Clinical Outcomes by Geographic Region for Patients Implanted with the Zotarolimus-Eluting Stent

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Abstract

Background: Differences between geographic regions in patient characteristics and outcomes, particularly for acute coronary syndromes, have been demonstrated in clinical trials. Clinical outcomes after percutaneous coronary interventions with the zotarolimus-eluting stent in a real-world population were assessed over time.

Objectives: The influence of geographic location on clinical outcomes with the zotarolimus-eluting stent was assessed in 3 regions: Asia Pacific, Europe, and Latin America.

Methods A total of 8,314 patients (6,572 Europe, 1,522 Asia Pacific, and 220 Latin America) were followed for 1 year; 2,116 of these (1,613, 316, and 187, respectively) were followed for 2 years. Patient and lesion characteristics, dual antiplatelet therapy, and clinical outcomes were compared between Latin America and the other regions.

Results: Patients in Latin America had the highest proportions of risk factors and prior myocardial infarction. Dual antiplatelet therapy usage rapidly declined in Latin America, from 44.9% at 6 months to 22.5% at 1 year and 7.8% at 2 years (Europe: 87.4%, 61.5%, 19.7%; Asia Pacific: 82.4%, 67.0%, 45.7%). There were no significant differences between Latin America and Europe or Asia Pacific for any outcome at either time point. The incidence of Academic Research Consortium definite and probable stent thrombosis was low (≤ 1.2%) among all patients at 1 year and 2 years.

Conclusions: Clinical outcomes were comparable between patients in Latin America and Europe, and Latin America and Asia Pacific, despite less favorable clinical subsets in Latin America, a higher risk profile, and markedly lower use of dual antiplatelet therapy over time. (Arq Bras Cardiol 2011;96(5):353-362)

Keywords: Eluting stents; multicenter studies; graft occlusion, vascular; coronary restenosis; angioplasty, transluminal, percutaneous, coronary.

Summary

Results from the E-Five Registry indicate that geographic location does not affect clinical outcomes in patients treated with the zotarolimus-eluting stent. Patients in Latin America had the highest proportions of risk factors and prior myocardial infarction. Use of dual antiplatelet therapy declined rapidly in Latin America as compared with Europe and Asia Pacific. However, there were no significant differences between Latin America and Europe or Asia Pacific for any outcome at either time point. The incidence of Academic Research Consortium definite and probable stent thrombosis was low (≤ 1.2%) among all patients at 1 year and 2 years.

Introduction

International differences in patient characteristics and clinical outcomes have been demonstrated in cardiovascular clinical trials, specifically in the acute coronary syndrome (ACS) population[1,2]. In thrombolytic studies, patients in the United States (US) tended to have shorter time to treatment, lower Killip class, and a higher proportion of inferior myocardial infarctions (MIs) than non-US patients. In studies comparing North American and Eastern European patients, North American patients were more likely to be male and to have fewer comorbidities, including hypertension, angina, heart failure, and abnormal electrocardiogram findings, than patients enrolled in Eastern Europe. Several trials in the setting of ST-elevation MI have demonstrated higher mortality rates in non-US than in US sites, particularly in Latin America[1].

Few data are available concerning international differences in the use of drug-eluting stents. Austin et al[3] demonstrated a wide variation in the application of drug-eluting stents across 4 countries (US, Canada, United Kingdom, and Belgium), but they did not report on differences in patient characteristics or clinical outcomes. The E-Five Registry, a large prospective, nonrandomized, multicenter, international registry, assessed the safety and effectiveness of the Endeavor zotarolimus-eluting stent (ZES; Medtronic CardioVascular, Santa Rosa, California, USA) in "real-world" patients with symptomatic coronary artery

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disease undergoing percutaneous coronary intervention (PCI)[4]. The size of this global cohort provides a unique opportunity to explore the existence of geographic differences and whether such differences may influence clinical outcomes in patients undergoing PCI and stent implantation outside the confines of a clinical trial. Furthermore, this cohort allows a view of differences in the use of dual antiplatelet therapy (DAPT) and the clinical impact of those differences.

Methods

Study design and objectives

The E-Five Registry is a prospective, nonrandomized, multicenter registry conducted in 37 countries around the world. For this study, we selected 3 regions, Asia Pacific (AP), the European Union (EU), and Latin America (LA), based on physical location. No attempt was made to ensure equality between the numbers of patients enrolled in each region or between member countries.

A total of 8,314 adult patients enrolled at 188 centers were followed for 1 year. In addition, a subset of 2,116 patients from 26 centers was followed for 2 years. These centers were selected on the basis of enrollment and willingness to continue follow-up. Outcomes were evaluated at 1 year and 2 years for the respective cohorts.

Analyses were performed to determine differences in demographic and baseline characteristics among patients from each region and the potential influence of these differences on clinical outcomes, including major adverse cardiac events (MACE), cardiac death, MI, target lesion revascularization (TLR), target vessel revascularization (TVR), and definite and probable stent thrombosis as defined by the Academic Research Consortium (ARC)[5].

Study population and protocol

The E-Five Registry contains data on adult patients who underwent single-vessel or multivessel PCI. Eligible patients had target lesions appropriate for stent intervention. Details of the study protocol were previously reported[4].

All patients completed follow-up visits at discharge, 30 days, 6 months, and 1 year, and selected centers followed patients for up to 2 years (Figure 1). Outpatient clinic visits were the preferred means of follow-up, although phone calls were allowed.

Countries included in the LA region were Brazil, Chile, Mexico, and Uruguay. The AP region included Australia, China, Hong Kong, India, Korea, Malaysia, New Zealand, Singapore, and Thailand. The EU region included Austria, Belgium, Bulgaria, Czech Republic, Egypt, Estonia, Finland, Germany, Greece, Hungary, Israel, Italy, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Switzerland, Turkey, and the United Kingdom.

This study was conducted under the ethics guidelines of the Declaration of Helsinki. Before study initiation at any clinical site, the study was approved by a medical ethics committee to protect human subjects, depending on regional requirements. Written informed consent was obtained from all patients.

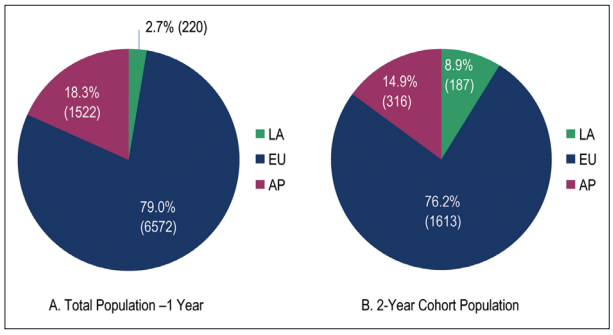

Figure 1 - Distribution of patients by region for year 1 and year 2 for (A) all patients enrolled in the E-Five Registry and (B) the subset of patients followed to 2 years. LA - Latin American region; EU - European region; AP - Asia Pacific region.

Device description

The Endeavor ZES (Medtronic) consists of a cobalt-alloy stent with an elution polymer-coated exterior that releases the antiproliferative drug zotarolimus (10 μg/mm stent length). The zotarolimus elution is designed to inhibit proliferation of smooth muscle cells; the phosphorylcholine-based polymer coating is designed to simulate red blood cells, thus mimicking the natural cell membrane[6]. These features are designed to reduce the typical biological response to an implanted device and enhance long-term safety. The ZES is available in diameters of 2.25 mm to 4.0 mm and in lengths of 8 mm to 30 mm.

Data collection and management

Electronic data capture by web-based case report forms was completed for all sites. To ensure quality control, random monitoring of clinical sites was conducted at prespecified intervals. Approximately 10% of the study data was reviewed to monitor compliance and to ensure accurate reporting of events, as well as accuracy of data.

The data designated for baseline collection included eligibility criteria, demographic characteristics, cardiac risk factors, current cardiac status, lesion characteristics, and results from pre-procedure angiography. Investigators were required to conduct a visual examination of the lesion to estimate lesion characteristics.

Documented clinical outcomes compared between regions included MACE, death, cardiac death, MI, TLR, TVR, TVR (nontarget lesion), and target vessel failure (TVF). Antiplatelet medication use was documented at 30 days, 6 months, and 1 year for all patients and at 2 years for those in the 2-year cohort.

MACE and stent thrombosis events were reviewed by a central clinical events committee (Cardialysis, Rotterdam, The Netherlands). Stent thrombosis events were evaluated using ARC definitions. Data management for this study and study monitoring were completed by Medtronic CardioVascular staff or a contract research organization designated by Medtronic.

Study endpoints

The primary endpoint for the overall E-Five Registry was the rate of MACE, defined as death, MI (Q-wave and non-

Q-wave), emergent cardiac bypass surgery, or TLR (repeat PCI or coronary artery bypass graft [CABG] surgery), at 1 year.

We report here clinical outcomes of MACE, all-cause death, cardiac death, MI, TLR, TVR, and TVF at 1 and 2 years of follow-up for each of the 3 regions. The rates of ARC-defined definite and probable stent thrombosis were analyzed for early (0 to 30 days), late (31 to 365 days), and very late (366 to 730 days) events.

Statistical analyses

Patient, lesion, and procedural characteristics were recorded at each site and summarized by region for the overall population at 1 year and for the long-term follow-up cohort at 2 years. Percentages are reported for categorical variables, and means ± standard deviations are reported for continuous variables. Antiplatelet therapy was detailed at 30 days, 6 months, and 1 year for all patients and at 2 years for the smaller cohort. All clinical outcomes (including MACE, all-cause death, death due to cardiac complications, MI, TLR, TVR, TVF, and ARC definite and probable stent thrombosis) were compiled by region for all available patients at the 1- and 2-year time points. Although the LA region had the smallest number of patients, it represented a unique population of patients with higher rates of cardiac risk factors and prior MIs, but the shortest duration of DAPT use; therefore, we used this region as the reference comparator for the other 2 regions.

Baseline variables were compared as follows: A 2-sided *t* test was used to calculate p values for continuous variables, and Fisher's exact test was used to determine p values for categorical variables. A p value of < 0.05 was considered statistically significant.

To adjust for differences in baseline characteristics in the 1-year and 2-year cohorts, the clinical outcomes at 1 year and 2 years were compared as follows: p values were based on logistic regression adjusted for propensity scores, which were calculated using the following baseline variables: age, sex, prior MI, prior percutaneous transluminal coronary angioplasty, prior CABG surgery, diabetes, acute MI (< 72 hours), hypertension, hypercholesterolemia, smoking, left anterior descending artery (*vs* non-left anterior descending artery), class B2/C (*vs* class A/B1), lesion length ≥ 27 mm (if any lesion is ≥ 27 mm, *vs* < 27 mm), and reference vessel diameter > 3.5 mm (if any lesion is > 3.5 mm, *vs* ≤ 3.5 mm).

The E-Five Registry is funded by the Medtronic Bakken Research Center, Medtronic CardioVascular, Maastricht, The Netherlands.

Results

Patient demographics and lesion characteristics

Overall population - the mean age of all patients enrolled in the E-Five Registry was 63.3 years. Patients in the EU region were older than patients in LA (64.2 *vs* 61.3 years, p < 0.001), and patients in LA were older than in AP, although this difference was not statistically significant (61.3 *vs* 59.9 years) (Table 1). The majority of patients in all regions were male: EU, 76.8%; AP, 77.1%; and LA, 70.0%. The most common comorbidities were hypercholesterolemia and hypertension. The prevalence of hypercholesterolemia was significantly higher in LA than in EU (75.0% *vs* 66.3%, p = 0.007) and AP (75.0% *vs* 47.6%, p < 0.001). The prevalence of hypertension was significantly greater in LA than in AP (76.4% *vs* 63.0%, p < 0.001) or EU (76.4% *vs* 69.6%, p = 0.036). The rate of prior MI also was higher in LA than in EU (47.3% *vs* 31.8%, p < 0.001) and AP (47.3% *vs* 31.5%, p < 0.001), as well as the rate of prior CABG (LA *vs* EU: 10.0% *vs* 8.3%, p = 0.384; LA *vs* AP, 10.0% *vs* 4.0%, p < 0.001). The prevalence of diabetes mellitus was more consistent between regions, with approximately one third of patients being affected: LA, 34.5%; AP, 37.4%; and EU, 31.6% (p = NS for LA *vs* EU and LA *vs* AP).

Target vessel location varied among the regions and is detailed in Table 1. Reference vessel diameter was similar for patients in LA and AP but smaller for patients in EU. There was a significantly lower rate of class C lesions (American College of Cardiology/American Heart Association system) in LA as compared with both EU (10.7% *vs* 24.5%, p < 0.001) and AP (10.7% *vs* 30.2%, p < 0.001).

2-Year cohort - the baseline demographic data of the subset of patients followed for 2 years was similar to data of the overall population (Table 2). Patients in LA were significantly younger than EU patients (61.3 *vs* 63.2 years, p = 0.02), but significantly older than AP patients (61.3 *vs* 56.7 years, p < 0.001). In the 2-year cohort, there were significantly fewer males in LA than in AP (69.0% *vs* 83.5%, p < 0.001) and EU (69.0% *vs* 77.1%, p = 0.018). The LA region also had the highest rates of common cardiac risk factors, including hypertension, hypercholesterolemia, previous MI, previous CABG, unstable angina, and diabetes, as compared with the other 2 regions.

Target lesion characteristics of the 2-year cohort were similar to those of the overall 1-year patient population. Vessel location, lesion length, and the proportion of class B2 and C lesions were all significantly different between the LA and EU regions and between the LA and AP regions (Table 2). LA patients were significantly more likely to have class B2 lesions than AP patients (54.5% *vs* 27.6%, p < 0.001) and EU patients (54.5% *vs* 36.7%, p < 0.001) and significantly less likely to have class C lesions than AP patients (10.3% *vs* 37.2%, p < 0.001) and EU patients (10.3% *vs* 25.9%, p < 0.001). Reference vessel diameter was similar between the LA region and the EU and AP regions, whereas lesion length was again shorter in LA (16.94 ± 8.46 mm) as compared with both EU (18.85 ± 10.72 mm, p = 0.001) and AP (21.75 ± 11.01 mm, p < 0.001).

Antiplatelet therapy

Postprocedure antiplatelet therapy, which was based on clinical standard practice, was common in all regions. Although most patients continued to take aspirin throughout the 2-year follow-up period, DAPT usage rates decreased considerably over time (Table 3). In particular, the most rapid and steep decline in DAPT usage was seen among LA patients: at 6 months, 44.9% of LA patients were receiving DAPT, whereas 87.4% of patients in EU and 82.4% of patients in AP continued

Table 1 – Patient and lesion characteristics by region in overall (1-year) population

	LA n = 220, 291 lesions	EU n = 6,572, 8,117 lesions	p-value LA *vs* EU	LA n = 220, 291 lesions	AP n = 1,522, 1,931 lesions	p-value LA *vs* AP
Age - years (mean±SD)	61.3±11.03	64.2±10.93	<0.001	61.3±11.03	59.9±10.92	0.073
Male - %	70.0	76.8	0.023	70.0	77.1	0.027
Prior MI - %	47.3	31.8	<0.001	47.3	31.5	<0.001
Prior PCI - %	26.8	27.8	0.818	26.8	14.5	<0.001
Prior CABG - %	10.0	8.3	0.384	10.0	4.0	<0.001
Current smoker - %	22.3	23.6	0.687	22.3	18.3	0.167
Hypercholesterolemia - %	75.0	66.3	0.007	75.0	47.6	<0.001
Hypertension - %	76.4	69.6	0.036	76.4	63.0	<0.001
Diabetes mellitus - %	34.5	31.6	0.377	34.5	37.4	0.455
Insulin dependent	5.0	9.2	0.031	5.0	4.3	0.597
Non-insulin dependent	29.5	22.4	0.014	29.5	33.1	0.318
Unstable angina - %	41.8	32.0	0.003	41.8	41.1	0.826
Target lesion location - %			0.027			0.051
Left anterior descending artery	44.0	45.7		44.0	50.6	
Left circumflex artery	18.6	22.5		18.6	20.5	
Right coronary artery	35.4	27.8		35.4	26.9	
Left main	1.4	2.1		1.4	1.1	
Saphenous vein graft	0.7	1.9		0.7	0.9	
Reference vessel diameter - mm (mean±SD)	2.99±0.42	2.92±0.47	0.009	2.99±0.42	2.97±0.45	0.480
Lesion length - mm (mean±SD)	17.31±9.07	18.22±10.64	0.096	17.31±9.07	19.92±10.57	<0.001
Lesion class - %						
Type B2 lesion	54.6	35.6	<0.001	54.6	29.8	<0.001
Type C lesion	10.7	24.5	<0.001	10.7	30.2	<0.001

LA - Latin American region; EU - European region; AP - Asia Pacific region; MI - myocardial infarction; PCI - percutaneous coronary intervention; CABG - coronary artery bypass graft; SD - standard deviation.

DAPT. By the 1-year time point, only 22.5% of LA patients were still using DAPT, compared with 61.5% of EU patients and 67.0% of AP patients. Among patients followed up through 2 years, DAPT usage dropped to 7.8% in LA, 19.7% in EU, and 45.7% in AP by 2 years (Figure 2).

Clinical outcomes

Overall outcomes at 1 year - there were no statistically significant differences in most of the clinical outcomes at 1 year between the LA region and the EU or AP region (Table 3). The 1-year rate of MACE was 4.3% for LA, 6.2% for AP, and 7.9% for EU patients (p = NS for both LA *vs* EU and LA *vs* AP). There were no MI events in the LA region and rates of only 1.6% in EU and 1.9% in AP (p = NS for LA *vs* EU and LA *vs* AP). Cardiac death and MI was statistically different for LA compared with AP (0.5% *vs* 3.5%, p = 0.039), but not for LA compared with EU. Rates of early (0 to 30 days) and late (31 to 365 days) ARC probable and definite stent thrombosis were low across all regions, and again, there were no significant differences between the LA region and the EU or AP region. There were no late ARC definite and probable stent thrombosis events in LA, compared with a rate of 0.5% in EU (p = 0.977) and 0.2% in AP at the same time point (p = 0.968).

2-year cohort outcomes - similar to the results of the entire E-Five cohort followed at 1 year, there were no statistically significant differences in clinical outcomes between the LA region compared with the EU or AP region throughout 2 years of follow-up (Table 4). Rates of MACE at 2 years were 6.3% in LA, 4.5% in AP, and 9.5% in EU patients. In all major cardiac endpoints, the outcomes and prevalence rates at 2 years were similar to the rates observed at 1 year. The rates of TVR were similar in the LA and EU regions (6.8% *vs* 6.6%, p = 0.795); however, the rate of TVR was lower in the AP region than in the LA region, although the difference did not reach statistical significance (6.8% *vs* 1.9%, p = 0.052). There were no very late (366 to 730 days) ARC definite and probable stent thrombosis events in the LA or AP regions among the 2-year cohort and only 2 (0.1%) in the EU region.

Discussion

The primary endpoint of MACE at 12 months and the secondary endpoint of MACE in the 2-year cohort, in

Table 2 – Patient and lesion characteristics by region in 2-year cohort

	LA n = 187, 253 lesions	EU n = 1,613, 2,006 lesions	p-value LA *vs* EU	LA n = 187, 253 lesions	AP n = 316, 355 lesions	p-value LA *vs* AP
Age - years (mean±SD)	61.25±11.15	63.19±10.74	0.020	61.25±11.15	56.72±10.44	<0.001
Male - %	69.0	77.1	0.018	69.0	83.5	<0.001
Previous MI - %	47.1	34.8	0.001	47.1	30.4	<0.001
Previous PCI - %	28.3	26.6	0.602	28.3	9.2	<0.001
Previous CABG - %	10.2	7.3	0.186	10.2	2.8	<0.001
Current smoking - %	21.4	23.9	0.468	21.4	22.2	0.911
Hypercholesterolemia - %	76.5	66.9	0.008	76.5	55.1	<0.001
Hypertension - %	77.0	70.0	0.051	77.0	63.0	0.001
Diabetes - %	36.4	28.1	0.021	36.4	36.1	1,000
Insulin dependent	5.9	8.5	0.261	5.9	5.1	0.687
Non-insulin dependent	30.5	19.7	<0.001	30.5	31.0	0.921
Unstable angina - %	44.9	25.9	<0.001	44.9	37.0	0.090
Target lesion location - %			0.035			<0.001
Left anterior descending artery	45.5	47.2		45.5	63.7	
Left circumflex artery	17.0	22.5		17.0	13.5	
Right coronary artery	36.0	27.5		36.0	20.0	
Left main	0.8	1.3		0.8	1.1	
Saphenous vein graft	0.8	1.6		0.8	1.7	
Reference vessel diameter - mm	2.98±0.40	2.91±0.47	0.021	2.98±0.40	3.00±0.43	0.563
Lesion length - mm	16.94±8.46	18.85±10.72	0.001	16.94±8.46	21.75±11.01	<0.001
Lesion class - %						
Type B2 lesion	54.5	36.7	<0.001	54.5	27.6	<0.001
Type C lesion	10.3	25.9	<0.001	10.3	37.2	<0.001

LA - Latin American region; EU - European region; AP - Asia Pacific region; MI - myocardial infarction; PCI - percutaneous coronary intervention; CABG - coronary artery bypass graft; SD - standard deviation.

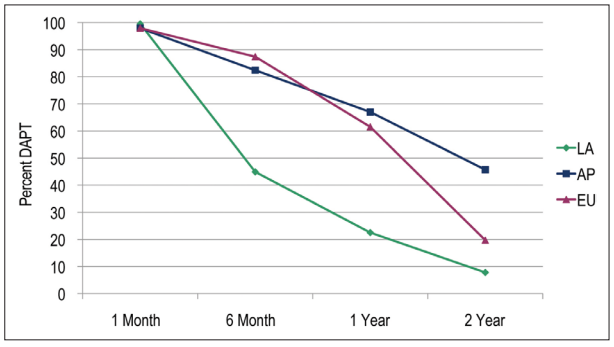

Figure 2 - *Use of dual antiplatelet therapy (DAPT) by region at 30 days, 6 months, 1 year, and 2 years. LA - Latin American region; EU - European region; AP - Asia Pacific region.*

addition to cardiac death, MI, TLR, TVF, and ARC definite and probable stent thrombosis at the same time points, were similar between the LA and EU regions, and the LA and AP regions, despite considerable variations in cardiac risk factors, lesion characteristics, and DAPT use. At 1 year, the lowest rate of MACE was observed in the LA region, even though this region had the lowest DAPT use at that time point. In the smaller 2-year cohort of patients, the lowest MACE rate was found in the AP region. Patients in the LA region had a greater incidence of prior MI, unstable angina, and previous revascularization (PCI and CABG) and higher rates of hypertension, hypercholesterolemia, and diabetes. It is possible that patients with a higher incidence of cardiac risk factors received more rigorous secondary preventive treatments, although these data are not available for analysis.

Within the E-Five Registry, stent thrombosis events were adjudicated to confirm per-protocol and ARC-defined outcomes. As previously reported[4], ARC definite and probable stent thrombosis events occurred more commonly early (0 to 30 days) than late (31 to 365 days). This held true for the subset of patients followed for 2 years in all regions, with extremely low rates of ARC probable and definite stent thrombosis reported. Premature cessation of DAPT may be related to increased risk of stent thrombosis[7], and the optimal duration of DAPT that is both safe and effective in reducing late stent thrombosis events remains an important unanswered question[8,9]. Despite the low rates of prolonged DAPT use in

Table 3 – E-Five Registry outcomes by region in the overall (1-year) population

	LA n = 220	EU n = 6,572	p-value* LA *vs* EU	LA n = 220	AP n = 1,522	p-value* LA *vs* AP
MACE - %	4.3	7.9	0.062	4.3	6.2	0.187
Death - %						
All	0.5	2.5	0.151	0.5	2.6	0.067
Cardiac	0.5	1.7	0.295	0.5	1.9	0.159
MI (all) - %	0.0	1.6	0.981	0.0	1.9	0.954
Death (cardiac) + MI (all) - %	0.5	3.0	0.085	0.5	3.5	0.039
ARC definite/probable stent thrombosis - %	0.0	1.2	0.976	0.0	1.1	0.965
0 to 30 days	0.0	0.7	0.980	0.0	0.9	0.969
31 to 365 days	0.0	0.5	0.977	0.0	0.2	0.968
TLR - %	3.8	4.9	0.362	3.8	2.5	0.473
TVR (non-TL) - %	0.9	0.7	0.930	0.9	0.3	0.535
TVR - %	4.7	5.5	0.489	4.7	2.7	0.282
TVF - %	5.2	7.7	0.178	5.2	5.6	0.563

*LA - Latin American region; EU - European region; AP - Asia Pacific region; MACE - major adverse cardiac events; MI - myocardial infarction; ARC - Academic Research Consortium; TLR - target lesion revascularization; TVR - target vessel revascularization; TL - target lesion; TVF - target vessel failure. *p-values were calculated using logistic regression adjusted for propensity scores, which were calculated using the following baseline variables: age, sex, prior MI, prior percutaneous transluminal angioplasty, prior coronary artery bypass graft surgery, diabetes, acute MI (< 72 hours), hypertension, hypercholesterolemia, smoking, left anterior descending artery (vs non–left anterior descending artery), class B2/C (vs class A/B1), lesion length ≥ 27 mm (if any lesion is ≥ 27 mm, vs < 27 mm), reference vessel diameter > 3.5 mm (if any lesion is > 3.5 mm, vs ≤ 3.5 mm).*

Table 4 – E-Five Registry outcomes by region in the 2-year cohort

	LA n = 187	EU n = 1,613	p-value* LA *vs* EU	LA n = 187	AP n = 316	p-value* LA *vs* AP
MACE - %	6.3	9.5	0.124	6.3	4.5	0.503
Death - %						
All	0.6	3.3	0.076	0.6	2.3	0.145
Cardiac	0.6	1.6	0.365	0.6	1.6	0.242
MI (all) - %	0.6	1.7	0.228	0.6	1.0	0.785
Death (cardiac) + MI (all) - %	1.1	3.1	0.168	1.1	2.3	0.329
ARC definite/probable stent thrombosis - %	0.0	0.9	0.972	0.0	0.3	0.947
0 to 30 days	0.0	0.6	0.965	0.0	0.3	0.947
31 to 365 days	0.0	0.2	0.967	0.0	0.0	N/A
366 to 730 days	0.0	0.1	0.975	0.0	0.0	N/A
TLR - %	5.1	5.7	0.545	5.1	1.9	0.150
TVR (non-TL) - %	1.7	1.1	0.848	1.7	0.0	0.945
TVR - %	6.8	6.6	0.795	6.8	1.9	0.052
TVF - %	8.0	8.7	0.581	8.0	3.9	0.143

*LA - Latin American region; EU - European region; AP - Asia Pacific region; MACE - major adverse cardiac events; MI - myocardial infarction; ARC - Academic Research Consortium; TLR - target lesion revascularization; TVR - target vessel revascularization; TL - target lesion; TVF - target vessel failure. *p-values were calculated using logistic regression adjusted for propensity scores, which were calculated using the following baseline variables: age, sex, prior MI, prior percutaneous transluminal coronary angioplasty, prior coronary artery bypass graft surgery, diabetes, acute MI (< 72 hours), hypertension, hypercholesterolemia, smoking, left anterior descending artery (vs non-left anterior descending artery), class B2/C (vs A/B1), lesion length ≥ 27 mm (if any lesion is ≥ 27 mm, vs < 27 mm), reference vessel diameter > 3.5 mm (if any lesion is > 3.5 mm, vs ≤ 3.5 mm).*

the LA region, stent thrombosis rates were not significantly different from those reported in the other 2 regions. LA patients generally had shorter and less complex lesions, which may have decreased the risk of stent thrombosis[7]. It is unclear how these multiple factors (early cessation of DAPT, less complex lesions, and more comorbidity) may have interacted and influenced the risk of stent thrombosis. This finding warrants further investigation.

Of note, ongoing prospective clinical trials are evaluating optimal DAPT duration. One such trial is the OPTIMIZE study for ZES, which randomized 3,120 patients to 3 months *versus* 12 months of DAPT and will report 1-year outcomes for death, MI, stroke, major bleeding, and ARC-defined stent thrombosis events[9].

In contrast to these findings, other analyses of international variations have shown differences in clinical outcomes by geographic region. In the Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, enrollment in LA was an independent predictor of mortality at 30 days (odds ratio 2.42; 95% confidence interval 1.60-3.67) and 6 months (odds ratio 2.5; 95% confidence interval 1.8-3.4)[10]. This finding was observed even after adjustment for differences in baseline risk, suggesting that the outcome difference may have been due to more conservative practice patterns (i.e., lower use of evidence-based therapies for acute MI, lower and later use of revascularization procedures, and less use of invasive management such as angiography). Other ACS studies have also reported significantly higher mortality rates among patients enrolled in LA centers. In these studies, mortality ranged from 10.4% to 12.4% in LA, compared with 5.7% to 7.8% in the US and Europe, respectively[1]. It has been hypothesized that low rates of coronary angiography and revascularization may explain these observed differences in clinical outcome[1].

Of note, however, Cardoso et al[11] evaluated the use of drug-eluting stents in Brazil from 2000 to 2005 and observed a progressive increase in use (from 0.14% to 14%) and after 2001, an increase in success rates (from 96.58% to 99.56%) and a decrease in hospital mortality rates (from 1.59% to 0.21%).

Our findings showing that DAPT use was lowest in the LA region are consistent with other reports. In PURSUIT, patients in LA were significantly less likely to receive in-hospital ticlopidine, heparin, angiotensin-converting enzyme inhibitors, oral beta-blockers, lipid-lowering agents, and oral nitrates. They were also prescribed fewer evidence-based discharge medicines, including antiplatelet agents, beta-blockers, lipid-lowering agents, and oral nitrates[10].

It is unclear why no differences in clinical outcomes were observed in the LA group in E-Five. It is possible that there is less opportunity for practice variation in PCI and stent implantation, as compared with ACS management, where differences have been observed. It is also plausible that the LA centers participating in the E-Five Registry may have been more clinically experienced than sites participating in ACS trials, so that practice variations that may have influenced outcome were minimal. Finally, patients enrolled in E-Five may have been at lower risk of events than patients enrolled in ACS trials, decreasing the likelihood that a difference in clinical events would have been observed.

Limitations

It should be noted that this study was not originally designed or powered to evaluate regional subgroups. The LA and AP regions together include fewer patients than the EU region and may not be representative of all patients presenting for implantation of a drug-eluting stent in those regions. In our analysis, even though we adjusted for baseline differences in the comparison tests of outcomes between regions, other patient-level factors that were unaccounted for could have affected outcomes independently of geographic region. The 2-year patient cohort is a subset of the overall E-Five population; thus, formal comparisons of baseline patient and lesion characteristics for the two groups are inappropriate, although it is nonetheless important to show the overall similarity of the patient groups at 1 and 2 years. Finally, because follow-up could be conducted by phone, extensive information on medical therapies and interventions specific to each region was not available.

Conclusion

Regional results from the E-Five Registry suggest that despite differences in patient and lesion characteristics and DAPT use between different geographic regions, outcomes, including rates of MACE, cardiac death, MI, and ARC-defined probable and definite stent thrombosis, are similar. Although DAPT use in LA was less than half that in the other regions, this did not result in increased rates of MACE or late stent thrombosis. The other cardiac and lesion outcomes at 1 year and 2 years were comparable between the LA and both the EU and AP regions.

These data suggest that considerable differences in lesion complexity and comorbidities across geographic regions do not translate into differences in outcomes after PCI. It may be that the risks of premature cessation of DAPT are partially mitigated by simpler lesion anatomy. These results provide evidence of the safety and effectiveness of the Endeavor ZES in real-world patients despite potential patient, lesion, and practice differences between the major geographic regions.

Potential Conflicts of Interest

Chaim Lotam served as a consultant for Angio Score Ltd. and Medtronic CardioVascular. Ian T. Meredith has served as an advisory board member for Boston Scientific and Medtronic CardioVascular. Fausto Feres has received honoraria for lectures from Medtronic CardioVascular, Terumo, and Sanofi-Aventis. A. Frutos García has received research support from Abbott Vascular, Medtronic CardioVascular, and Boston Scientific. Martin T. Rothman has served as a consultant to Abbott Vascular, Cordis Corporation, JenaValve Technology GmbH, Lombard Medical Technologies PLC, Medtronic CardioVascular, and Volcano Corporation; has received research/grant support from Abbott Vascular, Boston Scientific, CardioBridge GmbH, Cordis Corporation, and Medtronic CardioVascular; and since this paper was written, has become Vice President of Medical Affairs, Coronary and Peripheral Division, Medtronic CardioVascular.

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Study Association

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