Differences in cardiovascular risk factors and clinical outcomes between Western European and Southeast Asian patients treated with the Genous Bio-engineered R stent: an e-HEALING worldwide registry substudy

Margo Klomp[a], Peter Damman[a], Marcel A.M. Beijk[a], Kim H. Tan[b], Vruyr Balian[c], Giuseppe de Luca[d], Jan G.P. Tijssen[a], S. Silber[e] and Robbert J. de Winter[a] on behalf of the e-HEALING investigators

Objective **Percutaneous coronary interventions (PCIs) are increasingly being performed worldwide to treat patients with coronary artery disease. However, studies on the influence of ethnicity on clinical outcomes after PCI are scarce. In our current analysis, we evaluate the differences in baseline clinical, angiographic and procedural characteristics, and 12-month clinical outcomes in patients undergoing nonurgent PCI in Western Europe and in Asia.**

Methods **We analyzed all patients enrolled in the worldwide e-HEALING (electronic Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) registry living in Western Europe and Asia. All patients were treated with at least one endothelial progenitor cell capturing stent. The main study outcome was target vessel failure at the 12-month follow-up, defined as the composite of cardiac death or myocardial infarction and target vessel revascularization.**

Results **A total of 3504 patients, 2873 living in Western Europe and 731 living in Asia, were assessed in the current analysis. Almost all of the baseline clinical and angiographic characteristics differed significantly between both populations. Target vessel failure at the 12-month follow-up occurred in 11.4% of the Western Europe patients and in 5.6% of the Asian patients ($P < 0.01$).**

Conclusion **We conclude that differences exist in the baseline, angiographic, and procedural characteristics between Western European and Asian patients undergoing nonurgent PCI. In addition, the 1-year clinical outcomes differ significantly after PCI between Western European and Asian patients. Our results indicate that reports from studies performed worldwide should include both overall and regional subgroup outcomes.** ***Coron Artery Dis*** **23:271–277 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: endothelial progenitor cells, ethnicity, European patients, percutaneous coronary intervention, restenosis, risk factors, Southeast Asian patients

[a]Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [b]Sunway Medical Centre, Petaling Jaya, Selangor, Malaysia, [c]Ospedale Busto Arsizio, Varese, [d]Division of Cardiology, Eastern Piedmont University, Novara, Italy and [e]University of Munich, Munich, Germany

Correspondence to Robbert J. de Winter, MD, PhD, FESC, Department of Cardiology, Cardiac Catheterization Laboratory B2-137, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
Tel: +31 205 669 111; fax: +31 206 962 609; e-mail: r.j.dewinter@amc.uva.nl

Margo Klomp, Peter Damman, and Marcel A.M. Beijk contributed equally to the writing of this article.

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Introduction

Percutaneous coronary intervention (PCI) with stent placement has become the most common revascularization modality for coronary artery disease (CAD) worldwide [1]. Several studies have reported that the occurrence of cardiovascular risk factors [diabetes mellitus (DM), hypertension, hypercholesterolemia, and familial CAD] varies among different ethnic groups [2–5]. Although the influence of ethnicity on clinical presentation, procedure-related choices, and outcomes of coronary artery bypass grafting (CABG) has been described, studies on ethnicity and PCI are sparse [6–8]. To date, most studies evaluating the influence of ethnicity on the risk factors and clinical outcomes after PCI have been carried out in immigrants versus native inhabitants living in a European country or in North America [2,3,9–11]. In our current analysis, we evaluate the differences in the baseline clinical, angiographic, and procedural characteristics and the 12-month clinical outcomes in patients undergoing nonurgent PCI in participating centers in Western Europe and in Southeast Asia. We analyzed the data from the worldwide e-HEALING (electronic Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) registry evaluating the endothelial progenitor cell capturing stent (ECS).

Materials and methods

Source population

The current analysis is a post-hoc analysis of the worldwide e-HEALING registry evaluating the ECS. The study design, data collection and management, quality control, and list of sites/investigators have been

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described previously [12]. In brief, almost 5000 patients who received at least one ECS were enrolled between October 2005 and October 2007 in 144 centers in Europe, Asia/Pacific, Middle East, Africa, and Latin America. The e-HEALING registry complied with the principles of the Declaration of Helsinki on investigation in humans and was approved by the local institutional review board at each participating center. If considered necessary, written informed consent was obtained.

Device description

The ECS comprises a polysaccharide matrix coating with murine, monoclonal antihuman CD34+ antibodies covalently bonded to the surface of a 316L stainless-steel stent (Genous Bio-engineered R stent, OrbusNeich Medical Technologies, Fort Lauderdale, Florida, USA).

Study population and procedures

For the current analysis, all patients living in Western Europe and Southeast Asia were included (Appendix 1). The Southeast Asian centers were located in Singapore, Hong Kong, and Malaysia. Patients who underwent a nonurgent PCI with at least one lesion stented with an ECS (diameter 2.50–4.00 mm, length 9–33 mm) in accordance with the instructions for use were eligible for enrollment in the e-HEALING registry. The patients' race or ethnicity could not be filled out in the electronic case report form. The indication for PCI was left at the discretion of the operator. Patients were recommended to receive at least 2 weeks of statin therapy before PCI and dual antiplatelet therapy was recommended for at least 1 month after the procedure and aspirin indefinitely. The use of concomitant medication was left at the discretion of each treating physician.

Outcomes and data management

The main study outcome of our post-hoc analysis was target vessel failure (TVF) at the 12-month follow-up, defined as the composite of cardiac death or myocardial infarction (MI) unless unequivocally attributable to a nontarget vessel and target vessel revascularization (TVR). The secondary outcomes were the composite of cardiac death, MI, and clinically indicated target lesion revascularization (TLR) and the individual outcomes were all-cause death, cardiac death, MI (non-Q-wave or Q-wave), TLR, TVR, and stent thrombosis (ST) according to the definitions of the Academic Research Consortium [13]. The outcome definitions have been described previously [12].

All outcome events were assessed at discharge from initial hospitalization, at 30 days, at 6 months, and at 12 months. Trained and qualified clinical research associates monitored the registry throughout its duration remotely through the Internet-based database. Ten percent of the sites were selected randomly for on-site monitoring including full source data verification. The following events were adjudicated by an independent Clinical Event Committee whose members did not participate in the study: death, MI, TVR, TLR, and ST. The Clinical Event Committee was managed independently by a contract research organization (Cardialysis, Rotterdam, The Netherlands).

Baseline patient and lesion, procedure-related, and angiographic characteristics were collected and stored in a central Internet-based electronic data capture system (Eventa; KIKA Medical, Paris, France) with built-in queries to improve accuracy maintained by Cardialysis.

Statistical analysis

Categorical variables were reported with counts and percentages, and continuous variables were reported with the mean and SD. Cumulative event rates were estimated using the Kaplan–Meier method and compared with the log-rank test. Follow-up was censored at the last known date of follow-up or at 12 months, whichever came first. Hazard ratios (HRs) for the main outcome TVF were calculated in two sets of Cox proportional-hazards models: unadjusted in univariable analysis and adjusted for identified predictors for TVF in multivariable analysis. We previously identified the following predictors for TLR [14]. Predictors for the main outcome TVF were identified by backwards selection of baseline clinical and angiographic variables. A *P*-value of less than 0.1 by the likelihood ratio test was deemed significant. In an exploratory analysis, we identified predictors for TVF according to region. The statistical analysis was performed at the Academic Medical Center, University of Amsterdam using the Statistical Package for Social Sciences (SPSS) software version (version 16, SPSS Inc., Chicago, Illinois, USA).

Results

Of the 4996 patients entered in the e-HEALING registry, 52 patients were excluded because of missing procedure-related data ($n = 16$); no ECS was placed or ECS placement was unknown ($n = 36$). Five patients were excluded because of missing follow-up data. Of the remaining 4939 patients, 3604 patients were eligible for our analysis, all patients living in Western Europe (2873 patients, 3800 lesions) and all patients living in Southeast Asia (731 patients, 1057 lesions). The baseline characteristics of the study population are shown in Table 1. The average age of patients from Western Europe was 65.9 ± 11.2 years and that of Southeast Asian patients was 57.4 ± 9.9 years ($P < 0.01$). A total of 75% of the patients from Western Europe were men, compared with 85% in the Southeast Asian population ($P < 0.01$). Furthermore, 24% of the Western Europeans and 36% of the Southeast Asians were diabetic patients, respectively ($P < 0.01$). Of all other cardiovascular risk factors, only the occurrence of smoking did not differ significantly

Table 1 Baseline clinical characteristics and medication use

	Western Europe $N=2873$	Asia $N=731$	P-value
Demographics			
Age (years)	65.93 ± 11.15	57.35 ± 9.89	<0.01
Male sex	2158 (75%)	623 (85%)	<0.01
BMI (kg/m^2)	27.4 ± 5.1	25.9 ± 3.7	<0.01
Diabetes	684 (24%)	262 (36%)	<0.01
Non-insulin dependent	496 (73%)	241 (92%)	
Insulin dependent	188 (27%)	21 (8%)	
Hypertension	1946 (68%)	452 (62%)	<0.01
Hypercholestrolemia	1981 (69%)	640 (88%)	<0.01
Current smoker	677 (24%)	174 (24%)	0.89
Family history of coronary artery disease	803 (28%)	159 (22%)	<0.01
History			
History of MI	1150 (40%)	173 (24%)	<0.01
History of PCI	666 (23%)	120 (16%)	<0.01
History of CABG	215 (7%)	17 (2%)	<0.01
Medication use			
Aspirin	2298 (80%)	637 (87%)	<0.01
Clopidogrel	1440 (50%)	688 (94%)	<0.01
Angiotensin II receptor blocker	286 (10%)	99 (14%)	<0.01
Angiotensin-converting enzyme inhibition	1133 (39%)	172 (24%)	<0.01
β-Blockers	1703 (59%)	399 (55%)	0.02
Calcium antagonists	502 (17%)	112 (15%)	0.17
Nitrates	946 (33%)	133 (18%)	<0.01
Statins	2154 (75%)	647 (89%)	<0.01
Indication PCI			
Non-STEMI, ongoing instability	242 (8%)	12 (2%)	<0.01
Unstable angina pectoris, ongoing instability	523 (18%)	43 (6%)	<0.01
Post-STEMI	248 (9%)	50 (7%)	0.12
Post-non-STEMI	196 (7%)	24 (3%)	<0.01
Post-unstable angina pectoris	213 (7%)	25 (3%)	<0.01
Elective PCI	1184 (41%)	575 (79%)	<0.01
Others/unknown	268 (9%)	2 (0%)	<0.01
Multivessel PCI	439 (15%)	199 (27%)	<0.01
Coronary artery bypass graft	33 (1%)	8 (1%)	0.91
Left main	57 (2%)	9 (1%)	0.18
Lesions per patient	1.3 ± 0.6	1.5 ± 0.7	<0.01

No statistically significant differences were found between both groups.
Values are *n* (%) or mean ± SD
CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

between both populations ($P = 0.89$). Southeast Asians less often had a history of MI or revascularization.

Over 80% of all patients were on aspirin. Clopidogrel was administered in 50% of the Western Europeans versus 94% in Southeast Asians before the PCI procedure ($P < 0.01$). Furthermore, elective PCI for stable disease was performed in 41 and 79% of the patients, respectively ($P < 0.01$).

Table 2 shows the baseline angiographic characteristics. Almost all treated lesions were de-novo lesions and ~10% were bifurcation lesions. The average lesion length of the treated lesions was 16.30 ± 8.54 mm in Western European patients and 20.17 ± 9.72 mm in Southeast Asian patients ($P < 0.01$). The occurrence of treated ACC/AHA type B2/C lesions was 58 versus 37% ($P < 0.01$), with a mean stent use of 1.13 ± 0.47 versus 1.13 ± 0.44 stents per lesion ($P = 0.87$) in Western Europeans versus Southeast Asians, respectively.

Table 2 Baseline angiographic and procedural characteristics

	Western Europe $L=3800$	Asia $L=1057$	P-value
De-novo lesion	3681 (97%)	1049 (99%)	<0.01
Restenotic lesion	119 (3%)	8 (1%)	
Bifurcation	419 (11%)	105 (10%)	0.31
Lesion length (mm)	16.3 ± 8.54	20.17 ± 9.72	<0.01
Reference vessel diameter (mm)	3.04 ± 0.43	2.91 ± 0.41	<0.01
Stenosis preprocedure (% of vessel diameter)	86.71 ± 11.51	82.05 ± 12.83	<0.01
Preprocedure thrombus	567 (15%)	23 (2%)	<0.01
ACC/AHA lesion classification			
A	325 (9%)	206 (19%)	<0.01
B1	1306 (34%)	463 (44%)	
B2	1350 (36%)	106 (10%)	
C	819 (22%)	282 (27%)	
Preprocedure TIMI flow			
Grade 0	469 (12%)	87 (8%)	<0.01
Grade 1	243 (6%)	118 (11%)	
Grade 2	490 (13%)	216 (20%)	
Grade 3	2598 (68%)	636 (60%)	
Stent use			
Stents per lesion	1.13 ± 0.47	1.13 ± 0.44	0.87
Direct stenting attempted	1425 (38%)	289 (27%)	<0.01
Postprocedure TIMI flow			
Grade 0	11 (0%)	7 (1%)	<0.01
Grade 1	7 (0%)	5 (0%)	
Grade 2	46 (1%)	35 (3%)	
Grade 3	3736 (98%)	1010 (96%)	
Stenosispost procedure (% of vessel diameter)	3.5 ± 8.21	1.87 ± 8.44	<0.01

Values are *n* (%) or mean ± SD
L, number of lesions; TIMI, thrombolysis in myocardial infarction.

The clinical outcomes are summarized in Table 3. At the 12-month follow-up, the primary endpoint of TVF occurred in 11.4% of the Western European patients and in 5.6% of the Southeast Asian patients ($P < 0.01$). The cumulative event rate of TVF for both treatment arms is shown in Fig. 1. The TVR rates were 8.8 and 4.1% ($P < 0.01$), the MI rates were 2.6 and 1.4% ($P = 0.06$), and cardiac death occurred in 2.3 and 1.5% ($P = 0.20$) of the patients, respectively. Furthermore, definite ST was present in 0.9 and 0.3% of the patients ($P = 0.10$).

The unadjusted HR for TVF of Western European patients compared with Southeast Asian patients was 2.13 (95% confidence interval: 1.53–2.97, $P < 0.001$). After adjustment for identified predictors of TVF, the HR was 2.23 (95% confidence interval: 1.56–3.17, $P < 0.001$). In an exploratory analysis, we identified predictors for TVF according to region. Independent predictors of TVF in Western European patients were BMI, DM, a PCI before the index procedure, and the indication for PCI (Table 4). In Southeast Asian patients, an MI before the index procedure was an independent predictor of TVF within 1 year after the initial PCI. Complex lesions, defined as either AHA type B2 or type C lesions, were predictors of TVF in both Western European and Southeast Asian patients.

Discussion

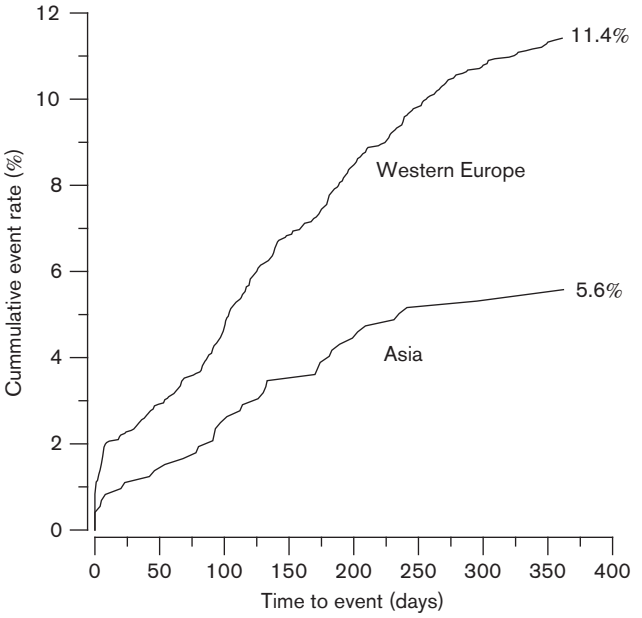
The current analysis is the first study comparing baseline clinical, angiographic, and procedural characteristics and

Table 3 One-year clinical outcomes

	Western Europe $N=2873$	Asia $N=731$	P-value
Primary efficacy endpoint			
Target vessel failure*	315 (11.4%)	39 (5.6%)	<0.01
Individual outcomes			
Death	91 (3.3%)	13 (1.8%)	0.05
Cardiac death	65 (2.3%)	11 (1.5%)	0.20
MI	73 (2.6%)	10 (1.4%)	0.06
Q-wave MI	12 (0.4%)	4 (0.6%)	
Non-Q-wave MI	62 (2.2%)	6 (0.8%)	
Clinically indicated TLR	207 (7.4%)	26 (3.8%)	<0.01
Percutaneous	190 (7.0%)	25 (3.7%)	
Surgical	23 (0.8%)	1 (0.1%)	
TVR	238 (8.8%)	28 (4.1%)	<0.01
Percutaneous	212 (7.8%)	25 (3.7%)	
Surgical	33 (1.2%)	3 (0.4%)	
Stent thrombosis			
Definite	25 (0.9%)	2 (0.3%)	0.10
Probable	19 (0.7%)	2 (0.3%)	0.22
Possible	35 (1.3%)	8 (1.1%)	0.78
Composite end points			
Device oriented: cardiac death, target vessel MI, TLR	291 (10.5%)	38 (5.4%)	<0.01
Patient oriented: death, MI, any revascularization	459 (16.5%)	52 (7.4%)	<0.01
Cardiac death, MI, TLR	298 (10.8%)	38 (5.4%)	<0.01
Death or MI	155 (5.5%)	18 (2.5%)	<0.01
Cardiac death or MI	131 (4.7%)	16 (2.2%)	<0.01

Values are *n* (%).
MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.
*Target vessel failure is defined as the composite of cardiac death, MI attributable to the target lesion, or clinically driven target vessel revascularization.

Fig. 1



Number at risk

Months	0	2	4	6	8	10	12
Western Europe	2873	2703	2623	2551	2418	2382	1898
Asia	731	709	697	682	669	639	378

Time-to-event curve for the primary endpoint of cardiac death, myocardial infarction, and clinically indicated target lesion revascularization.

clinical outcomes between Western European patients and Southeast Asian patients enrolled in a large stent registry. There are significant differences in patient and lesion characteristics between the patients treated in Western Europe and in Southeast Asia. When evaluating clinical outcomes 12 months after ECS implantation, TVF occurred in 11.4% of the Western European patients and in 5.6% of the Southeast Asian patients. The difference in the TVF rate among both populations was mainly driven by higher TVR in the Western Europeans.

Previous studies

Studies evaluating the occurrence of CAD in patients from different regions are rare. In the study by Anand *et al.* [2], patients living in Canada of South Asian, Chinese, or European origin were recruited by stratified random sampling and were evaluated for cardiovascular risk factors and subclinical atherosclerosis. When comparing the Chinese with the Europeans in line with the current analysis, the Chinese were younger, had a lower BMI, and less often had a history of MI, PCI, or CABG. No differences were found in the occurrence of DM, hypertension, or dyslipidemia. The study by Khan *et al.* [11] evaluated South Asian, Chinese, and White patients who had been admitted for acute MI in two centers in Canada comparing mortality rates, revascularization procedures, risk or recurrent MI, and hospitalization for heart failure among the selected patients. In this cohort, the Chinese patients were generally younger and more often had DM and hypertension than the White patients. Both studies may not be directly comparable because the compared patients were all living in the same region. In contrast, the study by Zheng *et al.* [5] analyzed clinical data on Chinese patients with CAD living in China and German patients with CAD living in Germany. In the Chinese patients, the average age and mean BMI were lower, and hypertension and dyslipidemia occurred less often. The occurrence of DM was equal between

Table 4 Cox regression analysis

Variable	HR (95% CI)	P-value
Western Europe		
BMI	0.97 (0.95–1.00)	0.03
Diabetes mellitus	1.36 (1.05–1.76)	0.02
Current smoker	0.75 (0.56–1.02)	0.07
History of PCI	1.32 (1.02–1.71)	0.03
Indication for PCI		
Reference	–	0.04
ACS	0.98 (0.77–1.25)	0.89
Other	0.45 (0.25–0.80)	<0.01
Minimal one type B2/C lesion	1.25 (0.98–1.59)	0.07
Asia		
Previous MI	2.77 (1.44–5.35)	<0.01
Minimal one type B2/C lesion	1.91 (0.99–3.71)	0.06

ACS, acute coronary syndrome; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

both groups. In the current analysis, Southeast Asian patients were younger, had a lower BMI, and had DM and hypercholesterolemia more often, whereas in Western European patients, hypertension, a history of MI, PCI, or CABG, and unstable angina as indications for PCI were more frequent. When comparing the above-mentioned studies, the White patients, in general, were older, with a higher BMI, more often had hypertension or a history of MI, PCI, or CABG, and less often had DM. However, a discrepancy was found in the occurrence of DM, dyslipidemia, and hypertension. This may be explained by the difference in the study population and the study design. Moreover, no data were available on race or ethnicity in our current analysis.

One study reported on angiographic characteristics and clinical outcomes after PCI in White and Chinese patients. In the study by Slater *et al.* [3] on Whites, Blacks, Hispanics, and Asian patients from 17 centers in the USA, the average lesion length was 12.2 mm in Whites versus 14.4 mm in Asians; 58.7 versus 57.6% were type B2/C lesions with 1.4 versus 1.6 lesions per patient attempted to treat. At the 1-year follow-up, the composite end point of death, MI, or CABG occurred in 15.8% of the Whites and in 21.2% of the Asians. Cardiac death rates were 5.2 and 7.6%, respectively. In our current analysis, treated lesions were more complex than in the study by Slater and colleagues. Interestingly, event rates at the 1-year follow-up were slightly higher in Asians than in Whites, in contrast to our findings. One explanation may be that the Southeast Asian patients in our study resided and were treated in Southeast Asia whereas the Asians in the above-mentioned study were immigrants. Another explanation may be that the Southeast Asian population in our cohort included patients living in Hong Kong, Malaysia, and Singapore, whereas the Asian population in the USA included Chinese-Mainland, Japanese, Indian, and Pakistani patients, thereby comparing patients with different ethnic backgrounds. Finally, there might be differences in revascularization strategies.

Outcomes

The patients from Western Europe had higher 12-month event rates than the Southeast Asian patients. A possible explanation for the observed higher event rates is that the European patients had more advanced CAD, corroborated by the higher frequency of previous MI, CABG, or PCI. Moreover, despite angiographically longer lesions in Southeast Asian patients, lesions in Western European patients were more complex, as evidenced by the ACC/AHA classification and number of restenotic lesions. Furthermore, initial presentation with acute coronary syndrome occurred more frequently in Western European patients. Finally, differences in medical treatment can explain the differences. In our current analysis, concomitant pharmacological therapy at baseline was lower in European patients. Data on revascularization strategies were not captured in e-HEALING. Regional differences in revascularization strategies could be attributed to the difference in outcomes. In the aforementioned analysis by Slater and colleagues, White and Asian patients who lived in the USA were subjected to the same treatment strategy. This may support the theory that the difference observed in the current study is (partly) due to the difference in the treatment strategies. Moreover, after adjustment for mostly baseline clinical and angiographic characteristics, the HR for TVF was materially unaffected in our analysis.

Implications

One of the major implications of our current study is that the external validity from Western European studies is potentially limited to Western European populations, as evidenced by the differences in patient and lesion characteristics and outcomes between Western European and Southeast Asian patients. This suggests that reports from studies performed worldwide should include overall outcomes according to regional subgroups. Further research is required to investigate the influence of genetic and environmental factors and the occurrence of CAD, treatment, and outcomes between different ethnic groups within regions.

Limitations

Some limitations deserve to be mentioned. First, the under-reporting of adverse events is a potentially important limitation of all large registries. The e-HEALING registry was organized with a comprehensive data-management plan that included remote monitoring of all sites and full event adjudication. Second, angiographic variables were obtained by visual estimation. Third, the patients' race could not be filled out in the electronic case report form. Furthermore, there may be a selection bias as patient enrollment was not performed on consecutive patients. Finally, we might have been underpowered to compare the study groups with respect to cardiac death, MI, and ST.

Conclusion

We conclude that differences exist in baseline, angiographic, and procedural characteristics between Western European and Southeast Asian patients undergoing nonurgent PCI. In addition, the 1-year clinical outcomes differ significantly after PCI between Western European and Southeast Asian patients.

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Conflicts of interest

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Appendix 1. Centers participating in the regional differences substudy of the e-HEALING registry

Western Europe (*N*=2873)

Austria: Med. Univ. Klinik Kardiologie Graz (H. Brussee) (190), University of Vienna (D. Glogar) (99), LKH-Graz West (D. Botegal) (57), LKH Salzburg II. Med (J. Altenberger) (42), SMZ-Ost/Danube Hospital (S. Weber) (8), LKH Bruck (K. Kaspar) (7), LKH Villach, Villach (H. Koller) (4), RZ Austria (G. Helmreich) (1).

Belgium: Virga Jesse Hospital (E. Benit) (28), Cliniques Universitaires Saint-Luc (N. Debbas) (22), CHU de Charleroi (J. Lalmand) (2).

Denmark: Rigshospitalet (S. Helqvist) (19), Odense University Hospital (P. Thayssen) (11).

Finland: Satakunta Central Hospital (A. Ylitalo) (7).

France: CMC Parly II (G. Dambrin) (27), CHU Caen (G. Grollier) (14), Polyclinique de Bois Bernard (A. Gommeaux) (4), CHU Mondor (E. Teiger) (4), Institut Jacques Cartier (M.C. Morice) (2), CH Sud Francilien (P. Goube) (2).

Germany: Ambulantes Herzzentrum Kassel (A. Utech) (107), Kardiologische Praxis und Praxisklinik (S. Silber) (75), Zentralklinik Bad Berka (B. Lauer) (26), Herzzentrum NRW Bad Oeynhausen (M. Wiemer) (17), Städtische Kliniken Neuss, Lukaskrankenhaus (M. Haude) (15), Universitätsklinikum Frankfurt am Main (V. Schächinger) (8), Deutsches Herzzentrum Berlin German Heart Institute (E. Fleck) (8), Klinikum Coburg (J. Brachmann) (4), Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum (W. Bocksch) (3), Universitätsklinikum Rostock (C. Nienaber) (1), Krankenhaus Dresden-Friedrichstadt (J. Eberhard) (1).

Ireland: Beaumont Hospital (D. Foley) (38).

Italy: Ospedale Busto Arsizio (V. Balian) (185), AUP Federico II University of Naples (G. De Luca) (126), Campus Biomedico University of Rome (A. Carcagní) (80), Azienda Ospedaliera Santi Antonio e Biagio e Cesare Arrigo (G. Carosio) (54), Ospedale Sant'Anna (M. Galli) (49), Mauriziano (M. De Benedictis) (45), S.Antonio Abate (G.B. Biondo) (39), Cannizzaro (A. Fiscella) (36), Hesperia Hospital (A. Benassi) (35), Policlinico del pozzo (G. GeracI) (33), Policlinico Tor Vergata (F. Romeo) (32), Cardiologia Clinicizzata Universitaria Novara (G. de Luca) (30), S.Giovanni Battista Molinette (M. D'amico) (30), Le Scotte (A. Bravi) (29), Ospedale Civile di Legnano (F. Barlocco) (21), Ospedale S. Spirito (Paloscia Leonardo) (13), Division of Cardiology Moscati Hospital (G.M. Cianciulli) (12), Maggiore della Carità Novara (A.S. Bongo) (12), Catholic Registry Campobasso (G. Angeloni) (11), Ospedale S. Giovanni Addolorata (A. appalardo) (10), Ospedale Civile Maggiore (M. Turri) (10), Ospedale di Cittadella (M. Zanchetta) (6), Ospedale di Circolo e Fondazione Macchi (G. Calveri) (1), Cardinal Massaia Asti (G. Defilippi) (2), Ospedale S. Andrea (G. Cossa) (2).

The Netherlands: Academic Medical Center (R.Jde Winter) (260), Isala Klinieken (H. Suryapranata) (90), Amphia Ziekenhuis (P. Den Heijer) (67), Rijnstate Hospital (H.A. Bosker) (36), Medisch Spectrum Twente (K.G. van Houwelingen) (10).

Portugal: Hospital de Santa Marta (L. Bernardes) (104), Centro Hospitalar de Gaia (P. Braga) (79), Centro Hospitalar de Coimbra (A.L. Marques) (34).

Spain: HCU de Santiago de Compostela (A.A. Cendon) (76), Hospital Do Meixoeiro (A. Iniguez) (74), Hospital Santa Creu i Sant Pau (V. Martin) (70), Universitario Valladolid (B. Ramos) (60), Hospital de la Vall d' Hebron (J.A. Ferrer) (16), Policlinica Miramar (M. Uson) (19), Hospital Del Mar (A. Serra) (5), Hospital de Leon (A. Perez De Prado) (1).

Switzerland: University Hospital Switzerland (F. Eberli) (23).

UK: Western Infirmary (K. Oldroyd) (24), Lister Hospital (D. Gorog) (24), The James Cook University (M.A. Debelder) (16), Morriston (D. Smith) (13), St. Georges Hospital (P. Lim) (7), SWBH (C. Varma) (6), Northern General Hospital (J. Gunn) (1), Glenfield Hospital (J. Kovac) (2).

Asia (*N*=731)

Hong Kong: Queen Mary Hospital (S. Lee) (50).

Malaysia: Sunway Medical Centre (K.H. Tan) (227), HSC Medical Center (C.S. Soo) (200), National Heart Institute (R. Zambahari) (80), Hospital Universiti Sains Malaysia (Z. Yusof) (45), Hospital Kebangsaan Malaysia (O. Maskon) (40), Sarawak General Hospital (K.H. Sim) (30), Hospital University Kuala Lumpur (W.A. Wan Ahmad) (20), Hospital Besar Pulau Pinang (O. Ismail) (7), Hospital Sultanah Aminah Johor Bahru (C.Y. Lee) (3).

Singapore: National Heart Centre (T.H. KOH) (28), National University Hospital (S.G. Teo) (1).

*Enrollment as of November 2007.