Temporal Trends in the Incidence of Intermittent Claudication from 1950 to 1999

Joanne M. Murabito1,2, Jane C. Evans1, Ralph B. D’Agostino, Sr.1,3, Peter W. F. Wilson4, and William B. Kannel1

1 Framingham Heart Study, National Heart, Lung, and Blood Institute, Framingham, MA.
2 Section of General Internal Medicine, School of Medicine, Boston University, Boston, MA.
3 Statistics and Consulting Unit, Boston University, Boston, MA.
4 Departments of Endocrinology, Diabetes, and Medical Genetics, Medical University of South Carolina, Charleston, SC.

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Declines in coronary disease and stroke mortality have occurred, but it remains unclear whether intermittent claudication (IC) incidence and mortality rates have changed. The authors sought to examine long-term trends for IC in the community. Cases of IC among Framingham Study participants aged ≥40 years were classified according to date of onset from the 1950s to the 1990s. IC was defined as the presence of exertional calf discomfort that was relieved with rest. Age- and sex-adjusted incidence rate ratios were estimated using log-linear Poisson regression, and 10-year survival was calculated using the Kaplan-Meier method. IC occurred in 668 participants (286 women). The age- and sex-adjusted incidence rate of IC fell from 282 per 100,000 person-years during the period 1950–1969 to 225 per 100,000 person-years in the 1990s. The decline in IC incidence across time periods was significant (p for trend = 0.01), with an initial increase in the 1970s being followed by declines of 16% in the 1980s and 18% in the 1990s. Approximately 40% of persons with IC died within 10 years of diagnosis, with no significant change occurring during the study period. IC incidence has declined since 1950, but mortality has remained high and unchanged. Factors contributing to the declining incidence of IC need clarification.

cardiovascular diseases; intermittent claudication; mortality

Abbreviations: CVD, cardiovascular disease; PAD, peripheral arterial disease.

Intermittent claudication is a symptomatic expression of peripheral arterial disease (PAD), a highly prevalent atherosclerotic condition affecting more than 5 million persons in the United States (1). Claudication is associated with increased risks of mortality, nonfatal cardiovascular diseases (CVDs) (myocardial infarction, congestive heart failure, and cerebrovascular disease), and impaired lower extremity function (2–6). All major CVD risk factors, including smoking, diabetes, hypertension, and an elevated cholesterol level, are associated with increased risk of intermittent claudication (7–9). It is unclear whether or not the incidence of intermittent claudication is declining in the US population in response to changes in smoking behavior and increased awareness and treatment of hypertension and elevated blood cholesterol (10–12).

Recent national data have shown a relatively low awareness of PAD among primary care physicians and less intensive treatments for modifiable risk factors in persons with the disease as compared with persons with other manifestations of CVD (13). Thus, given that secondary prevention efforts are utilized less in PAD patients, it is uncertain whether survival following the onset of intermittent claudication has improved in parallel with improvements in survival following the onset of other CVDs such as myocardial infarction and congestive heart failure (14, 15). Although antiplatelet drug therapies effectively reduce fatal ischemic events in patients with PAD (16), these therapies, as well as other secondary prevention efforts, appear to be underutilized in patients with the disease (13).

We examined temporal trends in intermittent claudication incidence and subsequent survival among participants in the Framingham Heart Study during the time interval from 1950 through 1999. Since its inception, the Framingham Heart...
Study has used standardized criteria in the ascertainment of intermittent claudication, and the study cohorts have been monitored continuously with respect to vital status and the occurrence of CVD endpoints.

MATERIALS AND METHODS

Study sample

The Framingham Heart Study was established in 1948, enrolling 5,209 men and women aged 28–62 years in a prospective epidemiologic cohort study. Members of the original cohort have undergone follow-up examinations every 2 years. In 1971, 5,124 offspring of the original cohort members and offspring spouses ranging in age from 5 years to 70 years were enrolled in the Framingham Offspring Study. Follow-up examinations are conducted approximately every 4 years. Study design and entry criteria have been reported elsewhere (17–20). Written informed consent was obtained from all study participants, and the institutional review board of Boston Medical Center approved the examination content for both the original cohort and offspring examinations.

Ascertainment of intermittent claudication

At each original cohort and offspring cohort examination, intermittent claudication was assessed using a standardized physician-administered questionnaire (8) that asked about the presence of exertional calf discomfort related to rapidity of walking or up hill walking and whether symptoms were relieved with rest. A second physician independently interviewed all participants suspected to have claudication. A review panel comprising three Framingham Heart Study investigators examined all available evidence (including hospital records and personal physician office records) and made the final diagnostic determination of the presence of intermittent claudication. The diagnosis was adjudicated solely on the basis of medical history. Confirmation with ankle-brachial blood pressure testing was not available. If the exact date of onset of claudication was unavailable, the midpoint between the date of the last symptom-free Heart Study examination and the date of the Heart Study examination at which claudication was identified was assigned. Persons with intermittent claudication at study entry were excluded. Lower extremity bypass, lower extremity angioplasty, and lower extremity amputation for ischemia were not considered, since these data were not available at all Heart Study examinations and thus could not be compared across all decades.

Measurement of risk factors and identification of CVDs

Each Heart Study examination included a standardized medical history interview, a physical examination, laboratory testing, and electrocardiography. Blood pressure was measured twice by the examining physician with the participant in the seated position. Two blood pressure measurements were averaged to determine the presence of hypertension. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medication. Height and weight were obtained using standard protocols, and body mass index was defined as weight in kilograms divided by height in meters squared. Participants were asked whether they had smoked cigarettes regularly during the year preceding each examination, and if the answer was yes, the number of cigarettes smoked per day was recorded. Diabetes was defined as a fasting blood glucose level of ≥126 mg/dl, a nonfasting blood glucose level of ≥200 mg/dl, or the use of insulin or oral hypoglycemic medication. Elevated blood cholesterol was defined as a total cholesterol level of ≥240 mg/dl or the use of cholesterol-lowering medication.

New CVD events were identified at each examination on the basis of a medical history interview, physical examination findings, electrocardiography, and review of outside medical records (hospital records, personal physicians’ records, and death certificates). A review panel of three physician investigators (or a panel of study neurologists for cerebrovascular outcomes) examined all available evidence and made the final determination of events using established Framingham Heart Study criteria. CVD outcomes included angina, coronary insufficiency, myocardial infarction, congestive heart failure, intermittent claudication, stroke and transient ischemic attack, and death from cardiovascular causes.

Statistical analysis

Cases of intermittent claudication among participants aged 40 years or older were grouped by date of onset: 1950–1969 (191 cases), 1970–1979 (191 cases), 1980–1989 (148 cases), and 1990–1999 (138 cases). Because crude trends were similar in men and women and there were no significant age-sex interactions, we pooled men and women for all analyses. Age- and sex-adjusted incidence rates of intermittent claudication and 95 percent confidence intervals for each time period were calculated using the direct method. Log-linear Poisson regression (PROC GENMOD in SAS) was used to estimate sex- and age-adjusted rate ratios for intermittent claudication incidence during the 1970s, 1980s, and 1990s, with the 1950–1969 time period being used as the reference period (21). A p value less than 0.05 was considered statistically significant.

We conducted prespecified subgroup analyses to examine whether the time period effects for intermittent claudication incidence differed by 1) smoking status (ever smoking vs. never smoking) or 2) prevalent CVD at diagnosis of intermittent claudication (yes/no). We chose to examine smoking status given the importance of this risk factor in the risk of intermittent claudication. Furthermore, prior work demonstrated a decline in the prevalence and incidence of claudication in association with a decline in smoking among Icelandic men between 1968 and 1986 (22). Stratification by baseline CVD allowed us to explore possible differences in intermittent claudication incidence related to primary versus secondary prevention efforts over time (a decline in claudication incidence among persons free of CVD would suggest primary prevention effects, whereas declines in claudication incidence in persons with CVD would suggest secondary prevention effects). Follow-up was restricted to
the 10-year period following the onset of claudication. Kaplan-Meier analysis was used to compare age group-adjusted (<60, 60–69, or ≥70 years at the time of intermittent claudication diagnosis) and sex-adjusted 10-year survival over the four time periods. The log-rank test was used to test for homogeneity across strata.

Risk factor profiles over the time periods of study for persons with incident intermittent claudication were compared using data from the last examination attended prior to the diagnosis. Adjustment for sex and 5-year age group was performed using the direct method. Time trends in risk factors in the full sample of men and women at risk of intermittent claudication were also examined; for each participant, risk factor values for all examinations attended within each time period were averaged. Linear regression, adjusting for 5-year age group and sex, was used to obtain least-squares mean values for each risk factor according to time period.

**RESULTS**

From 1950 through 1999, intermittent claudication occurred in 668 participants (43 percent women). The mean age at diagnosis of claudication was 61 years in the 1950–1969 time period; it rose to 69 years in the 1990–1999 time period. Age- and sex-adjusted risk factors for CVD at the time of diagnosis with intermittent claudication for each time period are shown in table 1. The majority of persons diagnosed with intermittent claudication were current or former cigarette smokers, and pack-years of smoking increased with each successive time period. Of note, from 1950 to 1969, 32 percent of cases with intermittent claudication had never smoked, but in the 1990–1999 time period, only 25 percent of intermittent claudication cases were never smokers. Among claudication cases, the prevalences of diabetes, obesity (body mass index >30), use of cholesterol-lowering medication, and hypertension increased across time periods. Age- and sex-adjusted prevalent CVD was present in approximately 40–60 percent of cases in the later time periods, as compared with only 27 percent of cases in the referent period.

The age- and sex-adjusted incidence rate of intermittent claudication in the 1950–1969 referent period was 282 per 100,000 person-years. In the 1970s, the rate rose to 345 per 100,000 person-years; it then fell in the 1980s and 1990s to 243 per 100,000 person-years and 225 per 100,000 person-years, respectively (figure 1). The results of age- and sex-adjusted log-linear Poisson regression analyses are shown in table 2. Overall, the incidence of intermittent claudication fell by 16 percent in the 1980s and by 18 percent in the 1990s relative to the 1950–1969 period (for trend across time periods, $p = 0.01$). Never smokers experienced a steeper decline in intermittent claudication incidence across the time periods than ever smokers (42 percent vs. 20 percent, respectively). In the subgroup of subjects without prevalent CVD, the incidence of intermittent claudication was 20 percent lower in the 1990–1999 time period than in 1950–1969 ($p$ for trend = 0.035), whereas in subjects with prevalent CVD, no significant decline in the incidence of claudication was observed ($p$ for trend = 0.31).

Temporal trends in risk factors from 1950 to 1999 among subjects at risk of developing intermittent claudication are shown in table 3. The age- and sex-adjusted prevalences of

**TABLE 1.** Age- and sex-adjusted data on cardiovascular disease risk factors at the time of diagnosis with intermittent claudication, by time period, Framingham Heart Study, 1950–1999

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<tbody>
<tr>
<td>Mean age (years)</td>
<td>61 (8)*</td>
<td>64 (9)</td>
<td>66 (10)</td>
<td>69 (10)</td>
<td></td>
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<tr>
<td>Male sex (%)</td>
<td>62</td>
<td>53</td>
<td>55</td>
<td>57</td>
<td></td>
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<tr>
<td>Cigarette smoking (%)</td>
<td></td>
<td></td>
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<tr>
<td>Current smoker</td>
<td>46</td>
<td>35</td>
<td>37</td>
<td>37</td>
<td>&lt;0.001</td>
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<tr>
<td>Former smoker</td>
<td>22</td>
<td>31</td>
<td>33</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>32</td>
<td>34</td>
<td>30</td>
<td>25</td>
<td></td>
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<tr>
<td>Pack-years of smoking (ever smokers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetes (%)</td>
<td>2</td>
<td>10</td>
<td>16</td>
<td>25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index† &gt;30 (%)</td>
<td>10</td>
<td>14</td>
<td>11</td>
<td>26</td>
<td>0.002</td>
</tr>
<tr>
<td>High cholesterol level (≥240 mg/dl) (%)</td>
<td>47</td>
<td>40</td>
<td>34</td>
<td>33</td>
<td>0.004</td>
</tr>
<tr>
<td>Cholesterol treatment (%)</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>0.012</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>41</td>
<td>59</td>
<td>53</td>
<td>62</td>
<td>0.004</td>
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<tr>
<td>Cardiovascular disease (%)</td>
<td>27</td>
<td>41</td>
<td>61</td>
<td>49</td>
<td>&lt;0.001</td>
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* Numbers in parentheses, standard deviation.
† Weight (kg)/height (m)².
diabetes, obesity, and antihypertensive treatment increased, whereas the prevalences of current smoking and high blood cholesterol declined in the study population over the four time periods. Of note, the prevalence of diabetes increased dramatically among persons with prevalent CVD, from 7 percent in the 1950–1969 time period to 22 percent in the 1990–1999 time period. The prevalence of CVD in the full sample was 12 percent in the first three time periods and 11 percent in the 1990–1999 time period.

Survival following the onset of intermittent claudication remained unchanged over the course of the study (figure 2) \( (p = 0.27) \). By 10 years following the onset of intermittent claudication, nearly 40 percent of claudicants had died. In subgroup analyses, no significant differences in mortality after claudication onset across time periods were observed in never or ever smokers or in claudicants with or without prevalent CVD at the time of intermittent claudication diagnosis.

### DISCUSSION

The age- and sex-adjusted incidence of intermittent claudication in our population-based sample declined by 16–18 percent in the 1980s and 1990s in comparison with the period 1950–1969. The decline in intermittent claudication incidence was steeper among never smokers, with rates in the 1990s being over 40 percent lower than rates in 1950–1969. Smokers may have experienced less of a decline in intermittent claudication incidence than nonsmokers, because some of the smoking-related adverse effects on the arterial wall may be cumulative and irreversible (23). By the time smokers enter middle age, the thickness of the peripheral arterial wall is already greater than that of nonsmokers (24). In our sample, the incidence of intermittent claudication also declined significantly among persons without prevalent CVD, suggesting that primary prevention efforts aimed at modifying risk factors were successful. Among persons at risk of intermittent claudication who were free of CVD, rates of smoking and high cholesterol decreased whereas blood pressure treatment rates increased during the latter two decades of our study (table 3). In the Reykjavik Study, declines in intermittent claudication among men from 1968 to 1986 have been linked to declines in smoking and serum cholesterol (22).

Despite reports that persons with CVD were more likely to receive treatment for risk factors (13), we did not find a significant decline in incidence of claudication among those with prevalent CVD. The reasons for the lack of improvement in claudication incidence among persons with CVD over the calendar decades studied are unclear. Although rates of smoking and high cholesterol decreased and blood pressure treatment increased greatly, prevalences of diabetes and obesity among persons with prevalent CVD progressively increased across calendar time. It is possible that emerging medical and surgical therapies for CVD over time resulted in improved overall function among persons with CVD. The improvement in function may have allowed participants to walk a distance great enough to develop symptoms of claudication, whereas in the past persons with CVD may have been too functionally limited by symptoms.


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<tr>
<td></td>
<td>RR*</td>
<td>95% CI*</td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Overall</td>
<td>1.0</td>
<td>1.16</td>
<td>0.95, 1.43</td>
<td>0.84</td>
<td>0.67, 1.04</td>
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<tr>
<td>Ever smoker</td>
<td>1.0</td>
<td>1.20</td>
<td>0.94, 1.53</td>
<td>0.81</td>
<td>0.63, 1.05</td>
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<tr>
<td>Never smoker</td>
<td>1.0</td>
<td>0.73</td>
<td>0.47, 1.13</td>
<td>0.60</td>
<td>0.37, 0.96</td>
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<tr>
<td>CVD* status</td>
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<tr>
<td>No CVD</td>
<td>1.0</td>
<td>1.43</td>
<td>1.10, 1.87</td>
<td>0.94</td>
<td>0.70, 1.26</td>
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<tr>
<td>Prevalent CVD</td>
<td>1.0</td>
<td>0.83</td>
<td>0.60, 1.16</td>
<td>0.70</td>
<td>0.50, 0.99</td>
</tr>
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* RR, rate ratio; CI, confidence interval; CVD, cardiovascular disease.
such as chest pain or shortness of breath to experience claudication symptoms. Furthermore, survival following the onset of coronary heart disease and cerebrovascular disease has improved, which may have permitted participants to develop claudication. The increasing prevalence of diabetes among persons with prevalent CVD, along with improvements in CVD treatment and survival over the time periods studied, may have resulted in the lack of significant improvement in incidence of intermittent claudication among persons with prevalent CVD in our study.

No temporal improvement in survival after the onset of claudication was observed. Approximately 40 percent of claudicants died within 10 years of onset in all time periods. The lack of improvement in survival following the diagnosis of intermittent claudication contrasts with the significant decline observed in rates of sudden and nonsudden cardiac death (25), as well as observed declines in mortality following the onset of other CVDs, including myocardial infarction, congestive heart failure, and stroke in the community (14, 15, 26, 27). Heart disease and stroke have been the focus of national prevention programs, with education efforts being directed at both physicians and the general public, whereas PAD has not yet emerged as a target for a national public health campaign.

Recent national data demonstrate that PAD is underdiagnosed in the primary care setting; with the exception of smoking, risk factors are less intensively treated in persons with PAD than in persons with other types of CVD (13). Survey data from primary care physicians, cardiologists, and vascular surgeons suggest that deficiencies in physician knowledge and attitude play an important role in the lower

### TABLE 3. Age- and sex-adjusted prevalence (%) of cardiovascular disease risk factors in persons at risk of intermittent claudication, Framingham Heart Study, 1950–1999

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<td>Full sample</td>
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</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>42</td>
<td>30</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>5</td>
<td>8</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Body mass index &gt;30</td>
<td></td>
<td>13</td>
<td>15</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Blood pressure treatment</td>
<td></td>
<td>15</td>
<td>21</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>High cholesterol level (&gt;240 mg/dl)</td>
<td></td>
<td>48</td>
<td>32</td>
<td>28</td>
<td>17</td>
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<tr>
<td>Persons with prevalent CVD</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>38</td>
<td>30</td>
<td>27</td>
<td>21</td>
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<tr>
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<td>7</td>
<td>14</td>
<td>16</td>
<td>22</td>
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<tr>
<td>Body mass index &gt;30</td>
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<tr>
<td>Blood pressure treatment</td>
<td></td>
<td>17</td>
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<td>55</td>
<td>54</td>
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<tr>
<td>High cholesterol level (&gt;240 mg/dl)</td>
<td></td>
<td>46</td>
<td>33</td>
<td>31</td>
<td>16</td>
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<tr>
<td>Persons free of CVD</td>
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<tr>
<td>Smoking</td>
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<td>42</td>
<td>31</td>
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<tr>
<td>Diabetes</td>
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<td>4</td>
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<td>Blood pressure treatment</td>
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<tr>
<td>High cholesterol level (&gt;240 mg/dl)</td>
<td></td>
<td>49</td>
<td>32</td>
<td>28</td>
<td>17</td>
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* p for trend < 0.001 for all risk factors in the full sample and in the samples stratified by cardiovascular disease status.
† Weight (kg)/height (m)².
‡ CVD, cardiovascular disease.

![FIGURE 2](https://academic.oup.com/aje/article-abstract/162/5/430/82433) Ten-year survival following the onset of intermittent claudication, by time period, Framingham Heart Study, 1950–1999. Shown are the results of Kaplan-Meier survival analysis adjusted for sex and age group at diagnosis of intermittent claudication.
intensity of risk factor modification efforts in PAD patients (28). It appears that PAD patients do not fully appreciate the increased risk of cardiovascular events associated with their disease and the benefits of risk factor reduction (29). Misperceptions on the part of PAD patients may contribute to the lower rates of risk factor control. Only a small number of randomized controlled trials of CVD risk reduction have been carried out in persons with PAD. Nevertheless, data support the beneficial effects of antiplatelet therapies and angiotensin-converting enzyme inhibitor therapies on cardiovascular outcomes in PAD patients (16, 30, 31). Moreover, in the Scandinavian Simvastatin Survival Study, lipid-lowering therapy with simvastatin in coronary heart disease patients resulted in a 38 percent reduction in new or worsening intermittent claudication (32), and a review of randomized trials of lipid-lowering therapies in PAD patients demonstrated a marked but nonsignificant reduction in mortality (odds ratio = 0.2, 95 percent confidence interval: 0.03, 1.17) associated with treatment (33). More recently, results of the Heart Protection Study demonstrated that simvastatin significantly reduced the risk of major vascular events by approximately 25 percent among persons with PAD (34). Furthermore, in a subgroup analysis of persons with vascular disease, including PAD, simvastatin substantially reduced the risk of stroke (35). Intensive blood pressure control in persons with both diabetes and PAD has been shown to be associated with a marked reduction in CVD events (36). These data suggest a beneficial role for modification of high blood cholesterol levels and high blood pressure in persons with PAD. Despite existing evidence demonstrating a clear benefit, antiplatelet therapies have been prescribed less frequently in PAD patients than in patients with other CVDs (13). Barriers to effective secondary prevention of CVD probably explain, in large part, the lack of improvement in survival among claudicants in recent decades, given that the majority of deaths among persons with the disease are due to coronary and cerebrovascular causes (2–4, 7).

Smoking is the single most important risk factor for PAD (7, 37, 38), and it is associated with disease progression and risk of limb amputation. Although, in our study, the decline in incidence of intermittent claudication was seen in both ever smokers and never smokers, the magnitude of the decline was greater in persons who had never smoked. The declining trend in intermittent claudication in the later decades is not surprising, given the concurrent decline in cigarette smoking in the population at risk. In the 1990s, the prevalence of current smoking in our study sample was 17 percent, less than half that observed in the 1950–1969 time period. Smoking cessation in the Quebec Cardiovascular Study was associated with a decline in risk of intermittent claudication such that men who stopped smoking for 1 year had a risk of claudication similar to that of nonsmokers (37). In the Reykjavik Study, a prospective study of Icelandic men, Ingolfsson et al. (22) also reported a marked decline in incidence and prevalence of claudication from 1968 to 1986 in association with a decline in smoking rates and a lowering of cholesterol levels in Iceland. However, other studies have demonstrated a persistent elevation in risk of PAD among former smokers (39). In addition to smoking, all other major CVD risk factors have been shown to be associated with risk of claudication (7). Thus, national efforts aimed at detection, treatment, and control of high blood pressure and high blood cholesterol have probably contributed to the observed decline in the incidence of intermittent claudication in our study. Of concern is recent national survey data demonstrating an increasing prevalence of multiple risk factors among adult men and women in the US population (40), which in turn may lead to a reversal of gains made in decreasing CVD incidence.

Our study had a number of potential limitations. First, the Framingham Study sample is not nationally representative and is primarily Caucasian; results may not be generalizable to other racial or ethnic groups. Studies of racially diverse samples have observed a higher prevalence of PAD among non-Hispanic Blacks than among Whites (1, 41, 42). Second, we studied intermittent claudication diagnosed only by classical medical history and did not have confirmatory testing. Thus, misclassification is possible, but diagnostic criteria remained the same over the decades studied. Any misclassification would therefore be expected to be random and result in a bias toward the null. Perhaps more importantly, most persons with PAD are asymptomatic (41, 43–45); some have atypical leg discomfort (46, 47), and others stop walking to prevent symptom onset. Our study was only able to observe incidence and mortality trends for the fraction of persons with PAD who develop classical symptoms. Finally, there have only been a few randomized controlled treatment trials in persons with PAD from which to establish the benefit of antiplatelet and risk factor reduction therapies (16, 31–36). Prior to these trials, physicians needed to extrapolate treatment benefits from observations in patients with CVD. We would not have been able to observe any recent improvements in mortality following the onset of claudication that may have occurred in response to the latest trial results.

In conclusion, the incidence of intermittent claudication has declined in the general population over the past 50 years, but mortality following the onset of claudication has not improved; approximately 40 percent of persons with intermittent claudication died within 10 years in all time periods studied. Improvements in primary and secondary prevention to modify CVD risk factors and increasing utilization of effective therapies in persons with PAD are needed.

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Conflict of interest: none declared.

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