Drug treatment of intermittent claudication: A critical analysis of the methods and findings of published clinical trials, 1965–1985

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1 All trials of drug therapy for intermittent claudication published in English during the period 1965–1985 were reviewed. A total of 75 trials had studied 33 different pharmacological agents. Treadmill exercise, the most reproducible method of evaluating symptoms in this condition, was used in 49% of trials.

2 Oxpentifylline was the drug that had been most frequently studied. In seven placebo-controlled trials the average response to oxpentifylline, compared with placebo and weighted for sample-size, was 65% improvement in claudication distance. There was, however, a significant negative relation between sample-size and response ($r_s = -0.79$, $P < 0.05$), suggesting that this estimate was likely to have been biased by non-publication of negative results.

3 One third of all trials were uncontrolled; 84% of these reported benefit from drug treatment, compared with 32% of placebo-controlled trials ($P < 0.001$). Sample-sizes varied from seven to 227 patients; 31% of trials reported data from less than 20 patients and these were likely to have had insufficient statistical power.

4 Overall, 57 of the 75 trials (76%) had at least one of the following deficiencies: an uncontrolled design; not double-blind; failure to use treadmill exercise; less than 20 patients included in the analysis. Thus, *a priori* three-quarters of all trials were unlikely to have made a satisfactory assessment of drug efficacy.

5 The information available does not establish convincingly that any drug consistently improves exercise performance in intermittent claudication. In view of the deficiencies in previous trials, we propose guidelines for future studies with regard to trial design, sample-size and methods of exercise testing.

Keywords intermittent claudication trial design exercise testing oxypentifylline

Introduction

The prevalence of intermittent claudication rises with age (Kannel & McGee, 1984) and may be as high as 10% in subjects aged 65 or more

(Widmer *et al.*, 1980). Most patients are managed conservatively, with only a small minority of individuals undergoing surgery or transluminal

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angioplasty (Ruckley, 1986). Regular exercise (Ekroth *et al.*, 1978; Clifford *et al.*, 1980) and stopping smoking (Quick & Cotton, 1982) may improve symptoms of claudication, and the latter also benefits associated coronary artery or cerebrovascular disease (Hughson *et al.*, 1978), which are the main determinants of prognosis in patients with peripheral vascular disease (Reunanen *et al.*, 1982). It is also customary to control concomitant hypertension and diabetes, although there is no evidence that either measure improves the symptoms of intermittent claudication.

Additionally, drugs of various classes are prescribed very widely for intermittent claudication. There appears to be a sharp divergence between ordinary medical practice and expert opinion, since the latter generally holds that drug therapy for intermittent claudication is of very limited or no value (Verstraete, 1982). Several explanations are possible, and differences in interpretation of drug trials are likely to be important. The results of trials which convince prescribers and even regulatory authorities do not seem to be acceptable to critical reviewers. We have reviewed all trials of drug treatment in intermittent claudication published in English during 20 years from 1965 to 1985. Our aims were to examine the methods used in these trials, to determine how the methods used influenced the outcome, and to propose guidelines for the future design and conduct of drug trials in intermittent claudication.

Methods

A computer and manual literature search was performed to identify all trials of drug treatment in patients with intermittent claudication published in English during the period 1965–1985 inclusive. Abstracts were excluded, as were papers which did not include data from symptom-limited exercise tests. Studies examining blood flow or rheological changes without formal assessment of exercise capacity were excluded because changes in calf muscle blood flow or ankle systolic pressure index are not necessarily paralleled by changes in exercise capacity (Clifford *et al.*, 1980). Six trials of β -adrenoceptor antagonists were included; although these agents were usually tested to examine the possibility of an adverse effect on exercise tolerance (the exception is Reichert *et al.*, 1975), they fulfilled the inclusion criteria. For each study we recorded the following: entry criteria; study design; sample-size; duration of treatment; drug(s) studied; methods of assessing exercise capacity; and outcome.

Results

A total of 78 reports (from 76 publications, a copy of the bibliography is available from H.A.C. on request) were identified and after exclusion of three cases of dual publication, 75 studies were included. There was a steady increase in the number of reports with time, from none in 1966 to a peak of 15 in 1984.

Entry criteria

Entry was restricted in some trials according to age, sex, weight or walking distance and 20 (27%) trials stipulated that certain investigations (e.g. angiography, Doppler ultrasound) should be performed. Sixty reports (80%) did not specify a minimum duration of symptoms.

Study design

There were 47 placebo-controlled trials (63%), three trials (4%) comparing two or more drugs and 25 trials (33%) which were uncontrolled. Thirty-six trials (48%) included a run-in phase but only in 17 of these was placebo treatment given during this phase. Of the placebo-controlled trials, 29 had a parallel-group design and 18 were cross-over studies.

Sample-size

The median number of patients per trial was 35 with a range from 7 to 227. After drop-outs, the median number of patients included in the analysis of exercise performance was 30 (range 7 to 166). Twenty-three trials (31%) analysed data from less than 20 patients. Fourteen trials had a sample-size of 80 or more and these trials usually had to recruit from more than one centre.

Statistical methods

Thirty-two of the 75 reports gave no details of the statistical methods used. The methods most frequently applied were *t*-tests (19), Wilcoxon rank sum test (14) and analysis of variance (12). Inappropriate use of statistical methods was particularly common in cross-over trials where assessment of the effect of order and tests for treatment-order interaction were often omitted.

Duration of treatment

The median duration of treatment (or treatment-phase in cross-over studies) was 12 weeks (range 1 day to 144 weeks). Thirteen trials lasted less than 1 month, of which five studied the

Table 1 Drugs assessed in claudication trials 1965–1985

Drug	Number of trials
Oxpentifylline	12
Isoxsuprine	6
Flunarizine	5
Naftidrofuryl	5
Suloctidil	5
Buflomedil	4
Cyclandelate	3
Inositol	3
Metoprolol	3
Nylidrin	3
Propranolol	3
Vitamin E	3

The following have also been tested: anacrod, aprotinin, captopril, cinnarizine, clofibrate, creatine phosphate, defibrate, dextran, dihydroergotamine, oestradiol-testosterone combination, ketanserin, γ -linoleic acid, methyl dopa, nialamide, nicergoline, nicotinic acid, papaverine, pyridinol-carbamate, rutosides, streptokinase and ticlopidine.

effect of a single dose. Eleven trials were of greater than 6 months duration and three trials did not have a fixed duration of treatment.

Drugs studied

Thirty-three drugs have been examined as possible treatment for intermittent claudication (Table 1). The list is notable for inclusion of drugs with a wide variety of pharmacological actions.

Methods of assessment

Thirty-seven trials used treadmill exercise, the remainder using static tests, subjective measures, pedometry or bicycle exercise. In those that used a treadmill test, there was no consistent pattern regarding speed or gradient. Of 32 reports that gave details, only two trials varied the walking speed on an individual basis, but most used a fixed gradient. The median number of tests during treatment was two (range 1 to 12).

Outcome

Of 75 trials assessed, 39 purported to show benefit from drug treatment in intermittent claudication. The probability of obtaining a positive result was, however, significantly related to trial design (Table 2). An uncontrolled trial was almost three times more likely than a placebo-controlled trial to be considered positive ($\chi^2_1 = 17.7$, $P < 0.001$), i.e. poor study design was associated with favourable results for the drug being tested. Fifteen placebo-controlled trials produced a positive result, but five of these were analysed without direct comparison of the groups. For example, they reported that claudication distance improved significantly in the active treatment group, but there was no significant change in the placebo group; such an analysis effectively relegated these trials to uncontrolled status. In some studies with a large sample-size, a relatively small response, which was of uncertain clinical importance, proved to be statistically significant.

Trials of oxpentifylline for intermittent claudication

This agent has been included in more studies than any other drug (Table 1), and these studies illustrate clearly some problems of trial methodology. Eleven out of 12 trials purported to show some benefit from oxpentifylline, but three of these trials were uncontrolled, and two were comparisons against other pharmacologically active agents (which themselves have no proven efficacy). There were seven placebo-controlled trials, four of parallel-group design (Donaldson *et al.*, 1984; Porter *et al.*, 1982; Roekaerts & Deleers, 1984; Bollinger & Frei, 1977) and three cross-over trials (Strano *et al.*, 1984; DiPerri & Guerrini, 1983; Roekaerts & Deleers, 1984).

The main findings in the seven placebo-controlled trials of oxpentifylline are summarised in Table 3. They involved a total of 252 patients who had a mean initial distance of 159 m. The average responses were +44 m with placebo and +148 m with oxpentifylline treat-

Table 2 Trial design in 75 studies of drug treatment in claudicants

Design	Number of trials	% claiming benefit
Uncontrolled	25	84
Placebo-controlled		
Parallel-group	29	34
Cross-over	18	28
Comparative	3	—

ment. The overall response to oxpentifylline compared with placebo was apparently an improvement of 104 m or 65% (Table 3). This seems impressive superficially and would be of clinical value, but inspection of Table 3 reveals important problems. Three trials showed improvement of more than 100% from oxpentifylline. The sample-sizes of these trials were small (16, 19 and 20). In contrast, two large trials reported relatively small differences between oxpentifylline and placebo. Porter *et al.* (1982) showed a 19% increase in claudication distance with a sample-size of 82 patients. This was statistically significant but is of little clinical relevance. The other large trial (Donaldson *et al.*, 1984), which had a sample-size of 73 patients, showed a 21% *worsening* of claudication distance with oxpentifylline.

In all seven studies there was actually a significant negative correlation between sample-size and response ($r = -0.79$, $P < 0.05$). Put simply, the larger the trial the worse the outcome. This may be explained by bias due to non-publication of small negative trials and perhaps also by premature stopping of trials when the results are favourable. The 65% increase in claudication distance estimated by these studies is therefore likely to be an overestimate. It seems probable that the true response to oxpentifylline in unselected populations would be small. Evidence to support the use of this drug for intermittent claudication is weak, even before taking into account reservations about individual trials, which are considered below.

The trial of Porter *et al.* (1982) was a multi-centre project which entered 128 patients. Forty-six patients (36%) were not included in

the analysis for a variety of reasons, a feature which is likely to have introduced bias. For claudication distance, the mean response to oxpentifylline was 19% ($P < 0.02$), from which the authors concluded that oxpentifylline was an effective treatment for chronic occlusive arterial disease. They published these data again 2 years later (Reich *et al.*, 1984) and the results from one of the centres have also been published separately (Porter & Bauer, 1982). Both studies of Roekaerts & Deleers (1984) did not use treadmill exercise and showed improvement of greater than 100% from oxpentifylline. The patients studied were elderly inmates of a nursing home (mean age 75 years), and their symptoms were apparently very mild (mean pain-free walking distance 330 m at randomisation). It would be inappropriate to generalise from these findings to other populations with markedly different characteristics.

In conclusion, there is more evidence to support the use of oxpentifylline for intermittent claudication than for any other drug. Superficially, this evidence is impressive but we have important reservations about the trials collectively and in some individual cases. Similar reservations apply to the trials of all other drugs that have been studied (see below).

Summary of important deficiencies in all 75 trials

The most serious inadequacies of drug trials in intermittent claudication were an uncontrolled or open design, failure to use treadmill exercise or a small sample-size (less than 20 patients included in the analysis). Fifty-seven trials

Table 3 Summary of placebo-controlled trials of oxpentifylline

Authors	Sample-size (number analysed)	Duration (months)	Maximum dose (mg day ⁻¹)	I.C.D.* (m)	% change
Donaldson <i>et al.</i> (1984)	73	2	600	103	-21%
Porter <i>et al.</i> (1982)	82	6	1200	114	+19%
Roekaerts & Deleers (1984)	16	6	1200	184	+168%
Bollinger & Frei (1977)	19	2	600	202	+188%
DiPerri & Guerrini (1983)	24	2 × 2†	1200	216	+28%
Strano <i>et al.</i> (1984)	18	3 × 2†	800	128	+29%
Roekaerts & Deleers (1984)	20	6 × 2†	1200	446	+100%

Combined analysis of all patients in the above trials:

Sample size—252 patients;

I.C.D.—159 m;

Mean response to treatment: placebo +44 m, oxpentifylline +148 m; % change with oxpentifylline, compared with placebo +65%.

*Initial claudication distance.

†Cross-over studies.

(76%) had at least one of these features and were *a priori* unlikely to have made a satisfactory assessment of efficacy.

Findings from trials with satisfactory methods

By the criteria stated above, eighteen trials were potentially satisfactory, of which six reported a positive result. One of these trials did not directly compare active and placebo treatment groups and may not have produced a result that was truly significant. The remaining five positive trials evaluated five different treatments (oxpentifylline, papaverine, ketanserin, suloctidil and buflomedil). To date there is no trial which has used adequate methods and produced a positive result which others have been able to confirm. For example, in the first published placebo-controlled trial of ketanserin, improvement of 127% was reported (DeCree *et al.*, 1984) but two subsequent trials with similar design found that ketanserin was worse than placebo (Bounameux *et al.*, 1985; Cameron *et al.*, 1987). In the latter study, 95% confidence intervals showed that the true response to ketanserin is unlikely to exceed 33%. The reasons for such disparate findings are not clear but until the initial finding is confirmed by others, the efficacy of ketanserin cannot be considered to have been proven.

The evidence that any agent consistently improves exercise performance in claudicants is unconvincing. Conversely, studies involving β -adrenoceptor antagonists do not substantiate the common belief that these drugs exacerbate symptoms of claudication (Cameron & Ramsay, 1983), although they should be avoided in the presence of impending gangrene.

Conclusions

The majority of trials of drug treatment for intermittent claudication have had important shortcomings. Studies with a poor design and small sample-size have produced most of the positive findings, which are unlikely to be due to the merits of the drugs studied. Publication bias has led to under-representation of negative trials in the literature. Despite 75 trials of 33 drugs it is still unclear whether any of these pharmacological agents has a clinically relevant effect on intermittent claudication, and it is probable that none of them has an important effect. It is desirable that future trials of new agents avoid the same pitfalls. In the following section we review the available evidence and propose guidelines for the design and conduct of trials in claudication.

Proposed guidelines

Entry criteria

The main inclusion criteria should be a history of leg pain typical of intermittent claudication with regard to site, relation to exercise and relief from rest, combined with loss of peripheral pulses. Absent posterior tibial artery pulsation is a better predictor of vascular disease than absence of the dorsalis pedis pulse, which is congenitally absent in 7–12% of normal individuals (Criqui *et al.*, 1985). To avoid inclusion of patients with spinal stenosis or severe venous disease, these clinical findings should be complemented by some objective evidence of peripheral vascular disease, e.g. reduced ankle systolic pressure index as measured by Doppler ultrasound. Invasive investigations such as angiography would not usually be performed before initiation of drug treatment and are best omitted from the protocol.

Any treatment which is shown to be efficacious in intermittent claudication is likely to be given to patients with all grades of disease severity and ideally any claudicant should be eligible for inclusion in randomised studies. However, subjects with rest pain should be excluded from trials because surgery may be indicated and the most important end-point of the exercise test (claudication distance) is not measurable. Subjects who walk over 500 m at the initial visit should also be excluded, because if their claudication improves they are likely to need to stop for other reasons (e.g. dyspnoea). It is essential that symptoms should have been present and reasonably stable for at least 6 months before entry, as it is well-recognised that claudication of recent onset may spontaneously resolve. Entry may also need to be limited for safety reasons (e.g. recent myocardial infarction, unstable angina, contraindications to the trial drug) but we believe that no other entry restrictions should be applied. Other drugs for claudication should be withdrawn and any other medication kept constant throughout if possible.

Study design

A large placebo response is common in claudication trials and uncontrolled studies cannot provide evidence for drug efficacy, whatever the outcome. It has been shown that suggestion may have a significant influence on claudication distance (Waller *et al.*, 1988) and because of the potential for serious bias, open trials are best avoided. All studies should be double-blind unless there is a good reason to the contrary.

Table 4 Placebo data from three published studies relating to the variability of treadmill exercise times over 3 months in claudicant patients

Reference	n	I.C.T.	s.d. difference	s.d. difference/I.C.T. $\times 100\%$
DeCree <i>et al.</i> (1984)	9	275*	95.0	35%
Hay <i>et al.</i> (1987)	10	60	28.3	47%
Cameron <i>et al.</i> (1987)	12	97	29.9	31%

n, number of patients treated.

I.C.T., Initial claudication time (s) or * distance (m).

s.d. difference, Standard deviation of difference between measurements 3 months apart.

A placebo run-in phase with several exercise tests should be included. This will enable the patients to become familiar with the exercise-testing protocol and will eliminate those who are unsuitable or who have side-effects during placebo treatment. Either a parallel-group or cross-over design may be used. In the former, patients should be allocated randomly to active treatment or placebo. A major imbalance between the groups for variables related to outcome can make interpretation of the findings difficult. This can be avoided by making stratifications for important variables (e.g. initial claudication distance) within the randomisation. Stratification to obtain an approximately equal division of each sex into the groups is also advisable.

In a cross-over trial the order of treatments should be determined by balanced randomisation. Variability ought to be less as each patient acts as his own control. Fewer patients may be required than for a parallel-group study, but an interaction between treatment and order may arise if the effect of treatment is prolonged. In this situation, data from the second phase may need to be discarded and the first phase may have to be analysed as for parallel-groups (Hills & Armitage, 1979). A wash-out period between the two treatment phases reduces the likelihood of this occurring, but the sample-size should probably be independent of trial design (see below).

Sample-size

The number of patients to be included in a trial should be calculated in advance by determining the difference in responses that would be considered clinically important, the statistical power required, and the level of significance which will be accepted. Once these parameters have been determined, the sample-size can be calculated from a nomogram (Altman, 1980), providing that the likely variability of the measurements to be performed is known. This

could be assessed from a pilot trial, but placebo data from three trials which used treadmill exercise suggest that the standard deviation of difference is generally around 30–50% of the initial claudication distance (Table 4). This figure might be reduced by taking the mean of several tests performed on different occasions but it seems likely that any increase in statistical power from duplicate exercise tests on the same day would be small. When placebo-treated subjects were exercised twice separated by a half-hour rest period, claudication distances showed little variation between the two tests (unpublished data, Table 5).

Table 5 Claudication times (s) from duplicate treadmill tests 0.5 h apart in placebo-treated patients (n = 9)

Patient	1st test	2nd test	Mean
1	130	141	135.5
2	71	69	70.0
3	80	90	85.0
4	48	44	46.0
5	137	100	118.5
6	106	114	110.0
7	78	95	86.5
8	29	28	28.5
9	241	232	236.5
Mean	102.2	101.4	101.8
s.e. mean	21.0	20.0	20.3

Choice of the size of difference that would be considered clinically important is arbitrary. In our opinion a difference of less than 40% between drug and placebo is unlikely to be of major importance and would not warrant widespread use of a drug. To provide an 80% chance of detecting a response of this magnitude as significant at the 5% level in a two-tailed test, a sample-size of 32 patients would be needed (assuming that the standard deviation of difference will be 40% of the initial value; Table 4). This estimate should be increased to allow

for a withdrawal rate of 10–20%, meaning that 40 patients would be a suitable number for most placebo-controlled studies. Larger studies would be needed to detect smaller differences (e.g. between two effective drugs) or to increase the power or level of significance, but increasing the sample-size has various disadvantages. Not only does it make trials more expensive and less feasible, but small differences between treatments, which may not be of any clinical importance, may be found to be statistically significant. Also, in studies which are primarily designed to test efficacy, it might be considered unethical to randomise more patients than are needed to achieve a conclusive answer.

Duration of treatment

Studies lasting less than 1 month are probably best avoided, because benefit from treatment may not occur immediately. Initially there is a need to demonstrate that therapy is effective in chronic dosing and that short-term tolerance does not occur. Until this is well established, patients should not be entered into long-term randomised trials. We suggest that a duration of 2–4 months is suitable for most preliminary studies of drug efficacy.

Methods of assessment

Treadmill exercise is the best method of assessing response to treatment because it is similar to normal walking. It is also reproducible (Hillestad, 1963; Peterson, 1967) and easily standardised. The intra-patient variability between tests can be reduced by walking on a gradient at the maximum speed at which he or she is comfortable (Peterson, 1967). This speed should be determined at the first assessment and thereafter kept constant. There is no particular advantage in varying the gradient and 10% (6°) seems to be generally suitable. All exercise tests should be conducted by the same observers, with the environment constant as regards temperature and humidity. Subjects should be asked to wear similar clothing and footwear at each visit, and rested for at least 15 min prior to exercise on the treadmill. They

should be asked to signal the onset of pain (claudication distance), but continue walking until it is too severe to continue (walking distance). Claudication distance is probably a more important measurement than walking distance, as it is less subjective and usually varies less between tests (Hillestad, 1983). In view of the high prevalence of ischaemic heart disease in claudicants and documented risk of arrhythmias during exercise (Carroll *et al.*, 1978) electrocardiographic monitoring should be undertaken and adequate resuscitation facilities need to be readily available.

Statistical analysis

In a cross-over study, run-in data will play only a limited part in the eventual analysis, but for a parallel-group design the results are best analysed as a between-group comparison of changes from the baseline by analysis of variance (Wallenstein *et al.*, 1980). The use of a mean of several run-in readings as a baseline tends to reduce variability and increase the statistical power (or reduce the width of confidence intervals). Cross-over studies should be analysed using the method for a quantitative response proposed by Hills & Armitage (1979).

Conclusions

Twenty years of drug trials in intermittent claudication leave much to be desired because the majority of trials were inadequately designed. Twelve trials of oxpentifylline included around 500 patients but failed to provide conclusive evidence of its efficacy. Definite evidence that any agent consistently increases exercise performance is not available. In future all studies should be controlled, should include an objective method of assessing exercise performance, and should be analysed appropriately. Until adequate evidence of their efficacy becomes available, prescribing of drugs for intermittent claudication should be abandoned.

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References

- Altman, D. (1980). Statistics and ethics in medical research. III How large a sample? *Br. med. J.*, **281**, 1336–1338.
- Bollinger, A. & Frei, C. (1977). Double-blind study of pentoxifylline against placebo in patients with intermittent claudication. *Pharmatherapeutica*, **1**, 557–562.
- Bounameaux, H., Holditch, T., Hellemans, H., Berent, A. & Verhaeghe, R. (1985). Placebo-controlled, double-blind, two centre trial of ketanserin in intermittent claudication. *Lancet*, **ii**, 1269–1271.
- Cameron, H. A. & Ramsay, L. E. (1983). Which beta blocker? *Br. med. J.*, **286**, 1439.

- Cameron, H. A., Waller, P. C. & Ramsay, L. E. (1987). Placebo-controlled trial of ketanserin in the treatment of intermittent claudication. *Angiology*, **38**, 549–555.
- Carroll, R. M., Rose, H. B., Vyden, J., Ogawa, T., Takano, T., Weisbeck, E. & Blackman, E. (1978). Cardiac arrhythmias associated with treadmill exercise testing. *Surgery*, **83**, 284–287.
- Clifford, P. C., Davies, P. W., Hayne, J. A. & Baird, R. N. (1980). Intermittent claudication. Is a supervised exercise class worthwhile? *Br. med. J.*, **280**, 1503–1505.
- Criqui, M. H., Fronek, A., Klauber, M. R., Barrett-Connor, E. & Gabriel, S. (1985). The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from non-invasive testing in a defined population. *Circulation*, **71**, 516–522.
- DeCree, J., Leempoels, J., Geukens, H. & Verhagen, H. (1984). Placebo-controlled double-blind trial of ketanserin in the treatment of intermittent claudication. *Lancet*, **ii**, 775–779.
- DiPerri, T. & Guerrini, M. (1983). Placebo-controlled double-blind study with pentoxifylline of walking performance in patients with intermittent claudication. *Angiology*, **34**, 40–45.
- Donaldson, D. R., Hall, T. J., Kester, R. C., Ramsden, C. W. & Wiggins, P. A. (1984). Does oxpentifylline have a place in the treatment of intermittent claudication? *Curr. med. Res. Opin.*, **9**, 35–40.
- Ekroth, R., Dahlof, A., Gundeval, B., Holm, J. & Schersten, T. (1978). Physical training of patients with intermittent claudication: Indications, methods, and results. *Surgery*, **84**, 640–643.
- Hay, C. R. M., Waller, P. C., Carter, C., Cameron, H. A., Parnell, L., Ramsay, L. E., Preston, F. E. & Greaves, M. (1987). Lack of effect of a 24-hour infusion of iloprost in intermittent claudication. *Thrombosis Res.*, **46**, 317–324.
- Hillestad, L. K. (1963). The peripheral blood flow in intermittent claudication. IV The significance of claudication distance. *Acta med. Scand.*, **173**, 467–478.
- Hills, M. & Armitage, P. (1979). The two-period cross-over clinical trial. *Br. J. clin. Pharmacol.*, **8**, 7–20.
- Hughson, W. G., Mann, J. I., Tibbs, D. J., Woods, H. F. & Walton, I. (1978). Intermittent claudication: factors determining outcome. *Br. med. J.*, **1**, 1377–1379.
- Kannel, W. B. & McGee, D. L. (1984). Update on some epidemiological features of intermittent claudication: The Framingham study. *J. Am. Geriatr. Soc.*, **33**, 13–18.
- Petersen, F. B. (1967). The effects of varying walking speed when measuring the claudication distance on horizontal and sloping levels. *Acta Chir. Scand.*, **133**, 627–630.
- Porter, J. M. & Baur, G. M. (1982). Pharmacologic treatment of intermittent claudication. *Surgery*, **92**, 966–971.
- Porter, J. M., Cutler, B. S., Lee, B. Y., Reich, T., Reichle, F. A., Scogin, J. T. & Strandness, D. E. (1982). Pentoxifylline efficacy in the treatment of intermittent claudication: Multicentre controlled double-blind trial with objective assessment of chronic arterial disease patients. *Am. Heart J.*, **104**, 66–72.
- Quick, C. R. G. & Cotton, L. T. (1982). The measured effect of stopping smoking on intermittent claudication. *Br. J. Surg.*, **69** (suppl.) S24–S26.
- Reich, T., Cutler, B. C., Lee, B. Y., Porter, J. M., Reichle, F. A., Scogin, J. T. & Strandness, D. E. (1984). Pentoxifylline in the treatment of intermittent claudication of the lower limbs. *Angiology*, **35**, 389–395.
- Reichert, N., Shibolet, S., Ador, R. & Gafni, J. (1975). Controlled trial of propranolol in intermittent claudication. *Clin. Pharmac. Ther.*, **17**, 612–615.
- Reunanen, A., Takkunen, H. & Aromaa, A. (1982). Prevalence of intermittent claudication and its effect on mortality. *Acta med. Scand.*, **211**, 249–256.
- Roekaerts, F. & Deleers, L. (1984). Trental 400 in the treatment of intermittent claudication: results of long-term, placebo-controlled administration. *Angiology*, **35**, 396–406.
- Ruckley, C. V. (1986). Claudication. *Br. med. J.*, **292**, 970–971.
- Strano, A., Davi, G., Avellone, G., Novo, S. & Pinto, A. (1984). Double-blind, crossover study of the clinical efficacy and haemorrhological effects of penoxifylline in patients with occlusive arterial disease of the lower limbs. *Angiology*, **35**, 459–466.
- Verstraete, M. (1982). Current therapy for intermittent claudication. *Drugs*, **24**, 240–247.
- Wallenstein, S., Zucker, C. L. & Fleiss, J. L. (1980). Some statistical methods useful in circulation research. *Circ. Res.*, **47**, 1–9.
- Waller, P. C., Solomon, S. A. & Ramsay, L. E. (1988). The acute effects of cigarette smoking on treadmill exercise distances in patients with stable intermittent claudication. *Angiology* (in press).
- Widmer, L. K., Grensher, A. & Kannel, W. B. (1980). Occlusion of peripheral arteries. A study of 6400 working subjects. *Circulation*, **30**, 836–842.

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