Cardiovascular risk profile and outcome of patients with abdominal aortic aneurysm in out-patients with atherothrombosis: Data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry

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Objective: **Datasets regarding patients with abdominal aortic aneurysm (AAA) have almost universally been restricted to single geographic regions. We aimed to obtain data on the risk factor profile and cardiovascular (CV) co-morbidity among multi-ethnic patients with known AAA in the global REACH (REduction of Atherothrombosis for Continued Health) Registry.**

Methods: **The REACH Registry is an international, prospective, observational out-patient registry enrolling out-patients ≥45 years of age with established coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral arterial disease (PAD) or with at least three atherothrombotic risk factors. This report includes observations pertaining to 68,236 out-patients enrolled in 44 countries.**

Main outcome measures: **Gender, ethnic origin, CV risk factors, established atherosclerotic disease (CAD, CVD and PAD) at baseline, and CV outcome events at 1-year were compared in patients with and without AAA.**

Results: **An AAA was reported in 1722 (2.5%) of 68,236 out-patients enrolled in the REACH Registry. Older age (73 ± 8 vs 68 ± 10, $P < .0001$), male gender (81% vs 63%, $P < .0001$), White ethnicity (79% vs 67%, $P < .0001$) and a history of smoking (81% vs 55%, $P < .0001$) were independently related to the diagnosis of AAA. There was a weaker association with hypertension or hypercholesterolemia, and an inverse relation with diabetes. Fatal and non-fatal coronary and cerebrovascular event rates were not different between the AAA and non-AAA cohorts, but individuals with AAA suffered increased rates of other cardiovascular deaths (1.39% vs 0.94%, $P = .0135$), hospitalizations for atherothrombotic events (14.1% vs 9.3%, $P < .0001$) due to increased rates of revascularization procedures, and new or worsening PAD (3.7% vs 1.3%, $P < .0001$) at 1-year follow-up.**

Conclusion: **This study, the largest published to date, presents the CV risk profile and outcome of patients with an established diagnosis of AAA from a cohort of patients with either overt manifestations of CV disease or multiple risk factors, and further defines these patients in a multi-ethnic, global context. (J Vasc Surg 2008;48:808-14.)**

Abdominal aortic aneurysms (AAA) compared with established atherothrombotic disease (ie, coronary artery [CAD], cerebrovascular disease [CVD], or peripheral arterial disease [PAD]) are characterized by distinct cardiovascular (CV) risk factor profiles, as demonstrated in the Aneurysm Detection and Management (ADAM) study[1,2] and the UK Small Aneurysm Trial.[3] These distinctions imply that the underlying pathophysiology of AAA differs from CAD, CVD, and PAD, and some studies support the hypothesis that AAA may not be a direct manifestation of atherothrombosis.[4-6] On the other hand, AAA and established atherothrombotic disease often coincide, with advanced age, male gender, smoking, and family history identified as common risk factors linking these disease entities.[4,5,7-9] The etiological role of dyslipidemia and hypertension remains less precisely defined,[2] with some studies claiming a relationship with AAA and others reporting a lack of association.[8]

Screening programs in the United States and Europe have shown that 5% of men older than 65 have an occult AAA.[10] Individuals with AAA detected by screening rarely present with an aortic diameter associated with a short-term risk of aneurysm-related death (eg, from rupture), but current data suggest that many individuals with AAA suffer co-existing atherothrombotic risk such that coronary heart

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disease and cerebrovascular ischemic events confer the major increased CV morbidity and mortality burden.[11,12] Late survival of patients with AAA is significantly lower than that of age- and sex-matched non-AAA populations, even after successful AAA repair.[13-15]

The objective of this analysis was to investigate the prevalence of atherothrombotic risk factors; concomitant non-aortic CV disease; and CV ischemic event rates in a large, prospectively defined population with an established diagnosis of AAA compared with the non-AAA population in the REduction of Atherothrombosis for Continued Health (REACH) Registry, the largest worldwide registry of out-patients at high risk of atherothrombotic events.

METHODS

The REACH Registry is a multinational, prospective, observational registry of out-patients at high risk of, or with established, atherothrombosis. The design of the REACH Registry has been published previously.[16,17] In summary, 68,236 consecutive out-patients aged 45 or older with established CAD, CVD, or PAD, or with at least three atherothrombotic risk factors were enrolled from Dec 2003 to Dec 2004, at over 5000 study sites in 44 countries throughout the world.[17] Baseline characteristics including age, gender, ethnic origin, history, and treatment of classical atherothrombotic risk factors, measured blood pressure, fasting blood glucose, total cholesterol, and presence of established atherothrombotic disease (ie, CAD, CVD, and PAD) were assessed in patients with an established diagnosis of known AAA (AAA population) and without diagnosis of AAA (non-AAA population) based on a pre-hoc hypothesis that differing baseline risk factors and CV outcomes would be observed during follow-up. Definitions of baseline characteristics were at the discretion of the treating physician, for example labelling was based on medical history or medication, suggesting that a minority of patients on lipid-lowering or antihypertensive drugs do not have the according risk factor. Polyvascular disease was defined as established atherothrombotic disease in more than one vascular territory (ie, CAD, CVD, and PAD). Risk factors that were documented in the medical record, or for which patients were receiving treatment at the time of study enrollment, were considered, including treated diabetes mellitus, systemic blood pressure $\geq$150 mmHg despite therapy for at least 3 months, hypercholesterolemia treated with medication, and current smoking (defined as $\geq$15 cigarettes per day on average within the last month before entry in the REACH Registry). The diagnosis of AAA was based on documentation by the treating physician and not on systematic screening. Primary aortic imaging was not performed in this large international cohort.

At 12 $\pm$ 3 months from enrollment, data were collected from participating physicians regarding patients' clinical outcomes, vascular procedures, weight, and current smoking, as well as chronic medications taken regularly since baseline. The current report is based on a database lock of July 21, 2006 for analysis of the 1-year follow-up. Events were not adjudicated, however, the diagnosis of ischemic stroke or transient ischemic attack (TIA) had to be based on a neurologist or hospital report. Any CV death included fatal stroke, fatal myocardial infarction (MI) and other CV death. "Other CV death" included other death of cardiac origin, pulmonary embolism, any sudden death including unobserved and unexpected death (eg, while sleeping) unless proven otherwise by autopsy, death following a vascular operation, vascular procedure, or amputation (except for trauma or malignancy), death ascribed to heart failure, death following a visceral or limb infarction, or any other death that was not definitely ascribed to a nonvascular cause or hemorrhage. Any MI or stroke followed by death, whatever the cause, in the subsequent 28 days was considered a fatal MI or fatal stroke. A new diagnosis of PAD was documented by an abnormal ankle-brachial index (ABI) or other objective test. Worsening of PAD included deterioration of pre-existing claudication, or new episode of chronic critical leg ischemia (Appendix, online only).

The REACH Registry complies with the Declaration of Helsinki; the study design was approved by the institutional review board according to local regulations in each participating country and all patients included in the analysis provided signed informed consent.

Statistical analysis. Continuous variables are expressed as mean (SD). Categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables were performed using the Pearson χ^2 test and trend test adjusted on age and sex were done using Cochran-Mantel-Haenszel statistics to compare across groups. The *t*-test was used to compare continuous variables. Adjustment for age and sex was made using a multiple logistic model giving odds ratio (OR) with their 95% confidence interval (CI) and the least-square mean of the adjusted logit for each percentage. All event rates are calculated with a Cox model after adjustment for age and sex. Statistical significance was considered a two-tailed probability of $<.05$. Statistical analysis was performed using a SAS software version 9 (SAS Institute Inc., Cary, NC).

RESULTS

Among 68,236 patients enrolled in the REACH Registry, 1722 (2.52%) patients had an established diagnosis of known AAA. The prevalence of AAA was more than doubled in patients with symptomatic atherothrombosis compared with patients with $\geq$3 atherothrombotic risk factors (1574 vs 148; 2.8% vs 1.2%, respectively).

An AAA diagnosis was absent or unknown in 60,057 and 6457 patients, respectively. Demographic baseline data were comparable in patients with either absent or unknown AAA status and these two groups were merged to represent the non-AAA population (n = 66,514). Indication of presence or absence of AAA was independent from physician specialty in 87% of known AAA cases enrolled, meaning that a similar proportion of cases with or without AAA were enrolled by a particular specialist group. A selection bias was noticeable in a small group of specialists enrolling 15% of the overall and 13% of the AAA REACH population, respectively. Endocrinologists enrolled 0.8% of all

Table I. Baseline demographic characteristics of the AAA and non-AAA populations in the REACH Registry

Characteristic	*AAA (n = 1722)*	*Non-AAA (n = 66,514)*	P-*value*
Male (%)	80.66	63.23	<.0001
Mean age ± SD (years)	73.36 ± 7.83	68.45 ± 10.12	<.0001
Smoking			<.0001
Current (%)	20.85	14.61	
Former (%)	60.16	39.85	
Never (%)	16.84	42.45	
Unknown (%)	2.15	3.09	
Diabetes			
History (%)	29.44	44.41	<.0001
Treated (%)	23.94	40.63	<.0001
FBS > 126 mg/dL (%)	20.31	30.90	<.0001
Mean glucose ± SD (mg/dL)	110.92 ± 32.64	121.39 ± 46.14	<.0001
Hypercholesterolemia			
History (%)	74.48	72.10	.0297
TC (>200 mg/dL), %	33.31	39.49	<.0001
Mean cholesterol ± SD (mg/dL)	186.25 ± 43.84	192.93 ± 46.73	<.0001
Hypertension			
History (%)	83.45	81.77	.0741
measured > 140/90 mmHg	44.78	50.15	<.0001
Mean systolic BP ± SD (mmHg)	135.86 ± 18.98	137.88 ± 19.46	<.0001
Mean diastolic BP ± SD (mmHg)	76.21 ± 11.24	78.46 ± 11.23	<.0001

FBS, fasting blood sugar; *TC,* total cholesterol; *BP,* blood pressure; *SD,* standard deviation, *AAA,* abdominal aortic aneurysm.

Table II. Ethnicity of the AAA and non-AAA populations in the REACH Registry

Ethnicity, % (95% CI)	*AAA (n = 1722)*	*Non-AAA (n = 66,514)*	*Total (n = 68,236)*
White	78.90 (76.78; 80.87)	66.92 (66.54; 67.29)	67.21 (66.84; 67.57)
Hispanic	2.29 (1.65; 3.17)	5.12 (4.95; 5.30)	5.06 (4.89; 5.23)
Asian	13.17 (11.57; 14.96)	20.33 (20.02; 20.65)	20.16 (19.85; 20.47)
African American	1.97 (1.38; 2.79)	4.65 (4.49; 4.82)	4.59 (4.42; 4.75)
Other/Multiple	3.67 (2.84; 4.74)	2.98 (2.84; 3.11)	2.99 (2.86; 3.13)
Not available	196	5254	5450
		$\chi^2 = 131.13$, $P < .0001$	

AAA, abdominal aortic aneurysm; *CI,* confidence interval.

patients with known AAA versus 3.0% of all patients without AAA; neurologists enrolled 2.8% vs 9.6%, indicating a proportional reduction in the expected frequency of a diagnosis of AAA; general surgeons enrolled 6.4% vs 2.1%; and vascular physicians enrolled 2.5% vs 1.1% indicating a proportional increase in the expected frequency of a diagnosis of AAA. This selection bias was negligible for the overall analysis as it represented only a small proportion of the total REACH population.[17]

Compared with the non-AAA cohort, the AAA cohort was older (73 ± 8 vs 68 ± 10 years of age, $P < .0001$), more often male (81% vs 63%, $P < .0001$; Table I, and of White ethnicity (79% vs 67% $P < .0001$; Table II).

The relative probability of AAA according to increasing age groups in the REACH Registry is shown in Fig 1 ($P < .0001$). Percentage of AAA by region (adjusted on age, sex, diabetes, hypertension, hypercholesterolemia, and smoking) is shown in Table III. In a multivariate logistic regression analysis including age, gender, and atherothrombotic risk factors, the relationship between AAA and ethnic origin remained independent and statistically significant. Smoking had a strong association with AAA after adjustment for age and gender (OR 3.40 [2.97-3.89], $P < .0001$). This association was less marked for hypertension (OR 1.29 [1.11-1.48], $P = .0006$), and hypercholesterolemia (OR 1.24 [1.10-1.40], $P = .0005$). Diabetes mellitus showed a strong and striking negative association with the diagnosis of AAA (OR 0.59 [0.53-0.66], $P < .0001$; Table IV).

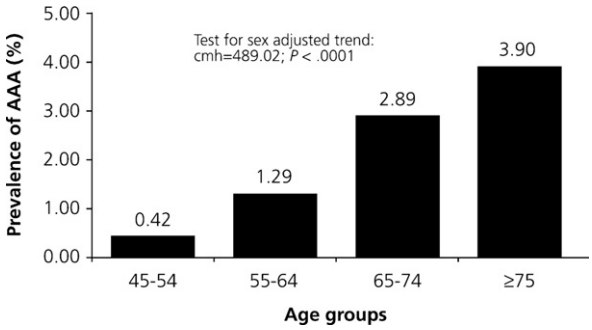

Fig 1. Increasing risk of AAA shown in sex adjusted age groups. cmd = Cochran-Mantel-Haenszel.

Table III. Percentage of AAA by region (adjusted on age, sex, diabetes, hypertension, hypercholesterolemia, and smoking)

North America	*Latin America*	*Western Europe*	*Eastern Europe*	*Middle East*	*Asia*	*Australia*	*Japan*
1.9%	1.4%	1.9%	0.6%	0.3%	0.5%	1.4%	1.7%

χ^2 $P < .0001$.

Table IV. Significant predictors related to the diagnosis of AAA (multivariate analysis)

Variable	*OR*	*CI 95%*	P-*value*
Age (>65 years)	1.07	[1.061; 1.073]	<.0001
Male sex	1.96	[1.713; 2.231]	<.0001
Ethnicity: White vs other	1.46	[1.282; 1.656]	<.0001
Diabetes	0.59	[0.525; 0.658]	<.0001
Hypertension	1.29	[1.113; 1.483]	.0006
Hypercholesterolemia	1.24	[1.099; 1.399]	.0005
Current or former smoker vs never smoker	3.40	[2.974; 3.894]	<.0001

OR, odds ratio; *CI,* confidence interval.

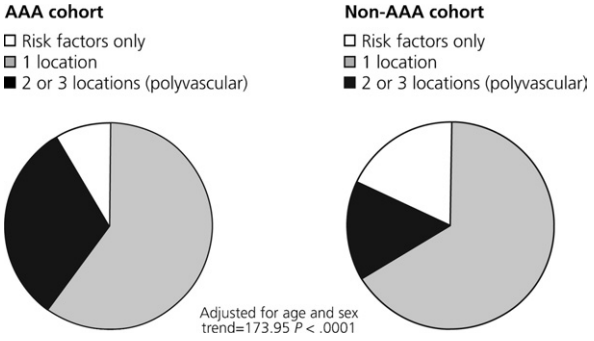

Fig 2. Proportional prevalence of asymptomatic (risk factors only), and established atherothrombotic disease in a single vascular bed or in more than one vascular bed (polyvascular disease) in patients with or without AAA in the REACH Registry. 1 location = established atherothrombotic disease in a single vascular bed (i.e. CAD, CVD or PAD); 2 or 3 locations = established atherothrombotic disease in two or three vascular beds (various combinations possible).

Amongst individuals with established atherothrombotic disease, the co-prevalence of AAA was highest among patients with PAD (6.6%, 550 of 8322 patients) compared with patients with CAD (3.0%, 1218 of 40,450 patients), or with CVD (2.2%, 425 of 18,992 patients), respectively. Polyvascular disease was twice as frequent in patients with AAA as in patients without: a third of patients with AAA also had established symptomatic atherothrombosis in more than one vascular bed, in addition to AAA (31.6% in the AAA vs 15.5% in the non-AAA cohorts, $P < .0001$; Fig 2).

More patients in the AAA population were treated with antihypertensive drugs and lipid lowering agents as compared with those without AAA (Table V). Patients with AAA were also more often treated with oral vitamin K antagonists (18.8% vs 12.2%, $P < .0001$), which explains the overall more frequent use of antithrombotics in the AAA group (89.0% vs 86.2%, $P = .0007$; Table V).

Table V. Baseline medications among AAA and non-AAA populations in the REACH Registry

Medication use, %	*AAA (n = 1722)*	*Non-AAA (n = 66,514)*	P-*value*
Aspirin	65.21	67.29	NS
Other antiplatelet	25.57	24.73	NS
Dual antiplatelet therapy	13.38	13.21	NS
Vitamin K antagonists	18.80	12.16	<.0001
Any antithrombotic therapy*	89.01	86.15	.0007
Statins	71.15	69.29	NS
Any lipid lowering drug	77.25	75.09	.0402
ACE-inhibitor	44.11	45.22	NS
Angiotensin II inhibitors	20.98	22.96	.0542
Calcium channel blockers	37.00	33.91	.0075
Diuretics	45.05	40.26	.0001
Betablockers	50.58	47.41	.0095
Any antihypertensive therapy	93.14	91.27	.0065

ACE, angiotensin converting enzyme; *AAA,* abdominal aortic aneurysm.
*Either oral vitamin K antagonists or antiplatelet agents.

One-year CV outcomes and other CV disease rates in the AAA cohort compared with the non-AAA cohort are presented in Table VI. Although rates of fatal and non-fatal coronary and cerebrovascular events were not significantly different between the AAA and non-AAA cohorts, there were significantly higher rates of other CV deaths (1.4% vs 0.9%, $P = .0135$), hospitalizations for atherothrombotic events (14.1% vs 9.3%, $P < .0001$) in particular revascularization procedures (coronary angioplasty [3.6% vs 2.6%, $P = .0197$], carotid surgery [0.82% vs 0.45%, $P = .024$], peripheral bypass surgery [2.6% vs 0.7%, $P < .0001$], other peripheral interventions [3.8% vs 1.0%, $P < .0001$]) and new or worsening PAD (3.7% vs 1.3%, $P < .0001$) in individuals with AAA (Table VI).

DISCUSSION

An AAA is prevalent, associated with atherothrombotic risk factors and clinical disease, and linked with high rates of CV ischemic events. However, previous datasets of patients with AAA have almost universally been limited to single geographic regions and comprised cohorts with limited ethnic diversity so that global validity remains to be shown.[1-3,18-20] The REACH Registry provides a unique opportunity to analyze these features of AAA in a global population as well as an opportunity to compare clinical characteristics in a very large cohort of 1722 patients with

Table VI. One-year cardiovascular outcome events (adjusted for age, sex and ethnicity) in the AAA and non-AAA populations of the REACH Registry

One-year outcome events, % [95% CI]	*AAA (n = 1629)*	*Non-AAA (n = 63,348)*	P-*value*
CV death	2.10 [1.36; 2.83]	1.63 [1.38; 1.88]	.0895
Fatal-MI	0.42 [0.10; 0.73]	0.43 [0.30; 0.55]	.9244
Fatal-stroke	0.37 [0.05; 0.69]	0.29 [0.18; 0.39]	.6116
Other CV death	1.35 [0.74; 1.94]	0.93 [0.74; 1.11]	.0412
Non-fatal stroke	1.52 [0.84; 2.19]	1.75 [1.49; 2.02]	.7775
Non-fatal MI	1.40 [0.73; 2.07]	1.20 [0.98; 1.41]	.4482
CV death/MI/stroke	5.02 [3.83; 6.19]	4.36 [3.96; 4.77]	.1046
CV death/MI/stroke/CV hospitalization	17.07 [14.98; 19.12]	12.26 [11.62; 12.88]	<.0001
Hospitalization	16.59 [14.53; 18.60]	12.13 [11.50; 12.76]	<.0001
Unstable angina/TIA/stroke	7.20 [5.73; 8.65]	7.12 [6.61; 7.62]	.7712
Other ischemic arterial event	2.82 [1.84; 3.79]	1.24 [1.02; 1.46]	<.0001
Bleeding	1.50 [0.83; 2.16]	0.86 [0.67; 1.04]	.0060
Coronary: Endovascular or surgical (CABG/ angioplasty/stenting)	4.27 [3.10; 5.43]	3.49 [3.13; 3.85]	.1212
Carotid: Endovascular or surgical (surgery or angioplasty/stenting)	1.05 [0.48; 1.63]	0.63 [0.49; 0.80]	.0499
New diagnosis or worsening of PAD	3.71 [2.55; 4.84]	1.28 [1.06; 1.49]	<.0001
PAD: Endovascular or surgical (bypass graft or amputation or other)	12.15 [10.52; 13.75]	8.39 [8.03; 8.75]	<.0001
	5.18 [3.80; 6.55]	1.64 [1.39; 1.88]	<.0001

AAA, abdominal aortic aneurysm; *CABG,* coronary artery bypass graft; *CI,* confidence interval; *CV,* cardiovascular; *MI,* myocardial infarction; *PAD,* peripheral arterial disease; *TIA,* transient ischemic attack.

an established diagnosis of AAA from a cohort of patients with either overt manifestations of CV disease or multiple risk factors. Analysis of REACH Registry data confirms that AAA occurs most frequently in older White males with a smoking history,[1,2,4,5,21] and a prevalence more than double in patients with symptomatic atherothrombosis compared with patients with atherothrombotic risk factors only.

A statistically significant ethnic association with AAA, independent from risk factor prevalence, age, and gender, was observed across all geographic regions in the REACH Registry. This observation supports previous studies implying that a genetic component contributes to the development of AAA, as has also been observed in first order relatives of individuals with known AAA.[22] The association of AAA with concomitant lower extremity PAD may be due to the strong pathophysiologic association of both AAA and PAD with smoking. Both the aorta and lower extremity arteries are especially susceptible to injury by exposure to all forms of tobacco and cigarette smoking in particular.[4,23-25] In accordance with prior studies, we found less robust evidence that hypercholesterolemia[8] or hypertension[9] are strongly related to the presence of AAA.[1,2,10,26-28] As medications prescribed for hypercholesterolemia and hypertension may have affected the development of AAA, the relationship between these risk factors and AAA presence is difficult to assess. Prospective studies have shown that, although hypertension has a weak association with AAA prevalence, mortality from AAA increases with high blood pressure. As a result, hypertension may be a relatively poor predictor of the risk of developing AAA in the general population, but an important risk factor for rupture in patients with established AAA.[29] An interesting observation from our analysis is the strong inverse relationship of AAA with diabetes, in accordance with a recent review by Weiss et al[30] who reported a lower prevalence of AAA in patients with diabetes in six studies. This is particularly notable, as PAD is related to smoking and diabetes, but with considerable differences in anatomical manifestation.[31] While the aorto-iliac segment seems to be particularly susceptible to injury by smoking, the distal arterial tree appears to be most susceptible to diabetes-related injury. It is unclear whether diabetic and non-diabetic individuals differ in abdominal aortic wall constitution or if other factors are more relevant, although this might help to further clarify the underlying pathophysiology and guide the development of novel pharmacological treatment options. Of note, whereas proteolysis and matrix destruction are characteristic of aneurysmal disease, the increased matrix volume characteristic of diabetic angiopathy might also be the case in the abdominal aorta.[32] Despite these observations, assessment of these differences has drawn little attention in AAA research.

Although these data confirm a high prevalence of classical atherothrombotic risk factors, such as smoking, hypertension, and hyperlipidemia within the AAA population, the relationship does not include diabetes, which was found to be significantly less prevalent in individuals with AAA than in patients with other atherothrombotic syndromes. Thus, this survey further underlines the hypothesis that AAA may represent an arterial disease with a pathophysiology dependent, only in part, on standard atherothrombotic risk factors.

The REACH Registry includes a very large population of individuals with known AAA from a cohort of 1722 patients with either overt manifestations of CV disease or multiple risk factors, and evaluates the outcome of these patients with regard to CV event rates. While clinicians and patients perceive AAA-related death (eg, rupture and periprocedural CV events) as the cause of mortality in large AAAs, data from the REACH Registry demonstrates that individuals with known AAA suffer from both fatal and

non-fatal MI or stroke, and from "other CV death", which likely includes the spectrum of AAA-related events and undiagnosed AAA rupture. Individuals with known AAA in the REACH Registry also suffered high rates of heart failure and hospitalization as a result of CV events and procedures, which contributed to the morbidity of patients with AAA. Data on surgical or endovascular AAA repair were not specifically collected in case report forms so it is not possible to evaluate the impact of AAA-repair on life expectancy or prognosis in this study.

While the REACH Registry data demonstrate that there was an intensification of use of risk-reduction medications in the AAA cohort compared with the non-AAA cohort, the actual fractional use of these medications was not very different from that used in the non-AAA cohort. The rationale for increased use of oral vitamin K antagonists is unknown, but could either relate to more vascular procedures performed or to more frequently recognized left ventricular systolic dysfunction, presence of atrial fibrillation, or a history of prior thromboembolic events in the AAA cohort (none of which was measured in this large Registry). The trend toward use of more aggressive risk reduction medication might be explained by a higher rate of polyvascular disease in one-third of the REACH Registry AAA population. Pharmacologic treatments recently suggested to prevent AAA expansion or rupture, namely statins and angiotensin converting enzyme inhibitors,[6,33,34] were not more commonly prescribed in the AAA compared with the non-AAA cohort in the REACH Registry.

Study limitations. Recruitment of patients into the REACH Registry was determined by a strategy to enroll individuals known to be at high risk of atherothrombotic events and not by the presence of an AAA at baseline. Although we cannot exclude potential selection bias at enrollment, AAA was not an inclusion criterion in REACH, so we can reasonably infer that AAAs in the REACH Registry are truly reflective of AAA in patients with atherothrombosis and the comparisons between the AAA cohort and non-AAA cohort for risk factors and extent of atherothrombosis are unlikely to be biased. A selection bias regarding diagnosis of AAA was noticed for some specialties. A diagnosis of AAA was obtained more frequently than expected by endocrinologists and neurologists but less frequently by general surgeons and vascular physicians. However, as this selection bias represents less than one-sixth of the REACH population, it was negligible for the overall analysis. Moreover, as primary imaging was not performed, a diagnosis of AAA may have been based on physical examination, although this is rather unusual.

The REACH Registry is not a prospective, population-based study and it provides a major platform for descriptive analysis of the natural history of patients with recognized AAA, but no data to describe the natural history of occult AAA, as might be obtained from a screening study. Furthermore, we note that subjects were classified as having an AAA by physician report, and not based on systematic use of any aortic imaging modality. The role of case misclassification is unknown. We presume that the actual prevalence of AAA is underestimated by a factor of 2 compared with systematic screening programs.[8,20] In an international study of this size, the costs and inconvenience associated with baseline and follow-up aortic imaging would not be sustainable. Another important limitation is the lack of capture of "AAA rupture" as a separate event in the case record form. Nonetheless, despite these limitations, findings from the REACH Registry appear consistent with insights derived from various regional AAA screening programs. Importantly, findings from the REACH Registry extend knowledge of AAA-associated risk factors, polyvascular arterial disease, and CV outcomes in this important aortic disease cohort to a global public health context.

CONCLUSIONS

In individuals at risk of atherothrombotic events, AAA is common in elderly, non-diabetic, White males with a history of smoking. Individuals with AAA from this large multinational cohort of patients with either overt manifestations of CV disease or multiple risk factors suffer higher rates of CV hospitalization and CV deaths than other patients with atherothrombosis. The high morbidity and mortality associated with AAA is derived not only from AAA-associated rupture and death, but is presumably due to the more advanced age, and a more widespread polyvascular manifestation of atherothrombotic disease in affected individuals. Results suggest that there is need to increase awareness of AAA and its consequences, and to implement screening protocols for patients at high risk for AAA. In order to facilitate screening, solid risk factors are mandatory to identify the population at risk.

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AUTHOR CONTRIBUTIONS

Conception and design: IB, AH, PC, PS, MAC, DB
Analysis and interpretation: IB, AH, MTA, PC, PS, MAC, DB
Data collection: DP, PS, DB
Writing the article: IB, AH, MTA, DP
Critical revision of the article: AH, PC, DP, PS, MAC, DB
Final approval of the article: IB, AH, MTA, PC, DP, PS, MAC, DB
Statistical analysis: DB, MAC
Obtained funding: PS, MAC, DB
Overall responsibility: IB, AH, PS, MAC, DB

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