Natural history of claudication: Long-term serial follow-up study of 1244 claudicants

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Objective: **The purpose of this study was to delineate the natural history of claudication and determine risk factors for ischemic rest pain (IRP) and ischemic ulceration (IU) among patients with claudication.**
Methods: **We prospectively collected data on 1244 men with claudication during a 15-year period, including demographics, clinical risk factors, and ankle-brachial index (ABI). We followed these patients serially with ABIs, self-reported walking distance (WalkDist), and monitoring for IRP and IU. We used Kaplan-Meier and proportional hazards modeling to find independent predictors of IRP and IU.**
Results: **Mean follow-up was 45 months; statistically valid follow-up could be carried out for as long as 12 years. ABI declined an average of 0.014 per year. WalkDist declined at an average rate of 9.2 yards per year. The cumulative 10-year risks of development of IU and IRP were 23% and 30%, respectively. In multivariate analysis using several clinical risk factors, we found that only DM (relative risk [RR], 1.8) and ABI (RR, 2.2 for 0.1 decrease in ABI) predicted the development of IRP. Similarly, only DM (RR, 3.0) and ABI (RR, 1.9 for 0.1 decrease in ABI) were significant predictors of IU.**
Conclusion: **This large serial study of claudication is, to our knowledge, the longest of its kind. We documented an average rate of ABI decline of 0.014 per year and a decline in WalkDist of 9.2 yards per year. Two clinical factors, ABI and DM, were found to be associated with the development of IRP and IU. Our findings may be useful in predicting the clinical course of claudication. (J Vasc Surg 2001;34:962-70.)**

Despite extensive study of claudication, the natural history of the disease is not fully known. Several large studies conducted before the 1980s demonstrated that intermittent claudication is a relatively benign process with a low incidence of disease progression.[1-4] These older studies documented a cumulative 10-year amputation rate of approximately 11% and improvement of distance in most persons over time. However, a shortcoming in these studies was patient inclusion based on symptoms alone and without any objective evidence that leg pain was a result of vascular disease. In contrast, studies done in the 1980s suggest a somewhat different picture for patients with claudication.[5-9] Although the reported amputation rates were still low, 30% to 40% of patients had symptomatic and/or objective deterioration over time as measured by ankle-brachial index (ABI). In addition, reported risk factors associated with disease progression in most of these studies include tobacco use and diabetes mellitus. However, the most important predictor of clinical outcome in all studies has been the severity of objectively determined arterial occlusive disease on initial evaluation. Based on these studies, generalizations can be made on the clinical outcomes affecting patients with claudication. Intermittent claudication can develop in five different ways— improvement, stabilization of the disease, worsening of the disease but with no revascularization required, worsening of the disease with revascularization required, and requirement of an amputation, usually after progression of disease.

We have previously analyzed mortality among 2777 patients with claudication.[10] This present work is based on a subset of the cohort reported in the previous work, because we restricted the current analysis to patients having serial follow-up of at least three studies during at least a 2-year follow-up period. The current study, one of the largest and longest of its kind, involves the analysis of prospectively collected data to delineate the natural history of intermittent claudication and determine risk factors for the development of ischemic rest pain (IRP) and ischemic ulceration (IU) among a male veteran cohort.

METHODS

We reviewed 28,000 lower-extremity vascular laboratory studies done between January 1983 and January 1998 at the Pittsburgh Veterans Administration (VA) Medical Center, representing 4669 patients. After initial referral to the laboratory, patients with claudication were asked to return at intervals of 6 to 12 months regardless of their clinical presentation. This was part of a strategy to prospectively follow these patients. The criteria used to identify patients with claudication have been previously

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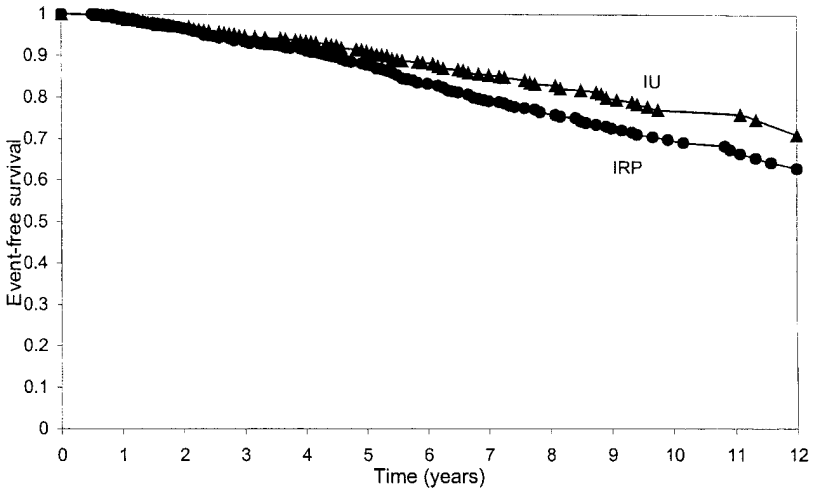

Fig 1. Kaplan-Meier event-free survival curves for the study cohort showing IU (*triangles*) and IRP (*circles*). For both curves, the standard error of the mean is less than 10% of the value of the survival function up to a follow-up of 12 years. Below the graph is shown the number of at-risk subjects at 0, 3, 6, 9, and 12 years.

published.[10] Briefly, both clinical and noninvasive criteria were used to identify 2777 patients with claudication. This cohort was also used in this analysis. We restricted the current study to patients having at least three studies with a minimum follow-up interval of 2 years between the first and last study. These follow-up criteria were applied so that the study would meet its objective of delineating the long-term natural history of claudication. A total of 1244 patients met both the criteria for claudication and the criteria for follow-up. Vascular laboratory nurses monitored all 1244 patients for IU and IRP. We defined IU as any form of pedal tissue loss that did not heal in 3 weeks. The diagnosis of IRP was made on the basis of the following criteria: (1) foot pain lasting at least 3 weeks; (2) pain severe enough to wake the patient at night; and (3) relief of pain with dependency. We were able to study serial progression of ABI among 1065 patients, after excluding patients with calcified vessels and missing ABI information. ABI was measured as the ratio between the ankle pressure (using the higher of the pressures measured over the dorsalis pedis and the posterior tibial artery) and the higher of the two brachial pressures. Pressure was measured by inflating a blood pressure cuff to 220 and then recording the value at which the distal Doppler signal returns upon slow cuff deflation. Patients were also interviewed before vascular laboratory testing and asked to report the distance they could walk (WalkDist) in yards before having to stop because of claudication. These data were sufficient to allow serial analysis in 779 of the 1244 patients (the remaining 165 patients could not provide a clear answer to this question).

Outcome events were extracted from the national patient care database as well as hospital records. The national VA database has been validated by studies showing accuracy rates >95% by comparison with direct patient record review (described at the Web site www.virec.research.med.va.gov). In the national database, revascularization and amputation procedures are tracked for all VA hospitals. This allowed us to track these outcomes wherever they may have occurred in the VA system. However, revascularization and amputation may be incomplete because of the possibility of veterans undergoing some procedures outside the VA. Missing data across the database were relatively

Table I. Clinical and demographic characteristics

Variable	
Age (y)*	64 (7)
Pack-years smoking*	52 (24.3)
ABI*	0.58 (0.2)
Race†	
White	87%
Nonwhite	13%
Diabetes†	
No diabetes	62%
Diet-controlled	7%
Oral hypoglycemic therapy	13%
Insulin therapy	18%
Smoking†	
Never smoked	6%
Past smoker	37%
Current smoker at study entry	57%
Hypertension†	
No hypertension	54%
Hypertension, no drug therapy	3%
Hypertension, drug therapy	42%
Angina†	22%
Myocardial infarction†	29%
Previous CVA†	17%

*Mean (SD).
†Frequency.
CVA, Cerebrovascular accident.

Table II. Univariate analysis: IRP

Variable	β	*RR (CI)*	P
Age (y)	–0.019	0.981 (0.96, 1.00)	NS
Smoking			
Never smoked	(baseline)		
Past smoker	0.620	1.859 (0.44, 7.81)	NS
Current smoker	1.342	3.829 (0.94, 15.53)	NS
Smoking (pack/year)	0.008	1.008 (1.00, 1.01)	.045
Race			
White	(baseline)		
Nonwhite	0.081	1.085 (0.65, 1.81)	NS
ABI*	–0.252	0.778 (0.71, 0.85)	.0005
Pulse pressure	–0.003	0.997 (0.99, 1.01)	NS
Systolic pressure	–0.006	0.994 (0.98, 1.00)	NS
Diastolic pressure	–0.008	0.992 (0.97, 1.01)	NS
Hypertension			
No hypertension	(baseline)		
Hypertension, no drug therapy	0.0399	1.490 (0.77, 2.87)	NS
Hypertension, drug therapy	–0.360	0.698 (0.47, 1.04)	NS
Diabetes			
No diabetes	(baseline)		
Diet-controlled	–0.950	0.367 (0.16, 0.96)	.039
Oral-hypoglycemic therapy	0.178	1.195 (0.63, 2.26)	NS
Insulin therapy	0.590	1.803 (0.71, 1.81)	.0202
Angina	–0.322	0.725 (0.43, 1.22)	NS
Previous myocardial infarction	–0.253	0.776 (0.52, 1.17)	NS
Previous CVA	0.126	1.134 (0.71, 1.81)	NS

*β and RR are shown for a 0.1-unit increase in ABI.
NS, Not statistically significant; *CVA*, cerebrovascular accident.

infrequent, ranging from 0% for the most fully populated field (patient identification) to 8% for the field with the greatest proportion of missing data (pulse pressure). Our analyses required Microsoft Access (Microsoft, Redmond, Wash) for descriptive statistics and SAS (SAS institute, Cary, NC) for Cox proportional hazards modeling, Kaplan-Meier plots, and parametric modeling. In performing our analysis, we used the baseline values (ie, the value obtained at the first vascular laboratory study) of all clinical variables, except where specified otherwise. β values and relative risk (RR) were calculated using the proportional hazards model (β is the natural logarithm of RR). For most of the continuous variables (age, smoking pack-years, pulse pressure, systolic pressure), the RR specifies the risk multiplier for a one-unit increase in the variable. For the continuous variable ABI, the β value and RR are shown for a 0.1-unit increase in ABI. In the case of the dichotomous (yes/no) variables, the RR indicates the increased RR associated with having the risk factor.

RESULTS

General demographics and clinical characteristics of the patient cohort are seen in Table I. Cohort characteristics include those typical of vascular patients—age, race, smoking, and other cardiovascular risk factors. The mean follow-up was 45 months, and the mean number of studies per patient was 5.2; statistically valid follow-up could be carried out for as long as 12 years.

Minor and major amputations occurred with a 10-year cumulative frequency of less than 10%. The 10-year cumulative frequency of surgical revascularization was 18%. Kaplan-Meier curves showing the occurrence of IRP and IU are shown in Fig 1. The cumulative 10-year risks of development of IU and IRP were 23% and 30%, respectively. We also found that ABI declined an average of 0.014 per year. This decline was slow but significantly different from zero ($P <$ .01). WalkDist declined at an average of 9.2 yards per year, a rate that again was significantly different from zero ($P <$ .01).

We next sought to delineate the factors that were associated with progression to IU and IRP among our patient cohort. Tables II and III depict the results of univariate Cox proportional hazards modeling of a number of potential predictors for both outcomes. The three factors that had significant predictive value for IRP were diabetes requiring insulin therapy, lower ABI, and higher pack-years of smoking. Lower ABI and diabetes requiring medication (either insulin or oral hypoglycemic therapy) were the only identified predictors for IU.

In the case of IU, because diet-controlled diabetes was not a significant risk factor and because the risk ratios were similar for diabetes requiring oral hypoglycemics and diabetes requiring insulin, it was clear that we should use the composite variable diabetes requiring medication for multivariate analysis of IU. In the case of IRP, we found that the results of multivariate analysis were very similar whether we used diabetes requiring insulin or the composite variable diabetes requiring medication. For the sake of simplicity, we therefore chose to use the composite variable diabetes requiring medication for the multivariate analysis of both IU and IRP. Our multivariate analysis showed that lower ABI and diabetes requiring medication

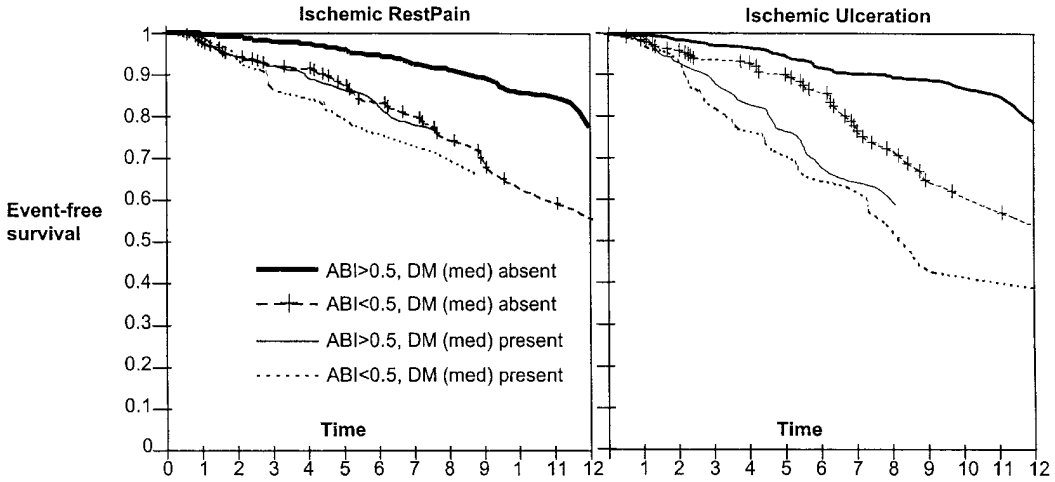

Fig 2. Kaplan-Meier curves for both IRP and IU outcomes stratified by the presence of diabetes requiring medication (*DM*) and baseline ABI.

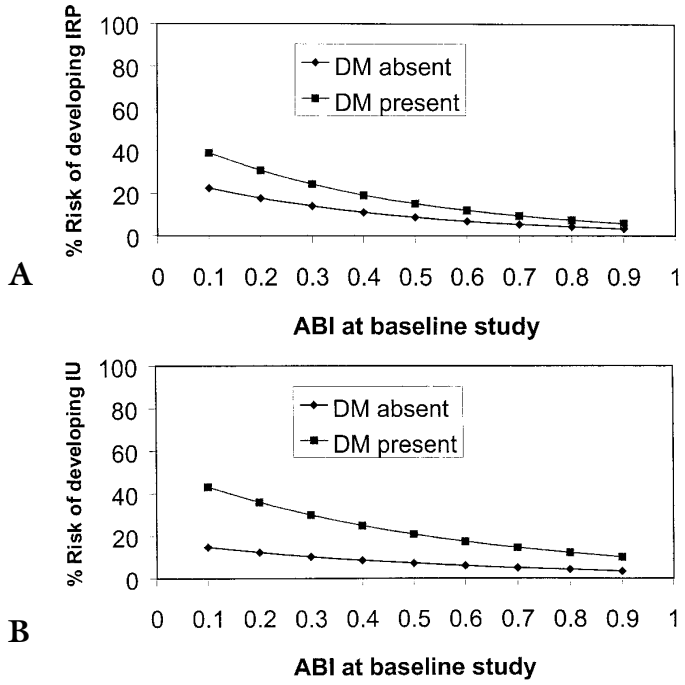

Fig 3. Predicted absolute risk for development of IRP **(A)** and IU **(B)**. *DM*, Diabetes requiring medication. See "Results" section for details.

were independent predictors of both IU and IRP (Tables IV and V). The smoking variable did not retain its predictive value for IRP in the final multivariate model. Fig 2 depicts relevant Kaplan-Meier curves for IRP and IU, stratified by the presence of diabetes requiring medication and baseline ABI. An arbitrary cutoff for ABI (0.5) was used to generate these curves. However, the effect of ABI was observable across its entire range, as indicated by the risk ratios shown in Table IV and V.

We have used our model parameters (Tables IV and V) and raw data to calculate the predicted absolute 5-year risk of developing IU and IRP (Fig 3). This contrasts with the RR ratios determined from the proportional hazards analysis. To perform these calculations, we used the actual 5-year incidence of development of these outcomes in a reference subgroup of patients not having diabetes and having ABI between 0.45 and 0.54 and then applied the RR multipliers shown in Tables IV and V.

DISCUSSION

This study represents one of the largest and longest analyses of the natural history of intermittent claudica-

Table III. Univariate analysis: IU

Variable	β	*RR (CI)*	P
Age (y)	–0.009	0.991 (0.97, 1.01)	NS
Smoking			
Never smoked	(baseline)		
Past smoker	–0.547	0.579 (0.32, 1.06)	NS
Current smoker	–0.589	0.555 (0.31, 1.06)	NS
Smoking (pack/year)	0.005	1.005 (1.00, 1.01)	NS
Race			
White	(baseline)		
Nonwhite	–0.205	0.815 (0.50, 1.33)	NS
ABI*	–0.217	0.805 (0.74, 0.87)	.0005
Pulse pressure	0.005	1.005 (1.00, 1.01)	NS
Systolic pressure	–0.004	0.996 (0.99, 1.00)	NS
Diastolic pressure	–0.018	0.982 (0.97, 1.00)	NS
Hypertension			
No hypertension	(baseline)		
Hypertension, no drug therapy	–0.0546	0.579 (0.26, 1.32)	NS
Hypertension, no drug therapy	–0.248	0.780 (0.57, 1.08)	NS
Diabetes			
No diabetes	(baseline)		
Diet-controlled	0.749	2.114 (1.31, 3.41)	NS
Oral-hypoglycemic therapy	0.992	2.698 (1.62, 4.50)	.0005
Insulin therapy	1.470	4.350 (3.11, 6.09)	.0005
Angina	–0.167	0.846 (0.55, 1.29)	NS
Previous myocardial infaction	–0.368	0.692 (0.48, 0.99)	NS
Previous CVA	0.197	1.218 (0.82, 1.81)	NS

*β and RR are shown for a 0.1-unit increase in ABI.
NS, Not statistically significant; *CVA*, cerebrovascular accident.
Symptomatic CAD is defined as the presence of either angina or prior myocardial infarction.

Table IV. Multivariate model: IRP

Variable	β	*RR (CI)*	P
DM	0.551	1.735 (1.19, 2.53)	.004
ABI*	–0.238	0.788 (0.72, 0.86)	.001
Smoking (pack/years)			NS

*β and RR are shown for a 0.1-unit increase in ABI.
DM, Diabetes requiring medication; *NS*, not statistically significant.

tion. Understanding its natural history is crucial to making clinical decisions, such as whether surgical revascularization is needed. In comparison with older, larger studies of patients with claudication, a strength of this current analysis is that patients were identified with both clinical and noninvasive criteria; thus, we avoided including patients with nonvascular leg pain. Our noninvasive criteria for diagnosing claudication are consistent with those of several other studies.[11-13]

Our previous work[10] documented a high mortality rate among patients with claudication (about 12% annualized risk of death). We found four key predictive risk factors for mortality, namely older age, lower ABI, stroke, and diabetes requiring medication. In the current work, we found that the 10-year cumulative risk of developing IRP is roughly 30%. The 10-year risk of developing IU is about 23%. We also found statistically significant but small annual reductions in ABI (0.014 units/year) and WalkDist (9.2 yards/year). In addition, we measured low cumulative rates of amputation (<10% at 10 years). Overall, our data support the concept that claudication is associated with a high rate of mortality but relatively benign lower-extremity outcomes among patients with claudication.

Our data are consistent with previous natural history studies. Even though atherosclerosis is pathologically a progressive process, large studies suggest that claudication is a surprisingly benign clinical entity with respect to lower-extremity outcomes.[11,14] The Basle study documented angiographic disease progression in 63% of patients 5 years after the initial diagnosis.[15] However, activity-limiting claudication still did not develop in 66% of those who survived after 5 years. In general, studies during the last 40 years suggest that only about a quarter of patients with intermittent claudication will ever deteriorate, most frequently during the first year of the diagnosis. Thereafter, deterioration is 2% to 3% annually.[8,11]

Table V. Multivariate model: IU

Variable	β	*RR (CI)*	P
DM	1.076	2.932 (2.12, 4.06)	.001
ABI*	-0.183	0.833 (0.77, 0.90)	.001

*β and RR are shown for a 0.1-unit increase in ABI.
DM, Diabetes requiring medication.

Stabilization of symptoms may occur secondary to collateral development, metabolic adaptation of ischemic muscle, or gait alteration favoring nonischemic muscle groups.[11] Reported major amputation rates of 7% during a 5-year period and 12% during a 10-year period are based on several population studies.[11] However, recent studies suggest that major amputations are relatively rare in these patients, with only 1% to 3.3% of patients needing major amputation during a 5-year period.[11] In addition, two large population-based studies found that less than 2% of patients with peripheral arterial disease required major amputation.[18,19]

The revascularization rate at our VA Medical Center, 18% cumulative frequency at 10 years, is at the higher end of the range reported in the literature. The reported proportion of patients who will ultimately require operative intervention varies in the literature from 3% to 22%, depending largely on the severity of the claudication of the patient enrolled in the study.[16,17] Thus, the lower figures are likely the truer reflection of what happens to all patients with claudication. Our relatively high revascularization rate likely reflects the fact that we studied patients with symptoms severe enough to warrant referral to a vascular laboratory.

Risk factors for the progression of claudication have been reported in many cohort analyses.[11] For disease progression, the reported risk factors include smoking, diabetes, and ABI.[11] In our analysis, the development of both IU and IRP was associated with diabetes and lower ABI. Although pack-years of smoking was associated with development of IRP in univariate analysis, it did not play a significant role when other factors were considered in the multivariate analysis. In this case, the issue may simply be that large numbers of our study group (94%) were current or past smokers. The small number of nonsmokers may have made it difficult to determine the true predictive value of smoking.

The importance of diabetes and its role in disease progression has been previously demonstrated.[5-9] We found that diet-controlled diabetes was not a significant predictor; however, diabetes that required either oral or insulin therapy was a strong predictor of the development of these outcomes. Diabetes in patients with peripheral arterial disease tends to portend a more aggressive course, with early large vessel involvement coupled with microangiopathy. McDaniel and Cronenwett[20] showed that these patients had a 35% risk of sudden ischemia and a 21% risk of amputation, compared with nondiabetic patients with claudication. This is consistent with our analysis, which suggests that diabetic patients with claudication have a 2.9-fold increased risk for development of IU and a 1.7-fold increased risk for development of IRP as compared with nondiabetic patients.

In our analysis, ABI was the strongest predictor for progression to IU and IRP. That is, the lower the ABI in a given patient, the higher the risk that patient had of developing limb-threatening ischemia. In Dormandy and Murray's[6] analysis of 1969 patients with claudication, the most significant predictor of disease deterioration was an ABI of less than 0.5 on presentation with a risk ratio of 2.3. In the current study, we analyzed ABI as a continuous variable. For IRP, the risk ratio for ABI is 1.25 for a 0.1 decrease in ABI. Likewise, for IU, the risk ratio for ABI is 1.21 for a 0.1 decrease in ABI.

A limitation of this and other hospital laboratory–based studies is the selection bias that may occur at multiple levels. Only a subset of patients with claudication will typically be referred to the vascular laboratory in the first place. Furthermore, despite our efforts to schedule every patient to return for follow-up regardless of clinical status, inevitably some patients fail to return. The net effect of this winnowing of patients is probably an over-representation of patients with worse and/or more progressive claudication. A further important limitation of our study population is the lack of female patients. This is virtually inevitable, given the setting of the study (VA hospital). In addition, our study included few Hispanic patients because of the makeup of the veteran population in the western Pennsylvania region. In other respects, however, the demographics and clinical characteristics of our study population (Table I) are not much different from those seen in other vascular laboratories. Female patients with claudication are likely to have a natural history different from that of male patients. Therefore, our results should only be extrapolated to other male patients with claudication of sufficient severity to be referred to a noninvasive vascular laboratory.

Even though the typical patient with claudication has a relatively benign prognosis with respect to lower-extremity outcomes, our data allow us to identify a subset of patients (diabetics with ABI <0.3) having a substantially elevated risk of adverse limb events (Fig 3). This raises the question of whether such patients are better served with early revascularization rather than waiting for the development of IU or IRP. Such a question can only be answered by a randomized trial, and we are currently examining the feasibility of such a trial. In the meantime, we suggest that the threshold for offering surgical revas-

cularization to diabetic patients with claudication with reduced ABIs should be lower than for other patients with claudication, as long as other important factors (such as medical risk factors and availability of conduit) are equal.

CONCLUSION

This prospectively followed cohort of male veteran patients with claudication with long-term national follow-up is one of the largest and longest of its kind. We documented an average rate of ABI decline of 0.014 per year and a decline in WalkDist of 9.2 yards per year. Two clinical factors, ABI and diabetes requiring medication, were found to predict risk of IRP and IU. Our findings may be useful in predicting the clinical course of claudication and in making informed decisions about patient selection for surgical intervention.

REFERENCES

1. Boyd AM. The natural course of arteriosclerosis of lower extremities. Angiology 1960;11:10-4.
2. Schadt DC, Hines EA, Juergens JL, Barleer NW. Chronic atherosclerotic occlusion of the femoral artery. JAMA 1961;175:656-61.
3. Peabody CN, Kannel WB, McNamara PM. Intermittent claudication—surgical significance. Arch Surg 1974;109:693-7.
4. McAllister FF. The fate of patients with intermittent claudication managed nonoperatively. Am J Surg 1976;132:593-5.
5. Cronenwett JL, Warner KG, Zelenock GB, Whitehouse WM Jr, Graham LM, Lindenauer M, et al. Intermittent claudication: current results of nonoperative management. Arch Surg 1984;119:430-6.
6. Dormandy JA, Murray GD. The fate of the claudicant—a prospective study of 1969 claudicants. Eur J Vasc Surg 1991;5:131-3.
7. Naschitz JE, Ambrosio DA, Chang JB. Intermittent claudication: predictors and outcome. Angiology 1988;29:16-22.
8. Jelnes R, Gaardstring O, Hougaard Jensen K, Baekgaard N, Tonnesen KH, Schroedder T. Fate of intermittent claudication: outcome and risk factors. Br Med J 1986;293:1137-40.
9. O'Riordan DS, O'Donnell JA. Realistic expectations for the patient with intermittent claudication. Br J Surg 1991;78:861-3.
10. Muluk SC, Muluk VS, Kelley ME, Whittle JC, Tierney JA, Webster MW, et al. Outcome events in patients with claudication: a 15-year study in 2777 patients. J Vasc Surg 2001;33:251-8.
11. TASC Working Group. Management of peripheral arterial disease (PAD). J Vasc Surg 2000;31:S1-S289.
12. McDermott MM, Feinglass J, Slavensky R, Pearce WH. The ankle-brachial index as a predictor of survival in patients with peripheral vascular disease. J Gen Intern Med 1994;9:445-9.
13. Wolf EA, Sumner DS, Strandness DE. Correlation between nutritive blood flow and pressure in limbs of patients with intermittent claudication. Surg Forum 1972;23:238.
14. Corgan AG, Warren R. Arteriographic changes in femoropopliteal arteriosclerosis obliterans. A five year follow-up study. N Engl J Med 1966;274:643.
15. Da Silva A, Widmer LK, Ziegler HW, Nissen C, Schweizer W. The Basle longitudinal study: report on the relation of initial glucose level to baseline ECG abnormalities, peripheral artery disease, and subsequent mortality. J Chron Dis 1979;32:797-803.
16. Breslau PJ, Jorning PJG, Dassen P. The natural history of intermittent claudication, a prospective study. Proceedings of the 2nd International Vascular Symposium; 1986 Sep.
17. Schildkraut JM, Myers RH, Cupples LA, Kiely DK, Kannel WB. Coronary risks associated with age and sex of parental heart disease in the Framingham Study. Am J Cardiol 1989;64:555-9.
18. Kannel WB, Skinner JJ Jr, Schwartz MJ, Shurtleff D. Intermittent claudication. Incidence in the Framingham Study. Circulation 1970;41:875-83.
19. Widmer LK, Biland L, Da Silva A. Risk profile and occlusive peripheral artery disease (OPAD). Proceedings of the 13th International Congress of Angiology; 1985 Jun 9-14; Athens, Greece.
20. McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. Ann Vasc Surg 1989;3:273-7.

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DISCUSSION

Dr Robert B. Patterson (Providence, RI). Thank you, Dr Brener and Dr Walsh, members and guests.

Dr Johnnides, I'd like to compliment you on a very nicely presented paper. This paper represents a reevaluation of the data that were presented to the SVS-AAVS in Toronto last spring, utilizing the endpoints of ischemic rest pain and ischemic ulceration rather than death and amputation.

Reading the manuscripts together raises some questions, perpetuates some weaknesses, and adds little to our corporate knowledge of claudication. The reported cohort has dropped from 2777 to 1244 patients. By requiring three vascular lab studies 2 years apart, are you selecting a biased cohort? The patients lost to follow-up may have symptom stabilization or improvement and not return for further clinic and lab visits. Or conversely, they may have sought care outside the VA system for more advanced vascular disease.

Where are the life tables and error bars to support 12-year validity? Mean follow-up of 45 months is a far cry from 12 years. How many patients actually had 12 years of follow-up? Did they also represent the most symptomatic and were thus more prone to return?

If ischemic ulceration and ischemic rest pain are considered limb-threatening endpoints, why did only 18% of the patients go to surgery when 23% and 30% developed limb-threatening symptoms? And if surgery was done primarily for claudication, as your senior author stated in his discussion in Toronto, how do you manage limb-threatened patients?

ABI decline was 0.14 per year. What does this mean when the standard deviation for ABI is plus or minus 0.10? Where is the life table or graph with error bars?

Self-reported walking distances, as you've already alluded to, without a validated instrument such as the walking impairment questionnaire, is notoriously unreliable. The decline in walking distance self-reported of 9 yards per year could be accounted by many factors. And I suspect an elderly population without claudication may experience a similar decrement.

With diabetes as an independent risk factor, how did you differentiate ischemic rest pain and ulceration from neuropathic pain and ulceration? Does this account for the disparity of symptom progression and revascularization?

The authors suggest the findings in this study will help determine the need for revascularization. Do they have any data to suggest that intervention in claudicants prior to the onset of limb-threatening symptoms alters the natural history with regard to limb loss and mortality? How about therapies directed toward relief of the claudication symptoms themselves? Our challenge today is not to demonstrate once again that untreated claudication infrequently leads to limb-threatening symptoms, but to

explore therapies that improve the lives of patients who are affected by the physical and social debilitation of claudication itself.

Thank you.

Dr Christopher Johnnides. I'd like to thank Dr Patterson for those comments. Looking at the list, I'll try to go one by one.

Is the cohort biased in the sense that we had patients go out to 12 years? If I understand the question correctly, are those patients likely to be more sick? I guess you could say that. The patients that we have had a range of follow-up. The longest did go out to 12 years, although all did not go out to 12 years. But when we analyze the data, we can generate useful information using Kaplan-Meier proportional Cox hazard methods based upon a range of ABIs or the presence or absence of diabetes.

The surgical indications; there is a disparity from the prior paper, if I understand your point correctly again, although the rate of revascularization in the February issue was 18%, and we have ischemic ulceration, ischemic rest pain for 30% here, which are usually operative indications. You also have to look at the rate of amputation on the first paper, which was approximately 10% at 10 years. I don't think we can get absolute agreement with numbers because you are going to lose some patients that do not want to have surgery or who die in the follow-up.

As far as ABI loss of 0.014 per year, and in terms of the error bars, some of the graphs I included, you may have noticed that some of the lines are truncated, that they didn't go out to all 12 years. We did it that way just to present a little bit more manageable graph. We presented those lines only if the error was within 10% of the mean. If it fell outside of 10%, then we didn't include that up to 12 years. We certainly can go back and include the error bars in those graphs.

The walking impairment questionnaire, again, as I pointed to in my talk, the more state-of-the-art way of identifying walking distance data would be treadmills, but I think that the average clinician in general uses information on self-reported walking distance versus treadmill data, so I still think this information is useful.

And Dr Patterson makes a good point in terms of the relative contribution of diabetes to ischemic ulceration. The greatly increased contribution, particularly in ischemic ulceration, probably is due to neuropathic and microvessel disease, and we didn't separate out for those two entities.

And how does this affect selection for surgery, how about treatment for claudication?

Dr Patterson raises a valid point. Some patients are going to stabilize and drop out and not be subject to follow-up. We collected these data as part of a prospective study to evaluate these patients in a research setting. We instructed these patients to follow up at 6-month and 12-month intervals based upon their clinical symptoms. Obviously we can only report data on those patients that did follow up, and it's logical to assume that those patients that don't follow up probably either died or the disease got better. So I'm not sure how we can improve upon that criticism.

Dr Satish C. Muluk. I'd just like to take a chance to add on to some of Chris's comments. I thought he did a fine job in responding to Dr Patterson's very insightful questions. I just have a few additions to make.

I think in terms of the issue of the biased cohort, perhaps the most important issue in terms of the validity of the data set, it's important to keep in mind that this is not simply a retrospective review of patients who just happened to come to the vascular lab. This was part of a prospective strategy initiated at our VA many years ago to bring patients routinely back regardless of their clinical situation, so that they were brought back with a prospective idea toward collecting data for future research and investigation.

And so, although there is always the possibility of a biased cohort, I would say that it is as close as one can get to following a large number of patients. Certainly if patients elected not to come back or moved from the area or died, there was not much that could be done. But this was not simply a retrospective review of data that was collected for other purposes.

The other issue, in terms of the error bars which Dr Patterson brought up, I think Chris did answer. But to emphasize, in order to make the figures manageable, we intentionally did not show the error bars. But the curves are limited to the data point, the time point, at which the standard error of the mean exceeds 10% of the survival distribution function, which is a fairly standard way of limiting the Kaplan-Meier curves and making the graphs a little more meaningful.

The other issues I thought were already answered, and I'll try not to be redundant therefore.

Dr Linda Harris (Buffalo, NY). I enjoyed your paper. I have a couple questions.

The first is since you found diabetes to be so important in the progression of disease, did you monitor how well the diabetes was controlled? Is there any evaluation of their hemoglobin A1c or any idea how well controlled their diabetes was, and did that impact their progression of disease?

Two, how did you treat the claudicants? Were they placed on smoking cessation programs, exercise protocols, or any medical management such as Pletal or Trental? And if you did those, how did those impact the progression of disease?

Dr Johnnides. Thank you for your comments.

We did not track hemoglobin A1c's or strict control diabetes. What we did is we divided the group into three groups, as I had stated—those without diabetes, those that were orally controlled, and those that were controlled with insulin. That could be worth looking at. Although I think it doesn't detract from the data, that those patients that we assumed would have worse diabetes, those that require medication, did worse than those that didn't require medication.

In answer to your second question, no, we did not look at the effect of medical treatment on the progression of disease in our population. That's something we could do, but it just wasn't included in this database.

Dr Daniel B. Walsh (Lebanon, NH). I wonder if I might ask, given all the variables you did look at, I'm interested that you didn't look at renal failure. And I wonder if you have other data or just some anecdotal knowledge to answer the question about the impact of renal failure on claudication.

Dr Johnnides. Not for this study. Basically the demographic characteristics I listed were the main characteristics. As far as anecdotal knowledge, I wouldn't be able to venture a guess.

Dr Bruce J. Brener (Millburn, NJ). Just focus on that question about bias again. The striking thing about your paper was the very large number of patients that developed ischemic rest pain and ulceration.

Dr Johnnides. Certainly. And I think we have to keep in mind, and this is why I pointed it out, the two glaring characteristics in our demographic data were that 100% were male and 94% smoked. I think that if you compare these to some of the prior studies in non-VA populations, there were slightly lower incidences. I think that reflects the fact that there were more women and fewer smokers probably in those populations.

Dr Muluk. I would like to make two additional comments.

One is that the nature of referral to a vascular laboratory does imply a certain degree of clinical severity. There must have been some reason for the patient to have been initially referred. So there is a bias in that respect. And it is quite conceivable that the average claudicant will be less ill and perhaps less prone to develop these problems. I don't know of any good way to get around that problem because it boils down to what we're capable of studying.

The second issue about the neuropathic pain is that all of these patients, in order to have a diagnosis of rest pain, had to indicate that their pain was improved with dependency in the hope of separating ischemic from neuropathic pain. Obviously, the ulceration question is a little more difficult. If someone with an ABI, say, of 0.7 were to develop an ulcer and had diabetes, there is no question that neuropathy is a contributor. But I think we all recognize in those patients that there is a combination of

factors—neuropathy, microvascular disease, and ischemia from major vascular occlusive disease.

Dr Michael P. Lilly (Baltimore, Md). I agree with your conclusion that because such a large proportion of your population are smokers you cannot draw any distinctions between smokers and nonsmokers.

However, a number of studies looking at large groups of claudicants and people with lower-extremity occlusive disease has shown that there is a strong relationship between progression of lower-extremity atherosclerosis and cumulative pack-years of smoking. Have you taken advantage of the large proportion of smokers in your study to stratify your data based on total pack-years smoking or perhaps examine the natural history of those who have actually quit?

It might be that there is a cohort of claudicants with a different natural history of their disease. That would be a very useful additional bit of information that could come out of this data set.

Dr Johnnides. Thank you for your comments, and I agree. Just one point that I would like to make, and I didn't include it in the slides, is that we did stratify, as I said, our smokers into those patients that currently smoked and had a history of smoking. There was no difference between significance in either group. That's why we lumped them together.

But I agree, I think that if we could get a larger cohort of the VA population that didn't smoke, we could definitely get some more useful information, especially in relation to those patients that stopped smoking and the supposed beneficial effect on the progression of disease.

Dr Brener. Did you separate patients with aortoiliac disease from femoropopliteal disease from combined disease? And do you think there is a different prognosis associated with the location of the disease?

Dr Johnnides. We did not separate in this paper, no. I think that people with more distal disease are thought to do worse, but actually we are looking at that in another paper we're preparing, the differences in proximal versus distal disease.