Risk-factor profile, drug usage and cardiovascular events within a year in patients with and at high risk of atherothrombosis recruited from Asia as compared with those recruited from non-Asian regions: a substudy of the REduction of Atherothrombosis for Continued Health (REACH) registry

S Goto,[1] Y Ikeda,[2] J C N Chan,[3] P W F Wilson,[4] T Cheng Yeo,[5] C S Liau,[6] M T Abola,[7] G Salette,[8] P G Steg,[9] D L Bhatt,[10] on behalf of the REACH Registry Investigators*

[1]Department of Medicine (Cardiology), Tokai University School of Medicine, Isehara, Japan
[2]Department of Life Science and Medical Bioscience, Waseda University, Tokyo, Japan
[3]Department of Medicine, The Chinese University of Hong Kong, Hong Kong, China
[4]Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine, Atlanta, GA, USA
[5]Department of General Medicine, National University Hospital, Singapore
[6]Department of Cardiology, Taiwan University Hospital and College of Medicine, Taipei, Taiwan
[7]Section of Vascular Medicine, Division of Clinical Cardiology, Philippine Heart Center, Quezon City, Philippines
[8]Sanofi-Aventis, Paris, France
[9]Department of Cardiology, Hôpital Bichat-Claude Bernard, Université Paris, Paris, France
[10]10VA Boston Healthcare System and Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA

Correspondence to
S Goto, Department of Medicine (Cardiology), Tokai University School of Medicine, Isehara 2591143, Japan;
shinichi@is.icc.u-tokai.ac.jp

*REACH Registry Executive Committee, REACH Registry Global Publication Committee are listed in the appendix 1.

ABSTRACT

Objective To clarify the differences in the baseline characteristics, prevalence and incidence of atherothrombosis in patients recruited from Asia versus non-Asian regions.

Design International Prospective Cohort Study.

Setting Region focused substudy.

Patients The Reduction of Atherothrombosis for Continued Health (REACH) Registry recruited 68 236 stable outpatients with established atherothrombosis or ≥3 atherothrombotic risk factors from 44 countries.

Interventions No intervention.

Main outcome measures Risk factors, use of medications, vascular disease bed location, and 1-year cardiovascular (CV) outcomes (CV death, myocardial infarction, stroke).

Results The percentages of patients recruited with CVD (Cerebrovascular Disease) were higher in Asia (41.0%) than in non-Asian regions (25.1%) (p<0.0001). The prevalence of diabetes mellitus was higher in Asia (46.6%) than in non-Asian regions (43.3%) (p<0.0001) despite the former having a lower body mass index (BMI) (24.4±3.9 vs 28.8±5.6) (p<0.0001). The combined endpoint of CV death/myocardial infarction/ stroke of patients recruited from non-Asian regions of 4.38% (95% CI 4.20 to 4.56) is equivalent to those from the Asian region excluding Japan of 4.65% (95% CI 4.04 to 5.25), but that is significantly lower in patients recruited from Japan of 3.40% (95% CI 2.76 to 4.04, p<0.05).

Conclusions There is a higher prevalence of CVD and higher prevalence of diabetus mellitus with lower body mass index in patients recruited from the Asian region as compared those recruited from non-Asian regions. The CV event rate in patients recruited from non-Asian regions is equivalent to that of patients recruited from the Asian region excluding Japan, but significantly lower in patients recruited from Japan.

INTRODUCTION

The prevalence and incidence of atherothrombotic diseases including myocardial infarction (MI) and ischaemic stroke along with the risk-factor profile of these diseases vary greatly across the regions of the world.[1–13] Regional differences in the prevalence and incidence of atherothrombotic disease may depend upon the genetic variability,[14 15] lifestyle difference[16] and regional differences in the medical care system, among others.

In the present study, we focus on risk-factor profiles, medication use and 1-year outcomes in patients with or at risk of atherothrombosis recruited from countries regionally located in Asia and those recruited from regions outside Asia. We used data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry, which enrolled an international, prospective cohort of patients with established atherothrombotic disease (coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral artery disease (PAD)) and patients who were at high risk of atherothrombosis.[17] The baseline characteristics of more than 68 000 patients (including >10 000 patients recruited from Asian countries),[18] their 1, 3 and 4-year cardiovascular (CV) outcomes,[19–21] and several substudy analyses have been published.[22–26] Here, we present a detailed analysis of the descriptive differences between patients recruited from Asia and those patients recruited from non-Asian regions using the same inclusion and exclusion criteria.

METHODS

The methods and rationale for the REACH Registry have been published previously.[17] Briefly, the REACH Registry recruited stable outpatients aged ≥45 years with either established atherothrombotic disease (CAD, CVD and/or PAD) or three or more risk factors for atherothrombosis (risk factors only (RFO)). The enrolment and exclusion criteria were predefined and have been published elsewhere.[17] Patients were recruited after study approval by the institutional review board in each country or hospital according to local requirements, and written informed consent was obtained.

We analysed the risk factors (age, gender; hypertension, hypercholesterolaemia, diabetes mellitus (DM) defined by local practice guidelines,

obesity assessed by both body mass index (BMI) and waist circumference, and smoking status) and usage of drugs for antithrombotic and correction for risk factors from the baseline database and the incidence of the primary endpoint of CV death, non-fatal MI and non-fatal stroke as well as major bleeding endpoints using the database of 1-year outcome of 10 692 patients (9122 symptomatic, 1570 asymptomatic) recruited from Asia compared with 54 285 patients recruited from 34 other countries outside Asia. Those patients from non-Asian regions were recruited primarily (>98%) from North and South America, Europe and Australia, and an additional 846 patients were recruited from the Middle East (44 089 symptomatic, 10 196 asymptomatic).

Statistical analysis

One-year event rates are expressed primarily as crude annualised event rates and percentages. One-year CV outcomes were adjusted for age, sex, key risk factors (15.2% smokers, 81.7% hypertension, 43.9% diabetes, 72.1% hypercholesterolaemia) and region of vascular disease (CAD, CVD, PAD). As we have already demonstrated in the REACH Registry that 1-, 3- and 4-year CV event rates in patients recruited from Japan differ substantially from those recruited from other regions,[19–21] a subanalysis was conducted, comparing patients recruited from Japan with patients recruited from the Asian region excluding Japan.

Comparisons between patients recruited from Asia (including Japan) and non-Asian regions, and between those recruited from Asia (excluding Japan) and Japan, were performed using the Pearson χ^2 test for qualitative variables, Student t test for quantitative variables and adjusted logrank test for event rates. Comparisons between patients recruited from Asia (excluding Japan), Japan and non-Asian regions were performed using an analysis of variance. The statistical analysis was performed using SAS v9 software.

Role of the funding source

All manuscripts in the REACH Registry are prepared by independent authors who are not governed by the funding sponsors and are reviewed by an academic publications committee before submission. The funding sponsors have the opportunity to review manuscript submissions but do not have authority to change any aspect of a manuscript.

RESULTS

In the 54 285 patients recruited from non-Asian regions, the majority of patients with symptoms (75.8%) had CAD. The percentages of patients recruited with CVD were higher in patients recruited from Asia (41.0%) than those recruited from non-Asian regions (25.1%) (figure 1, table 1). Among patients with symptoms, the percentages of patients recruited with polyvascular disease (two or more vascular regions) were significantly lower in patients recruited from Asia (13.9%) than in non-Asian regions (20.4%) (figure 1).

There were substantial differences in the risk-factor profiles of patients recruited from Asia and non-Asian regions (table 1). Patients recruited from Asia were younger and more predominantly male, with a lower prevalence of hypertension and hypercholesterolaemia but a higher prevalence of diabetes mellitus despite having a smaller waist circumference and a lower BMI (all p<0.0001). Details of the results in each vascular disease category (ie, RFO, CAD, CVD and PAD) are also summarised in table 1. The differences between patients recruited from Asia and non-Asian regions described above were consistent across all subcategories, except for no difference in age and sex in RFO patients and no difference in waist circumference in CAD and PAD patients.

Intraregional comparative analysis demonstrated that patients recruited from Japan were older and more predominantly male, with a lower prevalence of hypertension and

Figure 1 Proportions of patients with coronary artery disease, cardiovascular disease, peripheral artery disease and with risk factors only according to region of enrolment. CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease.
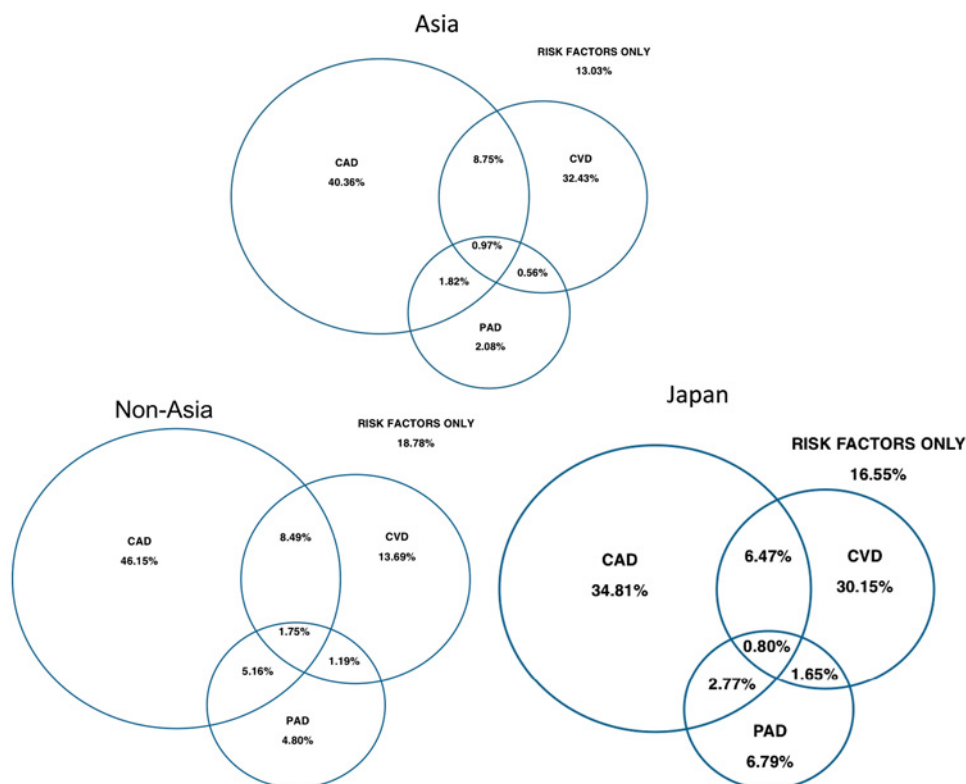
Table 1 Baseline risk-factor profile for patients recruited from Asia (including Japan) and non-Asian regions

	All patients (n=64 977)		Multiple risk factors only (n=11 766)		Coronary artery disease (n=38 602)		Cerebrovascular disease (n=18 013)		Peripheral artery disease (n=7911)	
	Asia (n=10 692)	Non-Asia (n=54 285)	Asia (n=1570)	Non-Asia (n=10 196)	Asia (n=5195)	Non-Asia (n=33 407)	Asia (n=4384)	Non-Asia (n=13 629)	Asia (n=911)	Non-Asia (n=7000)
Age (years)	67.5±9.7	68.8±10.2	68.9±9.1	69.2±10.0	66.8±9.7	68.6±10.2	67.9±9.7	70.0±10.2	70.1±9.0	69.2±10.0
p Value	<0.0001		0.31		<0.0001		<0.0001		0.0032	
Men	67.0	63.1	49.2	49.5	73.6	69.3	65.2	57.8	78.6	69.9
p Value	<0.0001		0.82		<0.0001		<0.0001		<0.0001	
Hypertension	75.2	83.0	79.9	91.7	72.9	81.3	78.0	84.8	78.4	81.5
p Value	<0.0001		<0.0001		<0.0001		<0.0001		0.022	
Hypercholesterolaemia	54.2	75.6	69.7	83.7	61.1	79.1	42.4	62.6	44.7	69.3
p Value	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
Diabetes	46.6	43.3	86.4	73.0	41.5	37.3	38.3	36.5	48.4	42.8
p Value	<0.0001		<0.0001		<0.0001		0.039		0.0014	
Waist circumference (cm)	87.3±11.9	100.1±15.9	87.3±12.1	102.6±16.9	88.0±11.9	100.1±15.5	86.9±11.8	98.6±15.9	86.3±12.3	99.3±15.4
p Value	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
Waist circumference*	49.5	52.8	50.3	64.4	51.1	50.3	48.5	51.5	46.5	48.5
p Value	<0.0001		<0.0001		0.34		<0.001		0.25	
BMI (kg/m^2)	24.4±3.9	28.8±5.6	24.9±4.0	30.5±6.4	24.7±3.9	28.7±5.4	24.2±3.8	28.1±5.3	23.2±3.5	27.6±5.1
p Value	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
BMI>30 (obesity)	6.5	34.5	9.3	47.1	6.9	33.1	5.2	29.3	3.5	26.3
p Value	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
Current smoker	14.7	15.3	21.6	18.8	11.8	13.1	14.0	14.3	19.4	25.0
Never smoker	48.7	42.0	60.5	51.1	45.8	39.0	50.4	46.1	27.6	24.0
Former smoker	36.6	42.7	17.9	30.1	42.4	47.9	35.6	39.6	53.0	51.0
p Value†	<0.0001		<0.0001		<0.0001		<0.0001		<0.001	

Data are mean±SD or %.

*Waist circumference in Japanese (men ≥85 cm/women ≥90 cm), Asian (men ≥90 cm/women ≥80 cm) and non-Asian (men ≥102 cm/women ≥88 cm) populations.

†Comparing smoking status: current; former; never.

Asia, patients recruited from Asian countries; BMI, body mass index; Non-Asia, patients recruited from regions other than Asia.

hypercholesterolaemia, a lower waist circumference and BMI, and a higher prevalence of former and current smokers than patients recruited from Asian countries excluding Japan (all p<0.0001) (table 2).

Pharmacological medications and control of risk factors

The use of chronic antiplatelet and anticoagulant therapy in patients recruited from Asia (excluding Japan), Japan and the non-Asian regions is shown in table 3. Use of antiplatelet in

Table 2 Baseline risk-factor profile for patients recruited from Asia (excluding Japan) and Japan

	Asia (ex. Japan) (n=5671)	Japan (n=5021)	p Value
Age (years)	65.1±9.8	70.3±8.7	<0.0001
Men	3689 (65.1%)	3477 (69.3%)	<0.0001
Diabetes	2685 (47.4%)	2298 (45.8%)	0.10
Hypertension	4479 (79.0%)	3559 (70.9%)	<0.0001
Treated hypercholesterolaemia	3460 (61.0%)	2331 (46.4%)	<0.0001
Waist circumference (cm)	89.6±13.2	84.9±9.7	<0.0001
Body mass index			
Overall (kg/m^2)	25.0±4.2	23.9±3.3	<0.0001
25 to <30 (overweight)	2098 (37.5%)	1474 (29.4%)	<0.0001
30 to <35 (class I)	404 (7.2%)	185 (3.7%)	
35 to <40 (class II)	60 (1.1%)	12 (0.2%)	
≥40 (class III)	30 (0.5%)	4 (0.1%)	
>30 (obese)	494 (8.8%)	201 (4.0)	<0.0001
Smoking status			
Current smoker	713 (12.8%)	804 (16.9%)	
Former smoker	1631 (29.3%)	2155 (45.2%)	<0.0001
Never smoked	3225 (57.9%)	1811 (38.0%)	

Data are mean±SD or number (%).

patients recruited from Asia excluding Japan is higher than those patients recruited from Japan and the non-Asian regions, but the use and dosage of aspirin in patients recruited from Asia or Japan were lower than those patients recruited from non-Asian regions. Moreover, the lower use of aspirin in patients recruited from Japan is notable. The use of dual antiplatelet therapy was similar in patients recruited from Asia and non-Asian regions. The use of anticoagulants was lower in Asia excluding Japan, even in patients who had atrial fibrillation (AF). The use of antiplatelet agent (and aspirin) plus an anticoagulant was lower in patients recruited from Asia excluding Japan as compared with those patients recruited from Japan and from non-Asian regions.

The use of lipid-lowering agents in patients with hypercholesterolaemia recruited from Japan was markedly lower than those patients recruited from Asia excluding Japan or patients recruited from non-Asian regions. Serum cholesterol concentrations in patients recruited from Asia were higher than those patients recruited from the non-Asian regions (table 3). The use of β-blockers, ACE inhibitors and diuretics in hypertensive patients was less frequent in patients recruited from Asia than those who were recruited from non-Asian regions, whereas the use of angiotensin-receptor blockers and calcium-channel blockers was much higher (table 3). Despite these different treatment strategies, systolic blood pressure was not different in patients recruited from Asia and non-Asian regions, while diastolic blood pressure was lower in patients recruited from Asia, especially from Japan. There was also a marked difference in the use of antidiabetic treatments: the use of sulfonylureas in patient with diabetes recruited from Asia excluding Japan is highest, followed by patients recruited from Japan and from non-Asian regions. The use of biguanides and of thiazolidinediones in patients recruited from Japan was markedly lower

Table 3 Medications used at baseline in patients recruited from Asia (excluding Japan), Japan and non-Asian regions

	Non-Asia (n=54 285)	Asia (excluding Japan) (n=5671)	Japan (n=5021)	p Value*	p Value†
Antithrombotic agents					
≥1 Antiplatelet agent	42 718 (78.8%)	4628 (81.6%)	3711 (73.9%)	<0.0001	<0.0001
Aspirin	37 282 (68.9%)	3606 (63.6%)	2737 (54.5%)	<0.0001	<0.0001
Aspirin dose (mg/day)	148.7±109.4	108.0±56.7	99.2±22.7	<0.0001	<0.0001
Other antiplatelet agent	12 579 (23.3%)	1745 (30.8%)	1589 (31.7%)	0.34	<0.0001
Any two antiplatelet agents	7143 (13.3%)	723 (12.8%)	615 (12.3%)	0.43	0.08
Oral anticoagulants	6749 (12.9%)	365 (6.5%)	625 (12.5%)	<0.0001	<0.0001
Oral anticoagulants and aspirin	2039 (3.9%)	131 (2.3%)	285 (5.9%)	<0.0001	<0.0001
Oral anticoagulants and antiplatelet agents	2404 (4.6%)	179 (3.2%)	440 (8.8%)	<0.0001	<0.0001
Antithrombotic agents	47 063 (87.2%)	4814 (85.0%)	3896 (77.6%)	<0.0001	<0.0001
Antiplatelet agents only	38 610 (71.2%)	4387 (77.4%)	3271 (65.2%)	<0.0001	<0.0001
Oral anticoagulants only	4334 (8.0%)	186 (3.3%)	185 (3.7%)	0.25	<0.0001
Oral anticoagulant in AF patients	3302 (54.8%)	112 (36.4%)	189 (53.5%)	<0.0001	<0.0001
Non-steroidal anti-inflammatory drugs	6918 (13.2%)	232 (4.1%)	147 (2.9%)	<0.001	<0.0001
Use of lipid-lowering agents in patients with hypercholesterolaemia					
≥1 Lipid-lowering agent	40 742 (90.8%)	3524 (88.5%)	2379 (74.2%)	<0.0001	<0.0001
Statins	37 831 (84.4%)	3219 (80.8%)	2127 (66.4%)	<0.0001	<0.0001
Other lipid-lowering agents	6454 (14.4%)	477 (12.0%)	399 (12.5%)	0.55	<0.0001
Serum cholesterol (mg/dl)	195.5±48.8	206.6±49.9	205.1±34.5	0.19	<0.0001
≥1 Antihypertensive agent in patients with hypertension	45 854 (96.4%)	4614 (95.7%)	3509 (89.1%)	<0.0001	<0.0001
β-blockers	24 618 (52.0%)	2018 (41.9%)	772 (19.6%)	<0.0001	<0.0001
ACE inhibitors	24 530 (51.9%)	1661 (34.5%)	794 (20.2%)	<0.0001	<0.0001
Angiotensin-receptor blockers	11 154 (23.7%)	1493 (31.0%)	1491 (37.9%)	<0.0001	<0.0001
Diuretics	22 872 (48.3%)	1233 (25.6%)	543 (13.8%)	<0.0001	<0.0001
Calcium-channel blockers	16 188 (34.3%)	2156 (44.7%)	2568 (65.2%)	<0.0001	<0.0001
Nitrates	11 133 (23.9%)	1306 (27.3%)	1045 (26.5%)	0.40	<0.0001
Other antihypertensives	5188 (11.0%)	462 (9.6%)	237 (6.0%)	<0.0001	<0.0001
Peripheral arterial claudication medications	3235 (7.0%)	250 (5.3%)	235 (6.0%)	0.15	<0.0001
Systolic blood pressure (mm Hg)	140.4±19.3	140.9±19.6	140.6±16.9	0.37	0.27
Diastolic blood pressure (mm Hg)	79.3±11.3	81.7±11.3	77.6±10.8	<0.0001	0.046
Use of antidiabetic agents in patients with diabetes mellitus					
≥1 Antidiabetic agent	21 238 (86.8)	2543 (88.7%)	1901 (78.7%)	<0.0001	<0.0001
Sulfonylurease	10 049 (41.4%)	1617 (56.8%)	1071 (44.3%)	<0.0001	<0.0001
Biguanides	10 166 (41.8%)	1441 (50.5%)	309 (12.8%)	<0.0001	<0.0001
Insulin	6595 (27.1%)	446 (15.6%)	565 (23.4%)	<0.0001	<0.0001
Thiazolidinediones	4519 (18.7%)	304 (10.7%)	153 (6.3%)	<0.0001	<0.0001
Other antidiabetic agents	2093 (8.8%)	399 (14.1%)	676 (28.0%)	<0.0001	<0.0001
Fasting blood glucose (mg/dl)	144.9±52.2	153.1±59.1	145.8±47.2	<0.0001	0.0002

Data are mean±SD or number (%).
*Japan versus Asia (excluding Japan).
†Non-Asia versus Asia versus Japan.

than those patients recruited from Asia excluding Japan and from non-Asian regions. Fasting blood-sugar concentration was lowest in patients recruited from non-Asian regions followed by patients recruited from Japan and those who were recruited from Asia excluding Japan.

One-year outcomes

The all-cause and CV mortality at 1 year of 2.69% and 1.72% in patients recruited from non-Asian regions are equivalent to those for patients recruited from Asia excluding Japan of 2.34% to 1.62% but lower in patients recruited from Japan of 1.60% to 0.81%, respectively (p<0.01 in both comparison). As shown in figure 2, the CV death rate of patients recruited from Japan was approximately half that in patients recruited from Asia (excluding Japan) and non-Asian regions. The rates of non-fatal MI in Japan and in Asia (excluding Japan) were approximately 80% of the rate in patients recruited from non-Asian regions,

while the rate of non-fatal stroke was higher in patients recruited from Asia than those patients recruited from Japan or the non-Asian regions. The combined endpoint of CV death/MI/stroke/in patients recruited from Japan of 3.40% (95% CI 2.76 to 4.04, p<0.05) was significantly lower than that of patients recruited from Asia excluding Japan of 4.65% (95% CI 4.04 to 5.25) and from non-Asian regions of 4.38% (95% CI 4.20 to 4.56), respectively (p<0.05 for both comparisons). The rate of serious bleeding events requiring both hospitalisation and transfusion in patients recruited from Japan of 0.42% was lower than that of patients recruited from Asia excluding Japan of 0.71% and from non-Asian regions of 0.90%, respectively (p<0.01 for both comparison).

DISCUSSION

Our study is the first detailed Asian-focused substudy arising from the vast, international, contemporary REACH database of
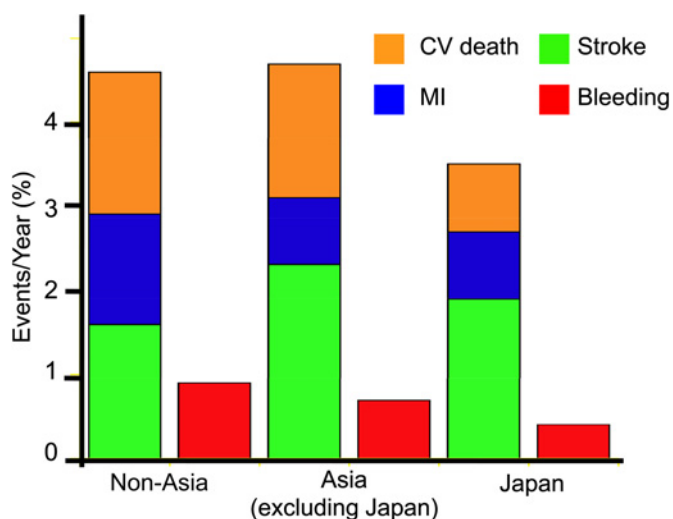
Figure 2 One-year cardiovascular and bleeding outcomes in patients recruited from Japan, Asia (excluding Japan) and from other regions of the world. CV, cardiovascular; MI, myocardial infarction.

patients with, or at high risk of, atherothrombosis. Our results have confirmed the finding of previous comparative, nation-specific cohort studies[7 13 27–29] and international case–control studies including the INTERHEART study,[2 8] Seven Country Study[10] and WHO Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) project[4 12] that the prevalence of CVD is higher in patients recruited from Asian countries at baseline than non-Asian regions. In accordance with the higher prevalence of CVD and lower prevalence of CAD in patients recruited from Asia, the annual incidence of CV death and non-fatal MI was lower in these patients than in those recruited from non-Asian regions. Of note, the rate of non-fatal stroke at 1 year in Japan was substantially lower than in the other Asian regions, although the prevalence of CVD was similar. This difference may be partly explained by the lower prevalence of DM, hypertension, hypercholesterolaemia and obesity, but not by use of drugs known to reduce the risk of atherothrombotic events such as antiplatelet agents or statins because their use in Japan is lower than Asia excluding Japan or in non-Asian regions. However, as shown in the previous WHO MONICA project,[12] further studies are necessary to clarify the quantitative contributions of the classical risk factors for future onset of stroke.

In the classical risk-factor profile, the markedly lower BMI and smaller waist circumference in patients recruited from Asia with higher prevalence of DM are notable. These results confirm previous findings that the reserve of insulin secretion in Asian patients (especially South Asian patients) is lower than in non-Asian patients.[30 31] As metabolic syndrome is a known risk factor for type II diabetes, these data support the need for region-specific criteria for this syndrome.[32 33]

There were substantial differences in medication use in patients recruited from Asia (excluding Japan), Japan and non-Asian regions. In addition to lower usage of aspirin, the dose of aspirin chosen in Japan is lowest followed by Asia (excluding Japan) and non-Asian regions. One possible explanation for the less frequent use of aspirin in Asia is the relatively lower prevalence of CAD (the disease category in which the clinical benefit for aspirin is most evident).[34] The lower use of oral anticoagulants in patients with a history of atrial fibrillation[23] in patients recruited from Asia (excluding Japan) is notable, but the reason

remains to be elucidated. Less frequent use of lipid-lowering agents and statins with a lower rate of MI and CV death in Asia despite higher serum cholesterol levels (especially in Japan) might also be explained by a lower prevalence of CAD in Asia. There are substantial differences in the use of antihypertensive agents, especially in Japan, such that the use of calcium-channel blockers was markedly higher, possibly because of a genetic deficiency in endothelial NO synthase[35] and a concomitant higher prevalence of vasospastic angina in Asia (especially Japan).[36]

The markedly lower rates of CV death, non-fatal stroke, the combined endpoint of CV death/MI/stroke and bleeding in Japan compared with Asia (excluding Japan) were notable, but the reason for these differences cannot be clarified in this study. These intraregional differences cannot be explained by either a predominance of CVD or extent of risk-factor control. The nationwide, homogeneous medical insurance system, patients' free access to experts without the need for referrals from general practitioners[37] and specific lifestyle factors such as the eating of raw fish containing omega-3 fatty acid,[38] may be contributory factors. The identification of factors that contribute to lower CV and bleeding events in Japan may be important for other regions of the world in the future.

We attempted to reduce inclusion bias by selecting physicians (comprising cardiologists, neurologists, general practitioners, etc) who reflected real-world practice in each country, but there remains the possibility of recruitment bias.

In conclusion, this substudy of the large, international REACH Registry provides specific characteristics of risk-factor profiles, medication use, risk-factor control, and CV and bleeding outcomes in patients recruited from Asian countries as compared with those recruited from non-Asian regions. This information is important in designing future international clinical trials that include substantial numbers of patients from Asian countries.

REFERENCES

1. **Parikh NI,** Pencina MJ, Wang TJ, et al. A risk score for predicting near-term incidence of hypertension: the Framingham Heart Study. *Ann Intern Med* 2008;**148**:102—10.
2. **Iqbal R,** Anand S, Ounpuu S, et al. Dietary patterns and the risk of acute myocardial infarction in 52 countries: results of the INTERHEART study. *Circulation* 2008;**118**:1929—37.
3. **McGorrian C,** Yusuf S, Islam S, et al. Estimating modifiable coronary heart disease risk in multiple regions of the world: the INTERHEART Modifiable Risk Score. *Eur Heart J* 2010;**32**:581—9.
4. **Tunstall-Pedoe H,** Kuulasmaa K, Mahonen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999;**353**:1547—57.
5. **McQueen MJ,** Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case—control study. *Lancet* 2008;**372**:224—33.
6. **Yusuf S,** Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case—control study. *Lancet* 2004;**364**:937—52.
7. **Kiyohara Y,** Kubo M, Kato I, et al. Ten-year prognosis of stroke and risk factors for death in a Japanese community: the Hisayama study. *Stroke* 2003;**34**:2343—7.
8. **Rosengren A,** Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case—control study. *Lancet* 2004;**364**:953—62.
9. **Teo KK,** Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case—control study. *Lancet* 2006;**368**:647—58.
10. **Verschuren WM,** Jacobs DR, Bloemberg BP, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. *JAMA* 1995;**274**:131—6.
11. **Kubo M,** Kiyohara Y, Kato I, et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. *Stroke* 2003;**34**:2349—54.
12. **Stegmayr B,** Asplund K, Kuulasmaa K, et al. Stroke incidence and mortality correlated to stroke risk factors in the WHO MONICA Project. An ecological study of 18 populations. *Stroke* 1997;**28**:1367—74.
13. **Goto S.** Cardiovascular risk factors in patients at high risk of atherothrombosis: what can be learned from registries? *Thromb Haemost* 2008;**100**:611—13.
14. **Jun ZJ,** Ping T, Lei Y, et al. Prevalence of factor V Leiden and prothrombin G20210A mutations in Chinese patients with deep venous thrombosis and pulmonary embolism. *Clin Lab Haematol* 2006;**28**:111—16.
15. **Ozawa T,** Niiya K, Sakuragawa N. Absence of factor V Leiden in the Japanese. *Thromb Res* 1996;**81**:595—6.
16. **Robertson TL,** Kato H, Rhoads GG, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Incidence of myocardial infarction and death from coronary heart disease. *Am J Cardiol* 1977;**39**:239—43.
17. **Ohman EM,** Bhatt DL, Steg PG, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events—study design. *Am Heart J* 2006;**151**:786.e1—10.
18. **Bhatt DL,** Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;**295**:180—9.
19. **Steg PG,** Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007;**297**:1197—206.
20. **Alberts MJ,** Bhatt DL, Mas JL, et al. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur Heart J* 2009;**30**:2318—26.
21. **Bhatt DL,** Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010;**304**:1350—7.
22. **Cacoub PP,** Abola MT, Baumgartner I, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis* 2009;**204**:e86—92.
23. **Goto S,** Bhatt DL, Rother J, et al. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J* 2008;**156**:855—63, 63 e2.
24. **Mehta RH,** Bhatt DL, Steg PG, et al. Modifiable risk factors control and its relationship with 1 year outcomes after coronary artery bypass surgery: insights from the REACH registry. *Eur Heart J* 2008;**29**:3052—60.
25. **Rother J,** Alberts MJ, Touze E, et al. Risk factor profile and management of cerebrovascular patients in the REACH Registry. *Cerebrovasc Dis* 2008;**25**:366—74.
26. **Wang TD,** Goto S, Bhatt DL, et al. Ethnic differences in the relationships of anthropometric measures to metabolic risk factors in Asian patients at risk of atherothrombosis: results from the REduction of Atherothrombosis for Continued Health (REACH) Registry. *Metabolism* 2010;**59**:400—8.
27. **Ueda K,** Hasuo Y, Kiyohara Y, et al. Intracerebral hemorrhage in a Japanese community, Hisayama: incidence, changing pattern during long-term follow-up, and related factors. *Stroke* 1988;**19**:48—52.
28. **Scheltens T,** Verschuren WM, Boshuizen HC, et al. Estimation of cardiovascular risk: a comparison between the Framingham and the SCORE model in people under 60 years of age. *Eur J Cardiovasc Prev Rehabil* 2008;**15**:562—6.
29. **Suka M,** Sugimori H, Yoshida K. Validity of the Framingham risk model applied to Japanese men. *Methods Inf Med* 2002;**41**:213—15.
30. **Abate N,** Chandalia M. The impact of ethnicity on type 2 diabetes. *J Diabetes Complications* 2003;**17**:39—58.
31. **Chandalia M,** Lin P, Seenivasan T, et al. Insulin resistance and body fat distribution in South Asian men compared to Caucasian men. *PLoS One* 2007;**2**:e812.
32. **Lee CM,** Huxley RR, Woodward M, et al. Comparisons of metabolic syndrome definitions in four populations of the Asia-Pacific region. *Metab Syndr Relat Disord* 2008;**6**:37—46.
33. **Patel A,** Huang KC, Janus ED, et al. Is a single definition of the metabolic syndrome appropriate?—a comparative study of the USA and Asia. *Atherosclerosis* 2006;**184**:225—32.
34. **Antithrombotic Trialists' Collaboration.** Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71—86.
35. **Yoshimura M,** Yasue H, Nakayama M, et al. A missense Glu298Asp variant in the endothelial nitric oxide synthase gene is associated with coronary spasm in the Japanese. *Hum Genet* 1998;**103**:65—9.
36. **Beltrame JF,** Sasayama S, Maseri A. Racial heterogeneity in coronary artery vasomotor reactivity: differences between Japanese and Caucasian patients. *J Am Coll Cardiol* 1999;**33**:1442—52.
37. **Chan JC,** Gagliardino JJ, Baik SH, et al. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). *Diabetes Care* 2009;**32**:227—33.
38. **Hoy SM,** Keating GM. Omega-3 ethylester concentrate: a review of its use in secondary prevention post-myocardial infarction and the treatment of hypertriglyceridaemia. *Drugs* 2009;**69**:1077—105.

APPENDIX 1

REACH registry executive committee: DL Bhatt, VA Boston Healthcare System and Brigham and Women's Hospital, Boston, Massachusetts, USA (chair); PG Steg, Hôpital Bichat-Claude Bernard, Paris, France (chair); EM Ohman, Duke University Medical Center, Durham, North Carolina, USA; J Röther, Klinikum Minden, Minden, Germany; PW Wilson, Emory University School of Medicine, Atlanta, Georgia, USA.

REACH registry global publication committee: MJ Alberts, Northwestern University Medical School, Chicago, USA; DL Bhatt, VA Boston Healthcare System and Brigham and Women's Hospital, Boston, Massachusetts, USA (chair); R D'Agostino, Boston University, Boston, Massachusetts, USA; K Eagle, University of Michigan, Ann Arbor, Michigan, USA; S Goto, Tokai University School of Medicine, Isehara, Kanagawa, Japan; AT Hirsch, University of Minnesota School of Public Health and Minneapolis Heart Institute Foundation, Minneapolis, Minnesota, USA; C-S Liau, Taiwan University Hospital and College of Medicine, Taipei, Taiwan; J-L Mas, Centre Raymond Garcin, Paris, France; EM Ohman, Duke University Medical Center, Durham, North Carolina, USA; J Röther, Klinikum Minden, Minden, Germany; SC Smith, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; PG Steg, Hôpital Bichat-Claude Bernard, Paris, France (chair); PWF Wilson, Emory University School of Medicine, Atlanta, Georgia, USA.