

Risk Factor Profile and Treatment Patterns of Patients with Atherothrombosis in Singapore: Insight from the REACH Registry

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Abstract

Introduction: Atherothrombosis is the leading cause of cardiovascular mortality. The Reduction of Atherothrombosis for Continued Health (REACH) Registry provided information on atherosclerosis risk factors and treatment. Singapore was one of the 44 participating countries in the REACH Registry. The objective of this study was to determine the atherosclerosis risk factor profile and treatment patterns in Singapore patients enrolled in the REACH Registry. **Materials and Methods:** The REACH Registry is an international prospective observational registry of subjects with or at risk for atherothrombosis. Patients aged 45 years or older with established vascular disease [coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral arterial disease (PAD)] or 3 or more atherosclerosis risk factors were recruited between 2003 and 2004. **Results:** A total of 881 patients (64.4% male) were recruited in Singapore by 63 physicians. The mean age was 64 ± 9.8 years (range, 45 to 95). Seven hundred and one (79.6%) patients were symptomatic (CAD 430, CVD 321, PAD 72) while 180 (20.4%) patients had ≥ 3 risk factors. Approximately 13% of symptomatic patients had symptomatic polyvascular disease. There was a high proportion of diabetes mellitus (57%), hypertension (80.6%) and hypercholesterolemia (80.1%). A substantial proportion of symptomatic patients were current smokers (14.1%). Approximately half of the patients were either overweight or obese [abdominal obesity, 54.3%; body mass index (BMI) 23-27.5, 45.9%; BMI ≥ 27.5 , 23.3%]. Patients were undertreated with antiplatelet agents (71.9% overall; range, 23.9% for ≥ 3 risk factors to 84.7% for PAD) and statins (76.2% overall; range, 73.6% for PAD to 82.1% for CAD). Risk factors remained suboptimally controlled with a significant proportion of patients with elevated blood pressure (59.4% for ≥ 3 risk factors and 48.6% for symptomatic patients), elevated cholesterol (40% for ≥ 3 risk factors and 24.4% for symptomatic patients) and elevated blood glucose (45% for ≥ 3 risk factors and 19.8% for symptomatic patients). **Conclusion:** Established atherosclerosis risk factors are common in Singapore patients in the REACH Registry; and obesity is a major problem. Most of these risk factors remained suboptimally controlled.

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Key words: Obesity, Undertreatment, Vascular disease

Introduction

Atherothrombosis is a global problem that affects every ethnic group. It can lead to ischemic stroke, myocardial infarction or vascular death.^{1,2} Patients with previous manifestations of atherothrombosis are at risk for recurrent

events in the same vascular territory as well as in other vascular beds.³⁻⁶ Thus, a patient with a previous myocardial infarction is not only at increased risk for another myocardial infarction, but also stroke or transient ischemic attack.

The disease burden and long-term prognosis of

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atherothrombosis can be gleaned from randomised controlled trials, meta-analyses on drug treatment⁷⁻¹¹ or observational studies and disease registries.¹²⁻¹⁵ Due to their strict inclusion and exclusion criteria, randomised controlled trials do not accurately reflect the true disease burden and long term prognosis of atherothrombosis. Observational studies and disease registries do not evaluate the entire population at risk for atherothrombotic events, only focusing on one manifestation of the disease, e.g acute coronary syndrome or are restricted to a particular region or country.

The Reduction of Atherothrombosis for Continued Health (REACH) is a prospective long term study in the real-life setting covering the entire spectrum of stable atherothrombotic syndromes: including those who are asymptomatic but have risk factors for atherothrombosis to those with established disease.¹⁶ This article presents the baseline characteristics of the Singapore patients in the REACH Registry.

Materials and Methods

The REACH Registry is an international prospective observational registry with long-term follow up of subjects at risk for atherothrombotic events. The design of the REACH Registry has been previously published.¹⁶ Briefly, the primary objective is to evaluate the long-term risk of atherothrombotic events in the global population and in different population subgroups. It also aims to compare outcomes within different subject profiles in order to evaluate the importance of cross risk of subjects at risk, and define predictors of risk for subsequent atherothrombotic events. Consecutive, eligible outpatients aged 45 years or older were recruited over a 7-month period between December 2003 and June 2004. Two groups of patients were recruited:

1. Symptomatic patients

These included patients with documented coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral artery disease (PAD)

2. Asymptomatic patients at high risk for atherothrombotic events

These included patients with at least 3 atherosclerosis risk factors: type 1 or 2 diabetes mellitus, diabetic nephropathy, ankle brachial index <0.9, presence of at least one carotid plaque by ultrasonography, asymptomatic carotid stenosis ($\geq 70\%$), systolic blood pressure ≥ 150 mmHg despite therapy for at least 3 months, hypercholesterolemia currently treated with medications, current smokers (>15 cigarettes per day) and male ≥ 65 years or female ≥ 70 years.

Patients were recruited from 44 countries including Singapore. Selection of physicians for the REACH Registry was determined at the country level. In Singapore, both general practitioners and specialists (in both the public and private sector) including cardiologists, neurologists, endocrinologists, vascular surgeons and internists were involved in the REACH Registry.

Data were collected centrally using a standardised international case report form. Baseline demographics, risk factor characteristics, medication history, height, weight, waist circumference, resting systolic and diastolic blood pressure, and available fasting blood glucose and cholesterol levels were obtained. Continuous variables are expressed as mean [standard deviation (SD)]. Categorical variables were expressed as frequencies and percentages. The *t*-test was used to compare continuous variables. Comparisons between categorical variables were performed using the χ^2 test. *P* <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 15.

Results

The baseline demographics are shown in Table 1. A total of 881 patients (64.4% male) were recruited. The mean age was 64 ± 9.8 years. Seven hundred and one (79.6%) patients were symptomatic (CAD 430, CVD 321, PAD 72) while 180 (20.4%) patients were asymptomatic with ≥ 3 risk factors. The majority of patients with symptomatic disease were under the care of specialists; conversely, most asymptomatic patients were under the care of general practitioners.

Major risk factors for atherothrombosis including diabetes mellitus, hypertension and hypercholesterolemia were present in a high proportion of patients. Among the symptomatic patients, diabetes mellitus was more common in patients with PAD. The prevalence of current smoking in symptomatic patients was 14.1% overall, and was higher in patients with PAD (19.4%). Obesity and overweight status was present in more than 50% of patients. Abdominal obesity as determined by waist circumference was present in 54.3% while 23.3% were obese as assessed by body mass index (BMI). Additionally, 21.3% were classified as obese by both criteria, 32.5% were considered obese by waist circumference but not by BMI while 13.1% were considered obese by BMI but not by waist circumference. Only 43.2% were considered not obese by both criteria which is lower than that reported for the global population (43.2% versus 49.2%).¹⁷

In general, atherosclerosis risk factors were not well controlled at baseline (Table 2). Approximately 50% of patients had elevated blood pressure readings ($\geq 140/90$ mmHg) and a significant proportion had elevated cholesterol

Table 1. Baseline Demographics of Singapore Population in the REACH Registry

	Percentage of population					
	Total (n = 881)	Symptomatic (n = 701)	CAD (n = 430)	CVD (n = 321)	PAD (n = 72)	Risk factors only (n = 180)
Age (y)						
Mean (SD)	64.4 (9.8)	64.1(9.9)	63.7 (9.6)	65.1 (10.1)	66.1 (8.6)	65.6(9.6)
Men	64.4	67.9	72.6	62.3	73.6	50.6
Diabetes*	57.0	49.6	55.1	45.8	61.1	85.6
Hypertension†	80.6	79.3	80.9	81.3	79.2	85.6
Hypercholesterolemia	80.1	78	84.7	72.6	76.4	88.3
Abdominal obesity (AO)‡	54.3	52.5	55.6	49.1	46.5	62.6
Normal weight (BMI <23)	30.0	31.4	29.5	31.2	42.9	25.7
Overweight (BMI 23-27.5)	45.9	46.1	47.6	45.4	41.4	46.9
Obesity (BMI ≥27.5)	23.3	22.5	22.9	23.3	15.7	27.4
Obesity (BMI ≥27.5) & AO	21.3	20.4	21.3	20.2	13	26.3
Smoker						
Former	26.6	29.7	31.4	29.3	41.7	14.4
Current	15.4	14.1	13.7	12.8	19.4	20.6
Physician type						
General practitioner (n = 286)	32.5	21.0†	24.4	17.8	32.5	77.2§
Specialist (n = 595)	67.5	79.0†	75.6	82.2	67.5	22.8§

BMI: body mass index (calculated as weight in kilograms divide by the square of height in metres); CAD: coronary artery disease; CVD: cerebrovascular disease; PAD: peripheral arterial disease; REACH: Reduction of Atherothrombosis for Continued Health; SD: standard deviation

* Patients with type 1 or 2 diabetes treated with hypoglycaemic agents or insulin or with history of diabetes

† Patients with hypertension as a risk factor or a history of hypertension

‡ Waist circumference >90 cm for male and >80 cm for female

§ P value significant at <0.001

Table 2. Undertreatment of Risk Factors in the Singapore Population of the REACH Registry

	Percentage of population								
	Elevated blood pressure*			Elevated cholesterol†			Elevated blood glucose‡		
	Overall	General practitioner	Specialist	Overall	General practitioner	Specialist	Overall practitioner	General	Specialist
Risk factor (n = 180)	59.4	58.3	63.4	44.5	48.4	30.3	52.7	50.4	61.3
Symptomatic (n = 701)	48.7	45.9	49.5	35.4	44.2	33.7	35.0	33.8	35.4
CAD (n = 430)	44.3	44.2	44.3	29.2	40.0	26.9	36.7	33.3	37.6
CVD (n = 321)	55.1	52.6	55.7	44.8	53.3	43.3	36.0	36.7	35.8
PAD (n = 72)	52.8	16.7	56.1	47.1	100.0	41.9	51.5	0.0	58.6

CAD: coronary artery disease; CVD: cerebrovascular disease; PAD: peripheral arterial disease; REACH: Reduction of Atherothrombosis for Continued Health

* Patients with a blood pressure of >140/90 mmHg

† Patients with a cholesterol level of >200 mg/dL

‡ Patients with a blood glucose level of >126 mg/dL

and blood glucose levels. These risk factors were not well controlled in both asymptomatic and symptomatic patients, regardless of physician type. Among the symptomatic patients, 12.9% had symptomatic polyvascular disease. Most patients with CAD or CVD had involvement of 1 or 2 vascular beds. In contrast, a higher proportion of patients

with PAD had involvement of all 3 vascular beds (Fig. 1).

Medications used are listed by disease groups (Table 3) and physician specialty (Table 4). Patients were undertreated with antiplatelet agents (71.9% overall; range, 23.9% for ≥3 risk factors to 84.7% for PAD), statins (76.2% overall; range, 73.6% for PAD to 82.1% for CAD), and other

	N	%
CAD alone	326	37.0
CVD alone	229	26.0
PAD alone	32	3.6
Risk factors only	180	20.4
CAD + CVD	74	8.4
CAD + PAD	22	2.5
CVD + PAD	10	1.1
CAD + CVD + PAD	8	0.9
Overall	881	100

CABG: coronary artery bypass graft; CAD: coronary artery disease; CVD: cerebrovascular disease; MI: myocardial infarction; PAD: peripheral arterial disease; REACH: Reduction of Atherothrombosis for Continued Health

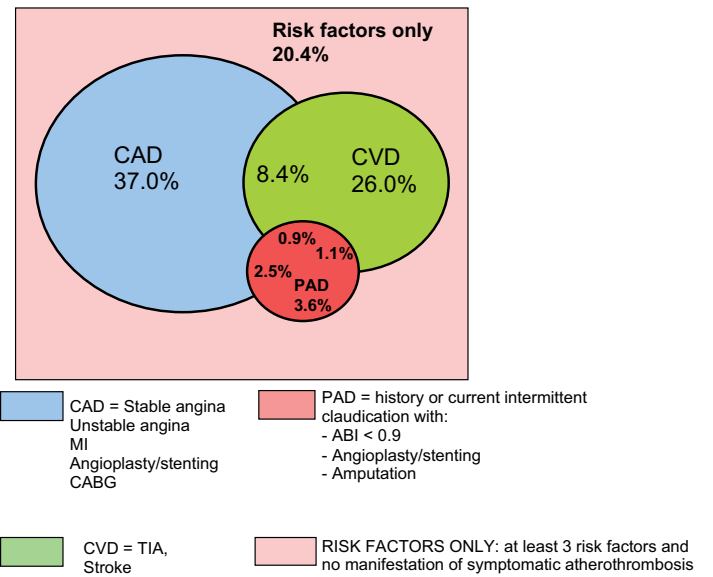


Fig. 1. Prevalence of polyvascular disease in the REACH registry.

Table 3. Medication Use Amongst the Singaporean Population in the REACH Registry by Disease Groups

	Percentage of population					
	Total (n = 881)	Symptomatic (n = 701)	CAD (n = 430)	CVD (n = 321)	PAD (n = 72)	Risk factors Only (n = 180)
No. of patients with diagnosed hypertension	710	556	348	261	57	154
At least 1 antihypertensive	98.7	98.2	99.1	97.7	96.5	100.0
β Blockers	55.4	61.7	74.4	46.7	49.1	32.5
ACE Inhibitors	39.0	39.9	38.2	40.6	35.1	35.7
Diuretics	26.2	25.2	27.9	23.4	26.3	29.9
Calcium Channel Blockers	37.5	39.2	41.1	35.6	45.6	31.1
Angiotensin II receptor blockers	33.7	29.0	33.6	23.4	33.3	50.6
Other antihypertensives	6.6	8.5	10.1	6.9	14.0	7.1
Antiplatelet therapy						
At least 1 antiplatelet agent	71.9	84.2	83.5	84.1	84.7	23.9
Acetylsalicylic acid	55.7	64.6	62.6	65.1	65.3	21.1
Other antiplatelet agents	24.5	30.0	32.6	29.6	31.9	3.3
Any 2 antiplatelet agents	8.4	10.4	11.6	10.6	12.5	0.6
No. of patients with Type I or Type II diabetes currently treated with hypoglycaemic agents or insulin or with history of diabetes	502	348	237	147	44	154
At least 1 diabetic medication	96.2	94.8	96.2	93.9	95.5	99.4
Sulphonylureas	56.0	50.9	57.4	44.9	34.1	67.5
Biguanides	59.8	55.5	51.9	52.4	56.8	69.5
Insulin	16.7	19.3	21.9	14.3	47.7	11.0
Thiazolidinediones	9.0	6.3	8.0	6.8	4.5	14.9
Other diabetic medications	17.7	19.3	19.4	20.4	11.4	14.3
Nitrates	24.1	29.4	43.4	17.2	20.8	3.3
NSAIDs	4.1	3.1	3.3	2.2	1.4	7.8
Lipid-lowering therapy						
At least 1 agent	83.0	81.7	87.9	77.0	80.6	87.8
Statin	76.2	76.8	82.1	74.8	73.6	73.9
Other lipid-lowering agents	13.4	11.6	14.9	5.9	13.9	20.6

CAD: coronary artery disease; CVD: cerebrovascular disease; NSAIDs: non-steroidal anti-inflammatory drugs; PAD: peripheral arterial disease; REACH: Reduction of Atherothrombosis for Continued Health

Table 4. Medication Use Amongst the Singaporean Population in the REACH Registry by Physician Specialty

	Percentage of Patient Population							
	General Practice	Specialist*	Internist	Cardiologist	Angiologist	Vascular Surgeon	Neurologist	Endocrinologist
No. of patients from each physician group	286	595	30	215	15	51	209	75
No. of patients with diagnosed hypertension	244	466	27	166	9	38	157	69
At least 1 antihypertensive	99.2	98.3	100.0	100.0	100.0	94.7	96.2	100.0
β blockers	41.0†	57.1†	48.1	69.9	55.6	52.6	42.7	65.2
ACE inhibitors	25.9†	40.0†	40.7	34.9	33.3	23.7	47.1	44.9
Diuretics	23.4	25.5	40.7	28.3	22.2	13.2	10.8	53.6
Calcium channel blockers	35.7	36.5	44.4	32.5	55.6	50.0	33.8	39.1
Angiotensin II receptor blockers	43.9†	26.0†	40.7	30.1	44.4	26.3	14.6	33.3
Other antihypertensives	2.9†	10.5†	7.4	15.1	0.0	18.4	2.5	15.9
Antiplatelet therapy								
At least 1 antiplatelet	43.4†	85.8†	96.7	86.5	86.7	88.2	86.1	69.3
Acetylsalicylic acid	35.7†	65.5†	73.3	65.1	46.7	66.7	65.1	64.0
Other antiplatelet agents	10.7†	30.5†	33.3	35.3	40.0	35.3	31.6	9.3
Any 2 antiplatelet agents	2.9‡	10.1‡	10.0	14.0	0.0	13.7	10.5	4.0
No. of patients with Type I or Type II diabetes currently treated with hypoglycaemic agents or history of diabetes								
At least 1 diabetic medication	95.4	90.6	93.3	86.8	90.9	92.9	86.2	100.0
Sulphonylureas	67.9†	45.9†	46.7	50.9	45.5	32.1	40.4	49.3
Biguanides	63.4§	53.8§	60.0	45.3	45.5	57.1	47.9	72.0
Insulin	8.2	20.7	26.7	8.5	36.4	46.4	6.4	42.7
Thiazolidinediones	16.0†	4.3†	26.7	8.5	0.0	3.6	0.0	0.0
Other diabetic medications	11.9§	20.1§	13.3	25.5	9.1	10.7	23.4	14.7
Nitrates	18.5	26.7	26.7	36.3	20.0	19.6	15.3	37.3
NSAIDs	9.1	1.7	3.3	0.0	0.0	2.0	0.5	9.3
Lipid-lowering therapy								
At least 1 agent	82.9	83.0	100.0	92.1	100.0	72.5	70.3	93.3
Statin	71.6§	81.5§	100.0	85.6	93.3	60.8	68.9	89.3
Other lipid-lowering agents	16.1	12.1	26.7	19.1	13.3	11.8	2.9	16.0

ACE: angiotensin-converting enzyme; NSAIDs: non-steroidal anti-inflammatory drugs; REACH: Reduction of Atherothrombosis for Continued Health

* Sum of observations from Internist, Cardiologist, Angiologist, Vascular Surgeon, Neurologist, Endocrinologist groups

† *P* value significant at <0.001.

‡ Significant *P* value = 0.001

§ *P* value significant at <0.05

evidence-based medications. There were significant variations in patients' medication use by physician's specialty. Specialists tended to prescribe more β-blockers, angiotensin-converting enzyme (ACE) inhibitors, antiplatelet agents and statins whereas general practitioners used more Angiotensin II receptor blockers.

Discussion

The REACH Registry is a prospective long-term study in

the real-life setting covering the entire spectrum of stable atherothrombotic syndromes. This report on the baseline characteristics of the Singapore patients in the REACH Registry gives us a glimpse of the demographics, risk factor profile and management of patients at highest risk for atherothrombosis in the outpatient setting in Singapore.

The proportion of Singapore patients who were symptomatic (79.6%) and asymptomatic (20.4%) mirror those seen in the global population.¹⁷ Similarly, the major

risk factors for atherothrombosis were seen in a high proportion of our patients and highlight the importance of treating these potentially modifiable factors (diabetes mellitus, hypertension, hypercholesterolaemia, obesity and cigarette smoking) that have been shown to contribute importantly to the development of atherothrombosis.¹⁸

Obesity is a major problem in the Singapore patients in the REACH Registry. Approximately 50% of our patients were considered overweight or obese by either BMI or waist circumference, indicating that the Singapore patients in the REACH Registry have a high “metabolic” risk burden. The thresholds at which obesity is linked with an increased cardiovascular risk vary across populations. Several epidemiologic studies in Asians have shown that Asians have a higher amount of body fat at lower BMIs and waist circumference compared with western populations,^{19,20} leading to a higher prevalence of cardiovascular disease risk factors at lower BMIs in Asian populations than Western populations.²¹⁻²⁴ Accordingly, we used the Asian criteria for waist circumference and BMI²⁵ to define obesity in our study.

There is a substantial gap between guideline recommendations and real life clinical practice in the management of patients with or at risk for atherothrombosis. There is general under-utilisation of proven medical therapies especially in the symptomatic patients. There is an overwhelming amount of data supporting the use of antiplatelet agents and statins in patients with or at high risk of atherothrombosis.⁹⁻¹¹ Despite this, these medications were not prescribed at ideal rates in our patients and a significant number of patients did not meet established targets recommended in guidelines for cholesterol reduction.²⁶⁻²⁸ Additionally, a significant proportion of patients had elevated blood pressure, blood glucose levels, increased body weights and were still using tobacco. These atherosclerosis risk factors were sub-optimally controlled in both asymptomatic and symptomatic patients regardless of physician type. Thus, although the specialists used more β -blockers, ACE inhibitors, antiplatelet agents and statins than general practitioners, these risk factors remained sub-optimally controlled.

Atherothrombosis is a diffuse disease. Accordingly, in patients with established atherothrombosis, symptomatic polyvascular disease was not uncommon. Most patients with CAD or CVD had involvement of 1 or 2 vascular beds. In contrast, a higher proportion of patients with PAD had involvement of all 3 vascular beds. This may indicate that patients with CAD or CVD seek treatment earlier than those with PAD or clinicians are diagnosing PAD later, only when the disease is in an advanced stage.

This study has several limitations. As with all registries, there may be recruitment biases. Although physicians were

instructed to recruit consecutive patients to reduce bias, logbooks were not mandatory or audited to ensure compliance. Because only stable outpatients were recruited, the enrolled patients may have been at lower risk than if inpatients had also been included. Cost reasons affecting lack of medication use and contraindications to medication use were also not documented.

Conclusion

This study showed that established atherosclerosis risk factors are common in Singapore patients in the REACH Registry. In particular, overweight and obesity is a major problem and was present in approximately 50% of patients. Significantly, most of these risk factors remained sub-optimally controlled. Symptomatic polyvascular disease was not uncommon, and these patients face cross risk in vascular beds other than their initial presenting vascular bed.

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