

## Atherosclerotic Vascular Disease Conference

### Writing Group I: Epidemiology

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Our knowledge of the epidemiology of coronary heart disease (CHD) is extensive. Although CHD mortality peaked in the 1960s and then declined dramatically,<sup>1,2</sup> CHD remains the leading cause of death in both men and women in the United States. The aging of the United States population contributes to the high prevalence of CHD. By the year 2020, it is estimated that ischemic heart disease will be the number one cause of disability and death worldwide.<sup>3</sup> Data on noncoronary atherosclerotic vascular disease (AVD) are far less available than data on CHD. Studies of the atherosclerotic process underlying ischemic stroke are hampered by the differing vascular mechanisms that lead to stroke, including large-artery atherosclerosis with occlusion and distal embolization and small penetrating arterial disease with lacunar infarction. Also, there are a considerable number of ischemic stroke events for which the mechanism is unclear and the infarct is of undetermined cause. What is known about the epidemiology of atherosclerotic disease in different territories tends to come from snapshots based on several prevalence studies, which often reflect a medical milieu very different from the one today in which many preventive interventions, including lipid-lowering therapy, hypertension control, and antiplatelet therapies, are more widely used. Epidemiologic, pathophysiological, and therapeutic studies of noncoronary atherosclerotic disease have tended to focus on individual territories rather than on the vascular tree in its totality. Although it is still important to understand critical differences among the different territories, it is also important that basic, epidemiologic, and clinical investigators recognize the links among vascular territories (namely, that atherosclerosis is a systemic disease) and that collection of current prevalence and incidence data for both clinical and subclinical vascular disease allows for robust comparisons and improved under-

standing of both the similarities and differences in atherosclerosis in different vascular territories.

The barriers that contribute to gaps in understanding include a basic problem with nomenclature. Clearly, adequate comparisons of data by different investigators require consistency in definitions, which has sometimes proved impossible. Furthermore, data gathering based on different criteria makes comparisons difficult as well. This reality is reflected in the data discussed in this report and those from the other writing groups. An additional problem is the differing definitions of the disease processes themselves, partly as a consequence of emerging understanding of clinical presentations and partly as a result of newer imaging techniques. For example, penetrating aortic ulcers, a condition widely recognized by clinicians who use aortic imaging to search for causes of embolic stroke, are virtually unrecognized by the epidemiologic community.

This report summarizes understanding of the epidemiology of noncoronary atherosclerosis in the following 4 specific arterial beds: cerebrovascular, aortic, renal, and peripheral (lower extremity). The level of epidemiologic understanding of disease differs by vascular territory; the writing group has attempted to summarize what is known in each case, beginning with a review of the epidemiology of territory-specific disease (eg, demographics and incidence of claudication in the presence of peripheral arterial disease [PAD]), followed by a review of general cardiovascular outcomes related to the presence of disease in specific territories (eg, the incidence of CHD events in patients with established PAD).

This territory-specific discussion is followed by specific recommendations for future research, American Heart Association programs, and advocacy efforts.

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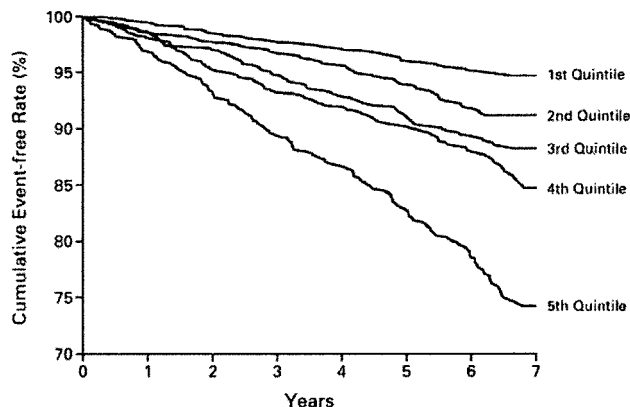
### Cerebrovascular Atherosclerotic Disease

Stroke is one of the leading health problems in the United States today, with 600 000 new or recurrent strokes occurring annually. Stroke is the third leading cause of death and the principal cause of long-term disability.<sup>4</sup> Approximately 85% of all strokes are ischemic; of these, most ( $\approx 60\%$  of all strokes) are attributable to atherothrombotic disease. The number of strokes related to carotid atherosclerosis is less certain but probably approaches 20% of all strokes. The absolute United States stroke mortality rate has declined for many years, reaching a low of  $\approx 144$  000 deaths from 1990 to 1992.<sup>5</sup> Since then, the absolute number of deaths attributed to stroke has begun to increase, probably because of a leveling off of the decline in stroke death rate as well as the aging of the United States population. As a consequence, in the United States, stroke deaths seem to have increased slightly to  $\approx 167$  000 per year.

Although it was recognized as early as 1914 that stroke could be caused by extracranial arterial occlusion,<sup>6</sup> it was not until the early 1950s and the work of C. Miller Fisher<sup>7</sup> that the role of carotid artery atherosclerosis as a more common cause of stroke began to be clarified. There is a predilection for clinical atherosclerosis in the internal carotid arteries as well as in the vertebrobasilar arteries. The prevalence of carotid artery stenosis has been estimated from high-resolution B-mode carotid ultrasonography. In the Framingham Heart Study cohort, >1000 subjects were studied, including 441 men and 675 women. The mean age of the sample studied was 75 years (range, 66 to 93). In this elderly community-based sample, 47% percent of women and 37% of men had carotid stenoses of 0% to 10%; 34% of women and 37% of men had carotid stenoses of 11% to 30%. Slightly more than 10% of the cohort had stenoses >40%, and most of these had lesions in the range of 41% to 60%. In this cohort, traditional risk factors were associated with carotid atherosclerosis, with age being the most powerful, followed by cigarette smoking, elevated systolic blood pressure, elevated cholesterol level, and alcohol consumption. Age-adjusted, mean systolic blood pressure was  $\approx 40$  mm Hg higher in patients with carotid stenosis  $\geq 50\%$  compared with those who had stenosis of 0% to 4%. Overall data from Framingham suggest that at the mean age of 75 years, 9% of men and 7% of women have a carotid stenosis >50%, whereas at age 50 years, <1% have carotid stenosis  $\geq 50\%$ .<sup>8</sup>

Follow-up from the medical therapy or conventional therapy groups from randomized trials of carotid endarterectomy allows for some understanding of the relation between carotid artery stenosis and subsequent stroke. For example, in the North American Symptomatic Carotid Endarterectomy Trial (NASCET),<sup>9</sup> at 2 years, stroke rate in the medical group was 26% when baseline carotid stenosis was >70%.

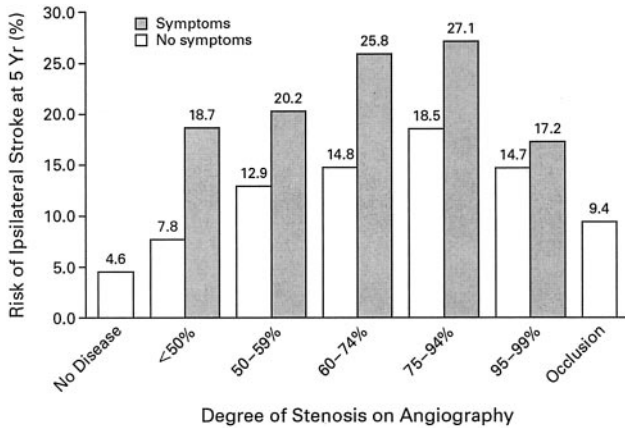
In the past decade, several large observational studies<sup>10–13</sup> have developed standardized views of the carotid intima and have measured carotid intima-medial thickness (IMT). Not surprisingly, increasing carotid IMT is associated with increasing prevalence of vascular end points, including stroke and CHD. This relationship appears graded, and although steeper for stroke, the relation is highly significant for CHD as well. In a prospective epidemiologic study of >4400



**Figure 1.** Carotid disease as a marker of cardiovascular risk, myocardial infarction, or stroke. Cumulative event-free rates for the combined end point of myocardial infarction or stroke according to quintile of combined IMT. The cumulative event rate for either event is shown for 5 separate quintiles of a large observational cohort ( $n=4476$ ) undergoing carotid ultrasound and precise measures of IMT. The estimated cumulative rate of the combined end point for the fifth quintile of the combined measure was >25% at 7 years compared with a cumulative rate of <5% for the first quintile. Reprinted with permission from Reference 14.

elderly subjects by O'Leary et al,<sup>14</sup> the rate of new myocardial infarction or stroke was dramatically higher over a 7-year period in the fifth quintile compared with the first quintile of IMT (Figure 1). These subjects were free of clinical evidence of vascular disease initially; by the seventh year of follow-up, >25% of patients in the fifth IMT quintile had experienced myocardial infarction or stroke, compared with <5% in the first quintile.<sup>14</sup> Compared with risk factor measurements evaluated in this study, carotid IMT was a stronger predictor of future cardiovascular events than all conventional cardiovascular disease (CVD) risk factors.<sup>14</sup> In 2 studies that evaluated IMT measures at different time points, progressive IMT was strongly associated with coronary events.<sup>15,16</sup>

The risk and mechanism of stroke vary by percent carotid stenosis and symptom status. For example, in NASCET, the risk of ipsilateral stroke at 5 years for patients with <50% stenosis on angiography was 18.7% and 7.8% for those with and without symptoms, respectively. For those with 75% to 94% stenosis, the rates were 27.1% and 18.5%, respectively (Figure 2).<sup>17</sup> Because NASCET enrolled symptomatic patients, however, understanding the implications of stroke rate on the side of an asymptomatic stenosis opposite a symptomatic stenosis is problematic.<sup>17</sup> The Asymptomatic Carotid Atherosclerosis Study (ACAS)<sup>18</sup> enrolled asymptomatic patients with stenosis  $\geq 60\%$ ; even without surgery, absolute stroke rates were low: 5.0% at 2 years with a 1.2% absolute risk reduction by carotid endarterectomy (to 3.8%) by the most highly skilled surgeons available. The authors cautioned that the benefits of carotid endarterectomy in the absence of symptoms may be overstated, both because of the relatively low risk of stroke with asymptomatic carotid stenosis and because in asymptomatic carotid stenosis (60% to 99% occlusion), it was estimated that 45% of strokes were attributable to cardioembolism or lacunes.<sup>17</sup>



**Figure 2.** The 5-year risk of a first ipsilateral stroke in patients with symptomatic and asymptomatic carotid-artery stenosis according to the degree of stenosis. The risk and mechanism of stroke varies by percent carotid stenosis and symptom status. Stenosis of 95% to 99% represents near-occlusion. The numbers of patients with symptomatic carotid-artery stenosis were as follows: <50% stenosis, 690; 50% to 59% stenosis, 238; 60% to 74% stenosis, 267; 75% to 94% stenosis, 196; and 95% to 99% stenosis, 58. For asymptomatic carotid-artery stenosis, the numbers of patients were as follows: no disease, 471; <50% stenosis, 1496; 50% to 59% stenosis, 108; 60% to 74% stenosis, 113; 75% to 94% stenosis, 74; 95% to 99% stenosis, 29; and occlusion, 86. Reprinted with permission from Reference 17.

Ethnic differences in stroke and carotid atherosclerosis have long been recognized. Black populations have a 38% higher adjusted incidence of ischemic stroke than white populations<sup>19</sup> and higher stroke mortality.<sup>20</sup> Black populations also have significantly greater common carotid IMT than non-Hispanic white populations.<sup>21,22</sup> In a retrospective multicenter Veterans Affairs study of patients presenting with stroke or transient ischemic attack, however, after adjusting for potential confounders, black subjects were less likely than white subjects to undergo carotid imaging.<sup>23</sup> Similarly, ethnic differences have been observed in use and outcome of carotid endarterectomy. For instance, white subjects were significantly more likely to undergo carotid endarterectomy,<sup>24</sup> and in one series, black women had significantly more postoperative strokes than other patients (16% versus 3%).<sup>25</sup> The genesis of ethnic differences in carotid atherosclerosis, diagnostic use, and outcome is undoubtedly multifactorial and complex. Data that show that black populations have a higher rate of stroke, undergo fewer carotid imaging studies, and experience worse outcome of carotid endarterectomy are persuasive evidence that additional study of ethnic differences in noncoronary atherosclerosis is essential.<sup>23</sup>

### Aortic Atherosclerotic Disease

Usually aortic atherosclerosis is not as clinically apparent as coronary, peripheral, or even carotid artery atherosclerosis. Occlusive disease of the aorta occurs only rarely, and the principal disease of aortic atherosclerosis, although rare, often presents as a medical catastrophe. Thus, most aortic atherosclerosis present in life can be classified as subclinical disease.

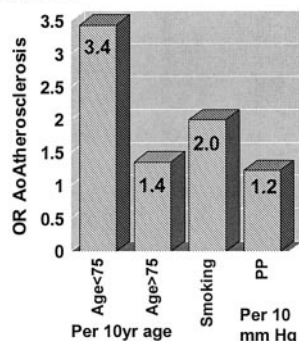
Thoracic aortic dissection, a common clinically recognized presentation of aortic disease, is generally not associated with

atherosclerosis as such. Thus, the principal clinical syndromes associated with aortic atherosclerosis are abdominal aortic aneurysms (AAAs), peripheral atheroembolization, and the relatively newly recognized clinical syndromes penetrating aortic ulcer and intramural hematoma. Necropsy studies from Sweden have found abdominal AAAs in 4.7% of men and 1.7% of women 56 to 74 years of age.<sup>26</sup> Thoracic aortic aneurysms seem to be much rarer, occurring in  $\approx$ 4 to 5 of 1000 autopsy studies,<sup>27</sup> and often are not related to atherosclerosis. The true prevalence of AAA in asymptomatic patients is not well described. Prevalence rates are critically dependent on the population studied, thus limiting the general viability of findings. Furthermore, studies have reported different definitions of AAA, ranging from  $\geq 3.0$  cm<sup>28</sup> to  $\geq 3.5$  cm<sup>29</sup> to  $\geq 4.0$  cm.<sup>30</sup> Indeed, when such differing diagnostic criteria for AAA are used to assess a given study population, there can be as much as a 4-fold variation in prevalence of AAA. Furthermore, although techniques for measurement of carotid IMT have been widely standardized, there is no similar level of agreement on appropriate methods for ultrasound screening or measurement of AAA. Finally, there is debate about the complex issue of whether diameters should be normalized for age, sex, or body size (body surface area, height, etc). Although it is clear that such factors will influence normal aortic size, it is also true, via Laplace's relationship, that absolute diameter is likely to affect risk of rupture independent of other factors. Given these issues, it is not surprising that clinical studies have reported AAA prevalence of 2.4% to 16.9% among men.<sup>31,32</sup> The relatively recent Aneurysm Detection and Management (ADAM) study of 16 Veterans Affairs medical centers is one of the largest prospective screening studies.<sup>33</sup> More than 125 000 patients from 50 to 79 years of age, the vast majority of whom were men, were screened by using the definition of AAA as  $\geq 3.0$  cm. Prevalence was 4.3% and 1.0% for men and women, respectively. However, only 1.3% and 0.1%, respectively, were found to have an AAA  $\geq 4.0$  cm. A similar but much smaller Norwegian study of >6300 subjects (25 to 84 years of age) identified an AAA  $\geq 3.5$  cm in 8.9% of men and 2.2% of women.<sup>29</sup> Prevalences were low for both men and women <50 years of age but rose sharply and linearly for men >50 years of age and for women >60 years of age, albeit less steeply.<sup>34</sup>

The presence of clinically silent atherosclerosis has most often been detected by screening x-ray examinations, computed tomography (CT), and echocardiography, particularly transesophageal echocardiography (TEE), which is regarded as the most sensitive technique for detecting clinically silent aortic atherosclerosis. TEE detects both thin and relatively thicker plaques (atheromas) and can define protruding or mobile plaque elements. Not surprisingly, the prevalence of aortic atheromas on TEE varies depending on the population studied. The prevalence of aortic atheromas among patients undergoing TEE for routine clinical indications is 8%; among those with known significant carotid disease, prevalence is 38%. Among those with documented obstructive coronary disease, TEE studies have demonstrated a prevalence of as much as 90%.<sup>35</sup> In a community-based TEE study of subjects  $\geq 45$  years of age in Olmsted County, Minnesota, aortic atherosclerosis was present in 51% of subjects, with a greater

### Ascending Aorta Atherosclerosis Risk Factors

- SPARC TEE random sample Olmsted County  $\geq 45$ yo
  - 581 (47%) eligible participated
- Aortic atherosclerosis
  - Any 53%
  - Complex 7.6%



**Figure 3.** Risk factors for ascending aortic atherosclerosis assessed by transesophageal echocardiography. The odds ratio (OR) of aortic (Ao) atherosclerosis from the SPARC Olmsted County random sample (581 eligible random participants,  $\geq 45$  years old) by age, smoking status, and pulse pressure (PP). Frequency of aortic atherosclerosis: any, 51.3%; complex, 7.6%. Reprinted with permission from Reference 36.

prevalence more distally in the aorta.<sup>36,37</sup> Complex atheromas (thickness  $\geq 4$  mm or with mobile elements) were present in 7.6% of subjects. Prevalence of both simple and complex atheromas increased with advancing age (Figure 3), smoking, and pulse pressure. Several TEE studies have found an association between the presence of aortic atheromas and both stroke and other peripheral embolic events, although true causality has not yet been proved. Nevertheless, one prospective report found that among those with protruding aortic atheromas on TEE, there was a 33% incidence of vascular embolic events over a 2-year follow-up period.<sup>38</sup>

Several studies have looked at the prevalence of aortic calcification on x-rays of the prelumbar region. By age 50 years,  $< 20\%$  of patients have radiographic evidence of calcification; by age 70 to 75 years,  $\approx 41\%$  have evidence of calcification, and prevalence continues to increase through age 80 years.<sup>39</sup> Similar studies that evaluated the presence of aortic calcification on routine chest x-rays have demonstrated that the prevalence of aortic plaques doubles with each decade of life.<sup>40</sup>

Penetrating atherosclerotic ulcers (PAUs) usually present symptomatically as acute aortic syndrome (with acute chest or back pain or both) but are sometimes discovered in asymptomatic patients as an incidental finding on a routine CT scan of the chest. An aortic PAU begins with ulceration of an aortic plaque that then erodes through the intima and into the media, typically producing a localized hematoma within the underlying aortic wall. This process may progress, producing a pseudoaneurysm, aortic dissection, contained rupture, or frank rupture. These lesions are generally present in patients with severe and diffuse aortic atherosclerosis. Patients tend to be elderly with a history of hypertension and smoking, and  $\approx 50\%$  of these patients will have an associated aneurysm of the abdominal or thoracic aorta. Because no large, prospective, observational studies have screened for PAUs, the true prevalence of PAUs remains unknown. However, it is known that PAUs were present in  $\approx 10\%$  of patients with symptoms of acute aortic syndrome (clearly a population at increased risk).<sup>41,42</sup>

Reasonably good territory-specific end point data exist only for aortic aneurysms. The risk of rupture of an aortic aneurysm increases as aneurysm diameter increases. Once an aneurysm is  $> 6$  cm in diameter, risk of rupture is  $\approx 25\%$  per year. Risk of CVD mortality unrelated to rupture is also proportional to aneurysm size.<sup>43</sup>

Framingham data also suggest that calcified plaques seen on chest x-ray are a significant predictor of future cardiac death. The presence of aortic calcification was associated with a 2-fold increase in risk of cardiac death in men and women  $< 65$  years of age, even after correcting for other risk factors.<sup>40</sup> Similarly, in a community-based study, after adjusting for potential confounders, abdominal aortic calcification was associated with a significantly increased risk of both CHD and CVD mortality.<sup>44</sup> In several studies, relative risk of sudden death was as high as 7-fold among men  $< 35$  years of age but fell with succeeding decades of life until there was no excess risk by age 70 years.<sup>39,40</sup> This curious finding is probably best explained by the fact that only a minority of younger patients had calcified aortic plaques on chest x-ray, so the finding was an effective marker of premature AVD. In patients 70 years of age and older, however, the presence of calcified aortic plaques is so common that it can no longer distinguish a group at distinctly higher risk.

### Renal Atherosclerotic Vascular Disease

Many of the same risk factors that have contributed to the CHD epidemic are also drivers of the emerging epidemic of chronic kidney disease (CKD). This is particularly true for obesity, hypertension, diabetes, and specific risk factors associated with these related conditions. Stages of CKD are based on levels of estimated glomerular filtration rate (eGFR).<sup>45</sup> Most renal risk for atherosclerosis begins at stage III CKD (eGFR  $< 60$  mL/min per  $1.73$  m<sup>2</sup>). Despite the known association between renal atherosclerosis and CKD, information on the prevalence of renal atherosclerosis in CKD is not well known. The relationship of renal artery stenosis to end-stage renal disease (ESRD) may be better understood. In 2000, the annual incidence of ESRD was estimated to be  $\approx 100$  000 and prevalence was estimated to be 372 407 and increasing rapidly. By 2010 it is estimated that there will be  $> 650$  000 cases of ESRD in the United States. Because of the confluence of risk factors, ESRD is frequently associated with atherosclerosis,<sup>46</sup> although actual prevalence of renal artery atherosclerosis, particularly significant renal artery stenosis in ESRD, is uncertain. One report estimates that renal artery stenosis is present in 2.1% of all new cases of ESRD.<sup>47</sup> Most ESRD cases are not screened for the presence of renal artery stenosis, however, and the presence of atherosclerotic disease is likely to be far more frequent. Other data on the prevalence of renal artery stenosis are derived from studies of patients undergoing cardiac catheterizations. In studies that varied in size from  $> 1400$  patients to only 170 patients, renal artery stenosis was estimated to vary from 6% to 8%; renal artery stenosis was defined as  $\geq 1$  renal artery with  $> 50\%$  to 70% occlusion.<sup>48–50</sup> An autopsy series of  $> 2000$  patients who died from stroke found that  $\geq 1$  renal artery had  $> 75\%$  stenosis in 10% of the series studied.<sup>51</sup>

Patients with ESRD have a greatly increased risk of CVD throughout the vascular tree. For instance, in the National Institutes of Health hemodialysis study,<sup>52</sup> prevalence of cerebrovascular disease, PAD, and CHD was 19%, 23%, and 40%, respectively. The diffuse atherosclerosis contributes to the continuum of increased cardiovascular mortality with increasingly severe renal disease. It is important to keep in mind that regardless of how renal disease severity is classified (degree of urine albuminuria or proteinuria, eGFR, or presence of ESRD), 10-year mortality for severe renal abnormalities is extraordinarily high (107 per 1000 person-years) compared with that predicted by Framingham data with multiple risk factors (25 per 1000 person-years).<sup>46</sup> Furthermore, as the epidemics of obesity and diabetes worsen and the level of hypertension control remains at a disappointing 27%,<sup>53</sup> it is likely that incidence of CKD will increase. Presumably the increasing incidence will be attributable in part to progressive renal artery atherosclerosis. Atherosclerosis has a causal role in producing ESRD; the presence of ESRD also likely contributes to atherosclerosis, because ESRD exacerbates many traditional atherosclerotic risk factors.

This concept is supported by results from a recent study of young adults with childhood-onset chronic renal failure, which showed an extraordinarily high prevalence of arterial abnormalities as measured by noninvasive techniques. CT scans showed that coronary artery calcifications were present in 92% of patients; carotid IMT measures were significantly increased compared with matched controls. The degree of coronary calcification and carotid IMT was significantly correlated with the duration of renal disease.<sup>54</sup>

Thus, the epidemiology for renal artery atherosclerosis, including prevalence, incidence, and contribution to both target organ and overall cardiovascular mortality, is less well understood compared with atherosclerosis in other territories. Nevertheless, it is quite clear that the emerging epidemic of CKD is intimately related to atherosclerosis and its progression as well as its risk factors.

Ethnic differences in CKD epidemiology are well known. Compared with white patients, black patients are more likely to have ESRD attributable to hypertension<sup>55</sup> and less likely to have renal artery stenosis.<sup>47</sup> Black patients tend to develop ESRD a decade earlier than their white counterparts.<sup>56</sup> Because of treatment discrepancies, black patients with ESRD are less likely to have the vascular access of choice, more likely to have arterial-venous fistulas,<sup>57</sup> less likely to receive peritoneal dialysis, and less likely to undergo renal transplantation.<sup>58</sup> Similarly, dialysis is likely to be initiated later for Asian and Hispanic patients with ESRD than for white patients with ESRD.<sup>59</sup> Once dialysis is initiated, however, white patients have a higher mortality rate than their black or Asian counterparts.<sup>60,61</sup>

### Peripheral Arterial (Lower-Extremity) Atherosclerotic Vascular Disease

Considerable confusion exists concerning the terminology used to define AVD of the lower extremities. Use of the most common term for this condition, *peripheral arterial disease* (PAD), has caused some confusion, because some investigators have included carotid disease in this definition. Others

**TABLE 1. Relative Prevalence of PAD and IC**

Age, y	Population	PAD	IC
40–59	68 886 000	2 100 000	901 000
60–69	19 862 000	1 600 000	803 000
≥70	24 808 000	4 700 000	2 530 000

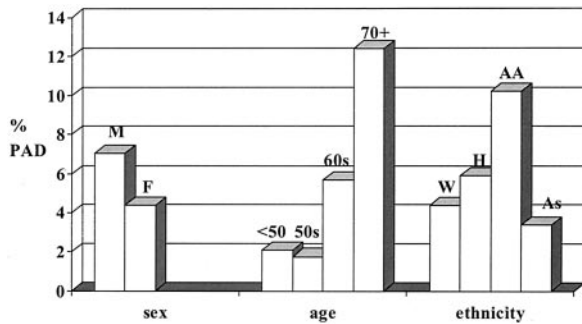
IC indicates intermittent claudication.

Data derived from References 67–69.

have used the term *peripheral vascular disease* (PVD). To some clinicians and investigators, however, this term includes venous as well as arterial diseases. Finally, more recently, the term *lower-extremity arterial disease* has been proposed. Although this term is specific, its use is not currently widespread; in this report, the term PAD is used to refer to lower-extremity arterial disease.

Although PAD has been defined by some as the presence of classic lower-extremity pain with exertion (claudication) or a physical examination demonstrating absent or markedly diminished pulses, most investigators currently use a broader but simultaneously more specific definition, namely, an abnormal ankle-brachial index (ABI). An ABI  $\leq 0.90$  is 90% sensitive and 95% specific for PAD.<sup>62</sup> Severe PAD associated with pain at rest or ulceration generally occurs with an ABI  $< 0.40$ . Three decades ago, the Framingham investigators reported an annual incidence of claudication of 53 per 10 000 persons in men 55 to 64 years of age and 54 per 10 000 persons in women 65 to 74 years of age.<sup>63</sup> Current data from the Framingham Heart Study suggest that the prevalence of PAD and its manifestations, intermittent claudication, lower-extremity bruits, and surgical intervention, have increased to 3.9%, 1.9%, 2.4%, and 1.4% in men and 3.3%, 0.8%, 2.3%, and 0.5% in women, respectively.<sup>64</sup> In defining PAD by abnormal results of noninvasive tests, including ABI, Criqui et al<sup>65</sup> found a 2% to 3% prevalence of PAD by age 50 years and  $\approx 20\%$  prevalence of PAD for persons  $\geq 75$  years of age. Of those with PAD,  $\approx 10\%$  had classic claudication, 50% had atypical leg pain, and the remaining 40% did not have exercise leg pain.<sup>66</sup> The relative risk of PAD in women versus men is 0.7. PAD seems to occur more frequently in Hispanic subjects (relative risk, 1.5) and African American subjects (relative risk, 2.5). Table 1 shows the relative prevalence of PAD and intermittent claudication as derived from several sources.<sup>67–69</sup>

Risk factors associated with development of PAD are similar to those of other atherosclerotic disease, although the association between elevated LDL cholesterol and PAD seems to be somewhat weaker than that for CHD. The dyslipidemia associated with PAD is frequently that of the metabolic syndrome and glucose intolerance: low HDL cholesterol and high triglycerides. Hypertension, cigarette smoking, and diabetes in particular are powerful risk factors for development of PAD. Using this information, Framingham investigators developed a clinical risk profile tool to help clinicians and patients predict onset of intermittent claudication.<sup>70</sup> Adjusted PAD prevalence by sex, age, and ethnicity is shown in Figure 4.<sup>71</sup> Progression of PAD over  $\approx 5$  years is predicted by both clinical factors (claudication, previous intervention, and PAD in the contralateral leg) and traditional

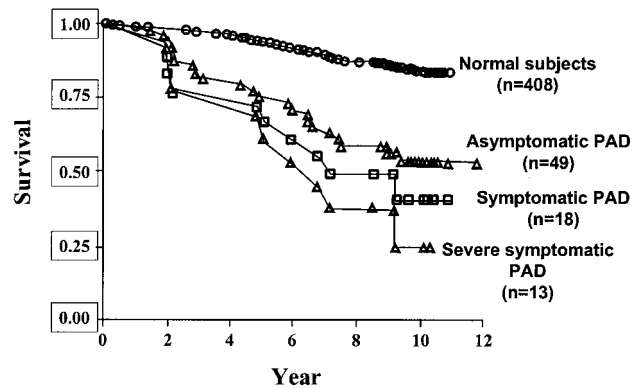


**Figure 4.** PAD prevalence in the multiethnic San Diego Population Study. Each variable adjusted for the other 2. M indicates male; F, female; W, white; H, Hispanic; AA, African American; and As, Asian. Reprinted with permission from Reference 71.

risk factors (age, diabetes, and cigarette smoking).<sup>72</sup> Among patients with PAD, prior evidence of CHD is common (35% by history and electrocardiography alone, 85% by angiography), as is the presence of cerebrovascular disease (60% of patients with PAD have >30% carotid stenosis on ultrasonography).<sup>73</sup>

In patients with established PAD associated with intermittent claudication, ≈5% to 10% undergo revascularization over 5 years, although there is wide regional variation in this outcome. Over the same interval, critical leg ischemia develops in 5% of patients, with 1% to 4% requiring amputation.<sup>74</sup> There is also wide ethnic variation in the latter outcome. In a recent study, being black or Hispanic was an independent risk factor for lower-extremity amputation in patients with PAD.<sup>75</sup> Similarly, in a state-based study, white subjects were more likely to receive aortoiliac surgery and less likely to receive lower-extremity amputations than other ethnic groups.<sup>76</sup> Multiple other studies have also demonstrated increased rates of amputation for black and Hispanic compared with white subjects.<sup>77–80</sup> Although the burden of traditional atherosclerotic risk factors was also higher in minority patients, the increased risk of amputation was not entirely explained by the higher prevalence of risk factors.

In 1990, among patients with PAD, 5-year mortality was ≈30%.<sup>67</sup> By the year 2000, mortality rates had decreased substantially through risk factor modification and other medical treatments. Nevertheless, the presence of PAD is a powerful predictor of cardiovascular mortality, even in pa-



**Figure 5.** Kaplan-Meier survival curves in PAD. Based on mortality from all causes among healthy subjects and subjects with symptomatic or asymptomatic large-vessel PAD. Reprinted with permission from Reference 67.

tients initially asymptomatic or without evident CHD. Not surprisingly, the more symptomatic the PAD patient, the worse the long-term prognosis. Survival curves comparing PAD patients with different symptomatic status are shown in Figure 5. Sex-specific mortality rates and relative risks are shown in Table 2. There seems to be no sex difference in relative risk of PAD for subsequent CVD mortality.<sup>67,80</sup>

In summary, many factors related to development, outcome, and prevention of atherosclerosis in cerebrovascular, aortic, renal, and peripheral arterial territories are shared with coronary atherosclerosis. Important differences remain, as do gaps in semantics, such as terminology, and fundamentals, such as data on the true prevalence of intramural aortic hematoma. Indeed, knowledge of the current epidemiology of noncoronary atherosclerosis is remarkably limited, although important information is available, as reviewed in this report. Through the sharing and dissemination of existing knowledge, considerable opportunity exists to dramatically improve both clinical and research efforts in the care and understanding of people with or at risk of noncoronary atherosclerosis. It is quite clear that once atherosclerosis is established in any territory, it is essential to make aggressive secondary prevention efforts to prevent clinical CVD events, because these persons are at dramatically increased risk of such events.

**TABLE 2. Crude, Sex-Specific Mortality Rates per 100 by PAD Status and Age-Adjusted Relative Risks\***

	Men				Women			
	NL	PAD	RR	95% CI	NL	PAD	RR	95% CI
N	183	34	...	...	225	33	...	...
All-cause	16.9	61.8	3.3	1.9–6.0	11.6	33.3	2.5	1.2–5.3
CVD	7.7	41.7	5.1	2.4–10	3.6	18.2	4.8	1.6–14.7
CHD	5.5	35.3	5.8	2.4–14	2.2	9.1	4.8	1.0–22.3
Other	9.3	14.7	1.6	0.6–4.5	8.0	15.2	1.6	0.6–4.4

NL indicates normal; RR, relative risk; and CI, confidence interval.

\*Adjusted by proportional hazards models for age and survival time.

## Recommendations

### Research Priorities

- The epidemiology of renal artery atherosclerosis, including incidence, prevalence, age, sex, and ethnic variation, is largely unexplored, and the relationship of subclinical renal artery atherosclerosis to subsequent development of renal disease is a critical target for future investigations.
- The relationship between aortic atherosclerosis, particularly aortic aneurysm development, and traditional atherosclerotic risk factors should be explored, as should the relationship between aortic atheromas detected noninvasively (asymptomatic) with risk factors and other cardiovascular disease outcomes, including development of PAUs. More knowledge is needed about the incidence and outcomes of PAUs and their relationship to other aortic atherosclerotic syndromes.
- Improvement is needed in understanding the impact of PAD and carotid disease on functional capacity in older persons. The association between epidemiologic measures of PAD (ABI) and newer imaging modalities should be evaluated.
- Understanding of the different determinants, presentation, and outcomes of AVD in different arterial distributions is needed.
- Temporal trends in both subclinical and clinical AVD in different territories should be investigated.
- Understanding of ethnic differences in incidence, prevalence, clinical presentation, use of diagnostic modalities and treatment, and outcomes of AVD and different vascular territories is needed.

### American Heart Association Programs

- Consensus conference on nomenclature, definitions, terminology, measurements
- Education of public and professionals on the importance of noncoronary AVD
- Increased awareness on the part of clinicians that detection of atherosclerosis in any vascular territory increases the likelihood of atherosclerosis in other territories and mandates aggressive efforts to control risk factors for secondary prevention
- Increased visibility of AVD issues at the AHA annual Scientific Sessions
- Increased reporting and statistics on AVD in the AHA publication *Heart and Stroke Facts*
- Consider integration of prevention and treatment of AVD into the AHA strategic plan

### Advocacy Priorities

- More funding for AVD research and prevention
- Reimbursement for broad-based secondary prevention strategies, including cardiovascular rehabilitation (beyond conventional cardiac rehabilitation) and risk factor modification in patients with AVD
- Improved reimbursement for appropriate and cost-effective detection of AVD

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