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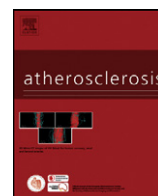
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Contribution of cardiovascular risk factors to coronary risk in patients with intermittent claudication in the PRIME Cohort Study of European men[☆]

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ABSTRACT

Background: Intermittent claudication (IC) is associated with an increased cardiovascular morbidity. The goal of the present study was to assess the contribution of conventional cardiovascular risk factors (CVRFs) to this increased risk.

Method: The PRIME Study is a multicenter Prospective Cohort Study of 10 602 men recruited in 1991–1993, aged 50–59 at baseline and followed over 10 years. At baseline, a questionnaire on socio demographic data was self-administered and CVRFs were measured. Composite outcome consisted of incident MI, effort angina, unstable angina and coronary death. The standardized questionnaire of the London School of Hygiene was used to identify claudicants. Data were analyzed using multivariate Cox models.

Results: Probable and possible cases of IC were reported by 1.4% (135) and 4.6% (442) of subjects, respectively. Compared to subjects with no claudication, the probable cases demonstrated higher rates of CVRFs. The incidence of CAD events was 7.23/1000 person-year. Compared to non claudicants, probable claudicants had an increased age and country adjusted risk of coronary events (HR (95% CI), 2.4 (1.5–3.7), $p < 0.0001$). After further adjustments for school duration, family history of early myocardial infarction, tobacco consumption, alcohol consumption, BMI, systolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, HDL-cholesterol, triglycerides and lipid-lowering treatment, participants with probable claudication had an increased risk of coronary events but this was no longer significant (HR (95% CI), 1.3 (0.8–2.1), $p = 0.23$).

Conclusion: IC is associated with an increased risk of developing coronary events. This association is largely explained by the coexistence of CVRFs.

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1. Introduction

Intermittent claudication (IC) is the most common symptom of peripheral arterial disease (PAD) in the lower extremities. The WHO Rose questionnaire was developed by the London school of Hygiene and Tropical Medicine in 1962 for use in epidemiological surveys

and was applied extensively to screen for IC as an expression of symptomatic PAD [1,2]. More recent studies identify symptomatic and asymptomatic PAD using the Ankle-Brachial Index (ABI) [3–8] but ABI use in routine general practice is limited.

Atherosclerosis of arteries is the principal physiopathological process of PAD and risk factors for coronary artery disease are elevated in patients with IC. Follow-up studies of patients with IC reveal a higher mortality rate than that in the general population [9–14] and approximately a twofold increase in age-adjusted risk of any coronary event [15,16]. Therefore, the coexistence of cardiovascular risk factors (CVRFs) and PAD could at least partially explain the increased coronary risk in PAD patients. While some studies suggest that there may be no increased risk of cardiac events from IC [9,12], others suggest that the risk remains elevated after adjustment for other CVRFs [13]. Therefore the goal of our study was to

Abbreviations: IC, intermittent claudication; PAD, peripheral arterial disease; MI, myocardial infarction.

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determine the contribution of CVRFs to coronary risk in IC patients in a Cohort Study of middle age European men.

2. Methods

2.1. Sample recruitment

The PRIME Study is a multicenter prospective cohort established in 1991 to identify risk factors for coronary heart disease (CHD) and to explain the gradient in CHD incidence between Belfast (Northern Ireland) and France. Participants were men, aged 50–59 at baseline, living in the areas covered by four collaborating WHO-MONICA centers: Belfast, Lille, Toulouse, and Strasbourg. Details on recruitment, baseline examination, and follow-up of the PRIME Study have been previously described [17]. Briefly, the recruitment was planned to broadly match the social class structure of the French and Northern Irish population and was based on volunteers working in industry or various employment groups or attending health-screening centers. A total of 10602 men aged 50–59 at baseline was recruited and followed-up for at least 10 years. For the purpose of this study, only 9779 patients free of cardiovascular disease at baseline were considered. Furthermore, 78 persons were excluded from analysis because information regarding the Rose questionnaire or adjustment variables was missing, leaving 9701 men considered for the analyses.

2.2. Baseline data collection

Standardized questionnaires related to demographic and socioeconomic factors were self-administered at home by the participants and checked with them by survey staff at the baseline visit. Data on school duration, personal and familial medical history, tobacco and alcohol consumption, drug intake and physical activity pattern were also collected. A medical examination with standardized anthropometric measurements (height, weight, waist circumference), blood pressure and heart rate measurement and a standard 12-lead electrocardiogram was performed. Finally, a blood sample was taken after 12 h overnight fast and biological measurements were performed in a core laboratory (total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol).

Family history of early myocardial infarction consisted of at least one episode of myocardial infarction before the age of 60 in first degree relatives. Smoking habits were determined from questions on present and past habits, number and type of cigarettes, cigars, or pipes smoked per day. Smoking status included the number of cigarettes per day smoked by former smokers and by current smokers. Subjects were categorized as “never smoker”, “former smoker <15 cigarettes per day”, “former smoker \geq 15 cigarettes per day”, “current smoker <15 cigarettes per day” and “current smoker \geq 15 cigarettes per day”. Alcohol consumption was assessed by a questionnaire in which the subject reported his mean consumption (in units) of wine, beer, cider, and spirits for each day of the week. Intake of alcohol was expressed in mL pure ethanol/day and subjects were classified into three categories: alcohol abstinent, alcohol drinkers with consumption <40 mL/day and alcohol drinkers with a consumption \geq 40 mL/day. Physical activity for leisure time was assessed and subjects were classified into two categories: they were considered physically active if they had practiced sport at least 12 times during the past year and physically inactive if they had not. Body mass index (BMI) was calculated as the ratio of weight/height². Hypertension was defined as a systolic blood pressure \geq 140 mmHg and/or diastolic blood pressure \geq 90 mmHg and/or antihypertensive treatment. Diabetes was defined by a reported history of diabetes and current blood glucose-lowering therapy by dietary or pharmacological means. Dyslipidemic subjects were participants with total cholesterol \geq 2.20 g/L and/or

triglycerides \geq 1.50 g/L, and/or participants on statin or fibrate therapy at baseline visit.

2.3. Definition of intermittent claudication

Intermittent claudication was defined using the Rose questionnaire. Subjects were classified in three mutually exclusive groups according to their answers to six questions among nine. To be classified as having “probable intermittent claudication”, subjects had to report that they developed leg pain while walking, that the pain occurred while walking uphill or hurrying, that they had not developed such pain when standing still or sitting, that they stopped walking when pain developed. They had to report that the pain had never disappeared while they were walking and that the pain disappeared when they stopped walking. To be classified as having “possible intermittent claudication”, subjects had to report that they developed leg pain while walking, and that the pain never occurred while standing still or sitting. Other subjects were classified as having no intermittent claudication.

2.4. Follow-up

Briefly, subjects were contacted annually by letter and asked to complete a clinical event questionnaire to be returned to the center in a prepaid envelope. For all subjects reporting a possible event, clinical information was sought directly from the hospital or family doctor's notes. In case of no reply, a phone contact was established with the subject or his general practitioner. An international medical committee was established, comprising one member from each PRIME center, one member from the coordinating center in Paris, three independent cardiologists (two from France and one from UK) and one neurologist. The committee's task was to validate each cardiovascular event occurring during the follow-up and each cause of death. Myocardial infarction (MI) was defined as previously described [18]. Definite coronary death was defined as death with a documented coronary event. When significant coronary atheroma was present at autopsy, the death was considered as definite coronary death. When a coronary death was suspected, with no other documentation or explanation, it was labeled possible coronary death. The three death categories were grouped together as coronary death. Effort angina was defined by the presence of chest pain as elsewhere described [18]. Unstable angina was defined as exertional chest pain (changing in frequency or severity) or appearance of chest pain at rest following pre-existing pain on exertion, with either enzymes changes or electrical changes. In the absence of enzyme or electrical data, the diagnosis was not upheld. The diagnosis of ischemic stroke was verified by one expert neurologist from the medical reports. Hemorrhagic strokes and transient ischemic attacks were excluded from the analyses. For survival analyses events were grouped into a composite endpoint of coronary events composed of incident MI, effort angina, unstable angina and coronary death.

2.5. Statistical methods

Baseline characteristics were analyzed with ANOVA tests (for continuous variables) and χ^2 tests (for categorical variables). Cox's proportional hazard regression models were used to assess the relationship between IC and coronary events. Three different models were used: (1) adjusted for age and country; (2) adjusted for age, country, school duration, family history of myocardial infarction, tobacco consumption, and alcohol consumption; (3) fully adjusted for age, country, school duration, family history of myocardial infarction, tobacco consumption, alcohol consumption, systolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, HDL-cholesterol, triglycerides, and lipid-lowering treatment.

Table 1Characteristics of men with probable, possible, or no intermittent claudication in the PRIME Study $n=9701$.

	Intermittent claudication			p^b
	No $n=9124$	Possible $n=442$	Probable $n=135$	
Age (years) ^a	54.8 ± 2.9	55.1 ± 2.8	55.0 ± 2.9	0.29
Country (%)				
Northern Ireland	25	15	32	<0.0001
France	75	85	68	
School duration (years)	11.4 ± 3.5	11.3 ± 3.6	10.1 ± 3.7	<0.0001
Family history of early MI (%)	9	10	13	0.27
Tobacco consumption (%)				
Never smokers	30	21	11	<0.0001
Exsmokers <15 cigarettes/day	17	17	13	
Exsmokers ≥15 cigarettes/day	26	27	32	
Current smokers <15 cigarettes/day	14	18	13	
Current smokers ≥15 cigarettes/day	13	17	31	
Alcohol consumption (%)				
Abstinent	17	16	27	0.006
<40 mL/day	45	42	35	
≥40 mL/day	38	42	38	
Physical activity (%)	82	81	68	0.0001
BMI (Kg/m ²) ^a	26.5 ± 3.4	26.8 ± 3.9	27.4 ± 4.1	0.003
Obesity (%)	14	18	27	<0.0001
Hypertension (%)	45	49	56	0.005
Systolic blood pressure (mmHg) ^a	133 ± 18.7	135 ± 19.2	141 ± 22.5	<0.0001
Antihypertensive treatment (%)	12	14	23	<0.0001
Diabetes (%)	3	5	7	0.001
Antidiabetic therapy (%)	2	3	7	0.002
Dyslipidemia (%)	64	69	72	0.03
Total cholesterol (g/L) ^a	2.21 ± 0.38	2.23 ± 0.37	2.23 ± 0.43	0.72
LDL cholesterol (g/L) ^a	1.44 ± 0.34	1.44 ± 0.34	1.43 ± 0.36	0.92
HDL cholesterol (g/L) ^a	0.49 ± 0.13	0.49 ± 0.13	0.43 ± 0.12	<0.0001
Triglycerides (g/L) ^a	1.48 ± 1.0	1.47 ± 0.86	1.90 ± 1.33	<0.0001
Lipid-lowering treatment (%)	8	11	13	0.04

^a Mean ± standard deviation.^b ANOVA or χ^2 .

A multinomial regression model was also used, to test the association between symptomatic PAD and three separate events: acute coronary syndrome, effort angina, and ischemic strokes. Statistical analyses were conducted using SAS 9.1[®]. The cut-off value of $p < 0.05$ was used for statistical significance.

3. Results

Probable and possible cases of intermittent claudication were reported by 1.4% (135) and 4.6% (442) of subjects, respectively. The clinical characteristics of the 9701 participants according to the presence of IC are shown in Table 1. Compared with subjects with no claudication, the probable cases were more prevalent in Belfast ($p < 0.0001$) and had fewer years of education ($p = 0.0001$). They tended to be more often heavy smokers or former heavy smokers ($p < 0.0001$) and alcohol abstinent ($p = 0.006$). They tended to be less physically active ($p = 0.0001$) and to have elevated BMI ($p = 0.004$). They were more likely to suffer from hypertension (0.005), diabetes ($p = 0.001$), or dyslipidemia (0.03). They had higher triglyceride levels ($p < 0.0001$) and lower HDL-cholesterol levels ($p < 0.0001$), and tended to be more often under antihypertensive treatment ($p < 0.0001$), antidiabetic therapy ($p = 0.002$), or lipid-lowering treatment ($p = 0.04$). Altogether, possible cases were likely to present an intermediate profile, except for alcohol and triglycerides.

Over the 10 years of follow-up, 653 coronary events (incidence 7.23/1000 person-years) occurred.

The incidence of coronary events was similar in possible claudicants and non claudicants, but was more than two fold higher in probable IC than non claudicants (Fig. 1)

No significant association was demonstrated between possible IC and coronary events, so only the results for probable claudicants are presented here. Three models are presented in Table 2 to assess the relationship between probable IC and coronary events. Age and country-adjusted Cox regression analysis found probable IC to be associated with a roughly 2.4 fold increased risk of coro-

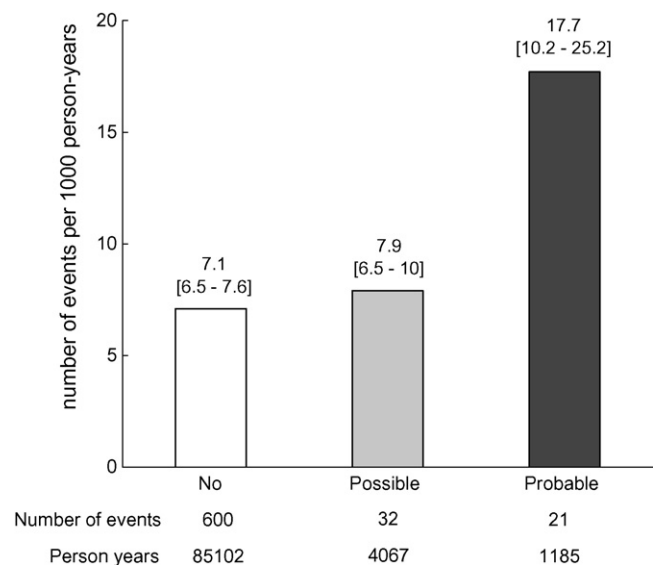


Fig. 1. Crude rates [95% confidence interval] of coronary events according to the presence of probable, possible and no intermittent claudication.

Table 2
Adjusted hazard ratios for coronary events in the PRIME Study $n=9701$.

	HR [95% IC]: Model 1	HR [95% IC]: Model 2	HR [95% IC]: Model 3
Probable intermittent claudication (vs. no IC)	2.4 [1.5–3.7]	1.9 [1.2–2.9]	1.3 [0.8–2.1]
Age ^a	1.3 [1.2–1.5]	1.3 [1.2–1.5]	1.2 [1.1–1.4]
Country (France vs. Ireland)	0.6 [0.5–0.7]	0.7 [0.6–0.8]	0.7 [0.6–0.9]
School duration ^a		0.9 [0.8–0.9]	0.9 [0.8–1.0]
Family history of early MI (yes vs. no)		1.7 [1.4–2.1]	1.6 [1.3–2.0]
Tobacco consumption (vs. never smokers)			
Former smokers <15 cigarettes/day		1.0 [0.8–1.3]	0.9 [0.7–1.2]
Former smokers ≥15 cigarettes/day		1.6 [1.3–1.9]	1.4 [1.1–1.8]
Current smokers <15 cigarettes/day		1.7 [1.3–2.1]	1.6 [1.2–2.0]
Current smokers ≥15 cigarettes/day		2.3 [1.8–2.9]	2.2 [1.8–2.9]
Alcohol consumption (vs. no alcohol)			
<40 mL/day		0.8 [0.7–1.0]	0.8 [0.6–1.0]
≥40 mL/day		0.6 [0.5–0.8]	0.7 [0.5–0.8]
BMI (Kg/m ²) ^b			1.05 [0.9–1.1]
Systolic blood pressure (mmHg) ^b			1.3 [1.2–1.4]
Antihypertensive treatment (yes vs. no)			1.5 [1.2–1.8]
Diabetes (yes vs. no)			1.7 [1.2–2.4]
Total cholesterol (g/L) ^b			1.3 [1.2–1.4]
HDL-cholesterol (g/L) ^b			0.7 [0.7–0.8]
Triglycerides (g/L) ^b			0.9 [0.8–1.1]
Lipid-lowering treatment (yes vs. no)			1.1 [0.8–1.4]

Model 1: adjusted for age and country. Model 2: adjusted for age, country, school duration, family history of early myocardial infarction, tobacco consumption. Model 3: adjusted for age, country, school duration, family history of early myocardial infarction, tobacco consumption, alcohol consumption, BMI, systolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, HDL-cholesterol, triglycerides, and lipid-lowering treatment.

^a Hazard ratios are presented for 5 year increase.

^b Hazard ratios are presented for 1 standard deviation increase.

nary events. Further adjustment on school duration, family history of myocardial infarction, tobacco consumption, and alcohol consumption decreased this association which remained significant (HR (95% CI), 1.9 (1.2–2.9), $p=0.005$). After full adjustment, the association decreased and was no longer statistically significant (HR (95% CI), 1.3 (0.8–2.1), $p=0.23$).

We also performed a multinomial logistic regression to assess the relationship between IC and 3 separate events in the same model: acute coronary syndrome, angina pectoris, and ischemic stroke. The results are shown in Table 3. After full adjustment, subjects with probable claudication had an increased risk of developing effort angina (OR (95% CI), 2.13 (1.01–4.55), $p=0.04$). No other result was significant.

4. Discussion

Patients with IC have raised levels of major cardiovascular risk factors, in particular of smoking and diabetes. Earlier studies have found an increased risk of coronary heart disease in patients with IC, but whether the increased risk is completely explained by the unfavorable cardiovascular risk profile is unclear. The results of the present study corroborate the association between IC and coronary risk but this association is no longer significant after adjustment for other cardiovascular risk factors suggesting that raised risk factors largely explain increased coronary risk in patients with IC.

In agreement with previous reports, IC patients were more likely to have elevated cardiovascular risk factors compared to those

without claudication [11]. They tended to be more often heavy smokers or former heavy smokers, had fewer years of education, were more likely to suffer from diabetes, hypertension, overweight, and had higher triglyceride levels and lower HDL-cholesterol levels [13,14,16].

The results of earlier studies that analyzed the contribution of CVRFs to coronary risk in IC patients have been inconsistent. The association remained statistically significant after adjusting for classical risk factors in some studies [19], while adjustment led to a large reduction of the risk in others [9,20,21]. These apparent disparities could be explained by differences in the selection, number, or definitions of covariates used for adjustment. As in the present study, adjustments have been performed for social and demographic variables, for tobacco status including number of cigarettes smoked per day, for total cholesterol [9,13], for alcohol intake [16], for antihypertensive treatment [22] in some but not all studies. In contrast, adjustments for family history of premature CAD, for HDL-cholesterol, or for lipid-lowering treatment were rarely performed. In the present study, adjustment for all these factors attenuated the association between IC and coronary risk, suggesting that the increased coronary risk was explained by the adverse cardiovascular risk profile in IC patients.

Further analyses using coronary endpoints separately showed no association between IC and acute coronary events or stroke, but a significant association with effort angina, after adjustment for cardiovascular risk factors. The reason for the later is not clear owing to the limited possibility of IC patients to walk fast. IC patients might

Table 3
Adjusted^a odds ratios for acute coronary syndrome, angina pectoris and ischemic stroke in men with probable or possible intermittent claudication $n=9701$.

	Total	Acute coronary syndrome			Effort angina			Ischemic stroke		
	<i>n</i>	<i>n</i>	OR [95% CI]	<i>p</i>	<i>n</i>	OR [95% CI]	<i>p</i>	<i>n</i>	OR [95% CI]	<i>p</i>
No	9124	409	1	–	202	1	–	107	1	–
Possible	442	24	1.11 [0.72–1.72]	0.62	8	0.72 [0.33–1.55]	0.40	4	0.90 [0.33–2.49]	0.84
Probable	135	12	1.18 [0.63–2.21]	0.61	9	2.13 [1.01–4.55]	0.04	3	0.94 [0.22–4.02]	0.96

^a Multinomial regression adjusted for age, country, school duration, family history of early myocardial infarction, tobacco consumption, alcohol consumption, BMI, systolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, triglycerides, and lipid-lowering treatment.

also benefit from better care, their on going disease bringing them to medical attention more often than healthy patients. Finally, due to the limited sample size, a play of chance is still possible.

In most national and European guidelines, PAD is considered a high-risk condition that commands intensive life-style and pharmacological secondary prevention measures. In the present study the 10 year cumulated risk of coronary events reaches 17.7%, supporting the recommendations. However, this value is just below the arbitrary risk threshold that defines high-risk in primary prevention. This apparently lower than expected value might be explained by a selection bias of patients included in the cohort (healthy worker effect). This is suggested by the comparison of event rates in men of the same geographical area and age that were found slightly lower in the PRIME cohort than in the reference population (for the French centers) [23]. Another possible explanation is that PAD patients have better cardiovascular prevention than healthy patients without symptomatic disease.

It appears that tobacco is particularly associated with the presence of a symptomatic PAD [24–27]. In our study, adjustment for smoking status included the number of cigarettes per day smoked by current smokers or by former smokers. As expected, adjustment for tobacco consumption strongly reduced the risk of coronary or cardiovascular events. Diabetes is strongly associated with PAD and adjusting for diabetes reduced cardiovascular risk. However, as diabetic patients could suffer from peripheral neuropathy, which may distort the perception of pain, it is possible that the Rose questionnaire may underestimate the actual number of diabetic claudicants.

This report has limitations. Firstly, the limited number of ICs (135 for probable and 442 for possible) resulted in a small number of coronary events (21 in the probable and 30 in the possible IC groups) and thus a limited statistical power allowing us to detect only major associations. As a consequence the residual relative risk associated with IC after full adjustment was still 30% higher but the confidence intervals were wide resulting in non-significant results. In the present study we used the Rose questionnaire instead of more modern means of PAD detection, such as ABI. We are aware that ABI can detect symptomatic and asymptomatic peripheral arterial disease with high precision. Unfortunately, at the time when this study was initiated, the use of ABI was not standard practice. We studied two categories of claudicants, probable cases and possible cases, as allowed by the Rose questionnaire [1]. Subjects in the group selected with relaxed criteria would be more likely to be “false positive” cases; this could explain why they were not at increased risk of coronary events. The identification of diabetic patients in PRIME was only based on subject reports. On the whole it seems that control for confusion caused by diabetes is not perfect in our report. Furthermore, unrecognized diabetes could result in misclassification of subjects. However, owing to satisfactory health offer, undiagnosed diabetes is rare in the background population of the same gender, age and geographical area. This study is restricted to men aged 50–59. The results thus could not be extrapolated to other groups or to women since those populations do not share the same characteristics and may differ in cardiovascular risk factors. Subjects included in PRIME were volunteers, and inclusion mostly took place in professional world, which could cause a healthy worker effect and limit the number of events in the cohort. CVRF data were only collected at the baseline visit. Consequently, changes in treatments or life-styles may have occurred during the 10 year follow-up, which may influence the relationship.

In conclusion, our results clearly show that IC is a strong predictor for coronary events over a period of 10 years. After full adjustment for cardiovascular risk factors, the relationship is substantially reduced, suggesting that accumulation of cardiovascular risk factors in IC patients strongly contributes to the excess coronary risk. However, PAD patients may suffer specific events, such as

acute peripheral ischemia, that still requires appropriate preventive measures.

Conflict of interest

There are no conflicts of interest to declare.

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