

Four-year Clinical Outcomes of Filipino Patients with or at Risk for Atherothrombotic Events from the REACH Registry

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Abstract

Introduction: Patients with established atherothrombotic disease (EAD) or those with only atherothrombotic risk factors are at high risk for cardiovascular events and death. There are scant data on the clinical profile of stable Filipino patients with or at risk for atherothrombosis and their long-term outcomes. The authors' objective is to present the baseline clinical profile and four-year cardiovascular outcomes in Filipino outpatients with EAD and those with multiple atherothrombotic risk factors in comparison to the Asian and Global populations

Methods: The Reduction of Atherothrombosis for Continued Health (REACH) registry is an international, prospective cohort of 68,236 patients aged at least 45 years old with either EAD or at least three atherothrombotic risk factors enrolled from 44 countries in 2003-2004. The Philippine cohort consists of 1040 outpatients with EAD (N=913) or at least three atherothrombotic risk factors (N=127) consecutively enrolled and followed up for at least one to four years for the occurrence of cardiovascular death (CVD), myocardial infarction (MI) and stroke.

Results: Nine hundred fifty-five Filipino outpatients (96)% completed the four-year follow-up. Mean age is 65.5 years

with similar sex distribution. Common risk factors included diabetes (46%), hypertension (87.4%), hypercholesterolemia (62.9%), and smoking history (29.7%). Ninety-two percent had EAD-- 43% with coronary artery disease, 45% with cerebrovascular disease (CVD) and four percent with peripheral artery disease (PAD). The combined primary endpoint of CVD/MI/stroke was 14.7%, but higher (19.8%) among those with polyvascular disease. Cerebrovascular disease (CVD) patients had the highest CVD/MI/stroke rates (17.6%); PAD patients had the highest CVD/MI/stroke and hospitalization rate (33.2%). Baseline medication usage is 81.1% for antiplatelet agents, 62.6% for statins and 69% for angiotensin-converting enzyme inhibitor/angiotensin receptor blocker but four-year follow-up medication usage rates were lower.

Conclusion: Filipino outpatients with or at risk for atherothrombosis experienced high long-term rates of CV events. This is the first report of long-term cardiovascular outcomes of stable Filipino outpatients with this high-risk profile.

Keywords: atherothrombotic disease, atherothrombosis, REACH Registry,

Introduction

Atherothrombosis results from atherosclerosis complicated by platelet-rich thrombus formation involving multiple vascular beds. This may present as coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral arterial disease (PAD) and its life- and limb-threatening complications of acute coronary syndrome, acute ischemic stroke and acute limb ischemia. Atherothrombosis remains as a leading cause of death globally and across different ethnic groups. In 2012, the World Health Organization (WHO) reported ischemic heart

disease (IHD) and stroke to be the overall top two leading causes of death globally (13.2% and 11.9%, respectively) and among the lower-middle to high income countries; lower-respiratory infections, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and diarrheal diseases top the list of causes of mortality in the low-income countries, but still followed by IHD and stroke.¹

The large multinational Reduction of Atherothrombosis for Continued Health (REACH) registry documented high rates of recurrent vascular events at three years in patients with symptomatic vascular disease.² For the composite endpoint of nonfatal myocardial infarction (MI), nonfatal stroke or vascular death, the one-year and three-year event rates were 4.7 and 12.0%, respectively, while for patients enrolled with atherosclerosis risk factors only, the one and three-year event rates for MI/stroke/vascular death were 2.3 and 6.0%, respectively.² A four-year analysis of REACH registry patients showed that among patients with atherothrombosis,

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those with a prior history of ischemic events at baseline had the highest rate of subsequent ischemic events (18.3%; 95% confidence interval (CI), 17.4%-19.1%).³

Ethnicity has been shown to be an independent predictor of various major adverse cardiovascular events.⁴ In a substudy analysis of the REACH registry, this time on patients recruited from the Asian region (N = 10,692), there is a higher prevalence of CVD and diabetes mellitus with lower body mass index compared to those from non-Asian regions. The one-year cardiovascular event rates were similar in patients from Asian and non-Asian regions but significantly lower in patients recruited from Japan.⁵ At two-year follow-up of REACH registry patients of various ethnic groups, cardiovascular death rate was significantly higher in Black patients compared with all other ethnic groups while cardiovascular death rates were significantly lower in all three Asian ethnic subgroups (East Asian, South Asian and other Asian subgroups which included Filipino patients).⁶

The Philippines is classified as one of the lower-middle income countries by the WHO and, as of their 2012 survey, IHD is the leading cause of death (15.4%) followed by stroke (11.1%), while diabetes mellitus (5.9%) and hypertensive heart disease (3.7%) are ranked fourth and fifth. Compared to 2000 data, these figures have remained the same for IHD but increased in the last decade for stroke, diabetes and hypertensive heart disease.¹ (WHO) The first Philippine National Nutritional Health Survey (NNHeS I, N = 4753) done in 2003 reported that the national prevalence rates of CAD based on previous diagnosis and angina questionnaire were 1.8% and 12.5%, respectively, prevalence rates of CVD based on previous diagnosis and stroke questionnaire as 1.4% and 1.9% respectively, and prevalence of peripheral artery disease based on previous diagnosis, claudication questionnaire and ankle-brachial index (ABI) as 0.4%, 4.2% and 5%, respectively.⁷ The second National Nutritional Health Survey (NNHeS II, N = 7700) done in 2008 reported that the overall age-adjusted prevalence rates of CAD, CVD, and PAD based on previous diagnosis indicated in interview questionnaires performed by medical personnel in 2003 were 1.1%, 1.4%, and 0.6% respectively and 1.1%, 0.9%, and 1.1% respectively.⁸

To date, there is no large prospective study of Filipino patients with or at risk for atherothrombosis that has been reported in Philippine literature. Knowing the natural history, risk factors and treatment of people with atherosclerosis risk factors and atherothrombotic events is of paramount importance to help determine measures to reduce mortality due to IHD and stroke and other vascular diseases. Our study aims to report the demographic and risk factor profile and four-year cardiovascular outcomes of stable Filipino outpatients with established atherothrombosis or only atherosclerosis risk factors enrolled in the REACH registry.

Methods

The REACH registry is an international, prospective, observational registry which enrolled 68,375 patients at baseline of which 45,227 patients had four-year outcomes. The Philippines was one of the countries where 1,040 patients were initially enrolled and 995 had four-year follow-up data. The design, including the strategy for selecting physicians, follow-up, ensuring data quality, and the baseline description of the REACH registry has been previously published.⁹⁻¹¹ This protocol was submitted to institutional review boards in each country according to the local requirements and signed informed consent was required for all patients. Consecutive outpatients aged ≥ 45 years with established CAD, CVD and/or PAD, or $\geq$ three atherothrombotic risk factors ("multiple risk factors only") were enrolled by their physicians over an initial seventh-month recruitment period on a worldwide basis between December 2003 and June 2004. Due to regulatory requirements in Japan, enrollment in that country was delayed and occurred between August 2004 and December 2004. The multiple risk factors category consisted of diabetes, diabetic nephropathy, ABI less than 0.9, asymptomatic carotid stenosis of 70% or more, carotid intima media thickness at least two times that at adjacent sites, systolic blood pressure of 150 mm Hg or higher despite treatment, hypercholesterolemia treated with medication, current smoking of 15 or more cigarettes per day, and age 65 years and older for men or 70 years and older for women. Documented CAD consisted of one or more of the following: stable angina, history of unstable angina, history of percutaneous coronary intervention, history of CABG, or previous MI. Documented CVD consisted of a neurologist report or hospital report with the diagnosis of ischemic stroke or transient ischemic attack (TIA). Documented peripheral artery disease consisted of current intermittent claudication with ABI of less than 0.9 and/or a history of intermittent claudication together with a previous intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass grafting, or other vascular interventions, including amputations. Diabetes was defined as any history of diabetes or current diabetes (diagnosed by at least two fasting blood glucose measures >126 mg/dL treated with medication, lifestyle, or both).

Follow-up

Detailed information was collected at baseline, with subsequent annual follow-up at one, two, three, and four years. Patients were enrolled between 2003 and 2004 and followed up until 2008. Final database lock was in April 2009. The initial follow-up was planned for up to two years and shortly before that point, an additional two-year extension was proposed. Not all countries and sites that were in the two-year follow-up cohort chose to continue participation in the registry, largely for financial reasons,

although the majority did decide to continue. Countries and sites that decided not to participate in the four-year follow-up were excluded from the results. Event rates of cardio-vascular death, MI, stroke, and cardiovascular hospitalization were calculated. The primary endpoint was the cardiovascular death/MI/stroke while secondary endpoints included the individual endpoints of all-cause mortality, cardiovascular death, nonfatal MI, nonfatal stroke, and the combined endpoint of the cardiovascular death/MI/stroke plus hospitalization for atherothrombotic events. Endpoints were not adjudicated. Cardiovascular death included fatal stroke, fatal MI, or other cardiovascular death. Other cardiovascular death included other deaths of cardiac origin; pulmonary embolism; any sudden death including unobserved and unexpected death (eg, death while sleeping) unless proven otherwise by autopsy; death following a vascular operation, vascular procedure, or amputation; death attributed to heart failure; death following a visceral or limb infarction; and any other death that could not be definitely attributed to a nonvascular cause or hemorrhage. Any MI or stroke followed by a death whatever the cause in the next 28 days was considered to be a fatal MI or fatal stroke. Cardiovascular hospitalization consisted of hospitalization for unstable angina, transient ischemic attack, worsening of claudication related to peripheral artery disease, other ischemic arterial event, CABG, coronary angioplasty/stenting, carotid surgery, carotid angioplasty/stenting, amputation affecting lower limbs, peripheral bypass graft, or angioplasty/stenting for peripheral artery disease. Groups based on the enrollment criteria of multiple atherosclerosis risk factors only (ROF) and stable established atherothrombotic disease (EAD) were compared. Polyvascular disease was defined as having atherothrombosis in two or three arterial beds (coronary, peripheral, cerebrovascular) at baseline.

Our study reports on the demographics, risk factor profile, and preventive medications taken by 995 Filipino patients enrolled in the REACH registry at baseline and the major cardiovascular outcomes at four-year follow-up.

Baseline Demographic Characteristics and Risk Factors

Data were collected centrally with the use of a standardized international case report form, completed at the study visit. Baseline seated systolic and diastolic blood pressure, and available fasting glucose and cholesterol levels were obtained. Subjects were considered to be "overweight" if their BMI was 25-29 kg/m² or "obese" if their BMI was ≥ 30 kg/m². Current smoking was defined as ≥ 15 cigarettes per day on average within the past month before enrollment; former smoking was defined as stopping smoking less than a month before enrollment. Weight, current smoking status, and chronic medications used at baseline were recorded. Employment status was described by whether

patients were still employed, or already unemployed, retired or incapacitated for work. Key outcome events as described above were likewise centrally recorded but were not adjudicated.

Statistical Analysis

Continuous variables are expressed as mean (standard deviation), and categorical variables are expressed as frequencies and percentages. Event rates are reported as annualized event rates. Cumulative incidence rates are reported after adjustment for age and sex using the corrected group prognosis method in the Cox proportional hazards model. Only patients with complete outcome and covariate information for a given end point were included in calculating the rates for that end point. Statistical significance was considered as a two-sided probability of less than .05. Statistical analyses were performed using SAS version 9 (SAS Institute, Cary, North Carolina).

Results

There were 1040 patients enrolled at baseline from outpatient clinics of 91 participating investigators--49 internists (53.9%), 26 neurologists (28.6%), eight cardiologists (8.8%), seven endocrinologists (7.7%) and one general surgeon (1.1%). Geographical representation of the patient population was determined by the practice base location of their physicians-- 79% from Luzon region, eighteen percent from Visayas region, and the remaining three percent from the Mindanao region. There were 913 patients with EAD or the symptomatic group (87.8%) and 127 with risk factors only (12.2%). Table I shows the distribution of patients to the different subgroups. Sixty-one percent of Filipino patients presented with any CVD, 48.7% with any CAD and 7.1% with any PAD. Forty-one percent of Filipino patients had CVD only, 31% with CAD only, and 1.8% with PAD only. Polyvascular disease was reported in 12.4% of the total population.

Mean age was 65.5 years (SD = 10.37), with virtually equal distribution to both genders. There were 46.2% with diabetes, 87.4% with hypertension, 62% with hypercholesterolemia, 7.4% with BMI > 30 , 30.4% who are former or current smokers. There were 43.4% with documented CAD, 15.5% with a prior MI and 11.4% with prior coronary revascularization-- percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), 53.2% had documented stroke and/or transient ischemic attack, and four percent with documented PAD, 0.7% with prior peripheral angioplasty/stenting/surgery (Table II). Majority of the patients at baseline were on at least one antiplatelet agent (81.1%), statin therapy (62.6%) and an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (69.2%) (Table III). However, at four-year follow-up, there were lower usage rates of at least one antiplatelet therapy (72.6%) and an ACE inhibitor

Table I. Distribution of filipino patients in the reach registry to subgroup according to atherothrombotic risk or vascular bed involvement

Population	N (%)
Global	1040 (100%)
Risk factors only	127 (12.2%)
Symptomatic	913 (87.8%)
CAD only	322 (31.0%)
CVD only	431 (41.4%)
PAD only	19 (1.8%)
CAD+CVD	95 (9.1%)
CAD+PAD	16 (1.5%)
CVD+PAD	18 (1.7%)
CAD+CVD+PAD	12 (1.2%)
CAD * among symptomatic	445 (48.7%)
CVD * among symptomatic	556 (60.9%)
PAD * among symptomatic	65 (7.1%)

* Patients can present more than one location of the disease

or Angiotensin receptor blocker (37.2%), with similar usage rate of statins (62.3%).

For four-year follow-up analysis, there were 995 patients who had at least one follow-up visit; 874 had EAD (87.8%) and 121 (12.2%) with risk factors only. During the follow-up interval, the primary endpoint of CVD/MI/stroke occurred in 14.7% in the total population, with an almost two-fold higher rate among patients with EAD (21%, CI 95% 16.1%-25.6%) compared to those with multiple risk factors only (12.7%, CI 95% 5.4-19.4%), p value = 0.02 (Table IV). Patients with CVD had the highest rates of CVD/MI/stroke (17.6%, CI 95% 12.1%-22.7%) compared to that of CAD patients (14.5%, CI 95% 9.4%-19.4%) and PAD patients (12.6%, CI 95% 1.3%-22.5%). (Table IV) The latter also had the highest rates of CVD/MI/stroke/ hospitalization for an atherothrombotic event (33.2%, CI 95% 14.5%-47.7%) followed by CAD patients (22.5%, CI 95% 16.6%-28%) and patients with CVD (20.8%, CI 95% 15.4%-25.8%). All-cause mortality rate was 13.9% (CI 95% 9.8%-17.8%), 78.4% of which were cardiovascular deaths (10.9%, CI 95% 7%-14.4%); these rates were similar between EAD and risk factors only groups. CAD patients had higher rates of nonfatal MI and those with CVD had higher rates of nonfatal stroke. Patients with polyvascular disease (12.4% of the total population) had higher rates of the primary endpoint CVD/MI/stroke (19.8%, CI 95% 11-27.7%), p -value = 0.00098, and of all secondary endpoints. (Table V)

Table VI shows the cardiovascular outcome rates from the first year to fourth year of follow-up. All event rates linearly increased throughout the four years of follow-up. Table VII reveals a comparison of major cardiovascular outcomes in the different geographical regions compared

Table II. Baseline profile of filipino patients in the REACH registry with four-year follow-up (N = 995)

Variable (Mean)	Patients SD (%)
Demographics	
Age	65.46 (10.37)
Men	492 (49.45 %)
Diabetes	460 (46.23%)
Hypertension	870 (87.44%)
Hypercholesterolemia	616 (61.91%)
Obesity (BMI>30)	72 (7.44%)
Former smoker	227 (23.28%)
Current smoker	69 (7.08%)
Never smoker	679 (69.64%)
Previous history of atherosclerotic disease	
Any history of symptomatic atherothrombosis	874 (87.8%)
History of CAD	432 (43.42%)
Stable angina with documented CAD	260 (26.34%)
Unstable angina with documented CAD	95 (9.71%)
History of MI	153 (15.50%)
History of PCI	44 (4.46%)
History of CABG	69 (6.98%)
History of CVD	529 (53.17%)
History of TIA	156 (15.95%)
History of Stroke	445 (45.13%)
History of PAD	40 (4.02%)
Claudication and ABI <0.9	35 (4.48%)
History of peripheral angioplasty/stenting/surgery	7 (0.70%)
Claudication and history of amputation	7 (0.70%)

Table III. Usage rate of preventive medications in filipino patients in the REACH registry at baseline and at four-year follow-up

Medication Use	Baseline N (%)	4-year Follow-up N (%)
At least one antiplatelet	807 (81.1%)	464 (72.61%)
Aspirin	524 (52.7%)	289 (45.23%)
Other antiplatelet agent	400 (40.2%)	210 (32.86%)
At least one lipid lowering agent	671 (67.4%)	422 (65.94%)
Statins	623 (62.6%)	398 (62.28%)
Other lipid lowering agents	64 (6.4%)	37 (5.83%)
ACE inhibitors	341 (34.3%)	142 (22.29%)
Angiotensin II receptor blockers	347 (34.98%)	228 (35.68%)
ACE inhibitor or Angiotensin II receptor blockers	689 (69.2%)	370 (37.18%)

Table IV. Four-year cardiovascular event rates for the total population and main subsets of Filipino patients in the REACH registry with four-year follow-up

Event	Total	Total EAD**	CAD	CVD	PAD	Multiple Risk Factor Only	p-value***
n	995	874	432	529	40	121	
CV death/MI/ stroke	14.66	15.43	14.52	17.61	12.65	8.97	0.03
CI 95%	10.39;18.69	10.91; 19.69	9.35; 19.36	12.10; 22.70	1.29; 22.54	1.99; 15.38	
All cause mortality	13.92	14.32	14.82	14.48	19.3	10.81	0.15
CI 95%	9.77; 17.82	9.98; 18.37	9.46; 19.77	9.64; 19.00	4.46; 31.36	3.31; 17.58	
CV death	10.88	11.06	11.95	11.61	13.04	9.23	0.29
CI 95%	7.09; 14.45	7.15; 14.74	6.92; 16.61	7.16; 15.76	1.15; 21.11	1.92; 15.83	
Non-fatal MI	1.08	1.22	2.21	NE	NE	NE	0.99
CI 95%	0.02; 2.28	0.03; 2.58	0.03; 4.68				
Non-fatal stroke	5.01	5.61	2.97	8.53	NE	NE	0.08
CI 95%	2.36; 7.58	2.64; 8.48	0.93; 4.96	3.99; 12.84			
CV death/MI/stroke or hospitalization for atherothrombotic event(s)	20.02	21.05	22.54	20.81	33.19	12.68	0.02
CI 95%	15.43; 24.35	16.19; 25.60	16.57; 28.05	15.40; 25.85	14.47; 47.70	5.41; 19.36	

*Calculated on the basis of the population of patients with non-missing outcomes and non-missing co-variables

** EAD: Established Atherothrombotic Disease

***p-value comparing Total EAD and Multiple Risk Factor Only

NE°:Event rates are non estimable (Number of event<5)

Adjusted on gender and age (using Cox model)

Table V. Major adverse cardiovascular events in Filipino patients in the REACH registry according to number of vascular disease bed location

Event	Total	Multiple Risk Factor Only	Established Atherothrombotic Disease			p-value
			1 location	2 locations	3 locations	
N	995	121	751	119	4	
CV death/MI/stroke	14.66	8.97	14.59	19.81	NE	0.00098
CI 95%	10.39-18.69	1.99-15.38	10.03-18.89	11.00-27.66		
All-cause mortality	13.92	10.81	13.76	16.84	NE	0.03145
CI 95%	9.77-17.82	3.31-17.58	9.35-17.89	8.67-24.11		
CV death	10.88	9.23	10.24	14.96	NE	0.01571
CI 95%	7.09-14.45	1.92-15.83	6.35-13.91	7.08-21.99		
Non-fatal MI	1.08	NE	0.94	NE	NE	0.00418
CI 95%	0.02-2.28		0.00-2.12			
Non-fatal stroke	5.01	NE	5.3	6.62	NE	0.00592
CI 95%	2.36-7.58		2.30-8.20			
CV death/MI/stroke or hospitalization for atherothrombotic event(s)	20.02	12.68	19.88	27.25	NE	0.00058
CI 95%	15.43-24.35	5.41-19.36	15.00-24.45	17.28-35.99		

*Calculated on the basis of the population of patients with non-missing outcomes and non-missing co-variables

NE°:Event rates are non estimable (Number of event<5)

Adjusted to gender and age (using Cox model)

to the Philippine cohort and that of the global population. The Eastern European population had the highest adverse cardiovascular event rates compared to the rest of the region, with CV death rates similar to that of the Philippine cohort. When compared to the overall Asian population, the Philippine population had higher CV death rates but similar cluster outcome rates.

Discussion

This global REACH registry population is a multinational diverse group of patients belonging to the wide spectrum of atherothrombotic risk and atherothrombotic disease that was prospectively followed up for at most four years. The Filipino cohort like the global population has approximately 90% with symptomatic or established atherothrombotic disease and the rest with multiple risk factors only. Sixty-one percent of Filipino patients presented with any CVD, 48.7% with any CAD and 7.1% with any PAD. The global REACH population, on the other hand, had 27.8% CVDs, 59.3% (CAD) and 12.2% (PAD), respectively.⁵ The Asian subgroup had 41% with CVD, 48.6% with CAD, and 8.5% with PAD.¹⁰ The higher prevalence of CVD as index event of Filipino patients in the REACH registry and the higher occurrence rate of nonfatal strokes among patients with CVD are consistent with observed higher rates of CVD, mainly strokes, in Asians, particularly those living perhaps in rural areas. Nonfatal stroke rates were more than two-fold greater among Chinese residing in mainland China compared to East Asians living in North America enrolled in the REACH registry, presumably related to the higher salt intake in mainland China.¹² Hypertension has been reported to be the strongest risk factor for both primary and recurrent stroke.¹²

Of note in the demographic and risk factor profile is the virtually equal distribution of patients to both sexes (49.4% males), with unexpectedly more females compared

to that of the global population with 63.7% male and that of the Asian subgroup with 67% male distribution.^{5,10} The Filipino cohort is also slightly younger (mean age of 65.5 years) compared to 68.5 years in the global cohort and 67.5 years in the Asian cohort. There is a higher prevalence of diabetes (46.2%) and hypertension (87.4%) in the Filipino cohort compared to that of the global cohort (44.3% and 81.8% respectively) and the Asian cohort with a lower rate of hypertension (75.2%).¹⁰ There are fewer Filipino patients with hypercholesterolemia (61.9%) compared to the global cohort (72.4%) but higher than that of the Asian cohort (54.2%). There are fewer Filipino patients who are current smokers (7.1%) compared to the global and Asian cohorts

Table VI. Annual rates of major adverse cardiovascular events in Filipino patients in the REACH registry

Outcome	one-year follow-up	two-year follow-up	three-year follow-up	four-year follow-up
N	804	859	869	874
All cause mortality	4.72	6.95	11.87	14.3
CI 95%		4.01-9.78	7.93-15.58	9.9-18.4
Major CV event				
CV death	3.15	5	9.27	11.06
CI 95%		2.46-7.45	5.69-12.66	7.15-14.74
Non-fatal MI	0.12	0.7	1.43	1.22
CI 95%		0.00 -1.73	0.02-3.02	0.03-2.58
Non-fatal stroke	3.95	4.26	4.55	5.61
CI 95%		1.86 - 6.61	2.09-6.94	2.64-8.48
CV death/MI/stroke	7	9.63	13.27	15.43
CI 95%		6.12-12.99	9.09-17.21	10.91-19.69
CV death/MI/stroke or hospitalization for atherothrombotic event(s)	11.68	14.19	19	21.05
CI 95%		10.30-17.90	14.36-23.38	16.19-25.60

Table VII. Three-year outcomes of patients from the different geographical regions compared to the Philippine and global populations*

Outcome	North America	Latin America	Western Europe	Eastern Europe	Middle East	Australia	Asia (including Philippines)	Japan	Philippines	Global
N	11604	1206	12218	4326	392	2551	3144	4234	869	39675
CV death	6.02	7.61	5.79	9.03	5.61	2.70	5.61	2.42	9.27	5.57
95% CI	8.97-10.61	9.47-13.47	8.53-9.96	10.36-12.97	5.08-10.53	5.80-7.90	8.51-11.16	4.47-5.94	5.69-12.66	5.15-5.99
CV death/MI/stroke	11.99	13.65	11.85	17.99	13.25	7.57	13.13	8.63	13.27	11.96
95% CI	11.08-12.90	11.46-15.77	11.06-12.64	16.47-19.47	9.70-16.44	6.44-8.69	11.68-14.56	7.67-9.58	9.09-17.21	11.37-12.54
CV death/MI/stroke or hospitalization for atherothrombotic event(s)	29.27	25.83	30.69	39.58	30.45	23.51	23.03	17.34	19	28.39
95% CI	28.09-30.43	23.24-28.32	29.62-31.75	37.90-41.21	25.85-34.77	21.68-25.29	21.38-26.44	16.10-18.56	14.36-23.38	27.62-29.16

*Adapted from Alberts, et al.²

(15.3% and 14.7%, respectively).^{5,10}

On follow-up, approximately one in seven patients (14.7%) in the stable population with established atherothrombotic disease had a major event (CV death, MI, stroke). There was an almost two-fold increase in major cardiac events (CVD/MI/stroke) suffered by patients with established disease compared to those with risk factors only. Cerebrovascular disease (CVD) patients had a higher rate of CVD/MI/stroke (17.6%) and incident recurrent nonfatal strokes compared to CAD and PAD patients. This is most likely related to the higher prevalence of hypertension in the Filipino cohort. Compared to the global and Asian cohorts, there were much higher rates of CVD in the Filipino cohort.^{5,10} This should alert the local health officials to not only monitor the higher rates of CVD but the increasing rates of adverse cardiovascular outcomes of CVD/MI/stroke among patients with CVD, especially, with the observed increasing prevalence of hypertension reported in the National Nutritional Health Surveys of 2003, 2008, and 2013.^{7,8,13}

However, one in three PAD patients (33.2%) had a major event or was hospitalized in this period of observation, yielding the highest rates of CVD/MI/stroke or hospitalization compared to those with CAD or CVD probably due to higher rates of hospitalization for an atherothrombotic event. Our findings are consistent with the reported event rates in the overall global REACH registry population.^{2-6,11-12} Although there is a low prevalence of PAD in the REACH registry global, Asian and Filipino cohorts, there were higher rates of adverse outcomes among PAD patients with polyvascular disease. PAD patients are underrecognized and undertreated and efforts to achieve early recognition and appropriate treatment of these PAD patients will contribute to the reduction of adverse cardiovascular outcomes.¹⁴

There was a linear increase in event rates throughout the four-year follow-up period. (Table V) This may be related to the lower usage rates of preventive medications like antiplatelet therapy, statins and ACE inhibitors/angiotensin II receptor blockers at four-year follow-up which was reported in the Filipino cohort. However, when compared to the Japanese cohort which had lower rates of antiplatelet therapy and statins but lower prevalence rates of hypertension, diabetes and hypercholesterolemia, their adverse event rates are also much lower than the other Asians enrolled in the REACH registry.³ Although reasons for this lower usage rate of preventive therapy were not determined, it is interesting to note that over 70% of these Filipino patients are being managed by internists, and the rest by neurologists. This lower usage rate may also result from lower treatment compliance rates due to financial constraints but this health information was not collected in this study.

When compared to the different geographical regions,

the Eastern European population had the highest adverse cardiovascular event rates compared to the rest of the regions; this could only be partially explained by higher prevalence rate of risk factors, i.e. 85% of symptomatic patients had hypertension, but >97% of these hypertensive patients were on at least one antihypertensive therapy.² The Philippine cohort had cardiovascular death rates similar to that of the Eastern European population but had much lower rates of the cluster outcomes of CV death/MI/stroke or hospitalization for atherothrombotic events. Compared to the overall Asian population and to the Japanese cohort, CV death rates in the Filipino cohort were higher while cluster outcome rates of CV death/MI/stroke, and that which included hospitalization for atherothrombotic events were similar, most probably reflecting the contribution of recurrent stroke events among patients with index stroke events and attendant rehospitalization. This could also be related to the higher prevalence rates of hypertension in the Filipino population compared to their Asian neighbors. This observation underscores the need for the National Health Agenda to prioritize measures addressing the early diagnosis, optimal treatment and effective control of hypertension and other atherothrombotic risk factors.

Limitations

Inherent to nonpopulation-based registry studies is the potential patient recruitment bias and the lack of adjudication of endpoints which may affect estimates of prevalence and incidence rates. Investigators were asked to recruit consecutively patients from their outpatient clinics but there was no systematic enlistment of patients. Reasons for medication use or non-use were not recorded systematically. There was an effort to enlist use of herbal medications and other supplements which may have replaced the appropriate medications to be taken but the reported numbers were low. There were also more investigators and hence, patients, recruited from the Luzon island compared to the other regions as a function of accessibility to study follow-up provided by the sponsor. There was an attempt to reduce recruitment bias by inviting physicians from various clinical specialties.

Conclusion

Data from this multiregional cohort of Filipino patients with or at risk for atherothrombosis confirm the high risk for developing adverse cardiovascular outcomes as early as one to four years of follow-up. Compared to the global population and even to other Asian countries, the Filipino cohort had higher prevalence rates of diabetes and hypertension and more patients with baseline CVD who, in turn, developed higher rates of adverse cardiovascular outcomes. Moreover, usage rate of optimal medical therapy to prevent adverse outcomes were comparatively lower

than those patients from other Asian countries and the rest of the global population. Efforts at controlling risk factors, especially hypertension, may contribute to the reduction of adverse events and deaths. More attention directed to early detection and more effective control of diabetes and hypertension, and use of secondary prevention measures of patients with CVD and peripheral artery disease by their physicians may also improve cardiovascular prognosis in these subgroups. To our knowledge, this is the first prospective study on the demographics, risk factor profile and adverse outcomes of a large number of Filipino patients with or at high risk for atherothrombosis.

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