Geographic variations and risk factors for systemic and limb ischemic events in patients with symptomatic peripheral artery disease: insights from the REACH registry

Jérémie Abtan, MD[1], Deepak L. Bhatt, MD, MPH[2], Yedid Elbez, MSc[1], Emmanuel Sorbets, MD[1,3], Kim Eagle, MD, MACC[4], Christopher M. Reid, PhD[5], Iris Baumgartner, MD[6], David Wu, PhD[7], Mary E. Hanson, PhD[7], Hakima Hannachi, MD[7], Puneet K. Singhal, PhD[7], Philippe Gabriel Steg, MD[1,8], Gregory Ducrocq, MD, PhD, FESC [1]* for the REACH Registry Investigators[†]

1. FACT (French Alliance for Cardiovascular Trials, an F-CRIN network, DHU-FIRE, Hôpital Bichat (Assistance Publique – Hôpitaux de Paris), Université Paris-Diderot, Sorbonne Paris-Cité and INSERM U-1148, Paris, France

2. Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA

3. Hôpital Avicenne (Assistance Publique – Hôpitaux de Paris), Université Paris 13

4. University of Michigan Cardiovascular Center, Ann Arbor

5. Monash University & Curtin University, Australia

6. University Hospital Bern, Switzerland

7. Merck & Co., Inc., Kenilworth, NJ, USA

8. NLHI, ICMS, Royal Brompton Hospital, Imperial College, London, United Kingdom.

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***Address for correspondence:**

G Ducrocq, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, Téléphone: +33 140256659, Fax: +33 140258865.E-mail: gregory.ducrocq@bch.aphp.fr

†A full list of the REACH Registry Investigators can be found in Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;295:180-189.

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Summary

Background: Patients with symptomatic peripheral artery disease (PAD) are at high risk of ischemic events. However, data about predictors of this risk are limited.

Hypothesis: We analyzed baseline characteristics and 4-year follow-up of patients enrolled in the international REACH registry with symptomatic PAD and no history of stroke/transient ischemic attack to describe annual rates of recurrent ischemic events globally and geographically.

Methods: The primary outcome was systemic ischemic events (composite of cardiovascular death, myocardial infarction or stroke) at 4 years. The secondary outcome was limb ischemic events (composite of lower limb amputation, peripheral bypass graft and percutaneous intervention for PAD) at 2 years. Multivariate analysis identified risk factors associated with recurrent ischemic events.

Results: The primary endpoint rate reached 4.7% during the 1st year and increased continuously (by 4% to 5% each year) to 17.6% by year 4, driven mainly by cardiovascular mortality (11.1% at year 4). Japan experienced lower adjusted ischemic rates ($p<0.01$) vs North America. Renal impairment ($p<0.01$), congestive heart failure ($p<0.01$), history of diabetes ($p<0.01$), history of myocardial infarction ($p=0.01$), vascular disease (single or poly; $P<0.01$) and older age ($p<0.01$) were associated with increased risk of systemic ischemic events while statin use was associated with lower risk ($p=0.03$). The limb ischemic event rate was 5.7% at 2 years.

Conclusion: Four-year systemic ischemic risk in patients with PAD and no history of stroke or TIA remains high, and was mainly driven by cardiovascular mortality.

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Abbreviations

CAD: coronary artery disease

MI: myocardial infarction

PAD: peripheral artery disease

TIA: transient ischemic attack

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Introduction

Over 202 million people worldwide were estimated to be living with peripheral artery disease (PAD) in 2010, with estimated prevalence rates of 9% in North America and 11% in Europe.[1] The spectrum of PAD includes acute and chronic limb ischemia, asymptomatic PAD, claudication, and critical limb ischemia.[2, 3] PAD is a strong predictor of myocardial infarction (MI), stroke, and death from vascular causes,[4, 5] with an annual incidence of approximately 5% for the composite endpoint of stroke, MI, and death in patients with PAD over 1 year.[6] Understanding the current trends in PAD prevalence and risk factors is critical in guiding preventive strategies to reduce the burden of PAD. However, contemporary, real-world data regarding patient profiles, treatment patterns and cardiovascular risks for PAD patients beyond 1 year are insuffcient, and are often limited to a single geographic region.

In order to address gaps in evidence for characterization of longer-term ischemic risk in PAD patients, we analyzed 4-year data from the REACH international registry of atherothrombosis[7-9] in patients with symptomatic PAD with no history of stroke or transient ischemic attack (TIA), focusing on both systemic (MI, stroke and CV death) and limb ischemic complications (lower limb amputation, peripheral bypass graft and percutaneous intervention for PAD). Patients with prior stoke or TIA were excluded because the risk and benefit balance of antithrombotic agents in this population is specific and has been previously published as a separate analysis.[10] The objectives of the present study were to 1) describe annual rates of systemic ischemic events (MI, stroke and CV death) over 4 years globally and by geographic region, and to identify associated risk factors; and 2) to describe limb ischemic

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event rates (a composite of lower limb amputation, peripheral bypass graft, and percutaneous intervention for PAD) over 2 years.

Methods

Population

The design, methods, and main results of the REACH registry, an international, prospective, observational study, have been previously described.[7, 11] Briefly, from December 2003 to June 2004, consecutive outpatients aged 45 years or older with established coronary artery disease (CAD), cerebrovascular disease, or PAD, or with at least 3 atherothrombotic risk factors were enrolled. Documented PAD was defined as 1 or more of the following: current intermittent claudication with ankle-brachial index of less than 0.9 or a history of intermittent claudication together with a previous and related intervention such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation. Documented CAD was defined as 1 or more of the following: stable angina with documented CAD, history of unstable angina with documented CAD, history of percutaneous coronary intervention, history of coronary artery bypass graft surgery, or previous MI.

Data were collated centrally using standardized case report forms. The initial follow-up period was 2 years, but centers were invited to participate in a 2-year extension. Only patients with PAD and no history of stroke or TIA were included in the present analysis. Signed informed consent was obtained from all patients and the institutional review board in each country approved the protocol.

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The population was divided into 7 geographical regions: North America, including Canada and United States of America; Latin America, including Brazil, Chile and Mexico; Western Europe, including patients from Austria, Belgium, Finland, France, Germany, Greece, the Netherlands, Portugal, Spain, Switzerland and the United Kingdom; Eastern Europe, including patients from Hungary, Romania, Russia and Ukraine; Middle East including patients from Israel and the United Arab Emirates; Asia including patients from China, Taiwan, Hong Kong, Malaysia, Philippines and Thailand; and Japan.

Outcomes

Following enrollment, detailed baseline characteristics, treatment and outcomes were collected annually. Endpoints were not adjudicated and were based on physician report at the time of follow-up. We analyzed 3 systemic ischemic outcomes over 4 years: non-fatal MI, non-fatal stroke, and cardiovascular death; and 3 limb ischemic outcomes at 2 years: lower limb amputation, peripheral bypass graft and percutaneious intervention for PAD. Limb ischemic outcomes were not adjudicated, but were tracked on a declarative basis at the end of followup. Consequently, due to missing data at 4 years, this endpoint was analyzed at 2 years.

The primary outcome was the composite of the 3 systemic ischemic events, and the secondary outcome was the composite of the 3 limb ischemic events. Other secondary outcomes of interest included CV death, MI, and stroke analyzed separately, as well as cardiovascular hospitalization.

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Stroke was verified by a neurologist consultation or hospital records. Cardiovascular death was defined as any MI or stroke followed by death in the next 28 days regardless of the cause, death from pulmonary embolism, heart failure, death following vascular surgery, following a visceral or limb infarction, or any sudden death unless proven to be non-cardiovascular by autopsy.

Statistical analysis

Descriptive statistics, including frequencies and percentages for categorical variables, and mean and standard deviation for continuous variables were calculated to describe the patients' baseline characteristics, medical history, and treatment patterns using the overall study population. Kaplan Meier estimates were used to assess cumulative incidence rates at each year of follow up. Patients from each region were also investigated as subgroups.

The exact date of each systemic ischemic event was systematically collected, whereas limb events were collected on a yearly basis during follow up visits, precluding assignment of a precise date. Therefore, systemic and limb ischemic outcomes were analyzed separately.

The risks of cardioascular events in each geographic region were estimated by Cox proportional hazards models adjusted for the REACH risk score predicting cardiovascular events,[12] after exclusion of the geographic items of the score. Multivariate Cox-regression models were used to assess the factors associated with cardiovascular risk in the study population. Univariate models were first built to assess the impact of each individual variable on cardiovascular outcomes. A set of variables was then selected according to their statistical significance in the univariate model (pd0.10), clinical significance and non-redundancy with

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other variables in the model, and was introduced into the multivariate models. In addition, clinically relevant factors with plausible clinical association with ischemic events were forced into the multivariate Cox-regression model.

Data were processed using the SAS software package (version 9.3; SAS Institute, Cary, NC, USA). Elbez Yedid had access to all the data in the study and takes responsibility for its integrity and the data analysis.

Results

Overall, 65,531 patients were initially enrolled in the REACH Registry in 44 countries and 5,587 centers. Of these, 8,322 had a history of symptomatic PAD, of whom 6,005 (76.7% [95% CI: 75.8% - 77.6%]) had no history of stroke or TIA and constituted the study population for this analysis. Two-year follow-up was completed in 5,336 (88.9%) patients and the 4-year follow-up was completed in 2,998 (49.9%) patients. The population included 1,785 (29.7%) patients from North America, 162 (2.7%) from Latin America, 2,702 (45%) from Western Europe, 441 (7.3%) from Eastern Europe, 38 (0.6%) from the Middle East, 213 (3.6%) from Asia, and 473 (7.9%) from Japan.

Baseline characteristics

In the overall population, the mean age was 70 ± 10 years, and 69.2% were men. At enrollment, 47.3% had diabetes mellitus; 66.2% had hypercholesterolemia, 89.1% had hypertension, 20.9% were current smokers and 18.7% were overweight/obese. Important

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differences in baseline characteristics were observed according to geographic region (Table 1).

Systemic ischemic events

The 2-year rate of systemic ischemic events (cardiovascular death, MI, or stroke) in the overall population was 9.1% and the 4-year rate was 17.6% (Figure 1). The rate of systemic ischemic events increased cumulatively by approximately 4% to 5% for each year of follow-up (Figure 1). The primary outcome was mainly driven by cardiovascular death, accounting for half of the composite outcome with an increase of ~3% each year (2.7%, 5.2%, 8.2%, 11.1%, Figure 2a). Non-fatal MI increased from 1.3% to 2.4% to 3.3% to 4.4% (Figure 2b) with each additional year of follow up, and non-fatal stroke from 1.0% to 2.3% to 3.3 to 4.5% (Figure 2c). Similarly, the rate of cardiovascular hospitalization increased cumulatively over the 4 years of follow-up from 17.8% the first year to 26.3% to 33.4% and 38.3% the fourth year (Figure 2d).

According to geographic region

Compared with North America, patients who were enrolled in Eastern Europe (HR=0.73 [95% CI: 0.55; 0.98], p=0.03), Western Europe (HR=0.83 [95% CI: 0.70; 0.98], p=0.02) or Japan (HR=0.53 [95% CI: 0.41; 0.67], p<0.01) had lower crude 4-year cumulative event rates (Figure 3). After adjusting for baseline characteristics, the only persistent

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difference was for Japanese patients, who experienced fewer ischemic events (HR 0.61 [95% CI: 0.45; 0.83], $p<0.01$; Figure 3). Complete analysis of outcomes according to geographic region are shown in **Figure 3**.

Risk factors associated with systemic ischemic events

Renal impairment (HR=2.98 [95% CI: 1.69; 3.12], $p<0.01$), heart failure (HR=1.65 [95% CI: 1.34; 2.02] $p<0.01$), history of diabetes (HR=1.50 [95% CI: 1.26; 1.78], $p<0.01$), history of MI (HR=1.33 [95% CI: 1.07; 1.64] $p=0.01$), vascular disease (single or poly; HR=1.36, 95% CI: [1.09, 1.70] $p<0.01$)], and older age (per additional year: HR=1.03 [95% CI: 1.02; 1.04], $p<0.01$) were associated with increased systemic ischemic events (Figure 3). No sex or race/ethnicity associations were observed. Statin use was associated with decreased systemic ischemic risk (HR=0.82 [95% CI: 0.69; 0.99]; $p=0.03$; Figure 4).

Limb ischemic events

The 2-year rate of the composite endpoint of limb ischemic events was 5.7%. Angioplasty and/or stenting for PAD accounted for 3.2% of these events, peripheral bypass graft accounted for 2.1%, and lower limb amputation accounted for 1.3% (patients could experience more than one event, explaining why the total was lower than the sum of each event). Overall, the composite outcome of systemic and limb ischemic events was 11.9% at 2 years.

Discussion

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This contemporary and geographically diverse study of patients with symptomatic PAD in routine clinical practice confirmed that the ischemic event rate remains high, with a cumulative 4-year systemic event risk of 17.6%, mainly driven by cardiovascular mortality. The rate increased over follow-up (~4% to 5% per year) and there were no major differences observed across the geographic regions except for Japan, where patients experienced a lower rate of ischemic events over time. PAD patients also experienced relatively high rates of severe limb ischemic events (approximately 6% at 2 years, including a 1.3% rate of major amputations). Independent risk factors associated with the increased systemic ischemic event rate were renal impairment, heart failure, single or poly vascular disease, a history of MI, a history of diabetes, and older age. Statin use was the only factor associated with a decreased risk of recurrent ischemic events over 4 years.

The factors associated with increased ischemic events observed in this analysis were consistent with the usual cardiovascular risk factors for atherosclerotic disease.[2, 13, 14] A previous analysis of the REACH registry[9] and other studies[15-18] suggest that patients with PAD do not achieve cardiovascular risk factor control as frequently as patients with other established atherothrombotic diseases, such as cerebrovascular disease or cardiovascular disease. In the REACH Registry, PAD patients with 3 to 5 controlled risk factors had fewer major cardiovascular events (i.e., MI, stroke, cardiovascular death) compared with PAD patients with poor control (0 to 2 risk factors controlled; 2.66% vs. 3.52% one-year rates; p=0.17).[19, 20]

In the present analysis, use of statin therapy was associated with reduced risk of ischemic events. European and US guidelines recommend LDL-cholesterol reduction in

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patients at high cardiovascular risk.[21, 22] A previous analysis of the REACH registry showed a reduction of adverse limb outcomes in patients treated with statins for symptomatic PAD as well as overall ischemic events.[23] The addition of more potent treatment regimens and more aggressive reduction of LDL-cholesterol could provide even greater risk reduction. One study that assessed a composite outcome of coronary heart disease, cerebrovascular disease and peripheral vascular disease events demonstrated that both statins and ezetimibe were associated with reductions in the risk of the composite outcome.[24] In addition, the new PCSK9 inhibitors, such as alirocumab or evolocumab, showed a reduction in LDL-cholesterol levels when added to maximally tolerated statin therapy. Post hoc analyses have also suggested a reduction in cardiovascular event rates in high risk patients with established cardiovascular disease receiving these agents,[25, 26] but results from ongoing clinical trials are needed[27, 28] and these agents have yet to be assessed in the specific population of PAD patients.

Residual ischemic risk was uniformly distributed over the different geographic areas, except for Japan, where patients experienced lower event rates. The explanations for such differences have been described previously.[29] Briefly, differences in disease management and medication use have been reported (in particular, the use of clopidogrel is substantially higher in Japan than in other regions of the world), which may have contributed to some extent in the improved outcomes in Japan, supported by evidence that clopidogrel use may be superior to aspirin in reducing major cardiovascular events in PAD patients.[30, 31] In addition, gaps in country-based payer policies and healthcare systems might explain differences in risk factor prevalence and management. Moreover, genetic susceptibilities and lifestyle differences may

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also play role in risk variation.[29] Nevertheless, residual risk remains high, and events accrued progressively over time across all geographic areas.

Antiplatelet agents are a cornerstone of the treatment of atherothrombotic disease. Patients with previous stroke or TIA were excluded from the present analysis as they present a specific risk to benefit balance of antithrombotic use.[10] However, antiplatelet agents were not associated with a statistically significant reduction in risk of systemic ischemic events in the present analysis. This may be related to the relatively lower efficacy of aspirin compared with clopidogrel or other antiplatelet agents in patients with PAD,[32, 33] the high proportion of patients in the REACH registry receiving aspirin as the antiplatelet agent, or that the analysis was not powered to show statistical significance.

More intensive antiplatelet treatment strategies might provide additional benefit in patients with PAD. A post hoc analysis of data from the CHARISMA trial in a subgroup of patients diagnosed with PAD showed a trend for a benefit of clopidogrel plus aspirin over aspirin alone in this population, with a reduction in MI rates.[19, 34] At the time the REACH registry was established, the novel oral antithrombotic agents prasugrel, ticagrelor, vorapaxar, or rivaroxaban were not available. Therefore, the present analysis cannot provide insights on the benefit of those agents.

Results of the EUCLID trial, which compared monotherapy with ticagrelor or clopidogrel in PAD patients without indication for dual antiplatelet therapy, did not show a reduction in composite ischemic or limb events or in major bleeding, although a reduction in ischemic stroke was observed.[35] Of note, patients who were homozygogous for loss of function alleles to clopidogrel were excluded, though this exclusion did not seem to be the

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cause of the overall neutral results for ticagrelor versus clopidogrel. Therefore, all patients included in the EUCLID trial were receiving effective antiplatelet therapy.[35]

The use of a dual antiplatelet therapy rather than a single antiplatelet therapy might provide additional benefit for PAD patients. A subgroup analysis of the PLATO trial showed that the benefit of ticagrelor over clopidogrel in acute coronary syndrome patients was consistent in the subgroup of PAD patients compared with the global population.[36] A similar analysis from the post-MI PEGASUS trial also showed a consistent benefit of ticagrelor over placebo in addition to aspirin in post MI patients with PAD.[37, 38] Similarly, a recent analysis from the DAPT trial showed clear benefit of prolonged dual antiplatelet therapy in PAD patients treated with coronary stents.[39] Recently, vorapaxar, a PAR1 platelet receptor antagonist has been evaluated in addition to aspirin in the TRA-2P-TIMI50 trial in a secondary prevention setting in patients with stable atherosclerosis (defined as prior MI or stroke within the previous 2 weeks to 12 months prior to randomization) or PAD (defined as claudication and abnormal ABI or prior revascularization). In that trial, vorapaxar demonstrated a reduction in ischemic events at 3 years, including hospitalization for acute limb ischemia and peripheral revascularization.[40] Another strategy to increase antithrombotic intensity could be the addition of an anticoagulant to aspirin. The COMPASS trial (NCT01776424) assesses the effect of the addition of rivaroxaban to aspirin versus rivaroxaban alone or aspirin alone in patients with established CAD or PAD and will provide information regarding potential benefits and risks of this approach.

There are some limitations to the present analyis. The collection of limb events and systemic events was not done in the exact same method, and there was no assignment of a

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precise date for limb events. Additionally, limb events were tracked on a declarative basis at the end of follow-up, leading to some missing data at the 4-year time point. Consequently, our analysis was underpowered to determine risk factors for these occurences. These analyses are drawn from an observational registry, the results presented here are therefore descriptive, and analyses on the determinants of residual risk as well as analyses on geographic differences must be interpreted cautiously. Clinical events were not adjudicated in the REACH registry, but measures were taken to select high quality physicians, and diagnoses were provided by hospitals and doctors based on their expertise. Patient adherence to medication was not captured in the registry and adherence could impact patient outcomes. Finally, although the data were taken from a large cohort, the analysis may have been underpowered for some comparisons.

In conclusion, this analysis of the REACH registry showed an important ischemic risk in patients with PAD, continuously increasing over the 4 years of follow-up and mainly driven by CV mortality. Limb ischemic events represent a substantial additional burden to that related to systemic ischemic events in this population. Secondary prevention strategies, including enhanced antithrombotic treatment and more intense lipid lowering, may be useful to improve prevention of ischemic and limb vascular events in this high-risk population.

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Figure legends

Figure 1. Cumulative incidence rates of primary outcome of cardiovascular death, MI or stroke for post-MI patients with no history of TIA/Stroke.

Figure 2. Cumulative incidence rates of cardiovascular outcomes in PAD patients with no history of stroke or TIA by year of follow up

Figure 3 Hazard Ratio for the primary outcome of cardiovascular death, MI, or stroke for post-MI patients with no history of TIA/Stroke according to geographic regions after adjustment with the REACH risk score.

Figure 4. Hazard ratios of determinants for the primary outcome of cardiovascular death, non-fatal MI, and non-fatal stroke estimated by multivariate Cox models in PAD patients with no history of TIA/Stroke.

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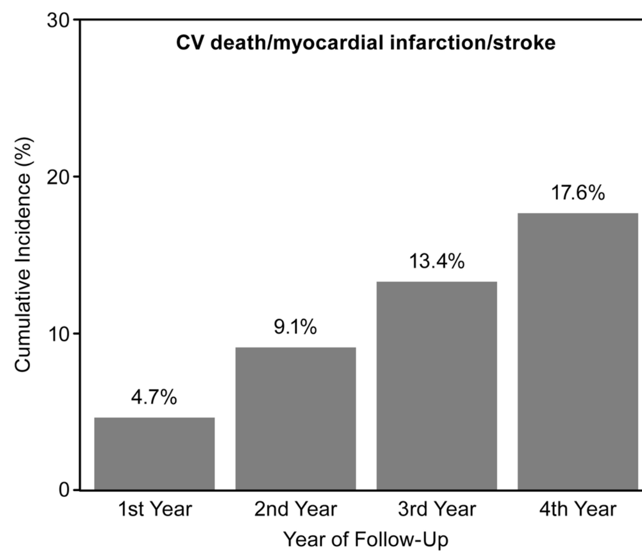

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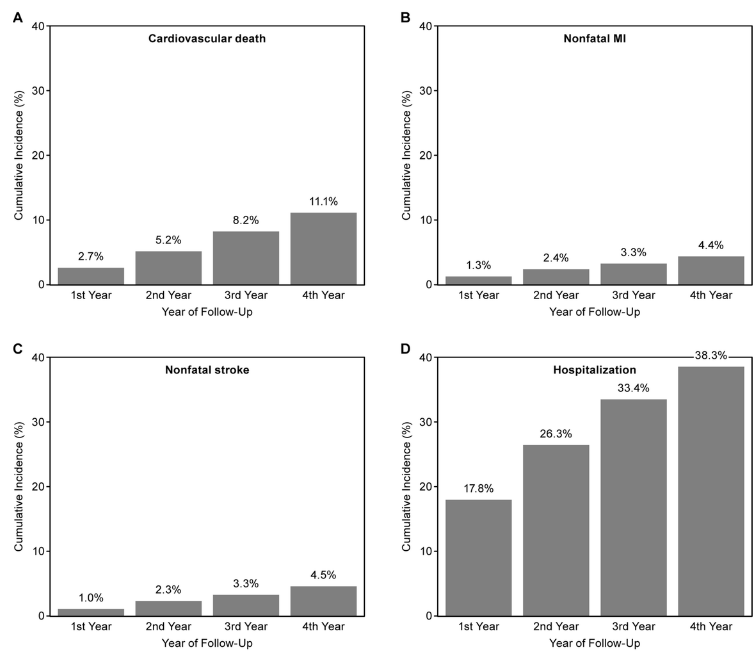

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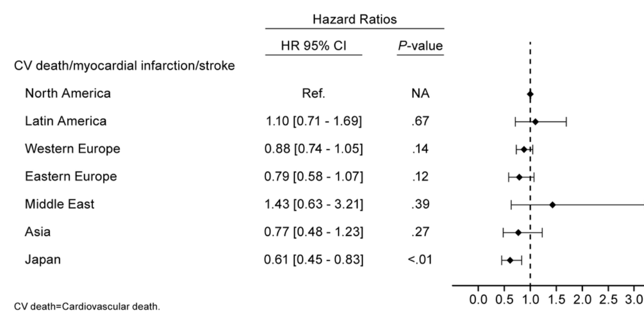

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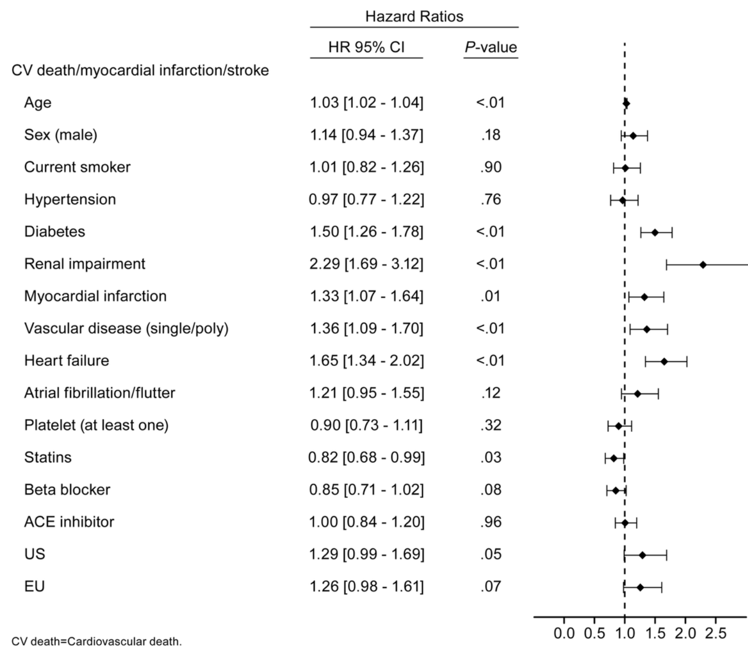

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Table 1. Baseline Patient Demographics and Clinical Characteristics

	PAD patient without history of stroke /TIA							
	North America n = 1785	**Latin America n = 162**	**Western EU n = 2702**	**Eastern EU n = 441**	**Middle East n = 38**	**Asia n = 213**	**Japan n = 473**	**Total N=6,005**
Age, mean (SD)	70.44 (10.1)	68.73 (10.73)	68 (9.71)	62.92 (8.65)	66.14 (10.84)	66.22 (9.27)	72.03 (8.04)	70.52 (9.52)
Median	71.3	69.1	68.5	63.5	66.8	66.7	73.0	71.39
Range (q1 – q3)	63.3 – 78.7	62.4 – 76.9	61.0 – 75.0	56.4 – 68.6	54.7 – 74.7	58.8 – 72.8	67.6 – 77.5	64.01 - 77.29
Men	1109 (62.1%)	100 (62.5%)	2057 (76.2%)	346 (78.5%)	30 (78.9%)	139 (65.3%)	394 (83.3%)	1261 (69.2%)
Diabetes	897 (50.5%)	96 (59.3%)	975 (36.4%)	152 (34.6%)	20 (52.6%)	148 (69.5%)	177 (37.4%)	855 (47.3%)
Hypertension	1540 (86.3%)	136 (84%)	2000 (74%)	325 (73.7%)	32 (84.2%)	166 (77.9%)	362 (76.5%)	1625 (89.1%)
Dyslipidemia	1437 (80.6%)	74 (45.7%)	1750 (64.8%)	237 (53.9%)	28 (73.7%)	133 (62.4%)	166 (35.1%)	1205 (66.2%)
Renal Impairment	69 (4.6%)	4 (4%)	35 (1.9%)	4 (1%)	2 (7.1%)	18 (10.9%)	31 (7.9%)	53 (3.7%)
Angina								
Stable Angina	502 (28.7%)	28 (17.7%)	639 (23.9%)	181 (41.3%)	10 (26.3%)	47 (22.6%)	78 (16.6%)	692 (38.7%)
Unstable Angina	214 (12.2%)	16 (10.1%)	195 (7.3%)	68 (15.6%)	4 (10.5%)	25 (12%)	24 (5.1%)	358 (20.1%)
Polyvascular Disease*	1072 (60.1%)	61 (37.7%)	1196 (44.3%)	260 (59%)	22 (57.9%)	97 (45.5%)	134 (28.3%)	1824 (100%)
History of MI								
<=1year	109 (6.2%)	4 (2.6%)	110 (4.1%)	41 (9.3%)	2 (5.4%)	11 (5.3%)	8 (1.7%)	122 (6.8%)
> 1year	473 (26.9%)	26 (17%)	517 (19.3%)	104 (23.6%)	10 (27%)	24 (11.6%)	43 (9.1%)	470 (26.2%)
Atrial Fibrillation/Flutter	218 (12.4%)	5 (3.2%)	250 (9.5%)	52 (11.9%)	2 (5.4%)	9 (4.3%)	35 (7.4%)	290 (16.3%)
Congestive heart failure	372 (21.1%)	8 (5%)	341 (12.9%)	57 (13.1%)	7 (18.4%)	27 (12.9%)	27 (5.7%)	407 (22.9%)
Obesity								
Overweight (BMI, 25->30)	677 (52.2%)	71 (74.7%)	1199 (67.5%)	178 (61.6%)	19 (65.5%)	61 (79.2%)	107 (93%)	717 (63.8%)
Class I (BMI, 30->35)	396 (30.5%)	22 (23.2%)	460 (25.9%)	96 (33.2%)	7 (24.1%)	14 (18.2%)	8 (7%)	278 (24.7%)
Class II (BMI, 35->40)	145 (11.2%)	1 (1.1%)	93 (5.2%)	13 (4.5%)	2 (6.9%)	2 (2.6%)	0 (0%)	89 (7.9%)
Class III (BMI≥40)	79 (6.1%)	1 (1.1%)	24 (1.4%)	2 (0.7%)	1 (3.4%)	0 (0%)	0 (0%)	40 (3.6%)
Smoker								
Former	962 (54.9%)	81 (52.3%)	1333 (51.1%)	168 (38.2%)	10 (28.6%)	85 (40.3%)	280 (61.4%)	859 (49%)
Current	395 (22.6%)	24 (15.5%)	741 (28.4%)	172 (39.1%)	14 (40%)	27 (12.8%)	98 (21.5%)	366 (20.9%)
Medication								
Acetylsalicylic acid	1303 (73.1%)	125 (77.2%)	1536 (57%)	328 (74.4%)	30 (78.9%)	118 (55.4%)	166 (35.1%)	1111 (61.4%)
At least one antiplatelet	1456 (81.6%)	138 (85.2%)	2170 (80.4%)	383 (86.8%)	35 (92.1%)	164 (77%)	384 (81.2%)	1513 (83.2%)
Angiotensin converting enzyme inhibitors	815 (46%)	58 (36.3%)	1097 (40.8%)	266 (60.3%)	17 (45.9%)	65 (30.5%)	88 (18.6%)	909 (50.4%)

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Angiotensin II receptor antagonists	448 (25.4%)	30 (18.8%)	493 (18.4%)	13 (3%)	8 (21.6%)	64 (30.2%)	139 (29.4%)	360 (20.1%)
Nitrates/other anti-angina	371 (21.4%)	22 (13.8%)	511 (19.3%)	156 (35.5%)	9 (24.3%)	52 (24.6%)	97 (20.5%)	493 (27.7%)
Statin	1371 (76.9%)	72 (44.4%)	1673 (62%)	242 (54.9%)	28 (73.7%)	134 (62.9%)	143 (30.2%)	1192 (65.5%)
Betablockers	943 (53.1%)	35 (21.7%)	1002 (37.3%)	203 (46%)	15 (40.5%)	80 (37.6%)	60 (12.7%)	731 (40.5%)

*Polyvascular disease was defined as coexistent symptomatic (clinically recognized) arterial disease in 2 or 3 territories (coronary, cerebral, and/or peripheral) within each patient.

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