (24.8)	
C	452 (19.5)	369 (19.9)	83 (17.8)	
Pre Dilatation L1 = TRUE (%)	2126 (91.7)	1666 (90.0)	460 (98.5)	<0.001
Pre Length Value L1 (median [IQR])	15.00 [12.00, 20.00]	15.00 [12.00, 20.00]	15.00 [13.00, 18.00]	0.203
Pre Diameter Value L1 (median [IQR])	2.50 [2.00, 3.00]	2.50 [2.00, 3.00]	2.00 [2.00, 2.50]	<0.001
Length b1 L1 (median [IQR])	20.00 [15.00, 30.00]	20.00 [15.00, 25.00]	25.00 [20.00, 30.00]	<0.001
Diameter b1 L1 (median [IQR])	2.50 [2.00, 3.00]	2.50 [2.25, 3.00]	2.50 [2.00, 2.50]	<0.001
Pressure b1 L1 (median [IQR])	10.00 [8.00, 12.00]	10.00 [8.00, 12.00]	7.00 [6.00, 9.75]	<0.001
Inflation Time b1 L1 (median [IQR])	60.00 [60.00, 60.00]	60.00 [60.00, 60.00]	60.00 [60.00, 60.00]	<0.001
Post Dilatation L1 = TRUE (%)	134 (5.8)	102 (5.5)	32 (6.9)	0.268
Complication L1 = TRUE (%)	41 (1.8)	33 (1.8)	8 (1.7)	1.000
Rotational L1 = TRUE (%)	13 (0.6)	13 (0.7)	0 (0.0)	0.084
Balloon Cut L1 = TRUE (%)	87 (3.8)	62 (3.3)	25 (5.4)	0.055
Thrombus Extract L1 = TRUE (%)	19 (0.8)	19 (1.0)	0 (0.0)	0.020
IVUS L1 = TRUE (%)	98 (4.2)	97 (5.2)	1 (0.2)	<0.001
OCT L1 = TRUE (%)	32 (1.4)	30 (1.6)	2 (0.4)	0.047
Stent Implant L1 (%)				<0.001
None	2058 (88.8)	1601 (86.5)	457 (97.9)	
POST DCB	179 (7.7)	170 (9.2)	9 (1.9)	
PRE & POST DCB	2 (0.1)	2 (0.1)	0 (0.0)	
PRE DCB	79 (3.4)	78 (4.2)	1 (0.2)	
FinalTIMIL1 (%)				0.137
0	16 (0.8)	11 (0.7)	5 (1.2)	

I	17 (0.8)	11 (0.7)	6 (1.4)	
II	19 (0.9)	13 (0.8)	6 (1.4)	
III	2032 (97.5)	1622 (97.9)	410 (96.0)	
Final DissectionL1 = TRUE (%)	74 (3.6)	46 (2.8)	28 (6.6)	0.001
Angiographic Success L1 = TRUE (%)	2264 (97.7)	1812 (97.9)	452 (96.8)	0.169
Device Malfunction = TRUE (%)	5 (0.2)	4 (0.2)	1 (0.2)	1.000
Procedural_success = 1 (%)	2223 (95.9)	1779 (96.1)	444 (95.1)	0.299

DCB=Drug coated balloon; IVUS= Intravascular ultrasound; ISR=In-stent restenosis; IQR= Interquartile range; MVD= Multivessel coronary artery disease; OCT=Optical coherence tomography; RVD=Reference vessel diameter; TIMI=Thrombolysis in myocardial infarction.

Supplementary Table 3. Caucasian and East Asian patients' clinical outcomes.

Outcomes	Overall	Caucasian	East-Asian	p
n	2,084	1,657	427	
All-cause death = 1 (%)	69 (3.3)	64 (3.9)	5 (1.2)	0.004
MI = 1 (%)	73 (3.5)	67 (4.0)	6 (1.4)	0.007
MACE = 1 (%)	240 (11.5)	207 (12.5)	33 (7.7)	0.005
TVR = 1 (%)	137 (6.6)	131 (7.9)	6 (1.4)	<0.001
TLR = 1 (%)	133 (6.4)	127 (7.7)	6 (1.4)	<0.001
Bleeding = 1 (%)	25 (1.2)	4 (0.2)	21 (4.9)	<0.001

MACE=Major adverse cardiovascular events; MI=Myocardial infarction; TLR=Target lesion revascularization; TVR= target vessel revascularization.