Intermittent claudication: From its risk factors to its long-term prognosis in men. The Quebec Cardiovascular Study

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BACKGROUND: The natural history of intermittent claudication, from its risk factors to its cardiovascular prognosis, has been reported in few prospective studies.
OBJECTIVE: To assess incident intermittent claudication, as well as its risk factors and long-term prognosis in men.
METHODS: A random sample of 4376 men 35 to 64 years of age from Quebec City (Quebec), who were free of cardiovascular disease (CVD), was evaluated in 1974 for CVD risk factors and followed until 1998. To assess the prognosis, the event rates between 1985 and 1998 were computed among men with incident claudication without other CVD, incident survivors of a first myocardial infarction (MI) without other CVD and men free of CVD between 1974 and 1985.
RESULTS: From 1974 to 1998, 300 men developed intermittent claudication. Tobacco consumption, high systolic blood pressure and diabetes at least doubled the adjusted RR (aRR) of intermittent claudication. In 1985, there were 80 claudicants, 2868 men free of CVD and 68 survivors of a first MI. During the 13-year follow-up, a new CVD occurred in 48.8% of the claudicants, in 18.9% of men without CVD (aRR 2.08; 95% CI 1.48 to 2.90) and in 45.6% of MI survivors (aRR compared with claudicants 1.12; 95% CI 0.69 to 1.79). There was also no significant difference between claudicants and MI survivors for fatal CVD, nonfatal CVD and total mortality.
CONCLUSIONS: Men with intermittent claudication are at high risk for CVD that may be equivalent to men with previous MI.

Key Words: *Cardiovascular disease; Intermittent claudication; Myocardial infarction; Risk factors*

La claudication intermittente : Des facteurs de risque au pronostic à long terme chez les hommes. L'enquête québécoise sur la santé cardiovasculaire

HISTORIQUE : Peu d'études portent sur l'évolution naturelle de la claudication intermittente, des facteurs de risque au pronostic cardiovasculaire.
OBJECTIF : Évaluer la claudication intermittente incidente ainsi que ses facteurs de risque et son pronostic à long terme chez les hommes.
MÉTHODOLOGIE : Un échantillon aléatoire de 4 376 hommes de 35 à 64 ans de Québec, sans maladie cardiovasculaire (MCV), a été évalué en 1974 afin d'établir les risques de MCV, puis suivi jusqu'en 1998. Pour déterminer le pronostic, les auteurs ont calculé le taux d'événements entre 1985 et 1998 chez les hommes présentant une claudication incidente sans autre MCV, les survivants incidents à un premier infarctus du myocarde (IM) sans autre MCV et les hommes sans MCV entre 1974 et 1985.
RÉSULTATS : De 1974 à 1998, 300 hommes ont développé une claudication intermittente. La consommation de tabac, la tension artérielle systolique élevée et le diabète doublaient au moins le risque relatif rajusté (RRR) de claudication intermittente. En 1985, on dénombrait 80 claudicants, 2 868 hommes sans MCV et 68 survivants d'un premier IM. Pendant le suivi de 13 ans, un nouvel MCV s'est manifesté chez 48,8 % des claudicants, 18,9 % des hommes sans MCV (RRR 2,08; 95 % IC 1,48 à 2,90) et 45,6 % des survivants d'un IM (RRR par rapport à celui des claudicants 1,12; 95 % IC 0,69 à 1,79). Par ailleurs, on ne remarque pas de différence significative entre les claudicants et les survivants à un MCV pour ce qui est des MCV fatals, des MCV non fatals et de la mortalité totale.
CONCLUSIONS : Les hommes sans claudication intermittente sont très vulnérables à un MCV, et cette vulnérabilité peut être équivalente à celle des hommes ayant déjà subi un MCV.

The natural history of intermittent claudication (1-9) and lower limb arterial disease detected by abnormal ankle-brachial index (10-13), has been documented in longitudinal studies identifying the contributing risk factors as well as fatal cardiovascular disease (CVD) and all-cause mortality outcomes. Although it is well known that patients with intermittent claudication are at high risk for cardiovascular death, the relationship with nonfatal CVD outcomes in a random population has been reported in only a few studies (8,14-16). Likewise, little data have been published comparing the prognosis between persons with intermittent claudication and persons with other CVD (16,17). The present study was performed to further assess the long-term effects of risk factors on the development of intermittent claudication among 4376 men selected at random and without CVD at entry in 1974 and followed until 1998. In addition, to assess the prognosis of intermittent claudication, we computed the event rates between 1985 and 1998 among incident claudicants identified between 1974 and 1985; these claudicants without CVD were compared with men free of CVD and men with a first incident myocardial infarction (MI) without other CVD.

METHODS

Setting and population

The population of the present study was previously described (18). In brief, from December 1973 to June 1974, 4637 men 35 to 64 years of age, representing 65% of a random sample of seven suburbs of Quebec City stratified according to age of men in the province of Quebec, answered a standardized medical questionnaire, and had their blood pressure measured and a blood sample taken for cholesterol determination. At entry, 245 men with CVD were excluded on the basis of a

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TABLE 1
Baseline characteristics of men with and without claudication during a 24-year follow-up

Variables	Intermittent claudication		P
	Yes (n=300)	No (n=4076)	
Age, years	49.7±7.2	46.2±7.8	<0.001
Systolic blood pressure, mmHg	147±20	138±18	<0.001
Diastolic blood pressure, mmHg	86±11	85±11	0.02
Total cholesterol, mmol/L	5.1±1.0	4.9±1.0	0.002
Smoking status, n (%)			
Nonsmokers	14 (4.7)	539 (13.2)	
Ex-smokers	24 (8.0)	733 (18.0)	
Pipe/cigars	12 (4.0)	220 (5.4)	<0.001
Cigarettes 1–19/day	81 (27.0)	990 (24.3)	
Cigarettes ≥20/day	169 (56.3)	1594 (39.1)	
Diabetes, n (%)	23 (7.7)	116 (2.9)	<0.001
Body mass index*, kg/m^2	25.7±3.7	25.9±4.1	0.5
Years at school	9.3±3.4	10.2±3.9	<0.001
Family history of CVD, n (%)	99 (33.0)	1046 (25.7)	0.005

*Data presented as mean ± SD unless otherwise indicated. *Body mass index was determined for 2108 men. CVD Cardiovascular disease*

complete medical and electrocardiographic examination. The remaining men were subsequently evaluated in 1980 and 1985, and answered a standardized questionnaire (letter or telephone) regarding their medical status in 1990 and 1997. Among the 4392 men, 16 (0.4%) were lost after the initial examination in 1974. Among the 4376 remaining men, 155 (3.5%) participants had an incomplete follow-up: the last update was in 1990 for 98 participants, in 1981 for three, in 1979 for 23, and in 1977 for 31. The study was approved by the institutional ethics committee, and participants provided written consent to consult their hospital chart.

Risk factors

Blood pressure was calculated as the mean of two consecutive measurements with a standard mercury column sphygmomanometer, using phase V as diastolic pressure, with the participant in the sitting position at rest for at least 5 min. Smoking status was self-reported and men were classified into five groups: nonsmokers at entry; ex-smokers (those who discontinued their habit at least one year before screening); pipe and/or cigar smokers; smokers of one to 19 cigarettes per day; and smokers of 20 cigarettes or more per day. A nonfasting blood sample was used to determine cholesterol levels. Diabetes was either self-reported or based on a fasting blood sugar level of 7 mmol/L or greater. Body mass index data were available in 2108 men. Education levels were divided according to the number of years at school: zero to seven years, eight to 12 years, and 13 years or more. CVD family history was defined as a history of fatal CVD, MI, stroke and angina among siblings, mother and father.

Diagnostic criteria for intermittent claudication and MI

The diagnosis of intermittent claudication was based on Rose and Blackburn's questionnaire (19), which was administered by a nurse at each visit, documenting cramping discomfort in one or both calves or thighs induced on exertion and relieved by rest; a cardiologist was required to validate the diagnosis based on the questionnaire. A diagnosis of MI required two of the following three findings: typical symptoms, electrocardiographic tracing with new Q waves or evolving ST segment elevation, or peak cardiac enzyme levels at least two times the upper limit of normal.

Cardiovascular outcomes and all-cause mortality

The outcome measures were fatal and nonfatal CVD (MI, unstable angina, typical effort angina and stroke), as well as all-cause mortality. Cardiovascular death included death due to coronary artery disease, stroke, congestive heart failure or other vascular diseases (such as aortic aneurysm rupture or pulmonary embolism). The diagnosis of MI required the same criteria as above. The diagnosis of unstable angina required acute typical symptoms plus an electrocardiographic tracing with ischemic ST-T changes. Typical effort angina was documented by a nurse using a standard questionnaire, and the diagnosis had to be confirmed by a cardiologist during the medical examination or telephone evaluation. Stroke required a sudden neurological deficit, lasting at least 24 h, that was of vascular origin, excluding trauma, tumour or malformation. Events were adjudicated by three cardiologists using the hospital charts; for death occurring outside the hospital, the family was contacted to document the circumstances of death, and confirmation was obtained with the death certificate or a note from the provincial registry or the physician attesting death.

Statistical analysis

Baseline patient characteristics were compared between groups using ANOVA F-tests or χ^2 tests. Cox proportional hazards models were used to estimate the risk of intermittent claudication associated with different predisposing factors. For CVD prognosis, the rates of fatal and nonfatal CVD and all-cause mortality during a 13-year follow-up were compared among men with no CVD in 1985; men with intermittent claudication documented between 1974 and 1985 and without other CVD; and men surviving a first MI documented between 1974 and 1985 without any other CVD. The 1985 evaluation was used as baseline data for these three groups. The Kaplan-Meier survival probability was calculated for each group for the different outcomes. The log-rank test was used to compare survival curves among the groups. Risks were adjusted for age, risk factors in 1985 and the person-time exposure between the diagnosis of claudication or MI, and the new outcome or the end of the study period using Cox proportional hazards models. Adjusted RRs (aRRs) are presented with their 95% CIs. Results were considered to be significant at $P \leq 0.05$.

RESULTS

Baseline characteristics

From 1974 to 1998, 300 men developed intermittent claudication, and all of the 162 (54%) who underwent angiographic study had a documented atherosclerotic narrowing of at least 50% in one of their lower limb arteries. Compared with the 4076 men without intermittent claudication, claudicants were older and had higher blood pressure, total cholesterol levels, prevalence of tobacco consumption, diabetes and family history of CVD, as well as fewer numbers of years at school (Table 1). There was no difference in body mass index.

Risk factors for intermittent claudication

Table 2 summarizes the aRR of intermittent claudication according to the different risk factors. Smoking 20 cigarettes or more per day was the dominant independent risk factor, increasing the risk of intermittent claudication by 4.6-fold. Those who stopped smoking at least one year before the study had an aRR that was not different from the one of never-smokers. Increased systolic and diastolic blood pressures (fifth versus first quintile) were associated with a 2.6 and 1.4 increased aRR of intermittent claudication, respectively. Diabetes and age were also independently associated with a 2.3 and 1.7 increased aRR of intermittent claudication, respectively. Elevated serum cholesterol levels (fifth versus first quintile) increased the aRR of intermittent claudication by 1.5-fold. Body mass index and years at school were not significantly related to intermittent claudication.

Cardiovascular events

During the 24-year follow-up of the cohort, there were 485 cardiovascular and 318 coronary deaths, 588 men had a nonfatal MI, 203 had unstable angina, 673 had a typical angina and 223 had a nonfatal stroke. Among the 300 claudicants, 95 (32%) had a CVD documented before the diagnosis, and 100 (33%) had a CVD documented after the

TABLE 2
Adjusted RRs of intermittent claudication according to different risk factors

Variables	Subjects, n	Intermittent claudication, n	Age-adjusted rates/ 10,000	RR (95% CI)*
Age, years				
<55	3568	218	29.1	1
≥55	808	82	62.3	1.73 (1.33–2.25)†
Systolic blood pressure, mmHg				
<124	811	37	21.4	1
124–132	860	45	23.8	1.13 (0.73–1.74)
133–140	852	43	22.9	1.08 (0.70–1.68)
141–152	957	57	27.4	1.23 (0.82–1.87)
>152	896	118	60.8	2.57 (1.75–3.76)†
Diastolic blood pressure, mmHg				
<77	858	56	31.9	1
77–82	804	47	28.2	0.91 (0.61–1.34)
83–87	860	46	25.7	0.82 (0.55–1.21)
88–92	861	63	36.1	1.24 (0.86–1.78)
>92	993	88	43	1.44 (1.02–2.03)‡
Serum cholesterol, mmol/L				
<4.11	843	44	25.7	1
4.11–4.65	873	49	25.2	0.97 (0.64–1.46)
4.66–5.12	909	66	34.4	1.25 (0.86–1.84)
5.13–5.66	911	68	33.8	1.27 (0.87–1.86)
>5.66	840	73	41.3	1.45 (1.00–2.12)‡
Smoking status at baseline				
Nonsmokers	553	14	11.5	1
Ex-smokers	757	24	12	1.14 (0.59–2.21)
Pipe/cigars	232	12	21.8	2.01 (0.93–4.35)
Cigarettes 1–19/day	1071	81	34	3.34 (1.89–5.90)†
Cigarettes ≥20/day	1763	169	48.8	4.64 (2.68–8.04)†
Diabetes				
No	4237	277	32.3	1
Yes	139	23	81.3	2.28 (1.48–3.50)†
Body mass index, kg/m^2				
<22.6	419	34	41.7	1
22.6–24.7	426	39	51.7	1.20 (0.75–1.91)
24.8–26.5	423	41	49.9	1.31 (0.82–2.07)
26.6–28.8	417	34	49.5	1.17 (0.72–1.89)
>28.8	423	34	43.5	1.00 (0.61–1.62)
Years at school				
<8	1279	101	41.6	1
8–13	2202	156	40.6	1.07 (0.83–1.38)
>13	884	43	30.1	0.82 (0.57–1.17)

**RRs are adjusted for age, body mass index, systolic blood pressure, diabetes, smoking status at entry, family history of ischemic heart disease and cholesterol levels at baseline; †P<0.001; ‡P<0.05*

TABLE 3
Characteristics of men according to claudication and myocardial infarction (MI)

Variables	No CVD (n=2868)	With claudication, no other CVD (n=80)	With MI, no other CVD (n=68)	P of ANOVA
Age, years	56.1±7.2	61.7±6.8*	60.0±7.8*	<0.001
Systolic BP, mmHg	133±18	141± 25*	135±19	0.001
Diastolic BP, mmHg	82±11	81±12	80±10	0.4
Total cholesterol, mmol/L	5.7±1.0	5.8±1.2	5.9±1.1	0.6
Smoking status, n (%)				
Nonsmokers	427 (14.9)	4 (5.0)	8 (11.8)	
Ex-smokers	1306 (45.5)	24 (30.0)	28 (41.2)	
Pipe/cigars	86 (3.0)	4 (5.0)	2 (2.9)	0.004
Cigarettes 1-19/day	356 (12.4)	12 (15.0)	13 (19.1)	
Cigarettes ≥20/day	693 (24.2)	36 (45.0)	17 (25.0)	
Diabetes, n (%)	157 (5.5)	11 (13.8)	6 (8.8)	0.008
Body mass index, kg/m^2	26.2±3.8	24.9±3.6*	26.0±4.5	0.02
Family history of CVD, n (%)	1492 (52.0)	40 (50.0)	46 (67.7)	0.02

*Data presented as mean ± SD unless otherwise indicated. *Different from the group 'no CVD'. Differences in the prevalence of smoking, diabetes, family history of CVD were determined by χ^2 test. BP Blood pressure; CVD Cardiovascular disease*

diagnosis of their peripheral artery disease. The mean (± SD) time periods of these cardiovascular outcomes were 5.6±5.4 years before and 6.7±5.4 years after the diagnosis of intermittent claudication.

In 1985, there were 80 claudicants without CVD, 2868 without CVD and 68 men who survived a first MI and had no other CVD. Ages were similar among the claudicants and the MI survivors, and lower in the group without CVD. Claudicants had the highest systolic blood pressure and rate of smokers, and the lowest body mass index (Table 3). Among the claudicants, survivors of a first MI and men without CVD, 21 (26.3%), nine (13.2%) and 250 (8.7%), respectively, were taking an antihypertensive medication (mainly beta-blockers and diuretics), and five (6.3%), three (4.4%) and 60 (2.1%), respectively, were taking a lipid-lowering agent (mainly cholestyramine). During a 13-year follow-up period, the 80 claudicants without CVD, compared with men without any CVD, had a significantly higher aRR of 1.9 for cardiovascular death, and 2.0 for nonfatal CVD (Table 4). During the 13-year follow-up period, the 68 men with an MI compared with the 80 claudicants had no difference in overall CVD (45.6% versus 48.8%, aRR 1.12 [95% CI 0.69 to 1.79]). There was also no significant difference in fatal or nonfatal CVD as well as all-cause mortality (Table 4 and Figure 1). Although there was no difference in individual non-CVD outcomes, the CIs were wide due to the small number of events, and are not presented.

DISCUSSION

Our study examined the natural history of intermittent claudication in a random population of men free of CVD at entry, from its risk factors to its fatal and nonfatal CVD events and all-cause mortality. Tobacco consumption was the dominant risk factor for intermittent claudication, followed by diabetes mellitus, increased blood pressure, age and cholesterol levels. Claudicants doubled their risk for fatal and nonfatal CVD events compared with men without CVD, a risk as high as the one of survivors of a first MI without other CVD.

Prospective studies have established tobacco consumption, diabetes, elevated blood pressure and cholesterol levels as the main predisposing factors to intermittent claudication (1-16,20-22). In most studies, tobacco consumption was the dominant risk factor. Our findings confirm these observations and are concordant with studies showing that intermittent claudication risk for ex-smokers is similar to men who never smoked (3,7).

Some large prospective studies with or without a random population sample have evaluated the fatal outcomes of intermittent claudication. All except one study (2) showed that during a three- to 38-year follow-up period, intermittent claudication, particularly in men, at least doubled the risk for CVD death and increased the risk of all-cause mortality by 1.5-fold (1-16). Our findings are concordant with these observations. Some studies reported much higher risks but several claudicants in these studies had CVD comorbidities such as angina or previous MI or stroke that worsened the cardiovascular prognosis. Even after excluding the patients with other CVD, some (10-12) but

TABLE 4
Adjusted RRs of cardiovascular events and total mortality in men with intermittent claudication and in men surviving a first myocardial infarction (MI)

	No CVD (n=2868)	With claudication, no other CVD (n=80)	With MI, no other CVD (n=68)
Cardiovascular mortality and morbidity			
n (%)	543 (18.9)	39 (48.8)	31 (45.6)
RR (95% CI)	1	2.08 (1.48–2.90)*	2.31 (1.60–3.51)*
RR (95% CI)	–	1	1.12 (0.69–1.79)
Cardiovascular death			
n (%)	139 (4.9)	15 (18.8)	17 (25.0)
RR (95% CI)	1	1.88 (1.08–3.29)***	3.80 (2.28–6.33)*
RR (95% CI)	–	1	1.65 (0.78–3.50)
Non-fatal CVD			
n (%)	465 (16.2)	30 (37.5)	20 (29.4)
RR (95% CI)	1	1.95 (1.34–2.86)*	1.76 (1.12–2.76)**
RR (95% CI)	–	1	0.78 (0.43–1.42)
Total mortality			
n (%)	459 (16.0)	35 (43.8)	26 (38.2)
RR (95% CI)	1	1.49 (1.04–2.12)***	1.80 (1.21–2.69)**
RR (95% CI)	–	1	1.07 (0.62–1.82)

*Nonfatal cardiovascular disease (CVD) included MI, stroke, coronary insufficiency and angina. RR adjusted for age, diabetes, systolic blood pressure, smoking and familial history of CVD. The RR between the group with MI and the group with claudication is additionally adjusted for exposure time between diagnosis of MI or MI to a new outcome or the study end. *P≤0.001; **P≤0.01; ***P≤0.05*

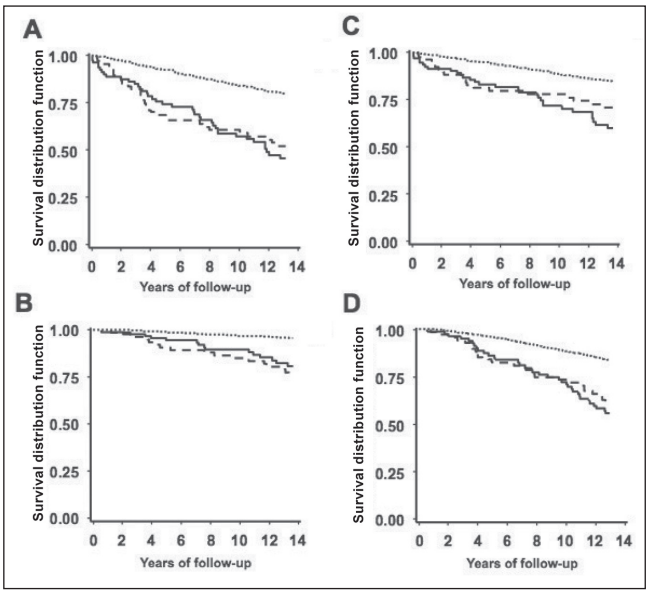

Figure 1) *Kaplan-Meier survival curves versus years for the three groups: the dotted line represents men without cardiovascular disease (CVD); the continuous line represents claudicants without other CVD; and the broken line represents survivors of a first myocardial infarction without other CVD.* **A** *First CVD fatal or nonfatal events;* **B** *Fatal CVD events;* **C** *Total mortality;* **D** *Nonfatal CVD events. Men without CVD had lower event rates than the two other groups (P<0.001). There was no significant difference in the event rates between the claudicants and the survivors of a first myocardial infarction*

not all (13) studies have also documented higher mortality rates in patients with peripheral artery disease, based on ankle-brachial index, than the rates reported in large epidemiological studies. The discrepancies may be explained by different methodologies (patient identification based on a questionnaire plus ankle-brachial index measurement versus a questionnaire alone), and more severe and longer duration of intermittent claudication in clinical studies.

Studies on the incidence of nonfatal cardiovascular events in claudicants are scarce. In an American sample (8) of 2812 persons aged 65 years or older, 2.4% of men and 1.5% of women had intermittent claudication, and their risk for nonfatal CVD was not significantly increased after a six-year follow-up period. Leng et al (14) found that among 1592 men and women aged 55 to 75 years randomly selected from registers of 10 general practices, 73 claudicants doubled their risk for angina and CVD death during a five-year follow-up period. Hooi et al (15) reported that among 3649 men and women 40 to 78 years of age, 138 had intermittent claudication at baseline and had a significant aRR of 1.40 for nonfatal CVD during a seven-year follow-up period. All of these studies were performed in prevalent cases of claudication. In our study, with a longer follow-up period, men with incident intermittent claudication, compared with men without CVD, had an aRR for nonfatal CVD of 1.95 (1.34 to 2.86).

Prognostic comparisons between persons with intermittent claudication or peripheral artery disease with other ischemic CVD have been limited. Patients with previous lower limb arterial surgery had a higher mortality than patients matched for risk factors and year of percutaneous coronary intervention (17). These results contrast with the findings of the Framingham Heart Study (16), which reported no major difference in the CVD prognosis between men and women with intermittent claudication and those with typical effort angina. Likewise, we observed similar prognostic findings between men with intermittent claudication and survivors of a first MI. The difference between these last two studies and the surgical cohort may be due to the populations of selected cases – incident cases in the two studies and prevalent cases for surgical patients without knowledge of the time of occurrence of the ischemic heart disease and the intermittent claudication.

Limitations

Our study has some limitations. In addition to the fact that the study group consisted of Caucasian men from Quebec only, the assessment of claudication based on a standardized questionnaire underestimates the prevalence of peripheral artery disease (23). In our study, the questionnaire on intermittent claudication was administered at each visit and was corroborated by a cardiologist's evaluation; furthermore, among the 300 claudicants, 54% had an angiographic study and all had significant atherosclerotic narrowing. We compared the CVD rates between claudicants with and without documented angiographic atherosclerosis, and observed no difference in CVD rates between the two groups; 62% (100 of 162) for those with and 69% (95 of 138) for those without documented atherosclerosis (P=0.2). Nevertheless, it is recognized that the questionnaire on intermittent claudication per se is not as powerful as low ankle-brachial index values to predict cardiovascular events. It is also recognized that our study lacked power for individual nonfatal CVD events compared with the Framingham Heart Study (16). Finally, our study was performed between 1974 and 1998, a period during which few effective CVD therapies, such as statins and renin-angiotensin system modulators, were widely known or used.

Intermittent claudication constitutes a major cardiovascular burden. Persons with intermittent claudication have a limited walking capacity and are exposed not only to local potential complications leading to revascularization or amputation of lower limbs but also to a high risk for CVD. Our study confirms this observation and strongly suggests that CVD risk for claudicants is as high as for survivors of a first MI. Considering the increased tobacco consumption in developing countries and the increased incidence of type 2 diabetes worldwide, we should expect an augmentation in intermittent claudication and its consequences. Health professionals and government

agencies may reduce this vascular burden by improving smoking cessation programs and managing other risk factors of intermittent claudication.

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