Carotid Atherosclerosis and Risk of Subsequent Coronary Event in Outpatients With Atherothrombosis

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Background and Purpose—The presence of carotid plaque reflects overall atherosclerotic burden and may predict coronary artery disease events. We examined the association among carotid atherosclerosis, history of atherothrombotic events, and risk of coronary events.

Methods—Among 45,227 patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry with 4-year follow-up, 23,364 patients with information on carotid atherosclerosis at baseline were analyzed. The primary outcome was the composite of first occurrence of cardiovascular death, myocardial infarction, or coronary hospitalization.

Results—The carotid atherosclerosis was present in 46% of patients (n=10,725) and was associated with increasing conventional cardiovascular risk factors and extent of symptomatic vascular disease. During 4-year follow-up, 4,304 patients experienced ≥1 coronary event. After adjustment for cardiovascular risk factors and geographic region, the risk of coronary events increased by 22% (95% confidence interval [CI], 14%–30%) in patients with versus without carotid atherosclerosis. The relative increase was 18% (95% CI, 7%–31%) in patients enrolled with multiple risk factors only, 25% (95% CI, 16%–35%) in patients with coronary artery disease, 46% (95% CI, 28%–65%) in patients with cerebrovascular disease, and 37% (95% CI, 17%–60%) in patients with peripheral artery disease. Carotid atherosclerosis was associated with increased risk, even among patients with previous myocardial infarction but no known stroke (P=0.001) or among patients with previous stroke but no known myocardial infarction (P<0.001).

Conclusions—Carotid atherosclerosis was an independent predictor of coronary events across all types of symptomatic vascular disease and had an incremental effect on risk regardless of risk factors or location of vessel disease. (Stroke. 2013;44:373-379.)

Key Words: atherosclerosis ■ carotid plaque ■ coronary disease

In recent years, several studies have assessed the relationship between the presence of atherosclerosis in carotid arteries and the risk of coronary artery disease (CAD) or cardiovascular events. Carotid artery disease, even in its preclinical stage, has been associated with CAD and an increased risk of cardiovascular events.1,2 Carotid artery intima media thickness (IMT) has been shown to be a strong predictor of incident myocardial infarction (MI) in the general population aged ≥55 years,3,4 and good correlation between increased IMT and the presence of CAD has been reported. Studies using postmortem examination and ultrasound techniques have found a close relationship between atherosclerosis in the carotid and coronary arteries.5,6

Studies using either systematic coronary angiography or noninvasive computed tomography coronary angiography have documented a high prevalence of coronary atherosclerosis in patients with nonfatal cerebral infarction and without history of CAD.7,8

It has been recently reported that IMT of the internal carotid artery adds predictive value to the Framingham risk score, and that the presence of plaque improves the prediction of new-onset cardiovascular disease.9 In a case–control study, carotid IMT, carotid plaques, and Framingham score were independently associated with stroke risk.10 This study showed that each of these explained part of the risk and that their evaluation is not redundant but may be synergistic.

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Like IMT, the presence of carotid plaque reflects the overall atherosclerotic burden and may predict cardiovascular death and nonfatal MI.11 So far, most of the information available on atherothrombosis risk has been derived from single-country studies or a single subtype of patient, and is generally limited to hospitalized patients or those in clinical trials. Using data from a large international registry of stable outpatients with or at risk for atherothrombosis, the Reduction of Atherothrombosis for Continued Health (REACH) Registry,12 we examined the association between the presence of carotid atherosclerosis, history of atherothrombotic events, and risk of subsequent coronary events.

Methods
The rationale, design, baseline, and follow-up data of the REACH Registry have been previously published.13-17 In brief, the REACH Registry is an international, prospective, observational registry designed to provide up to 24 months of clinical follow-up of >68,000 outpatients from 5473 sites in 44 countries. After the initial follow-up, an additional 2-year extension was proposed, and 29 countries (3647 sites enrolled 45,227 patients) decided to participate.16 The present study included patients with 4-year follow-up and available carotid plaque status at baseline. All participants provided informed consent, and ethics committees in each country approved the study.

Patients and Definitions
Patients aged ≥45 years with ≥3 risk factors for atherosclerosis or established CAD, peripheral artery disease (PAD), or cerebrovascular disease (CVD) were enrolled during 2003–2004 and followed-up until 2008. Risk factors were diabetes mellitus, diabetic nephropathy, ankle–brachial index <0.9, asymptomatic carotid stenosis ≥70%, presence of ≥1 carotid plaque, systolic blood pressure ≥150 mm Hg, despite treatment, hypercholesterolemia treated with medication, current smoking ≥15 cigarettes/day, and age ≥65 years (men) or ≥70 years (women). Documented CAD consisted of ≥1 of the following: stable angina; history of unstable angina; history of percutaneous coronary intervention; history of coronary artery bypass grafting; or previous MI. Documented CVD consisted of a neurologist/hospital report of the diagnosis of ischemic stroke or transient ischemic attack. Documented PAD consisted of current intermittent claudication with ankle–brachial index <0.9 and 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.

Data Collection
Detailed information (demographics, medical history, clinical examination, risk factors, and medications) was collected via standardized case report forms at baseline.12 Our study focused on the presence of carotid atherosclerosis (all patients with carotid plaque, regardless of the presence of lumen stenosis or not) reported by physicians as evidence of ≥1 carotid plaque, asymptomatic carotid stenosis ≥70%, or history of carotid revascularization. Focused on the distal part of the common carotid artery, the carotid bulb, or in the proximal parts of the internal or external carotid artery, carotid plaque was defined as a distinct area with an IMT exceeding twice that of the neighboring sites.13 Follow-up information, including medications, death, cardiovascular events, hospitalization, and vascular interventions, was systematically collected annually for 4 years.

Outcomes
The primary outcome for this analysis was the composite of first occurrence of cardiovascular death, MI, or coronary hospitalization. A secondary prespecified outcome was defined as the first occurrence of MI (fatal or nonfatal). Endpoints were not adjudicated. Cardiovascular death included fatal stroke, fatal MI, or other cardiovascular death (other death of cardiac origin; pulmonary embolism; any sudden death, including unobserved and unexpected death (eg, while sleeping) unless proven otherwise by autopsy; death after a vascular operation, vascular procedure, or amputation; death attributed to heart failure; death after 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, irrespective of the cause, in the next 28 days was considered to be a fatal MI or fatal stroke. Coronary hospitalization consisted of hospitalization for unstable angina, coronary artery bypass grafting, or coronary angioplasty/stenting.

Statistical Analysis
To assess the selection bias related to missing information on carotid atherosclerosis, we compared the baseline characteristics between the included and nonincluded patients using Student t test for continuous variables and the χ2 test for categorical variables. We also estimated the absolute standardized differences (expressed as percentages of pooled standardized differences) to identify the most important differences. An absolute standardized difference of ≤10% indicates inconsequential imbalance.

We calculated and compared the age- and sex-adjusted prevalence rates of carotid atherosclerosis across baseline characteristics using logistic regression analysis. The difference in prevalence according to number of symptomatic arterial disease locations was tested using the test for trend in the multiple logistic model.

We further investigated the impact of the presence of carotid atherosclerosis on 4-year coronary risk through the calculation of hazard ratios (HRs) for the selected end points using a Cox proportional hazards model adjusted for age and sex. Cox proportional hazard models were further adjusted on prespecified confounding variables, including cardiovascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, obesity, current smoking, heart failure, and atrial fibrillation) and geographic region. For a given end point, deaths that were not included in the end point were treated as censored events. The proportional hazard assumptions were checked using the log–log survival plots and by introducing a time-dependent variable into models. Adjusted event rates were calculated using the corrected group prognosis method;18 adjustment for age was made using the quartile values.

Our first analyses concerned the entire study group. Further analyses were performed for 4 subsets (patients with ≥3 risk factors only and those with CAD, CVD, or PAD) and were stratified according to the number of symptomatic arterial disease locations. Finally, to assess whether patients with ischemic stroke and carotid atherosclerosis were at similar risk as patients with CAD, we calculated and compared the carotid atherosclerosis–specific rates of coronary events in patients enrolled with ischemic stroke but no history of MI and those enrolled with MI but no history of ischemic stroke.

Statistical testing was performed at the 2-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute).

Results
Among 45,227 patients with a 4-year follow-up, carotid atherosclerosis status was available for 23,364 patients (52%) who were included in this analysis. Baseline characteristics for included and excluded patients are available in Table I in the online-only Data Supplement. The main difference between the groups was a higher rate of previous CVD in included patients (34% vs 22%; P<0.0001). Carotid atherosclerosis was present in 10,725 of 23,364 included patients (46%). Most patients with carotid atherosclerosis were recruited in Western and Eastern Europe (Figure 1).
Baseline Characteristics and Carotid Atherosclerosis

Baseline characteristics and the associated prevalence of carotid atherosclerosis are reported in Table 1. Except for diabetes mellitus, hypercholesterolemia, and obesity, all conventional cardiovascular risk factors were associated with an increased prevalence of carotid atherosclerosis. The highest prevalence was found for patients with PAD or CVD (Table 1). The use of antidiabetic drugs and angiotensin II receptor blockers was associated with a lower prevalence of...
carotid atherosclerosis, in contrast to other antihypertensive or antithrombotic drugs. With respect to lipid-lowering treatment, the prevalence of carotid atherosclerosis was similar between patients with or without statins.

Both the extent (ie, number of symptomatic arterial beds) and the severity of symptomatic vascular disease were associated with increased prevalence of carotid atherosclerosis. The age- and sex-adjusted prevalence rate increased significantly from 34% in patients with risk factors only to 80% in those with 3 vascular diseases (Figure 2).

Carotid Atherosclerosis and 4-Year Coronary Event Risk

During 4-year follow-up, there were 1406 cardiovascular deaths (including 374 fatal MIs), 723 nonfatal MIs, and 2956 coronary hospitalizations (including 2194 unstable angina cases). A total of 4304 patients experienced ≥1 coronary event, yielding an overall estimated 4-year risk of 21.3% (95% confidence interval [CI], 20.6%–21.9%).

Among the entire study population, 4-year age- and sex-adjusted coronary event rates were higher among patients with versus without carotid atherosclerosis (Table 2). In multivariable analysis, including all cardiovascular risk factors and geographic region, the greatest between-group difference was observed for nonfatal MI (HR, 1.52; 95% CI, 1.30–1.77) when carotid atherosclerosis was present. However, although the presence of carotid atherosclerosis was associated with an increased risk of coronary events in patients with previous symptomatic arterial disease, this effect was not observed among patients enrolled with multiple risk factors only (Table 2).

For any coronary event, the presence of carotid atherosclerosis resulted in adjusted HRs of 1.25 among patients with CAD, 1.46 among those with CVD, and 1.37 among those with PAD (Table 2). Similar results were found with respect to the major coronary outcome of nonfatal/fatal MI.

Regarding the number of symptomatic atherothrombosis disease locations, carotid atherosclerosis predicted risk of coronary events among patients with polyvascular disease, although they did not reach significance in patients with triple arterial disease (Figure 3). Adjusted HRs among patients with polyvascular disease (2 or 3 locations) were 1.34 (95% CI, 1.17–1.53) for any coronary event and 1.70 (95% CI, 1.29–2.23) for nonfatal/fatal MI.

Carotid Atherosclerosis in Stroke and Incremental Coronary Risk

Among patients enrolled with symptomatic atherothrombosis disease, 4652 had previous ischemic stroke without previous MI, and 5751 had previous MI without previous ischemic stroke. Coronary event rates in these 2 groups of patients with single major vascular disease are shown in Figure 4. In both groups, carotid atherosclerosis independently predicted coronary risk, with multivariable-adjusted HRs of 1.36 (95% CI, 1.13–1.63) in ischemic stroke patients and 1.32 (95% CI, 1.18–1.47) in MI patients for any coronary events. The corresponding multivariable-adjusted HR for major coronary end points were 1.54 (95% CI, 1.09–2.17) and 1.37 (95% CI, 1.11–1.70), respectively. Carotid atherosclerosis, therefore, had an incremental effect on the risk of coronary events, although the risk of any coronary events among ischemic stroke patients with carotid atherosclerosis was significantly lower than among MI patients without carotid atherosclerosis (age- and sex-adjusted HR, 0.61; 95% CI, 0.54–0.69). Further adjustment of cardiovascular risk factors and geographic region did not substantially affect the results (fully adjusted HR, 0.60; 95% CI, 0.53–0.69). This difference was attenuated with major coronary end points and was no longer significant after adjustment of cardiovascular risk factors and geographic region (fully adjusted HR, 0.85; 95% CI, 0.66–1.10; P=0.21).

Discussion

In this large cohort of outpatients with established atherosclerosis disease, we found an incremental risk of coronary events beyond the risk associated with conventional risk factors in patients with versus without carotid atherosclerosis.

The REACH Registry includes an international and contemporary cohort of outpatients with risk factors only or with established atherothrombotic disease treated according to current guidelines. Approximately 46% of patients presented with carotid atherosclerosis, although this varied widely by geographic region. Carotid atherosclerosis was associated with conventional cardiovascular risk factors, as has been reported.19,20 The rate of carotid atherosclerosis increased with the number of affected vascular territories, reaching 80% among patients with 3 vascular sites. These results confirm the overlap between cerebral, coronary, and peripheral atherosclerosis diseases.7

Four-year coronary risks were 23.2% and 19.3% in patients with and without carotid atherosclerosis, respectively. A greater difference between patients with and without carotid atherosclerosis was observed for nonfatal MI, with a relative risk increase of 52%. This is consistent with previous population-based studies showing that carotid plaque is an independent predictor of coronary events3,21,22 and improves the risk stratification for the occurrence of cardiovascular disease.5,23 To the best of our knowledge, no study has described the impact of carotid atherosclerosis on the long-term risk of coronary events by history of atherothrombotic events or vascular beds involved. We have shown that the presence of carotid atherosclerosis predicts the risk of coronary events in patients with a history of atherothrombotic events, irrespective of the arterial bed involved (CVD, CAD, or PAD). In addition,
its predictive value increased with the number of affected arterial beds.

It has been suggested that plaque formation in carotid and coronary arteries is closely related and has a common atherogenesis process. On the basis of studies of high-sensitivity C-reactive protein levels in patients with both CAD and echolucent carotid plaques, a common inflammatory process may be involved in plaque instability in carotid and coronary plaques. Furthermore, echolucent carotid plaques also have been associated with plaque instability, because they predict the existence of complex coronary plaques and future coronary events in patients with stable coronary disease. However, plaques seem to appear later in the carotids than in the aorta and coronary arteries. Therefore, the phase of plaque formation in the 2 arterial territories may differ. Our finding that the mere presence of carotid atherosclerosis independently increases the risk of coronary events across various disease locations is in favor of carotid atherosclerosis being a marker of disease severity.

The autopsy prevalence of silent myocardial ischemia has been reported to be as high as 40% in a large series of consecutive patients with fatal cerebral infarction, with a

Table 2. Four-Year Coronary Event Rates in Patients With and Without Carotid Atherosclerosis at Baseline for the Total Population and Main Subsets

<table>
<thead>
<tr>
<th>Event</th>
<th>CA (−)</th>
<th>CA (+)</th>
<th>P Value</th>
<th>HR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients n=12639</td>
<td>19.3</td>
<td>23.2</td>
<td>&lt;0.0001</td>
<td>1.22 (1.14–1.30)</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>6.6</td>
<td>8.2</td>
<td>&lt;0.0001</td>
<td>1.24 (1.11–1.39)</td>
</tr>
<tr>
<td>CV death</td>
<td>3.2</td>
<td>4.5</td>
<td>&lt;0.0001</td>
<td>1.52 (1.30–1.77)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>13.1</td>
<td>16.3</td>
<td>&lt;0.0001</td>
<td>1.24 (1.14–1.33)</td>
</tr>
<tr>
<td>Coronary hospitalization‡</td>
<td>4.8</td>
<td>6.3</td>
<td>&lt;0.0001</td>
<td>1.38 (1.21–1.57)</td>
</tr>
<tr>
<td>Patients with ≥3 risk factors only n=2600</td>
<td>10.9</td>
<td>10.4</td>
<td>0.69</td>
<td>1.18 (0.93–1.51)</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>5.2</td>
<td>3.8</td>
<td>1.00</td>
<td>1.27 (0.76–2.14)</td>
</tr>
<tr>
<td>CV death</td>
<td>2.6</td>
<td>2.6</td>
<td>0.77</td>
<td>1.37 (0.98–1.90)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>6.0</td>
<td>6.2</td>
<td>0.52</td>
<td>1.12 (0.72–1.74)</td>
</tr>
<tr>
<td>Fatal and nonfatal MI</td>
<td>3.7</td>
<td>3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with CAD n=7137</td>
<td>25.2</td>
<td>31.7</td>
<td>&lt;0.0001</td>
<td>1.25 (1.16–1.35)</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>7.5</td>
<td>10.1</td>
<td>&lt;0.0001</td>
<td>1.28 (1.12–1.47)</td>
</tr>
<tr>
<td>CV death</td>
<td>3.8</td>
<td>5.8</td>
<td>&lt;0.0001</td>
<td>1.61 (1.33–1.94)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>18.6</td>
<td>23.9</td>
<td>&lt;0.0001</td>
<td>1.25 (1.15–1.37)</td>
</tr>
<tr>
<td>Coronary hospitalization‡</td>
<td>5.7</td>
<td>8.4</td>
<td>&lt;0.0001</td>
<td>1.50 (1.28–1.75)</td>
</tr>
<tr>
<td>Patients with CVD n=3139</td>
<td>14.8</td>
<td>21.7</td>
<td>&lt;0.0001</td>
<td>1.46 (1.28–1.65)</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>6.6</td>
<td>9.3</td>
<td>0.0001</td>
<td>1.42 (1.16–1.73)</td>
</tr>
<tr>
<td>CV death</td>
<td>3.1</td>
<td>4.4</td>
<td>0.005</td>
<td>1.56 (1.17–2.08)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>8.0</td>
<td>13.8</td>
<td>&lt;0.0001</td>
<td>1.59 (1.35–1.88)</td>
</tr>
<tr>
<td>Coronary hospitalization‡</td>
<td>4.5</td>
<td>6.3</td>
<td>0.002</td>
<td>1.46 (1.15–1.86)</td>
</tr>
<tr>
<td>Patients with PAD n=1362</td>
<td>22.9</td>
<td>30.5</td>
<td>&lt;0.0001</td>
<td>1.37 (1.17–1.60)</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>9.6</td>
<td>13.1</td>
<td>0.004</td>
<td>1.28 (1.00–1.64)</td>
</tr>
<tr>
<td>CV death</td>
<td>3.8</td>
<td>6.5</td>
<td>0.003</td>
<td>1.82 (1.23–2.71)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14.0</td>
<td>20.7</td>
<td>&lt;0.0001</td>
<td>1.49 (1.22–1.82)</td>
</tr>
<tr>
<td>Coronary hospitalization‡</td>
<td>6.2</td>
<td>9.7</td>
<td>0.001</td>
<td>1.57 (1.15–2.15)</td>
</tr>
<tr>
<td>Fatal and nonfatal MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CA indicates carotid atherosclerosis; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; CVD, cerebrovascular disease; HR, hazard ratio; MI, myocardial infarction; and PAD, peripheral artery disease.

*Adjusted by age and sex.
†Calculated using Cox regression analysis adjusted for age, sex, cardiovascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, obesity, current smoking, heart failure, and atrial fibrillation), and geographic region (calculated on the basis of the sample of patients with nonmissing covariates: all patients, n=21929; patients with ≥3 risk factors only, n=3756; patients with CAD, n=12178; patients with CVD, n=7437; patients with PAD, n=3301).
‡Unstable angina or coronary revascularization procedure.
strong correlation between the presence of silent CAD and the presence of carotid plaque or stenosis, suggesting a strong relationship between cerebral and coronary atherosclerosis. The same correlation was found in a large series of patients with nonfatal cerebral infarction. As depicted in Figure 4, data from the REACH Registry show that the presence of carotid atherosclerosis in stroke patients and in patients with CAD independently predicts the risk of coronary events with an incremental effect.

Despite the high-quality data of the REACH Registry (with a large sample size from stable outpatients with various manifestations of atherothrombosis enrolled from different countries), several limitations must be considered. The REACH Registry was not a community-based study and involved a broad range of physicians from many specialties, including 40% family practitioners. Events were not adjudicated, which introduces a possible bias. More importantly, a selection bias may have been introduced because of the definition and missing information of carotid atherosclerosis, supported by the difference in baseline characteristics between patients with and without carotid atherosclerosis information. In addition, the lack of uniform standards for the evaluation of carotid plaques may limit the reliability of diagnosis and underestimate the predictive value of carotid atherosclerosis for subsequent coronary risk. Finally, we could not take into account of the severity and number of previous ischemic events, which may influence the risk of recurrent ischemic events.

Conclusions

The presence of carotid atherosclerosis is a marker of disease severity, being independently associated with an incremental effect on the risk of future coronary events across PAD, CAD, and CVD subgroups, and this incremental effect is increased with the number of vascular beds involved.

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References


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SUPPLEMENTAL MATERIAL
Supplemental Tables

Supplemental Table S1. Baseline Characteristics of Included and Non-Included Patients

<table>
<thead>
<tr>
<th></th>
<th>Included (n=23,364)</th>
<th>Not Included (n=21,863)</th>
<th>P-Value*</th>
<th>Absolute Standardized Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>68.5±10.0</td>
<td>68.3±10.0</td>
<td>0.009</td>
<td>2.4</td>
</tr>
<tr>
<td>Male</td>
<td>15,071 (64.6)</td>
<td>14,175 (64.9)</td>
<td>0.50</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9,725 (41.6)</td>
<td>9,974 (45.6)</td>
<td>&lt;0.0001</td>
<td>8.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19,249 (82.4)</td>
<td>17,503 (80.1)</td>
<td>&lt;0.0001</td>
<td>5.9</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>16,754 (71.8)</td>
<td>15,033 (68.8)</td>
<td>&lt;0.0001</td>
<td>6.5</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td>6,486 (28.1)</td>
<td>6,217 (28.7)</td>
<td>0.16</td>
<td>1.3</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3,571 (15.8)</td>
<td>3,268 (15.4)</td>
<td>0.31</td>
<td>1.0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3,204 (13.9)</td>
<td>2,881 (13.4)</td>
<td>0.15</td>
<td>1.4</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2,462 (10.7)</td>
<td>2,120 (9.9)</td>
<td>0.006</td>
<td>2.6</td>
</tr>
<tr>
<td>History of CAD</td>
<td>12,982 (55.6)</td>
<td>13,407 (61.3)</td>
<td>&lt;0.0001</td>
<td>11.7</td>
</tr>
<tr>
<td>History of CVD</td>
<td>7,973 (34.1)</td>
<td>4,832 (22.1)</td>
<td>&lt;0.0001</td>
<td>27.0</td>
</tr>
<tr>
<td>History of PAD</td>
<td>3,561 (15.2)</td>
<td>2,308 (10.6)</td>
<td>&lt;0.0001</td>
<td>14.0</td>
</tr>
<tr>
<td>≥ 1 antiplatelet drug</td>
<td>18,765 (80.4)</td>
<td>17,024 (77.9)</td>
<td>&lt;0.0001</td>
<td>6.1</td>
</tr>
<tr>
<td>Anticoagulant drug</td>
<td>2,873 (12.6)</td>
<td>2,376 (11.2)</td>
<td>&lt;0.0001</td>
<td>4.4</td>
</tr>
<tr>
<td>≥ 1 lipid-lowering drug</td>
<td>17,533 (75.1)</td>
<td>15,838 (72.5)</td>
<td>&lt;0.0001</td>
<td>6.0</td>
</tr>
<tr>
<td>≥ 1 antihypertensive drug</td>
<td>21,210 (90.8)</td>
<td>19,960 (91.4)</td>
<td>0.06</td>
<td>1.8</td>
</tr>
<tr>
<td>≥ 1 antidiabetic drug</td>
<td>8,749 (37.5)</td>
<td>8,990 (41.2)</td>
<td>&lt;0.0001</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Data are number (%) unless otherwise indicated.
*Student t test or Chi-Square test.

BMI indicates body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; SD, standard deviation.