The Course of Peripheral Vascular Disease in Non-insulin-dependent Diabetes

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The present report is an analysis of the course of peripheral vascular disease (PVD) in 619 patients with non-insulin-dependent diabetes (NIDDM) recruited within 1 yr of diagnosis and followed quarterly for up to 14 yr ($\bar{X}$ = 10.5 yr). At 13 yr duration, the actuarially determined cumulative risks for intermittent claudication (IC), nonpalpable dorsalis pedis pulse (NPUL), and arterial calcification (CALC) were, respectively, 37.9%, 34.5%, and 60.9% for men and 24.3%, 37.6%, and 32.2% for women. Major amputations (AMP) occurred in only 1.3% of the patients, equivalent to approximately one case per 1000 patients per year. The corresponding incidences of IC, NPUL, and CALC were, respectively, 29, 27, and 47 per 1000 men and 19, 27, and 25 per 1000 women per year. CALC and NPUL were strongly related to mortality. Baseline risk factors with probability levels that suggest a relationship to PVD were, in women, age versus CALC ($P < 0.01$), age versus NPUL ($P < 0.05$), weight versus NPUL ($P < 0.05$), systolic BP versus CALC ($P < 0.01$), summed glucose tolerance test versus CALC ($P < 0.01$), and triglyceride level versus CALC ($P < 0.05$). In men, the only significant risk factors were diminished vibration perception, which was related to NPUL ($P < 0.05$), and the serum triglyceride level, which was related to IC ($P < 0.05$). In patients who are carefully followed prospectively, IC is far more common, but AMP is far less common than has been generally appreciated. Further studies are needed to clarify the roles of the diverse risk factors that are possibly related. DIABETES CARE 1985; 8:235–43.

While it is generally recognized that diabetes predisposes to obliterative peripheral vascular disease (PVD) of the lower extremities, estimates of the scope of the problem vary widely[1–37] (Table 1). Most, but not all,[29,31] of the reported studies underestimate the problem because they are based on retrospective data from which prevalence rather than cumulative incidence or risk of PVD can be determined. In addition, it is often difficult to compare the findings of one study with those of another because of noncomparability of the populations that were investigated and lack of uniformity of the definitions and methodologies that were employed. For example, while in some studies the diabetes was of the insulin-dependent type (IDDM),[9,30] in others it was of the non-insulin-dependent type (NIDDM)[7,30,31,34] or not classified at all. Patient ages varied widely, i.e., < 40,[23] < 60,[16] 30+,[31] 40+,[7,28] 50+,[19] 60+ yr,[15] as did durations of diabetes, which were long in some reports[8,9,18,26,31] and short in others.[18,31] Some studies were of hospitalized patients whose diabetes might be more complicated,[11–13,35] while others were of outpatients[4,5,14,15,18,22,24,27,29–31,33,34,36] or of both inpatients and outpatients.[7–9,19,21,23] The situation is confounded even further by the fact that different manifestations of PVD are reported, i.e., amputation and/or gangrene,[4,5,12,15–17,22,24,35] intermittent claudication,[4,12,18,27,29,31] nonpalpable pedal pulses,[7,12,18,23,31] arterial calcification,[4,5,7,8,14,19,21] abnormal Doppler examinations,[30,33,34,36] or other miscellaneous findings.[8,11,15,25,26,37]

The present report describes the course of PVD among 619 patients of the University Group Diabetes Program (UGDP), a 14-yr prospective multicenter study of NIDDM.[38–45]

METHODOLOGY

Patients

Each study patient was recruited within 1 yr of initial diagnosis of diabetes and the diagnosis was confirmed by the demon-

TABLE 1
Reported prevalence or incidence of peripheral vascular disease

	Diabetic patients				Nondiabetic patients	
Definition of PVD	Outpatients	Inpatients	Outpatients + inpatients	Autopsies	Outpatients	Inpatients
Amputation or gangrene						
Prevalence	2.5–7.9%	0.05–1.8%		12–34%	0.007–0.3%	
Incidence	—	5.9/1000 PY*		—	3/1000 PY	
References	4,5	12,35		16,17	15,22,24	
Intermittent claudication						
Prevalence	0.3–5.5%	—			1–2%	
Incidence	8–12/1000 PY	6.6%			1.3–3.3/1000 PY	
References	4,18,31	12			27,29	
Nonpalpable dorsalis pedis pulse						
Prevalence	6–45%	17%	25–44%		0.3–4.8%	9–17%
Incidence	15–21/1000 PY	—	—		—	—
References	18,31	12	7,23		18,31	13
Arterial calcification						
Prevalence	24–61%		6–83%		3–9%	
Incidence	—		—		—	
References	4,5,18		7,9,19,21		14,18	
Abn. Doppler						
Prevalence	16–41%					
Incidence	—					
Reference	30,33,34,36					
Misc. "PVD"						
Prevalence	10–49.3%	53%	39%		1.2%	
Incidence	—	—	—		—	
References	25,26,37	11	8		15	

*PY = patient years.

stration of a positive glucose tolerance test in which the sum of the fasting, 1-, 2-, and 3-h glucose levels following 30 g glucose per m^2 body surface was equal to or greater than 500 mg/dl.[38] Patients with serious complications were excluded so that, in the judgment of the examining physician, life expectancy would be at least 5 yr. Each patient was then observed for 4 wk before enrollment on diet treatment only to exclude those who might be ketosis prone. Assignments were made randomly to either insulin variable (IVAR), insulin standard (ISTD), or placebo (PLBO) treatment. There were 204 patients in IVAR, 210 in ISTD, and 205 in PLBO. The insulin dosage in IVAR ranged from 10 to 200 U/day and was adjusted as frequently as deemed necessary by the treating physician in order to attain serum glucose levels of 110 mg/dl or less fasting and 210 mg/dl or less 1 h following a 50-g oral glucose load. ISTD treatment consisted of 12–16 U of lente insulin daily based on m^2 of body surface area. There were 166 men and 453 women, of whom 326 were white and 293 were nonwhite. At entry, the average age was 52.6 yr and the percent desirable body weight (%DBW) was 133.4.[46] During the study, 167 patients (27%) died and 105 (17%) left the program, resulting in a mean follow-up of 10.5 yr. A detailed description of the clinical course of the patients has recently been published.[45]

Examinations

The aspects of PVD that were evaluated in this study included amputation (AMP), intermittent claudication (IC), nonpalpable dorsalis pedis pulse (NPUL), and arterial calcification of the lower extremity (CALC). The numbers of patients examined each year are shown in Table 2. The decline in numbers of examinations, especially pronounced after year 10, is partially the result of loss of patients due to death or dropout but, to a larger extent, to the fact that although recruitment was from 1961 to 1965, the study ended for all remaining patients in 1971, which resulted in unequal periods of follow-up. Although there were 619 patients, the number of examinations at baseline was slightly less because in a very few instances the data were not complete due to such factors as amputation, unsatisfactory x-rays, etc.

Amputation. Major amputation at the thigh, leg, or foot of either limb was recorded. Information regarding amputa-

TABLE 2
Numbers of patients examined

	Year			
	0	5	10	14
Intermittent claudication				
Men	165	109	71	8
Women	451	346	249	28
Nonpalpable dorsalis pedis pulse				
Men	164	93	61	7
Women	451	307	214	20
Arterial calcification				
Men	165	72	36	5
Women	450	312	195	21

tions of toes was obtained from an actual count of the toes taken from the annual foot x-ray.

Intermittent claudication. Intermittent claudication was defined as a pain in either thigh or calf that occurs during exercise and forces cessation of the exercise to obtain relief from the pain. This definition of IC is similar to that accepted in the Framingham studies[29] and by the WHO.[32] The diagnosis was always made by an experienced physician who attempted to exclude leg pain that might be due to other causes such as peripheral neuropathy, arthritis, or venous insufficiency.

Nonpalpable dorsalis pedis pulse. The presence or absence of the dorsalis pedis (DP) pulse was determined by palpation and interpreted as absent if not palpable at any PVD examination. The shortcomings of pulse palpation are well known,[47] but the examination was included to provide data that could be compared with those of other studies.[31] Since the findings from the left and right sides were quite similar, only the findings from the right side will be presented.

Arterial calcification. X-rays were initially obtained of both the left and right lower extremities, but examination of the left side was discontinued when a preliminary analysis revealed very close agreement between findings obtained on the two sides. Film sets were periodically resubmitted to the radiologists blindly for study of interreader and intrareader agreement. The results of such a study performed on a subset of 157 cases are shown in Table 3. Although there was good intrareader agreement, interreader agreement was less than satisfactory; despite the observation that disagreements lessened with time, it was decided that films would be classified as positive only if both radiologists agreed that CALC was present.

TABLE 3
Reproducibility of x-ray readings*

	Reader A		Reader B	
	First reading	Second reading	First reading	Second reading
Thigh	43	40	21	22
Leg	38	35	23	21
Foot	43	33	32	28

*Percent of films from 197 patients read as positive for arterial calcification. Film sets were submitted blindly to two independent readers on two occasions.

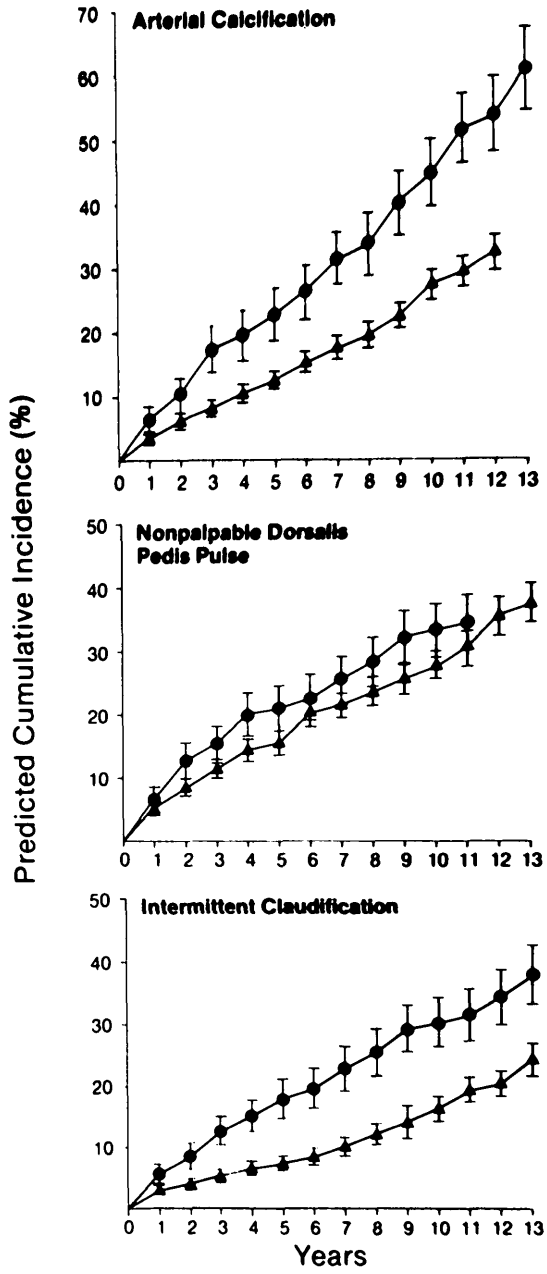

FIG. 1. Predicted cumulative incidence of peripheral vascular disease in NIDDM. ● *Men;* ▲ *Women;* $\bar{X} \pm SEM$.

TABLE 4
Prevalence and incidence of PVD

	Prevalence (%)				Cumulative incidence at year 13 (%)	Incidence/1000 patients/year
	0	5	10	14 yr		
Major amputation	—	—	—	—	1.3	1
Intermittent claudication	4.6	3.1	5.7	2.6	37.9 (M) 24.3 (F)	29 (M) 19 (F)
Nonpalpable dorsalis pedis pulse	10.3	7.4	11.3	15.9	34.5 (M) 37.6 (F)	27 (M) 27 (F)
Arterial calcification	16.2	22.6	34.4	30.6	60.9 (M) 32.2 (F)	47 (M) 25 (F)

Statistical Analyses

Predicted cumulative incidence (PCI) was actuarially determined by standard life table analysis,[48] and the risk factor data were examined by multivariate analysis using the log-linear exponent model.[49] Patients with IC, NPUL, or CALC already present at baseline were excluded from these analyses.

The following baseline risk factors were evaluated: age, %DBW, GTT (sum of fasting, 1-, 2-, and 3-h glucose values following 30 g glucose po/m^2 body surface), fasting serum triglyceride level, fasting serum cholesterol level, systolic blood pressure, diastolic blood pressure, assignment to PLBO, ISTD, or IVAR treatment, and vibration threshold at the right great toe, measured with the Biothesiometer (Bio-Medical Instrument Co., Chagrin Falls, Ohio), a calibrated rheostat-controlled vibrator.[50]

RESULTS

Amputation. At baseline, four patients (0.6%) had already suffered a major amputation unrelated to diabetes. During follow-up, 8 additional major amputations (1.3%) plus 11 amputations of toes (2.0%) were recorded. Amputations were too few to permit further statistical analyses.

Intermittent claudication. The prevalence of IC was 4.6% at baseline, 3.1% at year 5, 5.7% at year 10, and 2.6% at year 14. The predicted cumulative incidence (PCI) of IC at year 13 was 37.9% for men and 24.3% for women ($P = < 0.01$), equivalent to an incidence per 1000 patients per year of approximately 29 for men and 19 for women (Tables 4 and 5, Figure 1).

Nonpalpable dorsalis pedis pulse. The prevalence of NPUL was 10.3% at baseline, 7.4% at year 5, 11.3% at year 10, and 15.9% at year 14. The PCI of NPUL through year 13 was 34.5% for men and 37.6% for women (NS), equivalent to an incidence per 1000 patients per year of approximately 27 for men and 29 for women (Tables 4 and 6, Figure 1).

Arterial calcification of the lower extremity. The prevalence of CALC at baseline and years 5, 10, and 14 was 16.2%, 22.6%, 34.4%, and 30.6%, respectively. The PCI at year 13 was 60.9% for men and 32.2% for women ($P = < 0.01$), equivalent to an incidence per 1000 patients per year of approximately 47 for men and 25 for women (Tables 4 and 7, Figure 1). Although CALC was usually present in multiple sites, it was most common in the thigh and least common in the foot.

Relationship between PVD and mortality. During the course of the study, 40.3% of the 144 women who developed CALC died versus only 21% of the 300 in whom CALC was never observed ($P < 0.0001$), a relationship not seen among the men. NPUL was significantly related to mortality in both sexes, i.e., 50% of the 68 men with NPUL died versus only 27.6% of the 96 without NPUL ($P = 0.0053$) and 36.4% of the 173 women with NPUL died versus only 21.4% of the 280 without NPUL ($P = 0.0007$).

Risk factors and PVD. The results of the risk factor analyses are summarized in Table 5. No relationship was found in either sex between PVD and the initial serum cholesterol level, the average level of serum cholesterol, or the slope of the serum cholesterol during follow-up. On the other hand, the initial serum triglyceride level was related to CALC in women ($P < 0.01$) and to IC in men ($P < 0.05$).

Although not statistically significant, women with PVD had average serum triglyceride levels that were greater than those of men even though men as a group had higher initial as well as average serum triglyceride levels, i.e., 152 ± 11 versus 122 ± 4 mg/dl for initial values ($P = < 0.01$) and 165 ± 10 versus 141 ± 5 mg/dl for the average values ($P = < 0.01$). Serum triglyceride levels increased during follow-up in both sexes, i.e., the slopes were positive [0.195± 0.069 ($\bar{X}$ ± SEM) for men versus 0.190 ± 0.059 for women (NS)], but the slopes were not significantly related to PVD in either sex. Follow-up for men and women was comparable, i.e., an average of 5.57 annual fasting serum triglyceride levels were available for each of the 166 men and 6.13 for each of the 453 women.

Blood glucose control was best in IVAR and worst in PLBO,[45] but assignment to IVAR, ISTD, and PLBO was not related to subsequent PVD.

TABLE 5
Predicted cumulative incidence (PCI) of intermittent claudication in NIDDM

Year	Men			Women		
	No. of patients	No. of events	%PCI ($\bar{X}$ ± SEM)	No. of patients	No. of events	%PCI ($\bar{X}$ ± SEM)
1	147	4	5.8 ± 1.8	412	13	3.1 ± 0.8
2	135	6	8.6 ± 2.2	389	4	4.1 ± 1.0
3	123	3	1.9 ± 2.7	371	5	5.4 ± 1.1
4	118	4	15.1 ± 2.9	360	5	6.7 ± 1.2
5	109	2	18.1 ± 3.2	346	3	7.5 ± 1.3
6	102	4	19.7 ± 3.3	328	4	8.6 ± 1.5
7	95	3	23.0 ± 3.5	317	6	10.3 ± 1.5
8	86	4	25.6 ± 3.7	293	7	12.4 ± 1.8
9	79	1	29.2 ± 3.9	273	6	14.3 ± 2.8
10	71	1	30.2 ± 4.0	249	7	16.6 ± 2.0
11	59	2	31.3 ± 4.1	204	8	19.6 ± 2.1
12	35	2	34.3 ± 4.4	144	2	20.5 ± 2.2
13	17	0	37.9 ± 4.8	70	5	24.3 ± 2.6
14	8	1	— —	28	1	— —

DISCUSSION

Although it is difficult to make accurate comparisons of data derived from populations and methodologies that are dissimilar, the present findings support the conclusion that AMP is far less common and IC far more common than is generally appreciated.[29,35] At 13 yr of known NIDDM, the cumulative incidence of IC was 37.9% in men and 24.3% in women, equivalent to approximately 29 new cases per 1000 men and 19 new cases per 1000 women per year, which is in contrast with corresponding rates for IC reported at Framingham of 12.6% for men and 8.4% for women.[29] Possible explanations for the discrepancy include differences in sample size (239 subjects at Framingham versus 619 in the present study), in sex distribution (50% men at Framingham versus 27% in the present study), in frequency of follow-up (biannual at Framingham versus quarterly in the present study), and dissimilarities in the racial and socioeconomic characteristics. On the other hand, the prevalence of IC in the present study (which varied from 4.7% at baseline to 5.7% at year 14), is similar to prior estimates.[12,21,33] In a few instances, the year-to-year prevalence of IC, CALC, and NPUL actually decreased, reflecting loss of patients due to death or dropout.

Major amputations of the lower extremity, which likely are the result of PVD rather than neuropathy, were recorded in 1.3% of the patients, equivalent to only 1 amputation per

TABLE 6
Predicted cumulative incidence (PCI) of a nonpalpable dorsalis pedis pulse in NIDDM

Year	Men			Women		
	No. of patients	No. of events	%PCI ($\bar{X}$ ± SEM)	No. of patients	No. of events	%PCI ($\bar{X}$ ± SEM)
1	134	9	6.6 ± 2.0	396	21	5.2 ± 1.0
2	117	8	12.7 ± 2.8	365	13	8.5 ± 1.4
3	106	3	15.2 ± 3.0	339	11	11.4 ± 1.6
4	102	6	20.1 ± 3.4	333	11	14.4 ± 1.7
5	93	1	21.0 ± 3.5	307	4	15.5 ± 1.8
6	89	2	22.7 ± 3.6	291	16	20.1 ± 2.0
7	84	3	25.4 ± 3.8	269	5	21.6 ± 2.1
8	77	3	28.3 ± 4.0	246	7	23.7 ± 2.2
9	72	4	32.2 ± 4.2	233	6	25.6 ± 2.3
10	61	1	33.3 ± 4.3	214	6	27.7 ± 2.3
11	48	1	34.5 ± 4.4	169	8	30.7 ± 2.5
12	24	0	34.5 ± 4.4	110	10	35.8 ± 2.7
13	14	0	34.5 ± 4.4	49	2	37.6 ± 2.9
14	7	1	— —	20	0	— —

TABLE 7
Predicted cumulative incidence (PCI) of lower limb arterial calcification in NIDDM

Year	Men			Women		
	No. of patients	No. of events	%PCI ($\bar{X}$ ± SEM)	No. of patients	No. of events	%PCI ($\bar{X}$ ± SEM)
1	107	7	6.4 ± 2.3	393	14	3.5 ± 0.9
2	93	4	10.2 ± 2.8	370	10	6.1 ± 1.2
3	86	7	17.4 ± 3.6	344	8	8.2 ± 1.4
4	78	2	19.5 ± 3.8	328	8	10.4 ± 1.5
5	72	3	22.8 ± 4.1	312	8	12.7 ± 1.7
6	65	3	26.2 ± 4.3	292	9	15.3 ± 1.8
7	60	4	31.1 ± 4.6	275	7	17.4 ± 2.0
8	55	2	33.6 ± 4.8	250	6	19.3 ± 2.1
9	48	5	40.1 ± 5.1	230	9	22.4 ± 2.2
10	36	3	44.7 ± 5.3	198	13	27.2 ± 2.4
11	31	4	51.6 ± 5.5	152	5	29.3 ± 2.5
12	18	1	53.7 ± 5.7	104	5	32.2 ± 2.7
13	9	2	60.9 ± 6.4	51	0	32.2 ± 2.7
14	5	0	— —	21	2	— —

1000 patients per year. In contrast, Most and Sinnock estimated the risk of amputation among diabetic patients discharged from short-term U.S. hospitals to be considerably higher, i.e., 5.9 per 1000 patients per year.[35] It is likely that the low incidence of amputations observed in the present study results, at least in part, from the fact that the patients were examined by a physician every 3 mo and "minor" problems were adequately treated before they became major. It is also of great interest to note that IC seldom led to AMP, a finding similar to that described in nondiabetic patients by Juergens et al., who reported only a 3% progression from IC to AMP within 5 yr.[51] A possible explanation for the apparent lack of progression might be that the patients with IC die of coronary heart disease before they have a chance to develop gangrene,[52–58] an hypothesis that is supported by the correlations between PVD and mortality demonstrated in the present study. An important clinical implication of these findings is that surgery should be undertaken for IC if disabling symptoms do not respond to conservative measures and not for fear of imminent gangrene.

CALC is very common in NIDDM with a cumulative incidence at year 13 of 60.9% in men and 30.2% in women. Other investigations have estimated that CALC occurs in 30–80%.[4,7,9,14,18,19,21] Our findings agree with those of Nilsson et al. that CALC is more common in the thigh than in the foot[18] and with both Nilsson and Ferrier[14] that CALC is more common among men than among women. The correlation between CALC and NPUL suggests that CALC often indicates luminal narrowing.[30]

NPUL was noted in 10.3% of our patients at baseline and 11.3% at year 10, rates similar to those of 8% and 10%, respectively, reported by Melton et al.[31]

Although numerous studies have shown that aspect(s) of the diabetes syndrome are associated with an increased risk of PVD, the literature is quite confusing. PVD increases with increasing years of diabetes[18,31,33,37,59] as well as with increasing age,[30,31,33,60] but multivariate analysis suggests that the effect of diabetes duration is independent of that of age.[31,33] The present study and numerous prior studies show PVD to be more common among men than among women,[14,15,23,27,29,30,51,59] but adjustment for increased smoking among men tends to eliminate the difference,[58,59] which is noteworthy since smoking and PVD are strongly related[27,33] and reduction of cigarette smoking to fewer than 10 per day has been reported to result in improvement of IC.[27] Smoking histories were not taken in this study because at the time of its initiation the importance of cigarette smoking was not generally appreciated.

The GTT was correlated in women with both CALC and NPUL, in keeping with the findings at Tecumseh, Mich.,[61] Framingham, Mass.,[62] and Bedford, England[63] and of the WHO Multinational Study[64] of a relationship between PVD and hyperglycemia. Others, however, have shown no such relationship between PVD and blood glucose[26,30,33] or glycohemoglobin levels.[30] Although we report a correlation between %DBW and PVD, others disagree.[30,37,64] Hyperinsulinemia,[65] hyperuricemia,[27] and hyperfibrinogenemia[27] have also been suggested as possible risk factors for PVD.

Studies of lipids and lipoproteins have also given conflicting results, with serum cholesterol reported as related[51,62,66–68] or, as in the present study, unrelated[8,27,33,69,70] to PVD. We found relationships between serum triglycerides and IC in men and between triglycerides and CALC in women. Others both agree[66,67,69,70] and disagree.[33,37,68] Some authorities have even suggested that hypertriglyceridemia is related to more distal occlusive disease.[67,68] Hyperapobetalipoproteinemia,[71] hyperbetalipoproteinemia,[69] and decreased levels of HDL cholesterol[72] have also been incriminated. Excellent reviews of cholesterol, triglyceride, HDL cholesterol, and lipoprotein metabolism in diabetes are available.[73–76]

A relationship between hypertension and PVD has been

shown by many[27–30,51,59] but not all[77] studies. In the present study, systolic BP was related to CALC, but in women only. The absence of a relationship between PVD and diastolic BP has also been noted by others.[27,33] In the Framingham studies, PVD was related to left ventricular hypertrophy.[62] Finally, in the present study, an association was demonstrated in both sexes between neuropathy (decreased vibration perception) and NPUL. The significance of this observation is uncertain.

In the present study, the incidences of IC and CALC at 10 and at 13 yr were significantly ($P = < 0.01$) higher among men than among women. Although the observation might be of importance, its explanation is uncertain. The risk factor analyses suggested a relationship between intermittent claudication and the initial serum triglyceride levels, which were higher in men than in women but, as noted above, the data are difficult to interpret. Another explanation might be that there is more cigarette smoking among men than women, but since smoking histories were not taken in this study, further statements cannot be made. Finally, the fact that there were fewer men than women in the study might have obscured the role of certain risk factors in men.

A possible pitfall in these risk factor analyses as well as in many previously reported studies is the fact that the greater the number of possible risk factors investigated in this manner, the greater is the probability that some will be "significant" by chance alone. The risk factor findings should therefore be interpreted with caution and, in the opinion of the authors, are best viewed as leads for future primary prevention and/or intervention studies. The cumulative incidence rates for AMP, IC, NPUL, and CALC provided by the present study should prove helpful in the interpretation of such future studies.

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