RISK FACTOR STRATIFICATION OF PERIPHERAL ARTERIAL DISEASE IN THE UNITED KINGDOM

SHAUKAT N KHAN

DEGREE

MD

SUBMITTED

AUGUST 2005.

CONTENTS **Page No.**

Table of Figures and Tables

Abstract

Objective: To document the patient characteristics, primary care and hospital management and QoL in patients with intermittent claudication in the United Kingdom. Also to determine the appropriate use of prophylactic therapy, to determine markers of high and low risk and to suggest approaches to optimise the management of peripheral arterial disease.

Methods: 474 patients were recruited from 23 centres across the United Kingdom. Data was collected at baseline and at six months and risk factors profile was analysed.

Results: Symptomatic disease is more prevalent in men and those above 60. A high proportion of patients were hypertensive and control of blood pressure was not optimal. Use of antiplatelet agents and lipid lowering therapy was less than satisfactory though it improved following hospital referral. Life style modification advice was patchy and not uniform and intensive support for such programmes was lacking. Majority of patients improved not only on clinical parameters but also their QoL over a six month period. 35% underwent peripheral imaging and 7.8% had an interventional procedure. 14% had a vascular event over six months. Low ABPI, high systolic pressure and prior CHD were significantly associated with development of all vascular events.

Conclusions: Use of appropriate therapy to reduce the risk factor profile is less than optimal. There is a need for uniform national guidelines for appropriate management of peripheral arterial disease patients in the United Kingdom.

Acknowledgements

I am highly indebted to Professor Stansby, Professor of Vascular Surgery, Northern Vascular Centre & University of Newcastle, for his continuous support and guidance on this project. I also acknowledge the support of Dr. Marcus Flather, Director Clinical Trials And Evaluation Unit, Royal Brompton Hospital & Imperial College, London, in this respect and thank him for allowing me to interact with his wonderful team, especially Rebecca Mister. I received tremendous help from this unit and to simply thank the staff will be probably a limitation of my vocabulary to express my feelings.

Finally, I am thankful to my lovely wife, Iffat, who put up with me in my stressful days and remained a pillar of affection and support thorough out.

List of Abbreviations

AAA	Abdominal aortic aneurysm
ABPI	Ankle brachial pressure index
ACE	Angiotensin converting enzyme
BP	Blood pressure
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CD	Claudication distance
CPR	C – reactive protein
CT	Computed tomogram
CVA	Cerebrovascular accident
CVD	Cerebrovascular disease
EQ-5	Euroqol – 5
HDL	High density lipoprotein
IC	Intermittent claudication
IDDM	Insulin dependent diabetes mellitus
LDL	Low density lipoprotein
LREC	Local research ethics committee
MI	Myocardial infarction
MREC	Multi-centre research ethics committee
MRI	Magnetic resonance imaging
NIDDM	Non-insulin dependent diabetes mellitus
NRT	Nicotine replacement therapy
PAD	Peripheral arterial disease
PAQ	Peripheral arterial questionnaire
PTCA	Percutaneous transluminal coronary angioplasty
QoL	Quality of life
TC	Total cholesterol
TIA	Transient ischaemic attack

Chapter 1

Risk factor profile of patients with peripheral arterial disease and its current management: Review of the literature.

1.1 Introduction

Peripheral arterial disease (PAD) is a major public health problem. It is a hallmark of systemic pathology that not only affects the peripheral arterial system but also the coronary, cerebral and renal arteries.

The development of atherosclerosis is linked with a number of risk factors. Modification of these risk factors might reduce the development of PAD and in turn improve cardiovascular morbidity and overall mortality. However the management of patients with identical PAD varies widely between centres in the United Kingdom. In order to establish a national treatment strategy for PAD it is important to know the magnitude of the problem together with the likely outcomes in patients with differing severity of PAD. Hence, there is a need to establish the distribution patterns of PAD risk factors and further stratification of these in relation to progression of the disease process. This will help in developing a uniform action plan for the management of PAD.

The most common clinical presentation of PAD is intermittent claudication (IC). Assessment of claudicants can help to provide the detail of risk factors involved and their impact on the progression of disease over a period of time.

1.2 Intermittent Claudication

IC, the most frequent symptom complex of PAD, is characterised by calf, thigh or buttock pain and weakness brought on by walking, with the disappearance of the symptoms following a brief rest.

1.2.1. Clinical assessment

A good history and clinical examination forms the basis of clinical assessment in suspected cases of IC. Palpation of the peripheral pulses is a less sensitive measure of PAD [1-3]. Diagnostic accuracy may be improved by using a standard questionnaire such as the Edinburgh Claudication Questionnaire (ECQ) or the World Health Organisation / Rose questionnaire, though false-positive rates of up to 44% and false-negative rates of up to 19% have been reported after verification by non-invasive tests [4-7] .

1.2.2. Ankle: brachial pressure index (ABPI)

The most useful non-invasive test for the diagnosis of PAD is the ankle: brachial pressure index (ratio of best systolic blood pressure in dorsalis pedis or the anterior tibial arteries in the lower limb to systolic blood pressure in the brachial artery). A resting ABPI of 0.90 is considered to be 95% sensitive in detecting PAD and almost 100% specific in identifying apparently healthy individuals [8-14]. It may however be unreliable in case of diabetics due to calcification of the peripheral vessels resulting in incompressibility. An ABPI of greater than 0.90 is considered normal; 0.7 to 0.89 is considered mild disease; 0.5 to 0.69, moderate disease; and less than 0.5, severe disease [15]. A resting ABPI of less than 0.9 is usually associated with a 50% or greater vessel stenosis [16]. The Edinburgh Artery Study has shown an association between ABPI and severity of disease in the general population.

1.3 Epidemiology

PAD can broadly be divided into two groups,

i) symptomatic, presenting mainly as IC, and

ii) asymptomatic

1.3.1. Incidence of Intermittent Claudication

The number of new patients with PAD seen by a U.K. general practitioner per annum appears similar to the number of new cases of M.I or stroke seen [19]. However, many patients with IC are elderly and may consider their symptoms to be part of growing old and not consult a doctor. One half of all PAD patients older than 55 years are asymptomatic [18]. Of the symptomatic patients, approximately 80% experience IC, and 20% have critical limb ischaemia [19]. The proportion that consults their general practitioner varies from 10% in the inner city to 50% in rural communities [20, 21].

1.3.2. Prevalence of PAD

The prevalence of PAD differs depending on the study population and the diagnostic methods used [19, 21, 22-28] . Even when the same diagnostic criteria are used, this can result in different prevalence rates, depending on the

age, sex, and geographic location of the population studied (Table1.1). Thus, the reported prevalence rates for IC using the Rose questionnaire vary from 0.4% to 14.4% [22]. The PARTNERS programme found the prevalence of PAD in the population of patients older than 70 years and/or older than 50 years with co-morbidities (e.g., smoking and concomitant diabetes) to be 29%. Of the number of cases of PAD detected, as many as 44% were newly diagnosed with the use of the ABPI technique [29].

The prevalence of PAD increases rapidly with age, as does the hospital admissions rate [19, 25, 27]. In the male population the prevalence of IC is 3 - 6% around the age of 60 years. For the UK, the Edinburgh Artery Study has shown the prevalence to be 4.5% between 55 and 74 years of age [25]. Varied results relating to sex distribution have been produced by population based studies. Overall PAD has been shown to be higher in the male population for a given age and this ratio has ranged from 1 to 8 [30].

1.3.3. Prevalence of asymptomatic disease

The prevalence of asymptomatic disease can be estimated only by using non-invasive techniques, like the measurement of ankle systolic pressures [31-33] and duplex scanning, though the later has not been used widely in epidemiological surveys. The reported prevalence of asymptomatic disease ranges from 0.9% to 22% with the ratio of symptomatic to asymptomatic disease in individual studies varying between 1:0.9 to 1:6.0 [19, 23, 31-38].

Study	Location	Sample Size	Age	Prevalence (%)
Hughson et al, 1978 [20]	England	1716	45 – 69	2.2
De Backer et al, 1979 [34]	Belgium	8252	40 – 49 50 - 59	0.8 2.3
Reunanen et al, 1982 [22]	Finland	5738	30 – 39 40 – 49 50 - 59	0.9 1.6 4.6
Stoffers et al, 1991 [19]	Netherlands	3654	45 – 54 55 – 64 65 - 74	0.6 2.5 8.8
Fowkes et al, 1991 [23]	Scotland	1592	55 - 74	4.5
Smith et al, 1991 [24]	Scotland	10042	40 – 59	1.1
Novo et al, 1992 [28]	Palermo	1558	40 – 49 50 – 59	4.7 9.2
Aronow et al 2002 [25]	New York USA	3624	80 +/-8 81 +/-8	32 26
Murabito et al 2002 [39]	Massachusetts USA	3313	> 40 mean 59	3.9 3.3
Fowler et al 2002 [27]	Perth, Australia.	4470	65 - 83	15.6
Selvin et al 2004 [40]	Baltimore, USA	2174	40 + 70 +	4.3 14.5

Table 1.1: Prevalence of PAD in large population based studies

1.4. Risk Factors in PAD

The risk factors for developing PAD are similar to those for other atherosclerotic diseases. The influence of age and sex in the incidence and prevalence of IC has already been considered. The following risk factors are associated with development of PAD:

1.4.1. Smoking

All epidemiological studies of PAD have confirmed that cigarette smoking is a strong risk factor for the development of IC [20, 22-24, 41-48]. Symptomatic PAD is three times more common among smokers than non-smokers [49]. Epidemiological evidence has suggested that the association between smoking and PAD may be even stronger than that between smoking and coronary artery disease (CAD) [50-53]. In the Framingham study, the risk at all ages was almost double for PAD as compared to CAD [43]. The diagnosis of PAD is made up to a decade earlier in smokers than in non-smokers [46, 48, 51]. The severity of PAD tends to increase with the number of cigarettes smoked [43, 52-57] and heavy smokers have a fourfold risk of developing IC [43] .

Smoking is the most significant risk factor that is associated with disease progression. Cronenwett et al found that patients with IC who had smoked at least 40 pack-years required reconstructive vascular surgery over three times more frequently than those who had smoked less [58]. A major amputation rate of 6-11% has been reported in patients with IC who smoke compared with no major amputations in non-smoking claudicants [30, 59, 60]. The 5-year mortality rate for patients with IC who continue to smoke is 40% to 50% [60]. Smoking cessation has been associated with a rapid decline in the incidence of IC and the risk of IC for ex-smokers one year after quitting is approximately the same as that for non-smokers [55, 56]. However, the Edinburgh artery study found that the relative risk of IC was 3.7 in smokers compared with 3.0 in ex-smokers of more than 5 years [48].

1.4.2. Diabetes mellitus and impaired glucose tolerance

The association between diabetes mellitus and the development of PAD is now well established [43-45, 49, 61-65]. IC is about twice as common amongst

diabetic patients as among non-diabetic patients [30]. Insulin resistance seems to play a key role [64].

PAD in patients with diabetes is more aggressive, with early large vessel involvement coupled with microangiopathy. Diabetic patients with IC have a 35% risk of acute ischaemia and a 21% risk of major amputation, compared with 19% and 3%, respectively, in nondiabetic claudicant patients [65]. Similar results have been reported by Dormandy and Jelnes [21, 66].

1.4.3. Hypertension

Hypertension increases PAD risk by two to three fold and is particularly associated with the development of severe disease [39]. The Framingham study showed that hypertension carried a 2.5-fold age-adjusted risk in men and a 3.9-fold age-adjusted risk in women [43]. Similar evidence has been produced by the Edinburgh and the Basle studies [48, 61] though the Whitehall and the Finnish studies have found no association between the two [22, 67].

Hypertension may delay the onset of IC by elevating the central perfusion pressure. As a result newly diagnosed hypertensive may develop IC on initiation of antihypertensive therapy. Disease progression and deterioration has been related with higher systolic arterial pressure [66].

1.4.4. Hyperlipidaemia

Total cholesterol is a powerful independent risk factor for the development of PAD [43, 52]. In the Framingham study, a fasting cholesterol level greater than 7 mmol/L was associated with a doubling incidence of IC [45]. It appears that the ratio of total to high-density lipoprotein (HDL) cholesterol is a better predictor of occurrence of arterial disease [60]. Treatment of hyperlipidaemia reduces both the progression of PAD and the incidence of IC [68-70]. Interestingly postprandial hyperlipaemia has been reported in patients with normolipaemic PAD [71] and an association between PAD and hypertriglyceridaemia has also been reported [21, 20, 22, 43]. Hypertriglyceridemia may be associated with the progression and systemic complications of PAD [72]. Recently, Lipoprotein (a) (Lp[a]) has been reported to be a significant independent PAD risk factor [73].

1.4.5. Hyperhomocysteinaemia

Hyperhomocysteinaemia has been described to be an independent risk factor for the development of atherosclerotic lesions in peripheral arteries [74-76]. Raised homocysteine levels have been detected in 28-30% of patients with premature PAD [77,78]. Among vascular patients, the incidence of hyperhomocysteinaemia may be as high as 60% compared with 1% in the general population [79, 80] and has been observed as a stronger risk factor for PAD than coronary artery disease (CAD) [81]. However, Darius et al have found that elevated HC is only slightly more related to PAD than to CAD and cerebrovascular disease (CVD). After adjustment for known risk factors, they suggested that the effect size is small, and an association can no longer be observed between homocysteine and CAD and CVD [82].

1.4.6. Fibrinogen

High fibrinogen levels pose a high thrombotic risk. An increased fibrinogen level has been found to be associated with increased risk of PAD and also indicates an increased risk for poor outcome, particularly for fatal cardiovascular complications [20, 83-85]. A positive correlation has also been seen between elevated fibrinogen and asymptomatic PAD and to the future onset of PAD [86, 87].

1.4.7. Miscellaneous factors

Patients with IC have raised haematocrit levels and this may be a predictor of future graft occlusion [88-90]. This increase in haematocrit may be attributable to an association with smoking. Similarly, high plasminogen levels and raised mean corpuscular volume have also been found to be associated with PAD [91, 92]. Patients with PAD have also an altered coagulation state [93, 94], and their platelets show a tendency to increased aggregation and thrombus formation [95-97]. Recently, elevated D-dimers and C reactive protein (CRP) have also been associated with PAD [98, 99]. However it is unclear whether these factors are themselves involved in the pathophysiology of functional impairment or whether they are simply sensitive markers of the extent of systemic atherosclerosis. Other markers like serum amyloid A (SAA), the proinflammatory cytokine interleukin 6 (IL-6), the active and total fractions of the anti-inflammatory cytokine transforming

growth factor-beta (TGF-beta), the macrophage activation marker neopterin and the infection marker procalcitonin, constitute an inflammatory signature of advanced atherosclerosis and are correlated with the extent of disease [100]. These do not provide discriminatory diagnostic power over and above established risk factors.

1.4.8. Coexisting risk factors

The coexistence of risk factors increases the risk of PAD quite significantly. The Basle study reported that the relative risk increased from 2.3 in cigarette smokers alone to 3.3 in smokers with diabetes, and to 6.3 in smokers with systolic hypertension and diabetes [101]. The Framingham study reported that male sex, age and smoking were associated with a 1.5-fold increased risk for IC. Diabetes and hypertension conferred a >2-fold increased risk and CAD nearly tripled the risk for IC [45]. The probability of IC is increased in the presence of risk factors and smoking dramatically escalates it at any given risk factor level.

1.4.9. Genetic risk

Unlike CAD and CVD, a positive family history has not been confirmed as a significant risk factor in the development of PAD [83, 102, 103]. Individual risk factors may be elevated secondary to genetic predisposition. There seems to be some role of mutations in the genes coding for fibrinogen, Factor V and methylenetetrahydrofolate reductase and PAD [104]. Plasma fibrinogen levels are under substantial genetic control, as genetic polymorphisms account for some 20 -51% of variations in plasma fibrinogen levels [105].

1.4.10. Protective factors

Regular exercise and moderate alcohol intake have been shown to be positive protective factors for the development of IC [106, 107]. Increased level of high-density lipoproteins is also considered as a positive predictive factor in CAD but its role in such a capacity for PAD has yet to be substantiated. Clearly, the absence of a risk factor is protective in itself.

1.5 Co-existing vascular diseases

As mentioned previously, PAD is a marker of diffuse atherosclerosis, and is not surprising that it frequently occurs in conjunction with CAD and CVD. Epidemiologic and natural history studies have determined that PAD confers a high risk of fatal and nonfatal cardiovascular ischaemic events [30, 60, 108-111]. It is associated with a very high risk of myocardial infarction (MI), stroke, and other thromboembolic events, increased mortality, diminution of quality of life and a shortened five-year survival [21, 36, 108, 112, 113].

The calculated prevalence rate of CAD in patients with claudication is dependent upon the diagnostic criteria used [21, 45, 109, 114-124]. It ranges from 35% (questionnaire based – mainly symptomatic) to 90% (coronary angiogram – combined symptomatic and asymptomatic) [21,114]. A proportion of these patients may be asymptomatic if exercise is severely limited by claudication. Asymptomatic patients like the symptomatic group, are also at increased risk of MI, stroke and vascular death [35, 52]. Similarly individuals with CAD are more likely to suffer from PAD than the non-CAD individuals [22, 45]. However, the link between PAD and CVD seems to be weaker than that with CAD [109]. Although approximately half of all patients with IC have CAD, a much lower proportion have demonstrable CVD [21, 106, 109, 125]. Imaging techniques like duplex scanning reveal carotid disease in 26 – 50% of patients with IC [126-129]. Overall the current evidence suggests that approximately 40% of patients with CAD or CVD suffer from PAD. Similarly 60% of the patients with PAD have coronary or cerebrovascular disease [50, 130].

1.6. Natural history & progression of intermittent claudication

The progression of PAD can be considered in terms of the systemic outcomes like CAD and CVD events, and the local progression of disease in the limbs.

1.6.1. Local Disease

1.6.1.1. Improvement or stabilisation

In a majority of cases the clinical course of IC is benign [131]. Only a quarter of patients with IC ever deteriorate significantly [132]. The Basle study documented angiographic progression of the disease in 63% of patients 5 years after the

initial diagnosis [106]. Of those who had survived for 5 years after the diagnosis, 66% still had no limiting IC. This symptomatic stabilisation may be attributed to:

(i) the development of collaterals,

(ii) metabolic adaptation of ischaemic muscle by an increase in aerobic enzyme content,

(iii) increase in capillary density, or

(iv) altered gait of the patient to favour non-ischaemic muscle groups.

1.6.1.2. Worsening claudication

The highest risk of significant deterioration has been noted during the first year after diagnosis (7%–9%) compared with 2% to 3% per annum thereafter [66, 132]. Dormandy has shown approximately 6% deterioration in exercise tolerance over the first year in non-surgical hospital patients [133]. Hospital-based series tend to identify patients with IC who have more severe disease or whose symptoms are progressing. A resting ABPI of 0.5 or less has been postulated to be the most significant predictor of limb deterioration [133].

1.6.1.3. Need for intervention

In general, the indications for intervention are a significant deterioration in ability to carry out daily routines, increasing disability and increasing pain. Young patients with relatively better exercise tolerance than the elderly, whose livelihood is at risk because of inadequate performance of ambulant duties, are also good candidates for intervention. The frequency of local intervention has varied widely from 3% to 22% [134, 135]. The existing data suggest that only one fourth of all patients with IC deteriorate progressively, with an intervention rate of approximately 5% over 5 years for either severe claudication or deterioration to critical limb ischemia [30]. It is important to note here that a group of patients, who otherwise would be candidate for intervention, may not be considered for one because of poor cardio-respiratory status or impaired cognition.

1.6.1.4. Amputation

Major amputation is a relatively rare outcome of claudication. Only 1.0 - 3.3% of patients with IC need a major amputation over a 5-year period [134, 136]. The

Basle and Framingham studies report a major amputation rate of around 2% in claudicants [60, 101]. Earlier studies have reported an amputation rate of 7% at 5 years [115, 116]. The improved recent results reflect a successful intervention rather than the true natural progression of the disease.

1.6.2. Progression of Systemic Atherosclerosis

Patients with either asymptomatic or symptomatic PAD have a significantly increased risk of stroke, MI, and cardiovascular death as discussed in section 1.5. PAD should therefore be viewed as a sign of potentially diffuse and significant arterial disease. The Edinburgh Artery study has shown that patients with IC have a significantly increased risk of angina (relative risk, 2.31) whereas asymptomatic PAD patients have a slightly increased risk of MI and stroke [139]. Recent reports show a 1 - 3% annual incidence of nonfatal MI in these patients [133, 136]. The Edinburgh group has also reported an incidence of 8.2% of MI, 9.6% of angina and 6.8% of CVD during a follow up of five years [137]. There seems to be a general agreement that between 2% to 4% of patients with IC have a nonfatal cardiovascular event within the first year [30].

1.6.3. Mortality

The mortality rate of the claudicant population is on an average 2.5 times that of nonclaudicants [133]. A claudicant's life expectancy is estimated to be 10 years less than a control population [132]. PAD is associated with diminished QoL and a shortened five-year survival [23, 36, 108, 112, 113]. CAD is by far the most common cause of death among patients with PAD (40%–60%), while CVD accounts for 10-20% [138, 139]. Another 10% of PAD patients die due to other vascular causes like, aortic aneurysm. Thus, 20-30% of patients with PAD die of non-cardiovascular causes. The 5-, 10-, and 15-year mortality rates from all causes are approximately 30%, 50%, and 70%, respectively [30]. This emphasises that the real danger for the patient with IC is not the local disease itself but cardiac and cerebral complications or death. Claudicant patients with coronary ischaemia have survival curves similar to non-claudicants who had survived an MI [59, 114].

Smoking [140-142],diabetes [66, 116-119, 123, 133, 140], hypertension [66, 115, 133], white cell count [133, 141], asymptomatic carotid disease [142],

hypertriglyceridemia [72] and fibrinogen [141, 143] have all been reported as predictors of mortality. Smoking increases mortality rates among patients with IC by 1.5 to 3.0 [7]. Interestingly, diabetes seems to be less of a mortality risk than the progression of local disease in the legs. ABPI remains the most powerful tool for the prediction of all-cause mortality in the PAD population [144].

1.7. Interventions to reduce risk factor profile

Since individuals with PAD are at markedly increased risk of cardiovascular ischaemic events, early identification of this population and more aggressive medical interventions may potentially improve both morbidity and survival. Despite the known benefits of antiplatelet therapy and treatment of hypertension and hyperlipidaemia in reducing ischaemic event rates, PAD patients are less intensively treated than patients with CAD or CVD [29, 30, 145]. As discussed above vascular intervention is needed in a minority and most claudicants can be managed conservatively [134, 135]. Aggressive risk factor management is known to result in reduction of vascular events in patients with previous MI. Therefore it seems probable that early recognition and diagnosis of PAD combined with its appropriate life style modification and risk factor management may reduce overall risk of further adverse vascular events.

1.7.1.1. Life style modification

1.7.1.2. Smoking cessation

All patients with PAD should be strongly and repeatedly advised to stop smoking [7, 58, 59, 140-142]. Special programmes can enhance smoking cessation, though motivation remains the cornerstone. Counselling can give much-needed support and nicotine replacement therapy or Bupropion (Zyban - a norepinephrine, serotonin and dopamine neuronal uptake inhibitor) may help to reduce craving [146]. Nicotine replacement substitutes treat the very difficult withdrawal symptoms and cravings that 70% to 90% of smokers which is the main reason for not giving up cigarettes. By using a nicotine substitute, a smoker's withdrawal symptoms are reduced. Nicotine replacement therapy (NRT) gives a small dose of nicotime that helps to cut down the urge to use tobacco. Nicotine chewing gum, lozenges and patches are available over the counter. This therapy can also be prescribed as nasal sprays and inhalers. National Institute of

Clinical Excellence has recommended NRT and bupropion for smokers who have expressed a desire to quit smoking. NRT or bupropion should normally only be prescribed as part of an abstinent-contingent treatment, in which the smoker makes a commitment to stop smoking on or before a particular date (target stop date).

Success of smoking cessation is dependent on patient motivation and available support. Smokers should be offered advice and encouragement to aid their attempt to quit. Active intervention can achieve an abstinence rate of 16% at one year [147]. NRT increases the odds of smoking cessation by approximately 1.5 – 2 fold [148]. This appears to be largely independent of the intensity of any additional support for smoking cessation. Standard self-help materials may increase quit rates compared to no intervention, but the effect is likely to be small. Telephone and internet based quitlines and family and friends support can be helpful in smoking cessation programme. Group behavioural therapy has been reported to be more successful than the self help approach [149,150]. Several other strategies like hypnosis, acupuncture, filters and smoking deterrents have been employed with very little success [151,152].

1.7.1.2. Exercise

Trials have clearly demonstrated that walking capacity is increased by exercise training in patients with claudication [153-156]. Supervised exercise conducted for more than three months has shown increase in treadmill exercise performance [157-162]. A meta-analysis of structured exercise studies reported an average increase of 179% in initial claudication distance and a 122% increase in absolute walking distance on the treadmill [163]. This benefit may be lost if exercise is stopped. The predictors of response to the training programme include a high level of claudication pain during the training sessions and 6 months or longer of formal training and walking exercise as compared to other training modalities. Exercise rehabilitation itself has been associated with a minimal morbidity and mortality [164]. Peak exercise performance and peak oxygen consumption improves with treadmill training, the heart rate decreases along with an improvement of ventilation and oxygen consumption at a given sub-maximal workload [165, 166]. Efficient glucose metabolism, a reduction in

cholesterol and triglyceride concentrations and enhanced smoking cessation have also been reported with regular exercise [167]. It also has a positive impact on the QoL as it improves the functional status of the claudicant [168].

1.7.1.3. Weight control

Overweight patients with IC may benefit from reducing weight in terms of claudication distance by reducing work-load. Obesity is a recognised risk factor of most fatal and nonfatal cardiovascular events. Abdominal fat distribution, but not total body fat, has been associated with PAD, independently of concurrent cardiovascular risk factors [169].

1.7.2. Hyperlipidaemia

Analysis of data from several large trials suggests that rising vascular event rates correlate closely with increasing LDL cholesterol levels [170-172]. Elevated LDL cholesterol and triglyceride levels and low HDL cholesterol levels are of key importance in the development of PAD [48, 60, 69, 72, 171, 172]. Recent studies have supported the role of lipid modification in stabilisation or regression of arterial atherosclerosis [69, 70, 173-175].

The Scandinavian simvastatin (4S) study has shown that simvastatin reduces the risk of development or worsening of claudication by 38% [1]. The Heart Protection Study (HPS) with over 20000 participants aged 40-80 years, has also established the beneficial effect of statin therapy in several high risk populations [176]. Overall there was a highly significant 18% proportional reduction in the coronary death rate (5·7% *vs.*6·9%; p=0·0005) and a marginally significant reduction in other vascular deaths (1·9% *vs*2·2%; p=0·07) in patients taking simvastatin. It concluded that five years of 40mg once daily simvastatin would prevent about 70 -100 people per 1000 from suffering at least one of the major vascular events (including myocardial infarction, stroke and either coronary or peripheral arterial revascularisation). There was a significant reduction of cardiovascular events in the PAD subgroup ($p<0.0001$) and the need for peripheral revascularisation was also reduced. The benefit obtained with use of simvastatin in this study was across the board irrespective of cholesterol levels. A 1 mmol/L reduction in LDL cholesterol from about 4 mmol/L to 3 mmol/L reduced the risk of major vascular events by about one-quarter, and so too did

reducing it from about 3 mmol/L to 2 mmol/L. Perhaps this can be explainied by a pleotropic effect of statin therapy which is protective in nature and is independent of the total cholesterol and LDL levels. This reduction of cardiovascular events was to a greater extent than can be explained from effects of statins on serum inflammatory markers especially C-reactive protein. A recent meta-analysis has reported a statistically significant reduction of C-reactive protein levels by all statins [177]. This suggests a statin-mediated anti-inflammatory effect that perhaps contributes to the ability of statins to reduce risk for cardiovascular disease. 4S and Mondillo et al have also shown improved walking performance and claudication symptoms in PAD patients with the use of simvastatin [1, 178]. Similar results have been reported for other statins (157). Atorvastatin improves pain-free walking distance and community-based physical activity in patients with IC [176]. McDermott et al have recently shown that statin use is associated with superior leg functioning compared with no statin use, independent of cholesterol levels and other potential confounders [179]. Wilbert et al have observed that patients with PAD and a serum LDL cholesterol of $\geq$3.5mmol/L have a lower incidence of new coronary events if they were treated with statins as compared to those without (48%vs73%) [180]. Any patient with occlusive vascular disease be it coronary, cerebrovascular or PAD and baseline total cholesterol above 3.5mmol/l without contraindications should probably now receive a statin.

Generally patients with a high cholesterol and LDL levels should be advised dietary modification [72]. Dietary advice may be effective in treating hypertriglyceridaemia, which has been shown to enhance the progression of disease process [181]. Non-statin lipid lowering agents can also be employed in various clinical scenarios other than the intolerance and side effects of the statin therapy. Niacin may have a role in patients with low HDL cholesterol. Patients with low HDL and elevated triglyceride levels in which diet therapy has failed may benefit from fibrates [30].

Most of the studies looking at lipid lowering drugs have generally been conducted in CAD patients with subgroup analysis of PAD patients. This subgroup has been less intensely treated as compared to CAD [182]. Additional data is however required to establish the effects of statins and other lipid lowering therapy on development of future vascular events in PAD population.

Lp(a), a lipoprotein fraction has been shown to be an independent risk factor for PAD [73, 173]. Unfortunately, there are no specific treatments for elevated Lp(a) levels except to aggressively treat abnormalities in other lipid fractions.

1.7.3. Hypertension

Hypertension is associated with the development of atherosclerosis, particularly in the coronary and cerebral circulations. These patients also have a two- to threefold increased risk of IC [4, 45, 183, 184]. The effect of hypertension treatment on the natural history of peripheral atherosclerosis has yet to be evaluated. The evidence for the use of various anti-hypertensive drug classes in PAD is poor, and it is unknown whether significant benefit or risk accrues from their use. General consensus still supports the management of hypertension in PAD and the drug treatment of hypertension can follow the same guidelines as in patients without PAD [30]. A large decrease in systemic blood pressure in a group of patients may worsen the claudication [185]. Nevertheless, there is still a risk reduction of stroke, MI, and cardiovascular death by antihypertensives in PAD [183]. Mehler et al have reported that intensive blood pressure lowering to a mean of 128/75 mm Hg resulted in a marked reduction in cardiovascular events in PAD patients with diabetes [184].

Patients with PAD are at increased risk of renal hypertension, secondary to renal arterial atherosclerosis. Plasma creatinine level should therefore be measured prior to institution of hypertensive drug therapy, probably with Angiotensin converting enzyme (ACE) inhibitors.

Use of beta-blockers has not been shown to adversely affect mild to moderate claudication [186, 187]. ACE inhibitors have shown to improve endothelial function, cardiac and vascular remodelling, retard the anatomic progression of atherosclerosis, and reduce the risk of MI, stroke, and cardiovascular death [188]. In HOPE (Heart Outcome Prevention Evaluation) study subgroup analysis of 4051 patients with PAD from a total of 9297, showed ramipril, an ACE inhibitor, significantly reduced the rate of cardiovascular death, myocardial infarction, and stroke in a broad range of patients at high risk of cardiovascular death [relative risk [RR] = 0.78; 95% CI, 0.70 to 0.86; $P < 0.001$) [189]. These effects could not be explained due to the antihypertensive effect of ramipril alone.

1.7.4. Diabetes mellitus

Diabetes mellitus has a strong association with lower-extremity arterial disease and its progression [48, 49, 129, 190-192]. The United Kingdom Prospective Diabetes Study (UKPDS) has shown a significant reduction in any diabetes macrovascular (myocardial infarction, stroke, amputation including death from peripheral vascular disease) and microvascular (predominantly retinal photo-coagulation, neuropathy and nrephropathy) disease end points, following strict blood glucose control [192]. Metformin has also been associated with a reduction in diabetic complications and all-cause mortality [193]. It is recommended that patients with diabetes and PAD should have aggressive control and normalisation of blood sugar [30].

1.7.5. Hyperhomocysteinaemia

Despite increased plasma homocysteine levels being strongly associated with PAD [77], there are currently no randomised trials available to support the role of homocysteine lowering therapy in PAD [194] . Therapy with folic acid, vitamin B12, and vitamin B6 is effective in lowering homocysteine levels, but the effects on vascular disease severity and progression need further evaluation.

1.7.6. Antiplatelet therapy

Systematic reviews have demonstrated that patients with symptomatic PAD and those who have previously undergone intervention benefit from antiplatelet therapy for the reduction of MI and stroke [195, 196]. Aspirin is the 'first line' antiplatelet agent used in the UK as it is both cheap and effective, and evidence has demonstrated that aspirin reduces the rate of adverse vascular events by around 20% [197]. Over recent years there has been a trend towards prescribing lower doses of aspirin (75mg daily) in an attempt to reduce bleeding complications; however evidence supporting this move is yet to be clearly established.

The Peripheral Arterial Diseases Antiplatelet Consensus Group has recently recommended that all patients with IC should be considered for long-term antiplatelet therapy as evidenced by their ability to reduce future vascular events [197]. Although evidence supporting the use of aspirin in cardiac and cerebrovascular disease is good, there is a relative scarcity of data in PAD.

Much of the data used in meta-analyses to support the use of aspirin in PAD actually comes from other antiplatelet agents such as clopidogrel and ticlopidine [198]. In addition there is data suggesting that clopidogrel is a more effective agent than aspirin in patients with PAD [50]. Clopidogrel is a theinopyridine that blocks platelet ADP receptors, a more potent pathway of platelet activation than that of thromboxane (aspirin).

There is now growing interest in the use of combination antiplatelet agents to block multiple pathways of platelet activation, and interest in the identification of patients relatively resistant to aspirin therapy [128]. The CURE study has found the combination of aspirin plus clopidogrel to be more effective than aspirin alone in patients with acute coronary syndromes, and the European Stroke prevention study 2 demonstrated that the combination of aspirin plus dipyridamole was more effective in preventing strokes than either agent taken singly [199]. Although these results are promising, these data cannot be directly extrapolated to PAD, particularly when concerns over bleeding complications exist.

Current evidence and financial constraints would support the use of aspirin in all patients with PAD who are able to tolerate the drug. In patients intolerant of aspirin, clopidogrel is the drug of choice. Patients considered being at high risk of vascular events, and those who continue to have events whilst on aspirin should be considered for clopidogrel therapy, alone or in combination with aspirin.

1.7.7. Hypercoaguable states

Screening and treatment for thrombophilia in PAD is controversial. Patients with early onset PAD or those with a recent history or family history of thrombotic disorders should be screened for thrombophilia. Hypercoaguable states, when detected, should be discussed with a haematologist and in the majority of patients oral anticoagulation is the only available treatment. Use of oral contraceptives has been associated with increased risk of thrombosis in peripheral arteries. The RATIO study recently showed an adjusted odds ratio of 3.8 (95% CI 2.4-5.8) for PAD in women using any type of oral contraceptives vs. no use [200].

In patients primarily considered for surgical treatment, antiplatelet and anticoagulant drug therapy can be used as a means of promoting graft patency,

and beta-adrenergic blockers can be used as a means of reducing the perioperative risks associated with vascular surgery.

1.8 Pharmacotherapy of intermittent claudication

Patients with IC mostly receive drug treatment for risk factor modification, co-existing disease or as prophylaxis against thrombotic events associated with atherosclerosis. Pharmacotherapy has in general failed to produce sufficient reduction or elimination of symptoms in claudicants to gain widespread acceptance. However, pharmacotherapy is perhaps still helpful in the following scenarios:

i) in patients who have not sufficiently benefited from exercise and risk factor treatment,

ii) in patients who cannot or will not follow exercise therapy,

iii) as adjunct treatment where invasive therapy is not indicated,

Various clinical trials with drugs like pentoxifylline, buflomedil, naftidrofuryl and cilostazol have shown statistically significant improvement in walking distance but the average benefit is small [201-211]. Vasodilators have limited, if any, role to play. Cilostazol therapy may increase maximal and pain-free walking distances in IC [201]. Greater benefit may warrant a short course of therapy with continued use of such agents if sufficient improvement is observed. Currently there is insufficient data to recommend the routine use of pharmacotherapy in all patients with claudication.

- *Prostaglandins*

PGE1 and a prodrug of PGE1 (AS-013) have shown a significant increase in maximum walking distance as compared with placebo with an improvement in QoL [212, 213]. These improvements have remained virtually unchanged over 3 months' follow-up without treatment. Intravenous administration of these medicines is often not practical and side effects can limit therapy. A recently developed oral preparation, beraprost, a PGI2 analog may be more promising in this regard [214, 215]. Utility of this class of drug in claudication is presently being evaluated.

- *Vascular endothelial growth factor*

Vascular endothelial growth factor (VGEF) therapy is a new and exciting area. However a great deal of work and evaluation is required before it could be considered for routine treatment [216]. VEGF and basic fibroblast growth factor (bFGF) are mitogenic agents for the development of new collateral channels in models of peripheral ischaemia. VEGF has shown promise by augmenting collateral vessel development and increase capillary density in skeletal muscle animal models, via intra-arterial infusion and intramuscular injection [217].

A number of other pharmacological agents have been investigated for medical treatment of IC but show little consistent scientific evidence of efficacy.

1.9 Conclusion of introductory review

PAD is a considerable public health problem. It shares the similar risk factors as CAD and CVD. These risk factors can be modified to reduce the disease burden and its complications. There is a need to develop uniform guidelines to accomplish a desirable objective in PAD as has been done in CAD and CVD. This requires documentation of current practice patterns and outcomes in relation to risk factor profile in PAD.

Chapter 2

Protocol Overview

2.2. Objectives

The United Kingdom has a high burden of PAD. Unfortunately existing guidelines on management have largely focused on coronary and cerebrovascular disease. There is currently no uniform management protocol to treat these patients, not only in relation to the symptomatic disease process but also the underlying risk factors in a more effective and efficient way. As a result of this lack of agreement, many patients are currently denied risk-lowering therapy.

This study aimed to collect basic data on the current management of risk factors in claudicants at the primary care and also at the hospital level. This is expected to help in future health planning and improving the pattern of vascular practice.

The objectives of this study were:

1. To document the following in patients with PAD
    (a) Patient characteristics and distribution,
    (b) Practice patterns
    (c) 6 month outcomes
    (d) To understand the impact of PAD on patient-centred outcomes including disease-specific and generic measures of QoL and health status.

2. To determine markers of high and low risk affecting PAD.

3. To suggest approaches to optimise the management of the high-risk group and determine the use of risk factors therapy such as antiplatelet and lipid lowering agents.

4. To set a benchmark by which future practice may be improved.

2.2. Methods:

2.2.1. Study design

This study was a prospective, protocol-driven, multi-centre observational cohort study.

2.2.2.1. Identification of centres and enrolment of patients

Members of the Vascular Surgical Society of Great Britain and Ireland were contacted using a random sequence method and invited to take part. Efforts were made to ensure that there is appropriate representation from different regions of the United Kingdom and teaching and non-teaching hospitals were included. Initially, one tertiary centre and three district centres from each of the health regions were invited to participate. Due to recruitment difficulties in total 54 centres were invited. 31 of these refused over a period of time due to various reasons. Hence 23 centres were used (Appendix I: list of centres). A total of 474 patients were enrolled. Enrolment started in June 2002 and was completed in September, 2003. Follow up was completed in March 2004.

2.2.2.2. Eligibility

Potentially eligible patients were identified through vascular clinics of the participating hospitals as per the inclusion criteria. Patients enrolled on the study fulfilled the following eligibility criteria:

2.2.2.2.1. Inclusion criteria:

1. Good clinical history of intermittent claudication occurring within a walking distance of about 400 metres or quarter of a mile (i.e. Patients in Fontaine class II).
2. Ankle/brachial blood pressure index ≤ 0.9.
3. Presenting as a new referral to a vascular clinic of a participating hospital.
4. Patients with past history of vascular disease presenting as new referrals with an interval of two years at least.
5. Able to provide written informed consent.

2.2.2.2.2. Exclusion criteria:

1. Patients presenting with critical limb ischaemia including rest pain, necrosis or ulceration.
2. Spinal canal claudication.
3. Claudication that may be related to venous obstruction.
4. Patients presenting with another major medical condition where the claudication is incidental.
5. Participation in any other clinical trial.

2.2.2.3. Data collection and management:

Study-related information was collected on case report forms (CRFs). (Appendix 2: Case Record Form). All the data at entry was checked and any missing or unusually abnormal values were sent for edit query to the relevant centre. The data was cleaned and rechecked.

2.2.2.4. Follow-up:

Patients were followed up 6 months after enrolment to document the occurrence of major clinical events such as hospital admission, surgical or radiological intervention, and other vascular events like myocardial infarction, cerebrovascular accident, transient ischaemic attack or death. Six-month follow up was decided to observe the extent of outcomes within a short period of time in this high risk population. Hospital visit were encouraged, although telephone follow-up was used in patients who could not attend the outpatients. A small number of patients were seen earlier or later than planned, but median time for follow up remained 6 months.

2.2.2.5. Statistical issues

A sample size of 500 was initially proposed for this study. This was based primarily on the estimation that 10% of the population would develop a major event during the 6 month follow-up with a power calculation of 80% and secondarily on the feasibility of recruitment.

The following analysis plan was defined in advance of the study:

1) Descriptive Statistics

The characteristics and treatments recorded in the case report form including the baseline medical history, peripheral vascular disease history, employment and education, smoking status, results of the blood tests and medications will be tabulated. The following parameters will be assessed in the stratified analysis:

i.) Age
ii.) Gender
iii.) Ankle brachial index
iv.) Percentage taking an antiplatelet treatment
v.) The pack years smoked by the patient.

2) Exploratory analysis of interactions between various baseline characteristics and treatments

The following prognostically important variables will be considered. This list was not exclusive but contained the main factors to be used in exploratory analysis:

i) Age
ii) Gender
iii) Ankle brachial index
iv) Systolic blood pressure
v) Diabetes
vi) Hypertension
vii) Any prior coronary heart disease defined as the presence of a prior MI, prior CABG or prior PTCA or prior angina
viii) The absolute claudication distance
ix) The pack years smoked
x) Whether or not taking antiplatelet therapy
xi) Whether or not taking lipid-lowering therapy

This analysis would explore the relationship between age as an independent variable and the other variables. The second analysis would be based on gender as an independent variable and the others as dependant variables to determine the relationships. The third major factor would be ankle brachial index. A univariate analysis was proposed in the first instance and then a multivariate

model would be used to explore the inter-relationships between the various factors.

2.2.2.6. QoL

Patient centred outcomes were assessed at each visit. Effects of PAD on patients' QoL were assessed by a generic questionnaire, EuroQol – 5 (appendix 3) and a disease specific questionnaire Periphral Artery Questionnaire (PAQ) (appendix 4) [214, 215]. EuroQol – 5, developed by York University is widely used as a generic QoL tool and it was found to be an appropriate tool to be used in this setting. PAQ is a recently developed arterial disease specific tool that has been validated in the USA. Data from this study is also being used to estimate the cost burden of PAD in the UK and the possible impact of treatment modifications. This is being analysed in collaboration with health economist team from Massachusetts in the USA. This specific QoL tool i.e. PAQ, was found to be useful to document the impact of any intervention or progression of the disease and also sensitive to quantify the benefit in terms of management costs.

2.2.2.7. Ethical and Regulatory issues

The study protocol and any other relevant documents were submitted for approval to the Multi-Centre Research Ethics Committee (MREC) before being submitted to the Local Ethical Review Committee (LREC) in the participating institution. Patients were required to give written informed consent before their participation. No particular ethical concerns were raised, as this was an observational study.

2.3. Participating Centres

One tertiary centre and three district centres from each of the health regions were initially invited to participate. Tertiary centres were mainly based in the teaching centres. Initially 23 centres were invited to take part but due to local issues and difficulties many centres dropped out. Hence further centres were invited. A total of 54 centres were invited. 31 centres declined participation due to varying reasons. Most of these were peripheral hospitals where resources in terms of conducting a prospective study were not in place or the departments were too constrained due to service obligations.

2.3.1. Centre Recruitment Process:

Once identified the participating centre was invited. On expression of further interest the study protocol was forwarded to the centre. All the centres were provided with a copy of the Multicentre Research Ethics Committee (MREC) approval. The centres were required to get:

- Local Research Ethics Committee (LREC) approval
- Local Trust approval

A study coordinator (research nurse / doctor) was identified in each centre. Training Calls were conducted and once fully satisfied case record forms (CRF) were sent. All these activities were monitored and managed at the Clinical Trials and Evaluation Unit of the Royal Brompton Hospital, London in close association with the Northern Vascular Unit at Freeman Hospital, Newcastle upon Tyne.

At the time of recruitment patients were provided with an information leaflet (appendix 5). Any queries were answered and a written consent (appendix 6) was taken. The CRF was filled as per history given by the patient. Once enrolled the patient's details were sent to the study coordinating office. There the data was checked and cleaned. Any queries were edited and sent back to the centre for further clarification. Timelines of the study are displayed in table 2.1.

2.3.2. Profile of centres

In total 23 centers participated. Of these 13 were teaching hospitals while 10 were district hospitals.

2.3.2.1. Bed size:

The average number of beds in the recruitment centres was 1085 (teaching 1335, district 772) and average numbers of vascular beds in these centres were 27 (teaching 25, district 18).

2.3.2.2. Number of vascular surgeons:

The average number of vascular surgeons for the recruiting centres was 3.5 (teaching 4, district 3). Most teaching hospital surgeons were dedicated vascular

surgeons while most of the district hospital surgeons were general surgeons with an interest in vascular surgery.

2.3.2.3. Vascular workload:

The average number of patients seen per year in the outpatients of the recruiting centres was 1740 (teaching 2150, district 1400) and the average number of vascular emergencies was 191 (teaching 214, district 152).

2.3.2.4. Procedures:

The number of angioplasties and peripheral bypass procedures performed at the participating centres on average were 148 (teaching 165, district 127) and 62 (teaching 65, district 61) respectively.

2.3.2.5. Facilities:

All major diagnostic and therapeutic facilities were available at most centres which included treadmill, duplex scanning, diagnostic and interventional radiology, computed tomography (CT scan) and magnetic resonance imaging (MRI). Two of the centres were running nurse led claudication clinics. One district hospital had no vascular laboratory while MRI was not available in another.

MREC approved	March 2002
1st patient enrolled	June 2002
All centres recruiting	April 2003
Recruitment completion	September 2003
6 month follow-up completion	March 2004

Table 2.1: Timelines of the study

	Centres invited	**Centres confirmed**
Eastern	6	2
London	6	3
Northwest	5	0
Northern and Yorkshire	5	4
South East	9	1
South West	5	5
Trent	2	1
West Midlands	6	3
Scotland	6	1
Wales	2	2
Northern Ireland	2	1
Total	**54**	**23**

Table 2.2: Distribution of centres

Chapter 3

Baseline Characteristics

3.1. Baseline characteristics

As described in section 2.2.2.2.1. consecutive patients with a history of IC were recruited following consent to participate in the study. Study protocols were followed as per the inclusion and exclusion criteria. Patients with previous vascular history were included if they presented as new referral at least two years after the previous attendance to a vascular unit. A total of 474 patients were recruited. The baseline data relating to these patients is presented in this chapter.

3.2. Results

3.2.1. Age (Table 3.1)

The median age at enrolment was 68.37 years (interquartile range (IQR) 60.75 – 75.51). Age variable was divided into three groups i.e. less than 60, 60 – 70, more than 70 years of age, for further analyses. Median age of the female population was 71.93 years (IQR 63.03 – 77.44); for males it was 66.48 years (IQR 60.27 – 73.41) ($p < 0.001$, chi-square test).

3.2.2. Sex (Table 3.1)

The total number of males was 315 (66.5%) and females 159 (33.5%). The male to female ratio was 1.98 : 1. The preponderance of female claudicants as compared to males progressively increased from 1:2.5 in the less than 60 age group to 1:1.4 in the 70 plus age group. This was statistically significant (p 0.005, chi-square test).

3.2.3. Body Mass Index (BMI) (Table 3.2)

BMI is defined as weight in kg / height in meter^2. Normal BMI ranges between 20 and 25. Median body index in this population was 26.02 (IQR 23.45 – 29.64). Using standard charts 60% (282 / 470) of the patients were found to be overweight i.e. BMI of more than 25, and of these 5% (24 / 470) were grossly overweight, i.e. BMI > 35.

Age Group	Female n (% female) n = 159	Male n (% male) n = 315
< 60	30 (18.9%)	76 (24.1%)
60 – 70	40 (25.2%)	112 (35.6%)
> 70	89 (55.9%)	127 (40.3%)

Table 3.1: Age and sex distribution.

BMI	Percentage
15-20	5%
20-25	35%
25-30	38%
30-35	17%
35 +	05%

Table 3.2: Pattern of body mass index (bmi) distribution

	Median	Range (meters)
Initial CD	100.0	0 – 400
Absolute CD	150.0	10 – 1500

Table 3.3: Initial and absolute claudication distance characteristics

3.2.4. Ethnic origin

Most of the patients were Caucasians (97%), 3 were Afro-caribbeans, 8 (1.7%) South Asians and 1 East Asian.

3.2.5. Claudication:(Table 3.3)

All patients as per inclusion criteria were claudicants with initial claudication distance of less than 400 yards. 254 (53.6%) had bilateral claudication while 220 (46.4%) were symptomatic in one leg only. The distribution of initial and absolute claudication distances is shown in figure 3.1.

The median initial claudication distance in both unilateral and bilateral claudicants was 100 meters however the IQR was 50 – 200 for unilateral and 42.5 – 150 for the bilateral claudicants. The median absolute claudication distances were 176.0 (IQR 90 – 300) and 150 (IQR 70 – 205), respectively. These figures were statistically significant (p 0.01 and p 0.005, Kruskal – Wallis test).

3.2.6. Ankle Brachial Pressure Index (ABPI):(Table 3.4)

ABPI is the ratio of best ankle systolic pressure to systolic pressure in the brachial artery. The median ABPI on the left lower limb was 0.70 (IQR 0.57 – 0.85) and 0.75 (IQR 0.60 – 0.90) for the right lower limb. Lower of the two ABPI values was further grouped into four groups as shown in table 3.4.

The median ABPI in patients with bilateral claudication was 0.68 on left and 0.070 on the right while this was 0.75 and 0.80 respectively on the right (p <0.001 and <0.001, Kruskal – Wallis test).

3.2.7. Blood Pressure:

The median systolic blood pressure was 152 with a range of 75 – 234 mmHg. Even though only a single observation, systolic blood pressure of more than 140 mmHg was observed in 68.9% of the population. The median diastolic blood pressure was 80 with a range of 50 – 130. 19% had a single reading of more than 90 mmHg. The distribution patterns for the systolic and diastolic blood pressure are shown in tables 3.5 and 3.6.

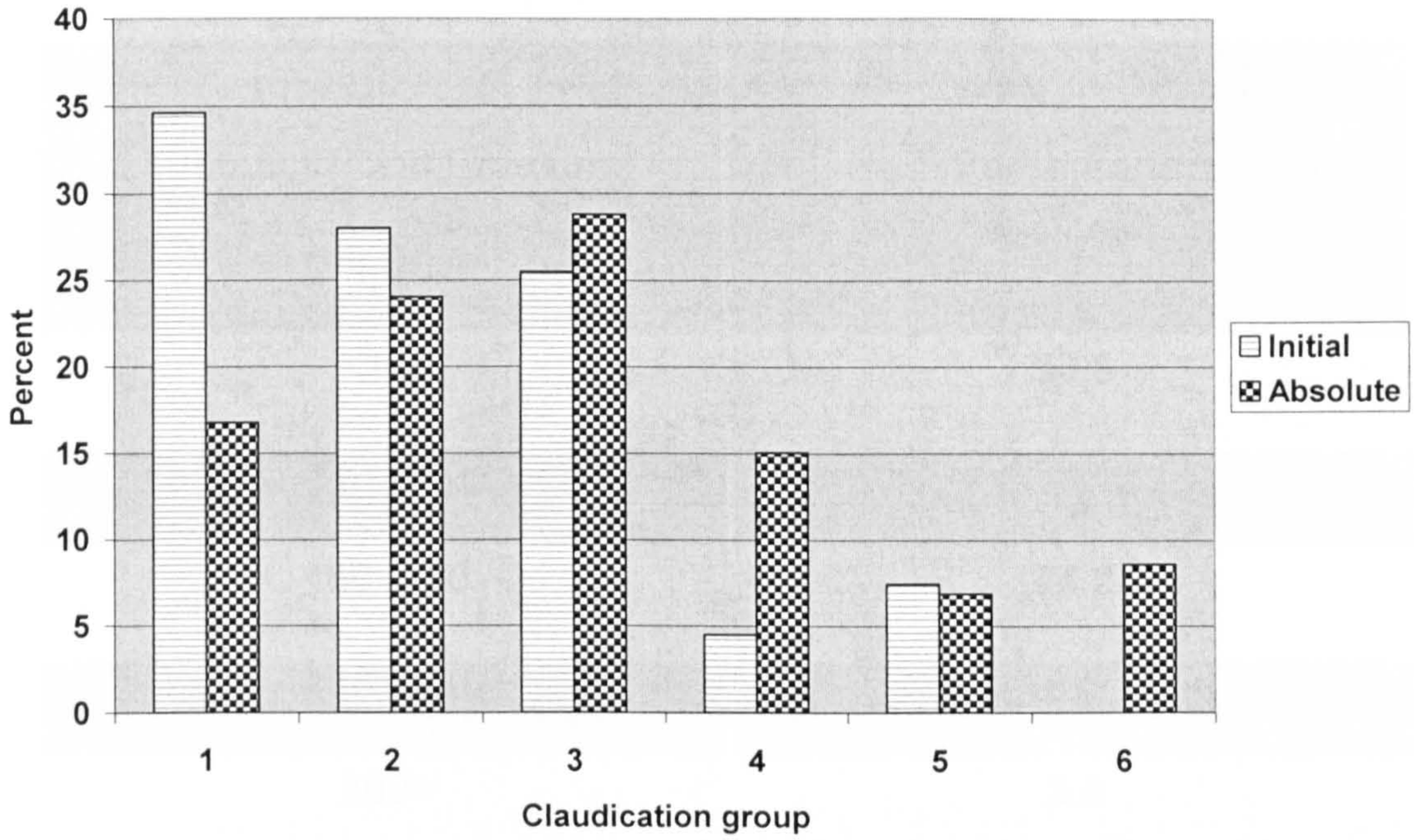


Figure 3.1: Initial and Absolute claudication: pattern of distribution

(1 = 0 – 50 meters, 2 = 51 – 100 meters, 3 = 101 – 200 meters, 4 = 201 – 300 meters, 5 = 301 – 400 meters, 6 = > 401 meters)

GROUP	Distribution (%)
I (ABPI 0.70 – 0.90)	34.8
II (ABPI 0.50 – 0.69)	46.7
III (ABPI 0.3 – 0.49)	16.3
IV (ABPI < 0.3)	02.2

Table 3.4: Ankle Brachial Pressure Index (ABPI) distribution pattern.

Systolic Blood Pressure (mmHg)	Percentage
<140	30.8
140 -160	33.1
160 -180	24.2
180 -200	8.5
200+	3.4

Table 3.5: Distribution pattern of systolic blood pressure

Diastolic Blood Pressure (mmHg)	Percentage
< 90	83.2
90 – 100	11.3
> 100	5.5

Table 3.6: Distribution pattern of diastolic blood pressure

3.2.8. Treatment for Hypertension:

A total number of 258 (54.4%) were receiving treatment for hypertension. 12 (6%) patients with a diastolic BP of more than 90 mmHg were not receiving any medication at all and 25 (12.6%) who were receiving treatment were either not well controlled on their medication or were non-compliant.

3.2.9.Treatment for Hyperlipidaemia: (Table 3.7)

214 (45.3%) were on lipid lowering therapy at the time of enrolment. 44% (208) were on statins and 1.3% (6) were on non-statin lipid lowering therapy.

73% (346) of the recruited population had their cholesterol checked. 193 patients had a cholesterol level more than 5.0 mmol/L. 145 of these patients with a cholesterol level of more than 5.0 mmol/L were not taking any lipid lowering medication. Cholesterol level was in excess of 5.0 mmol/L in 65 (43%) of the 151 patients who were on lipid lowering therapy.

There was a statistically significant difference in cholesterol levels of patients on statins as compared to those without ($p < 0.001$, Kruskal – Wallis test).

3.2.10. Previous Cardiovascular History: (Figure 3.2)

152 (32%) of the total 474 patients had a history of symptomatic cardiovascular disease other than hypertension. Of these 85 (18%) had angina, 68 (14.4%) MI, 34 (7.2%) CVA, 42 (8.8%) coronary artery bypass grafting (CABG) and 17 (3.6%) with prior percutaneous transluminal coronary angioplasty (PTCA).

Patients with prior coronary heart disease (CHD) history (defined as prior MI, angina, CABG or PTCA) were assessed in more detail. 139 (29.3%) patients had prior CHD history. These patients

- were older (p 0.014,chi-square test),
- had higher diastolic blood pressure (p 0.044)
- were more likely to have hypertension ($p<0.001$), and
- were more likely to be smokers (p 0.001).
- were more likely to be on antiplatelets, ACE inhibitors and beta-blockers ($p < 0.001$) (Table 3.8).

Statin use	208 / 474 (44%)
Other lipid lowering therapy	06 / 474 (1%)
Median total cholesterol (mmol/l)- pts on statin	4.9 mmol/L
Mean (sd) total cholesterol (mmol/l)- pts not on statin	5.7 mmol/L

Table 3.7: Lipid lowering therapy and cholesterol levels.

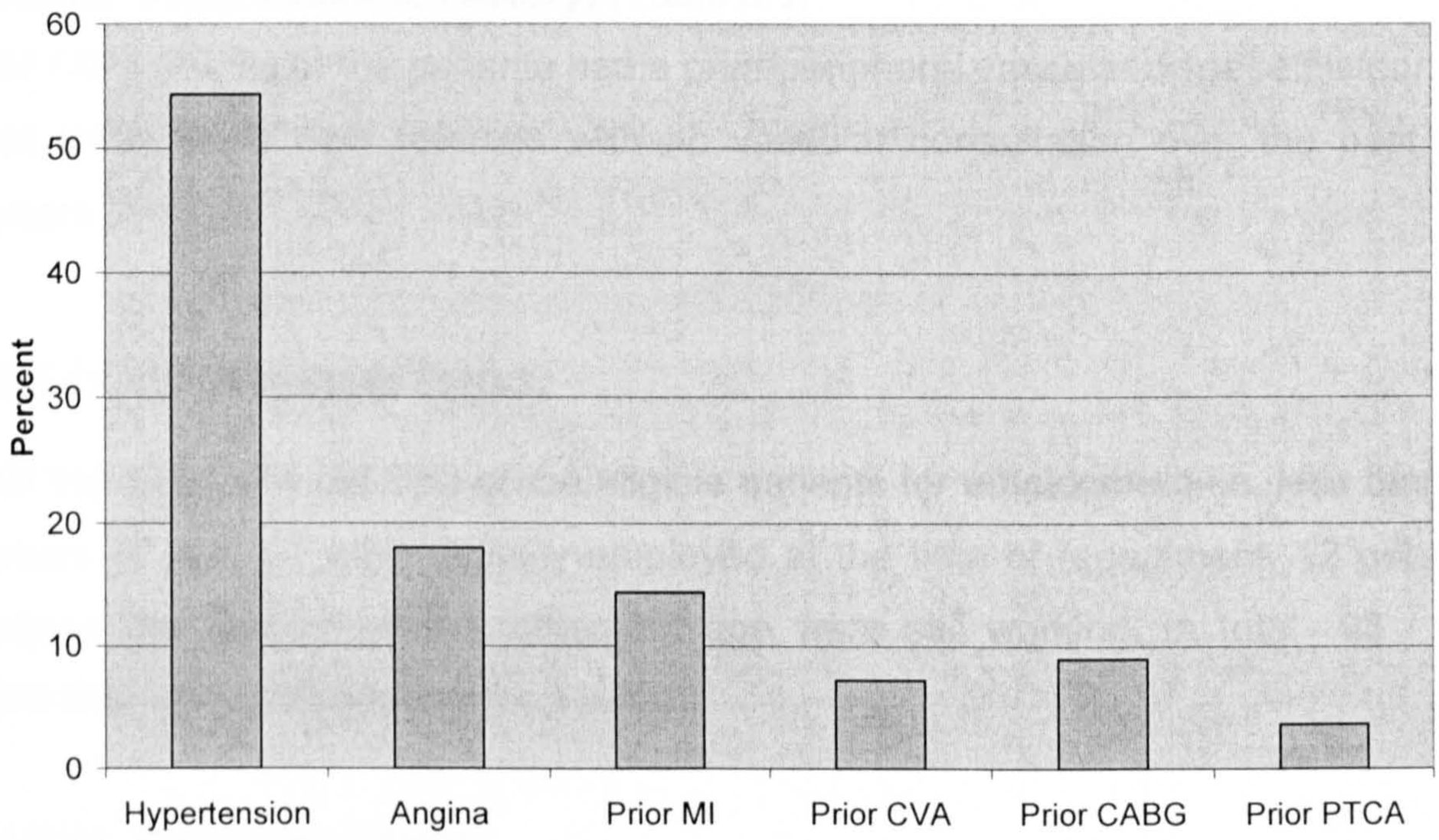


Figure 3.2: Cardiovascular history

- were more likely to be on lipid lowering therapy ($p < 0.001$)

These patients had a lower median cholesterol level as compared to those without a history of CHD (5.1 mmol/L vs. 5.6mmol/L, p 0.013, Kruskal – Wallis test) No association of prior CHD was found with the claudication distances and ABPI.

3.2.11. Diabetes:

94 (19.9%) of the patients were diabetics with 23 (4.9%) being insulin dependent and 71 (15.0%) non-insulin diabetics. Of the non-insulin dependent diabetics, 12 were diet controlled.

3.2.12. Prior Vascular History: (Table 3.9)

34 / 474 (7.2%) of the patients had a prior peripheral vascular disease history.
All these were new referrals with no vascular consultation over the past two years.

3.2.13. Employment Status:

Of the 179 / 474 (37.7%) of the eligible patients for employment i.e. less than 65 years of age, 81 were actively employed at the time of recruitment. 12 persons above the recommended retirement age were still working. In total 93 / 474 (19.6%) were still working for a living.

3.2.14 Education Status:

77/ 474 (16.3%) of the population continued their education beyond the minimum school leaving age and only 47/474 (9.9%) went on to attain a higher degree or a professional qualification.

3.2.15. Smoking:

413 / 474 (87.1%) had history of smoking. 42.1% were smoking at recruitment, 45.2% were ex-smokers and12.7% had never smoked. Median pack years (number of packs multiplied by the number of years smoked. One pack = 20 cigarettes) smoked were 40 (IQR 25 – 56).The total amount of

	Prior CHD (n=139)	No prior CHD (n=334)	p (x^2)
Antiplatelet [n(%)]	121 (87%)	210 (63%)	<0.001
Lipid lowering [n(%)]	96 (69%)	115 (35%)	<0.001
ACE inhibitor [n(%)]	53 (39%)	69 (21%)	<0.001
Beta blocker [n(%)]	49 (36%)	35 (10%)	<0.001
Angiotensin II antagonist [n(%)]	8 (6%)	24 (7%)	0.60

Table 3.8: Use of medication with prior CHD history.

Aortic aneurysm	12 (2.5%)
Internal carotid stenosis (>50%)	13 (2.8%)
Previous peripheral vascular graft	9 (1.9%)

Table 3.9: Prior vascular history.

tobacco smoked by non-cigarette smokers was 15.7 (median) grams per week. Patients who smoked cigars or rolled up their own cigarettes were approximated to an equivalent value of pack years.

113 of the smokers had attempted to stop smoking in the last six months and out of these only 2 were successful. A number of different methods were used as shown in table 3.11. Besides the main methods hypnosis, chewing gum and eating cold turkey were also used.

3.2.16. Antiplatelet Medication: *(Figure 3.4)*

331 (70%) of the patients were on antiplatelets. Of these 66.2% were on Aspirin, 3.6% on Clopidogrel, 2.3% on Dipyridamole and none on Ticlopidine. Eight (2.6%) persons were on both Aspirin and Dipyridamole. Six of these patients had a history of CVA. No person was on Dipyridamole alone. The most common dose of Aspirin was 75mg (90.1%) while 5.4% were on a dose of 150mg and 4.5% on 300mg once daily.

The common reasons for not taking antiplatelets are shown in table 3.12. Others included asthma, taking warfarin, bruising, colitis, history of gastritis and subarachnoid haemorrhage.

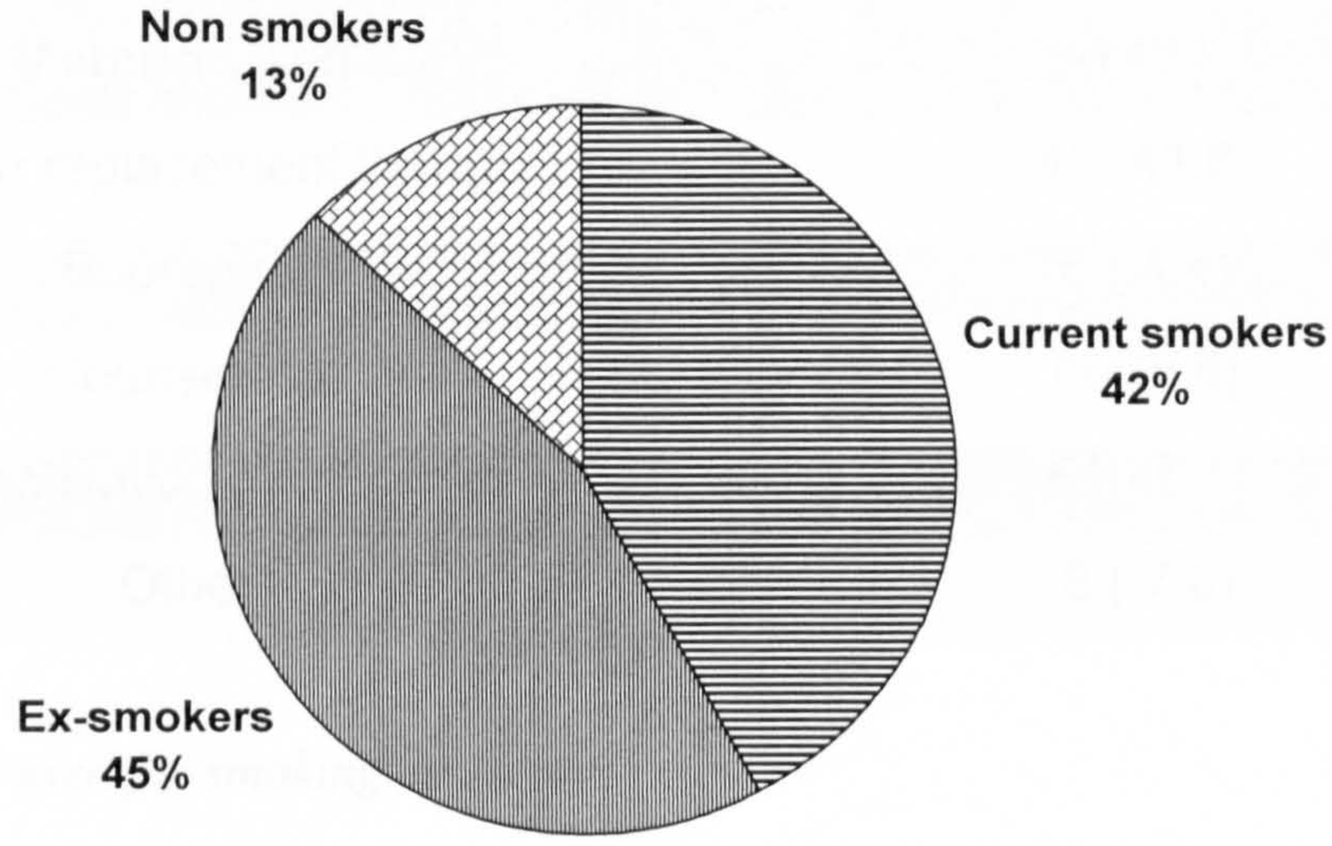


Figure 3.3: Smoking status of the population.

Pack-Years Smoked (Pack x No. of years)	Percentage (%)
1 – 20	19.5
21 – 40	34.6
41 – 60	29.8
61 – 80	8.2
80 +	7.9

Table 3.10: Pack years smoked

Method Used	n (%)
Nicotine replacement therapy	47 (41.6)
Bupropion	5 (4.4)
Counselling	10 (8.8)
Self motivation / Will power	51(45.1)
Other	8 (7.0)

Table 3.11: Methods used for smoking cessation.

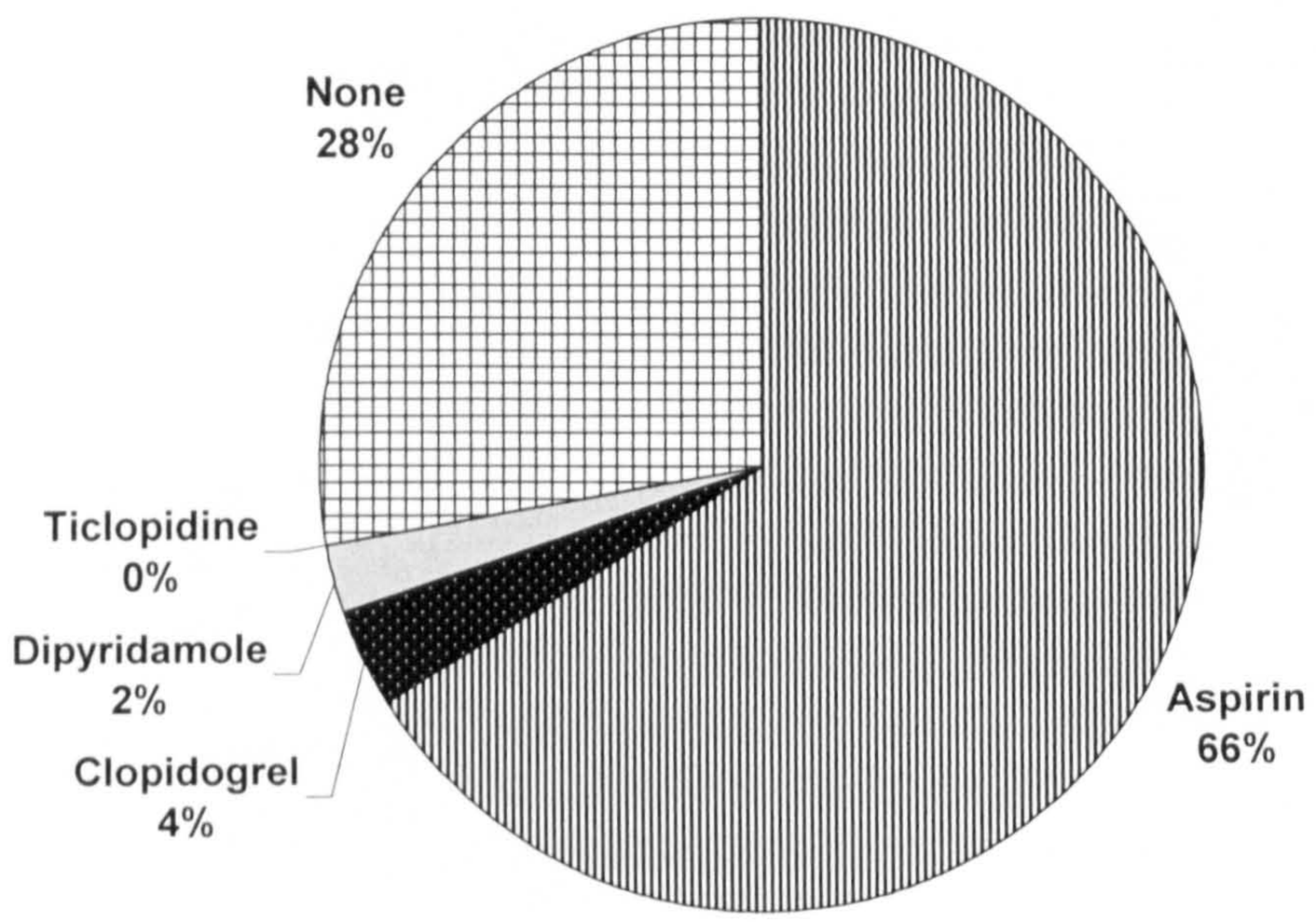


Figure: 3.4: Distribution pattern of antiplatelet medication.

History of ulcers	14 (3.0%)
Indigestion	9 (1.9%)
Allergy	1 (0.2%)
Never prescribed	93 (19.6%)
Non-compliance	4 (0.8%)
Other	21 (4.4%)

Table 3.12: Reasons for not taking antiplatelets.

Age	Female	Male	p-value
<60	18 / 30 (60%)	44 / 76 (57.9%)	</= 1
60-70	23 / 39 (60%)	85 / 112 (75%)	0.20
>70	65 / 89 (73%)	97 / 127 (76.4%)	</= 1
Total	106 / 158 (67.1%)	225 / 315 (71.4%)	</= 1

Table 3.13: Antiplatelet use by age and sex.

3.2.17. Laboratory Investigations:

3.2.17.1. Total Cholesterol: (Figure 3.5, Table 3.14)

346 / 474 (73.1%) patients had their cholesterol checked with a median of 5.4mmol/L (IQR 4.5 – 6.2). Median cholesterol in patients on lipid lowering medication was 4.9mmol/L and that without such medication was 5.7mmol/L.

3.2.17.2. High Density Lipoprotein (HDL):

HDL was checked in 180 / 474 patients (38%) with a median 1.3mmol/L (IQR 1.11 – 1.6).

3.2.17.3. Low Density Lipoproteins (LDL):

68 / 474 (23.7%) patients had their LDL levels checked. Median LDL was 3.2 (IQR 2.3 – 3.87).

3.2.17.4. Total cholesterol : HDL Ratio:

This was calculated in 180 / 474 (38%) of the patients. Median ratio was 3.87 (IQR 3.1 – 4.8). This was 3.5 for patients on lipid lowering therapy as compared to 4.1 who were without such medication.

3.2.17.5. Other blood tests:

Other baseline laboratory investigations are shown in table 3.15.

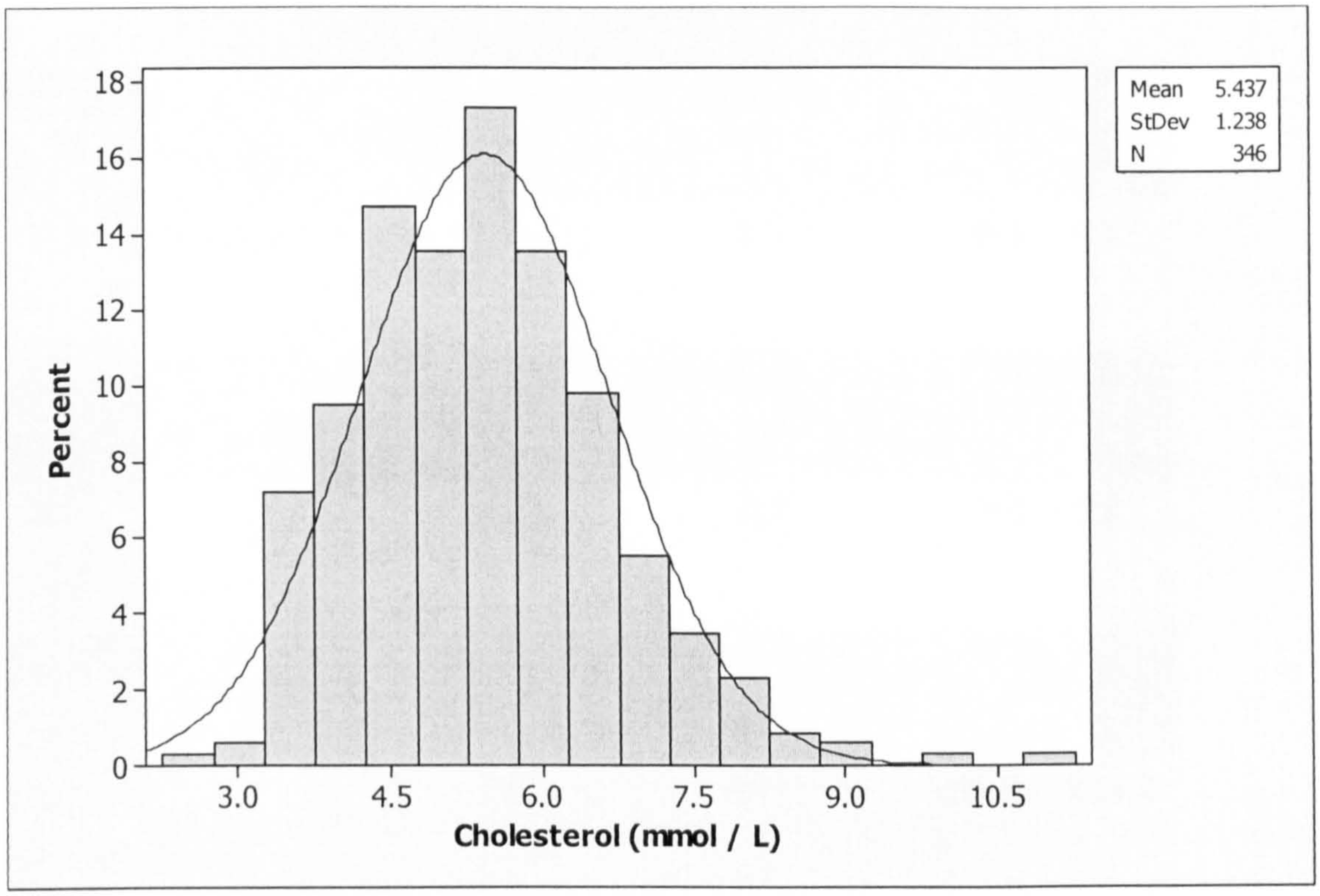


Figure 3.5: Total cholesterol distribution.

Cholesterol Level (mmol/L)	Percentage (%)
< 3.5	4.6
3.5 – 5.0	35.0
5.0 – 6.5	43.9
> 6.5	16.5

Table 3.14: Distribution pattern of total cholesterol.

Variable	Percent checked	Median	IQR
Total Cholesterol (mmol/L)	73.1	5.4	4.5 – 6.2
HDL (mmol/L)	38.0	1.3	1.1 – 1.6
LDL (mmol/L)	23.7	3.2	2.3 – 3.9
Glucose (mmol/L)	55.2	5.3	4.8 – 6.1
Creatinine (mmol/L)	67.1	96.0	83.0 – 109.0
Haemoglobin (mg/dl)	63.1	14.4	13.4 – 15.3
MCV	60.3	91.1	88.2 – 94.8
Platelets	63.1	254	209 – 304
White Cell Count (x 10^9/L)	62.6	8.1	7.1 – 9.4
CRP	14.3	3.6	2.9 – 6.7

Table 3.15: Baseline laboratory investigations

3.2.18. Drug History:

A medication history of several cardiovascular drugs was taken and is summarised in table 3.16.

Drug	Number	Percentage
Statins	208	44.0
Non-statins	06	1.3
Warfarin	17	3.6
ACE Inhibitors	122	25.8
B-blocker	84	17.8
Ca-antagonist	107	22.6
Angiotensin II antagonist	32	6.8
Nitrate	54	11.4
Vasodilator	39	8.2
Quinine	25	5.3
Diuretic	136	28.8
Oral hypoglycaemics	57	12.0
Insulin	25	5.3
Hormone Replacement Therapy (HRT)	12	2.5

Table 3.16: Medication used by the recruited patients.

3.3. Discussion:

Despite a high prevalence of PAD in the community, awareness of the condition and appropriate risk factor management in the primary care is not optimal [29, 151]. Some risk factors are associated more than others either with the incidence or the progression of PAD. In the present study we have accumulated risk factor data on claudicants at their initial visit to a vascular clinic in UK and have primarily documented the patient characteristics and prevalence of atherosclerotic risk factors in this population. This visit also audited the risk factor management at primary care level. Patient centred outcomes were also evaluated which are discussed in more detail in chapter 7.

Increasing age has been shown to be a risk factor for the development of PAD [19, 25, 27]. In the Framingham study each 10-year increment in age carried a 2.6-fold increase of developing PAD [39]. PAD has a predilection for the male population [60, 109, 112]. In this series more than 65% of the claudicants were above 65 years of age and 65% were men.

The usefulness of ABPI as a marker of generalised atherosclerosis is well documented [111, 137]. The Cardiovascular Health Study and the Framingham study have reported a graded inverse relationship of decreasing ankle-brachial index to cardiovascular disease end points and risk factor levels [39, 111]. In our study ABPI was found to have a significant association with angina, BMI, initial and absolute claudication distances and total cholesterol. An ABPI value of 0.78 has been linked with an approximate 30% 5-year risk of MI, ischemic stroke, and vascular death [29, 220]. Mean ABPI in this study was 0.62 (+/- 0.16). 65% had an ABPI of less than 0.70.

Antiplatelet agents are less frequently prescribed in PAD patients as compared to patients with a history of CAD or CVD [113, 221]. In this series 21% of the patients were not receiving any antiplatelet therapy. Patients with history of angina (p 0.001), MI ($p < 0.001$) or cardiac intervention (p 0.002) were more likely to be on antiplatelet therapy. Also patients on lipid lowering therapy (p 0.048) or antihypertensive therapy (p 0.047) or both (p 0.024), were more likely to be taking antiplatelet agents.

Smoking cessation has been shown not only to reduce disease progression but also the mortality risk in PAD [54, 222]. Nicotine replacement treatment approximately doubles the cessation rate in unselected smokers [223, 224]. Bupropion has a similar benefit when used with intensive support [152]. These are available on NHS and every patient with claudication should be offered one of the two as well as the appropriate counselling. Different delivery profiles available for the nicotine replacement may improve its compliance and effectiveness. Smoking cessation classes are helpful and recommended but therapies like acupuncture, hypnotherapy and 'aversive smoking' are of little benefit [225-227]. Unfortunately, rates of cessation are not encouraging and remain as low as 13% at two years [222].

87% of the patients had a history of smoking in this series; 42% current and 45% ex-smokers. Of the current smokers only 23.9% (n=113) had tried to stop within the three months of enrolment. 46 used nicotine, 5 bupropion and only 10 were counselled. There is an increasing need to counsel these patients at a younger age. The number of current smokers as compared to ex- or non-smokers declined as the age progressed ($p < 0.001$). Males were more prone to smoking whether at present or in the past (p-values 0.011 and 0.12, respectively).

Up to 20% of patients with intermittent claudication may have diabetes and approximately 50% of cases may be undiagnosed at the time of presentation [228]. It is a powerful risk factor for progression to critical limb ischaemia [229].In this series, 18.3% were diabetics. Only 45.5% had their blood glucose checked and 42% of these were known diabetics. As evident from the results blood glucose was not very well controlled in the diabetics and 6.5% of the 'non-diabetic' patients had a glucose level above7.0 mmol/L and needed further evaluation.

The United Kingdom prospective diabetes study has shown that intensive glycaemic control reduces the microvascular complications of type 2 diabetes [188]. Surgical intervention in diabetics may not achieve the desirable response, therefore a greater benefit from strict glycaemic control may be expected in this group for cardiovascular disease as compared to non-diabetic population [230]. Risk factors profile and management in our series was not much different as

compared to non-diabetic claudicants i.e., antiplatelet therapy was 73.6% vs. 70.7%, lipid lowering therapy was 63% vs. 63% and the number of ex-smokers was 50 vs. 47%.

The Heart Protection Study has shown that lowering total cholesterol and low density lipoprotein cholesterol by 25% with a statin reduces cardiovascular mortality and morbidity in patients with PAD by around a quarter, irrespective of age, sex, or baseline cholesterol concentration [68]. All patients should be on a statin. A protective effect of statins has been suggested that is independent of the total cholesterol and LDL levels which is likely to be mediated by influencing the inflammatory markers, i.e. C-reactive protein [177]. In our study, only 45% of the patients were on lipid lowering therapy. Patients with PAD only, were less intensively managed for hyperlipidaemia as compared to patients with prior history of MI or coronary intervention ($p = 0.012$ and 0.011, respectively). Lipid measurements were being done routinely only in 14 of the 23 centres. Patients on lipid lowering therapy had lower cholesterol and LDL levels as compared to those without such therapy (total cholesterol 5.0 vs. 5.8 mmol/L and LDL 2.7 vs 3.5 mmol/L, $p < 0.001$). 18% of the patients with a cholesterol level higher than 5.0 mmol were on lipid lowering therapy while 75% of the patients with cholesterol level higher than 5 were not receiving any treatment. It is important to mention over here that statin doses were not recorded and it is possible that many of the patients did not recieve the currently recommended therapeutic doses (e.g. 40mg of simvastatin rather than 10 mg.) and this may partly explain the inadequate control of lipid profile. In general practice most of the patients receive less than optimal dose of simvastatin; this may be inadequate and thus the ultimate benefit of such therapy is limited. However caution should be exercised in patients with hepatic dysfunction or myalgia. Liver function test and creatine kinase should be checked.

The Edinburgh, Basle and Framingham studies have shown an increased PAD risk in hypertension by two to four fold and is particularly associated with the development of severe disease [39, 45, 48, 61]. Control of hypertension was inadequate in our series. 54.7% of the patients had a history of hypertension and of these 73% of these had a reading higher than the British Hypertension Society

recommended high normal reading of 140/90 mmHg. Although these were single readings, decreasing the systolic pressure by 10mmHg (average declined described in hypertensive studies for the third reading as compared to first [231, 232], still 62% would have their systolic BP more than 140 mm Hg.

As expected the systolic pressure increased with age (p 0.02). Overall, approximately 77% of the patients receiving antihypertensive therapy had poor control of high blood pressure and around a quarter of the patients with a blood pressure of more than 140/90 were not receiving any antihypertensive medication. Patients above 70 were more likely to be on antihypertensive treatment (p 0.001) as compared to below 60. In general, patients with PAD only were not less frequently treated for high blood pressure than patients with documented CAD or CVD. This may be related to general suboptimal antihypertensive treatment of the entire group. These patients need further follow up and a better control of their blood pressure.

Antiplatelet agents are known to reduce the risks of CAD, CVD and vascular death [50, 233]. Antiplatelet therapy is therefore recommended for secondary disease prevention in patients with vascular diseases [234]. This study demonstrates the lower rate of administration of antiplatelet therapy in patients with PAD alone compared with those who had previous cardiovascular history and were on treatment for hypertension and hyperlipidaemia ($p < 0.001$). Around a quarter of the patients had never been prescribed any antiplatelet agent.

The Heart Outcomes Prevention Evaluation (HOPE) study has shown that ramipril, an angiotensin converting enzyme inhibitor, reduces cardiovascular morbidity and mortality in patients with peripheral arterial disease by around 25%. The observed risk reduction of adverse outcomes in PAD could not be accounted for by the relatively modest reduction in blood pressure. It is therefore expected that most PAD patients would benefit from an angiotensin converting enzyme inhibitor, provided that treatment is not associated with a deterioration of renal function due to occult renal artery stenosis. Further, use of beta blockers has not been associated with progression or worsening of IC [186]. In this study 46.6% of the patients receiving antihypertensive therapy were on ACE inhibitors and 21.4% on beta blockers.

These data confirm that the PAD population in the UK carries a high atherosclerosis risk factor burden and ischaemic risk. This increased mortality risk can perhaps be limited by lifestyle alterations and drug therapy within the setting of general practice. Risk factor modification in patients with PAD in the UK appears currently inadequate. These findings suggest that there is a need for increased awareness of risk factor assessment and its aggressive management at a primary care level.

Chapter 4

Age and peripheral arterial disease

4.1. Introduction

Increasing age is associated with an increased incidence and prevalence of PAD [21, 24, 30, 36, 47, 63, 139]. PAD is not common below the age of 50. The weighted mean incidence of intermittent claudication as based on large population based studies increases from 2/1000/year at age 35-39 to >7 /1000/year at age above 65 [32]. The risk of developing PAD can be predicted by age [147, 231]. The prevalence of PAD ranges from 3% in patients age >55, to 11% in patients age >65, to 20% in those age 75 and older [232]. This may be a result of prolonged exposure to causative risk factors. Majority of this prevalence is asymptomatic or if symptoms do occur in the elderly, this is taken as a part of being growing old; thus delaying the presentation to a clinician. Older patients with PAD are at high risk for coronary and cerebrovascular events and need to be closely monitored for the many presentations of systemic atherosclerosis.

Early-onset PAD is typically associated with multiple cardiovascular risk factors. The majority of these are smokers, with a strong family history of cardiovascular disease, usually presenting with IC. Often like the elderly these symptoms are attributed to other more common causes of leg pain in the young.

4.2. Methods:

474 consecutive patients with IC were recruited as per the inclusion criteria of the study to 24 vascular units across the United Kingdom (see section 2.2.2.2.1.). Age was documented at the initial visit. Use of risk factor therapy was recorded and analysed. Progression of disease patterns were noted over six months in the three different age groups.

4.3. Results

For analysis the population was stratified into three different age groups.

The relationship of age to different variables is described below.

Age	Age Group	Frequency
< 60	1	106 / 474 (22.3%)
60 – 70	2	152 / 474 (32.1%)
> 70	3	216 / 474 (45.6%)

Table 4.1. Distribution pattern of population as per age

Age Group	Female	Male
< 60	30 / 106 (28.3%)	76 /106 (71.7%)
60 – 70	40 / 152 (26.3%)	112 / 152 (73.7%)
> 70	89 / 215 (41.2%)	127 / 215 (58.8%)

Table 4.2. Sex distribution as per age.

Age Group	Body Mass Index (median)
< 60	25.67
60 – 70	27.04
> 70	25.66

Table 4.3. BMI in different age groups.

4.3.1. Sex: (Table 4.2)

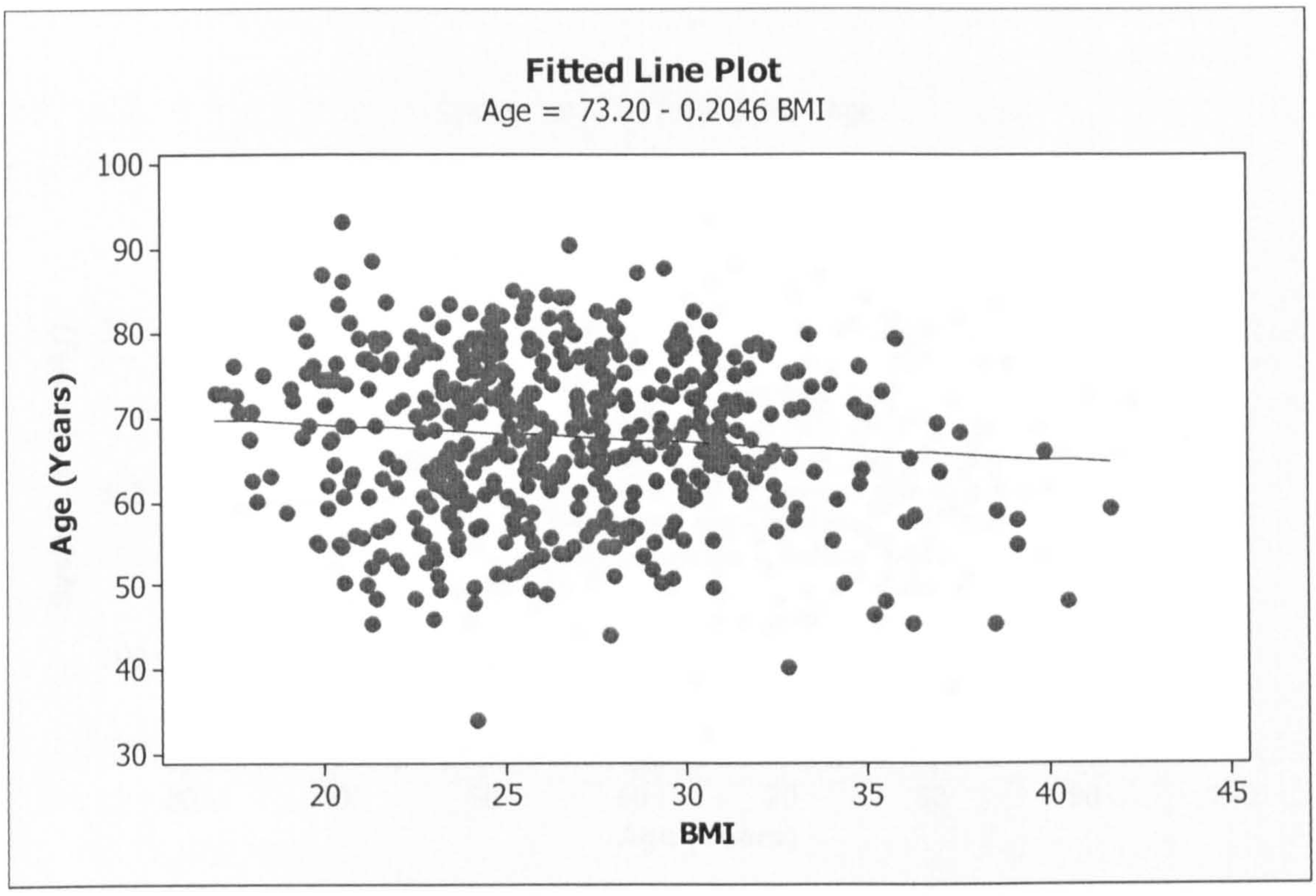
The female to male distribution in different age groups is shown in table 4.2. The relative proportion of the female population increased as the age progressed to above 70 (p 0.005, chi square test).

4.3.2. Body Mass Index (BMI): (Table 4.3)

The median BMI in this population in different age groups is shown in table 4.3. Regression of this data showed a negative correlation between increasing age and BMI (age = 73.2 – 0.20 BMI). This is shown graphically in figure 4.1.
There was no significant association among the three age groups in relation to BMI (p 0.058, Kruskal Wallis test).

4.3.3. Blood Pressure: (Table 4.4) (Figure 4.2)

The median blood pressure was 155/80 mmHg at recruitment and 150/82 at six month follow up. As per different age groups the median blood pressure is shown in table 4.4.
As expected the systolic blood pressure increased with age (systolic BP = 137.0 + 0.26 age) and this was found to be statistically significant for different age groups (p 0.019, chi-square test).
However diastolic blood pressure did not show a similar trend and infact decreased in this population as age increased (diastolic BP = 91.4 – 0.14).
In all 54.3% were receiving treatment for hypertension. In the elderly population more patients were likely to be on treatment for high blood pressure ($p < 0.0001$) as compared to below 60.
Treatment for high blood pressure in relation to age is shown in table 4.5 and figure 4.3.

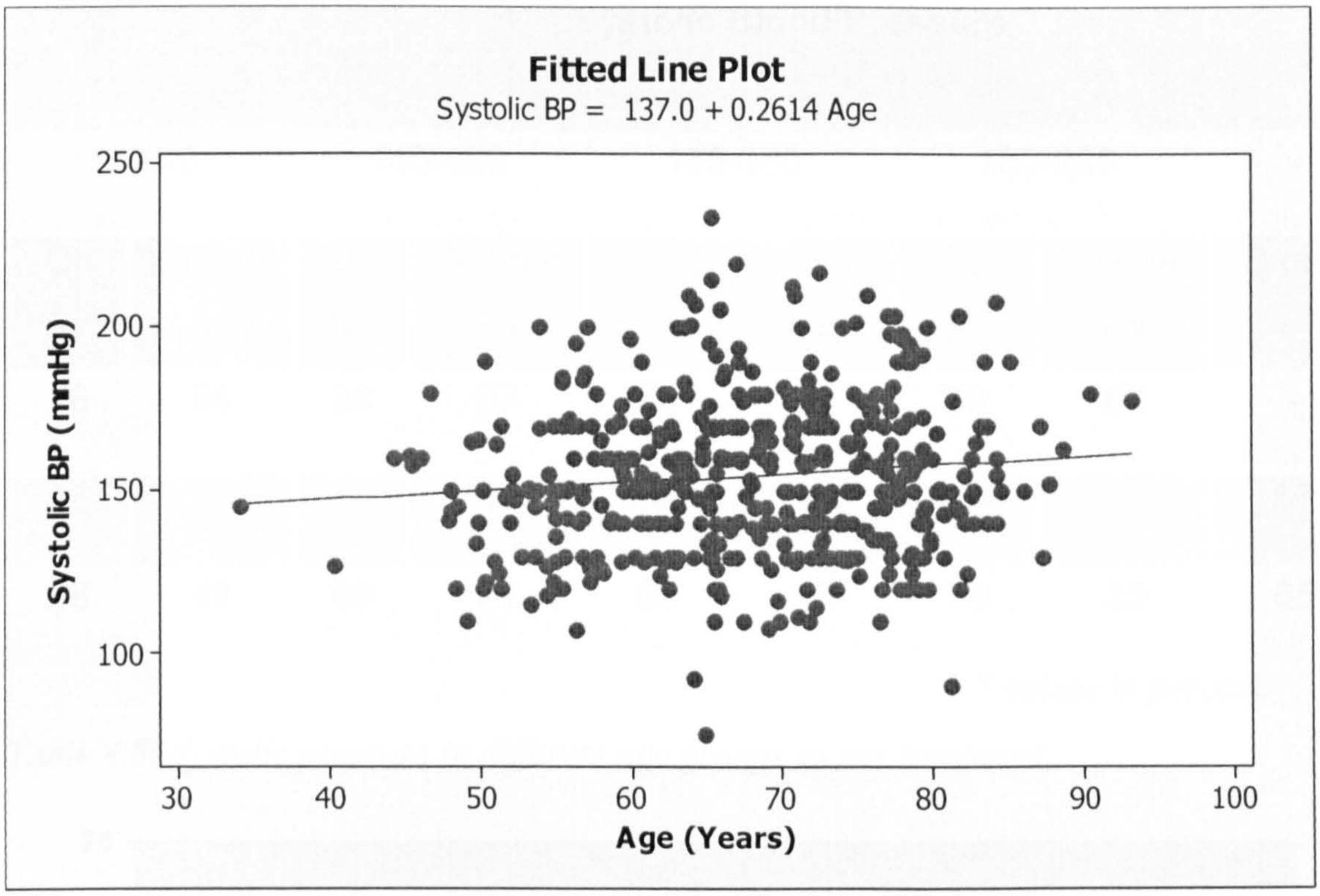


(Pearson correlation of BMI and Age = -0.100, P-Value = 0.031)

Figure 4.1. Correlation of BMI with age.

Age Group	Median Blood Pressure (mmHg) at initial visit	Median Blood Pressure (mmHg) at follow-up
< 60	150 / 83	146.5/82.5
60 – 70	156 / 80	150/81
> 70	155 / 80	152/82

Table 4.4. Blood pressure at initial visit and at follow-up as per age group.



(Pearson correlation of Systolic BP and Age = 0.108, P-Value = 0.019)

Figure 4.2. Systolic pressure trend as per increasing age.

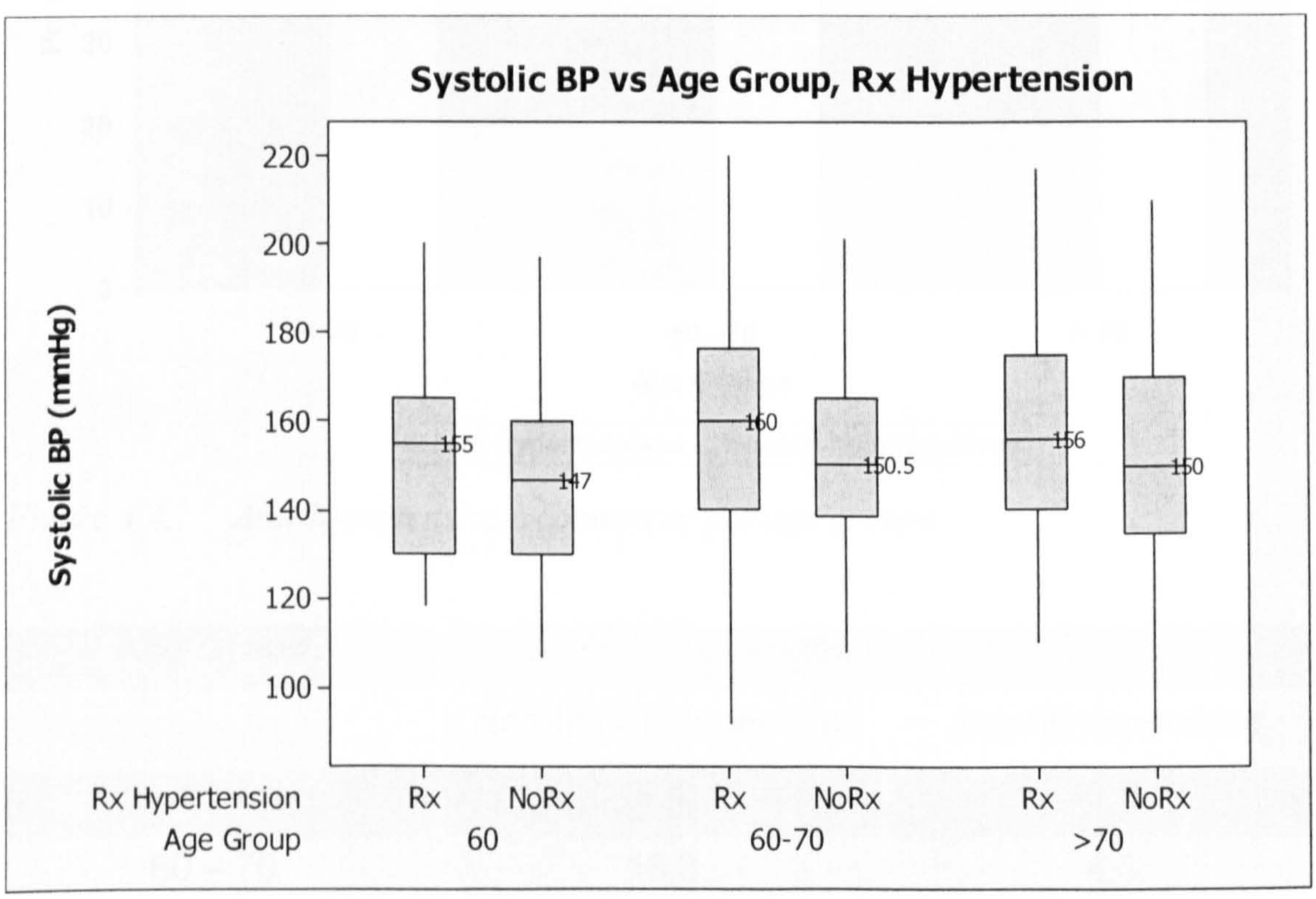


Figure 4.3: Systolic blood pressure in relation to treatment or no treatment in different age groups.

Age Groups	Systolic Blood Pressure									
	< 140		140-160		160-180		180-200		> 200	
	On Rx	Without Rx	On Rx	Without Rx	On Rx	Without Rx	On Rx	Without Rx	On Rx	Without Rx
< 60	36	64	33	67	50	50	33	67	-	-
60 – 70	43	57	48	52	59	41	73	27	57	43
> 70	58	42	69	31	63	37	75	25	65	35

** values in percent.*

Table 4.5: Systolic pressure in different age groups as per treatment.

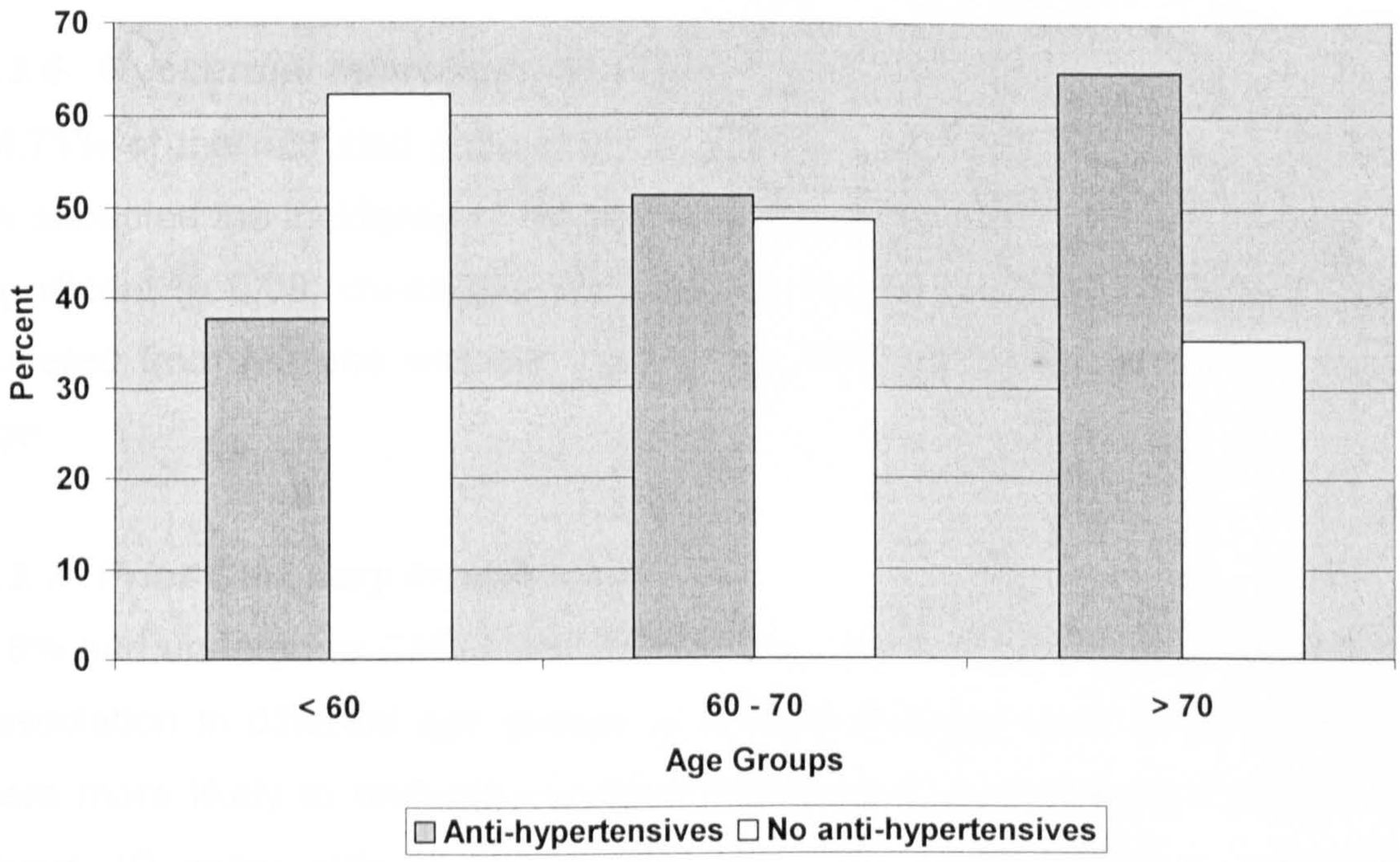


Figure 4.4. Anti-hypertensive treatment as per age groups.

Age Group	Diabetes Mellitus (%)	
	Non-Insulin dependent	Insulin dependent
< 60	9.4	5.7
60 – 70	18.3	4.6
> 70	15.3	4.7

Table 4.6. Distribution pattern of diabetics among different age groups.

4.3.4. Diabetes: (Table 4.6)

The distribution of diabetes in relation to age in this population is shown in table 4.6. Although there were more insulin dependent diabetics above 60 but no significant correlation of any of the age groups to history of insulin / non-insulin dependent diabetes was observed.

4.3.5. Angina: (Table 4.7)

Overall 22.5% patients suffered from angina. The younger patients had lower incidence of angina as compared to above 60, however, this was statistically not significant (p 0.08, chi-square test).

4.3.6. Myocardial Infarction (MI):(Table 4.8)

14.71% of the recruited population had history of MI with a median age of 68.5. As expected the incidence of MI with older age was higher though statistically not significant (p 0.08, chi-square test). By the end of six months five patients had suffered from MI; one was a 61 year old while others were above 70 years of age.

4.3.7 Prior Coronary Intervention:

8.8% had undergone CABG and 3.6% PTCA. There was no significant pattern of association in different age groups (p 0.24, chi-square test). 60 – 70 years old were more likely to undergo coronary intervention as compared to below 60 or above 70 years olds (3.3% vs. 0% and 1.3% at six months, respectively), however this was not statistically significant.

4.3.8. Prior Cerebrovascular Accident (CVA):

7.2% had history of CVA with a median age of 71, youngest being 55 year old and eldest 87. There was no significant difference (p 0.25, chi-square test). 1.5% of the 60 – 70 years old developed CVA over six months.

Age Group	Prevalence of angina (%)
< 60	12.3
60 – 70	18.4
> 70	20.5

Table 4.7. Distribution pattern of angina in different age groups.

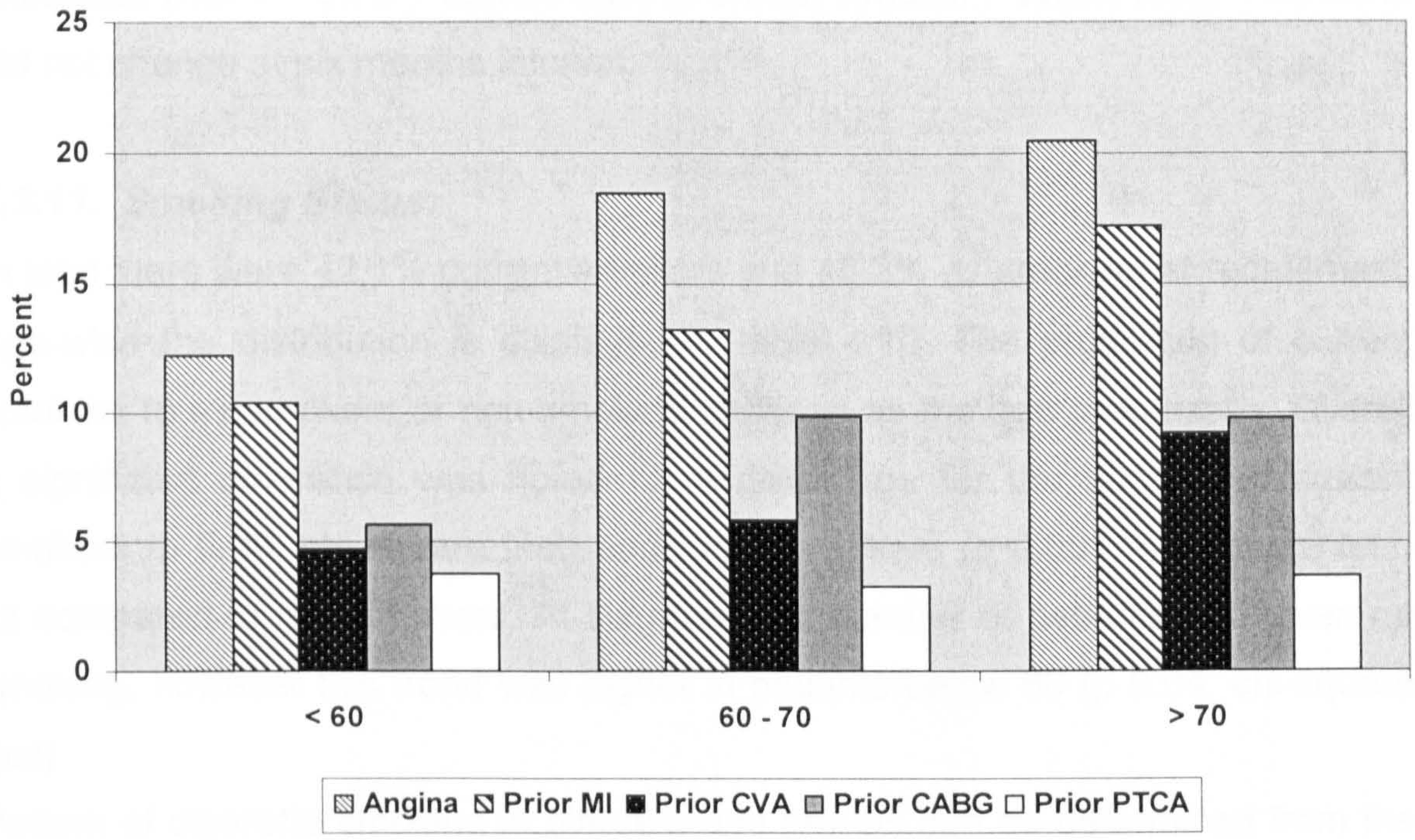


Figure 4.5. Pattern of previous cardiovascular history in different age groups.

Age Group	Prevalence of MI (%)
< 60	10.4
60 – 70	13.2
> 70	17.2

Table 4.8: History of MI in different age groups.

4.3.9. Claudication distance:

The distribution of initial and absolute claudication distances in different age groups is shown in table 4.9. No change was noted in relation to claudication distance in different age groups and improvement at six months was uniform for this population.

4.3.10. Ankle Brachial Pressure Index (ABPI):

The lower of the two ABPI values was taken. Its distribution in relation to age groups was as shown graphically in figure 4.5. ABPI decreased as the age group increased (ABPI = 0.78 – 0.0024 age) (p 0.008, Kruskal – Wallis test). This trend did not change at six months interval.

4.3.11. Smoking Status:

In total there were 42.1% current smokers and 45.2% ex-smokers at recruitment. Age-wise the distribution is displayed in table 4.10. The proportion of current smokers to ex-smokers or non-smokers declined as the age progresses. Overall a significant difference was noted for a given age for the number of current smokers (p 0.00, chi-square test) and for ex-smokers (p 0.001, chi-square test) as compared to non-smokers. At six months a number of patients had given up smoking, however this trend was higher in patients below 60 (p 0.04, chi-square test).

Pattern of cigarette smoking in different age groups can be determined from the number of pack years smoked by each individual.

No specific pattern of distribution was observed between the pack years smoked and age (p 0.47, Kruskal – Wallis test).

Age Group	Claudication Distance (meters) (Median) at 0 month		Claudication Distance (meters) (Median) at 6 months	
	Initial	Absolute	Initial	Absolute
< 60	100	150	150	200
60 – 70	100	150	150	200
> 70	100	150	150	200

Table 4.9: Initial and absolute claudication distances at 0 and 6 months.

:

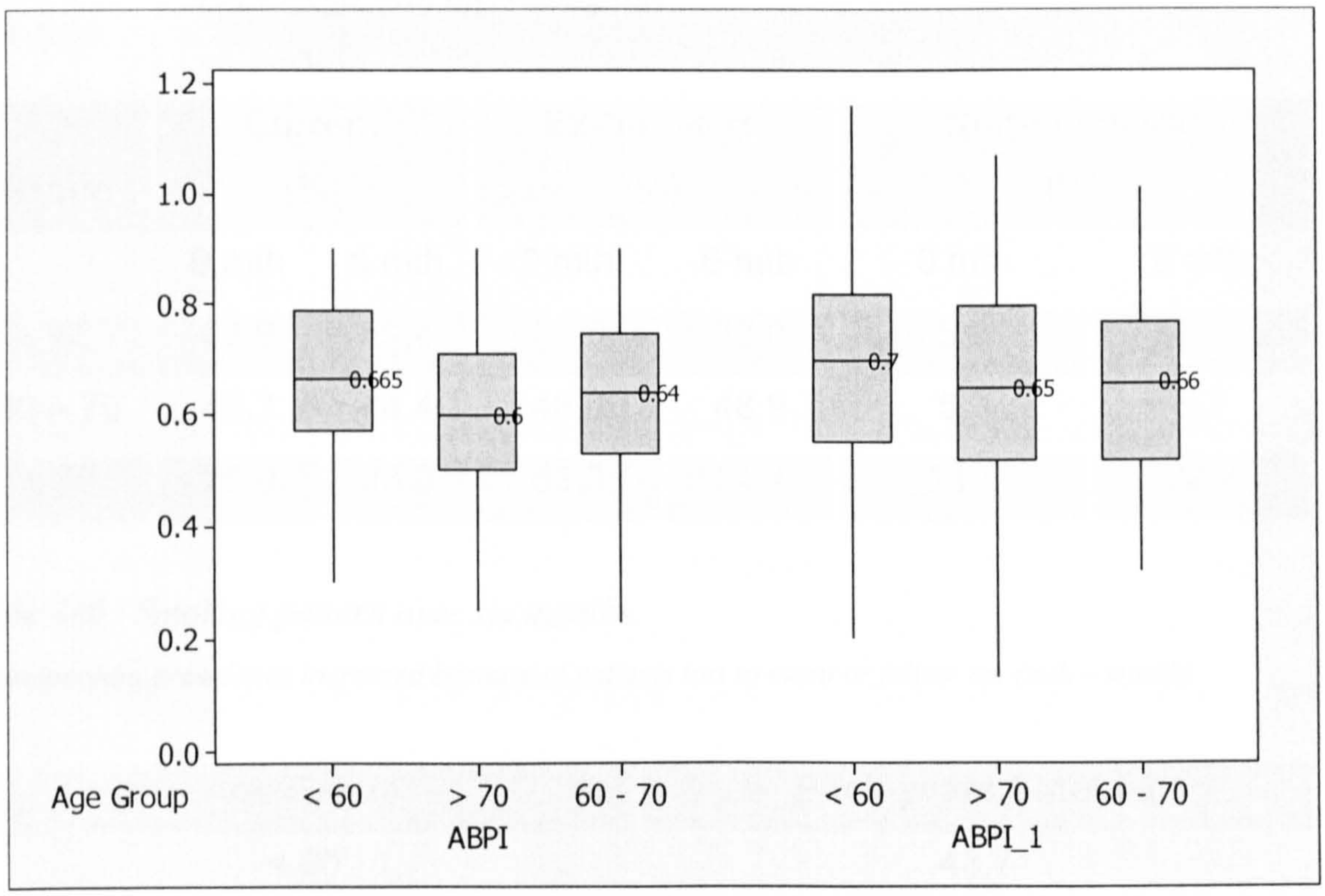
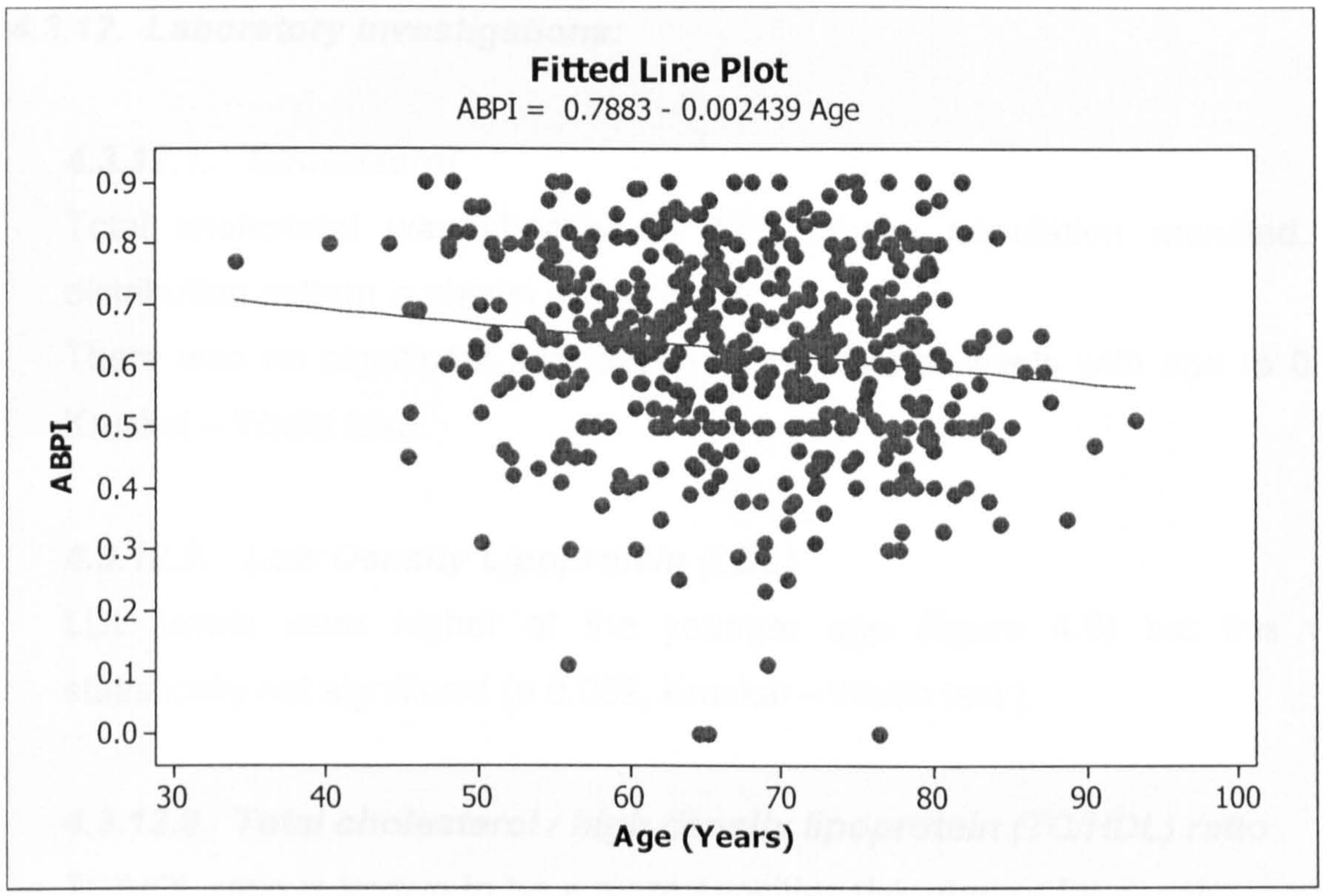


Figure 4.6: ABPI as per age groups at recruitment and at six months.

(ABPI – ankle brachial pressure index at 0 months, ABPI_1 – ankle brachial pressure at 6 months. Boxes represent the interquartile range with median values displayed; whiskers represent range.)



(Pearson correlation of ABPI and Age = -0.147, P-Value = 0.001)

Figure 4.7: ABPI trend with increasing age.

Age Group	Current (%)		Ex-Smokers (%)		Non-smokers* (%)	
	0 mth	6 mth	0 mth	6 mth	0 mth	6 mth
< 60	67.9	59.4	25.5	33.0	6.6	7.6
60 – 70	46.7	44.4	48.0	48.9	5.3	6.7
> 70	26.0	23.3	53.0	54.4	21.0	22.2

Table 410. Smoking pattern over six months.

** Non-smokers prevalence increased because of patients lost to event or follow up. (mth – month)*

Age Group	Pack-years Smoked
< 60	43.7
60 – 70	46.5
> 70	39.8

Table 4.11: Pack years smoked as per age group.

4.3.12. Laboratory Investigations:

4.3.12.1. Cholesterol

Total cholesterol was checked in 73% of the population recruited. Its distribution pattern is shown in figure 4.8.

There was no significant association of cholesterol levels with age (p 0.46, Kruskal – Wallis test).

4.3.12.2. Low Density Lipoprotein (LDL)

LDL levels were higher at the younger age (figure 4.9) but this was statistically not significant (p 0.052, Kruskal – Wallis test).

4.3.12.3. Total cholesterol / high density lipoprotein (TC/HDL) ratio

TC/HDL ratio is known to be a more sensitive risk marker for development of atherosclerosis. Age-wise pattern of distribution is represented in the table 4.12.

Again no significant association was noted between TC/HDL ratio and age (p 0.40, Kruskal – Wallis test).

4.3.13. Lipid lowering therapy:

Treatment for hyperlipidaemia was variable. 43.13% were receiving lipid lowering therapy. Percentage in each group taking lipid lowering therapy is shown in table 4.13.

Younger patients were less likely to be on lipid lowering therapy as compared to age above 60 (p 0.004, chi-square test) at the initial visit. The trend significantly improved in all age groups by six months ($p < 0.001$, chi-square test).

Further breakdown of the patients who were taking lipid lowering therapy at recruitment, as per their cholesterol levels was carried out as shown in table 4.14.

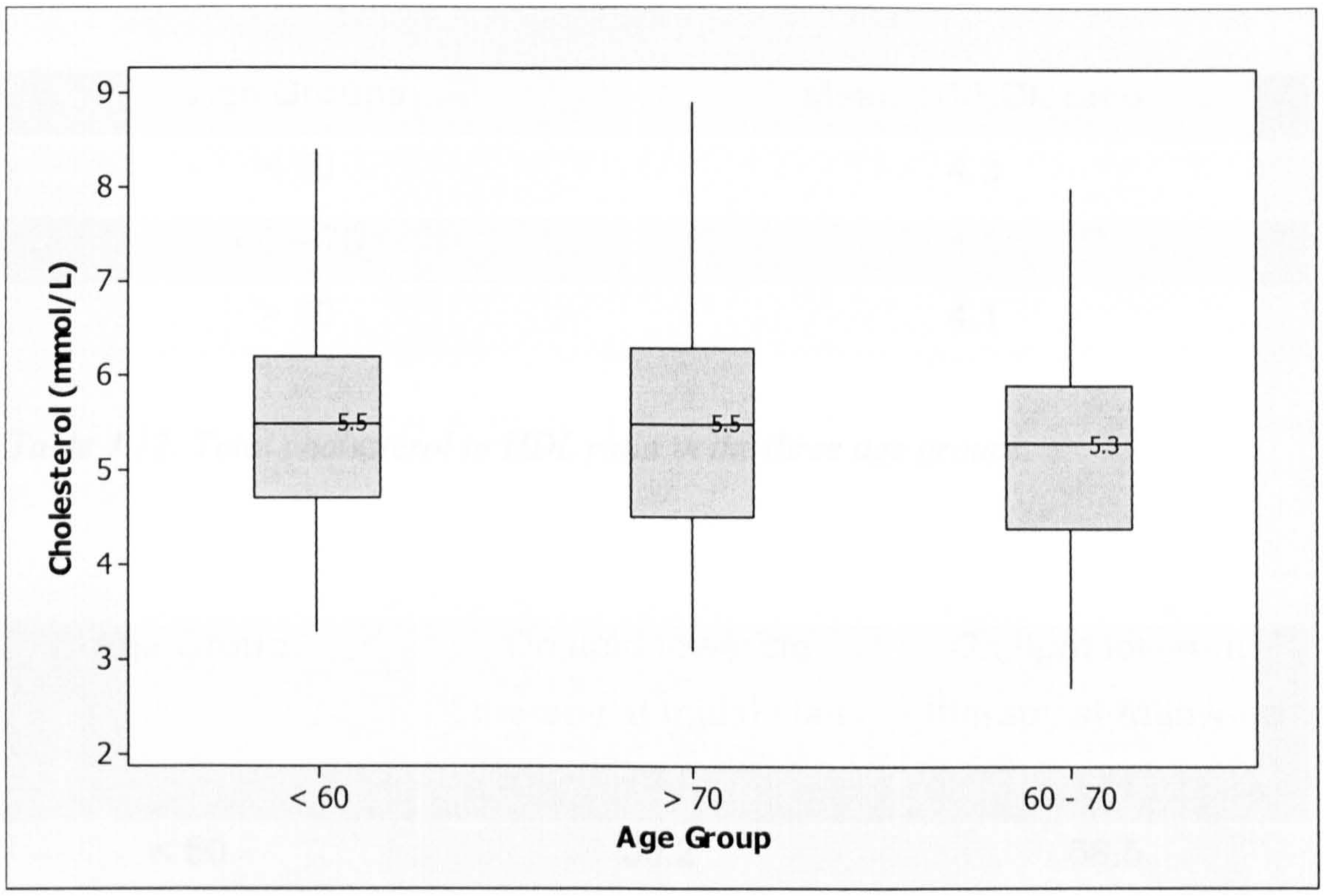
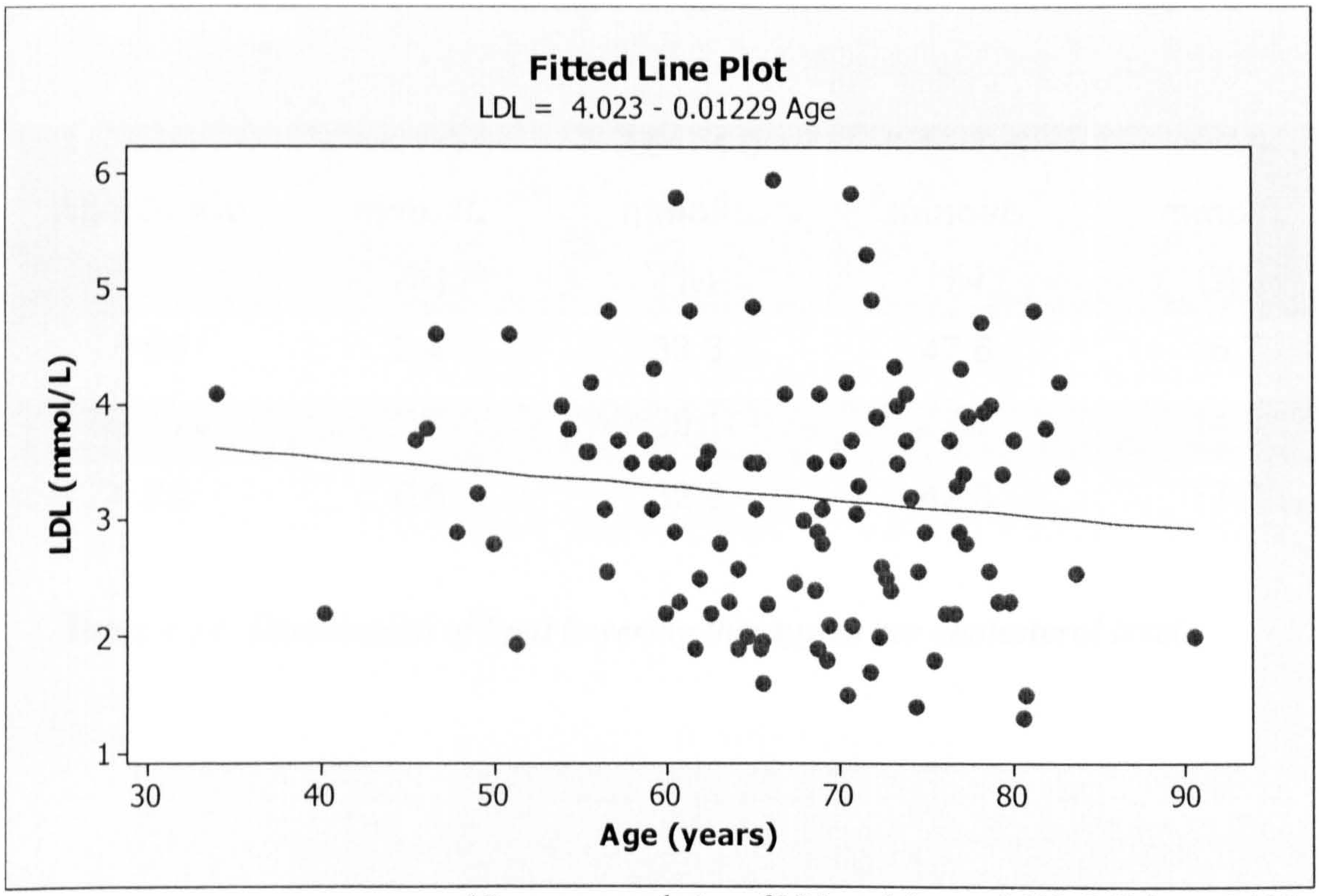


Figure 4.8: Cholesterol level as per different age groups.

(Box represents interquartile range with whiskers representing the range. Median values are displayed).)



(Pearson correlation of LDL and Age = -0.123, P-Value = 0.198)

Figure 4.9: LDL levels in relation to age.

Age Groups	Mean TC/HDL ratio
< 60	4.3
60 – 70	4.0
> 70	4.1

Table 4.12: Total cholesterol to HDL ratio in the three age groups.

Age Group	On lipid lowering therapy at initial visit (%)	On lipid lowering therapy at follow-up (%)
< 60	30.2	68.5
60 – 70	50.7	72.1
> 70	44.2	62.2

Table 4.13: Lipid lowering therapy as per age groups.

Age Group	< 3.5 mmol/L (%)	3.5 – 5.0 mmol/L (%)	5.1 – 6.5 mmol/L (%)	> 6.5 mmol/L (%)
< 60	2.4	33.3	47.6	16.7
60 – 70	3.7	39.1	42.7	14.5
> 70	6.6	32.9	42.8	17.7

Table 4.14: Distribution of lipid lowering therapy as per cholesterol levels.

4.3.14. Antiplatelet therapy: (Tables 4.15, 4.16)

Patients above the age of 60 were more likely to be on antiplatelet therapy (p 0.010, chi-square test) as compared to those below 60 at their initial visit. However at six months follow up patients across the population regardless of age group were taking antiplatelet agents (p 0.56, chi-square test).

More patients were on Aspirin in all age groups as compared to other anitplatalet agents.

Age Group	Antiplatelet therapy at initial visit (%)	Antiplatelet therapy at follow- up (%)
< 60	58.5	91
60 – 70	71.0	88.6
> 70	74.9	86.6

Table 4.15: Practice pattern of antiplatelet therapy in different age groups.

Age Group	Aspirin (%)	Clopidogrel (%)	Dipyridamole (%)
< 60	56.6	1.9	1.9
60 – 70	66.5	4.0	3.3
> 70	70.7	4.2	1.9

Table 4.16: Initial distribution of various antiplatelets as per different age groups

4.3.15. Drug History: (Table 4.17)

Following drug pattern was noted in different age groups:

	Age Groups		
Medicines	< 60	60 – 70	> 70
ACE-Inhibitors	22	27	27
B – blockers	17	16	20
Angiotensin II antagonists	7	6	7.5
Ca++ channel antagonists	13	24	26
Nitrate	6	11	14
Digoxin	1	1.3	5.6
Diuretics	17	21	40
Vasodilator	4.7	7	11
Warfarin	1	2.6	5.6
Oral hypoglycaemics	9.4	11.8	13.5
Insulin	5.7	5.3	5.1
Quinine	1.9	3.3	8.4

Table 4.17: Medicine pattern in different age groups.

** values in percent.*

*** 3 women were on hormone replacement therapy*

4.3.16. ***Peripheral Intervention:*** *(Table 4.18)*

Younger patients were more likely to undergo peripheral intervention as compared to the elderly (p 0.027, chi-square test). The mode of peripheral revascularisation i.e. angioplasty +/- stenting or surgery was uniform in all three age groups.

4.3.17. ***Events:*** *(Table 4.19)*

Patients above the age of 60 were more likely to develop an event other than the revascularisation which included MI, PTCA, CABG, TIA, CVA, amputation or death (p 0.001, chi-square test). No such event was seen over six months in less than 60 years of age.

Age Group	Peripheral Intervention (%)
< 60	12.26
60 – 70	8.55
> 70	4.17

Table 4.18: Peripheral revascularisation in relation to age groups.

Age Group	Event other than revascularisation (%)
< 60	0.0
60 – 70	6.58
> 70	7.41

Table 4.19: Occurrence of different events other than peripheral revascularisation in different age groups over six months.

4.4. Discussion:

As described earlier, age is a known risk profile for development of PAD and associated complications. The frequency of intermittent claudication increases dramatically with advancing age, ranging from 0·6% in individuals aged 45–54 years, to 2·5% in those aged 55–64 years, to 8·8% in patients aged 65–74 years [237]. The Rotterdam study, a population-based analysis of 7715 patients, documented a frequency of IC ranging from about 1% in those between the ages of 55–60 years to 4·6% in those between the ages of 80 and 85 years [38]

Since age is a uniform factor documented in all the population based studies, it was important to find out the significance of different risk factors in relation to age. Therefore for further evaluation, the age variable was divided into different age groups.

Male sex has always been at a higher risk of developing PAD as compared to females and at an earlier age. Incidence of symptomatic disease in women appears to catch up with that of the male population in the elderly [238]). In our study male to female ratio was 2.5:1 for less than 60 years of age as compared to above 70 years of age where this ratio was 1.4:1.

Systolic blood pressure is known to increase with age mostly secondary to arteriosclerosis [239]. As expected in our series, the systolic blood pressure was higher in the elderly population as compared to the younger age group (p 0.019). However, no similar association was found for the diastolic blood pressure. 55% of the patients were receiving treatment for high blood pressure and despite that a significant number (73%) had systolic blood pressure more than 140mm Hg. The pattern of distribution of high blood pressure was uniform across all age groups, however, patients above 70 years of age were more likely to be on anti-hypertensive treatment as compared to those below 60 ($p < 0.001$, chi-square test). There was no significant difference of systolic blood pressure in all groups between those who were on treatment and who were not. However the median values were higher than normal. This not only represent undiagnosed patients with hypertension but also those who were on medication, had inadequate control of high blood pressure. Elderly patients are more likely to have a significant past cardiovascular history and thus their treatment of risk factors is

more expected as compared to the younger population. Subsequent events are expected to be higher in the elderly population and not surprisingly, in this study we found a similar pattern of progression of PAD.

The role of diabetes in relation to age in claudication is not clear. The distribution of diabetes in different age groups was similar in this study though insulin dependent diabetics were proportionally more in the younger age group.

Claudication distances are expected to be higher in the younger patients. We did not notice such a difference in different age groups. It may be that the functional status of the patient is relatively more jeopardised than expected at a younger age as compared to the elderly. ABPI had an inverse relationship in relation to age. Gardner et al have reported a decline in ambulatory function and physical activity in patients 62 – 76 years of age based on their claudication distances at six months follow up despite no change in ABPI [240]. In our study infact the claudication distances improved across all age groups irrespective of the treatment with no significant change in ABPI.

Smoking is a foremost risk factor in development and progression of PAD. Younger patients are more likely to be smokers as compared to the elderly and PAD is diagnosed up to a decade earlier in smokers than in non-smokers [46,48, 51]. Smoking was a significant factor at any age in this series of claudicants. We also found that the smokers presented with claudication at an earlier age than those with history of no smoking. There was a significant association of current smoking to the younger age group as compared to those above 70 years of age ($p < 0.001$, chi-square test). Proportion of the current smokers decreased as the age increased and vice-versa.

Patients are more likely to modify their lifestyle if faced with functional disability. In our series patients under 60 were more likely to give up smoking as compared to the elder groups. It may be explained by the attitude of the elderly to life and chronicity of the problem.

Hyperlipidaemia has until now been treated as part the cardiac and other medical disease management only. Younger patients without a history of cardiovascular disease have not been seen as potential candidates for such a therapy. In our series we also found a similar trend. Cholesterol levels in age group 45 – 54 were significantly higher as compared to other groups (p 0.022, chi-square test). On the whole 63% of the patients had a cholesterol level higher than 5.0 mmol/L.

TC:HDL ratio, which is thought to be a more sensitive marker of development of atherosclerosis, was significantly higher in the younger population ($p < 0.001$,chi-square test). Overall the management of hyperlipidaemia was suboptimal and no age group was spared. With more awareness and current changing trends more and more people are now being offered statin therapy. We found an encouraging result at the end of the follow up as more patients from the lower age group were also offered the lipid lowering therapy.

A similar pattern has emerged in terms of antiplatelet therapy. Again the elder patients especially those with a previous CAD or CVD history are more likely to receive antiplatelet therapy. Majority of the patients were taking antiplatelet therapy at six months regardless of age signifying a significant input from the hospital and primary care.

Younger patients are economically more active and their interruption of daily life is going to weigh more in terms of intervention for symptomatic disease. Moreover the elderly population even with similar level of symptoms may be refused peripheral intervention especially surgery in presence of any significant morbidity. A similar pattern was observed in our study. Elderly population is more likely to suffer from a series of cardiovascular and other events. In our study we did not find any cardiovascular episode or death other than peripheral revascularisation occurring in the younger age group.

Younger patients in the UK may be overlooked in terms of primary prevention and therefore may not be benefiting from the risk reducing agents like statins and antiplatelet agents. Awareness of this problem is highlighted following a specialist unit referral. Smoking and higher serum cholesterol levels appear to play a more significant role in the younger claudicants. These patients should be provided adequate support in this regard as this group was keener to give up smoking. Elderly patients have a higher morbidity and mortality especially from the cardiovascular disease. There is a need for higher input from the physicians for adequate primary and secondary prevention of any cardiovascular morbidity in this group.

Chapter 5

Gender and peripheral arterial disease

5.1. Introduction:

Little attention has been focussed on gender differences in PAD. This is known to have predilection for men [30, 60, 112, 241]. Most studies report the prevalence of lower limb occlusive arterial disease to be lower in women than men [108, 237]. The extended longevity in industrialized nations coupled with the expanding elderly female population is predicted to lead to an increase in the prevalence of this condition. In females PAD has a delayed presentation and consequently referral is delayed with treatment starting at a more advanced stage.

5.2. Methods:

474 consecutive patients with IC were recruited as per the inclusion criteria of the study to 23 vascular units across the United Kingdom. Sex was documented at the initial visit. Use of risk factor therapy was recorded at recruitment and at six month follow – up. Outcomes at the end of six months were documented and analysed.

5.3. Results:

The available data was analysed in relation to important variables for either sex.

5.3.1. Age:

In this study there were 159 / 474 (33.54%) were females and 315 / 474 (66.46%) males. Median female age was 71.9 (range 40 – 87) while mean age in male population was 66.5 (range 34 – 93). Men were more likely to present with IC at an early age as compared to women ($p < 0.001$, Kruskal – Wallis test).

The sex distribution in different age groups is shown in fig 5.1.

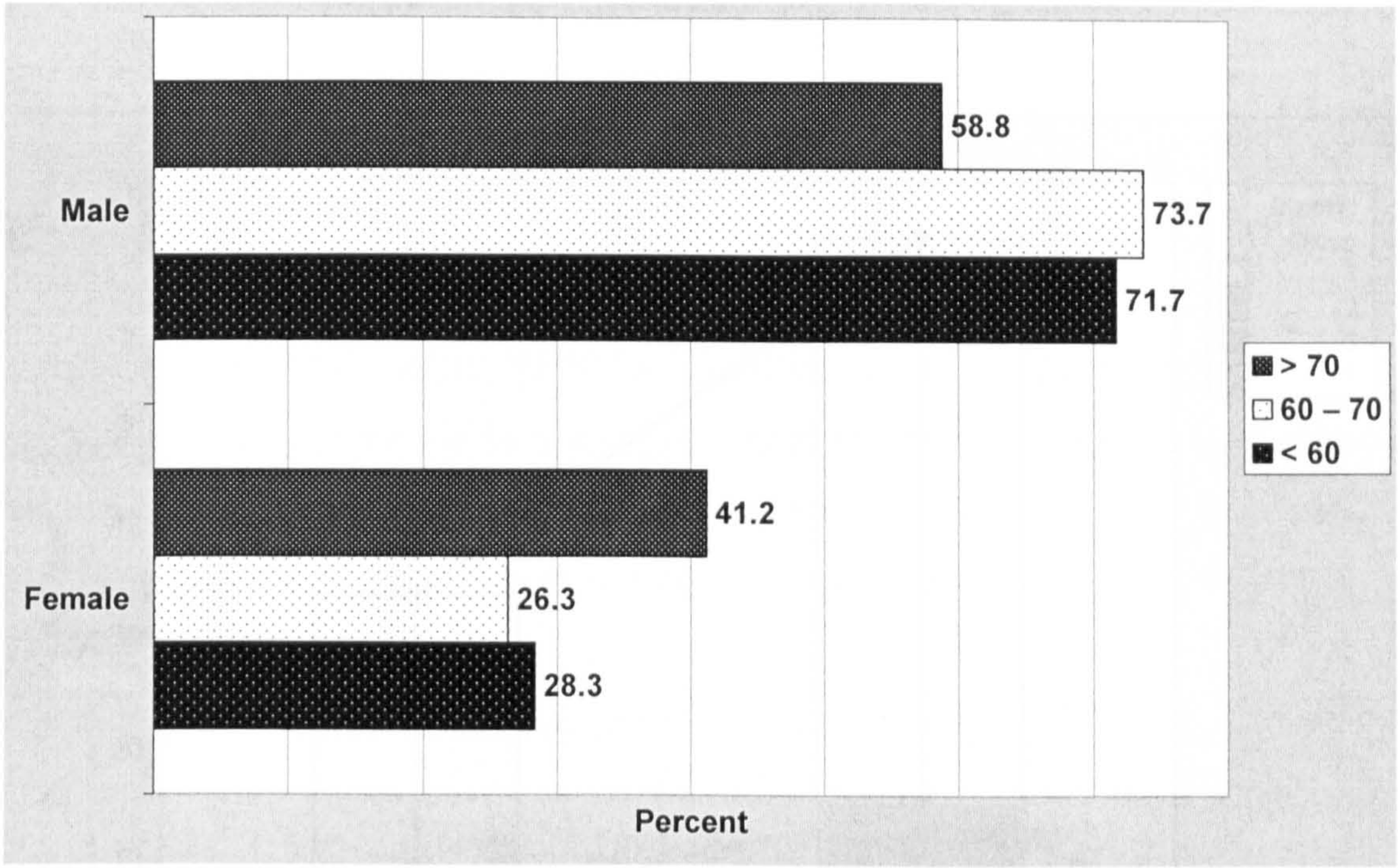
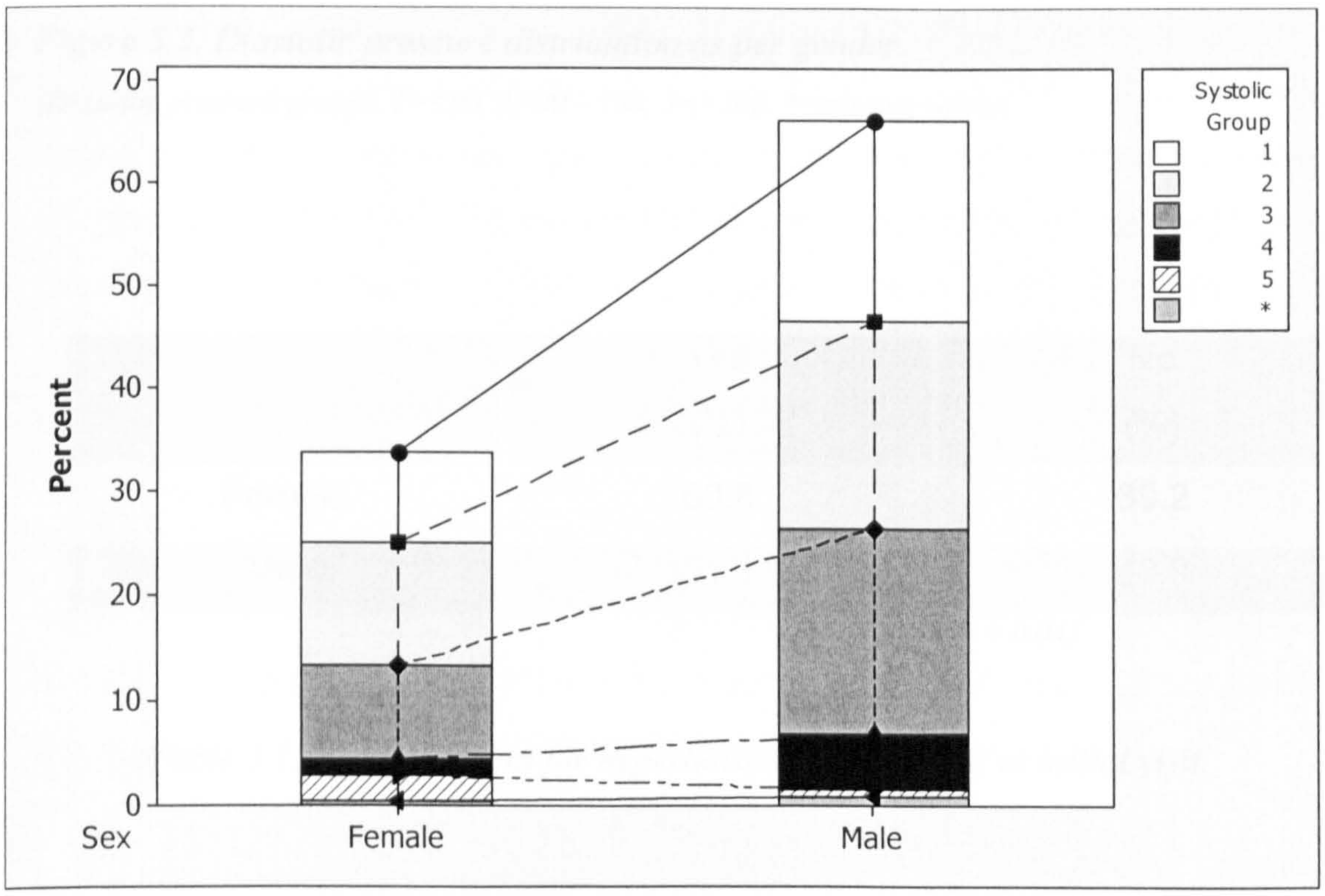


Figure 5.1: Age distribution as per sex.

(Age groups 1= <60, 2=60-70, 3=>70.)

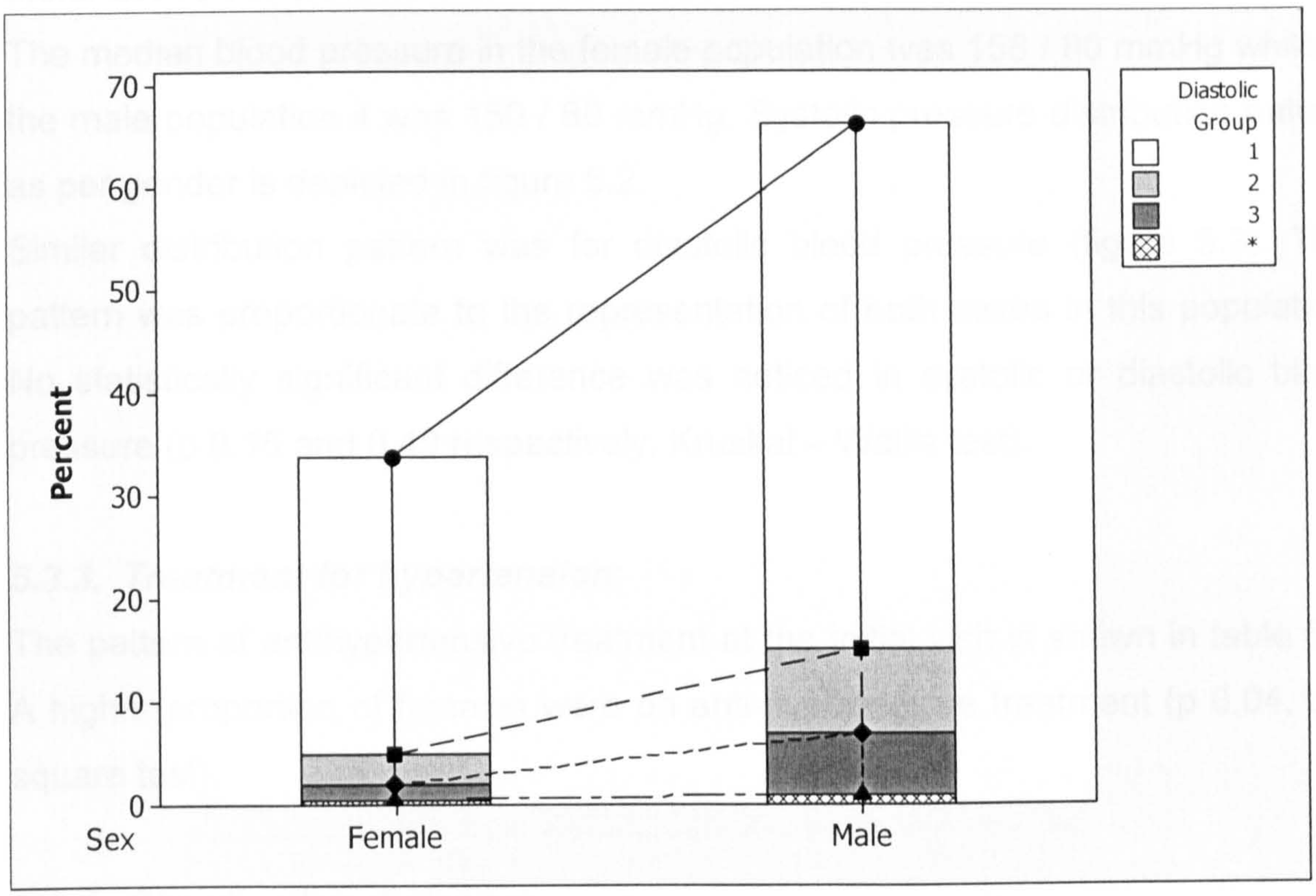


(p = 0.154)

Figure 5.2. Systolic pressure distribution as per gender.

(Systolic pressure groups 1=<140mmHg, 2=140 – 160, 3=160 – 180, 4=180 – 200, 5=>200.

** =missing value.)*



(p = 0.425)

Figure 5.3. Diastolic pressure distribution as per gender.

*(Diastolic pressure groups, 1=<90, 2=90 – 100, 3=>100, *=missing value).*

	Yes (%)	No (%)
Female	60.8	39.2
Male	51.1	48.9

(p = 0.04)

Table 5.1. Treatment for hypertension in either sex at initial visit.

5.3.2. Blood Pressure:

The median blood pressure in the female population was 158 / 80 mmHg while in the male population it was 150 / 80 mmHg. Systolic pressure distribution pattern as per gender is depicted in figure 5.2.

Similar distribution pattern was for diastolic blood pressure (figure 5.3). This pattern was proportionate to the representation of both sexes in this population. No statistically significant difference was noticed in systolic or diastolic blood pressure (p 0.15 and 0.49 respectively, Kruskal – Wallis test).

5.3.3. Treatment for hypertension:

The pattern of antihypertensive treatment at the initial visit is shown in table 5.1. A higher proportion of females were on anti-hypertensive treatment (p 0.04, chi-square test).

5.3.4. Claudication distance:

In females the median initial claudication distance was 80 meters as compared to a median of 100 meters in males (p 0.019, Kruskal – Wallis test) at recruitment. While a similar pattern was seen in absolute claudication distance where the values were 109.5 and 150 meters for females and males, respectively (p 0.010, Kruskal – Wallis test). At follow-up, however, there was no difference in the median initial and absolute claudication distances i.e. 150 and 200 meters respectively, for both the groups (p 0.56 and 0.35, Kruskal – Wallis test).

5.3.5. Ankle brachial pressure index:

Median ABPI at recruitment for both genders was 0.63 while at six months it was 0.65 for females and 0.67 for males. No significant difference was observed at six months (p 0.86, 0.43 respectively, Kruskal – Wallis test).

5.3.6. Lipid lowering therapy:

There was no significant difference of treatment for hyperlipidaemia in both sexes (p 0.97, chi-square test) at recruitment. Again at six months the proportion of either sex taking lipid lowering therapy did not change

	Yes (%)	No (%)
Female	43.0	57.0
Male	43.2	56.8

(p = 0.97)

Table 5.2: Treatment for hyperlipidaemia in either sex.

	Yes (%)	No (%)
Female	17.1	82.9
Male	18.4	81.6

(p = 0.72).

Table 5.3. Sex distribution in angina.

	Yes (%)	No (%)
Female	11.4	88.6
Male	15.9	84.1

(p =0 .19)

Table 5.4. Sex distribution in myocardial infarction.

significantly despite increase in total numbers taking such therapy (p 0.6, chi-square test).

5.3.7. Previous Cardiovascular History:

5.3.7.1. Angina:

There was no dominance of one sex to another in regards to angina. Sex distribution in relation to angina at recruitment is shown in table 5.3.
There was no significant association with either sex (p 0.72, chi-square test).

5.3.7.2. Prior myocardial infarction:

In patients with past history of myocardial infarction, sex pattern is shown in table 5.4. Proportion of males with prior history of MI was slightly more than the females (15.9% vs. 11.3%) but this was not statistically significant (p 0.18, chi-square test).During six months follow up 5 more patients suffered from MI, of these 4 were males.

5.3.7.3. Prior coronary intervention:

10 (6.3%) of the females and 32 (10.1%) of the males had previous history of coronary artery bypass grafting (CABG) while 6 (3.8%) of the females and 11 (3.5%) of the males had undergone percutaneous coronary angioplasty (PTCA). During six month follow up 9 patients underwent coronary intervention, 7 of them being males. Overall there was no predominance of either sex in relation to coronary revascularisation (p 0.25, chi-square test).

5.3.7.4. Prior Cerebrovascular accident (CVA):

10 (6.3%) females and 24 (7.6%) males had prior history of CVA. Two further males developed CVA during six month follow-up.

5.3.8. Diabetes mellitus (DM):

9 (5.7%) of the females had insulin dependent diabetes (IDDM) while 16 (10.1%) had non-insulin dependent diabetes (NIDDM). 14 (4.4%) of the males had IDDM and 55 (17.5%) had NIDDM. There was no significant association of diabetes with either sex (p 0.10, chi-square test).

5.3.9. Smoking:

Male and female distribution as per number of pack years smoked at recruitment is shown in table 5.5.

There were 116 (73.42%) females with history of smoking (61 current and 55 ex-smokers) at the initial visit. Among the male population 297 (94.29%) had history of active smoking (138 current and 159 ex-smokers) ($p < 0.001$, chi-square test). The median number of pack years smoked among females was 35 and for males 40. This was statistically significant (p 0.002, Kruskal – Wallis test). This changed to 38 and 42 respectively at six months.

At follow-up, 41.3% of the males were still smoking as compared to 33.3% of females. There was a significant relationship of male population to active smoking, past or present both at recruitment and at six month follow up ($p < 0.001$ and $p < 0.001$, respectively, chi-square test).

	Pack years smoked				
	< 20	**21 – 40**	**41 – 60**	**61 – 80**	**> 80**
Female	27.4	34.6	27.4	5.3	5.3
Male	16.2	34.6	30.8	9.4	9.0

** values in percent*

Table 5.5. Sex distribution as per pack years smoked.

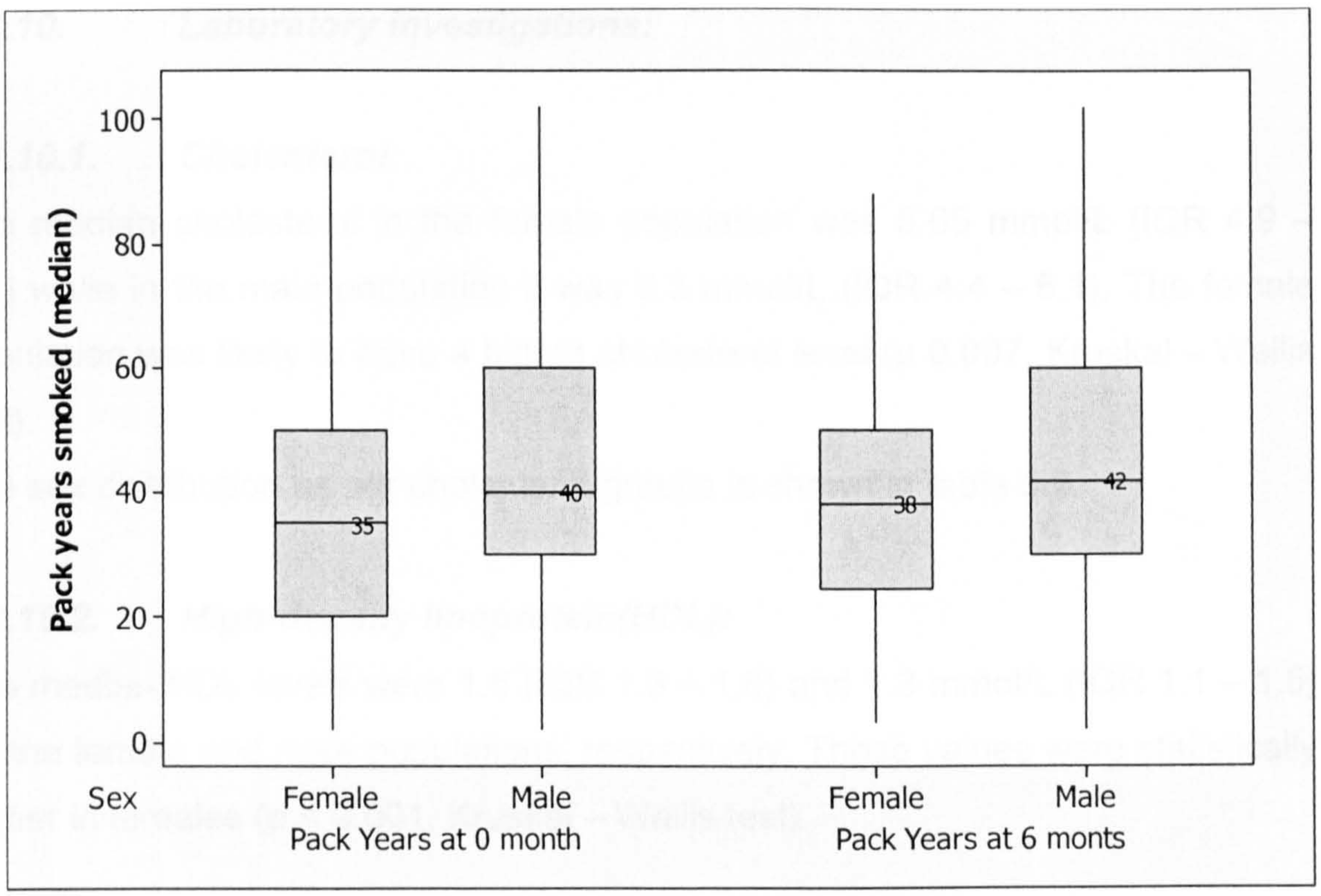


Figure 5.4: Boxplots of pack years in relation to gender at recruitment and follow-up. (Box = interquartile range, whiskers = whole range)

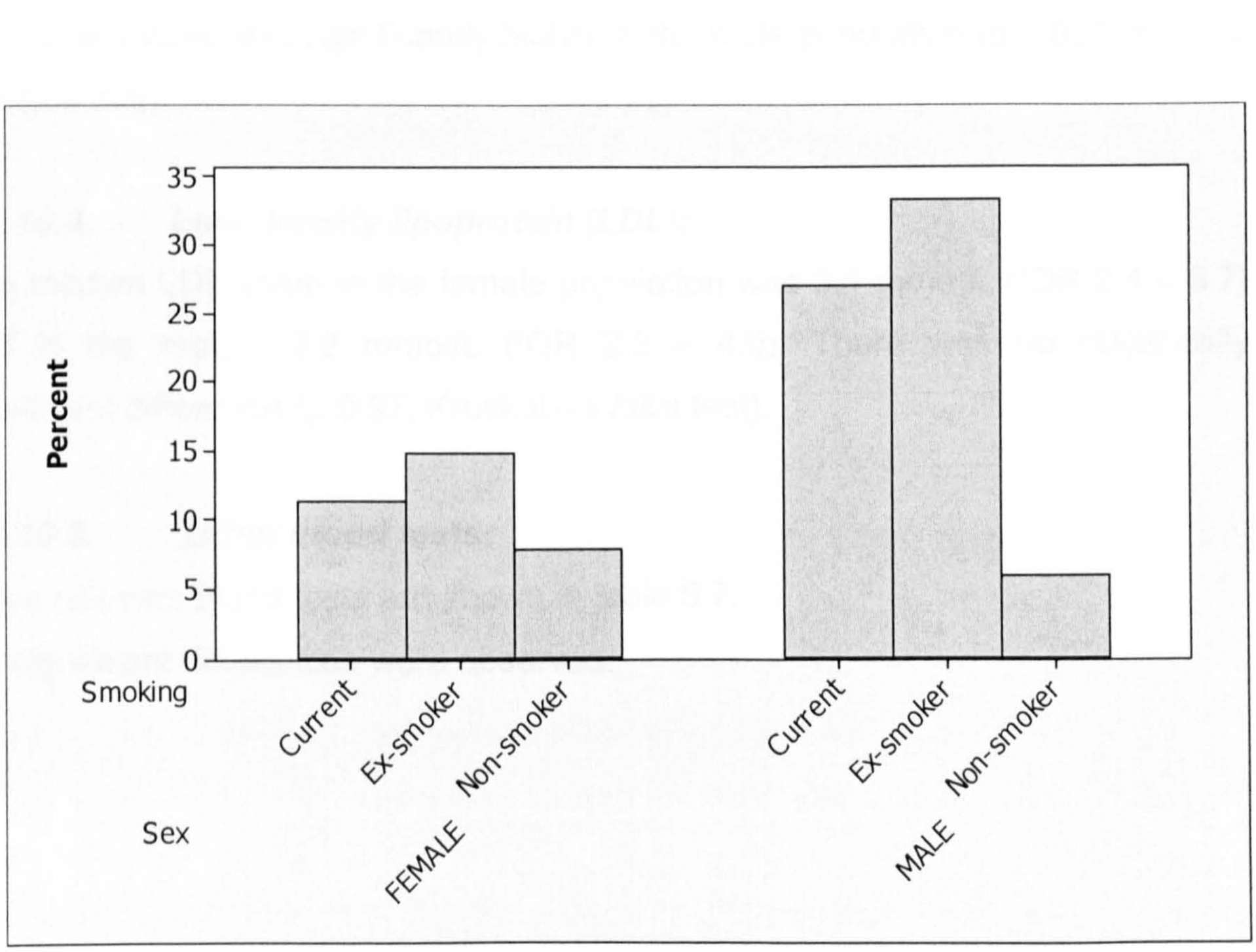


Figure 5.5. Percentage of each category in relation to sex at recruitment.

5.3.10. Laboratory investigations:

5.3.10.1. Cholesterol:

The median cholesterol in the female population was 5.65 mmol/L (IQR 4.9 – 6.4) while in the male population it was 5.3 mmol/L (IQR 4.4 – 6.1). The female population was likely to have a higher cholesterol level (p 0.007, Kruskal – Wallis test).

The sex distribution as per cholesterol groups is shown in table 5.6.

5.3.10.2. High-density lipoprotein(HDL):

The median HDL levels were 1.5 (IQR 1.3 – 1.8) and 1.3 mmol/L (IQR 1.1 – 1.5) for the female and male populations, respectively. These values were statistically higher in females ($p < 0.001$, Kruskal – Wallis test).

5.3.10.3. Total Cholesterol / HDL ratio (TC/HDL):

The median total cholesterol / HDL ratio in the female group was 3.6 (IQR 2.7 – 4.5) while in the males it was 4.0 (IQR 3.2 – 5.1). TC/HDL as contrast to individual values was significantly higher in the male population (p 0.026, Kruskal – Wallis test).

5.3.10.4. Low density lipoprotein (LDL):

The median LDL value in the female population was 3.1 mmol/L (IQR 2.4 – 3.7) and in the males, 3.2 mmol/L (IQR 2.2 – 4.0). There was no statistically significant difference (p 0.97, Kruskal – Wallis test).

5.3.10.5. Other blood tests:

Other relevant blood tests are shown in table 5.7.

No significant differences were observed.

Sex	Total cholesterol level (mmol/L)			
	< 3.5	3.5 – 5.0	5.0 – 6.5	> 6.5
Female	1.6	30.6	47.1	20.7
Male	6.2	37.3	42.2	14.3

** values in percent*

Table 5.6: Total cholesterol distribution as per gender.

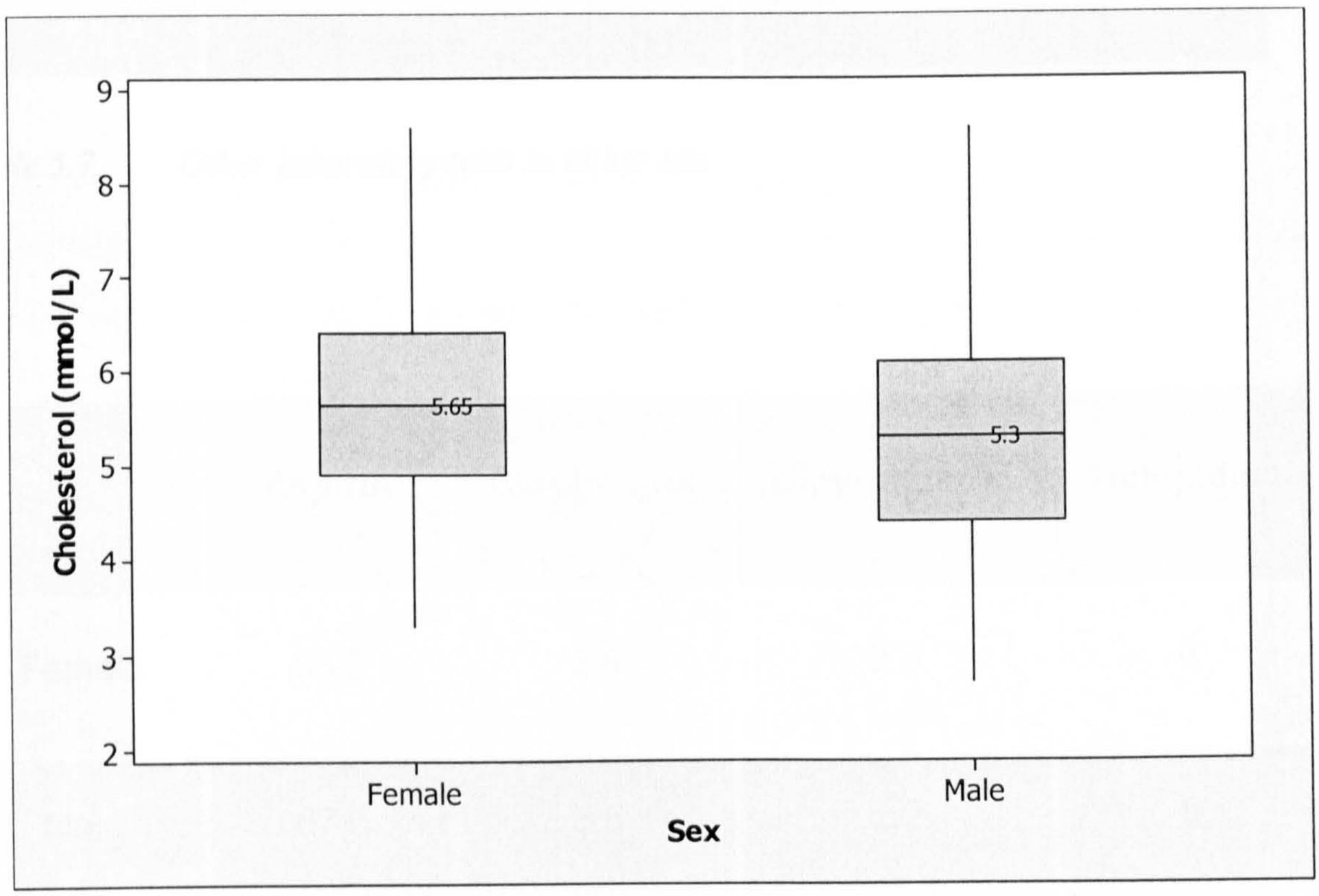


Figure 5.6. Boxplot of total cholesterol as per gender.

(Box represents the interquartile range and whiskers represent the range).

Test	Female (median)	Male (median)
Haemoglobin (gm/dL)	13.7	14.8
MCV	91.2	91.1
White cell count (*10^9/L)	8.0	8.2
Platelets	276.0	237.5
Glucose	5.1	5.4
Creatinine	88.0	98.0

Table 5.7. Other laboratory tests in either sex

	Aspirin	Clopidogrel	Dipyridamole	Ticlopidine
Female	63.3	3.8	2.5	0
Male	67.5	3.5	2.2	0

Table 5.8. Pattern of antiplatelet medication in either sex.

5.3.11. Antiplatelet therapy:

106 (67.1%) of the females and 225 (71.4%) of the males were on antiplatelet agents (p 0.33, chi-square test) at their initial visit. 32.9% females and 28.6% males were not taking any antiplatelet agent. By the time of follow-up, only 12.1% of the females and 11.6% of the males were not taking antiplatelet therapy.

Of those who were on aspirin, 92 (92%) females and 190 (89.2%) of males were using 75mg once daily. A similar pattern was noted at six months.

There was no significant trend of distribution for taking or not taking antiplatelet medication based on gender.

Reasons for not taking antiplatelet medication were almost similar (table 5.9).

5.3.12. Peripheral Intervention:

8.8% of the females and 6.7% of the males underwent peripheral revascularisation procedures. There was no significant trend in terms of gender for peripheral revascularisation (p 0.40, chi-square test).

5.3.13. Events other than revascularisation:

There was a similar proportion of either sex that suffered from cardiovascular or cerebrovascular events, amputation or death (5% females, 5.7% males;

p 0.76, chi-square test).

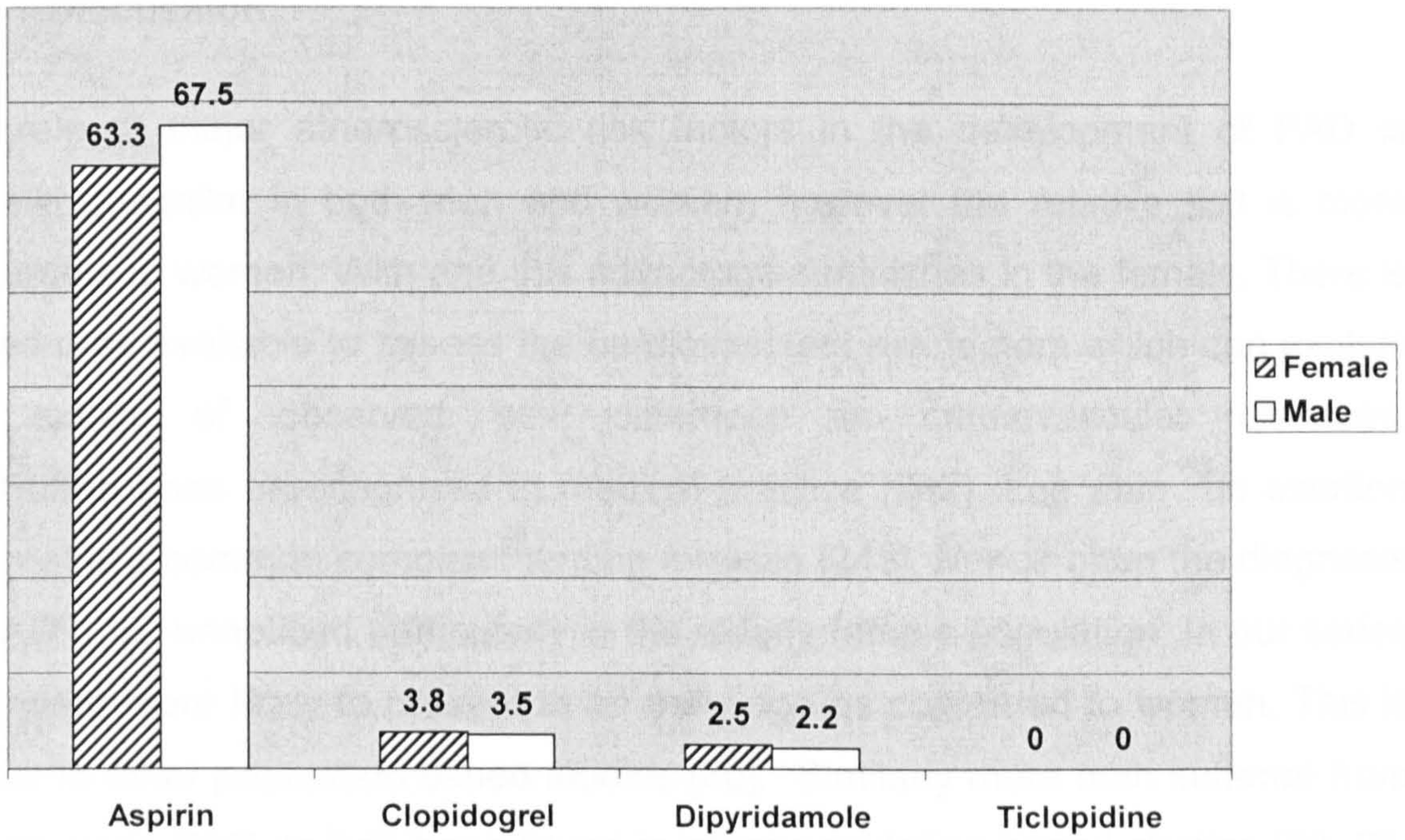


Figure 5.7. Gender-wise antiplatelet medication (in percentage)

	Female	Male
Never prescribed	18.6	20.3
Allergy	00	0.3
History of ulcers	3.8	2.6
Indigestion	3.8	1.0
Non-compliance	1.3	0.6
Other	5.7	3.8

** values in percent*

Table 5.9. Reasons for not taking antiplatelet medication

5.4. Discussion:

The role of major atherosclerotic risk factors in the development of PAD is somewhat similar in both men and women, however the relative risk is more favourable to women. With age this advantage diminishes in the female. There is limited data available to assess the cardiovascular risk factors which can explain the extent of observed sex difference in cardiovascular diseases. PAD often goes unrecognised in medical practice [242]. Leg pain on exertion and rest is a common complaint among females [243]. Hence often the diagnosis of PAD goes unnoticed particularly in the elderly female population. In our series men were more likely to present at an early age as compared to women. This is similar to other population based studies [30]. Similarly more men suffered from symptomatic PAD as has been found in other population based studies [22, 23, 27, 36]. Atherosclerosis is a cumulative process, starting at a fairly young age. Even though sex differences like serum lipid profile and blood pressure disappear with age, it is possible that the cumulative effects of these risk factors on arteriosclerosis remain larger in men than in women, because of the longer exposure time in men. Higgins et al claim that contrary to earlier beliefs, the prevalence of PAD is similar in women and men and that women may have more asymptomatic disease [244].

Female gender has been associated with reduced clinical improvement in terms of claudication distance and ABPI over short term [245]. Our findings show a similar pattern at the time of recruitment; however improvement at six months was across the board irrespective of gender with no significant difference. Gardner has suggested that the shorter claudication distances in women with PAD are explained by their lower cardiopulmonary fitness and poorer self-perceived physical ability [246]. However we feel that with appropriate treatment this difference in exercise tolerance can be overcome as shown in this study.

No statistical difference in terms of ABPI measurements was observed in the two groups. This parameter suggests that the functional impairment is independent of the ABPI measurement in the two genders. This has been attributed to greater leg strength in men [243]. Therefore, regular exercise therapy is recommended to improve the functional capacity of the caludicants especially in females.

Men are more likely to be smokers as compared to women. Also the number of pack years smoked was significantly higher in the male population. Smoking alone increases the development of PAD and this can be one of the major reasons for increased prevalence in the male population for a given age.

Nilsson et al have reported a higher level of total cholesterol and HDL levels in women [247]. Total cholesterol increases with age. This increase usually levels out in the male population in the second half of the fifth decade while in the female population it increases till the age of 50 – 65 [248].In this study female population had a higher cholesterol (p 0.007) a higher HDL level (p <0.001) and, hence, a higher TC/HDL ratio (p 0.02, chi-square). It appears that a higher HDL levels in the female population may offset the higher risk due to increased cholesterol level. TC/HDL ratio that is considered to be a more sensitive risk factor for development of atherosclerosis was found to be significantly higher in the male population largely due to low levels of HDL. Low HDL alone is a major determinant of the PAD risk and addition of smoking further decreases the HDL levels [249].

Females were more likely to be on anti-hypertensive therapy as compared to males. This can be explained by the fact that females tend to present with IC later in life than males. However no difference was found regarding lipid lowering therapy and antiplatelets in relation to gender.

Women with PAD have been associated with a 2-4 fold increases in cardiovascular morbidity and mortality [244]. This may be related partly to late presentation of PAD among females. We found an overall 13.3% event rate in women as compared to 11.7% in men. Events other than revascularisation were not significantly different in the two groups at six month follow up (5% females vs. 5.7% males).

Men generally have a higher interventional rate without salvage indications as compared to women [246]. This difference in revascularisation could be secondary to lower prevalence of IC in women. Besides, smaller arterial diameter in the female population is likely to deter any interventional procedure as it is more prone to further complications [251, 252]. However no such observation

was made in our series in this short period of time. A longer follow up will give a clearer picture on this aspect.

Even though the major cardiovascular risk factors are the same in both sexes, preventive strategies like the use of HRT in postmenopausal women has been proposed to reduce the risk of PAD [253]. Despite the cardioprotective effects, HRT cannot be recommended for all postmenopausal women. Literature has provided conflicting evidence of its use in PAD and overall cardiovascular protection. Current evidence indicates potentially no benefit of combined estrogen-progesterone HRT for primary or secondary prevention of vascular disease. Furthermore, HRT may be associated with adverse clinical events and outcomes in certain women. Combination HRT (estrogen-progesterone) reduces the beneficial effect of estrogens on coronary arteries, increases the progression of coronary artery atherosclerosis, increases the thrombotic potential of atherosclerotic plaques, and may significantly lower high-density lipoproteins, thereby decreasing the cardioprotective benefit of estrogen therapy. However, unopposed estrogen may provide some degree of vascular protection. Preliminary findings from current literature suggest that estrogen-only HRT may be a beneficial treatment. This information merits additional research to assess the impact of estrogen alone on PAD.

The problem of smoking, as emphasised earlier, should be more aggressively addressed in both sexes especially males.

In conclusion, differences in major cardiovascular risk factors, particularly in HDL cholesterol level and smoking rate may explain a substantial part of the sex difference in PAD risk.

Chapter 6

Six Month Follow Up

6.1. Introduction:

As per the protocol of this observational study, patients were followed up at six months. This time interval allowed to check on the occurrence of any major clinical events such as the need for hospital admission, amputation or bypass, and any other treatments besides the assessment of QoL and comparison of variables with those of baseline data.

6.2. Methods:

All patients were given a six-month follow up date at their initial visit. However, it was appreciated at the time of protocol setting that some of the patients may not be able to attend the outpatients; therefore, a telephone follow-up was allowed if this was the case.

435 (91%) patients were available for follow up. 64% visited the out-patients while 36% were contacted on telephone. Mean time to follow up was 200 (+/- 62) days. Objective parameters like blood pressure and ABPI were assessed where available.

6.3. Results:

6.3.1. Body Mass Index:

The median body mass index at follow up was 26.19 (IQR 23.52 – 29.53) (n = 337) as compared to baseline index of 26.02 (IQR 23.45 – 29.65) (n = 470).

6.3.2. Systolic Blood Pressure:

The median systolic pressure at six months was 150 mmHg (IQR 140 – 170) as compared to 152 mmHg (IQR 140 – 170) at the initial visit. Distribution of systolic blood pressures is shown in table 6.1.

6.3.3. Diastolic blood pressure:

The median diastolic pressure at follow up was 82 mmHg (IQR 76 – 90) as compared to baseline median of 80 mmHg (IQR 73 – 90). Further analysis is shown in table 6.2.

Systolic BP (mmHg)	Baseline n = 472	Follow Up n = 276
<140	30.8%	29.0%
140 -160	33.1%	38.4%
160 -180	24.2%	18.8%
180 -200	08.5%	08.7%
200+	03.4%	05.1%

Table 6.1. Systolic blood pressure distribution at baseline and 6 months.

Diastolic BP (mmHg)	Baseline n = 470	Follow Up n = 274
< 90	83.2%	81.7%
90 – 100	11.3%	13.9%
> 100	05.5%	04.4%

Table 6.2. Diastolic blood pressure pattern at base line and 6 months

	Baseline	Follow Up
Initial claudication distance (m) [median(IQR)]	100 (50 – 200)	150 (50 – 300)
Absolute claudication distance (m) [median(IQR)]	150 (75 – 250)	200 (100 – 400)
ABPI (Left) [mean (sd)]	0.71 (0.21)	0.74 (0.21)
ABPI (Right) [mean (sd)]	0.74 (0.21)	0.78 (0.22)

Table 6.3. Claudication status at baseline and 6 months.

6.3.4. Claudication Status:

Claudication distances and ankle brachial pressure indices at six months are shown in table 6.3. There was a significant difference in initial and absolute claudication distances (significant at 0.000 and at 0.000, respectively, Wilcoxon signed rank test) and also the ABPI (significant at 0.008, Wilcoxon signed rank test) at follow up.

Patients undergoing peripheral revascularisation [35 / 474 (7.3%)] had a significant improvement of their initial and absolute claudication distances. For peripheral angioplasty it improved from the median initial distance of 40 meters to 150 meters (significant at 0.001, Wilcoxon signed rank test) and for surgical procedures it improved from 100 meters to 300 meters (significant at 0.001, Wilcoxon signed rank test). Similarly the median absolute distances changed from 62.5 to 225 meters (significant at 0.001, Wilcoxon signed rank test) for angioplasty and 150 to 400 meters (significant at 0.001, Wilcoxon signed rank test) for surgical intervention.

6.3.5. Smoking:

At six months follow up, 159 / 409 (39%) were still smoking (figure 6.1). However there was no significant difference in the smoking status at follow up. 113 (59%) of the 192 current smokers at baseline attempted to stop smoking. Only 18/113 (15.9%) were successful. Of these 52% used nicotine replacement therapy, 5% bupropion, 24% counselling and 34% resorted to various other methods. The median pack years smoked at six month follow up were 45.65 as compared to baseline of 43.08.

6.3.6. Antiplatelet therapy:

360/408 patients (88%) were taking antiplatelet treatment as compared to 70% at the initial visit (significant at 0.001, Wilcoxon signed rank test) (table 6.5). 92% were on Aspirin and 91% of these were taking 75mg once daily. 48 (11%) were still not taking any antiplatelet agent.

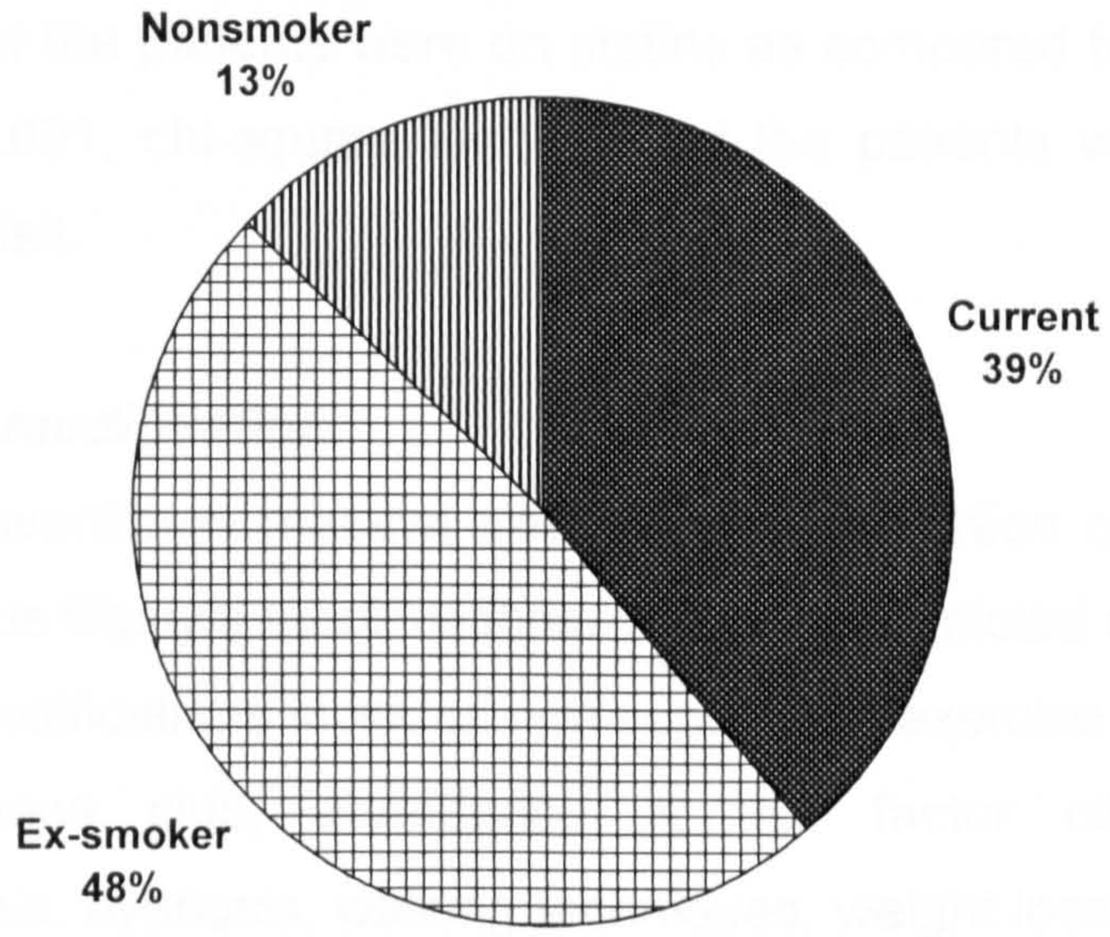


Figure 6.1. Smoking status at 6 months.

	Baseline n = 473	Follow Up n = 410
Current	42%	40%
Ex-smoker	45%	47%
Non-smoker	13%	13%

Table 6.4. Smoking status at 0 and 6 months.

	Baseline n = 474	Follow Up n = 408
Aspirin	66%	81%
Clopidogrel	4%	8%
Dipyridamole	2%	2%
Ticlopidine	0%	0%

(p = 0.001)

Table 6.5. Antiplatelet trend at baseline and 6 months.

6.3.7. Lipid lowering therapy:

281/421 (67%) of the patients were on statins as compared to 208/474 (44%) at baseline ($p < 0.001$, chi-square test). 1% of the patients were on non-statins similar to initial visit.

6.3.8. Lifestyle modification:

Besides the conventional medical treatment, a proportion of the patients also underwent various lifestyle modifications. These are depicted in table 6.6.
Other lifestyle modifications included non supervised exercise at home and gymnasium, dance club, attendance at risk factor clinic and vascular rehabilitation clinic, hypnosis, walking techniques, weight loss and getting written and verbal information on diet and exercise from clinician, nurse and internet.

6.3.9. Drug history:

Compared to baseline the medication pattern of patients is shown in table 6.7.
There was no significant change in pattern of medication at six months apart from the statins as discussed above.

6.3.10. Major Investigations:

A number of patients underwent further investigations with a view to further evaluation and management. Major investigations performed were duplex scanning, peripheral angiogram, MR angiogram and coronary angiogram. This is shown in table 6.8.

Lifestyle change	%
Smoking cessation class	17
Exercise class run by the vascular unit	13
Cardiac rehabilitation class	03
Dietary advice from dietician	09
Written advice on risk reduction	26
Other	36

Table 6.6. Life style modifications employed during six months.

Drug	Baseline (%)	Percentage (%)
Statins	44	69
Non-statins	01	01
Warfarin	04	06
ACE Inhibitors	26	29
B-blocker	18	18
Ca-antagonist	23	24
Angiotensin II antagonist	07	06
Nitrate	11	10
Vasodilator	08	08
Quinine	5	3
Diuretic	29	33
Oral hypoglycaemics	12	13
Insulin	05	06
HRT	03	03

Table 6.7. Medication patterns at initial visit and 6 month follow-up.

Investigation	Percent
Peripheral duplex scan	27
Peripheral arterial angiogram	34
Coronary angiogram	05
Magnetic resonance imaging	03

Table 6.8. Major investigations performed in 6 months.

Event	n (%)
All vascular events	57 (14%)
Death	17 (4%)
Non fatal MI	5 (1%)
Non fatal CVA	2 (<1%)
TIA	2 (<1%)
Congestive cardiac failure	3 (1%)

Table 6.9. Major events in 6 months since recruitment.

Vascular Event	n (%)
Angioplasty / Stent	27 (7%)
Peripheral Vascular Surgery	7 (2%)
Amputation	1 (< 1%)
CABG	5 (1%)
PTCA	2 (< 1%)

Table 6.10. Vascular interventions in 6 months

6.3.11. Events since enrolment:

Events were defined as any vascular event ending in radiological or operative peripheral revascularisation, amputation, non fatal MI, coronary revascularisation (CABG or PTCA), TIA, CVA and death. A list of major events occurring over a period of six months is displayed in table 6.9.

Interventions and revascularisation procedures in the first six months of enrolment were:

There were in total 64 hospital admissions. These were not only for vascular reasons but also for a number of medical conditions.

6.4. Multivariate analysis:

Multivariate analysis was carried out to assess the impact of different risk factors in relation to development of events.

These are summarised on the following page.

Variable		Vascular event (n = 58)	No vascular event (n = 473)	p chi^2
Age	< 60	12 (21%)	94 (23%)	0.58
	60 – 70	22 (38%)	129 (31%)	
	> 70	24 (41%)	192 (46%)	
Sex (% male)		37 (64%)	278 (68%)	0.63
APBI	< 0.3	6 (10%)	4 (1%)	0.003
	0.3-0.5	11 (19%)	65 (16%)	
	0.5-0.7	25 (43%)	191 (47%)	ns
	0.7-0.9	16 (28%)	146 (36%)	ns
Systolic BP	< 140	22 (38%)	123 (30%)	0.015
	140 – 160	24 (41%)	132 (32%)	
	160 – 180	11 (19%)	102 (25%)	ns
	180 – 200	1(2%)	39 (9%)	ns
	> 200	0 (0%)	16 (4%)	ns
Diabetes (%)		14(24%)	79 (19%)	0.18
Rx hypertension (%)		31 (53%)	226 (54%)	0.88
Prior CHD (%)		27 (47%)	109 (26%)	0.002
Antiplatelet use (%)		45 (78%)	286 (69%)	0.17
Lipid lowering therapy use (%)		31 (53%)	180 (43%)	0.15

Variable		Vascular event (n = 58)	No vascular event (n = 473)	p chi^2
Absolute claudication distance	< 50m	16 (28%)	62 (15%)	0.25
	50-100m	13 (23%)	99 (24%)	ns
	100-200m	15(26%)	119 (29%)	ns
	200-300m	5(9%)	64 (16%)	ns
	300-400m	3 (5%)	29 (7%)	ns
	> 400m	5 (9%)	35 (9%)	ns
Smoking	Current	24 (41%)	174 (42%)	0.53
	Ex-smoker	24 (41%)	191 (46%)	ns
	Non-smoker	10 (17%)	50 (12%)	ns
Total Cholesterol (mmol/L)	< 3.5	3 (7%)	13 (4%)	0.86
	3.5 – 5.0	16 (36%)	103 (34%)	ns
	5.0 – 6.5	18 (40%)	136 (45%)	ns
	> 6.5	8 (18%)	48 (16%)	ns
		** 13 not checked*	**113 not checked*	
TC / HDL	< 3.0	7 (23%)	34 (23%)	0.58
	3.0 – 4.5	11 (37%)	68 (46%)	ns
	> 4.5	12 (40%)	46 (31%)	ns
		**28 not checked*	**267 not checked*	

Table 6.11. Multivariate analysis in relation to all vascular events.

6.4.1. *All vascular events:* *(Table 6.11)*

Multiple variables analysed in relation to the outcome, in this case events as described earlier. A low ABPI and a history of coronary heart disease were significantly associated with any form of event..

6.4.2. *Death:* *(Table 6.12)*

Advanced age, a low ABPI, a previous CHD history and a high TC / HDL ratio were significantly associated with death.

Variable		Death (n = 13)	No death (n = 469)	p
Age	< 60	0 (0%)	105 (23%)	0.014
	60 – 70	3 (23%)	146 (32%)	-
	> 70	12 (77%)	205 (45%)	-
Sex (% male)		13 (77%)	303 (66%)	0.41
APBI	< 0.3	1 (8%)	9 (2%)	0.007
	0.3-0.5	5 (38%)	71 (16%)	
	0.5-0.7	5 (38%)	212 (47%)	ns
	0.7-0.9	2 (15%)	160 (35%)	ns
Rx Hypertension (%)		7 (54%)	249 (55%)	0.95
Prior CHD (%)		8 (62%)	127 (28%)	0.013
Antiplatelet use (%)		11 (85%)	317 (70%)	0.21
Lipid lowering therapy use (%)		7 (54%)	202 (44%)	0.49
Absolute claudication distance				
	< 75m	4 (25%)	95 (24%)	0.56
	75-150m	7 (44%)	113 (28%)	
	150-250m	2 (13%)	92 (23%)	
	>250m	3 (19%)	98 (25%)	

Variable		Death (n = 13)	No death (n = 469)	p
Smoking	Current	4 (31%)	192 (42%)	0.22
	Ex-smoker	5 (38%)	208 (46%)	ns
	Non-smoker	4 (31%)	56 (12%)	ns
Total Cholesterol	< 3.5	0 (0%)	16 (5%)	0.74
	3.5 – 5.0	4 (50%)	115 (34%)	ns
	5.0 – 6.5	3 (37%)	152 (45%)	ns
	> 6.5	1 (13%)	55 (16%)	ns
		** 5 not checked*	**123 not checked*	
TC / HDL	< 3.0	0 (0%)	41 (24%)	0.018
	3.0 – 4.5	1 (20%)	79 (45%)	ns
	> 4.5	4 (80%)	54 (31%)	ns
		**8 not checked*	**287 not checked*	

Table 6.12. Multivariate analysis in relation to death, MI and CVA.

6.5. Discussion:

Follow up of this cohort of patients allowed an assessment of the progression of IC, documentation of various clinical outcomes and practice patterns. Role of various risk factors in relation to IC also came under review. Management of the claudicants following initial visit allowed to document the current hospital based practice patterns.

Atherosclerotic risk factors are common in patients with PAD. However, the intensity of lifestyle modification and the use of evidence-based medical therapy in this high-risk cohort remain suboptimal. There is a significant opportunity to improve the appropriate use of secondary preventive therapy in these high-risk patients and improve patient compliance with education and empowerment. Six month follow up allowed us to study this aspect across the UK.

Hypertension as discussed in section1.4.3. is associated with 2-3 fold risk of PAD and is associated with severe disease [39]. We found inadequate management of hypertension in this group over six months. Systolic BP was more than 140 mmHg in 71% at six months versus 69.2% at baseline while diastolic pressure above 90 mmHg was 18.3% versus 16.8%. As management of hypertension is generally considered to fall under the domain of a general practitioner and physician, therefore, most of the times its management is not altered by the vascular units. Hence no change in blood pressure readings at six months audits the trends of management at general practice level rather than the specialist vascular centre. A persistent high blood pressure reading is a worrying trend and calls for effective communication between the general practitioner and the vascular unit.

Smoking is a major risk factor not only in development of PAD but also in its progression (see section 1.4.1). At six months follow up 40% of the patients were still smoking as compared to 42% at recruitment. It appears that every patient was conveyed the message to stop smoking as more than half (59%) of the current smokers did attempt to give up smoking. However complete cessation results were disappointing. Although verbal advice was provided in most cases, it was not followed up with further supportive actions. Persistent and more

intensive support is required in this group of patients. Patient's compliance with any treatment aimed at secondary prevention always remains a significant problem. Any lack of support is enough reason for the patients to carry on their normal lifestyle.

Diabetes is well associated with disease progression and complications. In this series it did not show a significant pattern of progression of disease or higher risk of complications than the non-diabetics at six months. This is similar to findings of the Framingham and Strong Heart studies [26, 248].

Heart protection study has highlighted the role of statins in prevention of serious cardiovascular complications [68]. Statins have been associated with improved walking distances [176]. This message seems to be getting across as lipid lowering therapy increased from 44% to 69% ($p < 0.001$) at six months in our series. Improvement in exercise tolerance partly may have resulted from use of such a therapy.

As mentioned earlier lipid measurements were being done routinely only in 14 of the 23 centres at the initial visit. Patients on lipid lowering therapy had lower cholesterol and LDL levels as compared to those without such therapy (total cholesterol 5.0 vs. 5.8 mmol/L and LDL 2.7 vs 3.5 mmol/L, $p < 0.001$). At follow up lipid profile was not recorded though these were not routinely checked at most centres. Most of the patients receiving lipid lowering therapy were on simvastatin 20mg per day. Currently in view of heart protection study the recommended dose is 40mg. This may explain the inadequate control of lipid profile and thus limited benefit of such therapy. Caution should be exercised in patients with hepatic dysfunction or myalgia. Liver function test and creatine kinase should be checked in symptomatic patients. Routine liver function tests measurement has not recommended [68].

This trends needs attention as patients with IC may be denied of the benefit of lipid lowering therapy especially when this group is a high risk for future cardiovascular morbidity. Checking cholesterol routinely may also help to not only diagnose but follow these patients and assess the benefit of lipid lowering therapy.

Over 70% patients were counselled and underwent various lifestyle modifications. Although general advice was available, there was a noticeable lack of uniform package for further counselling for smoking cessation, risk factor modification and supervised exercise programmes.

Dormandy has pointed out that the majority of claudicants tend to stabilise or improve over a period of time [229]. It was not surprising to find that the median initial claudication distances increased over six months (initial CD 100 versus 150 $p < 0.001$, absolute CD 150 versus 200 $p < 0.001$). This symptomatic stabilisation or improvement may be explained by changes at cellular level and development of local compensatory mechanisms and also improvement in modification of risk factors and lifestyle of the patients.

PAD Antiplatelet Consensus Group has recommended that all patients with IC should be on an antiplatelet agent for long term [234]. Hirsch et al have reported antiplatelet use of 33% only in newly diagnosed patients with PAD as compared to 54% of known PAD patients in a survey of 6979 patients across the United States [29]. We observed a significant improvement in antiplatelet use in our series at six months (88% versus 70%, p 0.001). This signifies an increasing awareness on part of the different health professionals involved in the management of PAD.

In this study a relatively high percentage of patients underwent further imaging, i.e. 27% had a duplex scan and 34% underwent peripheral angiogram. This is explained on the basis of a local practice pattern at one or two participating centres rather than a universal pattern. This may represent a regional trend in terms of patients' characteristics, disease severity or the varied management trend in a few institutions.

Frequency of local intervention varies widely from 3% to 22% in different studies [134, 135]. As discussed earlier (section 1.6.1.3.) only one fourth of all patients with IC deteriorate progressively, with an intervention rate of approximately 5% over 5 years for either severe claudication or deterioration to critical limb ischemia [30]. However in our series within a timescale of six months only, 7.8% of patients underwent peripheral intervention (angioplasty 6.2%, surgery 1.6%).

These patients either had troublesome claudication or were treated as per the treatment centre's policy of early intervention. Low ABPI, absolute claudication distance and number of pack years smoked were more likely to be associated with peripheral revascularisation. These varying policies call for uniform intervention indications as this will not only help to compare the results of different regions but also allow the cost implications in the management of PAD at national level.

Low ABPI, high systolic pressure and prior CHD were significantly associated with development of all vascular events. 14% of the patients suffered from a vascular event during a short period of six months. An inverse relationship was also observed between ABPI and the development of cardiovascular events. Similar results have been reported by the Framingham Offspring Study and the Cardiovascular Health Study [39, 111]. These findings confirm the usefulness of the ABPI as a useful marker of generalized atherosclerosis as observed in other studies [23, 254].

2 – 4% of patients with IC are expected to develop a nonfatal cardiovascular event within the first year [30]. In this series 2.1% presented with a nonfatal MI, CVA or TIA and 1.6% underwent coronary revascularisation within six months. 50 – 80% of the PAD patients die due to cardiovascular events [138, 139]. 13 patients died during the six month follow-up. 60% deaths were related with cardiovascular events. Besides low ABPI, age, high systolic blood pressure and prior CHD were significantly associated with death, MI or CVA.

National cardiac guidelines recommend that patients with IC should be managed in the same way as those with established coronary heart disease [251]. Cassar et al have reported a sub-optimal management of major risk factors in claudicants by the vascular surgeons in the UK [256]. Routine laboratory risk factor profile is not being checked at the referral centres and the chance to detect and manage new cases or cases with uncontrolled diabetes or hyperlipidaemia are being missed or sub-optimally managed.

Claudication improves with conservative measures in the majority of patients over a period of time. However, PAD patients are under treated for risk factors as

compared to CAD and CVD. This is especially so at the primary care level. There is a need for guidelines for uniform management of IC. Provision of a national risk reduction programme and life style modification package is urgently needed for this group of high-risk patients.

Chapter 7

Quality of life

7.1. Introduction:

Symptomatic disease of any sort often leads to diminished QoL (QoL) and PAD is no different. The symptoms of PAD are especially likely to persist over a prolonged period and this limited functional status limits the functional capacity significantly as compared to the healthy population [257]. Claudication not only limits the distance walked but also results in substantial impairment of social functioning, emotional and mental health [258, 259]. This limitation in QoL is only partially determined by the severity of walking limitation as the presence of cardiac and associated morbidity also plays a role in IC [260].

QoL has become increasingly important as an outcome measure in PAD because any interventional or conservative treatment should be aimed at improving the quality rather than just the quantity of life. Clinicians predict the QoL of claudicants less accurately than patients do themselves [258, 261]. Hence, several measurement tools are available to look objectively at any change in QoL status. The instruments used for measuring health-related QoL are expected to be valid (ability to measure what it is supposed to measure), reliable (reproduce a stable pattern of scores), feasible (easy to answer and administer for the respondent and investigator, respectively), responsive (ability to detect a clinical change or treatment effect) and to have cultural and language adaptations such as standardised translations, linguistic evaluations and attention to cultural issues.

7.2. Quantification of QoL:

QoL measures can be broadly divided into two groups:

a) generic

b) disease – specific

7.2.1. Generic Health Status Questionnaires:

Generic instruments tend to measure the global QoL dimensions, generally looking at

- functional status – ability to perform routine daily activities,
- perceived health – patient's perspective of his/her current health status,

- psychological status – patient's mental response to his/her present disease,
- role function – ability of a patient to perform his obligatory duties.

These tools may overlook the specific effects of the disease on QoL and thus may not detect any subtle though important variations. These also do not analyse disease specific symptoms [262]. However the principal objective of using the generic measures is that these allow comparison of the results of treatment across different diseases and also are useful for comparing different treatments in Health Ecomonic analysis.

Various generic tools for measurement have been developed. The following have commonly been employed in vascular studies:

- Euro Qol (EQ5D)
- Medical Outcomes Study Short-Form 36 (SF-36)
- RAND – 36
- Sickness Impact Profile (SIP)
- McMaster Health Index Questionnaire (MHIQ)
- Functional Status Questionnaire
- Health Utilities Index (HUI) and utilities (HUI2 and HUI3)
- Nottingham Health Profile (NHP).

7.2.2. Disease-specific Questionnaires:

A disease-specific health status questionnaire is generally used to measure baseline disease-specific health status. It concentrates on QoL domains affected by the symptoms of the disease in question. These are also used to measure any changes in the symptomatic disease. Disease-specific are more responsive [262, 263]. A number of these have been used in different centres to measure the patient oriented outcomes.

- Walking Impairment Questionnaire (WIQ)
- Peripheral Arterial Questionnaire (PAQ)
- VascuQol
- Physical Activity Recall
- Claudication Scale (CLAU-S)
- CCCQ (Charing Cross Symptom Specific Questionnaire)

- Artemis (Assessment of QoL in lower limb arteriopathy)
- Intermittent Claudication Questionnaire (ICQ)
- ECQ (Edinburgh Claudication Questionnaire)
- PAVK-86 [264] and
- Spitzer QL-index (a combined generic- and disease-specific questionnaire).

7.3. Methods:

In this study the generic QoL tool Euroqol – 5 (EQ-5) and the specific QoL tool the Peripheral Arterial Questionnaire (PAQ) were employed at the time of initial visit and then at the follow up. The patients generally answered these questionnaires independently. Where any help was required the patients were given an adequate explanation.

The EuroQol (EQ-5) is a 5-item questionnaire that can be used to measure health utility and health related QoL [218]. The EQ-5 defines health in five dimensions (mobility, self-care, usual activities, pain and discomfort, and anxiety or depression). In each dimension a respondent can belong to one of three categories—no problem, moderate problem, or severe problems. A utility value is therefore ascribed to an individual's health state based on the absence or presence of moderate or severe problems in the five dimensions. The EQ-5 also has a visual analogue scale that enables respondents subjectively to assess their health on a scale ranging from 0 (worst possible health state) to 100 (best possible health state) *(see appendix 3).*

Each of the five dimensions is divided into the levels of perceived problems:

Level 1 : No problem

Level 2 : Some problem

Level 3 : Extreme problem

Each health state was defined by combining one level from each of the five dimensions. These health states were converted to scores using the values based on the data collected from a representative survey of the UK general public.

The visual scale analogue "Thermometer" generated a self-rating current health-related QoL. This had end points at top of 100 (best imaginable health state) and

at bottom 0 (worst imaginable health state). Each respondent rated the health status by drawing a line from the box marked "Your own health state today" to the appropriate point on the "thermometer" scale.

PAQ is a recently validated, disease specific related QoL questionnaire with 21 items in 5 domains of patient symptoms, physical and social limitation, treatment satisfaction and QoL, specific to peripheral arterial disease *(see appendix 3)*. The PAQ is scored by assigning 1 point to the response suggesting the most limited function and an additional point for each higher response in the item. Scale scores are generated from summing the individual items within a domain and subtracting the lowest possible score for that domain, dividing by the range of that domain and multiplying by 100. All domains range from 0 to 100, where higher scores indicate less physical limitation, fewer symptoms, greater treatment satisfaction, or better QoL. Combining the physical limitation, symptom frequency/burden, social function, and quality-of-life domains derives a summary score.

These questionnaires were repeated at six-month interval at the follow-up visit.

7.4. Results:

7.4.1. Euroqol – 5. (Table 7.1)

The EQ – 5 generated profiles that can be measured against the important risk factors. Overall limitations of usual activities, pain or discomfort and anxiety or depression were of more concern than mobility and self care. The median health score was 0.69 (IQR 0.59 – 0.73) and self reported health status was 65 (IQR 50 – 76) on a scale of 0 – 100 at the initial clinic visit.

At follow-up the median health score was 0.69 (IQR 0.62 – 0.76) ($p < 0.0013$, Mann – Whitney test) and median health status 'thermometer' was 70 (IQR 50 – 80) (p 0.037, Mann – Whitney test).

Mobility and pain were the most commonly reported domains that affected the QoL.

Dimension	No problem (%)		Some problem (%)		Extreme problem (%)	
	0 month	6 month	0 month	6 month	0 month	6 month
Mobility	7.4	19.8	92.4	79.7	0.2	0.5
Self Care	90.4	90.2	8.9	9.5	0.7	0.3
Usual activities	35.9	48.8	59.9	44.6	4.2	6.6
Pain / Discomfort	7.2	20.1	70.6	68.1	22.2	11.8
Anxiety / Depression	63.6	66.7	32.2	27.8	4.2	5.5

Table 7.1. Distribution pattern of level of disability of the five life domains at initial visit and at six months.
(Values are quantified EQ-5 scores for each domain).

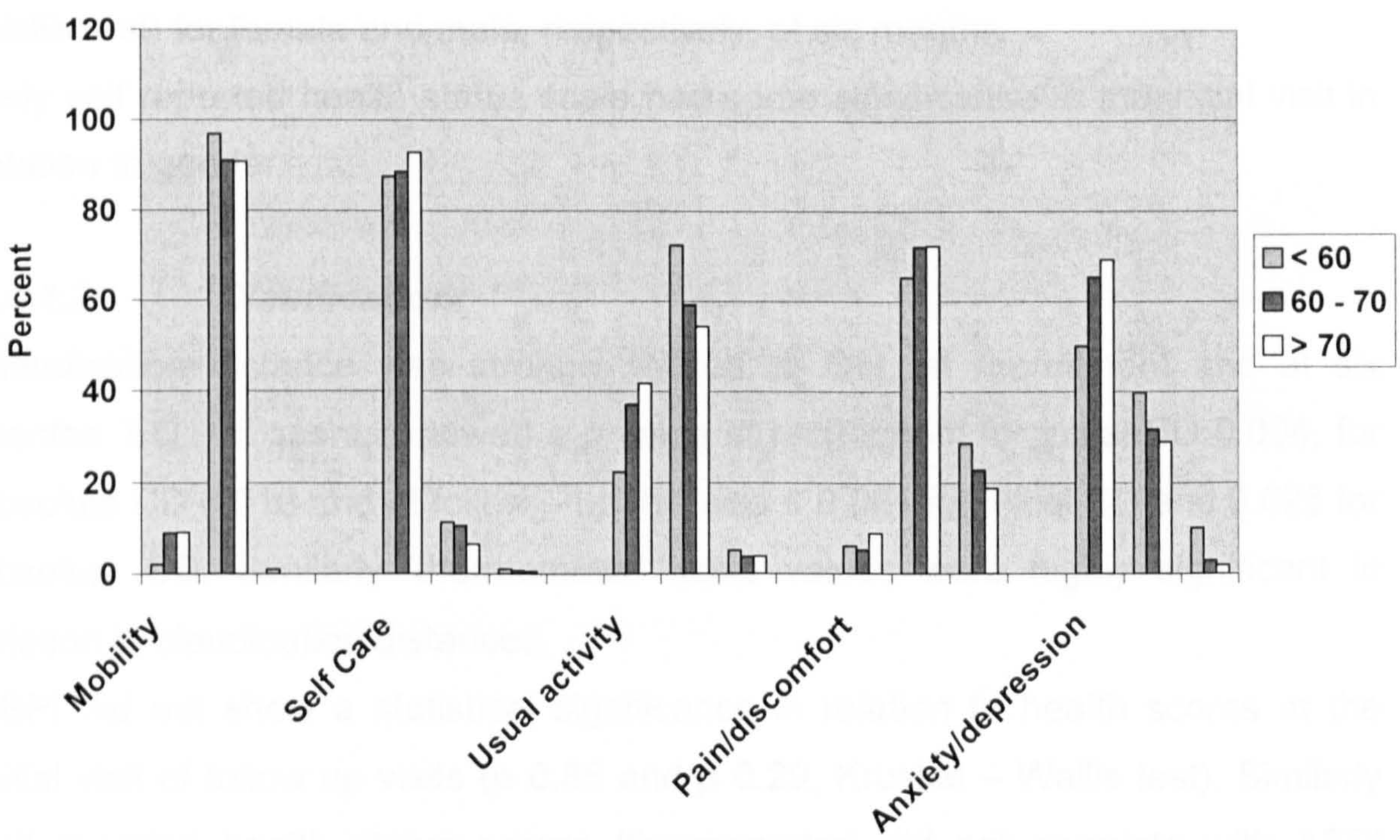


Figure 7.1. Distribution of euroqol – 5 domains at initial visit as per age group.

7.4.1.1. Age:

The life quality profile generally appears to remain unchanged in relation to age. No significant differences were observed in the three age groups in relation to different life quality parameters.

Interestingly the EQ – 5 scores were better in the above 70 years group as compared to below 60 (p 0.003, chi-square test). Self reported health status scores were not significantly different in the three age groups: 65, 70, 70 were the median scores in <60, 60 -70, > 70, respectively.

At follow-up EQ – 5 scores were 0.69, 0.69 and 0.69 and 'thermometer' means were 70, 70 and 65 for age groups < 60, 60 – 70 and > 70, respectively. These were not statistically significant for each age group.

7.4.1.2. Sex:

The median health status scores were 0.66 and 0.69 for female and male at recruitment (p 0.058, Kruskal – Wallis test) and 0.69 for both at follow-up. Self reported health status medians were 60 and 65 (p 0.035, Kruskal – Wallis test) on the thermometer scale at initial visit. These were 65 and 70 (p 0.40, Kruskal – Wallis test) for female and male, respectively, at six months.

Only self reported health status scale had some significance at the initial visit in relation to gender.

7.4.1.3. Claudication:

Claudication distance was strongly related to QoL at recruitment and at six months. EQ – 5 scores showed a p value at recruitment for initial CD 0.004, for absolute CD 0.016 and at follow – up this was < 0.001 for initial CD and 0.025 for absolute CD. Similarly 'thermometer' scale values were highly significant in relation to claudication distances.

ABPI did not show a statistical significance in relation to health scores at the initial visit of follow up visits (p 0.85 and p 0.29, Kruskal – Wallis test). Similarly self reported health status scores (thermometer) did not correlate with ABPI value at recruitment or follow up visit.

Health scores in patients with bilateral claudication were not significantly different as compared to unilateral claudicants except for the self reported

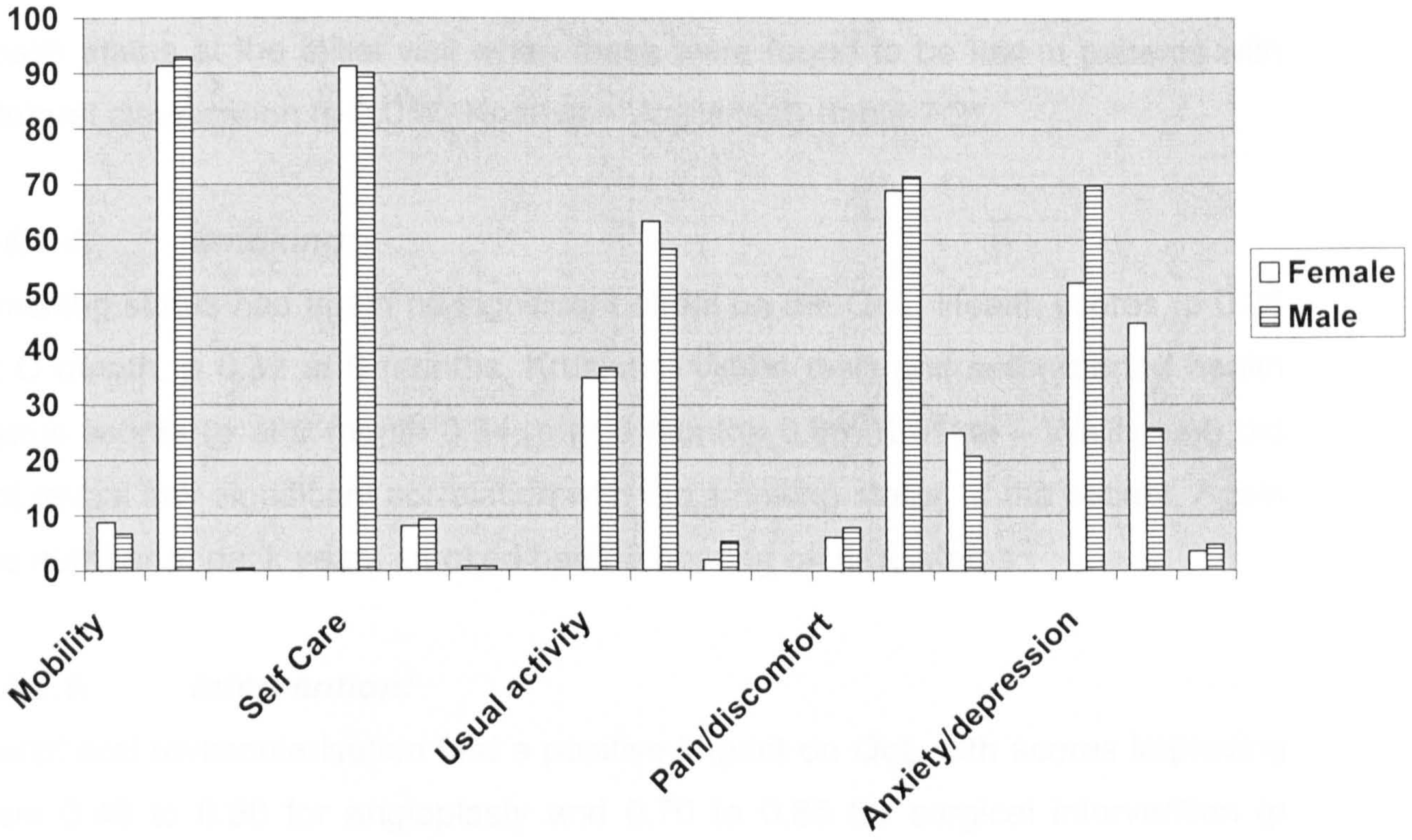


Figure 7.2. Distribution of health related domains (in percent) as per gender at recruitment.

Bilateral claudication	Score (median)		Thermometer (median)	
	0 month	6 month	0 month	6 month
No	0.69	0.69	69	60
Yes	0.69	0.69	70	65

Table 7.2. QoL in relation to uni- or bi-lateral claudication.

health status at the initial visit when these were found to be low in patients with bilateral claudication (p 0.017, Kruskal – Wallis test) (table 7.2).

7.4.1.4. Smoking:

Smoking status had again no significant effect on the QoL. Health scores (p 0.36 at O month, p 0.32 at 6 months, Kruskal – Wallis test) and self reported health status scores (p at 0 month 0.34, p at 6 months 0.65, Kruskal – Wallis test) did not reveal any significant correlation with the smoking status of the patient. Again the number of pack years smoked had no bearing on QoL status.

7.4.1.5. Intervention:

Peripheral revascularisation had a positive impact on QoL with scores improving from 0.48 to 0.50 for angioplasty and 0.70 to 0.86 for surgical intervention (p 0.005, chi-square test). Similarly 'thermometer' score improved from 62.8 to 67.9 for angioplasty and 58.8 to 77.0 for surgery ($p < 0.001$, Chi-square test).

7.4.1.6. Others:

Use of any medication or any blood investigation was not related to any significant change in QoL. Also, there was no effect of minimum school education as compared to more educated on different measures of life quality at baseline and at follow-up.

7.4.2. Peripheral artery questionnaire (PAQ):

PAQ was conducted in 338 (81.8%) patients at baseline and 299 (63%) at six months. In 287 (60.5%) patients this was conducted both at recruitment and at follow-up.

Domain	Baseline mean value	Follow-up mean value	Mean difference	p
Physical limitation	34.2	38.8	4.6	< 0.001
Symptom burden	41.4	50.1	8.7	< 0.001
Symptom stability	36.7	45.7	9.0	< 0.001
Social limitation	48.2	51.7	3.5	0.007
Treatment satisfaction	81.8	77.7	- 4.1	0.005
QoL	43.8	53.2	9.3	< 0.001
Summary Score	42.2	48.0	5.8	< 0.001

Table 7.3. PAQ scores at baseline and follow up.

Age group	Mean summary score at baseline	Mean summary score at follow-up
< 60	37.4	46.7
60 – 70	44.6	48.4
> 70	42.8	49.3

Table 7. 4 . Mean summary scores at baseline and follow-up.

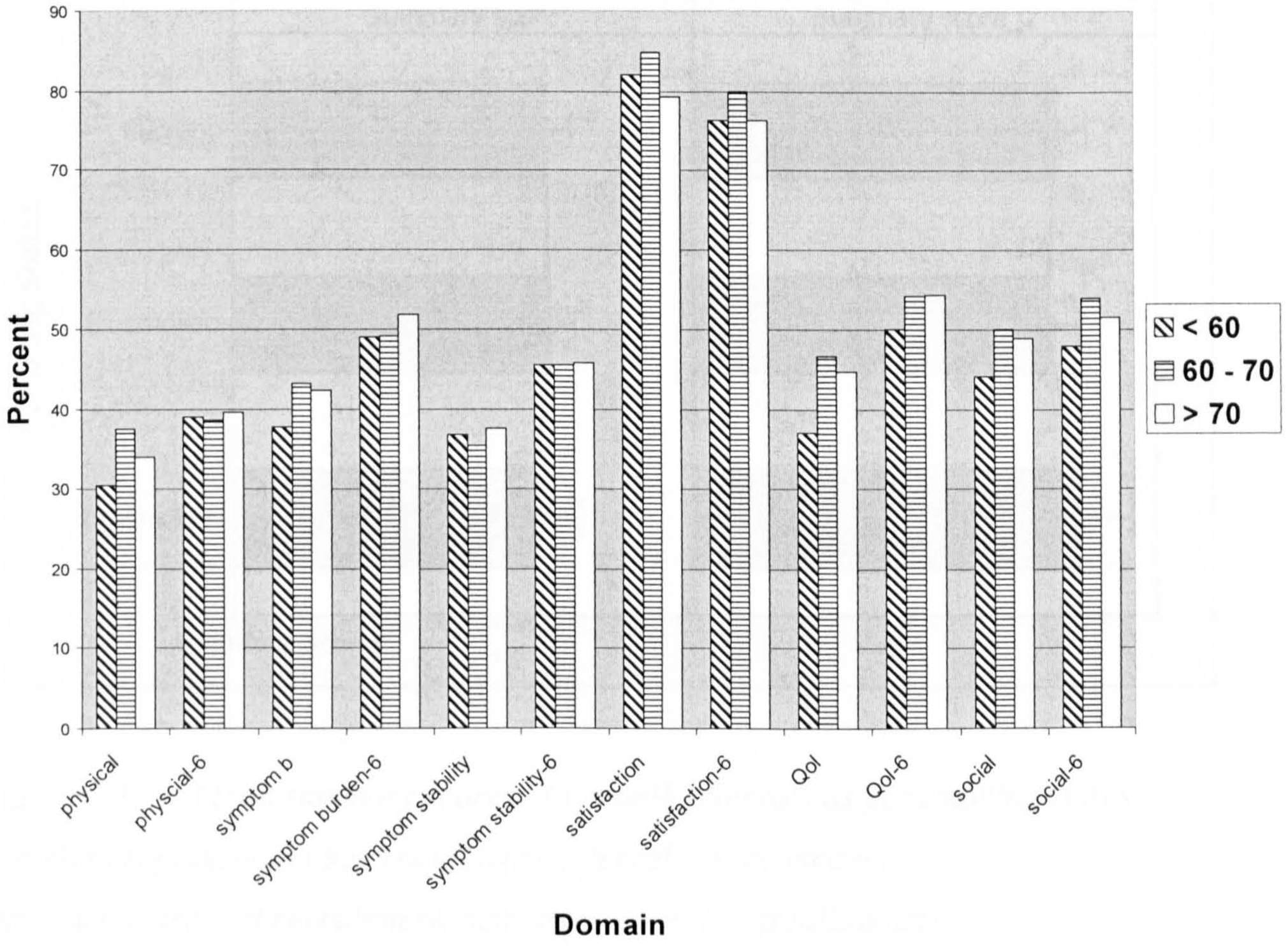


Figure 7.3. Domain pattern at baseline and at follow up for different age groups. (PAQ domains on X-axis at recruitment and at 6 months: physical, symptom burden, symptom stability, treatment satisfaction, QoL, social).

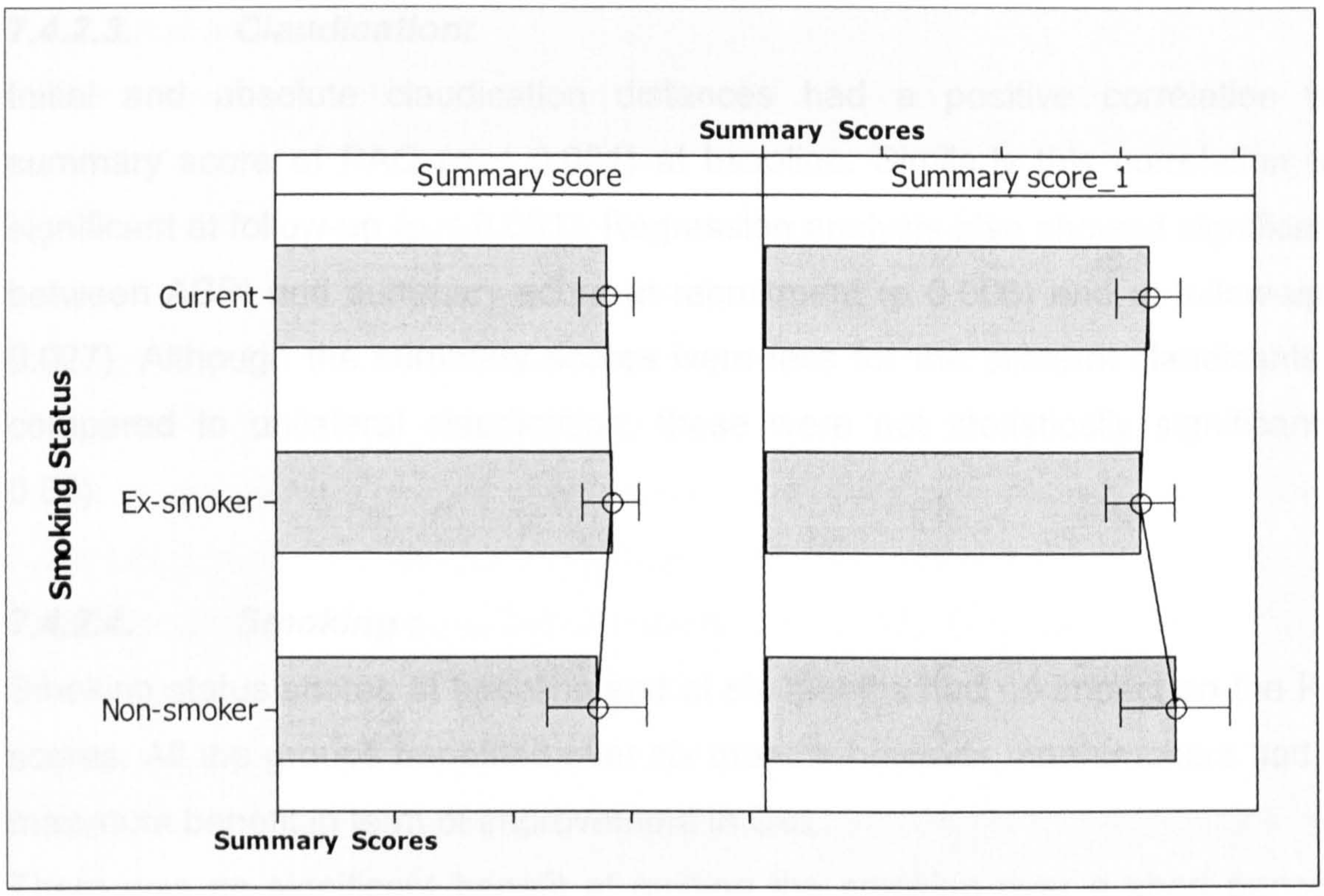


Figure 7.4. Mean summary scores at 6 month intervals as per smoking status. (whiskers represent the 95% confidence intervals of the means; Summary score – at recruitment, Summary score_1 – at follow-up).

7.4.2.1. Age:

The mean summary scores for each of the age group are displayed in table 7.4. Distribution pattern of various domains as per age group is shown in the figure 7.4.

7.4.2.2. Sex:

The mean (+/- sd) summary scores for female at baseline and follow up were 38.9 (+/- 18.6) and 45.6 (+/- 20.9); for male these were 43.7 (+/- 19.0) and 50.0 (+/- 22.6). The summary scores were not significant in relation to sex at baseline and follow-up although the mean scores were higher in males (p 0.056 and 0.121). The change in scores was significant in both sexes at follow-up in comparison to baseline.

7.4.2.3. Claudication:

Initial and absolute claudication distances had a positive correlation with summary score of PAQ ($p < 0.001$) at baseline. Similarly this correlation was significant at follow-up ($p < 0.001$). Regression analysis also showed significance between ABPI and summary score at recruitment (p 0.006) and at follow-up (p 0.027). Although the summary scores were less for the bilateral claudicants as compared to unilateral claudication, these were not statistically significant (p 0.06).

7.4.2.4. Smoking :

Smoking status scores at baseline and at six months had no impact on the PAQ scores. All the groups benefited over six months however, non-smokers had the maximum benefit in term of improvement in QoL.

There was no significant benefit of quitting the smoking over a short period in terms of improvement in QoL as the change in mean scores was not significant.

7.4.2.5. Peripheral intervention:

Peripheral intervention had a positive impact on summary scores. These changed from 44.3 to 69.7 for surgical intervention and from 30.6 to 45.6 for angioplasty ($p < 0.001$).

7.4.3. EQ – 5 and PAQ:

There was significant association of the scores of EQ – 5 and PAQ both at recruitment ($p < 0.001$) and at follow up ($p < 0.001$). Similar was true for the 'temperature' scale of EQ – 5.

7.5. Discussion:

As discussed earlier IC not only limits the blood flow to the lower limb but also is an indicator of systemic atherosclerosis. Hence it exerts a global impact on the patient. This impact besides the limited ambulatory disability, also translates into generalised decreased functional capacity. Using generic and disease specific QoL instruments this functional disability can be quantified. The use of both clinical and patient-based parameters is essential to assess the complete outcome of management of claudication. Generally clinical outcome measures have been used to evaluate the efficacy of any treatment but these appear to have a poor correlation with QoL measures [265, 266]. Barletta et al have shown a significant impairment of general health and low scores for physical and emotional dimensions in patients with IC as compared to controls [262]. This study confirms these findings with general QoL scores on EQ – 5 scales were 0.55 (range 0.05 – 1.00) and 63 (range 0 -100) at the initial visit. On the PAQ scale the summary score was 42 (range 0 – 100) at recruitment.

PAD patients have generally performed poorly on QOL measurement scales [267, 268]. Limitation of daily physical activity in performing routine activities and pain are the major dimensions in patients with IC that effect the QoL [269]. However depression is also common [270]. Patients rate their health status approximately one third lower than the perfect health state. Self reported health status in our series was 63 at recruitment.

Claudicants have greater perception problems in the areas of energy, pain, emotional reactions, sleep, and physical mobility [259]. Pain and mobility were the main domains that had a bearing on QoL in this series. Physical and social limitations and the symptom burden on PAQ scale were the main domains affecting the QoL.

In clinical practice objective disease criteria may not be an appropriate tool to assess the QoL in PAD patients. Uwe Müller et al have reported that QoL in PAD patients is independent of the peripheral Doppler pressure and the angiographic severity of the disease [271]. The most important criterion is the functional disability. However the same study concludes that the absolute claudication distance and body mass index are the most predictive variables for the QoL. Impairment in QoL in patients with IC correlates poorly with the reduced exercise capacity assessed by the treadmill test [266]. In our series we did find a

significant direct association of QoL scores with that of exercise tolerance. These scores had variable correlation with the ABPI. Any conclusion drawn on QoL from ABPI measurements would be inappropriate. A correlation has been established between the clinical indicators and QoL but not sufficient to assume that variations in clinical indicators result in reciprocal variations in QoL [265].

Patients over time become well equipped with the knowledge and understanding of the disease process. They tend to adjust or adapt to the problems faced in relation to claudication. This helps in the improvement of QoL. In this study we report an improvement of QoL measurements in a majority of patients over a six-month period regardless of the management format. There were significant improvements in health related QoL scores, both generic and disease specific, at six months. This can be related to overall lifestyle and overall risk factor modifications in this cohort over a six-month follow up.

Supervised exercise programmes have shown to increase the walking distance [155, 162, 163, 272]. Exercise is usually advised to patients with IC. In a recent study, QoL scores employing SF-36 and Charing Cross Symptom Specific Claudication Questionnaire (CCCQ) were significantly better in patients with supervised exercise than the advice group alone at 9 months (43% vs. 16%, $p < 0.05$) [273]. Tsai et al have reported an improvement of perception of health-related QoL from 12% to 178% on a 12 week supervised exercise programme [274]. A Swiss study reports similar results with pain, mood and functional status subscales on PAVK-86 improving significantly in patients with IC after 12 week exercise training [275].

One may predict that an older population might have a poor QoL not only from claudication but also from other co-morbid pathologies. We found significantly low scores at baseline in less than 60 year old patients as compared to older people but this levelled at six months follow up. Claudication perhaps limits the life pattern more in a young active patient. Claudication and PAD have a greater impact on women than on men and may result from the higher prevalence of mood disturbance and bodily pain reported by women [276]. Despite the similarity in disease severity, women have decreased physical functioning, more bodily pain and greater mood disturbance [276]. A recent study reported a statistically significant reduction in QoL of young women with PAD [271]. All domains of RAND-36 in comparison with QoL in healthy age-matched control

subjects were found to be diminished in this group. In another study male gender was associated with better scores for energy and fatigue, and for sleep and rest [260]. However, in our series we did not find a significant difference at recruitment or at follow up though mean scores were higher in males. Females were more anxious or depressed on EQ – 5 scale and had difficulty in social interactions as compared to males (p 0.014).

Smoking increases PAD progression. Quitting smoking may not only slows this progression but is expected to improve the QoL. We did not find a significant difference in QoL among current or ex-smokers and non-smokers over six month follow up. Cessation of smoking for a short period of time had no impact on QoL scores. However, improvement in non-smokers' QoL was much more than those with history of smoking over a six-month period.

Pharmacotherapy may have a positive impact on QoL. Cilostazol, naftidrofuryl and prostaglandin E1 have been shown to improve the QoL in claudicants [201, 211, 277, 278]. Statins have been reported to increase the walking ability in patients with IC but were not associated with improvement of QoL measures [276]. We did not observe any association of medication patterns with improvement in QoL scores. The effect of 'claudication improving' medicines, like cilostazol was not assessed in our study.

Many studies of invasive procedures have also been reported to have variable effects on QoL[280-282]. In our series we observed a very clear and positive impact of revascularisation procedures on the patient centred outcomes. EQ – 5's health and 'thermometer' scores and PAQ's summary scores improved significantly following angioplasty or surgical intervention. Whilst not surprising, this data might support the value of such intervention in PAD. Improvement of mobility with no claudication explains this better QOL scores.

For the success of any management plan, it is important to consider the patient centred outcomes as well. This may be the ideal outcome of any management plan. Physicians in charge of the care of claudicants should have a thorough understanding of the specific and overall effects of IC so that they can develop therapeutic plans suited to individual needs. Mobility may be an important aspect for a young claudicant in order to pursue his or her career while an elderly patient with a similar level of disease may not have any deterioration in QoL. Successful

management outcomes must therefore include the patient centred outcomes. A uniform strategy in this regard is suggested at a national level. The results of such outcomes may be more easily comparable than for complex clinical parameters.

Chapter 8

Conclusions

The risk factors for PAD are well defined; however, the management of these risk factors and the overall management of PAD remains variable, not only at the primary care level but also in specialist vascular units. IC is the major form of presentation of this disease. We studied 474 claudicants from 23 centres across the UK. This is the largest study of its kind in the UK to date documenting current practices in the management of IC and its associated risk factors. From an analysis of baseline data we discovered that male sex and increasing age impart a high risk for developing PAD, as previously reported in other studies. Patients with bilateral claudication are also more likely to have significantly less absolute exercise tolerance as compared to unilateral claudicants. ABPI was found to have a significant association with angina, BMI, initial and absolute claudication distances and total cholesterol. We have discovered that patients with PAD are under treated for their risk factors as compared to those with prior or coexistent coronary or cerebrovascular disease. We have found that one quarter of claudicants were not on antiplatelet therapy at referral from the General Practitioner and those with a past history of CAD or lipid lowering or anti-hypertensive therapy were more likely to receive anti-platelet agents. Cholesterol levels were not checked in 9 of the 23 centres and the management of this risk factor was quite erratic. Many of the patients with significantly higher levels of cholesterol were not receiving any treatment at the initial visit. Similarly anti-hypertensive treatment appeared unsatisfactory as 13% of patients had inadequately controlled hypertension and 6% of the patients needed further assessment of their high blood pressure. Effective communication is required in this regard between the specialist vascular team and the referring General Practitioner. Surprisingly risk factor profiles and management of diabetics in our series was not much different as compared to non-diabetic claudicants. Again progression of the disease in this group was similar to the rest of the population at six months.

A worryingly high proportion of claudicants were found to be smokers and disappointingly the smoking cessation rate was low at six-month follow up. The prevalence of smoking was much higher in the male population especially the younger age group. HDL levels were also found to be significantly lower in this

group. These two factors may partially be responsible for the increased incidence of IC among the males.

Although we found a higher serum cholesterol levels among the females, the TC: HDL ratio was also higher as compared to the males. We did not find any difference in terms of management or progression of claudication in relation to gender as has been suggested by some other reports.

Certain age related differences were noted which may have further clinical implications. We report that the younger population is less likely to be treated for their adverse risk factors as compared to the elderly or those with past history of cardiovascular disease. Younger claudicants were also found to be smoking currently in the majority of cases. Understandably the proportion of these current smokers decreased with age. Younger smokers were more likely to attempt to stop smoking as compared to the elderly; however, we feel that this group was not provided with enough smoking cessation support. Moreover, younger patients also had a higher serum cholesterol and TC:HDL levels as compared to the elderly; hence emphasising the need to check the lipid profile in all the patients.

At six months follow up certain improvements were noted. These were not only in clinical parameters but also in terms of risk factor management. Improvement in relation to claudication distance at six months was across the board irrespective of age group or gender contrary to some earlier reports. A satisfying element of the six-month follow up was the significant improvement in the use of statins and antiplatelets.

The overall pattern of management varied among different centres. Relatively higher numbers of patients underwent various forms of imaging and thus subsequent interventions as expected. This related more to the local practice pattern than the national management trends. Low ABPI and pack years smoked had a significant correlation with peripheral intervention. Again low ABPI was significantly associated with development of all vascular events along with the

high systolic pressure and history of CHD. Further morbidity and mortality rates were in line with the reported literature.

Patients with IC are two to three times more likely to develop a fatal cardiac event than non-claudicants. We feel that a national risk factor management protocol or guidelines should be established. The current delivery of risk modifying interventions has been found to be very patchy. This was certainly the case at the initial visit when patients were referred from primary care. However at six month follow up we observed a significant improvement in the use of lipid lowering therapy and antiplatelets over a six month time period. Creating increasing awareness and education programmemes especially at the primary care level for the prevention and treatment of risk factors will go a long way in reducing further local and cardiovascular events. Besides the involvement of General Practitioners, perhaps nurse led risk factor clinics in the community may prove helpful in this regard.

As many of the risk factors in PAD are common with those of CAD and CVD, establishment of risk lowering strategies "under one roof" would be a logical way forward. We believe that establishing national guidelines will enhance this benefit. "Risk lowering clinics" have been established in a few peripheral vascular centres already. Such an initiative is also needed at the national level. In a few countries like USA and Sweden such clinics have been established and provide a comprehensive risk factor lowering strategy and help in all aspects of PAD. These clinics, besides the diagnosis and management of treatable risk factors, should also have the facilities for the support of smoking cessation and supervised exercise programmes. Physicians, nurse practitioners, registered nurses, exercise physiologists, behavioural scientists, dieticians and social workers should staff or be involved in these clinics. Lifestyle modification also needs maximal support from relatives, friend and the community besides the therapist. This will require education of the public about PAD. Cost benefits in terms of reduction of future vascular events also need to be documented.

It is recommended that a national database of risk factors in patients with IC should be established and the outcomes in relation to particular risk factors

should be analysed. Such an outcome can be reached by extension of the present study over a longer period of time. This may also help to establish a 'vascular risk factor score' in relation to outcome in each patient. It is important to point out the group of patients that is likely to be at a higher level of risk of progression of disease. Such a score may become an effective tool in pinpointing this group of patients, as this will portray not only the severity of the disease process but also its prognosis. Perhaps a preventive strategy can be established in these patients on the basis of their risk factor profile.

Using the present template, in an extension to the current PRPARED study, data is also being collected to analyse the health costs of PAD at present in the UK. It will be interesting to see the effect of cost benefits of employing a uniform strategy for the management of PAD in the UK. This data can also differentiate the cost effectiveness of different modalities of treatment and interventions. This economic evaluation can relate the costs of a diagnostic or therapeutic strategy to its outcomes.

The clinical outcome of treatment does not directly correlate with QoL outcomes. An optimal interventional result represents a step toward the achievement of an improved functional status, but it is not indicative of an overall improvement in the patient's QoL. Agreed QoL parameters should also be used to assess the outcome of procedures or treatment on the patient.

Little has been done to study the effect of various modalities of treatment of PAD in IC in relation to QoL indicators. Randomised controlled studies to quantify these effects would help to determine the future direction of treatment of these patients.

Data from this study documents the patient characteristics, current trends of management in terms of risk factors and the disease specific treatments and marks out the high risk factors in relation to specific subgroups. This data could help to focus the treatment to a specific target population in relation to their risk factor status or disease state. The current deficiencies highlighted above may help determine new benchmarks to improve future practice. Resources will have to be mobilised in order to meet these objectives. General practitioners are at the

forefront of any primary prevention. It is worrying that in the current new GMS contract for General Practitioners there are no points concerning the primary management of PAD. There is an urgent need to rectify this.

APPENDICIES

APPENDIX 1: Centres participated in the study.

Institution	Consultant	Co-ordinator
Aberdeen Royal Infirmary	Ms Brittenden	
Addenbrookes Hospital	Mr Varty	Cathy Pitman
Belfast City Hospital	Mr Hannon	Kathy McGuigan
Birmingham Heartlands Hospital	Prof Bradbury	Yvonne Hall
Derriford Hospital	Mr Ashley	Chryz Cosgrove
Ealing Hospital	Mr Geroulakos	Stella Daskalopou
Freeman Hospital	Prof Stansby	Shiela Dugdill
Frimley Park Hospital	Mr Gerrard	Claire King
Gloucestershire Royal Hospital	Mr Earnshaw	Donna Parkin
Gwent Healthcare NHS Trust	Mr Blackett	Jayne Warren
Hull Royal Infirmary	Prof McCollum	Jenny Bryce
Ipswich Hospital	Mr Osman	Katie Weedon
Leicester Royal Infirmary	Prof London	
Morriston Hospital	Mr Gibbons	Rachel Harvard
Pinderfields Hospital	Mr Curley	
Queen Elizabeth Hospital	Mr Bhattacharya	Marcus Cleanthis
Royal Bournemouth Hospital	Mr Parvin	Sara Baker
Royal Free Hospital	Mr Baker	Phyl Morris-Vincent
Royal United Hospital	Prof Horrocks	Tulin Bodamyali
Selly Oak Hospital	Mr Vohra	Chris Lee
Southampton General Hospital	Prof Shearman	Jenny Williams
St Marys Hospital	Mr Cheshire	Louise Williams
Walsgrave Hospital	Mr Higman	Carol Bick

APPENDIX 2: Case Record Form (CRF)

PATIENT DETAILS

1	First name	
2	Middle name	
3	Surname	
4	Hospital Number	
5	Gender	
6	Date of Birth	__ __/__ __/__ __ __ __
7	Telephone number	

DETAILS OF RELATIVE NOT AT THE SAME ADDRESS

8	Relative family name:	
9	Relative first name:	
10	Address: Street:	
11	City:	
12	Postal code:	
13	Country:	
14	Telephone number:	

PATIENT DETAILS

1	Initials (first, last)	_ _ _ _ _ _ _ _
2	Date of birth	_ _ / _ _ / _ _ _ _
3	Sex	Male [ ] Female [ ]
4	Date of visit	_ _ / _ _ / _ _ _ _
5	Height	_ _ _ cm
6	Weight	_ _ _ . _ kg
7	Resting heart rate	_ _ _ bpm
8	Systolic blood pressure	_ _ _ mmHg
9	Diastolic blood pressure	_ _ _ mmHg
10	Ethnic origin[←]	Caucasian [ ] Afro-Carribean [ ] East-Asian [ ] South Asian [ ] African [ ] Other [ ] specify

INCLUSION CRITERIA

11	History of intermittent arterial claudication[↑]	Yes [ ] No [ ] ***stop***
12	New referral to vascular clinic[→]	Yes [ ] No [ ] ***stop***
13	Ability to provide written informed consent	Yes [ ] No [ ] ***stop***
14	Ankle/brachial blood pressure index ≤ 0.9[↓]	Yes [ ] No [ ] ***stop***

If No do not include this patient

EXCLUSION CRITERIA

15	Critical limb ischaemia[°]	Yes [ ] ***stop*** No [ ]
16	Spinal canal claudication probable[±]	Yes [ ] ***stop*** No [ ]
17	Claudication probably related to venous obstruction[″]	Yes [ ] ***stop*** No [ ]
18	Other acute major medical/surgical condition[≥]	Yes [ ] ***stop*** No [ ]
19	Patient taking part in any other studies	Yes [ ] ***stop*** No [ ]

If Yes do not include this patient

BASELINE MEDICAL HISTORY

1	Treatment for hypertension	Yes [ ] No [ ]
2	Treatment for hyperlipidaemia	Yes [ ] No [ ]
3	Angina[←]	Yes [ ] No [ ]
4	Diabetic[↑]	NIDD [ ] IDD [ ] No [ ]
5	Prior MI[→] (if yes date [mm/yyyy])	Yes [ ] __ __/__ __ __ __ No [ ]
6	Prior CVA[↓] (if yes date [mm/yyyy])	Yes [ ] __ __/__ __ __ __ No [ ]
7	Prior CABG[⌐] (if yes date [mm/yyyy])	Yes [ ] __ __/__ __ __ __ No [ ]
8	Prior PTCA[±] (if yes date [mm/yyyy])	Yes [ ] __ __/__ __ __ __ No [ ]

PERIPHERAL VASCULAR DISEASE HISTORY

9	Claudication bilateral[″]	Yes [ ] No [ ]
10	Estimated initial claudication distance[≥]	__ __ __ m
11	Estimated absolute claudication distance[×]	__ __ __ m
12	Ankle brachial pressure index – Left[∝]	
13	Ankle brachial pressure index – Right[∝]	
14	Previous peripheral vascular graft[11]	Yes [ ] No [ ]
15	Known internal carotid stenosis (>50%)[12]	Yes [ ] No [ ]
16	Aortic aneurysm[13]	Yes [ ] No [ ]
17	Has a treadmill Doppler test been carried out[14]	Yes [ ] No [ ]

EMPLOYMENT AND EDUCATION HISTORY

18	Is patient currently in paid employment	Yes [ ] No [ ]
19	If Yes, give average hours worked	__ __ Hours per week
20	Did education continue post minimum school leaving age	Yes [ ] No [ ]
21	Degree/equivalent professional qualification	Yes [ ] No [ ]

SMOKING STATUS

1	Smoking history ←	a) Current [ ] Go to Q3 b) Ex-smoker [ ] Go to Q2 c) Non-smoker [ ] Go to Q8 d) Smoker other [ ] Go to Q4
2	If ex-smoker, date stopped (mm/yyyy)	__ __ / __ __ __ __
3	Pack years smoked ↑	
4	If other, please give total amount smoked/week ↓→	NA [ ]
5	Has patient attempted to stop in last 6 months	Yes [ ] No [ ] NA [ ]
6	If Q5 is Yes, please specify method used	a) Nicotine replacement therapy ↓ [ ] b) Bupropin (Zyban) [ ] c) Counselling [ ] d) Other [ ]
7	If Other please specify	

BLOOD TESTS

8	Total Cholesterol	mmol/L NA [ ]
9	HDL	mmol/L NA [ ]
10	LDL	mmol/L NA [ ]
11	Triglycerides	mmol/L NA [ ]
12	Glucose	mmol/L NA [ ]
13	Creatinine	umol/L NA [ ]
14	Haemoglobin	g/dL NA [ ]
15	MCV	fL NA [ ]
16	Platelets	10^9/L NA [ ]
17	White cell count	10^9/L NA [ ]
18	CRP	mg/L NA [ ]
19	Fibrinogen	g/L NA [ ]
20	Homocysteine	umol/L NA [ ]

ANTIPLATELET MEDICATIONS

1	Is patient taking any antiplatelet medication[←]	Yes [ ] go to Q2 No [ ] go to Q4
2	If Yes, specify agent	a) Aspirin Yes [ ] No [ ] b) Clopidogrel Yes [ ] No [ ] c) Ticlopidine Yes [ ] No [ ] d) Dipyridamole Yes [ ] No [ ]
3	If taking aspirin, average daily dose	___ ___ ___ mg
4	If Q1 is No, please give reason	a) History of ulcers [ ] b) Indigestion [ ] c) Allergy [ ] d) Aspirin never prescribed/recommended [ ] e) Non-compliance [ ] f) Other [ ]
5	If Other, please specify	

OTHER MEDICATIONS

6	Lipid lowering (statin)	Yes [ ] No [ ]	14	Nitrate (oral/patch)	Yes [ ] No [ ]
7	Lipid lowering (other)	Yes [ ] No [ ]	15	Vasodilator[◇]	Yes [ ] No [ ]
8	Warfarin[↑]	Yes [ ] No [ ]	16	Quinine	Yes [ ] No [ ]
9	Digoxin	Yes [ ] No [ ]	17	Diuretic	Yes [ ] No [ ]
10	ACE inhibitor[↓→]	Yes [ ] No [ ]	18	Oral hypoglycaemic	Yes [ ] No [ ]
11	Beta blocker[↓]	Yes [ ] No [ ]	19	Insulin	Yes [ ] No [ ]
12	Calcium antagonist	Yes [ ] No [ ]	20	HRT[±]	Yes [ ] No [ ]
13	Angiotensin II antagonist	Yes [ ] No [ ]			

FOLLOW-UP DETAILS

21	EuroQoL completed (if yes date)[✓]	Yes [ ] __ __ / __ __ / __ __ __ __ No [ ]
22	PVD QoL completed (if yes date)[✓]	Yes [ ] __ __ / __ __ / __ __ __ __ No [ ]
23	VascuQoL completed (if yes date)[✓]	Yes [ ] __ __ / __ __ / __ __ __ __ No [ ]
24	If Q21-23 is No, please give reason	
25	Name of person completing CRF	
25	Date CRF completed	__ __ / __ __ / __ __ __ __
26	Date of planned follow-up[≥]	__ __ / __ __ / __ __ __ __

Please check this form carefully and complete any missing data. The top copy of these pages along with the completed questionnaires should be sent to the CTEU using the labels provided within 2 days of the patient being enrolled into the study

6 MONTH FOLLOW-UP

1	Date of follow-up	__ __ / __ __ / __ __ __ __
2	Method of follow-up	Hospital visit [ ] Telephone [ ]
3	Weight	__ __ __ . __ kg
4	Resting heart rate	__ __ __ bpm
5	Systolic blood pressure	__ __ __ mmHg
6	Diastolic blood pressure	__ __ __ mmHg
7	Claudication bilateral[←]	Yes [ ] No [ ]
8	Estimated initial claudication distance[↑]	__ __ __ m
9	Estimated absolute claudication distance[→]	__ __ __ m
10	Ankle brachial pressure index – Left[↓]	
11	Ankle brachial pressure index – Right[↓]	

ANTIPLATELET MEDICATIONS

12	Is patient taking any antiplatelet medication[°]	Yes [ ] go to Q13 No [ ] go to Q15
13	If Yes, specify agent	a) Aspirin Yes [ ] lo [ ] b) Clopidogrel Yes [ ] lo [ ] c) Ticlopidine Yes [ ] lo [ ] d) Dipyridamole Yes [ ] lo [ ]
14	If taking aspirin, average daily dose	___ ___ ___ mg

ALL MEDICATIONS

15	Lipid lowering (statin)	Yes [ ] No [ ]	23	Nitrate (oral/patch)	Yes [ ] No [ ]
16	Lipid lowering (other)	Yes [ ] No [ ]	24	Vasodilator[×]	Yes [ ] No [ ]
17	Warfarin[±]	Yes [ ] No [ ]	25	Quinine	Yes [ ] No [ ]
18	Digoxin	Yes [ ] No [ ]	26	Diuretic	Yes [ ] No [ ]
19	ACE inhibitor[″]	Yes [ ] No [ ]	27	Oral hypoglycaemic	Yes [ ] No [ ]
20	Beta blocker[≥]	Yes [ ] No [ ]	28	Insulin	Yes [ ] No [ ]
21	Calcium antagonist	Yes [ ] No [ ]	29	HRT[∝]	Yes [ ] No [ ]
22	Angiotensin II antagonist	Yes [ ] No [ ]			

EVENTS SINCE ENROLMENT

1	Has patient died (if yes date)	Yes [ ] __/__/____ No [ ]
2	If yes give main cause of death↙←	
3	MI (if yes date)↑	Yes [ ] __/__/____ No [ ]
4	CVA (if yes date) if No, go to Q7↙→	Yes [ ] __/__/____ No [ ]
5	Type of CVA	a) Haemorrhagic [ ] b) Non-haemorrhagic [ ] c) Not known [ ]
6	Level of disability	a) Major [ ] b) Minor [ ] c) Full recovery [ ]
7	TIA(if yes date)↓	Yes [ ] __/__/____ No [ ]
8	Coronary angioplasty(if yes date)°	Yes [ ] __/__/____ No [ ]
9	CABG (if yes date)±	Yes [ ] __/__/____ No [ ]
10	Peripheral arterial revascularisation″	Yes, Major [ ] Yes, Minor [ ] No [ ]
11	If yes give date	__/__/____
12	Congestive heart failure (if yes date)≥	Yes [ ] __/__/____ No [ ]
13	Last known creatinine and date performed	____ __/__/____ NA [ ]
14	Was dialysis required (if yes, date)×	Yes [ ] __/__/____ No [ ]

OTHER HOSPITAL ADMISSIONS SINCE ENROLMENT

15	Hospitalisation for other reason∝	Yes [ ] No [ ]
16	If yes, reason for admission 1	NA [ ]
17	If yes, reason for admission 2	NA [ ]
18	If yes, reason for admission 3	NA [ ]

SMOKING STATUS

1	Smoking history	a) Current [ ]	Go to Q3
		b) Ex-smoker [ ]	Go to Q2
		c) Non-smoker [ ]	Go to Q8
		d) Smoker other [ ]	Go to Q4
2	If ex-smoker, date stopped (mm/yyyy)	__ __ / __ __ __ __	
3	Pack years smoked		
4	If other, please give total amount smoked/week		
5	Has patient attempted to stop in last 6 months	Yes [ ] No [ ] NA [ ]	
6	If Q5 is Yes, please specify method used	a) Nicotine replacement therapy [ ]	
		b) Bupropin (Zyban) [ ]	
		c) Counselling [ ]	
		d) Other [ ]	
7	If Other please specify		

PATIENT'S SYMPTOMS

8	Compared to the time of first recruitment into the study have the patient's symptoms	a) Improved substantially [ ]	
		b) Improved slightly [ ]	
		c) Not changed [ ]	
		d) Deteriorated slightly [ ]	
		e) Deteriorated substantially [ ]	
9	Similarly has the patient's ability to mobilise (with respect to his or her peripheral arterial disease)	a) Improved substantially [ ]	
		b) Improved slightly [ ]	
		c) Not changed [ ]	
		d) Deteriorated slightly [ ]	
		e) Deteriorated substantially [ ]	
		f) Deteriorated for reasons other than PAD [ ]	

FOLLOW-UP DETAILS

1	EuroQoL completed (if yes date)	Yes [ ] __ __/__ __/__ __ __ __ No [ ]
2	PVD QoL completed (if yes date)	Yes [ ] __ __/__ __/__ __ __ __ No [ ]
3	VascuQoL completed (if yes date)	Yes [ ] __ __/__ __/__ __ __ __ No [ ]
4	If Q1-3 is No, please give reason	
5	Name of person completing CRF	
6	Date CRF completed	__ __/__ __/__ __ __ __
7	Date of planned follow-up	__ __/__ __/__ __ __ __

INVESTIGATORS DECLARATION

By signing below, I declare that the information presented in this Case Record Form accurately reflects the medical records, including the results of tests and evaluations performed on the dates specified.

8	Date	__ __/__ __/__ __ __ __
9	Name of investigator	
10	Signature of investigator	

Please check this form carefully and complete any missing data. The top copy of these pages along with the completed questionnaires should be sent to the Clinical Trials and Evaluation Unit, Royal Brompton Hospital using the labels provided within 2 days of this visit

APPENDIX 3: Euroqol – 5 Questionnaire

Please indicate which statement best describes your own health today.

1 Mobility

I have no problems walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

2 Self care

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

3 Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

4 Pain / Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

5 Anxiety/ Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

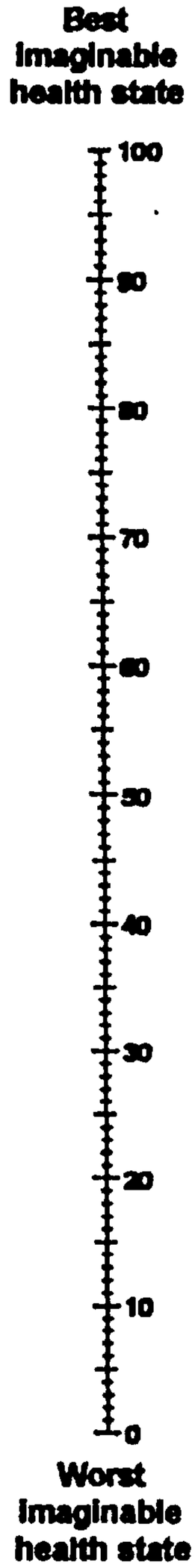
I am extremely anxious or depressed ☐

Your own health state today

To help people say how good or bad their health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you could imagine is marked by 0

We would like you to indicate on the scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box to whichever point on the scale indicates how good or bad your current health state is.

Your own health state today



APPENDIX 4: Peripheral Artery Questionnaire

The Peripheral Arterial Questionnaire

The following questions refer to blockages in the arteries of your body, particularly your legs, and how that might affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. Blockages in the arteries, often referred to as **peripheral vascular disease**, affect different people in different ways. Some feel cramping or aching while others feel fatigue. Which leg (or buttock) causes you the most severe **discomfort, fatigue, pain, aching, or cramps**?

the **Right** leg (buttock)	the **Left** leg (buttock)	**Both** are the same	Neither
☐	☐	☐	☐

2. Please review the list below and indicate how much limitation you have due to **your peripheral vascular disease** (discomfort, fatigue, pain, aching, or cramps in your calves (or buttocks)) over the past 4 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Walking around your home	☐	☐	☐	☐	☐	☐
Walking 1-2 blocks on **level ground**	☐	☐	☐	☐	☐	☐
Walking 1-2 blocks **up a hill**	☐	☐	☐	☐	☐	☐
Walking 3-4 blocks on level ground	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐
Vigorous work or exercise	☐	☐	☐	☐	☐	☐

3. Compared with 4 weeks ago, have your symptoms of **peripheral vascular disease** (discomfort, fatigue, pain, aching, or cramps in your calves (or buttocks)) changed?

My symptoms have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I have had no symptoms over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, how many times did you have **discomfort, fatigue, pain, aching, or cramps in your calves (or buttocks)**?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 4 weeks
☐	☐	☐	☐	☐	☐	☐

5. Over the past 4 weeks, how much has **discomfort, fatigue, pain, aching, or cramps in your calves (or buttocks)** bothered you?

It has been ...

Extremely bothersome	**Moderately** bothersome	**Somewhat** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no leg discomfort**
☐	☐	☐	☐	☐	☐

6. Over the past 4 weeks, how often have you been awakened with **pain, aching, or cramps in your legs or feet?**

Every night	3 or more times per week but not every night	1-2 times per week	Less than once a week	Never over the past 4 weeks
☐	☐	☐	☐	☐

7. How satisfied are you that everything possible is being done to treat your **peripheral vascular disease?**

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. How satisfied are you with the explanations your doctor has given you about your **peripheral vascular disease?**

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Overall, how satisfied are you with the current treatment of your **peripheral vascular disease?**

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

10. Over the <u>past 4 weeks</u>, how much has your **peripheral vascular disease** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

11. If you had to spend the rest of your life with your **peripheral vascular disease** the way it is <u>right now</u>, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

12. Over the <u>past 4 weeks</u>, how often have you felt discouraged or down in the dumps because of your **peripheral vascular disease?**

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
☐	☐	☐	☐	☐

13. How much does your **peripheral vascular disease** affect your lifestyle? Please indicate how your **discomfort, fatigue, pain, aching, or cramps in your calves (or buttocks)** may have limited your participation in the following activities over the past 4 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐

14. If you have wanted to have sexual relations, how much difficulty have you had in doing this over the past 4 weeks?

It has been....

Extremely difficult	**Moderately** difficult	**Somewhat** difficult	**Slightly** difficult	**Not at all** difficult	I have **not had** or **wanted** to have sexual relations
☐	☐	☐	☐	☐	☐

APPENDIX 5: Information Sheet for Patients

Title of project:

(PREPARED-UK) Prospective Registry and Evaluation of Peripheral Arterial Risks, Events and Distribution in the UK

Invitation to participate:

You are being asked to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it involves. This information sheet is designed to help you decide whether you would like to participate in this study. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study and why have I been chosen?

You have been referred to this hospital because you are suffering from Peripheral Arterial Disease (PAD). This is both a common and important condition. The purpose of this letter is to ask for your permission to use information about your medical condition for a registry study. A registry study records information on patients medical history and treatments, it does not change your medical care in any way. This study will be carried out in about 25 hospitals throughout the country and will document a few important medical details of patients like yourself. This will provide valuable information to help doctors understand more about peripheral arterial disease and will guide future research to improve the treatment of patients with these conditions.

Do I have to take part

No, you do not have to take part. It is up to you whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you do decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part?

We will record information about your medical condition, this data will be recorded anonymously. We would expect this to take less than one hour. Participation in this study will have no effect on the care you receive at any time. You will not undergo any extra tests or receive any extra treatments as a result of this study, and most of the information will be obtained from your medical records. Brief details of your state of health 6 months after you agree to take part need to be recorded. This can either be done at a routine clinic appointment or by telephone. We may contact you again up to 2 years after you agree to take part to see how you are and what, if any, new medical problems you have had. Longer term follow-up is important because it provides valuable information about the effects of peripheral arterial disease on your health status over a number of years. We will also ask you to complete 2 short questionnaires which ask questions about your quality of life at each visit.

We will write to your GP to inform them that you are taking part in this study. We will also continue to gather some very limited information about your health in the longer term. This may be for up to twenty years after your enrolment into the study and will not involve us contacting you in any way. This is done by a process called 'flagging' which involves giving your name to the Office of National Statistics (they also collect the information in the UK census). This process does not involve you in any extra contact with your hospital or with doctors. The information given to the Office of National Statistics (name, address and NHS number) is kept strictly confidential and they will not contact you or your family directly.

What are the possible benefits of taking part?

You are unlikely to benefit directly from participation in this study, however, any knowledge gained from your taking part is likely to be of benefit to others. The results of this study will be used to improve future treatments and care for patients like you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Information collected will not be used for any other purpose than that explained in this explanation.

What happens to the results of the research study?

The main findings of this registry will be submitted for publication in prominent journals and presented findings at scientific meetings. They will be used as a standard by which future practice may be improved. If you wish to obtain a copy of the results you should contact the research co-ordinator when the research is completed (after July 2003). You will not be identified in any reports or publications arising from this research.

Who is organising and funding the research?

This study is being organised and co-ordinated by the Clinical Trials and Evaluation Unit at the Royal Brompton Hospital in London and the Northern Vascular Unit at the Freeman Hospital in Newcastle. Your doctor will be paid a small amount for including you in this study.

Who has reviewed the study?

The Multi Centre Research Ethics Committee have reviewed and approved this study.

Consumers for Ethics in Research (CERES) publish a leaflet entitled "Medical Research and You." This leaflet gives more information about medical research and looks at some of the questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London, N16 0BW.

Thank you for taking the time to read this information sheet. The doctors and nurses involved in this study will be pleased to discuss any questions or concerns that you may have. If you have any further questions about this research please contact your consultant at the address provided.

APPENDIX 6: Consent Form

Centre Number: :

Study Number:

Patient Identification Number for this trial:

CONSENT FORM

Title of Project:

PREPARED UK. Prospective Registry and Evaluation of Peripheral Arterial Risks, Events and Distribution in the UK

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet dated 8th August 2002 (version 6) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from Clinical Trials and Evaluation Unit, Royal Brompton Hospital or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

5. I give consent for my details to be sent to the Office of National Statistics and for this information to be accessed for up to 20 years for the purposes of this study only. ☐

6. I give consent for my GP to be informed of my participation in this study ☐

Name of Patient	Signature	Date
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Signature	Date

1 for patient; 1 for researcher; 1 to be kept with hospital notes

REFERENCES AND BIBLIOGRAPHY

1. The Scandinavian Simvastatin Survival Study (4S), *Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).* Lancet, 1994. **344**(8934): p. 1383-1389.

2. Meade TW, Gardner MJ, Cannon P, Richardson PC., *Observer variability in reading the peripheral pulses.* British Heart Journal, 1968. **30**(5): p. 661-665.

3. Ludbrook J, Clarke AM, McKensie JK., *Significance of absent ankle pulse.* British Medical Journal, 1962. **5294**: p. 1724-1726.

4. Vogt MT, Cauley JA, Newman AB, Kuller LH, Hulley SB., *Decreased ankle/arm blood pressure index and mortality in elderly women.* JAMA, 1993. **270**(4): p. 465-469.

5. Marinelli MR, Beach KW, Glass MJ, Primozich JF, Strandness DE., *Non-invasive testing vs. clinical evaluation of arterial disease: a prospective study.* JAMA, 1979. **241**(19): p. 2031-2034.

6. Stoffers HE, Kester AD, Kaiser V, Rinkens PE, Knottnerus JA., *Diagnostic value of signs and symptoms associated with peripheral arterial occlusive disease seen in general practice: a multivariate approach.* Medical Decision Making, 1997. **17**: p. 61-70.

7. Leng GC, Fowkes FGR., *The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys.* Journal of Clinical Epidemiology., 1992. **45**: p. 1101-1109.

8. Bernstein EF, Fronek A., *Current status of noninvasive tests in the diagnosis of peripheral arterial disease.* Surgical Clinics of North America, 1982. **62**(3): p. 473-87.

9. Hummel BW, Hummel BA, Mowbry A, Maixner W, Barnes RW., *Reactive hyperaemia vs. treadmill exercise testing in arterial disease.* Archives of Surgery., 1978. **113**(1): p. 95-98.

10. McDermott MM, Greenland P,Liu K,Guralnik JM,Celic L,Criqui MH,Chan C,Martin GJ,Schneider J,Pearce WH,Taylor LM,Clark E., *The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study.* Annals of Internal Medicine., 2002. **136**(12): p. 873-83.

11. Yao ST, *New techniques of objective arterial evaluation.* Arch Surg, 1973. **106**: p. 600-604.

12. Winsor T, *Influence of arterial disease on the systolic blood pressure gradients of the extremity.* American Journal of Medical Sciences., 1950. **220**: p. 117-126.

13. Laing S, Greenhalgh RM., *The detection and progression of asymptomatic PAD.* British Journal of Surgery, 1983. **70**: p. 628-630.

14. Carter SA, *Indirect systolic pressures and pulse waves in arterial occlusive disease of the lower extremities.* Circulation, 1968. **37**(4): p. 624-638.

15. Tabet S, Berg AO., *Screening for PAD. In: Guide to clinical preventive services: report of the US Preventive Services Task Force.* 1996, US Preventive Services Task Force.: Baltimore.

16. Hiatt WR, Hoag S, Hammen RF., *Effect of diagnostic criteria on the prevalence of peripheral artery disease. The San Luis Valley Diabetes Study.* Circulation, 1995. **91**(5): p. 1472-1479.

17. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, Strandness DE Jr, Taylor LM., *Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review.* Circulation, 1996. **94**(11): p. 3026-49.

18. Reid DD, Brett GJ, Hamilton PJS, Jarrett RJ, Keen H, Rose G, et al., *Cardiorespiratory disease and diabetes among middle aged male civil servants.* Lancet, 1974. **i**: p. 469-473.

19. Stoffers HE, Rinkens PE, Kester AD, Kaiser V, Knottnerus JA., *The prevalence of asymptomatic and unrecognised peripheral arterial occlusive disease.* International Journal of Epidemiology, 1996. **25**: p. 282-290.

20. Hughson WG, Mann JI, Garrod A., *Intermittent claudication: prevalence and risk factors.* British Medical Journal, 1978. **1**(6124): p. 1379-1381.

21. Dormandy J, Mahir M, Ascady G, Balsano F, De Leeuw P, Blomberg P, et al., *Fate of the patient with chronic leg ischaemia.* J Cardiovasc Surg, 1989(30): p. 50-57.

22. Reunanen A, Takkunen H, Aromaa A., *Prevalence of intermittent claudication and its effect on mortality.* Acta Med Scand, 1982. **211**: p. 249-256.

23. Fowkes FGR, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ., *Edinburgh Artery Study: prevalence of asymptomatic and symptomatic PAD in the general population.* International Journal of Epidemiology, 1991. **20**(2): p. 384-392.

24. Smith WCS, Woodward M, Tunstall-Pedoe H., *Intermittent claudication in Scotland.*, in *Epidemiology of peripheral vascular disease.*, F. FGR, Editor. 1991, Springer-Verlag: London. p. 109-115.

25. Aronow WS, Ahn C, Gutstein H, *Prevalence and incidence of cardiovascular disease in 1160 older men and 2464 older women in a long-term health care facility.* J Gerontol A Biol Sci Med Sci., 2002. **57**(1): p. M45-6.

26. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW., *Prevalence and clinical correlates of PAD in the Framingham Offspring Study.* American Heart Journal., 2002. **134**(6): p. 961-965.

27. Fowler B, Jamrozik K, Norman P, Allen Y., *Prevalence of peripheral arterial disease: persistence of excess risk in former smokers.* Australian & New Zealand Journal of Public Health., 2002. **26**(3): p. 219-24.

28. Novo S, Avellone G, Di Garbo V, Abrignani MG, Liquori M, Panno AV, et al., *Prevalence of risk factors in patients with PAD: a clinical and epidemiological evaluation.* International Angiology, 1992. **11**: p. 218-229.

29. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR., *Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care.* JAMA, 2001. **286**(11): p. 1317-1324.

30. Dormandy JA, Rutherford RB., *TransAtlantic Inter-Society Consensus (TASC). Management of PAD.* Journal of Vascular Surgery., 2000. **31**(1): p. S1-S296.

31. Schroll M, Munck O., *Estimation of peripheral arteriosclerotic disease by ankle blood pressure measurements in a population study of 60-year-old men and women.* Journal of Chronic Diseases., 1981. **34**: p. 261-269.

32. Gofin R, Kark JD, Friedlander Y, Lewis BS, Witt H, Stein Y, Gotsman MS., *PAD in a middle-aged population sample. The Jerusalem Lipid Research Clinic Prevalence Study.* Isr J Med Sci, 1987. **23**(3): p. 157-167.

33. Widmer LK, Greensher A, Kannel WB., *Occlusion of peripheral arteries: a study of 6400 working subjects.* Circulation, 1964. **30**: p. 836-842.

34. De Backer IG, Kornitzer M, Sobolski J, Denolin H., *Intermittent claudication: epidemiology and natural history.* Acta Cardiol, 1979. **34**: p. 115-224.

35. Diamantopoulos EJ, Nanas S, Moulopoulos SD. *Detection of peripheral arterial occlusive disease in a representative sample of the Athens population.* in *14th World Congress of the International Union of Angiology.* 1986. Munich, Germany: Angio Arch.

36. Meijer WT, Hoes AW, Rutgers DM Bots ML, Hofman A, Grobbee DE., *Peripheral arterial disease in the elderly: the Rotterdam study.* Arterioscler Thromb Vasc Biol, 1998. **18**(2): p. 185-192.

37. Widmer LK, Biland L, Da Silva A. *Risk profile and occlusive periphery artery disease (OPAD).* in *13th International Congress of Angiology.* 1985. Athens, Greece.

38. Novo S, *Classification, epidemiology, risk factors, and natural history of PAD.* Diabetes, Obesity & Metabolism, 2002. **4**(Suppl 2): p. S1-6.

39. Murabito JM, E.J., Nieto K, Larson MG, Levy D, Wilson PW, *Prevalence and clinical correlates of PAD in the Framingham Offspring Study.* American Heart Journal., 2002. **143**(6): p. 961-5.

40. Selvin E, Erlinger TP., *Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000.* Circulation, 2004. **110**(6): p. 738-43.

41. Erb W, *Klinische Beitrage zur Pathologie des Intermittierenden Hinkens.* Munch Med Wochenschr, 1911. **2**: p. 2487.

42. Kannel WB, *Risk factors for atherosclerotic cardiovascular outcomes in different arterial territories.* J Cardiovasc Risk, 1994. **1**: p. 333-339.

43. Kannel WB, McGee DL., *Update on some epidemiological features of intermittent claudication.* Journal of American Geriatric Society, 1985. **33**: p. 13-18.

44. Kannel WB, McGee DL., *Diabetes and cardiovascular disease: the Framingham study.* JAMA, 1979. **241**: p. 2035-2038.

45. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF, *Intermittent claudication: a risk profile from the Framingham Heart Study.* Circulation, 1997. **96**(1): p. 44-49.

46. Kannel WB, Shurtleff D, *The Framingham Study: cigarettes and the development of intermittent claudication.* Geriatrics, 1973. **28**: p. 61-68.

47. Birkenstock WE, Louw JH, Terblanche J, Immelman EJ, Dent DM, Baker PM., *Smoking and other factors affecting the conservative management of peripheral vascular disease.* South African Medical Journal, 1975. **49**(28): p. 1129=1132.

48. Fowkes GR, Housley E, Riemersma RA, Macintyre CA, Cawood EH, Prescott RJ, Ruckley CV., *Smoking, lipids, glucose intolerance and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study.* American Journal of Epidemiology, 1992. **135**(4): p. 331-340.

49. Gordon T, Kannel WB, *Predisposition to atherosclerosis in the head, heart and legs: the Framingham study.* JAMA, 1972. **221**(7): p. 661-666.

50. CAPRIE Steering Committee, *A randomised, blinded, trial of clopidigrel versus aspirin in patients at risk of ischaemic events (CAPRIE).* Lancet, 1996. **348**(9038): p. 1329-1339.

51. De Palma RG. *Patterns of peripheral atherosclerosis: implications for treatment.* in *Atherosclerosis: Developments, Complications and Treatment: Proceedings of the International Symposium.* 1987. Perthshire, Scotland: Elsevier Science,Elsevier Science.

52. Bainton D, Sweetman P, Baker I, Elwood P., *Peripheral arterial disease: consequences for survival and association with risk factors in the Speedwell prospective heart disease study.* British Heart Journal, 1994. **72**(2): p. 128-132.

53. Bowlin SJ, Medalie JH, Flocke SA, Zyzanski SJ, Goldbourt U., *Epidemiology of intermittent claudication in middle-aged men.* American Journal of Epidemiology, 1994. **140**: p. 418-430.

54. Jonason T, Bergstrom R, *Cessation of smoking in patients with intermittent claudication: effects on the risk of peripheral vascular complications, myocardial infarction and mortality.* Acta Med Scand, 1987. **221**: p. 253-260.

55. Ingolfsson IO, Sigurdson G, Sigvaldason H, Thorgeirsson G, Sigdusson N., *A marked decline in the prevalence and incidence of intermittent claudication in Icelandic men 1968-1986: a strong relationship to smoking and serum cholesterol-the Reykjavik Study.* Journal of Clinical Epidemiology., 1994. **47**(11): p. 1237-1243.

56. Dagenais GR, Maurice S, Robitaille NM, Gingras S, Lupien PJ., *Intermittent claudication in Quebec men from 1974-1986: the Quebec Cardiovascular Study.* Clin Invest Med, 1991. **14**: p. 93-100.

57. Powell JT, Edwards RJ, Worrell PC, Franks PJ, Greenhalgh RM, Porter NR., *Risk factors associated with the development of PAD in smokers: a case control study.* Atherosclerosis, 1997. **129**: p. 41-48.

58. Cronenwett JL, Warner KG, Zelenock GB, Whitehouse WM, Graham LM, Lindenauer M, Stanley JC., *Intermittent claudication. Current results of nonoperative management.* Archives of Surgery., 1984. **119**(4): p. 430-436.

59. Juergens JL, Barker NW, Hines EA., *Arteriosclerosis obliterans: review of 520 cases with special reference to pathogenic and prognostic factors.* Circulation, 1960. **21**: p. 188-195.

60. Kannel WB, Skinner JJ Jr, Schwartz MJ, Shurtleff D., *Intermittent claudication. Incidence in the Framingham Study.* Circulation., 1970. **41**: p. 875-883.

61. Widmer LK, Da Silva A., *Historical perspectives and the Basle study.*, in *Epidemiology of PAD.*, F. FGR, Editor. 1991, Springer-Verlag: London. p. 69-83.

62. Van der Velden J, de Bakker DH, Claessens AAMC, Schellens FG., *Dutch National Study of Morbidity and Intervention in General Practice.* 1992, Netherlands Institute of Primary Health Care: Utrecht.

63. Stout RW, *Diabetes, atherosclerosis and aging.* Diabetes Care, 1990. **13**(Suppl. 2): p. 20-23.

64. Reaven GM, *Banting Lecture: Role of insulin resistance in human disease.* Diabetes Care, 1988. **37**: p. 1595-1607.

65. McDaniel MD, Cronenwett JL., *Basic data related to the natural history of intermittent claudication.* Annals of Vascular Surgery, 1989. **3**(3): p. 273-277.

66. Jelnes R, Gaardsting O, Hougaard Jensen K, Baekgaard N, Tønnesen KH, Schroeder T, et al., *Fate in intermittent claudication: outcome and risk factors.* British Medical Journal, 1986. **293**: p. 1137-1140.

67. Smith GD, Shipley MJ, Rose G., *Intermittent claudication, heart disease risk factors, and mortality: the Whitehall study.* Circulation, 1990. **82**: p. 1925-1931.

68. Heart Protection Study Collaborative Group, *MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial.* Lancet, 2002. **360**(9326): p. 23-33.

69. Duffield RGM, Lewis B, Miller NE, Jamieson CW, Brunt JN, Colchester AC., *Treatment of hyperlipidaemia retards progression of symptomatic femoral atherosclerosis: a randomised controlled trial.* Lancet, 1983. **2**(8351): p. 639-642.

70. The Lipid Research Clinics Coronary Primary Prevention Trial Results, *Reduction in incidence of coronary heart disease.* JAMA, 1984. **251**: p. 351-364.

71. Lupattelli G, Pasqualini L, Siepi D, Marchesi S, Pirro M, Vaudo G, Ciuffetti G, Mannarino E., *Increased postprandial lipemia in patients with normolipemic peripheral arterial disease.* American Heart Journal., 2002. **143**(4): p. 733-738.

72. Smith I, Franks PJ, Greenhalgh RM, Poulter NR, Powell JT., *The influence of smoking cessation and hypertriglyceridaemia on the progression of PAD and the onset of critical ischaemia.* European Journal of Vascular and Endovascular Surgery, 1996. **11**: p. 402-408.

73. Cheng SWK, Ting ACW, Wong J., *Lipoprotein (a) and its relationship to risk factors and severity of atherosclerotic PAD.* European Journal of Vascular & Endovascular Surgery, 1997. **14**(1): p. 17-23.

74. Kang SS, Wong PW, Malinow MR., *Hyperhomocysteinaemia as a risk factor for occlusive vascular disease.* Annu Rev Nutr, 1992. **12**: p. 279-298.

75. Fermo I, Vigano d'Angelo, Paroni R, Mazzola G, Calori G, D'Angelo A., *Prevalence of moderate hyperhomocysteinemia in patients with early onset venous and arterial occlusive disease.* Annals of Internal Medicine., 1995. **123**(10): p. 747-753.

76. Caldwell S, McCarthy M, Martin SC, et al., *Hyperhomocysteinaemia, PAD and neointimal hyperplasia in elderly patients.* British Journal of Surgery., 1998. **85**: p. 685-715.

77. Clarke R, Daly L, Robinson K, Naughton E, Cahalane S, Fowler B, Graham I., *Hyperhomocystinaemia: an independent risk factor for vascular disease.* New England Journal of Medicine, 1991. **324**(17): p. 1149-1155.

78. Boers GHJ, Smals AG, Trijbels FJM Fowler B, Bakkeren JA, Schoonderwaldt HC, Kliejer WJ, Kloppenborg PW., *Heterozygotes for homocystinuria in premature peripheral and cerebral occlusive arterial disease.* New England Journal of Medicine, 1985. **313**(12): p. 709-715.

79. Van de Berg M, Boers GHJ., *Homocysteinuria: what about mild hyperhomocysteinaemia?* Postgraduate Medical Journal, 1996. **72**: p. 513-518.

80. Currie IC, Wilson JS, Scott J, Day A, Stansbie D, Baird RN, Lamont PM, Tennant WG., *Homocysteine: an independent risk factor for the failure of vascular intervention.* British Journal of Surgery, 1996. **83**(9): p. 1238-1241.

81. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AGI., *A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes.* JAMA, 1995. **274**(13): p. 1049-1057.

82. Darius H, Pittrow D, Haberl R, Trampisch HJ, Schuster A, Lange S, Tepohl HG, Allenberg JR, Diehm C., *Are elevated homocysteine plasma levels related to peripheral arterial disease? Results from a cross-sectional study of 6880 primary care patients.* European Journal of Clinical Investigation, 2003. **33**(9): p. 751-7.

83. Kannel WB, Wolf PA, Castelli WB, D'Agostino RB., *Fibrinogen and risk of cardiovascular disease: the Framingham Study.* JAMA, 1987. **258**: p. 1183-1186.

84. Kannel WB, D'Agostino RB, Belanger AJ., *Update on fibrinogen as a cardiovascular risk factor.* Annals of Epidemiology, 1992. **2**: p. 457-466.

85. Doweik L, Maca T, Schillinger M, Budinsky A, Sabeti S, Minar E., *Fibrinogen predicts mortality in high risk patients with peripheral arterial*

disease. European Journal of Vascular & Endovascular Surgery, 2003. **26**(4): p. 381-386.

86. Smith FB, Lee AJ, Hau CM, Rumley A, Lowe GD, Fowkes FG., *Plasma fibrinogen, haemostatic factors and prediction of peripheral arterial disease in the Edinburgh Artery Study.* Blood Coagulation & Fibrinolysis, 2000. **11**(1): p. 43-50.

87. Fowkes FGR, *Fibrinogen and peripheral arterial disease.* European Heart Journal, 1995. **16**(Suppl A): p. 36-40.

88. Lee AJ, Fowkes FG, Rattray A, Rumley A, Lowe GD., *Haemostatic and rheological factors in intermittent claudication: the influence of smoking and extent of arterial disease.* British Journal of Haematology, 1996. **92**: p. 226-230.

89. Bouhoutsos J, Morris T, Chavatzas D, Martin P., *The influence of haemoglobin and platelet levels on the results of arterial surgery.* British Journal of Surgery., 1974. **61**(12): p. 984-986.

90. Handa K, Takao M, Nomoto J, Oku J, Shirai K, Saku K., *Evaluation of the coagulation and fibrinolytic systems in men with intermittent claudication.* Angiology, 1996. **47**: p. 543-548.

91. Mueller T, Luft C, Haidinger D, Poelz W, Haltmayer M., *Erythrocyte mean corpuscular volume associated with the anatomical distribution in PAD.* Vasa, 2002. **31**(2): p. 81-85.

92. Haltmayer M, Mueller T, Horvath W, Luft C, Poelz W, Haidinger D., *Impact of atherosclerotic risk factors on the anatomical distribution of PAD.* International Angiology., 2001. **20**(3): p. 200-207.

93. Ward AS, Porter N, Preston FE, Morris-Jones W., *Platelet aggregation in patients with PAD.* Atherosclerosis, 1978. **29**: p. 63-68.

94. Collins GJ Jr, Heymann RL, Zajtchuk R., *Hypercoaguability in patients with peripheral vascular disease.* American Journal of Surgery, 1975. **30**(1): p. 2-6.

95. Robless P, Okonko D, Jagroop A, Mansfield A, Mikhailidis D, Stansby G., *Dextran-40 reduces in vitro platelet function in PAD.* British Journal of Surgery., 1999. **86**(suppl. 1): p. 6.

96. Barradas MA, Stansby G, Hamilton G, Mikhailidis DP., *Diminished platelet yield and enhanced platelet aggregability in platelet-rich plasma of PAD patients.* International Angiology, 1994. **13**(3): p. 202-211.

97. Mohan IV, Berwanger CS, Mirekandari M, Okonko D, Cheshire NJ, Mansfield A, Wolfe J, Mikhailidis D, Stansby G., *Platelet activation after bypass for critical limb ischaemia and the role of pharmacotherapy to increase graft survival.* British Journal of Surgery., 1999. **86**(suppl. 1): p. 15.

98. McDermott MM, Greenland P, Green D, Guralnik JM, Criqui MH, Liu K, Chan C, Pearce WH, Taylor L, Ridker PM, Schneider JR, Martin G, Rifai N, Quann M, Formage M., *D-dimer, inflammatory markers, and lower extremity functioning in patients with and without peripheral arterial disease.* Circulation, 2003. **107**(25): p. 3191-3198.

99. Ridker PM, Stampfer MJ, Rifai N., *Novel risk factors for systemic atherosclerosis: a comparison of C - reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease.* JAMA, 2001. **285**(19): p. 2481-2485.

100. Erren M, Reinecke H, Junker R, Fobker M, Schulte JO, Kropf J, Kerber S, Breithardt G, Assmann G, Cullen P., *Systemic inflammatory parameters in patients with atherosclerosis of the coronary and peripheral arteries.* Atherosclerosis, Thrombosis and Vascular Biology., 1999. **10**(19): p. 2355-2363.

101. Da Silva A, Widmer LK, Ziegler HW, Nissen C, Schweiger W., *The Basle longitudinal study; report on the relation of initial glucose level to baseline ECG abnormalities, peripheral artery disease, and subsequent mortality.* Journal of Chronic Diseases., 1979. **32**: p. 797-803.

102. Goldbourt U, Neufield HN., *Genetic aspects of arteriosclerosis.* Arteriosclerosis, 1986. **6**: p. 357-377.

103. Wilhelmson L, Svardsudd K, Korsan-Bengsten K, Larsson B, Welin L, Tibblin G., *Fibrinogen as a risk factor for stroke and myocardial infarction.* New England Journal of Medicine, 1984. **311**: p. 501-505.

104. Lee AJ, *Genetic polymorphism and peripheral vascular diseases.* Critical Ischaemia, 1998. **8**(3): p. 68 - 75.

105. Humpheries SE, Cook M, Dubowitz M, Stirling Y, Meade TW., *Role of genetic variation ar the fibrinogen locus in determination of plasma fibrinogen concentrations.* Lancet, 1987. **1**(8548): p. 1452-1455.

106. Housley E, Leng GC, Donnan PT, Fowkes FGR., *Physical activity and risk of PAD in the general population: Edinburgh Artery Study.* J Epidemiol Commun Health, 1993. **47**(6): p. 475-480.

107. Carmargo CA, S.M., Glynn RJ, Gaziano JM, Manson JE, Goldhaber SZ, et al., *Prospective study of moderate alcohol consumption and risk of PAD in US male physicians.* Circulation, 1997(95): p. 577-580.

108. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D., *The prevalence of PAD in a defined population.* Circulation, 1985. **71**(3): p. 510-515.

109. Aronow WS, Ahn C., *Prevalence of coexistence of coronary artery disease, PAD, and atherothrombotic brain infarction in men and women 62 years of age.* American Journal of Cardiology., 1994. **74**: p. 64-65.

110. Newman AB, Sutton-Tyrrell K, Rutan GH, Locher J, Kuller LH., *Lower extremity arterial disease in elderly patients with systolic hypertension.* Journal of Clinical Epidemiology., 1991. **44**: p. 15-20.

111. Newman AB, Siscovick DS, Manolio TA, et al., *Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study.* Circulation, 1993. **88**: p. 837-845.

112. Criqui MH, Denenberg JO, Langer RD, Fronek A., *The epidemiology of PAD: importance of identifying the population at risk.* Vascular Medicine., 1997. **2**(3): p. 221-226.

113. Hirsch AT, Halverson SL, Treat-Jacobson D, Hotvedt PS, Lunzer MM, Krook S, Rajala S, Hunninghake DB., *The Minnesota Regional PAD Screening Program: toward a definition of community standards of care.* Vascular Medicine, 2001. **6**(2): p. 87-96.

114. Hertzer NR, Young JR, et al., *Coronary artery disease in peripheral vascular patients: A classification of 1000 coronary angiograms and results of surgical management.* Annals of Surgery, 1984. **199**: p. 223-233.

115. Begg TB, Richards RL., *The prognosis of intermittent claudication.* Scott ish Medical Journal, 1962. **7**: p. 342-352.

116. De Weese JA, Rob CG., *Autogenous vein grafts ten years later.* Surgery, 1962. **6**: p. 775-784.

117. Malone JM, Moore WS, Goldstone J., *Life expectancy following aortofemoral arterial grafting.* Surgery, 1977. **81**(5): p. 551-555.

118. Hertzer NR, Lees CD., *Fatal myocardial infarction following lower extremity revascularisation: two hundred and seventy-three patients followed 6-11 years after operation.* Annals of Surgery, 1981. **193**: p. 492-498.

119. Szilagyi DE, E.J., Smith RF, Reddy DJ, McPharlin M, et al., *A thirty-year survey of the reconstructive surgical treatment of aortoiliac occlusive disease.* J Vasc Surg., 1986(3): p. 421-436.

120. Szilagyi DE, Hageman JH, Smith RF, Elliott JP, Brown F, Dietz P., *Autogenous vein grafting in femoropopliteal atherosclerosis: the limits of its effectiveness.* Surgery, 1979. **86**: p. 836-851.

121. von Kemp K, van den Brande P, Peterson T, Waegeneers S, Scheerlinck T, Danau W., *Screening for concomitant diseases in peripheral vascular patients.* International Angiology, 1997. **16**: p. 114-122.

122. Vecht RJ, Nicolaides AN, Brandao E, et al., *Resting and treadmill electrocardiographic findings in patients with intermittent claudication.* International Angiology, 1982. **1**: p. 119-121.

123. Crawford ES, Bomberger RA, Glaeser DH, Salen SA, Russell WL., *Aortoiliac occlusive disease: factors influencing survival and function following reconstructive operation over twenty-five year period.* Surgery, 1981. **90**: p. 1055-1067.

124. Brewster DC, Okada RD, Strauss HW, Abbott WM, Darling RC, Boucher CA, et al., *Selection of patients for preoperative coronary angiography: use of dipyridamole stress-thallium myocardial imaging.* J Vasc Surg., 1985(2): p. 505-510.

125. Ögren M, Hedblad B, Isacsson SO, Janzon L, Jungquist G, Lindell SE., *Ten year cerebrovascular morbidity and mortality in 68-year-old men with asymptomatic carotid stenosis.* British Medical Journal, 1995. **310**: p. 1294-1298.

126. Turnipseed WD, Berkoff HA, Belzer FO., *Postoperative stroke in cardiac and peripheral vascular disease.* Annals of Surgery, 1980. **192**(3): p. 365-368.

127. Hennerici M, Aulich A, Sandeman W, Freund H-J., *Incidence of asymptomatic extracranial arterial disease.* Stroke, 1981. **12**(6): p. 750-758.

128. Klop RBJ, Eikelboom BC, Taks ACJM., *Screening of the internal carotid arteries in patients with PAD by colour-flow Duplex scanning.* European Journal of Vascular Surgery, 1991. **5**: p. 41-45.

129. Katsilambros NL, Tsapogas PC, Arvanitis MP, Tritos NA, Alexiou ZP, Rigas KL., *Risk factors for lower extremity arterial disease in non-insulin-dependent diabetic persons.* Diabetes Med, 1996. **13**: p. 243-246.

130. Aronow WS and G.H. Ahn C, *Prevalence and incidence of cardiovascular disease in 1160 older men and 2464 older women in a long-term health care facility.* J Gerontol A Biol Sci Med Sci., 2002. **57**(1): p. M45-6.

131. Coran AG, Warren R., *Arteriographic changes in femoropopliteal arteriosclerosis obliterans. A five-year follow-up study.* New England Journal of Medicine, 1966. **274**: p. 643.

132. Bloor K, *Natural history of arteriosclerosis of the lower extremities.* Annals of Royal College of Surgeons England., 1961. **28**: p. 36-51.

133. Dormandy JA, Murray GD., *The fate of the claudicant: a prospective study of 1969 claudicants.* European Journal of Vascular Surgery, 1991. **5**(2): p. 131-133.

134. Breslau PJ, Jorning PJG, Dassen P. *The natural history of intermittent claudication, a prospective study.* in *2nd International Vascular Symposium.* 1986.

135. Schildkraut JM, Myers RH, Cupples LA, Kiely DK, Kannel WB., *Coronary risks associated with age and sex of parental heart disease in the*

Framingham Study. American Journal of Cardiology., 1989. **64**: p. 555-559.

136. Gilliland EL, L.C., Goss DE, Lewis JD. *The morbidity and mortality of stable claudicants: results of five-year follow-up*. in *2nd International Vascular Symposium*. 1986.

137. Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dumba J, Housley E, et al., *Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general populaton.* International Journal of Epidemiology, 1996. **25**: p. 1172-1181.

138. O'Riordain DS, O'Donnell JA., *Realistic expectations for the patient with intermittent claudication*. British Journal of Surgery., 1991. **78**: p. 861-863.

139. Eagle KA, Rihal CS, Foster ED, Mickel MC, Gersh BJ., *Long-term survival in patients with coronary artery disease: importance of PAD. The Coronary Artery Surgery Study (CASS) Investigators*. Journal of American College of Cardiology, 1994. **5**: p. 1091-1095.

140. Leng GC, *Questionnaires.*, in *Epidemiology of peripheral arterial disease.*, F. FGR, Editor. 1991, Springer-Verlag: London. p. 29-40.

141. Violi F, Criqui M, Longoni A, Castiglioni C., *Relation between risk factors and cardiovascular complications in patients with PAD. Results from the A.D.E.P. study*. Atherosclerosis, 1996. **120**: p. 25-35.

142. Biland L, Da Silva A, Zemp E, Widmer LK. *Occlusive peripheral artery disease (OPAD): mortality and risk profile.* in *13th International Congress of Angiology*. 1985. Athens, Greece.

143. Banerjee AK, Pearson J, Gilliland EL, Goss D, Lewis JD, Stirling Y, Meade TW., *A six year prospective study of fibrinogen and other risk factors associated with mortality in stable claudicants.* Thromb Haemost, 1992. **68**(3): p. 261-263.

144. McDermott MM, Feinglass J, Slavensky R, Pearce WH., *The ankle-brachial index as a predictor of survival in patients with peripheral vascular disease.* J Gen Intern Med, 1994. **9**(8): p. 445-449.

145. Hirsch AT, Gotto AM Jr., *Undertreatment of dyslipidemia in peripheral arterial disease and other high-risk populations: an opportunity for cardiovascular disease reduction.* Vascular Medicine., 2002. **7**(4): p. 323-331.

146. Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, Silagy C, van Spiegel PI, Astbury C, Hider A, Sweet R., *Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study.* European Heart Journal., 2003. **24**(10): p. 946-955.

147. Pisinger C, Vestbo J, Borch-Johnsen K, Jorgensen T.,*Smoking cessation intervention in a large randomised population-based study. The Inter 99 study.* Preventive Medicine, 2005.**40**(3) 285-292

148. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. *Nicotine replacement therapy for smoking cessation.* The Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD000146.

149. Stead LF, Lancaster T. *Group behaviour therapy programmes for smoking cessation.* The Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD001007.148.

150. Lancaster T, Stead LF. *Self-help interventions for smoking cessation.* The Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD001118.

151. White AR, Rampes H, Ernst E. *Acupuncture for smoking cessation.* The Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD000009.

152. Abbot NC, Stead LF, White AR, Barnes J. *Hypnotherapy for smoking cessation.* The Cochrane Database of Systematic Reviews 1998, Issue 2. Art. No.: CD001008.

153. Jonason T, Ringqvist I, Oman-Rydberg A., *Home-training of patients with intermittent claudication.* Scand J Rehabil Med, 1981. **13**: p. 137-141.

154. Clifford PC, Davies PW, Hayne JA, Baird RN., *Intermittent claudication: is a supervised exercise class worth while?* British Medical Journal, 1980. **280**(6230): p. 1503-1505.

155. Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR., *Hospital vs home-based exercise rehabilitation for patients with peripheral arterial occlusive disease.* Angiology, 1997. **48**: p. 291-300.

156. Mannarino E, Pasqualini L, Menna M, Maragoni G, Orlandi U., *Effects of physical training on peripheral vascular disease: a controlled study.* Angiology, 1989. **40**(1): p. 5-10.

157. Larsen OA, Lassen NA., *Effect of daily muscular exercise in patients with intermittent claudication.* Lancet, 1966. **2**: p. 1093-1096.

158. Ericsson B, Haeger K, Lindell SE., *Effect of physical training on intermittent claudication.* Angiology, 1970. **21**(3): p. 188-192.

159. Lundgren F, Dahllof AG, Schersten T, Bylund-Fellenius AC., *Muscle enzyme adaptation in patients with peripheral arterial insufficiency: spontaneous adaptation, effect of different treatments and consequences on walking performance.* Clinical Science, 1989. **77**(5): p. 485-493.

160. Lundgren F, Dahllof A, Lundholm K, Schersten T, Volkmann R., *Intermittent claudication: surgical reconstruction or physical training? A*

prospective randomised trial of treatment efficiency. Annals of Surgery, 1989. **209**(3): p. 346-355.

161. Mannarino E, Pasqualini L, Innocente S, Scricciolo V, Rignanese A, Ciuffetti G., *Physical training and antiplatelet treatment in stage II peripheral arterial occlusive disease: alone or combined?* Angiology, 1991. **42**(7): p. 513-521.

162. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG., *Superiority of treadmill walking exercise vs. strength training for patients with PAD. Implications for the mechanism of the training response.* Circulation, 1994. **90**(4): p. 1866-1874.

163. Gardner AW, Poehlman ET., *Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis.* JAMA, 1995. **274**(12): p. 975-980.

164. Williams LR, Ekers MA, Collins PS, Lee JF., *Vascular rehabilitation: benefits of a structured exercise/risk modification program.* Journal of Vascular Surgery., 1991. **14**: p. 320-326.

165. De La Haye R, Diehm C, Blume J, Breddin K, Gerlach H, Rettig K, et al., *An epidemiological study of the value and limits of physical therapy/exercise therapy in Fontaine stage II arterial occlusive disease.* VASA, 1992. **38**: p. 1-40.

166. Gardner AW, Killewich LA., *Association between physical activity and endogenous fibrinolysis in PAD: a cross-sectional study.* Angiology., 2002. **53**(4): p. 367-374.

167. Hall JA, B.J., *The effects of an intensive 26-day program of diet and exercise on patients with peripheral vascular disease.* J Cardiac Rehabil, 1982(2): p. 569-574.

168. Hiatt WR, Regensteiner JG, Brass EP. Vascular Clinical Trialists., *Clinical trials for claudication: assessment of exercise performance, functional status,and clinical end points.* Circulation, 1995. **92**: p. 614-621.

169. Planas A, Clara A, Pou JM, Vidal-Barraquer F, Gasol A, de Moner A, Contreras C, Marrugat J, *Relationship of obesity distribution and peripheral arterial occlusive disease in elderly men.* International Journal of Obesity & Related Metabolic Disorders., 2001. **25**(7): p. 1068-1070.

170. West of Scotland Coronary Prevention Study, *Identification of high-risk groups and comparison with other cardiovascular intervention trials.* Lancet, 1996. **348**(9038): p. 1339-1342.

171. Pomrehn P, Duncan B, Weissfeld L, Wallace RB, Barnes R, Heiss G, et al., *The association of dyslipoproteinemia with symptoms and signs of PAD: the lipids research clinics program prevalence study.* Circulation, 1986. **73**(Suppl I): p. I-100 - I-107.

172. Drexel H, Steurer J, Muntwyler J, Meienberg S, Schmid HR, Schneider E, Grochnig E, Amman FW., *Predictors of the presence and extent of peripheral arterial occlusive disease.* Circulation, 1996. **94**([9 suppl I]): p. II-199-II-205.

173. Valentine JR, Grayburn PA, Vega GL, Grudy M., *Lp(a) lipoprotein is an independent, discriminating risk factor for premature atherosclerosis among white men.* Archives of Internal Medicine, 1994. **154**: p. 801-806.

174. Olsson AG, Ruhn G, Erikson U., *The effect of serum lipid regulation on the development of femoral atherosclerosis in hyperlipidaemia: a non-randomised controlled study.* Journal of Internal Medicine., 1990. **227**: p. 381-390.

175. Blankenhorn DH, Azen SP, Crawford DW, Nessim SA, Sanmarco ME, Selzer RH, Shircore AM, Wickham EC., *Effects of colestipol-niacin therapy on human femoral atherosclerosis.* Circulation, 1991. **83**(2): p. 438-447.

176. Mohler ER 3rd, Hiatt WR, Creager MA., *Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease.* Circulation, 2003. **108**(12): p. 1481-6.

177. Balk EM, Lau J, Goudas LC, Jordan HS, Kupelnick B, Kim LU, Karas RH., *Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review.* Annals of Internal Medicine., 2003. **139**(8): p. 670-82.

178. Mondillo S, Ballo P, Barbati R, Guerrini F, Ammaturo T, Agricola E, Pastore M, Borrello F, Belcastro M, Picchi A, Nami R., *Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease.* American Journal of Medical Sciences., 2003. **114**(5): p. 359-364.

179. McDermott MM, Guralnik JM, Greenland P, Pearce WH, Criqui MH, Liu K, Taylor L, Chan C, Sharma L, Schneider JR, Ridker PM, Green D, Quann M., *Statin use and leg functioning in patients with and without lower-extremity PAD.* Circulation., 2003. **107**(5): p. 757-61.

180. Aronow WS, Ahn C., *Frequency of new coronary events in older persons with peripheral arterial disease and serum low-density lipoprotein cholesterol 125 mg/dl treated with statins versus no lipid-lowering drug.* American Journal of Cardiology., 2002. **90**(7): p. 789-791.

181. Cooke JP, Ma AO., *Medical therapy of peripheral arterial occlusive disease.* Surgical Clinics of North America, 1995. **75**: p. 569-579.

182. Ramdev P, Rayan SS, Sheahan M, Hamdan AD, Logerfo FW, Akbari CM, Campbell DR, Pomposelli FB Jr., *A decade experience with infrainguinal revascularization in a dialysis-dependent patient population.* Journal of Vascular Surgery., 2002. **36**(5): p. 969-974.

183. National Institutes of Health-National Heart, L., and Blood Institute., *National High Blood Pressure Education Programme.* Indian Heart J, 1999(51): p. 381-396.

184. Mehler PS, Coll JR, EStacio R, Esler A, Schrier RW, Hiatt WR., *Intensive blood pressure control reduces the risk of cardiovascular events in patients with PAD and type 2 diabetes.* Circulation, 2003. **107**(5): p. 753-756.

185. Solomon SA, Ramsay LE, Yeo WW, Parnell L, Morris-Jones W., *â blockade and intermittent claudication: placebo controlled trial of atenolol and nifedipine and their combination.* British Medical Journal, 1991. **303**: p. 1100-1104.

186. Radack K, Deck C., *Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with PAD: a meta-analysis of randomised controlled trials.* Archives of Internal Medicine, 1991. **151**: p. 1769-1776.

187. Ubbink DT, Lie HK, Legemate DA., *Effect of [beta]-blockers on peripheral skin microcirculation in hypertension and peripheral vascular disease.* Journal of Vascular Surgery, 2003. **38**(3): p. 535-540.

188. Hirsch AT, Duprez D., *The potential role of angiotensin-converting enzyme inhibition in peripheral arterial disease.* Vascular Medicine, 2003. **8**(4): p. 273-8.

189. Yusuf S, Sleight P, Pogue J, et al., *Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin converting enzyme inhibitor on death from cardiovascular causes.* New England Journal of Medicine, 2000. **342**: p. 145-153.

190. Hittel N, Donnelly R., *Treating PAD in patients with diabetes.* Diabetes, Obesity & Metabolism, 2002. **4**(Suppl 2): p. S26-31.

191. Beckman JA, Creager MA, Libby P., *Diabetes and atherosclerosis: epidemiology, pathophysiology, and management.* JAMA, 2002. **287**(19): p. 2570-81.

192. UK Prospective Diabetes Study (UKPDS) Group, *Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes.* Lancet, 1998. **352**(9131): p. 837-853.

193. UK Prospective Diabetes Study (UKPDS) Group, *Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS).* Lancet, 1998. **352**(9131): p. 854-865.

194. Hansrani M, Stansby G., *Homocysteine lowering interventions for PAD and bypass grafts (Cochrane Review).* Cochrane Database of Systematic Reviews(3), 2002. **3**: p. CD003285.

195. Antiplatelet Trialists' Collaboration, *Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.* British Medical Journal, 2002. **324**(7329): p. 71-86.

196. Robless P, Mikhailidis M, Stansby G., *Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with PAD.* British Journal of Surgery., 2001. **88**: p. 787-800.

197. Peripheral Arterial Diseases Antiplatelet Consensus Group, *Antiplatelet therapy in peripheral arterial disease. Consensus statement.* European Journal of Vascular & Endovascular Surgery, 2003. **26**(1): p. 1-16.

198. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators (CURE). *Effects of clopidogrel in addition to aspirin in patents with acute coronary syndromes without ST-segment elevation.* New England Journal of Medicine, 2001. **345**(7): p. 494-502.

199. Diener HC, Forbes C, Sivenius J, Smets P, Lowenthal A., *European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke.* Journal of Neurological Sciences, 1996. **143**(1-2): p. 1-13.

200. Van Den Bosch MA, Tanis BC, Mali WP, Helmerhorst FM, Rosendaal FR, Algra A, Van Der Graaf Y., *The RATIO study: oral contraceptives and the risk of peripheral arterial disease in young women.* J Thromb Haemost, 2003., 2003. **3**(1): p. 439-444.

201. Thompson PD, Zimet R, Forbes WP, Zhang P., *Meta-analysis of results from eight randomised, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication.* American Journal of Cardiology., 2002. **90**(12): p. 1314-1319.

202. Waters KJ, Craxford AD, Chamberlain J., *The effect of naftidrofuryl (Praxilene) on intermittent claudication.* British Journal of Surgery., 1980. **67**(5): p. 349-351.

203. Porter JM, Cutler BS, Lee BY, Reich T, Reichle FA, Scogin JT., *Pentoxifylline efficacy in the treatment of intermittent claudication: Multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease patients.* American Heart Journal., 1982. **104**: p. 66-72.

204. Adhoute G, Andreassian B, Boccalon H, Cloarec M, di Maria G, Lefebvre O, et al., *Treatment of stage II chronic arterial disease ofthe lower limbs with the serotonergic antagonist naftidrofuryl: results after 6 months of a controlled, multicenter study.* Journal of Cardiovascular Pharmacology, 1990. **16**(Suppl 3): p. S75-S80.

205. Kriessmann A, Neiss A., *Demonstration of the clinical effectiveness of naftidrofuryl in intermittent claudication.* Vasa, 1988. **24**: p. 27-32.

206. Trübestein G, Bohme H, Heidrich H, Klüken N, Muller-Weifel H, Unkel B, et al., *Naftidrofuryl in chronic arterial disease: resultsof a controlled multicenter study.* Angiology, 1994. **11**(35): p. 701-708.

207. Trübestein G, Balzer K, Bisler H., *Buflomedil in arterial occlusive disease: results of a controlled multicentre study.* Angiology, 1984. **35**(8): p. 500-505.

208. Diamantopoulos E, Grammoustianos GS, Stavreas NP. *Controlled trial of Buflomedil in diabetic peripheral occlusive disease.* in *International Symposium on Ischemic Disease and the Microcirculation.* 1989. Frankfurt: Zuckschwerdt.

209. Donnelly R, *Evidence-based symptom relief of intermittent claudication: efficacy and safety of cilostazol.* Diabetes, Obesity & Metabolism, 2002. **4**(Suppl 2): p. S20-25.

210. Money SR, Herd JA, Isaacsohn JL, Davidson M, Cutler B, Heckman J, Forbes WP., *Effect of cilostazol on walking distances in patients with intermittent claudication caused by PAD.* Journal of Vascular Surgery., 1998. **27**(2): p. 267-275.

211. Regensteiner JG, Ware JE Jr, McCarthy WJ, Zhang P, Forbes WP, Heckman J, Hiatt WR., *Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials.* Jounal of American Geriatric Society, 2002. **50**(12): p. 1939-1946.

212. Belch JJF, Creissen D, et al., *Randomised, placebo-controlled, double-blind study evaluating the efficacy and safety of AS-013, a prostaglandin E1 prodrug, in patients with intermittent claudication.* Circulation, 1997. **95**: p. 2298-2302.

213. Diehm C, Bisler H, Bulling B, Camci M, Creutzig A, et al., *Efficacy of a new prostaglandin E1 regimen in outpatients with severe intermittent claudication: results of a multicenter placebo-controlled double-blind trial.* J Vasc Surg, 1997. **25**: p. 537-544.

214. Lievre M, Azoulay S, Lion L, Mornd S, Girre JP, Boissel JP., *A dose-effect study of beraprost sodium in intermittent claudication.* Journal of Cardiovascular Pharmacology, 1996. **27**: p. 788-793.

215. Melian EB, Goa KL., *Beraprost: a review of its pharmacology and therapeutic efficacy in the treatment of PAD and pulmonary arterial hypertension.* Drugs, 2002. **62**(1): p. 107-133.

216. Rajagopalan S, Trachtenberg J, Mohler E, Olin J, McBride S, Pak R, Rasmussen H, Crystal R., *Phase I study of direct administration of a*

replication deficient adenovirus vector containing the vascular endothelial growth factor cDNA (CI-1023) to patients with claudication. American Jounal of Cardiology, 2002. **90**(5): p. 512-516.

217. Tsurumi Y, Takeshita S, Chen D, Kearney M, Rossow ST, Passeri J, et al., *Direct intramuscular gene transfer of naked DNA endoding vascular endothelial growth factor augments collateral development and tissue perfusion.* Circulation, 1996. **94**: p. 3281-3290.

218. EuroQol Group, *EuroQol: a new facility for the measurement of health-related quality of life.* Health Policy, 1990. **16**(3): p. 199-208.

219. Spertus J, Jones P, Poler S, Rocha-Singh K., *The Peripheral Artery Questionnaire: A new disease-specific health status measure for patients with peripheral arterial disease.* American Heart Journal, 2004. **147**(2): p. 301-308.

220. McDermott MM, *Ankle brachial index as a predictor of outcomes in peripheral arterial disease.* Journal of Laboratory Clinical Medicine, 1999. **133**(1): p. 33-40.

221. McDermott MM, Mehta S, Ahn H, Greenland P., *Atherosclerotic risk factors are less intensively treated in patients with peripheral arterial disease than in patients with coronary artery disease.* Journal of Gen Internal Medicine., 1997. **12**(4): p. 209-215.

222. Hirsch AT, Treat-Jacobson D, Lando HA, Hatsukami DK., *The role of tobacco cessation, anti-platelet, and lipid-lowering therapies for the treatment of peripheral arterial disease.* Vascular Medicine., 1997. **2**(3): p. 243-251.

223. Tang JL, Law M, Wald N., *How effective is nicotine replacement therapy in helping people to stop smoking?* BMJ., 1994. **308**(6920): p. 21-26.

224. Silagy C, Mant D, Fowler G, Lodge M., *Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation.* Lancet., 1994. **343**(8890): p. Lancet.

225. Abbot NC, Stead L, White A, Barnes J, Ernst E., *Hypnotherapy for smoking cessation.* Cochrane Database of Systematic Reviews, 2000. **2**: p. CD001008.

226. White AR, Rampes H, Ernst E., *Acupuncture for smoking cessation.* Cochrane Database of Systematic Reviews, 2000. **2**: p. CD0000098.

227. Hajek P, Stead LF., *Aversive smoking for smoking cessation.* Cochrane Database of Systematic Reviews, 2004. **3**: p. CD000546.

228. Burns P, Gough S, Bradbury AW., *Management of peripheral arterial disease in primary care.* BMJ., 2003. **326**(7389): p. 584-588.

229. Dormandy J, Heeck L, Vig S., *The natural history of claudication: risk to life and limb.* Semin Vasc Surg, 1999. **12**: p. 123-137.

230. Gutteridge W, Torrie EPH, Galland RB., *Cumulative risk of bypass, amputation or death following percutaneous transluminal angioplasty.* European Journal of Vascular and Endovascular Surgery., 1997. **14**(2): p. 134-139.

231. Bovet P, Gervasoni JP, Ross AG, Mkamba M, Mtasiwa DM, Lengeler C, Burnier M, Paccaud F., *Assessing the prevalence of hypertension in populations: are we doing it right?* Journal of Hypertension., 2003. **21**(3): p. 509-17.

232. Schulze MB, Kroke A, Bergmann MM, Boeing H., *Differences of blood pressure estimates between consecutive measurements on one occasion: implications for inter-study comparability of epidemiologic studies.* European Journal of Epidemiology., 2000. **16**(10): p. 891-8.

233. Antiplatelet Triallists' Collaboration, *Collaborative overview of randomised trials of antiplatelet therapy. II: Maintenance of vascular graft or arterial patency by antiplatelet therapy.* British Medical Journal, 1994. **308**(6922): p. 159-168.

234. Peripheral Arterial Diseases Antiplatelet Consensue Group., *Antiplatelet therapy in peripheral arterial disease. Consensus statement.* Eur J Vasc Endovasc Surg., 2003. **26**(1): p. 1-16.

235. Kallio M, Forsblom C, Groop PH, Groop L, Lepantalo M., *Development of new peripheral arterial occlusive disease in patients with type 2 diabetes during a mean follow-up of 11 years.* Diabetes Care., 2003. **26**(4): p. 1241-1245.

236. Dillavou E, Kahn MB., *Peripheral vascular disease: Diagnosing and treating the 3 most comon peripheral vasculopathies.* Geriatrics, 2003. **58**: p. 37-42.

237. Stoffers H, Kaiser V, Knottnerus J., *Prevalence in general practice*, in *Epidemiology of Peripheral Vascular Disease*, F. Fowkes, Editor. 1991, Springer Verlag: London. p. 109-115.

238. Jensen SA, Vatten LJ, Romundstad PR, Myhre HO., *The prevalence of intermittent claudication. Sex-related differences have been eliminated.* European Journal of Vascular and Endovascular Surgery, 2003. **25**(3): p. 209-212.

239. Vokonas PS, Kannel WB, Cupples LA., *Epidemiology and risk of hypertension in the elderly: the Framingham Study.* Journal of Hypertension, 1988. **6**(Suppl.1): p. S3-9.

240. Gardner AW, Montgomery PS, Killewich LA., *Natural history of physical function in older men with intermittent claudication.* Journal of Vascular Surgery, 2004. **40**(1): p. 73-78.

241. Aronow W S, Ahn C., *Prevalence of coexistence of coronary artery disease, PAD, and atherothrombotic brain infarction in men and women 62 years of age.* American Journal of Cardiology., 1994. **74**: p. 64-65.

242. McDermott MM, Kerwin DR, Liu K et al., *Prevalence and significance of unrecognized lower extremity peripheral arterial disease in general medicine practice.* Journal of General Internal Medicine, 2001. **16**: p. 384 - 390.

243. McDermott MM, Greenland P, Liu K, Criqui MH, Guralnik JM, Celic L, Chan C., *Sex Differences in Peripheral Arterial Disease: Leg Symptoms and Physical Functioning.* Journal of the American Geriatrics Society, 2003. **51**(2): p. 222 - 228.

244. Higgins JP, Higgins JA, *Epidemiology of peripheral arterial disease in women.* Journal of Epidemiology., 2003. **13**(1): p. 1-14.

245. Amighi J, Sabeti S, Schlager O, Francesconi M, Ahmadi R, Minar E, Schillinger M., *Outcome of conservative therapy of patients with severe intermittent claudication.* European Journal of Vascular & Endovascular Surgery, 2004. **27**(3): p. 254-8.

246. Gardner AW, *Sex differences in claudication pain in subjects with peripheral arterial disease.* Med Sci Sports Exerc., 2002. **34**(11): p. 1695-1698.

247. Nilsson PM, Theobald H, Journath G, Fritz T., *Gender differences in risk factor control and treatment profile in diabetes: a study in 229 swedish primary health care centres.* Scand J Prim Health Care, 2004. **22**(1): p. 27-31.

248. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P., *Twenty-year dynamics of serum cholesterol in middle-aged population of eastern Finland.* Annals of Internal Medicine., 1996. **125**: p. 713-722.

249. Tuomilehto J, Tanskanen A, Salonen JT, Nissinen A, Koskela K., *Effects of smoking and stopping smoking on serum high-density lipoprotein cholesterol levels in a representative population sample.* Prev Med., 1986. **15**: p. 35-45.

250. Feinglass J, McDermott M, Foroohar M, Pearce W., *Gender differences in interventional management of peripheral vascular disease: evidence from a blood flow laboratory population.* Annals of Vascular Surgery, 1994. **8**(4): p. 343-349.

251. Magnant J, Cronenwett J, Walsh D, Schneider J, Besso S, Zwolak R., *Surgical treatment of infrainguinal arterial occlusive disease in women.* Journal of Vascular Surgery., 1993. **17**(1): p. 67-78.

252. Norman PE, Semmens JB, Lawrence-Brown M *et al.*, *The influence of gender on outcome following peripheral vascular surgery: A review. Cardiovascular Surgery*, 2000. **8**: p. 111-115.

253. Westendorp I, 't Veld BA, Grobbee DE, Pols HA, MeijerWT, Hofman A, Witteman J. 160(16):2498-2502, 2000., *Hormone Replacement Therapy and Peripheral Arterial Disease: The Rotterdam Study.* Archives of Internal Medicine., 2000. **160**(16): p. 2498 - 2502.

254. Fabsitz RR, Sidawy AN, Go O, Lee ET, Welty TK, Devereux RB, Howard BV., *Prevalence of peripheral arterial disease and associated risk factors in American Indians: the Strong Heart Study.* American Journal of Epidemiology, 1999. **149**(4): p. 330-338.

255. Wood D, Durrington P, Poulter N, McInnes G, Rees A, Wray R., *Joint British Recommendations on prevention of coronary heart disease in clinical practice.* Heart, 1998. **80**(Suppl. 2): p. S1-S29.

256. Cassar K, Belch JJ, Brittenden J., *Are national cardiac guidelines being applied by vascular surgeons?* European Journal of Vascular & Endovascular Surgery, 2003. **26**(6): p. 623-628.

257. Klevsgard R, Hallberg IR, Risberg B, Thomsen MB., *Quality of life associated with varying degrees of chronic lower limb ischaemia: comparison with a healthy sample.* European Journal of Vascular & Endovascular Surgery., 1999. **17**(4): p. 319-325.

258. Pell JP on behalf of Scottish Vascular Audit Group, *Impact of intermittent claudication on quality of life.* European Journal of Vascular & Endovascular Surgery., 1995. **9**(4): p. 469-472.

259. Khaira HS, Hanger R, Shearman CP., *Quality of life in patients with intermittent claudication.* European Journal of Vascular & Endovascular Surgery., 1996. **11**(1): p. 65-69.

260. Breek JC, Hamming JF, De Vries J, van Berge Henegouwen DP, van Heck GL., *The impact of walking impairment, cardiovascular risk factors, and comorbidity on quality of life in patients with intermittent claudication.* Journal of Vascular Surgery, 2002. **36**(1): p. 94-99.

261. Hicken GJ, Lossing AG, Ameli M., *Assessment of generic health-related quality of life in patients with intermittent claudication.* European Journal of Vascular and Endovascular Surgery., 2000. **20**(4): p. 336-341.

262. Beattie DK, Golledge J, Greenhalgh RM, Davies AH, *Quality of life assessment in vascular disease: towards a concensus.* European Journal of Vascular & Endovascular Surgery., 1997. **13**(1): p. 9-13.

263. Chetter IC, Dolan P, Spark JI, Scott DJ, Kester RC., *Correlating clinical indicators of lower-limb ischaemia with quality of life.* Cardiovascular Surgery., 1997. **4**(5): p. 361-366.

264. Bullinger M, Cachovan M, Creutzig A, Diehm C, Gruss J,Heidrich H, Kirchberger I, Leoprecht H, Rogatti W., *Development of an illness-specific instrument for assessment of quality of life in patients with arterial*

occlusive disease (Peripheral Arterial Occlusive Disease 86 Questionnaire). Vasa., 1996. **25**: p. 32-40.

265. Chetter IC, D.P., Spark JI, Scott DJ, Kester RC., *Correlating clinical indicators of lower limb ischaemia with quality of life.* Cardiovascular Surgery, 1997(4): p. 361-366.

266. Barletta G, Perna S, Sabba C, Catalano A, O 'Boyle C, Brevetti G., *Quality of life in patients with intermittent claudication: relationship with laboratory exercise performance.* Vascular Medicine., 1996. **1**(1): p. 3-7.

267. Schneider JR, McHorney CA, Malenka DJ, McDaniel MD, Walsh DB, Cronenwett JL., *Functional health and well-being in patients with severe atherosclerotic peripheral vascular occlusive disease.* Annals of Vascular Surgery, 1993. **7**(5): p. 419-428.

268. Bosch JL, Hunink MGM., *The relationship between descriptive and valuational quality-of-life measures in patients with intermittent claudication.* Medical Decision Making, 1996. **16**(3): p. 217-225.

269. McDermott MM, Greenland P, Guralnik JM, Liu K, Criqui MH, Pearce WH, Chan C, Schneider J, Sharma L, Taylor LM, Arseven A, Quann M, Celic L., *Depressive symptoms and lower extremity functioning in men and women with peripheral arterial disease.* Journal of General Internal Medicine, 2003. **18**(6): p. 461-467.

270. Muller-Bahl U, Engeser P, Klimm HD, Wiesmann A., *Quality of life and objective disease criteria in patients with intermittent claudication in general practice.* Family Practice, 2003. **20**(1): p. 36-40.

271. Bloemenkamp DG, Mali WP, Tanis BC, van den Bosch MA, Kemmeren JM, Algra A, van der Graaf Y., *Functional health and well-being of relatively young women with peripheral arterial disease is decreased but stable after diagnosis.* Journal of Vascular Surgery., 2003. **38**(1): p. 104-110.

272. Gardner AW, Killewich LA, Montgomery PS, Katzel LI., *Response to exercise rehabilitation in smoking and nonsmoking patients with intermittent claudication.* Journal of Vascular Surgery, 2004. **39**(3): p. 531-8.

273. Cheetham DD, Burgess L, Ellis M, Williams A, Greenhalgh RR, Davies AA., *Does supervised exercise offer adjuvant benefit over exercise advice alone for the treatment of intermittent claudication? A randomised trial.* European Journal of Vascular & Endovascular Surgery., 2004. **27**(1): p. 17-23.

274. Tsai JC, Chan P, Wang CH, Jeng C, Hsieh MH, Kao PF, Chen YJ, Liu JC., *The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease.* Journal of Internal Medicine., 2002. **252**(5): p. 448-455.