Incidence, Natural History and Cardiovascular Events in Symptomatic and Asymptomatic Peripheral Arterial Disease in the General Population

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Background. Intermittent claudication is associated with a poor prognosis, but less is known of the risks associated with asymptomatic peripheral arterial disease. The aims of this study were to determine the incidence and natural history of claudication, and the incidence of cardiovascular events in symptomatic and asymptomatic peripheral arterial disease.

Methods. In 1988, 1592 subjects aged 55–74 years were selected randomly from the age-sex registers of 10 general practices in Edinburgh, Scotland. The presence of peripheral arterial disease was determined by the World Health Organization questionnaire on intermittent claudication, the ankle brachial pressure index and a reactive hyperaemia test. This cohort was followed prospectively over 5 years for subsequent cardiovascular events and death.

Results. One hundred and sixteen new cases of claudication were identified (incidence density 15.5 per 1000 person-years). Of those with claudication at baseline, 28.8% still had pain after 5 years, 8.2% underwent vascular surgery or amputation, and 1.4% developed leg ulceration. Claudicants had a significantly increased risk of developing angina compared with normals (RR : 2.31, 95% CI : 1.04–5.10), and asymptomatic subjects had a slightly increased risk of myocardial infarction and stroke. Deaths from cardiovascular disease were more likely in both claudicants (RR : 2.67, 95% CI : 1.34–5.29) and subjects with major (RR : 2.08, 95% CI : 1.13–3.83) or minor asymptomatic disease (RR : 1.74, 95% CI : 1.09–2.76). Subjects with major asymptomatic disease also had an increased risk of non-cardiovascular death (RR : 2.19, 95% CI : 1.33–3.59), and therefore had the highest overall risk of death (RR : 2.44, 95% CI : 1.59–3.74).

Conclusions. Subjects with asymptomatic peripheral arterial disease appear to have the same increased risk of cardiovascular events and death found in claudicants.

Keywords: natural history, peripheral atherosclerosis, mortality, morbidity, epidemiology

Some degree of lower limb atherosclerosis is likely to be present in most of the adult population.[1-3] By late middle age, almost 8% demonstrate significant asymptomatic disease on non-invasive testing, and 5% experience intermittent claudication.[4,5] Studies of hospital patients with claudication suggest that 25% ultimately require bypass surgery or amputation, with at least half experiencing an improvement in symptoms.[6,7] In addition to the morbidity associated with lower limb

disease, claudicants are almost three times more likely to die than the general population[6] primarily from concomitant heart disease and stroke.[7,8] However, relatively little is known of the morbidity and mortality associated with asymptomatic peripheral arterial disease.

Mortality over a period of 10 years was examined in patients with peripheral arterial disease and subjects with hyperlipidaemia in a Lipid Research Clinics study.[9] Patients with large vessel disease had an increased risk of death from cardiovascular causes, although these mortality rates may have been increased by inclusion of the hyperlipidaemic group. In the general population, elderly subjects with subclinical atherosclerosis, including coronary and carotid disease as well as lower limb atheroma, also had an increased risk of subsequent

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cardiovascular events.[10] However, a low ankle arm index alone was sufficient to indicate an increased risk of death in patients with known peripheral arterial disease.[11] Less is known, however, of the risk of non-fatal cardiovascular events in subjects with asymptomatic peripheral arterial disease in the general population.

To examine the prevalence of symptomatic and asymptomatic peripheral arterial disease in the general population, a cross-sectional survey was conducted in Edinburgh in 1987.[4] A total of 1592 subjects aged 55–75 years were examined for the presence of peripheral arterial disease and associated risk factors. All subsequent fatal and non-fatal events were recorded to determine the incidence of cardiovascular events and death. Five years after recruitment, a re-examination was performed to determine any change in disease status, thus providing information on the incidence of disease in the general population.

This paper presents the first results from the 5-year follow-up of this cohort. The aims are: (i) to examine the incidence and prevalence of intermittent claudication; (ii) to determine the natural history of peripheral arterial disease in terms of clinical outcome and change in underlying disease; and (iii) to determine whether the incidence of fatal and non-fatal cardiovascular events is related to the presence of symptomatic and asymptomatic peripheral arterial disease at baseline.

METHODS

Study Population

The Edinburgh Artery Study began in 1988 as a cross-sectional survey of 1592 men and women aged 55–74 years. This population was selected at random from 10 general practices serving a range of socioeconomic and geographical areas throughout the city. The sample size of 1500 participants was estimated on the basis of the number required to conduct a subsequent follow-up study with adequate power to detect differences in the incidence of vascular events according to baseline characteristics. In order to produce at least 1500 participants, 272 subjects were selected from each practice: 34 males and females from each 5-year age group. The response rate was 65%, and follow-up of a sample of non-responders showed no substantial bias. Details of the study recruitment have been described previously.[4] The participants were followed up over a 5-year period for cardiovascular events and death, and were invited to attend for a second medical examination at the end of that time. The study was approved by the Lothian Health Board Ethics Committee, and informed consent was obtained from each participant.

Identification of Cardiovascular Events

Information about the following cardiovascular events was obtained during the 5-year follow-up period: myocardial infarction, angina, stroke, transient ischaemic attacks, intermittent claudication, critical limb ischaemia, thrombo-embolism, vascular surgery, angioplasty and coronary artery bypass grafting. Criteria to define these events were adapted from the American Heart Association,[12] and an event was recorded only if these criteria were fulfilled (see Appendix).

To identify all deaths occurring in the study cohort, each participant's record was flagged at the United Kingdom National Health Service Central Registry, thus ensuring any death certificates would be automatically forwarded for all subjects dying within the UK. All cardiovascular deaths were further investigated using hospital or general practitioner records to ensure that the protocol criteria were fulfilled.

To obtain details on non-fatal events, information was sought from general practitioners, hospitals, the Information and Statistics Division of the Scottish Office Home and Health Department and the subjects themselves. At the start of the study, a card was prepared with participant details and attached to the front of subjects' general practitioner records to be returned following a cardiovascular event. The card was also returned if the patients had changed address or general practitioner, in which case they were traced through the Primary Care Division. The Information and Statistics Division provided computer printouts of all hospital discharges occurring for subjects in Scotland. For those discharges with relevant ICD-9 codes (International Classification of Diseases, 9th revision), the medical records were investigated at the appropriate hospitals. In addition, the Royal Infirmary of Edinburgh supplied lists of new referrals to the peripheral vascular clinic, and of vascular operations coded according to a system designed by the Surgical Audit Committee.[13]

Each participant also received an annual questionnaire enquiring about the development of the following conditions in the previous year: heart attack, stroke, chest and leg pain, loss of power in arms or legs, and hardening of the arteries. Information was also sought on hospital attendances and general practitioner visits. Depending on the positive responses received, they were followed up by asking the participant to complete the World Health Organization (WHO) angina and intermittent claudication questionnaires,[14] contacting the general practitioner, or examining the relevant

hospital records to determine whether the event criteria were fulfilled.

Five Year Follow-up Examination

Invitation to attend.   Participants still residing in the Edinburgh area were sent a letter of invitation asking if they wished to attend the second examination, and if so, whether they would travel to the clinic (expenses were offered) or if they would prefer to be examined at home. Participants who lived outside the area were offered overnight accommodation as well as travelling expenses, but not home visits. Those who did not wish to attend, who missed appointments, or did not respond after three invitations, were sent a self-administered questionnaire. If the questionnaire was not returned, they were first telephoned, and then visited at home and asked to complete the questionnaire. Participants whose letters were returned by the Post Office were traced through Lothian Health Board, and the invitation procedure repeated.

Examination.   Examinations were carried out by three specially trained nurses between November 1992 and March 1994. Subjects completed a self-administered questionnaire, including the annual questions concerning cardiovascular events, plus personal characteristics, the WHO angina and intermittent claudication questionnaires,[14] smoking history, medications (including aspirin) and age at menopause.

After resting for 5 minutes, brachial systolic and diastolic (Phase V) blood pressures were measured in the right arm using a Hawksley random zero sphygmomanometer. The femoral, posterior tibial and dorsalis pedis arteries were palpated in both legs. Ankle pressures were measured using a Sonicaid Doppler ultrasound probe. Standing height was measured once to the nearest 5 mm without shoes, using a free-standing metal ruler on a heavy base. Weight, without shoes and outer clothing, was measured once to the nearest 100 g on a digital Soehnle scale. These measurements were made on the same equipment as that used in the baseline survey. In addition, ultrasound scans of the abdomen and neck were performed to detect the presence of aortic aneurysm and carotid artery disease (results to be reported in future papers).

Each subject underwent recording of an electrocardiogram (ECG) using a Hewlett Packard 12 lead portable 'pagewriter'. All ECG were subsequently coded using the Minnesota code[15] by two observers independently. If a discrepancy occurred, a final decision was made by a consultant cardiologist. Finally, 30 ml of venous blood were withdrawn for subsequent analysis of haemostatic, rheological and genetic factors.

Data Analysis

Information on the questionnaire and recording forms was checked by the clinic staff, coded and entered onto a DBASE IV database. Error rates were determined by dual entry of all data, and any discrepancies were checked by reference to the original records.

The cumulative incidence of intermittent claudication was calculated by taking the number of new cases as the numerator, and the total initial population minus deaths and number of claudicants at baseline as the denominator. Person-years at risk of developing intermittent claudication were calculated from the baseline appointment date to either the date of death, date of claudication event, loss to follow-up or the end of the study period. Incidence density was calculated as the number of new cases divided by person-years at risk.

The ankle brachial pressure index (ABPI) for each leg was calculated by dividing the ankle pressure by the brachial pressure. The lower of the indices obtained for the two legs was used as the measure of disease severity in the subsequent data analysis. The mean ABPI of the study population at baseline was compared with the mean ABPI at follow-up using a paired t-test.

The incidence of cardiovascular events and death was examined within four descriptive groups, based on the severity of peripheral arterial disease at the baseline examination. These categories were determined by the presence of claudication, and by results of the reactive hyperaemia test and the ABPI: (i) intermittent claudication (WHO questionnaire positive); (ii) major asymptomatic disease (ABPI $\leq$ 0.9 and drop in ankle pressure during reactive hyperaemia > 20% or ABPI $\leq$ 0.7 or reactive hyperaemia > 35%); (iii) minor asymptomatic disease (ABPI $\leq$ 0.9 or reactive hyperaemia > 20%); and (iv) normals (none of the above).[4] This classification has not been used in other studies, but results comparing the ABPI and reactive hyperaemia test separately with angiography[16] would suggest that the classification had adequate face validity. Multiple events of the same type occurring in the same subject, such as two myocardial infarctions, have been reported only once. Relative risks of fatal and non-fatal events were calculated by comparing the incidence rates in diseased groups with incidence in normal subjects, and adjusting for age.

RESULTS

Study Population

At the baseline examination in 1988, 1592 subjects (809 men and 783 women) aged 55–74 years were recruited to the Edinburgh Artery Study. Five years

TABLE 1 *Natural history of peripheral arterial disease over 5 years in a random sample of the general population, aged 55–74 years at baseline*

	Baseline category of peripheral arterial disease			
	Intermittent claudication (n = 73)	Major asymptomatic (n = 105)	Minor asymptomatic (n = 240)	Normal (n =1080)
Baseline characteristics				
Sex, % female (n)	51 (37)	47 (49)	50 (120)	47 (508)
Age, mean ± standard error	66.9 ± 0.6	67.7 ± 0.5	65.6 ± 0.4	64.1 ± 0.2
Intermittent claudication				
at 5 years, % (n)	28.8 (21)	15.2 (16)	7.1 (17)	3.2 (35)
Events during follow-up, % (n):				
Arterial reconstruction	4.1 (3)	–	0.4 (1)	0.4 (4)
Amputation	4.1 (3)	–	–	0.1 (1)
Angioplasty	–	1.0 (1)	0.4 (1)	–
Leg ulcer	1.4 (1)	–	–	–

later, 1156 (72.6%) attended for a second examination and completed a questionnaire, and a further 131 (8.2%) subjects completed a questionnaire only. In addition there were 203 deaths (12.8%), making a total of 1490 (93.6%) subjects who were almost completely followed up. Of the remaining 102 subjects: 18 did not wish to take part; 14 were unable to attend due to illness or hospitalization; seven subjects were given appointments, but failed to attend; nine letters were returned by the Post Office; and 54 subjects failed to answer any correspondence and were not at home when visited by a nurse. However, during the entire 5-year follow-up period, there were only 13 (0.8%) subjects for whom no additional information was available after the initial baseline examination.

Incidence of Intermittent Claudication
One hundred and sixteen new cases of claudication were identified during the 5-year follow-up period. This includes positive responses to the WHO claudication questionnaire either at the annual mailing or the 5-year examination, and notifications from the general practitioner. Seventeen (14.7%) had grade 1 claudication (pain only walking uphill or hurrying), 28 (24.1%) had grade 2 (pain walking at an ordinary pace on the level), 57 (49.1%) had probable claudication, and 14 (12.1%) had a general practitioner diagnosis of intermittent claudication but no WHO questionnaire evidence. The cumulative incidence of intermittent claudication was 9.0% with an incidence density of 15.5 per 1000 person-years. Overall, the incidence was higher among men (8.7%) than among women (6.6%) and showed some evidence of an increase with age, but this was not statistically significant.

Of the 1287 subjects who completed a WHO questionnaire at 5 years, 92 subjects had intermittent claudication, a prevalence of 7.1%. Sixteen (17.4%) had grade 1 claudication, 27 (29.3%) grade 2, and 49 (53.3%) had probable claudication.

Natural History of Peripheral Arterial Disease
The natural history of peripheral arterial disease was examined within categories of lower limb disease determined at the baseline examination. Full details of the characteristics of these groupings have been described previously;[17] the mean age and sex at baseline are shown in Table 1. The minor asymptomatic disease group and the normals were slightly younger than the other groups, but the sex distribution was similar. Ninety-four subjects could not be classified after the baseline visit, primarily because of unwillingness to undergo a reactive hyperaemia test.

Of the 73 defined as claudicants at baseline, 28.8% still had pain after 5 years, 8.2% had undergone vascular surgery or amputation, and 1.4% had developed a leg ulcer. Similarly, 15.2% of the 105 major and 7.1% of the 240 minor asymptomatic group had developed claudication during the follow-up period, whilst only 3.2% of the 1050 normals had done so. During the follow-up period, a total of eight subjects underwent arterial reconstructions, four had an amputation, two had lower limb balloon angioplasty and one developed a leg ulcer.

The change in mean ankle brachial pressure index over the 5-year period, according to baseline category of disease, is shown in Figure 1. In all disease groups, there was no statistically significant change in ABPI with time. However, a significant decline occurred
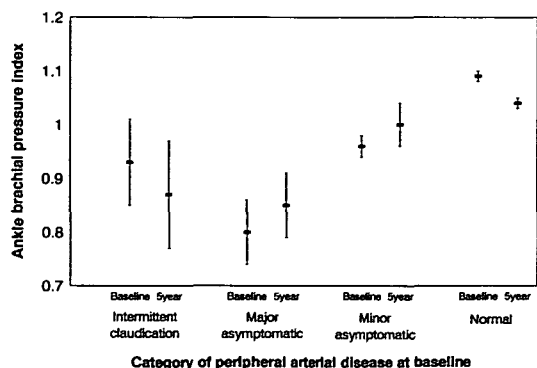
FIGURE 1 *Change in mean ankle brachial pressure index over 5 years by category of peripheral arterial disease in 1592 subjects aged 55–74 years at baseline. Lines represent mean and 95% confidence intervals*
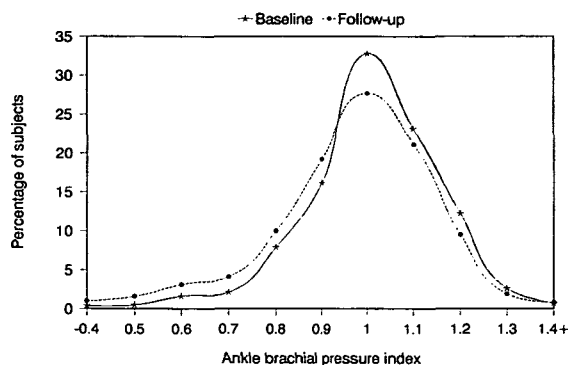

FIGURE 2 *Distribution of the ankle brachial pressure index in 1592 subjects aged 55–74 years at baseline and at 5-year follow-up*

in those who were normal or unclassified at baseline ($P \leq 0.001$). The distribution of the ABPI in the population as a whole at the 5-year follow-up examination showed a slight negative skewness (Figure 2). The mean ABPI was 1.02 (standard error [SE] 0.01), which was a reduction of 0.04 (SE 0.010) since the baseline examination ($P \leq 0.001$).

Non-Fatal Cardiovascular Events

The incidence of non-fatal cardiovascular events by category of peripheral arterial disease at baseline is shown in Table 2. A total of 37 subjects (2.3%) had a definite myocardial infarction during the follow-up period, and 44 subjects (2.8%) had a possible infarction. Silent myocardial infarctions occurred in 37 subjects (2.3%), and were more common in the group with minor disease and the normals, in whom over 30% of the total infarctions were asymptomatic. Overall, 92 subjects (5.8%) developed symptoms of angina, 28 subjects (1.8%) suffered a definite or possible stroke, and 25 (1.6%) a transient ischaemic attack during follow-up. In addition, seven subjects underwent coronary angioplasty, 13 had coronary artery bypass grafting and 14 suffered a thrombo-embolic episode (six pulmonary emboli, four deep vein thromboses and four arterial emboli).

In claudicants, there were raised relative risks (RR) for all types of cardiovascular event, but only the development of angina was statistically significant (RR : 2.31, $P \leq 0.05$). In both major and minor asymptomatic groups, there was a slight increase in risk of coronary and cerebrovascular events ($P > 0.05$).

TABLE 2 *Five-year incidence of non-fatal cardiovascular events in a random sample of the general population, aged 55–74 years at baseline*

	Baseline category of peripheral arterial disease						
	Intermittent claudication (n = 73)		Major asymptomatic (n = 105)		Minor asymptomatic (n = 240)		Normal (n =1080)
	Events (%)	Relative risk[a]	Events (%)	Relative risk[a]	Events (%)	Relative risk[a]	Events (%)
Myocardial infarction[b]	8.2	1.20 (0.52–2.76)	10.5	1.43 (0.77–2.68)	8.7	1.25 (0.80–1.95)	6.7
New angina	9.6	2.31* (1.04–5.10)	4.8	0.94 (0.38–2.32)	7.5	1.41 (0.87–2.29)	5.3
Stroke or TIA[b]	6.8	2.00 (0.80–4.99)	5.7	1.44 (0.59–3.54)	3.4	1.14 (0.56–2.31)	2.8
Others[c]	4.1	1.70 (0.53–5.42)	1.0	0.44 (0.06–3.15)	2.9	0.94 (0.42–2.10)	1.5

[a] Relative risk of event adjusted for age; 95% confidence intervals shown in parentheses.
[b] Includes both definite and possible events.
[c] Coronary interventions, thrombo-embolism and aneurysm.
* $P \leq 0.05$.

TABLE 3 *Five-year cardiovascular and non-cardiovascular mortality in a random sample of the general population, aged 55–74 years at baseline*

	Baseline category of peripheral arterial disease						
	Intermittent claudication (n = 73)		Major asymptomatic (n = 105)		Minor asymptomatic (n = 240)		Normal (n =1080)
	Mortality (%)	Relative risk[a]	Mortality (%)	Relative risk[a]	Mortality (%)	Relative risk[a]	Mortality (%)
Total deaths	19.2	1.55 (0.86–2.82)	30.5	2.44*** (1.59–3.74)	13.8	1.19 (0.82–1.73)	10
Non-cardiovascular deaths	5.5	0.70 (0.25–1.92)	19.0	2.19** (1.33–3.59)	5.4	0.78 (0.44–1.36)	6.4
Cardiovascular deaths:	13.7	2.67** (1.34–5.29)	11.7	2.08* (1.13–3.83)	8.4	1.74* (1.09–2.76)	3.6
Myocardial infarction[b]	5.5	–	6.7	–	5.0	–	2.6
Stroke[b]	1.4	–	2.9	–	2.1	–	0.8
Other	6.8	–	1.9	–	1.3	–	0.2

[a] Relative risk of death adjusted for age; 95% confidence intervals shown in parentheses.
[b] Includes both definite and possible events.
[c] Coronary interventions, thrombo-embolism and aneurysm.
* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$.

Mortality

There were 203 deaths during the follow-up period, 137 male and 66 female (death rate 169 per 1000 males and 84 per 1000 women). Overall, there were 89 cardiovascular-related deaths and 114 deaths due to a non-cardiovascular cause. In both sexes, there was an increasing trend in mortality across each of the four 5-year age groups (under 10% of the deaths were from the 55–59 year age group compared with about 40% from the 70–74 year age group).

The 5-year mortality rates in the 203 subjects by category of peripheral arterial disease at baseline are shown in Table 3. In those with intermittent claudication at baseline, there was a significant risk of dying from cardiovascular causes (RR : 2.67, $P \leq 0.01$, but not for overall death. However, in subjects with major asymptomatic disease there was a highly significant risk of death (RR : 2.44, $P \leq 0.001$), including both non-cardiovascular (RR : 2.19, $P \leq 0.01$) and cardiovascular causes (RR : 2.08, $P \leq 0.05$). The 20 non-cardiovascular deaths in those with major disease were primarily due to neoplasms (70%), of which most were bronchogenic; three deaths were due to chronic obstructive airways disease and three due to infective causes. Those with minor asymptomatic disease at baseline had an increased risk of cardiovascular death only (RR : 1.74, $P \leq 0.05$). In all groups, myocardial infarction was the main cause of cardiovascular death, except in claudicants where half of the subjects died from other cardiovascular causes, predominantly ruptured aortic aneurysm.

DISCUSSION

A fundamental problem in all cohort studies is bias resulting from loss to follow-up, particularly when losses are large. To restrict losses from the Edinburgh Artery Study cohort, several safeguards were implemented at recruitment which included flagging at the NHS Central Registry, tagging the general practitioner's records, sending out an annual questionnaire and obtaining relevant information from local hospitals. These methods, plus the relatively low mobility in a population of this age group, ensured that basic 5-year follow-up information was available on 93.6% of the initial cohort. This does not guarantee that all non-fatal events were notified, but in view of the different approaches used to obtain data it is likely that any omissions were negligible. Complete mortality data were available on the entire sample, as this was supplied as a result of initial flagging at the NHS Central Registry. These results therefore provide important information on the morbidity and mortality associated with both symptomatic and asymptomatic peripheral arterial disease in the general population.

Incidence of Intermittent Claudication

The 5-year cumulative incidence of intermittent claudication was 9.0%, higher than the 5-year rate of 6% found in men aged 65 years and over in the Basel study.[18] However, the observed trend for incidence to increase with age and to be higher in men than women agrees with findings from the Basel and Framingham longitudinal studies.[18–20] The prevalence of intermittent

claudication at the 5-year follow-up was 7.1%, higher than the 4.5% prevalence identified in the sample at baseline. Few studies have examined the prevalence of claudication in such an elderly sample, but one study in rural Cambridgeshire found a prevalence of 5.3% in subjects aged 66–96 years.[21]

The relatively large proportion of claudicants in the Edinburgh population compared with other studies may reflect true differences in disease prevalence, but unfortunately valid comparisons cannot be made because of different age structures of the populations, and because different methods have been used to define claudication. Many studies do not include 'probable' claudicants, a definition described by Criqui[22] to increase the sensitivity of the WHO questionnaire, and may therefore underestimate the true prevalence of disease.

Natural History of Peripheral Arterial Disease

Of the 73 subjects identified as suffering from intermittent claudication at the baseline examination, only 21 (28.8%) still had claudication after 5 years. This was not unexpected as studies of hospital patients suggest that most newly diagnosed claudicants will stabilize and that only a quarter deteriorate significantly.[7] Just over 4% of the baseline claudicants proceeded to amputation in the subsequent 5 years, less than the 7% rate demonstrated by several hospital-based series,[23–25] probably because hospital patients present at a more advanced stage of disease. However, the amputation rate of 4.1% was high compared with two other population studies where only 1.6%[20] and 1.8%[18] of patients who developed claudication came to amputation. This difference may be because of the relatively small number of claudicants studied here, or may reflect differences in regional patterns of disease or differences in surgical practice.

As peripheral atherosclerosis increases with age,[6] the overall decline in ABPI over the 5-year period in the normal and claudication groups was not unexpected. However, slight improvements in ABPI occurred in those with asymptomatic arterial disease at baseline, although these were not statistically significant. This improvement was not explained by excess deaths in subjects with more severe disease, and may therefore reflect the development of a collateral circulation. However, the mean ABPI at 5 years remained much higher in the normal group than in those with major disease, and is in keeping with the finding that fewer normal subjects developed claudication.

Non-Fatal Cardiovascular Events

Coronary atherosclerosis is frequently associated with peripheral arterial disease, and may be present in at least 90% of hospital patients.[26] A high incidence of non-fatal coronary events would therefore be expected in all categories of peripheral arterial disease, and indeed approximately 7% experienced a myocardial infarction over the 5-year period (Table 2). Similarly, in the Basel study, 16% of those with evidence of arterial disease had a non-fatal cardiac event after 11 years,[27] and in a hospital-based series 7% of claudicants had a non-fatal infarction after 10 years.[8] However, despite the relatively high incidence of cardiovascular events, only angina in claudicants showed a statistically significant risk compared with normals, possibly because in many cases the absolute numbers of events were small.

Silent myocardial infarctions were generally infrequent, but were much more likely in those classified as asymptomatic or normal at baseline, possibly because of a decreased awareness of the risk of disease, or no previous experience of cardiac pain. Little is known of the prevalence of silent myocardial infarction, but in the Framingham study 53% of the total infarctions were asymptomatic, and were again unlikely if the patient had prior angina.[28] Interestingly, in this study, interventions for coronary ischaemia, including angioplasty and bypass grafting, were more common in those with least lower limb disease, possibly because these subjects were considered more suitable for surgery.

Cerebrovascular disease was also more common in those with lower limb disease, but occurred less frequently than coronary events. Similarly in the Basel study, the 11-year incidence of cerebrovascular complications was 12% compared with 16% for coronary events.[27]

Mortality

The death rates in this population were higher than expected compared with average Scottish figures, particularly for men (standard male death rates range from only 17 per 1000 aged 55–64 years, to 101 per 1000 aged 75–84 years[29]). The higher than expected death rates in the Edinburgh Artery Study population may reflect an increased tendency for subjects to participate if they had a history of cardiovascular disease. The increased mortality from cardiovascular disease in claudicants agrees with other studies of hospital patients,[7,8] and the similar increase in cardiovascular deaths associated with asymptomatic disease might also have been anticipated. However, the excess of non-cardiovascular deaths in those with major disease was not expected, most of which were due either to respiratory disease or smoking-related neoplasms. High cigarette consumption in this group may therefore have been partly responsible, but non-cardiovascular deaths

were uncommon in claudicants who had similar smoking habits at baseline.[17] A detailed multivariate analysis, including other risk factors, will be presented in a subsequent paper.

The presence of either symptomatic or asymptomatic peripheral arterial disease is therefore an important indicator of subsequent morbidity and mortality. In claudicants, the incidence of cardiovascular events can be reduced by low-dose aspirin therapy,[30] and it is likely that antiplatelet agents will also benefit those with less severe asymptomatic disease.[31] However, such patients are unlikely to present to medical services, suggesting that screening middle-aged and elderly subjects for asymptomatic disease may be required before prophylactic treatment can be instituted. Prior to adopting this procedure, it will also be necessary to ensure that treatment is effective in reducing morbidity and mortality, and that any benefits outweigh the costs of screening.

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APPENDIX

CRITERIA FOR CARDIOVASCULAR EVENTS

Myocardial Infarction

1) *Non-fatal myocardial infarction*

   a) *Definite myocardial infarction* was coded if two of the following three criteria were present:

   i) Prolonged cardiac pain, anywhere in the anterior chest, left arm or jaw (possibly also involving back, shoulder, right arm or abdomen) and lasting at least 20 minutes.

   ii) Diagnostic ECG codes, including Minnesota Codes: 1.1.1–1.2.5; 1.2.7; or 9.2 plus 5.1 or 5.2.

   iii) Elevated enzyme levels: creatine phosphokinase greater than twice the upper limits of normal, and one of the following also greater than twice the upper limits of normal: lactate dehydrogenase, glutamic oxalo-acetic transaminase, or the MB isoenzyme of creatine phosphokinase. The enzymes must have been measured within 72 hours of an acute event.

   b) *Possible myocardial infarction* was coded if:

   i) One of the above definite criteria was present, plus either:
   – equivocal ECG codes: 1.2.8–1.3.6; 4.1–4.3; 5.1–5.3; or 9.2.
   – equivocal enzyme levels: above normal but not twice normal, or one was above twice normal but could be attributed to another cause.

   ii) Equivocal ECG codes and equivocal enzyme levels.

   c) *Silent myocardial infarction* was coded if:
   – ECG codes were diagnostic in the absence of elevated enzyme levels or cardiac pain.

2) *Fatal myocardial infarction*

   a) *Definite myocardial infarction* was recorded if one of the following criteria was present:

   i) Post mortem evidence of acute myocardial infarction.

   ii) Definite criteria for myocardial infarction were present within the 4 weeks prior to death.

   iii) ICD-9 codes for cause of death were: 410–414 plus participant had a history of a definite or possible myocardial infarction; or 410–414 plus definite or possible criteria for myocardial infarction immediately preceding death; or 410–414 plus post mortem evidence of severe coronary atherosclerosis or previous myocardial infarction.

   b) *Possible myocardial infarction* was coded if:
   – death certificate codes were 410–414 but no other evidence could be found.

Angina pectoris

A diagnosis of angina during the follow-up period required that there was no WHO evidence of angina at baseline examination, plus either:

   i) Evidence of angina on the WHO angina questionnaire[14] and recall of a doctor's diagnosis of angina.

   ii) WHO angina plus ECG ischaemia.

   iii) Clinical diagnosis of angina investigated by the general practitioner or a hospital.

Stroke

1) *Non-fatal stroke*

   a) *Definite stroke* was coded if one of the following criteria was present:

   i) A history of onset of symptoms of less than 48 hours, plus clinical confirmation of a focal or global disturbance of cerebral function lasting more than 24 hours.

   ii) Computerized tomography scan showed evidence of cerebral infarction or haemorrhage.

   b) *Possible stroke* was coded if:
   – primary or secondary discharge diagnosis included ICD-9 codes of 431, 432, 434, 436 or 437.

2) *Fatal stroke*

   a) *Definite stroke* was coded if one of the following was present:

      i) Post mortem evidence of cerebral infarction or haemorrhage.

      ii) Criteria for definite stroke were met within the 6 weeks prior to death.

   b) *Possible stroke* was coded if:

      – death certificate codes of underlying or immediate cause of death were ICD 431–437, but no other evidence was available.

Transient Ischaemic Attack

A transient ischaemic attack was defined as a 'history of rapid onset of clinical signs of focal or global disturbance of cerebral function lasting less than 24 hours'.

Intermittent Claudication

Intermittent claudication was diagnosed using the WHO questionnaire.[14] Grade 1 was recorded if calf pain occurred when walking uphill or hurrying, and Grade 2 if the pain also occurred while walking at ordinary pace on the level. 'Probable' claudication was defined as calf pain present on exercise but not at rest that otherwise did not fully meet the WHO criteria.

Thrombo-embolism

Thrombo-embolism was coded if the diagnosis was confirmed by laboratory, radiological or surgical evidence.

Amputation/Surgery/Angioplasty

A code of amputation referred to the amputation of any part of the lower limb, due to diabetes or vascular causes only. Vascular surgery, angioplasty, rest pain/ulcer/gangrene and coronary artery bypass grafts could be coded when these events were noted in participants' records.