Eur J Vasc Endovasc Surg (2011) **42**, S4—S6

Reprinted Article "The Fate of the Claudicant—A Prospective Study of 1969 Claudicants"☆

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Accepted 14 November 1990

KEYWORDS
Intermittent claudication;
Cardiovascular events

Abstract A prospective study of 1969 patients with intermittent claudication receiving placebo medication for a minimum of 1 year is reported. Patients were carefully monitored and only four patients were lost to follow-up. Annual mortality was 4.3%. Thirty-six patients developed a definite myocardial infarction, 27 a major stroke, 32 required a major amputation and 111 required surgical or radiological intervention for deteriorating ischaemia of the leg. The entry characteristics of the patients were analysed as a predictor of serious cardiovascular events. The most sensitive predictors of total mortality were age, history of coronary heart disease and an ankle/arm pressure ratio below 0.5. Of the laboratory measurements performed only the initial white cell count was a significant predictor of myocardial infarction, stroke and vascular deaths.

Introduction

The PACK (Prevention of Atherosclerotic Complications with Ketanserin) trial is the largest, although not the longest, carefully documented study of intermittent claudicants.[1] The primary aim was to investigate in a double-blind study of 3899 claudicants whether ketanserin, a serotonin receptor antagonist,[2] significantly altered the incidence of serious cardiovascular events. The main conclusions in terms of treatment effects have already been reported.[1] This is a report of the short-term fate of the 1969 claudicants who received a placebo. The authors of PACK had previously reviewed the existing literature on the fate of the claudicant, and the vast majority of publications on patients with ischaemic disease in the legs are concerned with their surgical treatment.[3] Very few previous studies have looked at the fate of an unselected group of claudicants in terms of mortality and cardiovascular morbidity. Analysis of the 1969 patients in the placebo group of PACK allows the accurate documentation of all the serious complications of the claudicant and assessment of the importance of various risk factors in relation to these complications.

Patients and Methods

1969 patients were randomised to the placebo group and all further data refer solely to this group of patients. Patients

☆ This article has been previously published in *Eur J Vasc Endovasc Surg* 1991;**5**:131—33.

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1078-5884/$36 © 2011 Published by Elsevier Ltd on behalf of European Society for Vascular Surgery.
doi:10.1016/j.ejvs.2011.06.014

were recruited using the same protocol in 147 hospitals in 14 countries. All patients gave a typical history of intermittent claudication due to atherosclerosis, confirmed by ankle/arm pressure ratio below 0.85 in both ankle arteries of at least one leg. Patients who had fulfilled those criteria in the past, but did not at the time of randomisation because of a successful arterial reconstruction, were also admitted to the study. The only important exclusion criteria were patients on beta blockers or platelet active drugs and patients with rest pain or gangrene. Following randomisation all patients were monitored for the following cardiovascular events for a minimum of 1 year; only four patients were lost to follow-up. (1) Definite myocardial infarction, fatal and non-fatal. (2) Definite major stroke, fatal and non-fatal. (3) Major amputation above the ankle, fatal and non-fatal. (4) Definite non-vascular death. (5) Other deaths presumed to be vascular, apart from fatal myocardial infarction, stroke or amputation, which were included in events 1,2 and 3. (6) Deterioration of arterial disease in a leg requiring surgical intervention or angioplasty.

Detailed documentation of every possible event, whether fatal or not, was reviewed by an international validation committee, who frequently requested additional data until a definite diagnosis could be made. All surviving patients were followed for a minimum of a year with a total follow-up of 2129 patient-years.

The data were analysed using the Cox proportional hazards regression model. Univariate models were fitted for each of the factors considered and multivariate models were fitted using the forward and backward stepping procedure of BMDP program P2L.[4]

Results

The entry characteristics of the patients are shown in Table 1. Table 2 shows the frequency of the various cardiovascular events during the follow-up period. Some patients had multiple events. (This explains the slight discrepancies from the analogous table in the main publication[1] which looked at trial end-points, that is the first event for each patient.) In total 92 patients died during the follow-up period, which was equivalent to an annual mortality of 4.3%.

A major value of such a large longitudinal study is to determine the features of a patient with established claudication, which are markers for severe cardiovascular complications. The entry characteristics were therefore analysed individually (univariate analysis) and in combination (multivariate analysis) as a predictor of the following three end-points, (a) All cause mortality. (b) All major strokes and definite myocardial infarctions, fatal or non-fatal, plus other presumed vascular deaths (events 1, 2 and 5 in Table 2). (c) Deterioration of leg ischaemia as evidenced by the need for an amputation, arterial reconstruction or angioplasty (events 3 and 6 in Table 2).

The results of the univariate analysis are expressed as relative hazards, that is the event rate with the risk factor relative to the rate without the factor, and are shown in Table 3. Apart from age, only a history of coronary disease and an ankle/arm pressure ratio below 0.5 are significant predictors of "All cause mortality" at a p value less than 0.01. The same three risk factors were significant in a multivariate analysis at a level of $p = 0.05$ or less. For all vascular deaths plus non-fatal major stroke and definite myocardial infarction the same three factors with the addition of hypertension and diabetes were significant at the same level. For "Deterioration of leg ischaemia" only

Table 1 Patient characteristics at randomisation.

	Placebo $n = 1969$
Age, years (mean, S.D.)	63.2 (9.1)
Sex, male	1572 (80%)
MAP[a] (mmHg) (mean, S.D.)	107 (13)
MAP > 120 mmHg	275 (14%)
Hypertension (>160 and/or 95 mmHg or receiving antihypertensive medication)	1113 (57%)
Ankle/arm ratio <0.05	316 (16%)
Ankle SBP[b] <70 mmHg	189 (10%)
Ankle/arm ratio >0.85	189 (10%)
Race, Caucasian	1922 (98%)
Regular smokers up to at least 6 months previously	1396 (71%)
Diabetes	277 (14%)
Clinical evidence of previous disease	
Coronary disease	539 (27%)
Cerebrovascular disease	168 (9%)
Arterial reconstruction for leg ischaemia	785 (40%)
Laboratory measurements	
Haemoglobin (G%)	14.8 (S.D. 1.4)
White cell count (10^9/1)	7.7 (S.D. 2.3)
Cholesterol (mmol/1)	6.5 (S.D. 1.5)
Concomitant medication	
None	537 (27%)
Digitalis	166 (8%)
Anti-arrhythmics	47 (2%)
Anti-anginals	411 (21%)
Anticoagulants	172 (9%)
Antidiabetics	201 (10%)
Diuretics	444 (23%)
Antihypertensives	256 (13%)
ECG	
Normal	1051 (53%)
Myocardial infarction	203 (10%)

[a] Mean arterial pressure.
[b] Highest systolic blood pressure on the worse leg.

Table 2 Frequency of events in 1969 patients.

1 Definite myocardial infarction	36 (12 fatal)
2 Major stroke	27 (8 fatal)
3 Amputation above ankle	32 (1 fatal)
4 Non-vascular death	28
5 Other vascular death	43
6 Deterioration of arterial disease in legs requiring intervention	111

Table 3 Predictive value of various risk factors—univariate analysis showing relative hazard and 95% confidence limits.

	All cause mortality	Deterioration of leg ischaemia
Age (per 10 year)	2.08 (1.61—2.68)	1.18 (0.97—1.42)
Ankle/arm pressure ratio (≤0.5)	2.02 (1.27—3.24)	2.31 (1.57—3.40)
Coronary disease	2.03 (1.33—3.10)	1.27 (0.87—1.85)
Hypertension	1.77 (1.12—2.78)	0.98 (0.68—1.39)
Diabetes	1.67 (1.0—2.80)	1.30 (0.82—2.08)
Sex	1.29 (0.73—2.26)	1.66 (0.99—2.79)
C.V.A.	1.06 (0.51—2.23)	1,83 (1.10—3.04)
Smoking (to 6 months ago)	0.80 (0.51—1.25)	1.40 (0.91—2.16)
Previous vascular surgery	0.55 (0.34—0.90)	1.72 (1.21—2.44)

the ankle/arm ratio and previous vascular surgery are significant hazards at a p value less than 0.01 both in univariate and multivariate analysis.

The haemoglobin concentration, haematocrit and cholesterol at entry were also analysed but showed no correlation with mortality or deterioration of leg ischaemia. The initial white cell count however was a significant predictor of myocardial infarction, stroke and vascular mortality ($p = 0.05$).

Discussion

In addition to some expected results, such as older patients are more likely to die, there are some surprising positive and negative findings in relation to mortality. Patients with previous arterial surgery on the leg or smokers are not more likely to die. By contrast, the ankle/arm pressure ratio (below 0.5) is as good a predictor of total mortality or cardiovascular events as a history of previous coronary disease and a better predictor than diabetes, smoking, hypertension or the plasma cholesterol level. It is less surprising that the ankle/arm pressure ratio is the best predictor in terms of deterioration of leg ischaemia. A much smaller but much longer Danish study of similar patients also showed the ankle systolic blood pressure to be a significant risk factor for mortality as well as deterioration in the leg circulation.[5] The absence of a significant predictive value for mortality of the classical risk factors such as hypertension, diabetes, smoking or high plasma cholesterol suggests that these primary risk factors for the development and early progression of atherosclerosis are not necessarily risk factors in the final stages of the disease. The predictive value of the initial white cell count supports the recently described significance of the leucocyte in ischaemic disease.[6] The significance of the ankle/arm systolic pressure ratio is possibly simply a reflection of the fact that the legs are the only territory affected by atherosclerosis where the severity of the disease can be accurately and easily quantified by a non-invasive method. The findings may have implications for the treatment policy of patients presenting with intermittent claudication.

Acknowledgement

This paper was written on behalf of the Prevention of Atherosclerotic Complications with Ketanserin Group.

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