ANGINA PECTORIS AND AMBULATORY MYOCARDIAL ISCHAEMIA IN THE GENERAL POPULATION

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by

Manish M Gandhi MBChB MRCP

Medicine I (Cardiology), University of Southampton
Royal South Hants Hospital, Southampton

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

TABLE OF CONTENTS

List of Tables **Page**

List of Figures **Page**

Page

Dedicated with love to my sister, wife and parents

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SUMMARY

Since the original population study of angina pectoris which commenced in Framingham in 1949, there has been no contemporary study of this common disease in relation to incidence, clinical characteristic and prognosis. The overall objective of this study was to investigate new cases of angina in the population presenting for the first time with this symptom of coronary disease. Specifically the objectives were to measure the clinical incidence of angina and to assess the patients' clinical characteristics with particular reference to ambulatory and exercise electrocardiography and the relationship of these physiological variables to prognosis.

A random sample of 17 general practices was drawn from within the boundary of the city of Southampton and all 117 general practitioners agreed to refer every new patient $\leq$ 70 years with no previous CHD presenting for the first time with suspected angina to an open access chest pain service. Of 110 consecutive patients presenting with typical angina, 70 were male and 40 female. The crude annual incidence rate (95% confidence interval) of angina pectoris in this representative population sample was 0.83 (0.66, 1.0) per thousand population aged 31-70 years; for men and women the rates were 1.13 (0.85, 1.40) and 0.53 (0.33, 0.72) respectively. The incidence of angina pectoris in the United Kingdom is estimated from this study to be at least 22,600 patients per annum. Ninety-six of 110 angina patients and 95 age, sex and practice matched asymptomatic healthy controls underwent 24 hour ambulatory ECG monitoring prior to antianginal therapy. All tapes were analysed blind. Ischaemic ST segment depression, defined as $\geq$ 1mm horizontal/downsloping shift from baseline at J+80 msec lasting $>$ 1 min, was prevalent in 34 of 64 (53%) men with angina vs 7 of 59 (12%) male controls, and in 16 of 32 (50%) women with angina vs 2 of 36 (6%) controls. In logistic regression analysis, serum cholesterol ($p = 0.02$) and exercise ischaemia ($p = 0.003$) were independently associated with the presence of ambulatory ischaemia in men with angina, but only the latter was significant in women; this may reflect a different pathophysiological basis for ambulatory ischaemia in women. At a median follow-up of 15.8 (range 7-30) months, angina remitted spontaneously in 12 (11%) patients, 20 (18%) patients underwent revascularisation, 8 (8%) sustained a non-fatal myocardial infarction, and 4 (4%) died. In Kaplan-Meier survival analysis, there was no significant difference in event-free survival from

coronary angioplasty, coronary artery bypass grafting, myocardial infarction or death between patients with and without ambulatory ischaemia (66% vs 72%, p=NS).

This is the first contemporary population study of new patients with angina pectoris since the advent of widespread non invasive electrocardiographic assessment, coronary arteriography and revascularisation. Angina is common and while in the majority of patients the resting electrocardiogram is normal at presentation, exercise induced ischaemia ($\geq$ 1mm) is found in 64% (42 of 66) of men and in 57% (21 of 37) of women. Ambulatory ischaemia is present in over half of new patients presenting with angina, but appears to be of no prognostic value. The prognosis of incident angina despite appropriate cardiological assessment and management is not benign. The study thus raises an important question which should be answered by a randomised controlled trial - does early cardiological assessment and coronary revascularisation reduce the morbidity and mortality of incident angina pectoris?

CHAPTER 1

INTRODUCTION

Cardiovascular disease is the most frequent cause of death in the United Kingdom. Coronary heart disease (CHD) accounts for 65% of cardiovascular deaths in men and for about half of deaths in women (OPCS, 1989). In both sexes up to the age of 65 years, cardiovascular diseases account for up to a quarter of all years of working life lost (OPCS, 1987).

Coronary heart disease commonly presents as angina pectoris. Angina affects over one million men and women under 65 years age in the United Kingdom (Shaper, 1984; Smith, 1990). It is the initial clinical manifestation of CHD in over a third of men and in about two-thirds of women (Kannel, 1972). The first description of angina pectoris as a clinical syndrome over 200 years ago (Heberden, 1772) was followed by the anatomical association with coronary atheroma and establishment of the ischaemic theory of angina (Proudfit, 1983). It is now recognised that although there is a close relationship between angina, myocardial ischaemia and coronary atherosclerosis, any one of these three can exist on its own, or in combination with one or both of the other two entities.

The majority of patients with angina pectoris present to their general practitioner and are managed in the community but little is known about the frequency, prognosis and optimum investigation and management of this manifestation of coronary disease in the population. Prevalence of angina has been estimated in many cross-sectional surveys using questionnaires, but incidence is less well documented and there has been no contemporary incidence study since the advent of revascularisation. Clinical characteristics of patients presenting with angina pectoris in the general population beyond a resting ECG have not been defined.

Electrocardiography - resting, exercise and ambulatory - features foremost among the investigations for patients presenting with angina pectoris. Continuous ambulatory electrocardiographic monitoring was introduced nearly two decades ago, yet despite extensive investigation, its frequency and prognostic value in patients presenting with angina pectoris in the general population have not been documented.

This chapter reviews the prevalence and incidence of angina pectoris and the frequency and prognostic significance of resting, exercise and in particular, ambulatory electrocardiography in patients with angina. Careful attention is paid to the method of patient selection in the reported studies to assess whether their results can be applied to the generality of stable angina patients encountered in clinical

practice. The limitations of available data are discussed, and the objectives of the present study are outlined.

1.1 Prevalence of Angina

Prevalence of angina has been estimated in three large studies (Table 1.1) using a chest pain questionnaire and ranges from 4.8% in middle-aged men to 8.5% in women. Epidemiological methods have to be simple and cheap so most surveys are limited to captive populations in particular employments (Reid et al, 1974) and to specific age groups (Shaper et al, 1984; Smith et al, 1990).

	Whitehall (1967-69)	BRHS* (1978-80)	SHHS† (1984-86)
Patients	Civil Service	random, general practice	random, general practice.
Sex	Men	Men	Men and women
Age (years)	40-64	40-59	40-59
n =	18,403	7,735	10,359
Prevalence (%)	4.8	4.8	men 6.3 women 8.5

* BRHS = British Regional Heart Study
† SHHS = Scottish Heart Health Study

Table 1.1 Prevalence of angina pectoris

Two other community based surveys of patients under treatment for ischaemic heart disease also report angina prevalence. In a 4-month survey in 1979 by the Royal College of General Practitioners, 51 general practitioners in Newcastle covering a population of 125,000 recorded patients aged 30-59 years that they treated for angina, and concluded that prevalence in their population was 1.1% (RCGP research committee, 1982). The methods used in this survey include memory recall to identify treated cases and a diagnosis which includes a 'suggestive' history of angina. Both methods have obvious limitations.

A more reliable estimate of prevalence comes from a survey of prescriptions for nitrates in Nottingham (population 612,800). During a 6-month period in 1984-5 15,451 nitrate prescriptions for 6,856 patients were identified (Cannon, 1988). Estimated prevalence of angina was 1.5% in men under 65 years age and 0.6% in

women under 60 years. However this may be an overestimate of the true prevalence as the diagnosis of angina examined in a sub sample of patients was incorrect in a significant proportion. In that study, prevalence increased sharply in men over the age of 65 years to 7.1% and to 4.4% in women over 60 years old.

1.2 Incidence of Angina

Incidence of angina pectoris has proved difficult to measure. To date, only the Framingham study has estimated incidence in a representative sample of men and women in the general population (Kannel, 1972). A cohort of 5,127 residents of Framingham, USA underwent biennial clinical examination between 1949 and 1966. From 303 cases of angina arising in men and women aged 33 to 69 years over this period, incidence estimates in men ranged between 2/1000 population/year in the 40-44 year age group to 11/1000/year in the 55-59 year age group. Corresponding rates in women were 0.5/1000/year to 2/1000/year.

The incidence of angina has also been reported in three other areas (Table 1.2) - in an occupational cohort of 9,764 Israeli male civil service and municipal employees (Medalie, 1976), in a single London general practice population (Fry, 1976) and in a population of men from selected general practices in Edinburgh with easy access to a special clinic (Duncan, 1976).

No conclusions about the real extent of variation in incidence rates of angina can be drawn from these reports because of wide differences in composition and size of patient populations, method of diagnosis and period of study. The most recent incidence estimate available is from a study reported 17 years ago. No current data is available.

1.3 Resting Electrocardiography

Due to a lack of population based studies of angina pectoris, information about clinical and electrocardiographic (ECG) characteristics in the generality of patients with this disease is limited. Available evidence suggests that less than 20% of patients receiving medical treatment for angina from general practitioners are referred for hospital investigation (Cannon, 1988). Extrapolation of results from hospital patients to the general population of angina patients is therefore inappropriate because selection

	study period	subjects	population at risk	annual incidence*
Framingham USA[a]	1949-66	men and women 33-69 yrs	5,130	4.2
Israel[b]	1963-68	men over 40 yrs	9,764	5.7
London GP[c] UK	1950-75	men and women over 40 yrs	2,755	5.0
Edinburgh[d,e] UK	1970-72	men 35-69 yrs	28,400	1.8

* crude rate per thousand population at risk

Table 1.2 Reported incidence of angina pectoris in selected populations 1949-72 (*a* Kannel, 1972; *b* Medalie, 1976; *c* Fry, 1976; *d* Fulton, 1972; *e* Duncan, 1976)

bias leads to spurious associations which cannot be compensated for even by very large studies (Evans, 1991).

The frequency of ischaemic changes on resting electrocardiography have been reported in two population based prevalence studies of patients with angina. Major resting electrocardiographic abnormalities (flat or downsloping ST segment depression of $\geq$ 0.6mm or T wave inversion) in recordings using only three orthogonal leads were evident in 5.2% of 40-59 year old men in the British Regional Heart Study who had definite angina diagnosed by questionnaire (Shaper, 1984). This compared to a prevalence of 2.6% for similar ECG abnormalities in asymptomatic men.

The Whitehall study showed that although there was a significant increase in 5-year coronary heart disease mortality in men with symptoms and resting limb lead electrocardiographic abnormalities compared to asymptomatic men with such abnormalities, the 5-year CHD mortality rate in men with either ECG abnormalities or chest pain was low at only around 3%. Interestingly, men with ECG abnormalities who were under the care of a doctor had up to fourfold higher age-adjusted CHD mortality rates compared with those who were not under medical care (Rose, 1978), suggesting that presentation per se to a doctor is associated with a worse prognosis regardless of questionnaire responses or ECG abnormalities.

Self selected presentation by patients to the primary care physician is thus the first stage in risk stratification of angina pectoris in the general population. An important implication of this observation is that patients diagnosed as having angina solely on the basis of responses to a chest pain questionnaire are a lower risk group than those who present to their general practitioner.

1.4 Ambulatory Electrocardiography

Transient ST segment depression associated with chest pain in active subjects was first described by Holter in 1961 (Holter, 1961), but due to concerns about reliability of the poor low frequency response of recorders, further research interest did not develop until the 1970s when Stern and Tzivoni described frequent transient episodes of ST segment depression during daily living activities, many of which not accompanied by chest pain (Stern, 1974). Since then, extensive research using ambulatory monitoring in selected patients with angina confirms that transient episodes of ST segment depression occur with and without chest pain (Selwyn, 1978; Deanfield, 1983; Shea,

1985; Cecchi, 1983; Mulcahy 1988).

Most studies of ambulatory ST segment monitoring are based on angina patients with positive exercise tests and angiographically proven coronary artery disease. In such patients, it is considered that ST segment changes often represent true ischaemia because of a high correlation with simultaneous perfusion defects on positron emission tomography (Deanfield, 1983 and 1984), myocardial dysfunction (Chierchia, 1983), and to a lesser extent with rises in pulmonary artery diastolic pressure (Levy, 1986). But data which directly correlates monitoring tracings with impaired myocardial perfusion to validate ST segment depression as representing the myocardial ischaemia are limited.

Variability

The inherent variability of ST segment response during daily living which clearly affects interpretation of clinical studies of ambulatory ischaemia has received limited attention (Khurmi, 1987; Deanfield, 1983; Nabel, 1988). In exercise test-positive patients with at least 5 episodes of typical angina per week, the reproducibility between two occasions of 24 hour monitoring 6 weeks apart was surprisingly good for the number, total duration and extent of ST segment depression recorded in the two leads CM5 and CC5 (Khurmi, 1987). However within and between patient variability was not quantified. By contrast, a marked day-to-day and long-term variability in the number of episodes of ST depression was reported in a study of 30 patients with similar characteristics (Deanfield, 1983), but not quantified.

The best quantitative assessment of variability was undertaken in 42 patients with stable angina and angiographically proven coronary artery disease who had at least one episode of ST depression during an initial 48 hour monitoring period (Nabel, 1988). A between patient variability contributed to 40% of the variance in frequency of episodes, and a similar variance within patients resulted from monitoring between different weeks. This large spontaneous variability was not normally distributed.

In all studies, monitoring was carried out at least twice on each patient using standard amplitude or frequency modulated equipment with an adequate frequency response and uniform criteria for the presence or absence of ischaemic ST segment change. In each case, a clear description of lead positioning was provided, and physicians verified abnormalities found during the test. All studies evaluated patients

with known chronic stable angina and a positive exercise test. Antianginal medication was kept constant, but factors such as physical activity could not be controlled.

Based on these findings, Nabel and colleagues (1988) have proposed guidelines for how much change should be attributed to random variation and how much to treatment or progression of disease. The variability of ambulatory ischaemic changes in these select groups of hospital patients with frequent angina, may however be different from other unstudied clinical subgroups and the precise extent of variability in the general population of angina patients is not known.

Prevalence

The reported prevalence of ambulatory ischaemia in patients with angina pectoris ranges from 19% to 92% (Figure 1.1).

All studies include selected tertiary cardiac centre patients with a positive exercise test at low workloads (Campbell, 1086; Rocco, 1988; Mody, 1988; Tzivoni, 1989; Deedwania, 1990), and with a history of a previous myocardial infarction in varying proportions (Cecchi, 1983; Von Arnim, 1985; Quyyumi, 1987; Mulcahy, 1988; Deedwania 1990). Almost all consist of patients with angiographically proven coronary artery disease on entry (Cecchi, 19832; Shea, 1985; Campbell, 1986; Mulcahy, 1988; Rocco, 1988; Tzivoni, 1989) or with disease severe enough to warrant angiography (Stern, 1974; Von Arnim, 1985; Tzivoni, 1986; Quyyumi, 1987; Mody, 1988; Deedwania, 1990; Hoberg, 1990). With the exception of two studies, one where usual antianginal treatment was continued (Deedwania, 1990), and another where long acting nitrates and calcium antagonists were stopped but an unspecified number continued taking beta blockers (Von Arnim, 1985), only short acting nitrates were used during the monitoring period. The duration of recording was 48 hours in some studies (Shea, 1985; Quyyumi, 1987; Mulcahy, 1988; Rocco, 1988), 24 hours in the rest, and not specified in one (Tzivoni, 1989).

In all of the above studies, ambulatory monitoring was performed on carefully selected patients referred for hospital investigation, so the true frequency of transient ischaemic episodes in unselected patients with stable angina pectoris remains unknown.

Prognosis

Likewise there are conflicting reports about the prognostic value of ambulatory ST

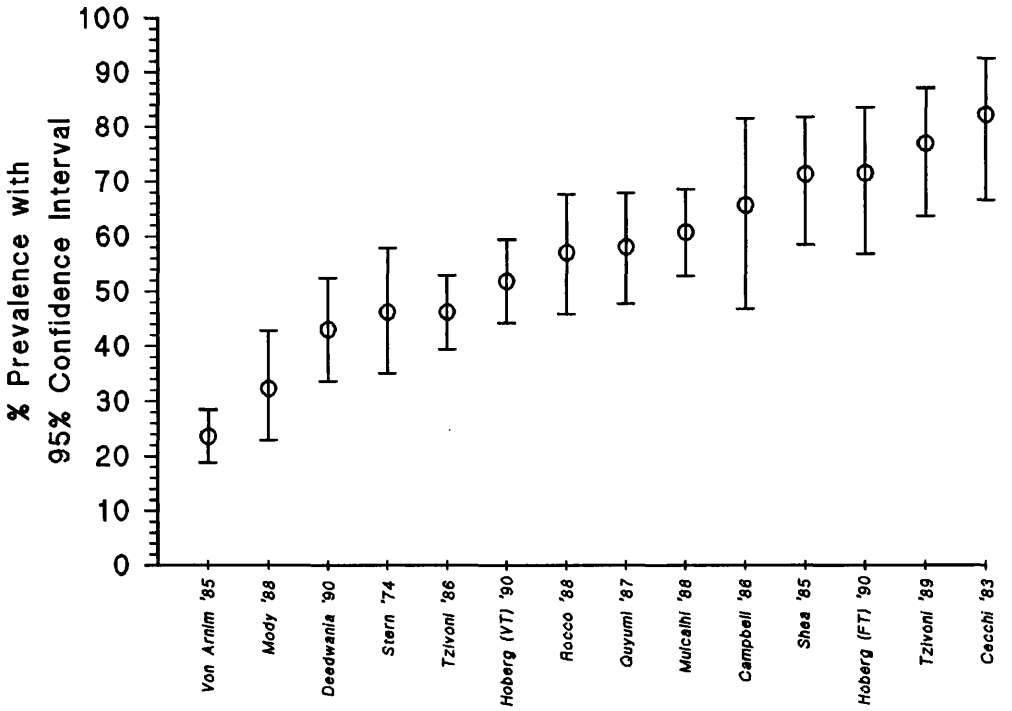


Figure 1.1 Reported prevalence of ambulatory ischaemia

segment analysis. Studies assessing the prognostic importance of ambulatory myocardial ischaemia in various subgroups of patients with stable coronary heart disease have varied from showing an independent predictive value of silent ischaemia for cardiac mortality (Deedwania, 1990), or for all cardiac events in the short term (Rocco, 1988; Tzivoni, 1989) but not for cardiac mortality and myocardial infarction in the long term (Yeung, 1991), to more recent studies showing a lack of prognostic value of ambulatory ischaemia (Mulcahy, 1992; Quyyumi, 1993).

Although the studies purportedly represent "unselected" patients with stable angina, the study populations differ in many respects. The number of patients vary from 56 in a study in which the inclusion criterion of 'at least one year of follow up' suggests that it was retrospective (Tzivoni, 1989), to 172 in a prospective study of non-consecutively selected outpatients from two centres (Mulcahy, 1992). The proportion of men included ranges from 79% (Yeung, 1991) to 100% (Deedwania, 1990), and mean age varies from 58 to 63 years. Four of the five studies do not include consecutive patients (Rocco, 1988; Tzivoni, 1989; Yeung, 1991; Mulcahy, 1992), and in the one that does, only 107 men were recruited over a twenty-one month period (Deedwania, 1990) reflecting selective inclusion of patients. Most cardiology clinics would probably assess several hundred patients with angina over this time course.

Like the prevalence studies discussed earlier, the prognostic studies also used similar selection criteria including an exercise test positive for ischaemia at low workloads (Rocco, 1988; Tzivoni, 1989; Deedwania, 1990; Yeung, 1991) and the presence of angina on exercise (Rocco, 1988; Yeung, 1991). A variable number of patients took antianginal therapy which was stopped prior to monitoring by some (Rocco, 1988; Yeung,1991), but not others (Deedwania, 1990). The proportion of patients with a previous myocardial infarction varied from none (Tzivoni,1989) to 52% (Deedwania, 1990), and of patients with previous CABG from 13% (Mulcahy, 1992) to 23% (Rocco, 1988).

Patient selection based on a low workload-positive exercise test may exaggerate the prognostic importance of ambulatory ischaemia, because a positive exercise test not only predicts the presence of ambulatory ischaemia (Campbell, 1986; Danza, 1991), but is also independently associated with reduced survival (Weiner, 1984; ECSSG, 1982). It follows therefore that in prognostic studies of ambulatory

monitoring in which patients are selected on the basis of a low workload positive exercise test, the patients with angina who have a high probability of having detectable ischaemic episodes are also the ones most likely to experience a cardiac event. In such studies, patients who experience a cardiac event would have a higher frequency of demonstrable ambulatory ischaemia than patients not selected on the basis of a positive exercise test. This is indeed the case (Figure 1.2) and 67-100% of patients who experienced myocardial infarction or death in studies which included only exercise test positive patients had demonstrable ambulatory ischaemia (Rocco, 1988; Tzivoni, 1989; Deedwania, 1990; Yeung, 1991) compared with 13-22% who had ischaemia and experienced similar end-points but were not selected on the basis of a positive exercise test (Mulcahy, 1992; Quyyumi, 1993). In this situation, the inclusion criterion of a low workload positive exercise test results in a spurious association of ambulatory ischaemia with adverse prognosis.

If results from studies of outpatients recruited from cardiology clinics are applied to the general population of patients with stable angina, then they should be representative of the broad spectrum of patients seen in clinical practice. If this were the case, then the rate of objective cardiac end-points such a myocardial infarction and cardiac death would be broadly similar among the different study populations. However the estimated annual rate of myocardial infarction and cardiac death varies by over four-fold in studies of stable angina patients (Tzivoni, 1989; Mulcahy, 1992) in spite of similar follow-up periods (Figure 1.3). The reported studies of ambulatory monitoring represent extremes of either 'low' (Mulcahy, 1992; Quyyumi, 1993) or 'high' risk (Deedwania, 1990) groups.

The differences in outcome are, in part, explained by differences in clinical practice. For example in the study by Deedwania and Carbajal (1990), although 77 patients had two or more coronary arteries diseased at baseline angiography, including 13 patients who had left main stem disease, a total of only 2 patients underwent revascularisation at a mean follow-up period of 23 months. During this period 16 out of the total study population of 107 patients died, resulting in a total mortality of 15%, and of 25% in those with episodes of ambulatory ischaemia. It is difficult and inappropriate to extrapolate conclusions from this study to patients seen in usual clinical practice because rate of revascularisation in patients with severe disease can be expected to be much higher and the mortality in stable angina patients lower

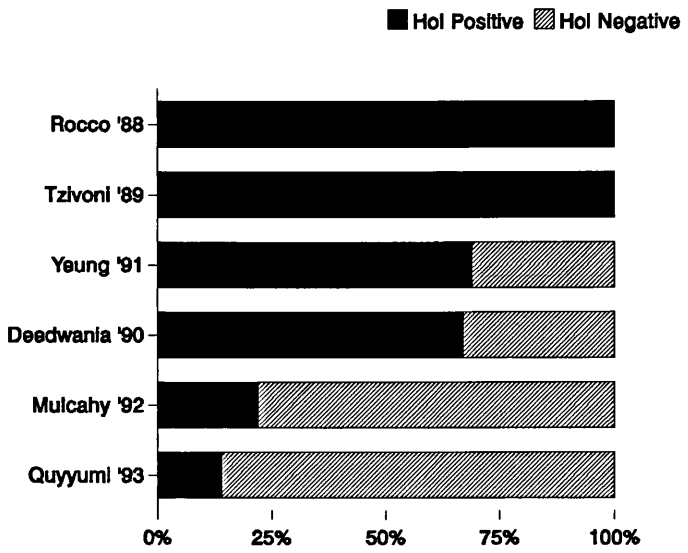


Figure 1.2 Prevalence of ambulatory ischaemia in stable angina patients who experienced the end-points of myocardial infarction or death in prognostic studies of holter monitoring

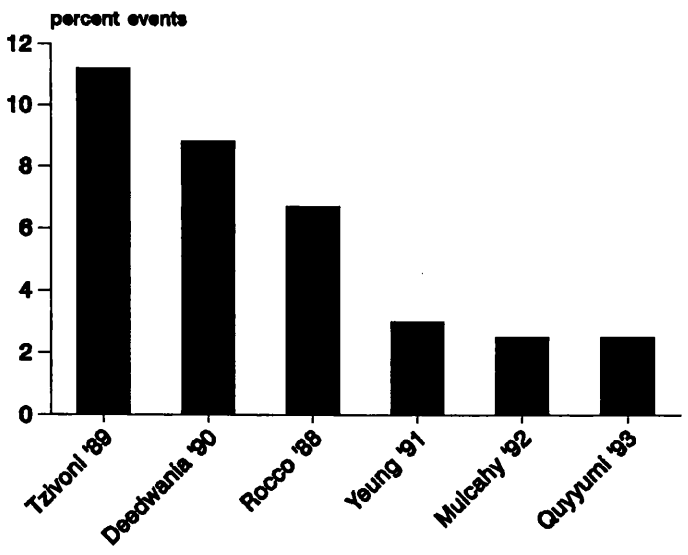


Figure 1.3 Variation in event rate for the combined end-points of myocardial infarction and death in studies assessing prognostic value of ambulatory ischaemia

(Kannel, 1972). An unusually low rate of coronary intervention in angina patients with ambulatory ischaemia with the likelihood of the resultant higher mortality may exaggerate the prognostic value of ambulatory ischaemia.

A spurious association in the reverse direction can result when patient selection is biased towards a low-risk group. In a study which did not require the presence of exercise ischaemia for inclusion (Mulcahy, 1992), patients with an exercise test negative for ischaemia experienced almost twice as many myocardial infarctions or deaths compared with the positive exercise test group. In that study, the *absence* of ambulatory ischaemia was associated with a two-fold higher event-rate compared with patients who had transient ischaemic episodes (2.8% vs 7.0%). In that study, in which patients were selected non-consecutively from two different centres, only 2 of 63 (3.2%) patients with both exercise and ambulatory ischaemia experienced a myocardial infarction or died compared with 5 of 59 (8.5%) patients without evidence of ischaemia who sustained a myocardial infarction. The apparent prognostic benefit associated with the presence of ambulatory and exercise induced electrocardiographic ischaemia is at variance with previous reports which have shown reduced survival in patients with exercise induced ischaemia (ECSSG, 1982), and almost certainly reflects the arbitrary selection of a 'low risk' patient population.

Finally, another important caveat of studies of ambulatory ST segment monitoring is the failure to demonstrate the independent contribution of ambulatory ischaemia to prognosis. The inclusion of varying proportions of patients with prior myocardial infarction - ranging from 0% (Tzivoni, 1989) to 52% (Deedwania, 1990) - confounds outcome because in patients with angina, a history of previous myocardial infarction is independently associated with reduced survival (Weiner, 1984). Thus spurious associations result because multivariate analysis to take account of important differences in baseline clinical characteristics between the comparison groups is not used (Tzivoni, 1989; Mulcahy, 1992).

1.5 Exercise Electrocardiography

Despite a large number of investigations including radionuclide scanning and echocardiography that are now available, the treadmill exercise test remains the most widely used for diagnostic and prognostic evaluation of patients with suspected coronary heart disease. Available evidence suggests however, that less than 10% of

medically treated angina patients in the general population undergo exercise testing (Cannon, 1988).

Many studies report the frequency and prognostic implications of exercise induced ischaemia in patients with angina, but large differences in selection criteria and reported results make it inappropriate to draw any conclusions about exercise characteristics of angina patients in the general population. A meta-analysis of 150 studies reported between 1966 and 1987 from 117 institutions involving 24,094 patients (Detrano, 1989) shows that the sensitivity of an exercise test for $\geq$ 50% coronary artery stenosis ranges from 20% to over 90% (mean 68 $\pm$ 16%) with a similar range in specificity (mean 77 $\pm$ 15%). The authors used over 40 variables in both linear and logistic regression analysis but were able to explain less than 35% of the variance. The major problem was inability to quantify bias from patient selection in the studies reviewed.

The influence of this bias on prevalence and prognostic implications of exercise induced ischaemia is illustrated by reports from the Coronary Artery Surgery Study (CASS), one of the largest prospective multicentre studies of patients with stable CHD (Killip, 1981). Data analysis in various reports from this study was based on a registry of 24,959 consecutive patients with suspected or proven coronary artery disease referred for cardiac catheterisation to 15 centres. Most patients usually undergo exercise testing prior to referral for catheterisation. This initial work-up bias (Philbrick, 1980) is not discussed in any of the reports on exercise testing from the CASS study, but the authors acknowledge the limitations of extrapolating results from a catheterised population to the wider spectrum of patients with angina (Weiner, 1984).

The reported prevalence of exercise-induced ischaemic ST segment depression among patients drawn from the CASS registry ranges from 41% in medically treated men and women (Weiner, 1984) to 80% in men with definite angina (Weiner, 1979), and based on symptom category, from 30% to 79% in patients with non-ischaemic chest pain and definite angina respectively (Weiner, 1979). Among the four CASS reports, the proportion of male patients included in the studies varies from 72% (Weiner, 1979) to 90% (Ryan, 1985) and of patients with previous myocardial infarction from 0% (Weiner, 1979) to 60% (Ryan, 1985). Prevalence of angiographic coronary artery disease varies from 58% (Weiner, 1979) to 100% (Ryan, 1985).

Although drawn from a single registry, patient selection results in wide variation of clinical characteristics. No single study represents the broad spectrum of patients with coronary heart disease encountered in clinical practice. Nevertheless conclusions from such studies are often erroneously interpreted as representative of the generality of patients with coronary heart disease.

The CASS reports conclude that exercise variables are helpful in assessing prognosis (Weiner, 1984) and in predicting improved survival following bypass surgery (Weiner, 1986). In both these observational studies from the CASS registry, multivariate analysis clearly shows a stronger independent association of a history of prior myocardial infarction with reduced survival than any of the exercise variables considered. The important confounding effect of prior myocardial infarction, the prevalence of which is significantly different between the comparison groups in one case (Weiner, 1986) and between survivors and non survivors in another (Weiner, 1984), is ignored by the authors.

These observations underline two important limitations which affect much of the literature about electrocardiographic ischaemia and prognosis: (i) the failure to take account of a history of prior myocardial infarction which is a strong independent predictor of reduced survival, and (ii) the failure to consider the *independent* contribution of all baseline clinical variables which often leads to misleading conclusions about the relative importance of electrocardiographic variables for risk stratification or for predicting intervention related survival.

An additional aspect of study design and methodology which limits generalisability of results is the number of patients eventually selected from the pool of all eligible patients at outset. For example, of the four CASS reports cited, any one study included only 3% to 21% of all patients on the registry. The randomised study included only 37% of all patients eligible for randomisation and ultimately consisted of only 3% of patients on the registry. Likewise in prospective studies assessing the prognostic implications of exercise induced ischaemia in mildly symptomatic patients with coronary artery disease (Bonow, 1984 and 1987) or in patients with recent onset angina undergoing cardiac catheterisation (Castener, 1990), the inclusion of a maximum of 131 patients over four years indicates a recruitment rate of about 32 patients per year. Assuming a thousand patients per year undergo angiography for coronary heart disease at any given centre, as a conservative estimate this figure

represents less than 5% of all catheterised patients. Conclusions from such studies are therefore not applicable to all patients with angina in the clinical setting.

Although an exercise test is frequently used in the primary care setting for risk stratification of new patients in the general population presenting with chest pain, and for selecting patients for cardiac catheterisation, its prognostic value has not been validated in an unselected patient population.

1.6 Conclusion

Angina pectoris is prevalent in over one million men and women in the United Kingdom. It affects many daily living activities and results in absence from work. Patients presenting with angina pectoris in the general population have a threefold increased risk of developing unstable angina, myocardial infarction or death within two years of first presentation.

Despite the significant morbidity and mortality, there is surprisingly no contemporary data about the incidence and prognosis of angina pectoris in the general population. Studies of hospital patients are unrepresentative because even though a patient with angina consults a general practitioner two or three times a year, less than a fifth of patients treated by general practitioners are referred for hospital cardiological evaluation.

In patients with angina, electrocardiographic evidence of ischaemia has conventionally been regarded as an important indicator of subsequent prognosis. In particular, the 'total ischaemic burden', that is, ischaemic ST segment depression with and without anginal chest pain detected by continuous ambulatory electrocardiographic monitoring is thought to represent a more complete picture of ischaemic heart disease activity. Extensive investigation of ambulatory ischaemia in hospital outpatients with stable angina over the past two decades has, however, produced controversial results with a wide range in reported frequency (24% to 82%) and discrepant results about its prognostic value - ranging from an eleven-fold increased risk for myocardial infarction or death to a risk reduction of 70% for the same end points.

A study of men and women in the general population was initiated to quantify incidence of angina pectoris, to describe its natural history and outcome in the revascularisation era, and to assess the frequency and prognostic value of ambulatory ischaemia in the generality of unselected angina patients. The specific objectives of

this study and its design are outlined in the next section.

1.7 Aims

1.7.1 To determine the frequency and clinical significance of ambulatory myocardial ischaemia in unselected men and women presenting for the first time with typical angina pectoris.

Secondary aims

1.7.2 To determine the clinical incidence and short-term prognosis of angina pectoris in the general population.

1.7.3 To investigate the prognostic value of an exercise test in patients presenting with angina pectoris in the general population.

1.7.4 To assess general practitioners' perceptions of current investigation and management of angina pectoris.

1.8 Study Design

- survey of incident angina pectoris from a registered randomly selected general practice population
- case-control comparison of the frequency and characteristics of ambulatory ischaemic changes in incident cases of angina with asymptomatic age, sex and practice matched healthy subjects
- prospective follow-up of patients to assess clinical outcome

and a

- postal questionnaire survey of unselected general practitioners.

CHAPTER 2

METHOD

2.1 Area of Study

Southampton, a port 76 miles south-west of London, is part of the Wessex Regional Health Authority area which serves a total population of three million. The population of Southampton is 422,000 (OPCS 1989). Compared with the national average, the standardised mortality ratio for ischaemic heart disease in this region is 8% lower in men and 12% lower in women (OPCS, 1991).

2.2 Questionnaire Survey of General Practitioners

A postal questionnaire survey of all 217 general practitioners listed with the Hampshire Family Health Services Authority in the Southampton area was undertaken over a three month period to assess perceptions about the current investigation and management of angina pectoris; specifically about the value of exercise testing, coronary angioplasty and coronary artery bypass grafting, and to estimate the proportion of angina patients reportedly referred for a consultant opinion. All practices were in an area close to a regional cardiac centre in Southampton. To maximise response rates, a follow up questionnaire was posted after three weeks if no reply had been received. Confidentiality was maintained by number coding the questionnaires (Appendix 1).

The questions concerned the importance of symptom frequency and duration as a guide to disease severity, a 'usefulness' rating for different indications of exercise testing, confidence at correctly interpreting a resting and exercise electrocardiogram, knowledge about scientific evidence of benefits of revascularisation, and referral of patients with angina for hospital cardiological assessment.

2.3 Pilot Study

Four practices were recruited during an initial three month period to estimate referral rates and to finalise documentation including the questionnaire and examination forms.

2.4 Selection and Recruitment of General Practices

The 64 general practices in the Southampton area under the Hampshire Family Health Services Authority were stratified according to the number of partners per practice, and 25 had five or more partners. Using a Minim program for randomisation on an IBM PC50 computer, 17 of these practices were randomly selected in 3 stages

between June and December 1990. Eight practices were recruited by August 1990, 12 by October 1990 and 17 by December 1990.

Recruitment was undertaken by arranging a meeting with the general practitioners at the individual practices. The research objectives as well as the method of operation of the Chest Pain Clinic and the service to be provided were explained in detail in the presence of all practice partners. It was emphasised that because the incidence of angina was being measured, it was essential for all patients with suspected angina to be referred to the Clinic. General Practitioners were specifically asked to refer men and women up to the age of 70 years presenting for the first time with chest pain which in their opinion could be stable angina. This included any patient for whom a trial of antianginal therapy like sublingual nitrates would be prescribed, or who would be referred to a hospital physician for assessment. GPs were specifically advised not to refer patients with acute chest pain suspected to be unstable angina or evolving myocardial infarction who would be admitted directly to a coronary care unit in the usual way.

The partners and trainees in each of the 17 practices agreed by a consensus decision to participate in the study (Appendix 2). To maximise referral rates, a letter reminding each of the 117 participating partners and trainees of the need to refer all new patients with suspected angina to the Chest Pain Clinic was sent every month. Attached to this was an anonymous report of referral rates by individual practices, with the breakdown of patients referred by each partner within the practice.

2.5 The Study Population

2.5.1 Criteria for referral to clinic

a) Men and women up to and including 70 years of age registered with one of the participating general practitioners.

b) All patients presenting for the first time with chest pain which in their general practitioner's opinion could be angina pectoris.

c) Patients prescribed a trial of sublingual nitrates.

d) Patients presenting with recurrent chest pain if previous episodes were not originally suspected to be coronary heart disease.

2.5.2 Exclusion criteria

a) Patients already on long term antianginal therapy for stable angina.

b) Patients with any previous diagnosis of coronary heart disease, eg unstable angina or myocardial infarction.

c) Patients with known congenital or valvular heart disease or cardiomyopathy.

d) Patients presenting with acute chest pain thought to be unstable angina or myocardial infarction who in the opinion of the general practitioner required hospital admission.

2.5.3 Selection of controls

For every patient with typical angina (Section 2.9.1), up to two age, sex and practice-matched asymptomatic subjects were drawn at random from a computerised register of the study population and were invited to attend a screening examination (Appendix 3). Individuals with a current or past history of coronary heart disease, or any of the above exclusion criteria were not studied.

2.6 Chest Pain Clinic

An open access Chest Pain Clinic was established at the Royal South Hants Hospital which is one of two teaching hospitals in Southampton and has 238 acute admission beds including a 9-bed coronary care unit. The regional cardiac centre for Wessex (population 3 million) is located at the Southampton General Hospital where the consultant cardiologists provide a predominantly tertiary referral service.

The Chest Pain Clinic was based in the department of Non Invasive Cardiology staffed by 3 full time cardiac technicians, 1 part time technician, 2 cardiographers and a secretary. The investigative services for the hospital and district outpatient centre included resting, exercise and ambulatory electrocardiography, echocardiography and ambulatory blood pressure monitoring. This facility had three rooms; one used for clinical examination of patients, another for exercise testing and echocardiography, and a third room for administration.

The Chest Pain Clinic was run as an open access service to which patients were referred by their general practitioner without prior appointment between 9am and 1pm Monday to Friday. When patients presented outside clinic hours, the GP referred them to the next available clinic. A referral form stating the patient's name, address and current medication, and a chest X-ray request card was completed by the GP, and given to the patient to take to the clinic (Appendix 4). A map showing the location of the clinic within the hospital was provided.

2.7 Consent

The study was granted ethical approval by the regional Ethics Committee. Written informed consent for participation in the study and for the use of results for research purposes was obtained from all patients and controls (Appendix 5).

Each patient initially completed a questionnaire (Section 2.8). A chest X-ray and resting electrocardiogram (Section 2.11.1) were then obtained. After a full clinical examination, each patient was classified on the basis of the history detailed in Section 2.9. Further investigations including exercise and ambulatory electrocardiography (Section 2.11.2 and 2.11.3) were then undertaken in patients with angina pectoris.

2.8 Questionnaire (Appendix 6)

All patients and controls completed a self administered questionnaire which covered the following:

a) demographic data
b) past medical history
c) current medication
d) smoking history
e) history of alcohol ingestion
f) Rose chest pain questionnaire
g) for women, questions relation to gynaecological history and hormone replacement therapy.

2.9 Clinical Classification

A complete structured history of the presenting complaint including the site, character, precipitating and relieving factors was recorded together with the frequency and duration of symptoms. This was done blind to the questionnaire data and prior to the exercise test. On the basis of the history, each patient was assigned to one of the following categories:

2.9.1 Typical angina pectoris

Defined according to an anatomically (Weiner, 1979) and prognostically (Murabito, 1990) validated definition as:

a) recurrent

b) brief episodes of chest pain (up to 15 minutes)

c) precipitated by exertion or exertion and emotion

d) relieved by rest or nitroglycerin

e) character and radiation consistent with the diagnosis

2.9.2 Other categories

a) Possible angina:

When 'c' and any one or more (but not all) of the other characteristics listed in 2.9.1 were present, the patient was classified as having possible angina.

b) 'Atypical Pain ? Cause':

This classification was used when the history was not consistent with typical or possible angina, but where the exact cause of pain was uncertain.

c) Non cardiac pain:

When the history and examination were totally inconsistent with the diagnosis of coronary heart disease or suggested an alternative cause of pain.

d) Unstable angina or myocardial infarction:

Patients with a history of rest pain suggestive of unstable angina or acute myocardial infarction with our without electrocardiographic changes were admitted directly from the clinic to the coronary care unit.

e) Exclusions:

Patients with any of the criteria listed in Section 2.5.2 were re-referred, as appropriate, to a medical outpatient clinic for assessment.

2.10 Clinical Examination

Each patient underwent a complete general and cardiovascular clinical examination. The findings were recorded on an examination form (Appendix 7) and included:

a) weight in kilogrammes

b) height in metres

c) heart rate and rhythm

d) signs of hyperlipidaemia

e) jugular venous pressure, position of cardiac apex, character of heart sounds, presence of any murmurs, bruits and the presence or absence of peripheral pulses.

f) blood pressure (Korotkoff phase V) was measured at least ten minutes after the patient was seated. If the systolic blood pressure was $\geq$ 160 mmHg and/or diastolic

blood pressure was ≥ 95 mmHg, the reading was repeated after fifteen minutes rest. A third reading was obtained for patients who subsequently returned for an exercise test. The lowest reading obtained was used in the analysis.

2.11 Investigations

The management scheme for patients assessed at the chest pain clinic is outlined in Figure 2.1. Except where contraindicated, patients with typical angina underwent the following investigations: a venous blood sample to measure a random cholesterol and glucose level; both were analysed at the hospital's biochemistry laboratory.

If indicated, echocardiography and doppler studies were carried out to exclude significant valvular heart disease. Spirometry was carried out to assess chronic airflow limitation.

2.11.1 Resting Electrocardiogram (ECG)

A standard 12-lead resting ECG was recorded at a paper speed of 25mm/sec using a Hewlett Packard pagewriter, Model HP 4750A. When Q waves or T wave inversion were evident in the inferior leads, a further recording was obtained during inspiration. All ECGs were coded blind by independent observers on data entry forms using a modification of the Minnesota code (Rose,1982) detailed in Appendix 8.

2.11.2 Exercise Electrocardiography

An exercise test was carried out at a median of 3 days (range 2-6 days) following the patient's initial clinic assessment.

a) All tests were performed prior to prescription of regular antianginal medication. Sublingual nitrates were prescribed in the interim period. Beta blockers prescribed for hypertension were tailed off and stopped 24 - 48 hours prior to exercise.

b) A Marquette Electronics Inc. Microcomputer Augmented Cardiograph II/ST stress test system was used. Careful attention was paid to skin preparation for electrode attachment to obtain low impedance. In men the attachment sites were shaved, cleaned with an alcohol swab, and after drying, gently wiped with gauze. The 12 standard electrocardiogram leads - limb, augmented and precordial chest leads (I, II, III, aVR, aVL, aVF, and V1-6) were used. Prior to commencing exercise, a 12-lead ECG was recorded with the patient supine, standing and following hyperventilation.

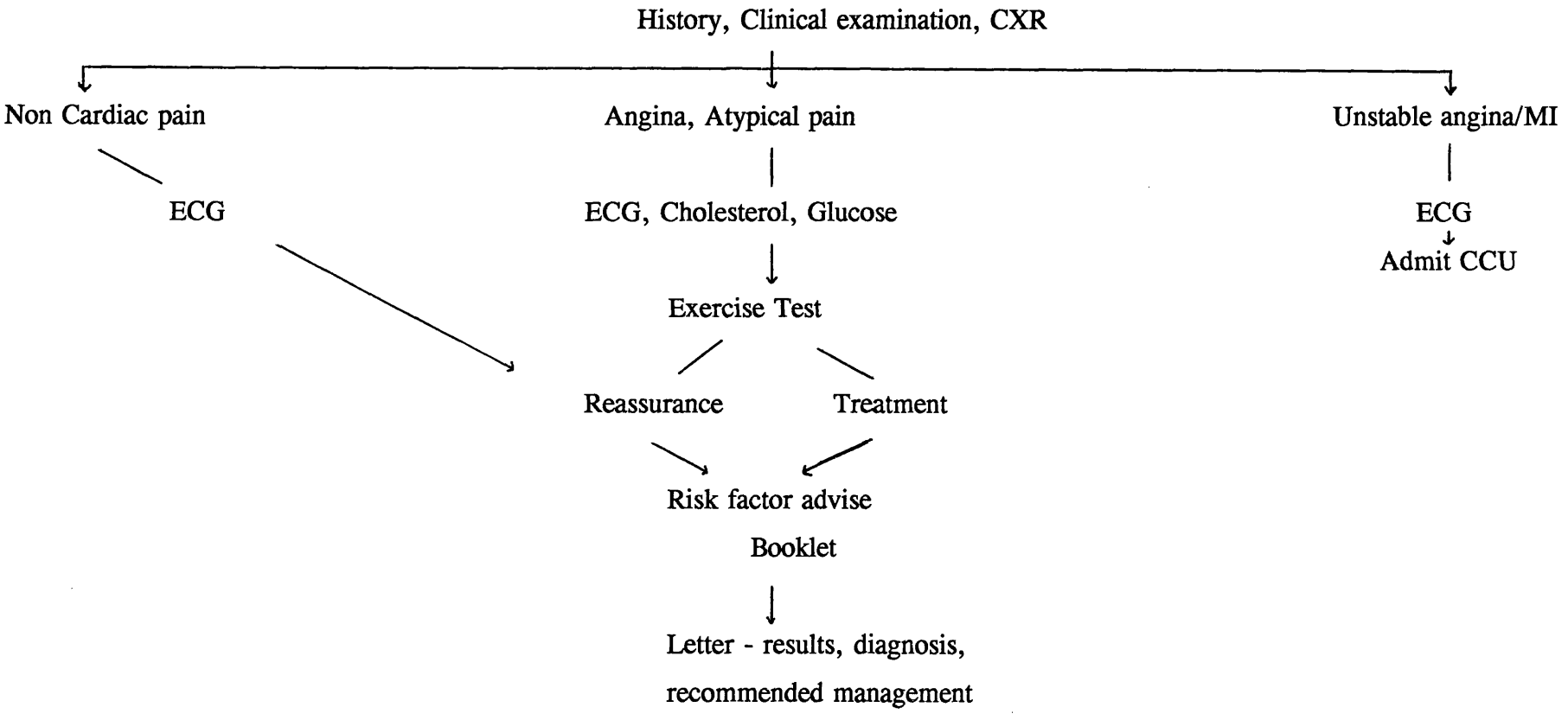


Figure 2.1. Chest pain clinic management scheme

c) A maximal symptom-limited exercise test was carried out according to the Bruce Protocol with three minute incremental stages (Table 2.1).

Stage	Time	Speed	Elevation	METS
1	3	1.7	10.0	4
2	3	2.5	12.0	7
3	3	3.4	14.0	10
4	3	4.2	16.0	13
5	3	5.0	18.0	17
6	3	5.5	20.0	20
7	3	6.0	22.0	23

Table 2.1. Stages of the Bruce Protocol (Bruce, 1971)

Blood pressure was recorded using a suitable sized cuff at rest and at three minute intervals throughout the test, at peak exercise and during recovery. A 12-lead ECG was recorded at similar time intervals and at the onset of any symptoms. Three leads (I,III, V5) were continuously monitored during exercise and additional recordings were obtained during ectopic activity or arrhythmia. ECG recordings were obtained for ten minutes into the recovery period, or until any changes reverted to the pretest baseline.

d) Test end-points included the development of severe angina, dyspnoea, exhaustion, hypotension, complex ventricular arrhythmia, a hypertensive response defined as a systolic blood pressure greater than 230 mmHg or a diastolic pressure of more than 120 mmHg, horizontal or downsloping ST segment depression of $\geq$ 4mm in one or more leads, or at the patient's request. If a patient developed chest pain during the test, the time of onset and relief were recorded.

e) At the end of recovery, a final report consisting of median complexes saved during pre-exercise manoeuvres (with patient supine, standing, post-hyperventilation) during exercise and at peak exercise, and also at the time of maximum ST segment depression was obtained.

f) All exercise ECG recordings were analysed blind by an experienced independent observer with visual interpretation overriding computer analysis (Appendix 9). ST segment depression was coded according to a modified version of the Minnesota code for post-exercise records (Rose, 1982). In addition, the extent of

maximum horizontal or downsloping ST segment depression 80 milliseconds after the J point in each set of leads was recorded. An ischaemic response was defined as 0.1 mV or greater horizontal or downsloping ST segment depression relative to the PR segment measured at J + 80 milliseconds.

2.11.3 Ambulatory electrocardiographic monitoring

Continuous 24 hour two-channel ambulatory electrocardiographic recordings were obtained on magnetic tapes using Tracker recorders. The recorders had a frequency response range between 0.05-100 Hz, conforming to the American Heart Association's standard for evaluation of the ST segment (Pipberger, 1975). Ambulatory monitoring was carried out prior to commencing regular antianginal medication. Sublingual nitrates were used if required. Two pairs of bipolar electrodes recorded (i) an anterior CM5 lead with the exploring electrode at the 'V5' position on the precordium, and the indifferent electrode over the manubrium, and (ii) a modified inferior lead with the exploring electrode over the left iliac fossa and the indifferent electrode to the right of the manubrium (Appendix 10). A small quantity of electrode gel was applied to the attachment sites and the skin was abraded with gauze to reduce impedance. Monitor leads were attached to pregelled electrodes (Medicotest a/s, Type T-00-S) and secured with adhesive tape leaving stress loops. A 0.1mV calibration signal was recorded at the beginning of each tape followed by electrocardiogram recordings in the supine, standing, left and right lateral positions and after hyperventilation to ensure that the ST segment was not affected by postural changes. The time at the end of the manoeuvres was noted.

Patients were encouraged to continue their normal daily living activities and were provided with a diary to record any exertional activity. They were instructed to press the 'event' button on the recorder and to note the time of onset, duration and character of any chest discomfort during the recording period. A typewritten sheet stating the above instructions was also provided (Appendix 10).

All tapes were visually analysed in a blinded fashion at 60 times the normal speed on a Reynolds Pathfinder III analyzer which had software incorporated for ST segment analysis. After initialisation, the cassette was calibrated with the pre-recorded signal. A reference mark was placed on the isoelectric part of the PR segment, the ST1 marker was positioned at the J-point and the ST2 marker at 80 milliseconds after the J-point. Significant ST segment depression was defined as 1 mm or more

horizontal or downsloping ST segment shift 80 milliseconds from the J-point lasting at least one minute. Two episodes were separated by the ST segment returning to baseline for at least one minute. Significant ST segment elevation was defined as an upward shift of the ST segment of $\geq$ 1mm above the isoelectric line. ST segment elevation during sleeping hours was noted separately. The presence or absence of anginal symptoms during episodes of ST segment change was noted from the patient's diary.

Areas of interest on the ambulatory electrocardiogram were printed out at 25 mm/second. These included the beginning of the record to exclude postural ST segment shift, and immediately preceding the onset, at the onset, at maximum ST segment shift and at the termination of an episode of significant ST segment change. Regular printouts of the baseline were obtained throughout the 24 hour period, as were traces of any arrhythmic events. A printout of the 24 hour trend of ST segment change was obtained with normal and with expanded time axes. The total number and duration of episodes per 24 hours were recorded. For individual episodes, the heart rate before onset, at onset and at peak ST segment change was recorded, as was the maximal degree of ST segment change, duration of episode and association with any symptoms (Appendix 11). Changes in the T wave vector in isolation were not regarded as evidence for ischaemia.

2.12 Management

When clinical investigations were complete, a preliminary handwritten report to the general practitioner on a typed pro forma summarising clinical findings, exercise test results and recommended management was handed to the patient. A full typewritten summary was subsequently posted to the patient's general practitioner.

Advice on dietary and lifestyle changes to modify cardiac risk factors including cigarette smoking and hypercholesterolaemia were provided together with explanatory leaflets.

Referral to the regional centre to consider cardiac catheterisation was advised when appropriate, but any such referral and follow-up was ultimately the responsibility of the general practitioner. The chest pain clinic was not situated on the same site as the regional cardiac centre. The decision to undertake coronary angiography and revascularisation was made independently by a cardiologist at the regional centre

unaware of the objectives of this study.

2.13 Follow-up

Follow-up data was undertaken for all patients with typical angina. Deaths were ascertained through the patient's general practitioner. A questionnaire requesting information about current medication, chest pain, attendance at an outpatient clinic and hospital admissions was posted to all remaining patients (Appendix 12). A copy of the questionnaire was posted after three weeks to the non-responders. Where possible, information from non-responders was obtained by telephone interview.

All questionnaire responses were corroborated with the patient's hospital clinical records. A search of the registers in the cardiac catheterisation laboratories at the regional centre identified patients who had undergone coronary angiography. Copies of clinical summaries were obtained from records of all patients reviewed at the cardiac centre, and a note was made of any percutaneous transluminal coronary angioplasty or coronary artery bypass grafting procedures undertaken. Hospital records of patients admitted with chest pain were reviewed, and myocardial infarction documented by the admitting team based on the history and a two-fold rise in cardiac enzymes and/or characteristic electrocardiographic changes was recorded.

2.14 Statistical Analysis

2.14.1 Incidence

Incidence rates per thousand per year with 95% confidence intervals were calculated for the total population aged 31-70 years and for age and sex specific sub groups. These were calculated as the number of cases of typical angina divided by the number of person-years at risk during the study period x 1000. The age and sex distribution of the population at risk was obtained from the registers of the participating general practices. Age and sex specific incidence rates were applied to the 1991 United Kingdom population projections to estimate the number of new angina cases per year (OPCS, 1993). Clinical outcome was assessed in relation to the first of the following events: death, myocardial infarction, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting. A survival curve was constructed using the Kaplan-Meier technique to demonstrate the cumulative probability of event-free survival during the follow-up period.

2.14.2 Ambulatory and exercise ischaemia

Normally distributed data was summarised by mean and standard deviation and skewed data by a median and range. Comparisons between subgroups were made using a χ^2 test (without continuity correction) for categorical data and a t-test for continuous data. The Mann-Whitney U-test was used for comparison of non-normally distributed data between subgroups. Logistic regression analysis was used separately in men and women to determine the independent association of clinical characteristics and exercise parameters with ambulatory ischemic activity. A stepwise procedure was used to build the model using a cutoff of $p=0.05$ to determine entry. Clinical variables entered first in the analysis were frequency and duration of symptoms, age, sex, systolic and diastolic blood pressure, current cigarette smoking, and serum cholesterol. Exercise variables then added were presence of ischemia (ST segment depression $\geq$ 1mm), peak rate pressure product and total exercise duration. Statistical significance was tested using the likelihood ratio statistic. Survival curves were constructed using the Kaplan-Meier technique to examine the cumulative probability of an adverse event (death, myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) in those with and without ambulatory ischemia, and compared by the log-rank method (Armitage, 1987). All analyses were performed using Statistical Analysis System, version 6 (SAS Institute Inc, Cary, NC.).

The analysis between exercise variables and outcome was performed in a similar way using Kaplan-Meier survival curves. Patients were stratified according to the presence or absence of $\geq$ 1mm exercise ST segment depression and also according to a total exercise duration of $\leq$ or $>$ 6 minutes. Data was explored for interaction due to gender. A Cox proportional hazards regression model including age, sex, serum cholesterol, current smoking habit, hypertension, symptom frequency $\geq$ once daily, duration of symptoms $\leq$ 1 month, peak rate pressure product and the presence of exercise ischaemia were included to assess the independent contribution of baseline clinical characteristics and exercise variables to subsequent prognosis. Separate analyses were carried out with and without revascularisation procedures as end-points in addition to death and myocardial infarction.

CHAPTER 3

GENERAL PRACTICE QUESTIONNAIRE SURVEY

3.1 Introduction

The management of angina has altered radically over the last two decades. In the past a prescription of sublingual nitrates sufficed (Fry, 1976), but with the advent of revascularization and its benefits in relieving symptoms (Parisi, 1992), improving quality of life (CASS, 1983) and prolonging survival (Varnauskas, 1988) in selected patients, the onus is now on general practitioners to choose patients with angina for cardiological evaluation with a view to coronary angioplasty or bypass surgery.

Whether or not management of angina in general practice has altered to reflect advances in cardiological management is uncertain. The aim of this questionnaire survey was to assess general practitioner opinion about the investigation and treatment of angina. Specifically, the objective was to estimate the proportion of patients who are reportedly referred for a Consultant opinion, and to assess general practitioners' perceptions about the value of exercise testing, coronary angioplasty and coronary artery bypass grafting.

The method of this questionnaire survey is outlined in Section 2.2.

3.2 Results

A total of 171 general practitioners returned the questionnaire giving a response rate of 79%.

Figure 3.1 shows the importance attached to the frequency and duration of angina in assessing severity of underlying coronary artery disease. About half of the general practitioners considered frequency of angina to be a reliable guide to disease severity, but an equal number did not. Their views differed similarly in relation to the duration of angina prior to presentation.

In patients with suspected cardiac symptoms, general practitioners commonly perform a resting electrocardiogram. Their reported confidence at correctly interpreting it for signs of ischaemia and infarction varied with three quarters stating they were usually or almost always confident, but a quarter stating that they were only sometimes (19%) or almost never (6%) confident (Figure 3.2). By contrast the majority were almost never (56%) or only sometimes (24%) confident at correctly interpreting an exercise test.

3.2.1 Exercise testing

The 'usefulness rating' of an exercise test for making a correct diagnosis and for assessing prognosis is shown in Figure 3.3. The majority thought an exercise test was useful in making a diagnosis but only half considered it useful for assessing prognosis in patients with angina. In assessing other indications for exercise testing, the percentage of general practitioners who gave ratings of 'frequently or almost always useful' varied from 8% for screening asymptomatic patients, 45% for reassurance, and 78% for selecting patients for coronary angiography.

3.2.2 Revascularisation

The majority of general practitioners agreed there was scientific evidence for benefit from coronary angioplasty in relieving symptoms (Figure 3.4), and 71% thought this applied to all age groups. In addition, a fifth were of the opinion that prolongation of survival with coronary angioplasty has also been demonstrated, but 40% were unaware of what the current evidence was in relation to angioplasty and survival.

Almost all (96%) were satisfied that coronary artery bypass surgery relieved symptoms and the majority (70%) considered this to be the case for all age groups. But there was more uncertainty about improved survival with bypass surgery and 38% either didn't know, or thought there was no evidence for this (Figure 3.4). Among those who thought bypass surgery prolongs survival, 44% thought this applied to all age groups but about a third (32%) considered the evidence applied to the under 65 year age group only.

3.2.3 Hospital investigation

In deciding whether or not to refer patients presenting with angina for cardiological assessment, frequency and duration of symptoms were considered important by 93% and by 78% respectively. While age was considered very important by 68%, gender was of little or no importance to 72% of general practitioners when deciding to refer a patient to a cardiologist.

Figure 3.5 shows reported estimates of the proportion of patients with stable angina referred for investigation. Seventy-two percent of general practitioners report referral of only a quarter of all their patients with stable angina to a hospital physician. Fewer patients are referred directly to a cardiologist at the regional centre, with 80% referring a maximum of only 10% of patients.

When they do refer a patient with angina to an outpatient clinic for an exercise test, 46% of general practitioners report a period of three months or longer before the results and management plan become available.

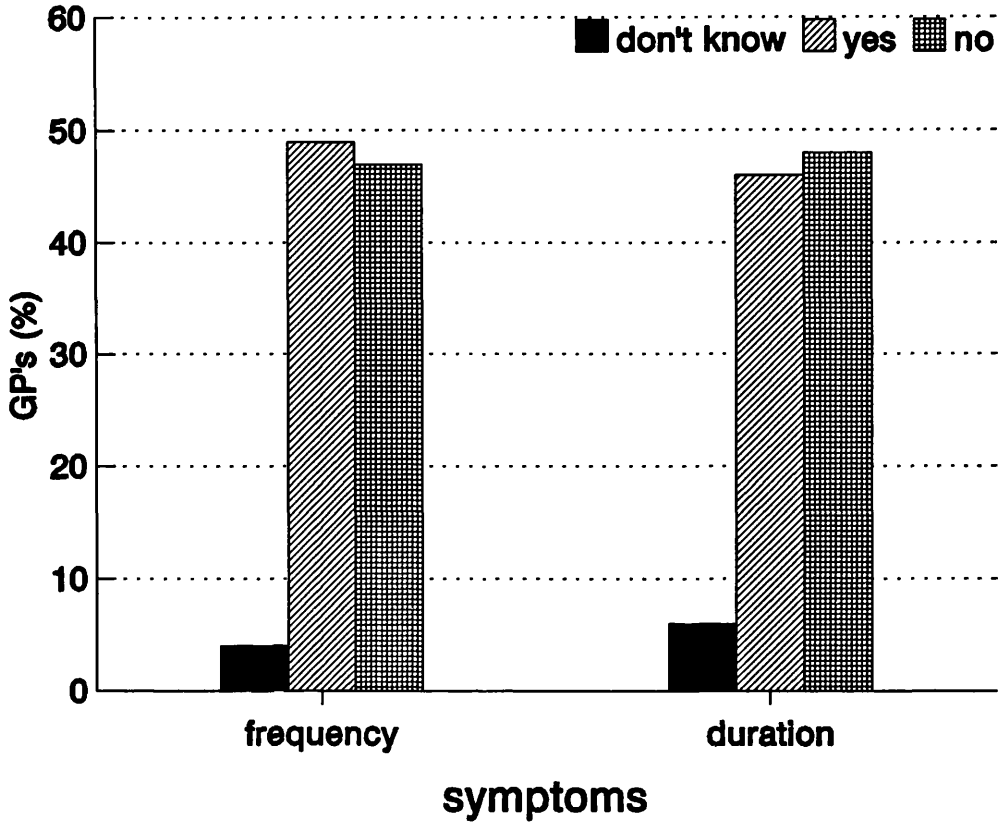


Figure 3.1 General Practitioners' responses to the question 'In a patient with stable angina do you consider symptom characteristics in terms of frequency and duration a reliable guide to the severity of underlying coronary artery disease?' (n = 171 respondents)

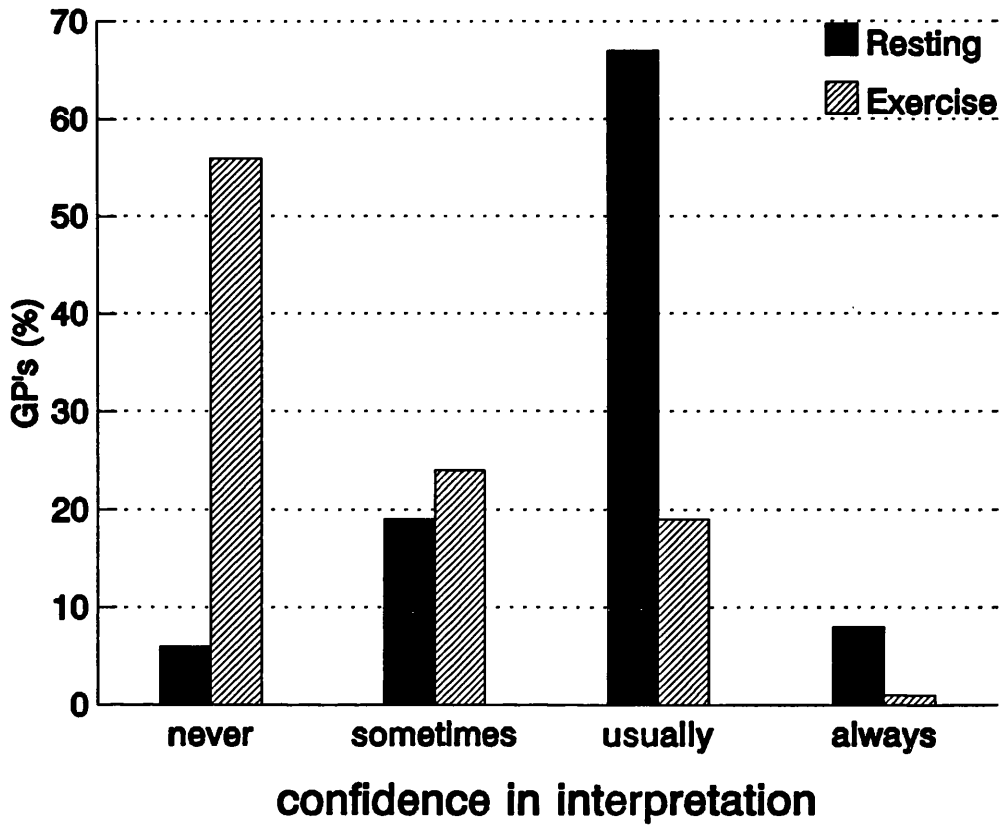


Figure 3.2 General Practitioners' reported confidence in correctly interpreting a resting and exercise electrocardiogram (n = 169 respondents).

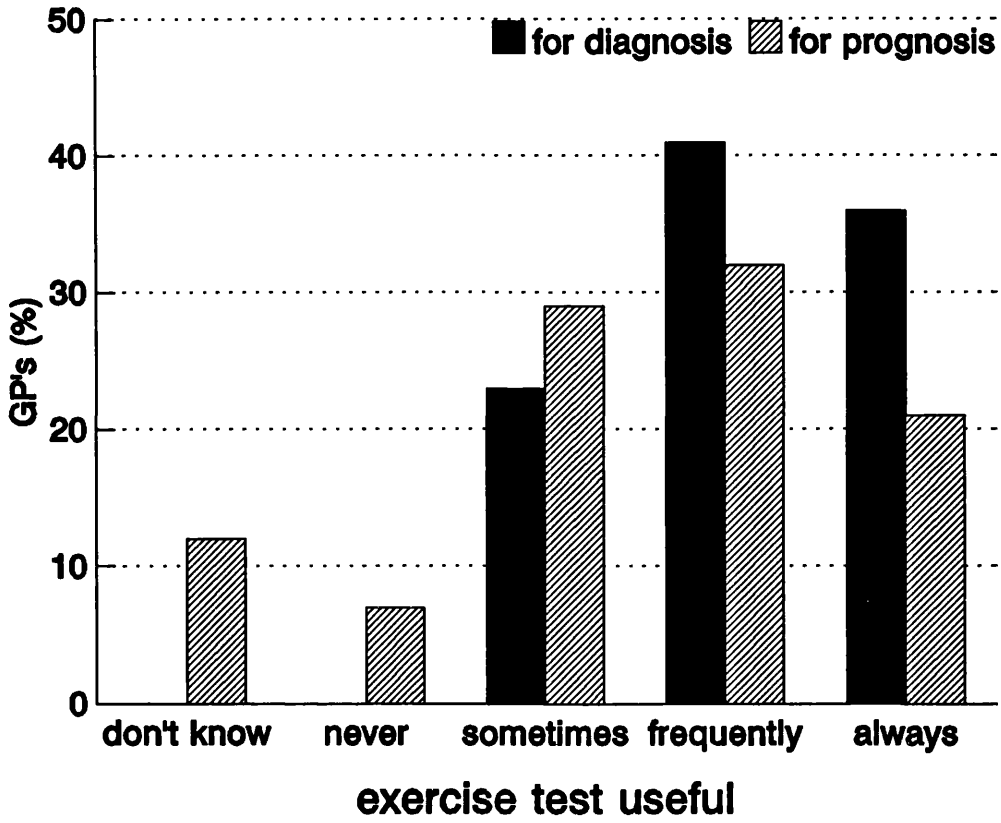


Figure 3.3 Ratings given by General Practitioners for the 'usefulness' of an exercise test for diagnosis and for assessing prognosis in patients with angina (n = 171 respondents).

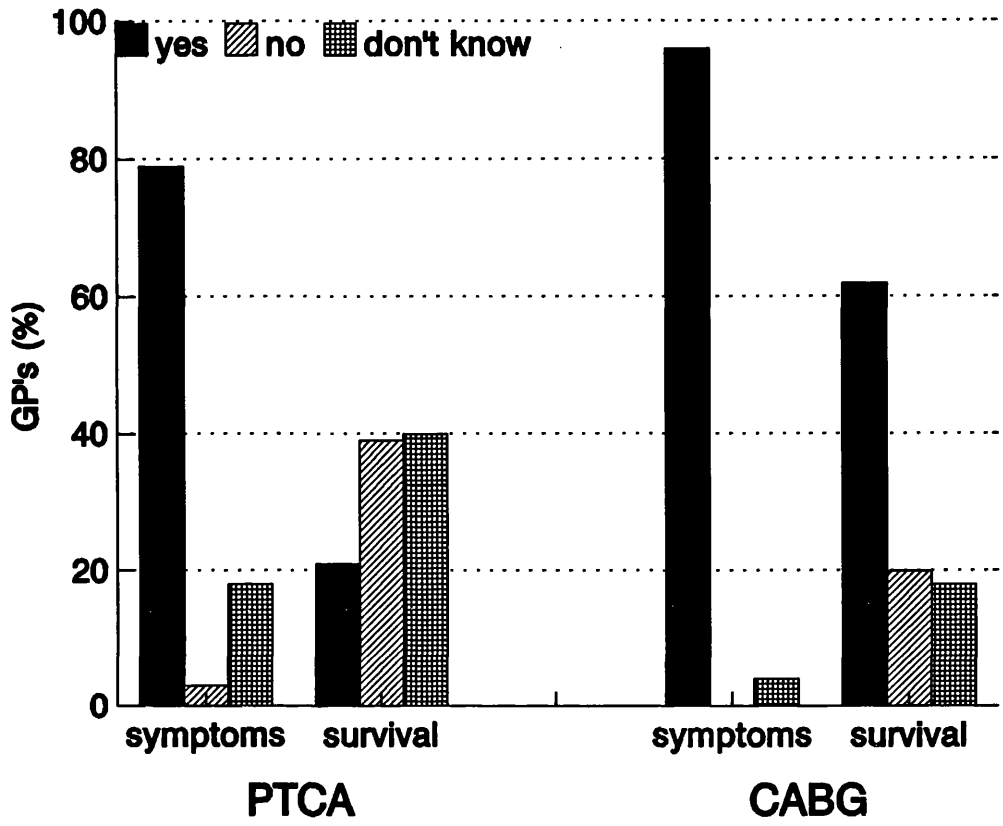


Figure 3.4 **Responses to questions about revascularisation: 'In your opinion, for patients with stable angina, is there scientific evidence to show that percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) a) relieve symptoms and b) prolong survival?' (n = 171 respondents)**

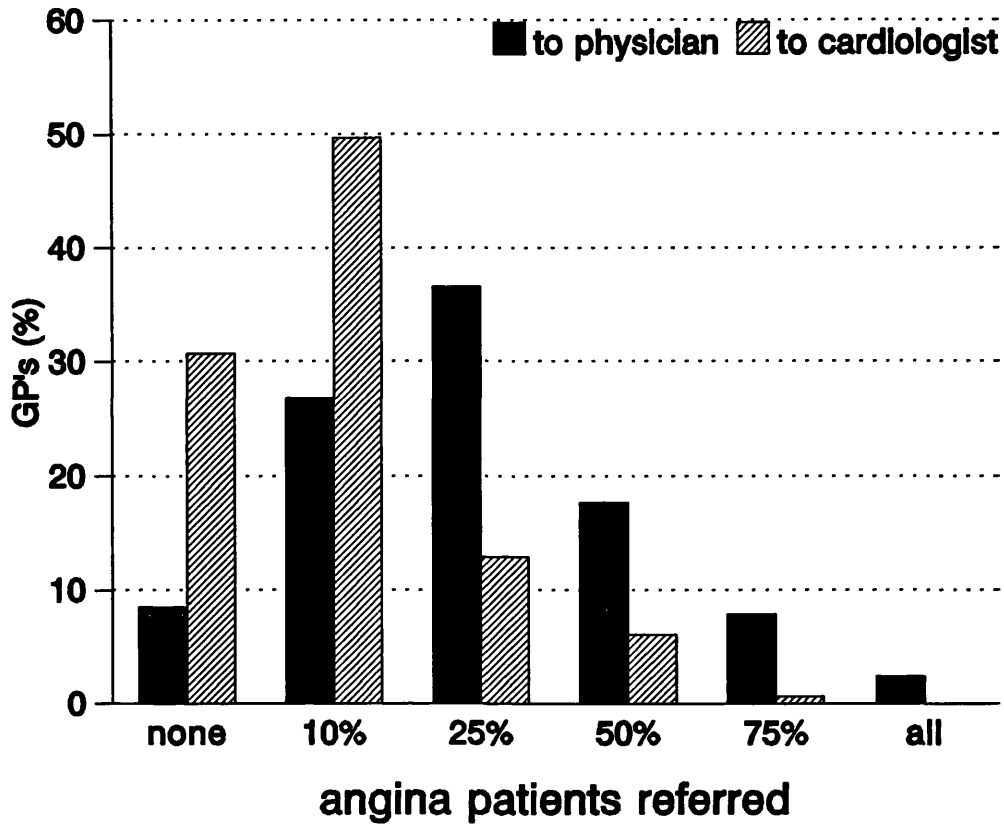


Figure 3.5 **'What proportion of your stable angina patients are referred a) to a general hospital physician b) directly to a cardiologist at the regional centre?' (n = 171 respondents)**

CHAPTER 4

PATIENT CHARACTERISTICS AND CHEST PAIN CLINIC

4.1 Patients referred

The open access Chest Pain Clinic was set up solely for the purposes of this study. A total of 489 patients were referred to this clinic between June 1990 and March 1992. At all ages, there were more male than female patients. Twenty-two patients did not meet the criteria for eligibility for clinic referral. Of these, 12 were aged 71 years or over, 7 patients had a past history of coronary heart disease, and 3 patients were referred from outside the registered study population.

One hundred and ten consecutive patients who presented with typical angina pectoris (section 2.9.1) were included in the study. Sixty-three per cent (n=70) were male, and 37% (n=40) were female.

The remainder of referrals were classified as follows (section 2.9): n=63 (13%) with possible angina; n=63 (13%) with 'atypical pain ? cause'; n=204 (44%) with non-cardiac pain, and 27 (6%) patients were admitted to the coronary care unit because the history and/or electrocardiogram was consistent with unstable angina or myocardial infarction.

4.2 Demography

The age and sex structure of 110 patients with typical angina is shown in Figure 4.1 The majority (92%) of the patients had lived in the area of study for over 10 years, representing a stable study population (Figure 4.2).

The social class distribution in Figure 4.3 shows that the vast majority of patients presenting with angina belonged to the manual or non-manual skilled occupations.

4.3 Symptom Characteristics

The duration of angina symptoms reported prior to initial assessment at the Chest Pain Clinic was variable (Figure 4.4). Although the majority of patients were assessed within 24 hours of their general practitioner first suspecting a diagnosis of coronary heart disease, 61% of patients reported experiencing angina for longer than one month prior to the clinic visit. Ten per cent reported the presence of symptoms for more than one year.

The majority reported experiencing anginal pain daily or up to two or three times a week. (Figure 4.5).

4.4 Cardiac Risk Factors

4.4.1 Hypertension

Hypertension was defined as a systolic blood pressure of ≥160 mmHg and/or a diastolic blood pressure of ≥100 mmHg on at least two recordings, or when the patient was receiving antihypertensive medication. A higher cut-off for diastolic blood pressure was used to allow for clinic readings.

Prevalence of hypertension in patients with angina (Figure 4.6) was 48% (53 of 110). In the 53 patients with hypertension, raised blood pressure had been previously undetected in 26%, detected but not treated in 34%, and inadequately treated in 17%.

4.4.2 Hypercholesterolaemia

The distribution of random serum cholesterol measurements is shown in Figure 4.7. Total serum cholesterol level was ≥ 6.5 mmol/L in 75% of patients with typical angina, and ≥ 9 mmol/L in 12% of these patients. There was no significant difference in the proportion of patients with a family history of coronary heart disease among those with a cholesterol level ≥ 6.5 mmol/L compared with a level < 6.5 mmol/L (53% vs 38%, p = 0.15). In all but one patient, hypercholesterolaemia had been previously unrecognised.

4.4.3 Smoking, diabetes, and obesity

The prevalence of current cigarette smokers among patients with typical angina was 30%. A further 38% were ex-smokers, 23% lifelong non smokers and 9% pipe or cigar smokers. Ex-smokers had given up smoking for at least one year.

Obesity, defined as a body mass index ≥ 30 kg/m^2, was prevalent in 27% (30 of 110) of patients with typical angina.

A random plasma glucose level > 11 mmol/L was detected in two patients with angina who were not known diabetics. A further 7 (6%) patients had previously diagnosed diabetes mellitus.

The proportion of patients presenting with typical angina in the general population who had major cardiovascular risk factors was high: 82% of patients had one risk factor, and almost a third (32%) had two major cardiovascular risk factors.

4.5 Clinic Workload

Over 95% of patients were assessed at the clinic within 24 hours of referral by the general practitioner. Patients seen at the weekend were referred to the next available clinic.

The mean referral rate was 28 patients per month. The overall referral rate to the Chest Pain Clinic was 193 patients per 100,000 population under 70 years of age per year.

A total of 317 patients assessed at the clinic during the 1991 calender year contributed to 4.4% of the department's resting electrocardiography workload. Twenty-three per cent (139 of 595) of exercise tests carried out in the department during 1991 were generated by the chest pain clinic.

A full typewritten summary stating clinical findings, investigation results, diagnosis and recommended management was posted to the general practitioner within 7 days in 72% of cases, and within two weeks of referral in 90% of cases (Figure 4.8). Management recommendations to the general practitioner included advice about risk factor modification and medical therapy.

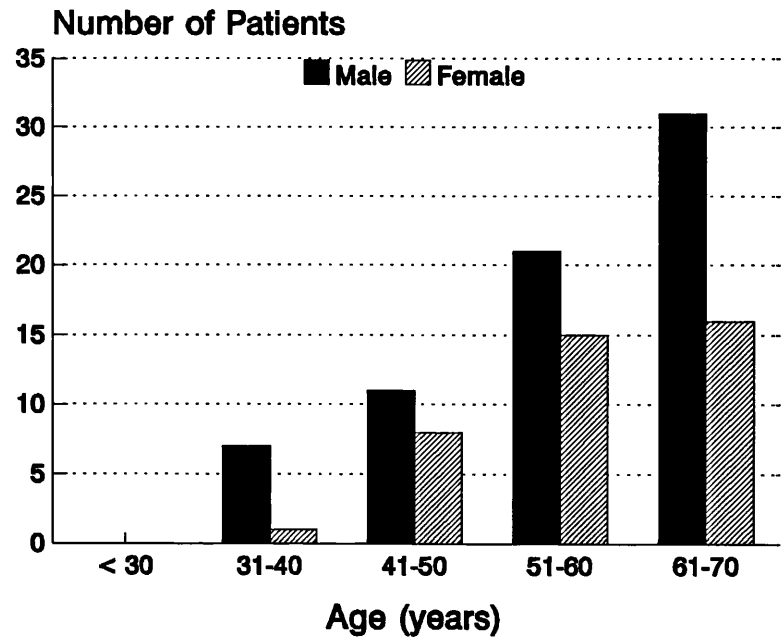


Figure 4.1 **Age and sex of 110 consecutive patients with typical angina pectoris**

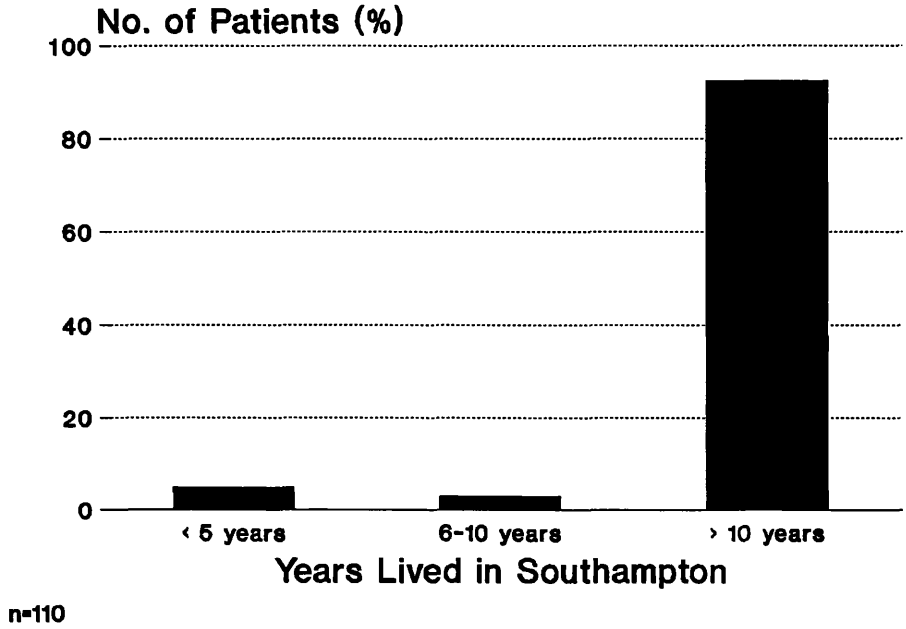


Figure 4.2 Number of years resident in area of study.

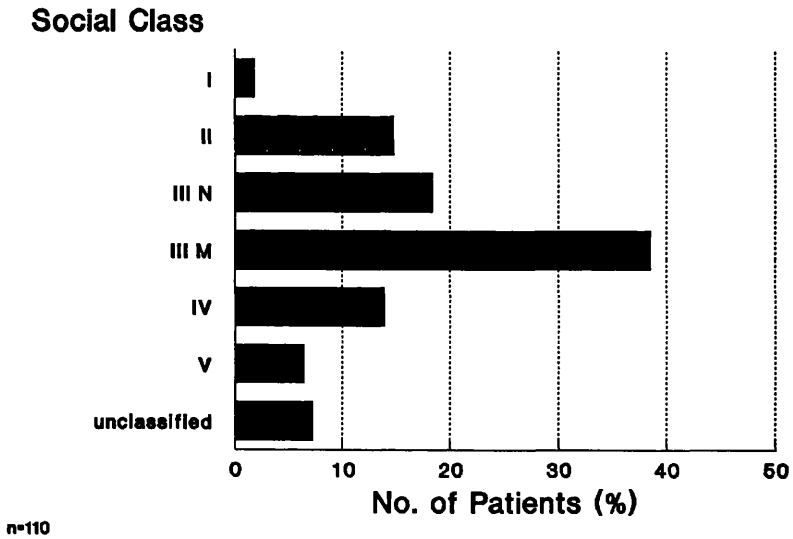


Figure 4.3 Social class distribution of patients with typical angina pectoris.

(I=professionals; II=intermediate occupations; IIIN=skilled occupations - non-manual; IIIM=skilled occupations - manual; IV=partly skilled occupations; V=unskilled occupations; unclassified=occupation not stated)

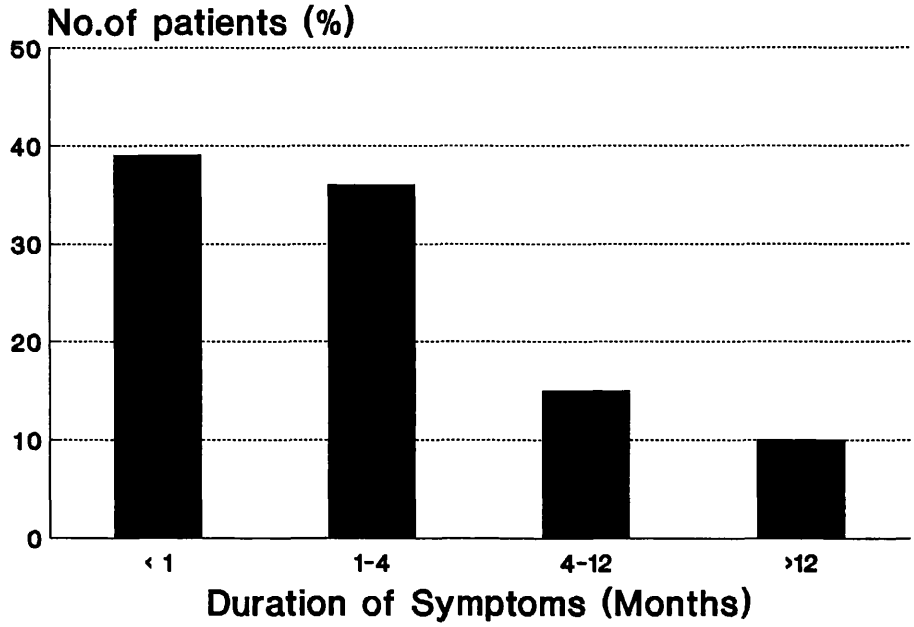


Figure 4.4 **Duration of typical angina symptoms reported by 110 patients prior to clinic visit.**

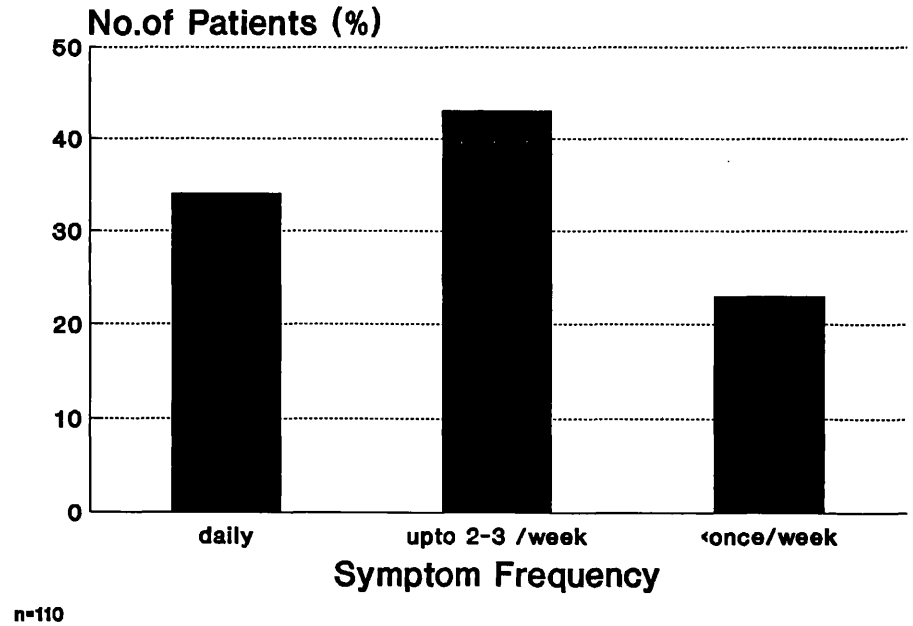
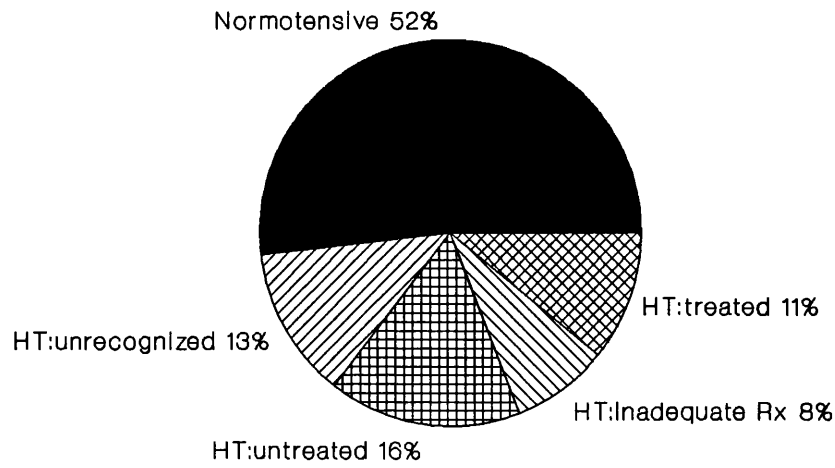
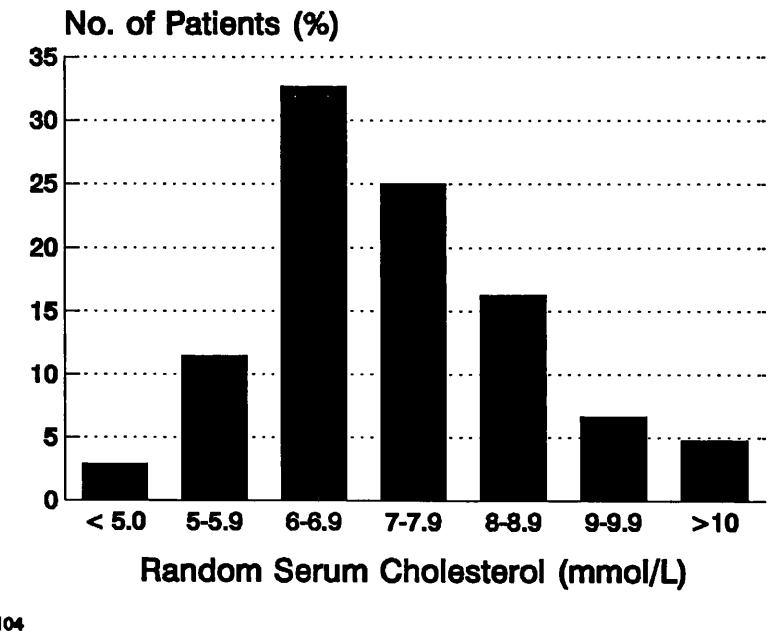


Figure 4.5 **Symptom frequency in patients presenting with typical angina.**



HT = BP > 160/100 mmHg or current Rx

Figure 4.6 Hypertension in 110 new patients with angina pectoris.



n = 104

Figure 4.7 Distribution of random serum cholesterol in patients presenting with angina pectoris in the general population.

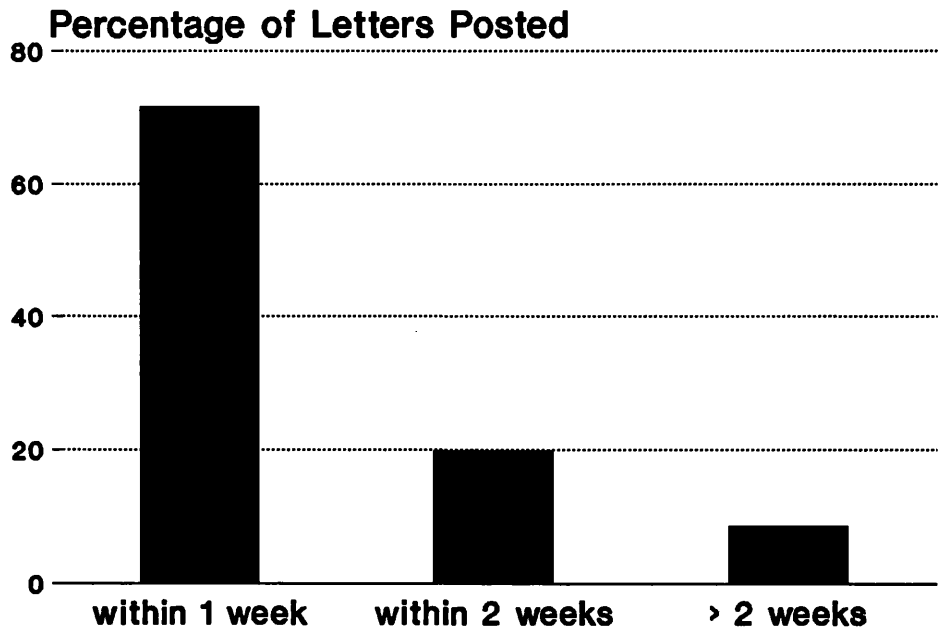


Figure 4.8 Time to general practitioner letter.

CHAPTER 5

INCIDENCE AND SHORT TERM PROGNOSIS OF ANGINA PECTORIS

5.1 Introduction

Little is known about the incidence or natural history of angina pectoris in the general population. The Framingham Study which commenced in 1949 was unique in recording incidence of angina in both men and women in the general population (Kannel, 1972) but its data is now outdated since a better understanding of cardiovascular risk factors, the availability of modern pharmacological agents, and the development of technology for coronary intervention procedures has coincided with a concomitant decline in both incidence and mortality of cardiovascular diseases (Sytkowski, 1990).

One of the aims of this study was therefore to estimate the clinical incidence of angina pectoris and to investigate the outcome of this disease following diagnosis.

5.2 Incidence

One hundred and ten consecutive patients presenting for the first time with typical angina were identified between June 1990 and March 1992 from a total registered population of 191,677. Of these 70 were male and 40 were female. The mean age was 57.4 (SD 9.6) years, range 34-70 years. Ninety-two per cent of the patients had been resident in the area of study for over 10 years.

Age and sex specific incidence rates for typical angina (Figure 5.1) were derived from the known age and sex structure of the study population (Appendix 2b). The crude annual incidence (95% confidence interval) in men and women aged 31-70 years was 1.13 (0.85, 1.40) and 0.53 (0.33, 0.72) per thousand population per year respectively. The overall crude annual incidence of typical angina was 0.83 (0.66, 1.0) per thousand patients aged 31-70 years per year.

The age and sex structure of the randomly selected study population was almost identical to the United Kingdom population (Figure 5.2). Applying these rates to the United Kingdom population gives an estimate of 22,570 (95% CI 17840, 27030) new patients presenting to their general practitioner with typical angina each year in the UK (Table 5.1).

As treadmill exercise testing was carried out on all patients with typical angina who did not have contraindications, separate estimates were derived for incidence of patients with angina and an ischaemic exercise test response. Of the 103 patients who underwent exercise testing, 63 (61%) had an ischaemic response with

≥ 1mm horizontal or downsloping ST segment depression. In the United Kingdom, the annual incidence of new patients with typical angina pectoris and exercise induced ischaemic ST segment depression is estimated at 9,370 (95% CI 7,760, 11,450) men and 4,250 (95% CI 2,890, 5,330) women.

5.3 Outcome

The median duration of follow-up was 15.8 months (range 7-30 months). Complete data was available for 107 of 110 (97%) patients with typical angina. The 3 patients lost to follow-up had moved without a forwarding address.

Table 5.2 shows outcome and Figure 5.3 the cumulative survival for the total cohort of patients with typical angina. Eleven per cent of patients presenting with angina died (n=4) or experienced non-fatal myocardial infarction (n=8) and 18% (n=20) underwent revascularisation. One of the deaths occurred in a patient with a low workload positive exercise test who also had co-existing prostatic malignancy. There were no special arrangements with the regional cardiac centre for assessment of patients included in the study and the decision for elective revascularisation was made independently by the cardiologists concerned based on their usual clinical practice.

Figure 5.4 shows the outcome among the 75 surviving patients who had not undergone revascularisation or experienced a non-fatal myocardial infarction at the time of follow-up. Angina resolved spontaneously in 12 (11%) patients, and with medical therapy in a further 21 (19%). About a third (32%) reported continuing symptoms in spite of medication and a further 4 patients were awaiting elective revascularisation.

Age (years)	Male	Female
Up to 40	1,580	240
41-50	2,360	1,760
51-60	4,370	2,570
61-70	6,940	2.750
Total	15,250	7,320
95% confidence interval*	(11,310, 18,630)	(4,530, 9,880)

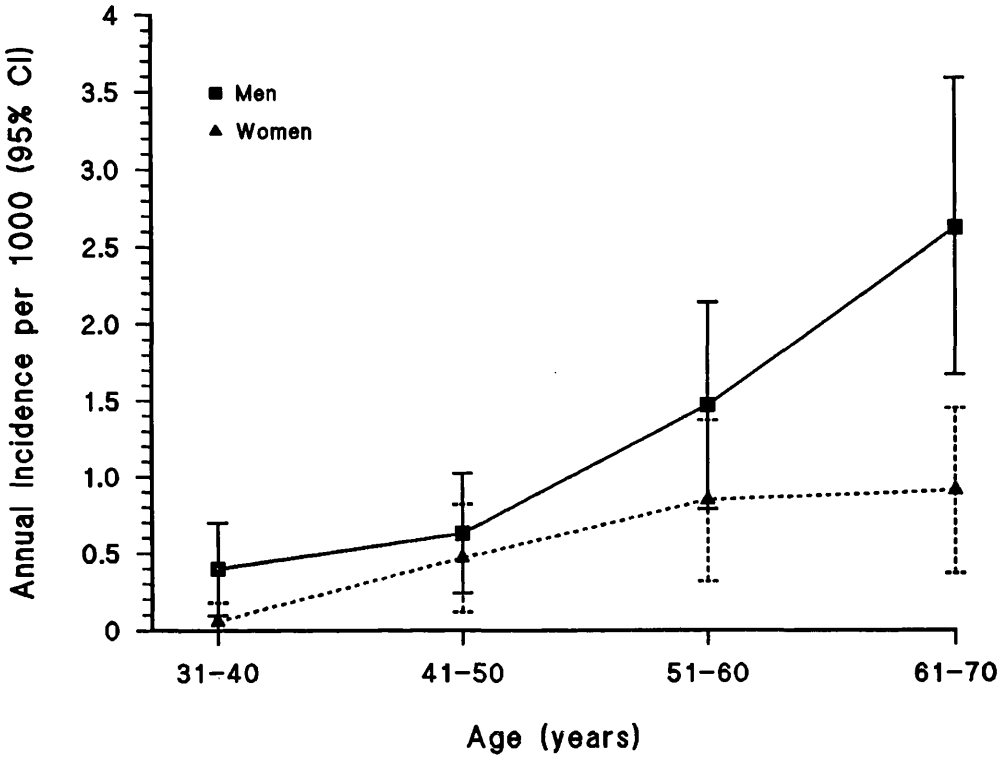
* derived from crude incidence rates

Table 5.1 Estimated number of patients presenting annually in the United Kingdom with typical angina pectoris.

			OUTCOME	
	Male (n = 70)	Female (n = 40)	Months to event (median)	Total Events (%)
Death (*n*)	4	0	2.6	3.6
Myocardial infarction (*n*)	6	2	1.6	7.3
PTCA* (*n*)	9	3	2.9	10.9
CABG† (*n*)	8	0	7.5	7.3

* excluding n=1 female patient on waiting list
† excluding n=1 female and n=2 male patients on waiting list
PTCA = percutaneous transluminal coronary angioplasty
CABG = coronary artery bypass grafting

Table 5.2 Outcome of 110 patients presenting with angina pectoris in the general population.



	Age (years)			
	31-40	41-50	51-60	61-70
Male	0.4 (0.10, 0.70)	0.63 (0.24, 1.02)	1.47 (0.79, 2.14)	2.62 (1.67, 3.58)
Female	0.06 (0, 0.18)	0.47 (0.12, 0.82)	0.85 (0.32, 1.37)	0.91 (0.37, 1.45)

Figure 5.1 Annual age and sex specific incidence of angina pectoris.

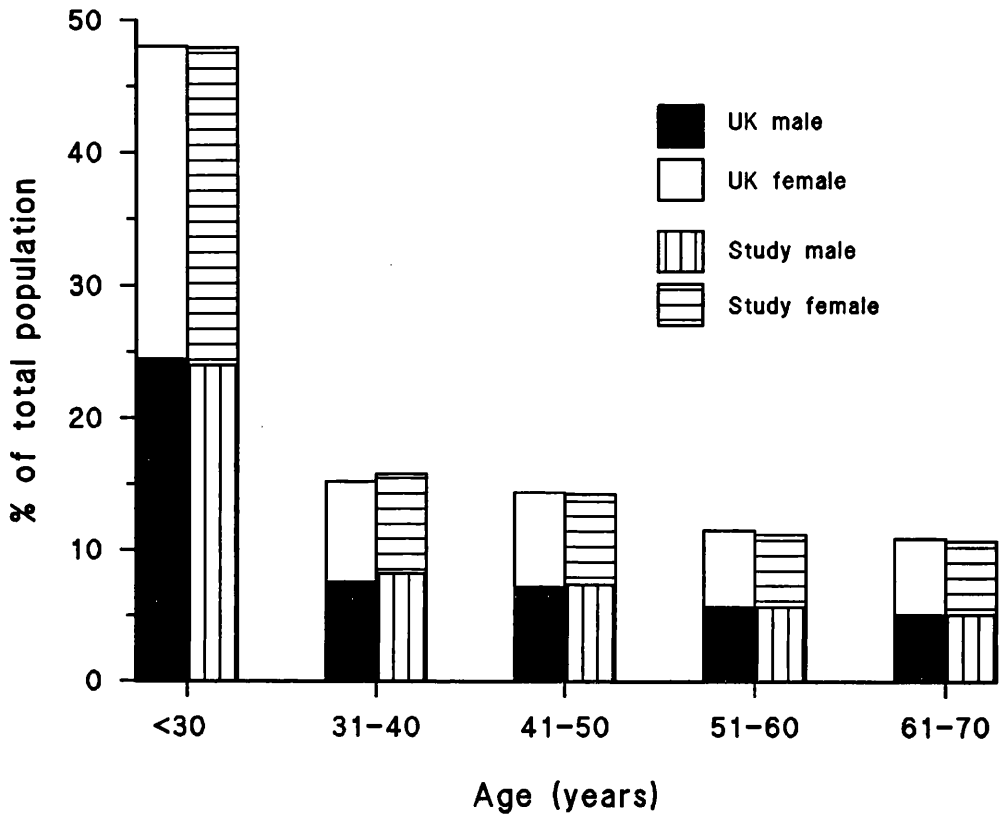


Figure 5.2 Structure of United Kingdom and study population by age and sex.

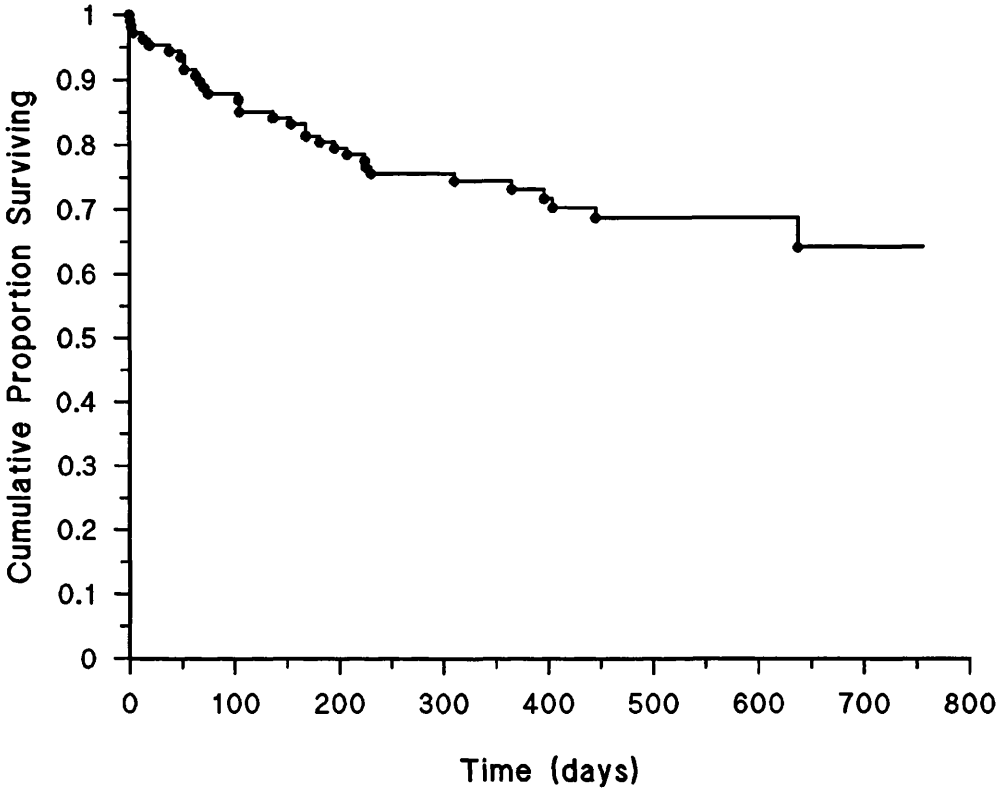
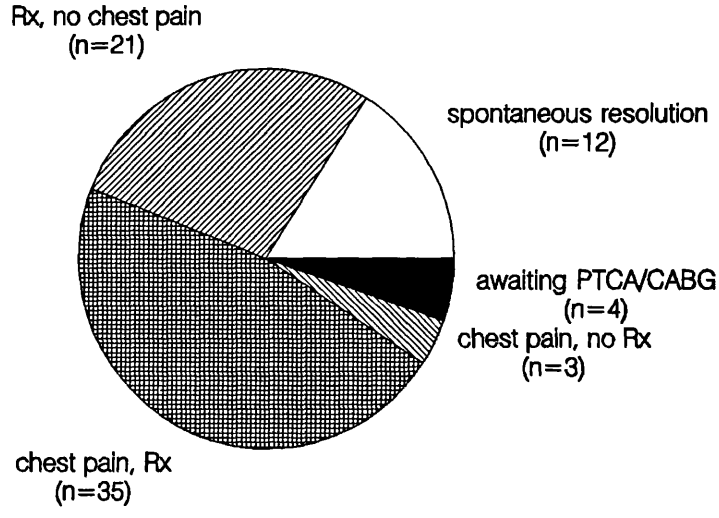


Figure 5.3 Event-free survival of patients with angina pectoris at a median of 15.8 months after first presentation (events = PTCA, CABG, myocardial infarction, death).



Rx = on antianginal medication

Figure 5.4 Outcome at a median of 15.8 months in n=75 angina patients who did not experience events listed in Table 5.2.

CHAPTER 6

EXERCISE TEST CHARACTERISTICS AND PROGNOSTIC VALUE

6.1 Introduction

An exercise test is used routinely in clinical practice to evaluate patients who present with exertional chest discomfort. Its diagnostic value is greatest in patients with atypical chest discomfort but, in those with typical angina, especially men in whom there is a high pre-test likelihood of disease, a positive exercise test contributes little additional diagnostic information (Detry, 1977; Patterson, 1984). In such patients the main reason for performing an exercise test is for prognostic risk stratification.

Some prognostic scores based on the treadmill exercise test suggest that exercise induced ST segment depression and total exercise duration may contribute to predicting survival in patients with angina (Mark, 1991; Morrow, 1993), but this finding is not consistent and in other studies exercise ischaemia was shown to be of no prognostic value (Duback, 1988).

The inconsistency in prognostic importance of exercise variables can be largely attributed to 'work up bias' (Philbrick, 1980). In a cohort of male veterans selected for coronary angiography, exercise induced ST segment depression was independently associated with reduced survival, but in patients referred to the same institution who were not selected for cardiac catheterisation, exercise ischaemia had no prognostic value (Brown, 1992). Patient selection criteria have a strong influence on whether or not an exercise variable will be of prognostic importance. Patients included in prognostic studies are often highly selected and misrepresent the intended population (Philbrick, 1982).

In spite of the widespread use of exercise testing for risk stratification, the prognostic value of total exercise workload and exercise induced ischaemia has not been validated in the generality of patients presenting with angina pectoris.

One of the secondary objectives of this study was therefore to describe the exercise characteristics of a representative sample of new patients with angina pectoris and to investigate the prognostic value of exercise test variables in such patients. In order to compare exercise characteristics, the normal response to exercise was evaluated in a broad spectrum of population based healthy men and women who were randomly selected from general practice registers (section 2.5.3).

The exercise protocol and the method of follow-up is described in sections 2.11.2 and 2.13 respectively.

6.2 Patients

Of 110 patients with typical angina, 7 were excluded for the following reasons: n=1 permanent pacemaker, n=1 left bundle branch block, n=1 intermittent claudication, n=2 hospital admission prior to exercise test, n=1 on digoxin and n=1 because of an abnormal chest x-ray.

Of the 103 consecutive patients with typical angina who were prospectively enroled, 66 (64%) patients were male and 37 (36%) female. Mean age of the study population was 57.9 (SD 9.8) years.

6.3 Controls

Selection of controls is described in section 2.5.3. Of 110 eligible asymptomatic healthy controls, 107 did not have contraindications to exercise testing. There were 65 men with a mean (SD) age of 56.3 (9.9) years and 42 women, mean age 57.7 (8.3) years. No subject had a current or past history of coronary heart disease, was taking beta blockers, or developed arrhythmia during the test.

6.4 Exercise Characteristics of Angina Patients

Ischaemic ST segment depression, defined as $\geq$ 0.1 mmol horizontal/downsloping ST shift from baseline at J+80msecs, was induced in 42 of 66 (64%) men and in 21 of 37 (57%) women with angina. Marked exercise induced ischaemia, that is $\geq$ 3mm ST segment depression, was prevalent in 29% of angina patients (20 male, 10 female). Mean (SD) exercise duration of patients with $\geq$ 3mm ST segment depression was 5.9 (2.2) minutes. Silent ischaemia was prevalent in only 11 of 103 (11%) patients.

Peak rate pressure product was equally and significantly reduced in those with and without ischaemia (Figure 6.1).

Total exercise duration or workload attained was also significantly reduced in patients with (6.5 min vs 9.8 min in controls) and without (7.0 mins vs 10.4 mins in controls) ischaemia; this difference was found in both men and women (Figure 6.2). The mean exercise duration on the Bruce protocol in men with angina was 7.0 (2.8) minutes compared with 11.0 (2.9) minutes in healthy male controls, and in women with angina it was 6.3 (2.4) minutes compared with 9.0 (2.1) minutes in female controls; $p < 0.001$ for both sexes.

A multivariate analysis including all baseline clinical characteristics was

carried out to determine whether frequency and duration of angina could predict a low workload positive exercise test. Only systolic blood pressure was weakly associated with a low workload positive exercise test (OR 1.03, 95% CI 1.0, 1.05).

6.5 Total Exercise Workload, Exercise Ischaemia, and Prognosis

6.5.1 Clinical characteristics

The 103 patients with angina pectoris who underwent an exercise test were divided into two groups according to final exercise stage reached: Group 1 consisted of n=43 patients whose total exercise duration was $\leq$ 6 minutes ie a maximum exercise workload of $\leq$ 7 METS on the Bruce protocol, and Group 2 consisting of n=60 patients who were able to exercise for $\geq$ 6 minutes on the Bruce protocol.

Table 6.1 compares the baseline clinical characteristics of Group 1 and Group 2 patients. Patients in Group 1 were older, had a higher mean serum cholesterol, more frequent angina and a lower peak rate pressure product compared with Group 2. All remaining clinical characteristics including the proportion of male patients and mean body mass index were similar between the two groups.

6.5.2 Survival curves

During 15.8 months of follow-up (range 7-30 months), there were 4 deaths (one non-cardiac), 6 myocardial infarctions, 11 coronary angioplasty and 8 coronary artery bypass graft procedures. Of the 42 patients in Group 1 who did not exceed Stage II of the Bruce protocol exercise test ($\leq$ 7 METS), 21 (50%) experienced one of these end-points (Table 6.2). By comparison there were only 8 (14%) events in Group 2 patients who reached Stage III or more of the exercise test.

Kaplan-Meier actuarial analysis of cumulative survival for both total events and separately for the combined end-points of non-fatal myocardial infarction and death revealed significantly reduced survival in patients with a lower exercise capacity (Figures 6.3 and 6.4). Total event-free survival in Group 1 was 50% compared with 86% in Group 2 (log rank $p < 0.0001$), and survival free from non-fatal myocardial infarction or death was 83% in Group 1 vs 95% in Group 2 (log rank $p < 0.05$).

The effect of exercise induced ST segment depression on the clinical end-points of myocardial infarction and death was evaluated in a separate analysis. There was no significant difference in survival free from myocardial infarction and death between patients with and without inducible ischaemia (Figure 6.5). This difference remained non significant even after women were excluded from the analysis.

	Total Exercise Duration	
	Group 1 ≤ 6 min	Group 2 > 6 min
mean Age (yr)	60.8 (7.5)	54.9 (10.5)*
male (%)	63	65
cigarette smokers (%)	21	37
hypertension (%)	53	47
serum cholesterol mmol/L	7.6 (1.4)	7.0 (1.2)†
diabetes 9%	7	8
body mass index (kg/m^2)	28.8 (4.2)	27.4 (3.3)
Symptoms		
frequency ≥ once daily (%)	47	25†
duration ≤ one month (%)	40	45
Exercise		
STD ≥ 1mm (%)	70	55
rate pressure product (x 10^3))	26.6 (5.9)	29.2 (5.7)†

value in parentheses is standard deviation
STD = ST segment depression
* $p<0.01$ † $p<0.05$

Table 6.1 Baseline clinical characteristics of n=43 patients with angina who completed ≤ 6 minutes (Group 1) compared with n=60 patients who completed > 6 minutes (Group 2) on the Bruce protocol treadmill exercise test.

6.5.3 Multivariate analysis

A multivariate Cox's hazard function analysis was carried out to assess the independent contribution of clinical and exercise variables listed in Table 6.1 to prognosis. Decreasing age, male gender and a total exercise duration less than six minutes emerged as the only independent predictors of reduced event-free survival (Table 6.3). Exercise induced ischaemia was not associated with reduced survival.

Because interventions such as PTCA and CABG which are censored in the survival analysis may be linked to a reduced exercise workload, the cox proportional hazards analysis was repeated to assess the relationship between baseline clinical characteristics and outcome with only non-fatal myocardial infarction and death as end-points. Total exercise duration $\leq$ 6 minutes remained an independent predictor of adverse outcome (Relative Risk 3.6 95% CI 0.9, 13.9), but exercise induced ST segment depression made no significant contribution to predicting myocardial infarction or death.

The positive predictive value of an exercise workload $\leq$ 7 METS for clinical events, that is, the proportion of angina patients whose total exercise duration was 6 minutes or less on the Bruce protocol and who experienced a clinical event during follow-up, was 50%. Combining the presence of exercise induced ST segment depression $\geq$ 1mm with exercise capacity $\leq$ 7 METS increased the positive predictive value for all endpoints from 50% to only 53%, and the specificity from 70% to 80%, but reduced sensitivity for predicting adverse events from 72% to 55%.

6.6 Exercise Capacity in Asymptomatic Controls

Variables measured during the Bruce protocol treadmill exercise test among asymptomatic control subjects were plotted against age, separately for men and women, to determine any correlations.

A statistically significant correlation was found among both sexes between age and peak systolic blood pressure (Figure 6.6). For both men and women, significant inverse correlations were found between peak heart rate and total exercise duration (Figures 6.7 and 6.8). These were independent of body mass index, and in each case, the relationship was stronger in men.

Regression equations for the exercise variables as a function of age were derived for both sexes (Table 6.4).

	Group 1	Group 2
Death *(n)*	3	1
Myocardial infarction *(n)*	4	2
PTCA *(n)*	8	3
CABG *(n)*	6	2

Table 6.2 Clinical outcome in n=58 patients who did (Group 2) and n=42 patients who did not (Group 1) exceed Stage II of the Bruce protocol exercise test.

	Relative Risk (95% CI)	p value
Decreasing age *	1.1 (1.0, 1.1)*	0.03
Male gender	4.3 (1.5, 12.5)	0.008
Exercise duration ≤ 6 min (≤ 7 METs)	8.3 (3.0, 23.1)	0.0001

* For each year of decreasing age.

Table 6.3 Multivariate analysis showing the independent association of baseline clinical characteristics with outcome: relative risks for PTCA, CABG, non-fatal myocardial infarction or death.

	Men	Women
Exercise Duration (minutes)	19.13 -(0.14 x age)	15.53 -(0.113 x age)
Peak Heart Rate (beats per min)	234.8 -(1.13 x age)	202.9 -(0.619 x age)
Peak Systolic Blood Pressure (mmHg)	143.6 +(0.91 x age)	121.4 +(0.978 x age)

Table 6.4 Regression equations for exercise variables as a function of age in asymptomatic healthy subjects performing the Bruce protocol treadmill test.

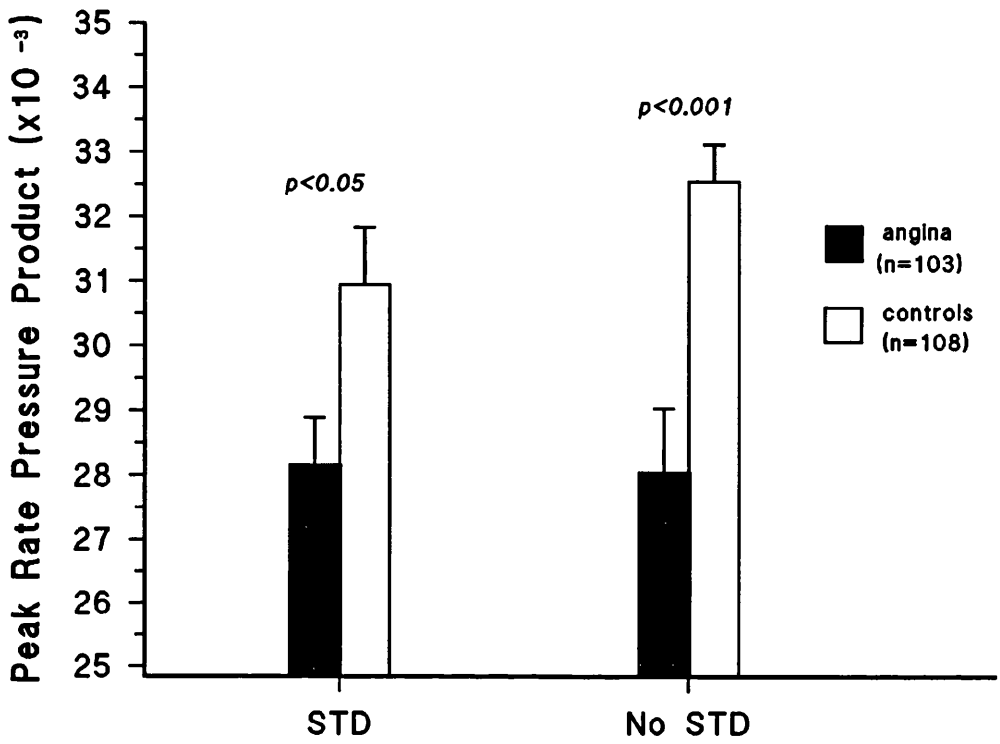


Figure 6.1 **Reduced peak exercise rate pressure product (x 10^3) in angina patients with (28.2 vs 30.9 in controls, p <0.05) and without (28.1 vs 32.5 in controls, p <0.001) ischaemia.**

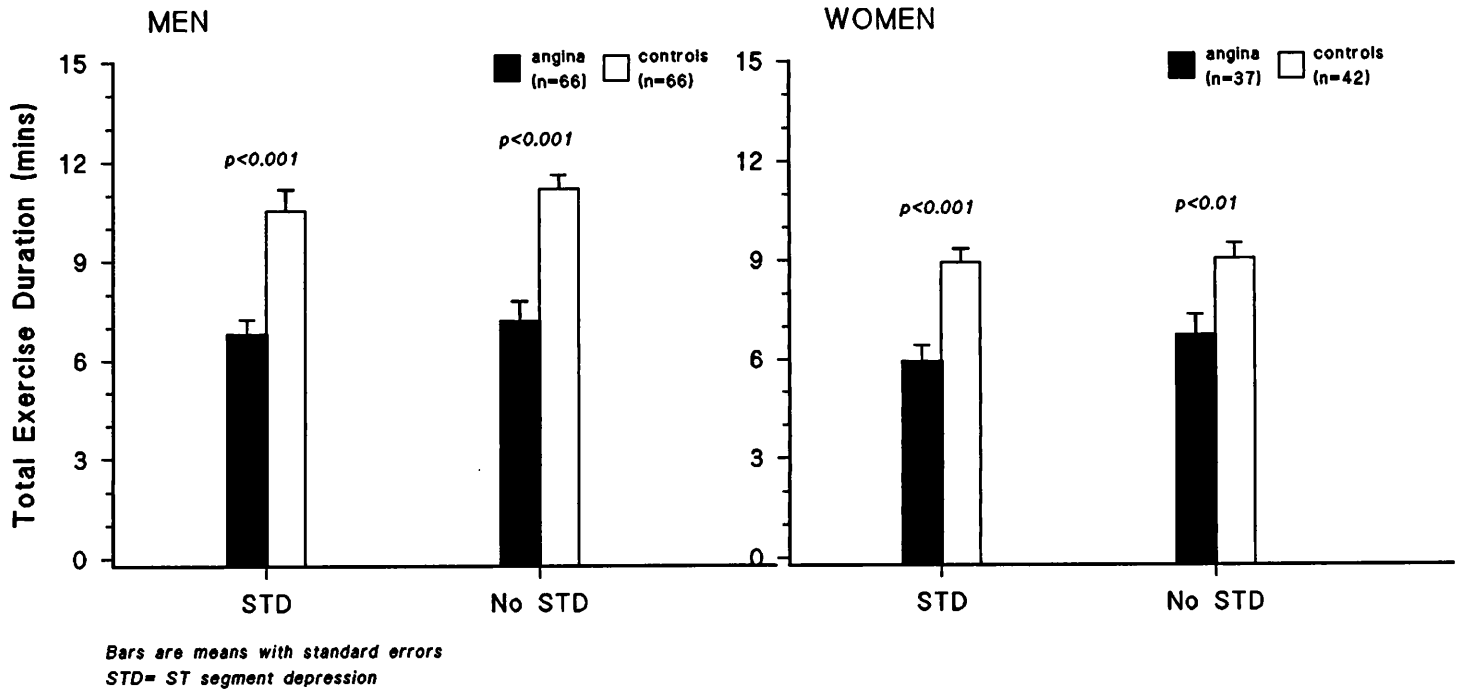


Figure 6.2 Reduced exercise duration (workload attained) in angina patients with and without inducible ischaemia on the Bruce protocol treadmill test.

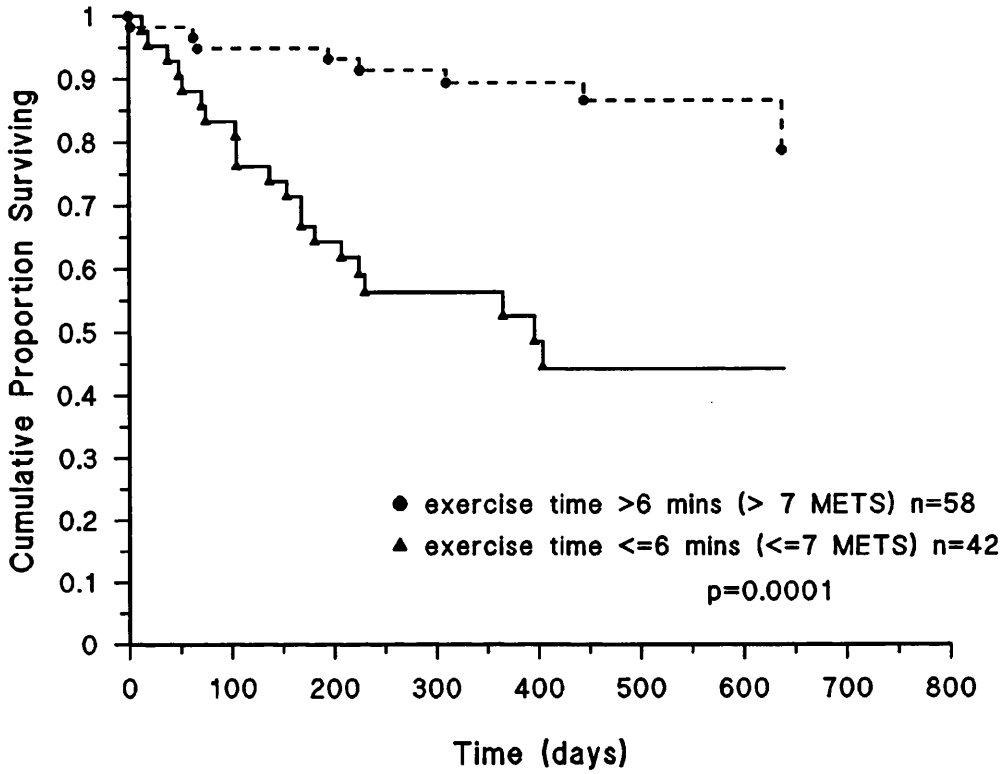


Figure 6.3 Survival free from PTCA, CABG, MI and death according to exercise workload attained (50% in Group 1 vs 86% in Group 2, log rank p <0.0001).

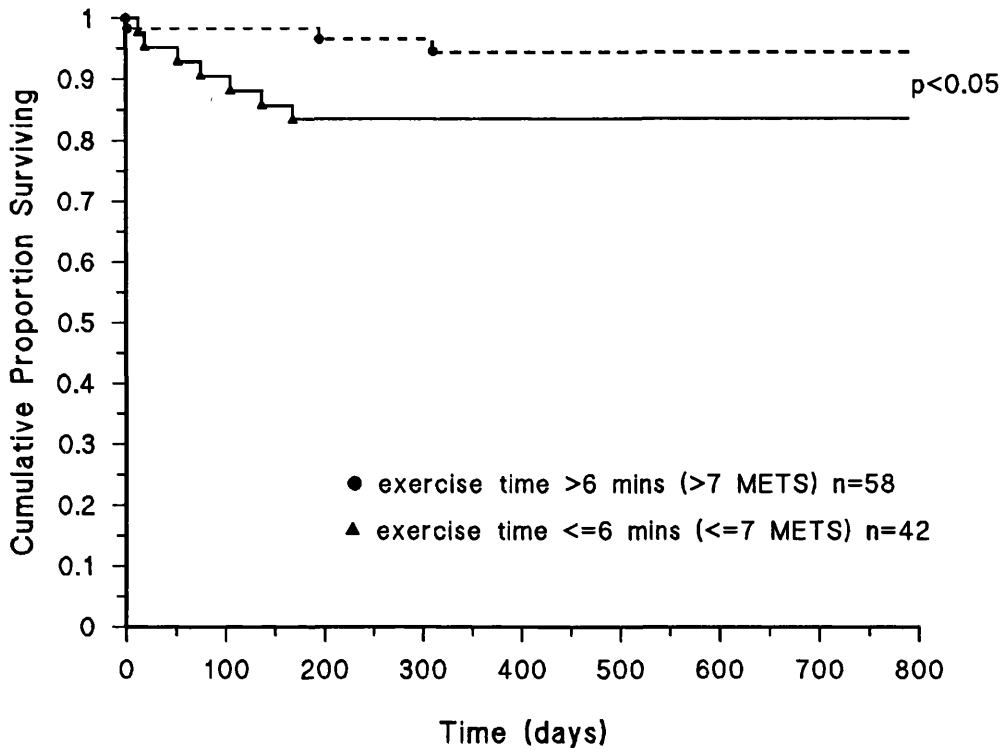


Figure 6.4 Survival free from myocardial infarction and death according to exercise workload attained (83% in Group 1 vs 95% in Group 2, log rank $p < 0.05$)

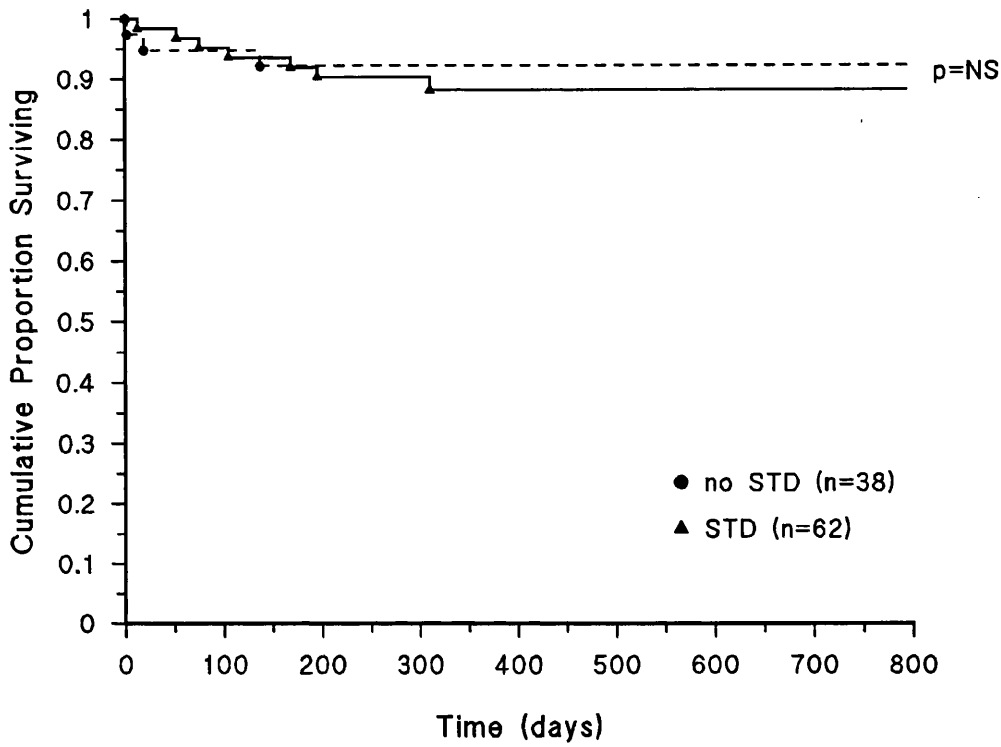


Figure 6.5 Event-free survival from non-fatal myocardial infarction and death in 62 angina patients with and 38 patients without inducible ischaemia (88% vs 92% respectively, log rank p = 0.6).

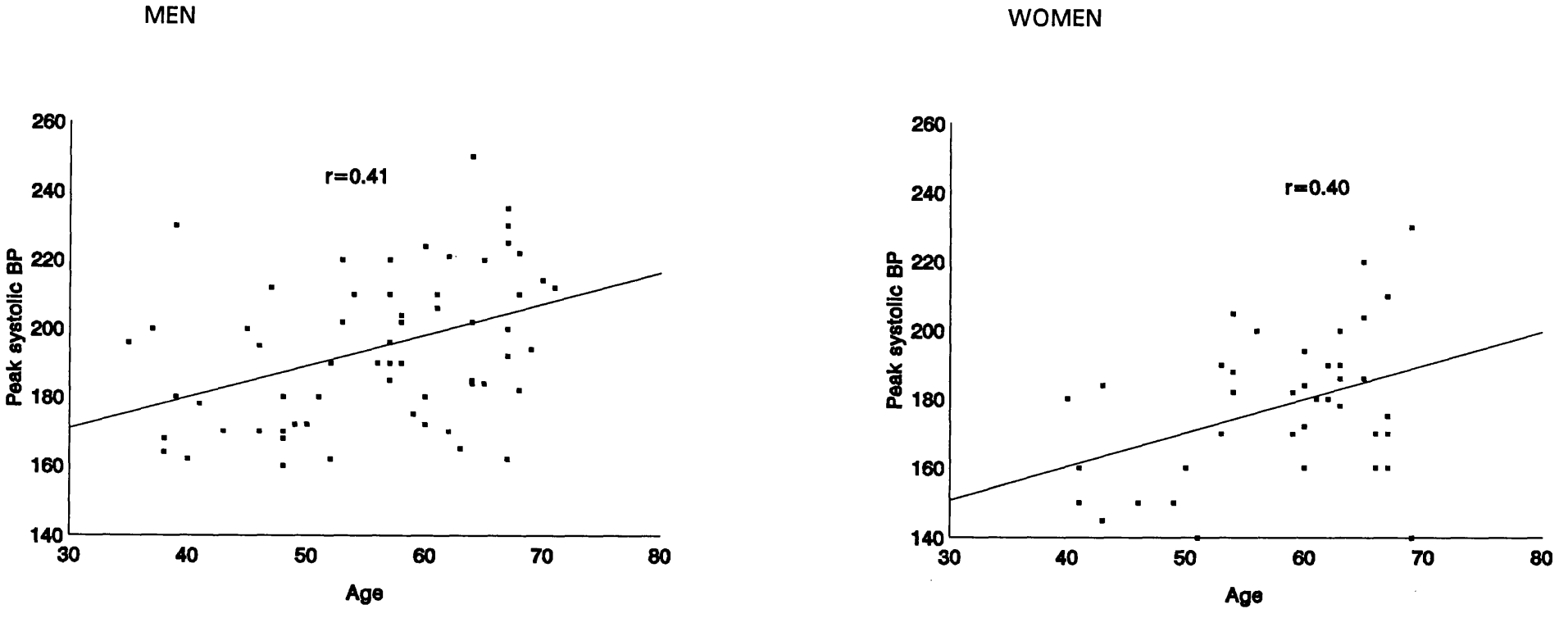


Figure 6.6 Correlation of peak exercise systolic blood pressure response with age in healthy men (left) and women (right) in the general population (in men $p < 0.001$, in women $p < 0.01$).

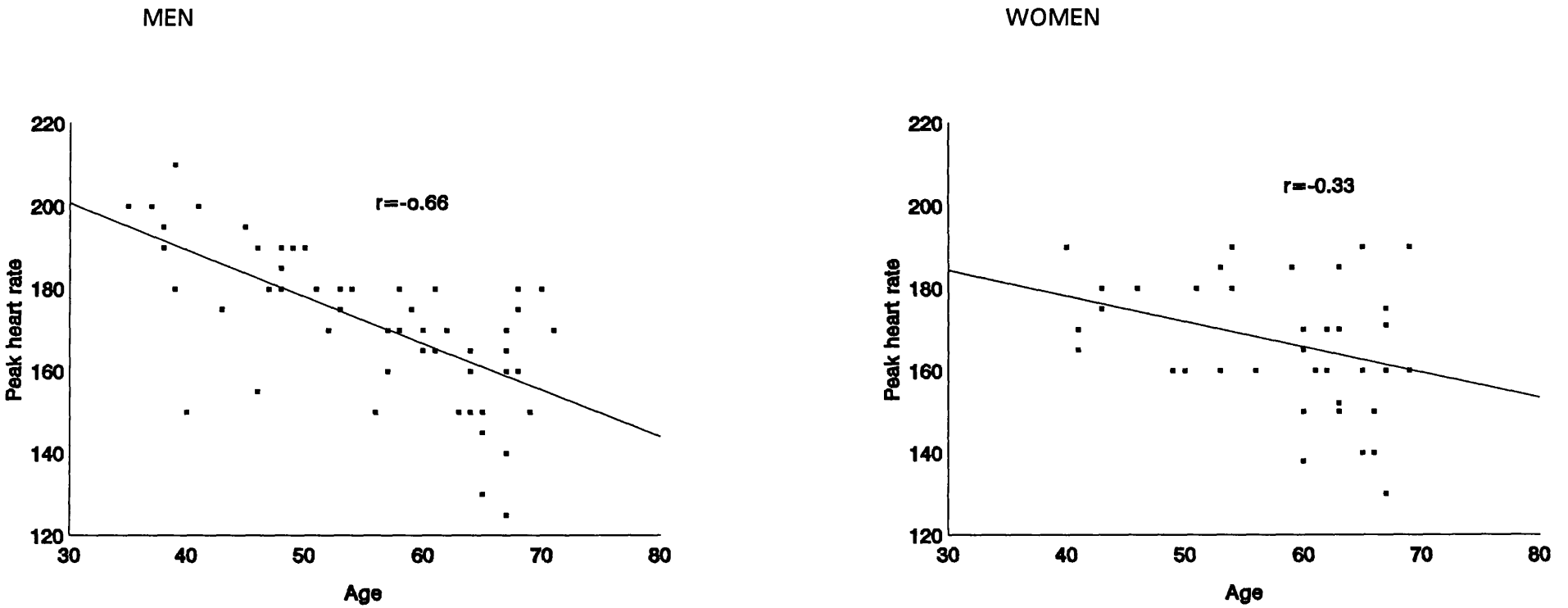


Figure 6.7 **Inverse correlation of peak exercise heart rate with age in asymptomatic controls (in men $p < 0.001$, in women $p = 0.03$).**

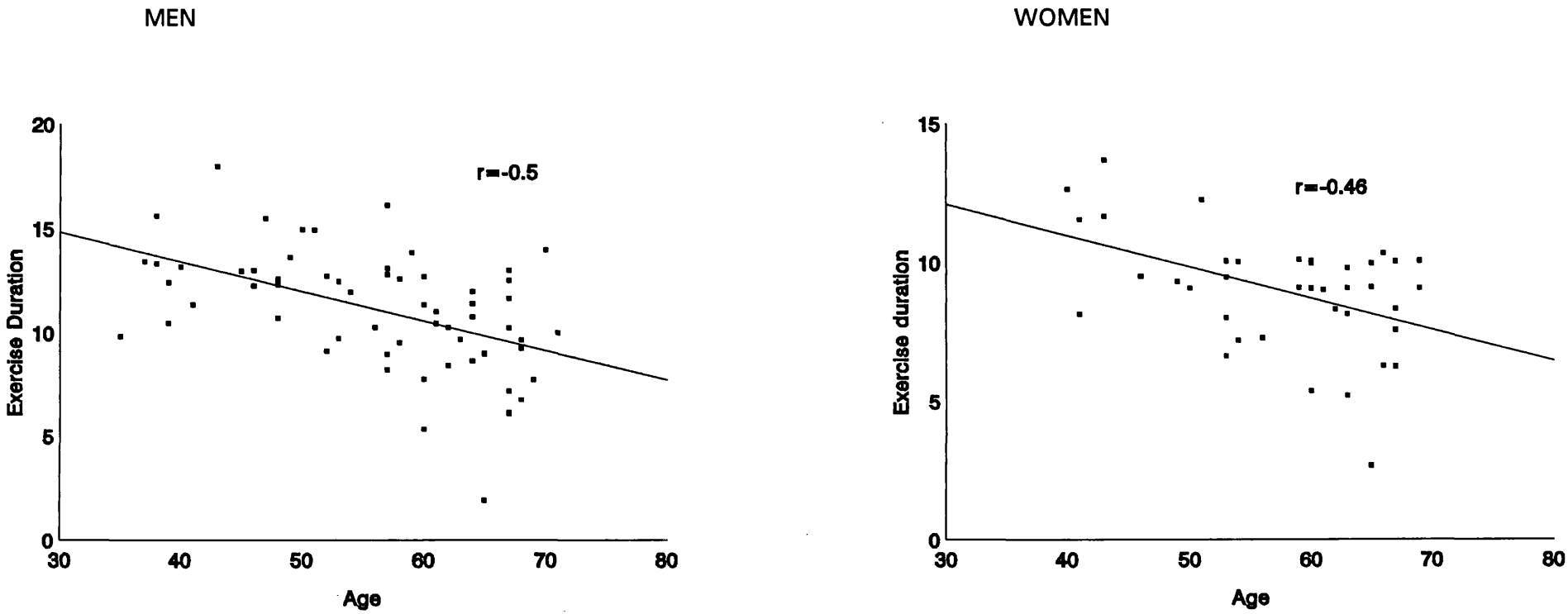


Figure 6.8 Inverse correlation of total exercise duration (maximum workload attained) with age in healthy controls (in men $p < 0.001$, in women $p < 0.01$).

CHAPTER 7

AMBULATORY MYOCARDIAL ISCHAEMIA

7.1 Introduction

Transient episodes of ischaemic ST segment depression detected by continuous ambulatory electrocardiographic monitoring have been extensively investigated, but the true frequency and clinical importance of ambulatory ischaemia in patients with stable coronary heart disease remains controversial. In selected hospital patients with positive exercise tests and angiographic coronary artery disease, some studies reported the majority of patients with angina to have ambulatory silent ischaemia (Cecchi, 1983; Shea, 1985), but others found this not to be the case (Mulcahy, 1988). The proportion of patients with stable angina in whom ambulatory ischaemia is detected ranges from under 25% (von Arnim, 1985; Thadani, 1992) to over 80% (Cecchi, 1983). Gender differences in ischaemic activity have been poorly defined, and apart from smoking (Barry, 1989), the effect of cardiovascular risk factors is unclear.

There are conflicting reports about the prognostic importance of ambulatory ischaemia in patients with stable coronary heart disease. In selected patients with stable angina, ischaemic episodes detected by ambulatory monitoring were previously reported to be associated with a higher risk of subsequent fatal and non-fatal cardiac events (Rocco, 1988; Tzivoni, 1989; Deedwania, 1990), but more recent studies suggest the reverse is true with a higher rate of myocardial infarction or cardiac death in patients with no ischaemia on ambulatory monitoring compared to those with ischaemic changes (Mulcahy, 1992; Quyyumi, 1993).

These differences in prevalence of ambulatory ischaemia and its prognostic significance may be due to careful patient selection which results in arbitrary 'low' and 'high' risk study groups unrepresentative of the broad spectrum of angina patients seen by most cardiologists - the 'sickest of the sick and the wellest of the well' (Diamond, 1986). A striking four-fold difference in the annual rate of myocardial infarction or death between two studies which employed different patient selection criteria supports this view (Tzivoni, 1989; Mulcahy, 1992). Results from studies which select patients with longstanding angina (Mulcahy, 1992), low workload exercise tests (Rocco, 1988; Tzivoni, 1989; Deedwania, 1990; Yeung, 1991), and which include non consecutive referrals (Tzivoni, 1989; Mulcahy, 1992; Yeung, 1991) cannot be extrapolated to the generality of patients with angina pectoris. A physician needs to know the significance of ambulatory myocardial ischaemia in the type of patient with angina pectoris who presents in clinical practice. If ischaemia during daily activities at the time of initial

presentation and work up is frequent, and if its presence can predict subsequent coronary events, then ambulatory monitoring would be valuable in risk stratification of new patients with angina.

A primary objective of this study was therefore to prospectively determine the frequency and prognostic significance of ambulatory myocardial ischaemia, and its relationship to cardiovascular risk factors, in previously untreated patients presenting for the first time with typical angina pectoris. Because the aim was to study a representative sample of patients with typical angina drawn from the general population, the demonstration of a positive exercise test or angiographic coronary artery disease was not a prerequisite. Prevalence of ambulatory ischaemia is described relative to the frequency of ischaemic ST segment changes in age and sex matched asymptomatic individuals drawn at random from the same population.

The method of ambulatory electrocardiographic monitoring is described in section 2.11.3, follow-up in section 2.13, and selection of controls in section 2.5.3.

7.2 Patients

Consecutive patients presenting with typical angina (section 2.9.1) were included. No patient had a prior myocardial infarction or a history of any other manifestation of coronary heart disease, or was taking long acting antianginal medication. Patients were excluded if they had baseline electrocardiographic abnormalities known to influence the ST segment such as left ventricular hypertrophy, bundle branch block or mitral valve prolapse, were on medical treatment likely to affect the ST segment, or had technically unsuitable ambulatory recordings. A total of 96 patients who did not meet any of the above exclusion criteria underwent 24 hour ambulatory ST segment monitoring prior to commencing antianginal therapy. Six patients were taking beta blockers for hypertension during the monitoring period.

Mean age of the 96 patients with typical angina pectoris was 57.5 (SD 9.9) years (range 34-70 years). Sixty-four were male and 32 female.

7.3 Ambulatory Electrocardiography in Patients with Angina

Fifty of ninety-six (52%) patients with angina had one or more episodes of significant ST segment depression during the 24 hour monitoring period. Prevalence of ambulatory ischaemia in men was 53%, and in women it was 50%. Of a total of 225

ischaemic episodes recorded, 159 (71%) were not accompanied by chest pain. There was no gender difference in the proportion of silent episodes - 70% in men and 73% in women. Of the 159 silent episodes, 89 (56%) were detected among 13 (14%) patients. Twenty-two per cent of angina patients had silent episodes only, and 24% had both silent and painful episodes (Figure 7.1).

The distribution of the number of ischaemic episodes recorded in men and women was similar (Figure 7.2). Among patients with ischaemic ST segment depression, men had a median of 3 (range 1-15) episodes and women 4.5 (range 1-15) episodes per 24 hour period respectively (p=NS). In men, the frequency of ambulatory ischaemia increased with age. Only 31% (5 of 16) of men up to the age of 50 had ischaemic episodes compared with 60% (29 of 48) of 51-70 year old men who had transient ischaemic episodes ($p < 0.05$). There was no statistically significant difference between men and women in the duration (median 59 vs 98 minutes) or extent (mean 2.4 vs 2.5mm) of ischaemic ST segment change. In women, silent episodes lasted significantly longer than painful episodes (median 19 vs 11 minutes, $p < 0.05$), but in men, painful episodes tended to be longer (median 14.5 vs 10 minutes) although this difference did not reach statistical significance. However there was a large variation between patients in the total duration of ischaemia which ranged from 1 to 782 minutes with a median of 66 minutes (Figure 7.2). The circadian distribution of ischaemic episodes in both sexes was similar, with a primary peak between noon and 6pm (Figure 7.3). Sixty-one per cent of episodes in men and 70% in women were accompanied by an increase in heart rate at onset.

7.4 Ischaemic ST Segment Depression in Asymptomatic Controls

Of 110 eligible asymptomatic controls, 95 subjects who did not have any of the exclusion criteria stated in section 7.2 underwent 24 hour ambulatory ECG monitoring. Mean age was 56.4 (SD 9.6) years, range 35-71 years; 59 were male and 36 female.

Significant ischaemic ST segment depression was detected in 7 of 59 (12%) men and 2 of 36 (6%) women. Mean age of the 9 subjects with ischaemic changes was 64.3 (SD 4.6) years. A total of 21 episodes were detected during 2,453 hours of monitoring, and their circadian distribution was similar to that of angina patients, with an afternoon peak between noon and 6pm when 52% of the episodes were recorded.

Median duration of episodes was 26 minutes (range 4-193 min.), and mean extent of ST segment depression 2.5 (SD 0.9) mm.

7.5 Symptoms, Cardiac Risk Factors and Ischaemic Activity

Table 7.1 shows the baseline clinical and exercise test characteristics of angina patients with and without ambulatory ischaemia. There were no significant differences between the two groups in frequency and duration of angina, gender or the major cardiovascular risk factors. Patients with ischaemia on ambulatory monitoring tended to be older and had a higher prevalence of exercise induced ST segment depression, but total exercise duration and the peak rate pressure product did not differ significantly between the two groups.

When the two groups were compared separately by gender, age, serum cholesterol and prevalence of exercise induced ST segment depression were significantly higher in men with ambulatory ischaemia (Table 7.2), but in women, only the latter was significantly higher. A stepwise multiple logistic regression analysis adjusting for age confirmed the independent association of serum cholesterol level with ambulatory ischaemic activity in men (Table 7.2).

7.6 Ambulatory Ischaemia and Event-free Survival

Follow up was complete for 93 of 96 (97%) angina patients. The remaining 3 patients had moved without a forwarding address. During a mean follow up period of 15.8 months (range 7-30 months), there were 3 deaths, 8 myocardial infarctions, 7 coronary artery bypass graft operations and 11 coronary angioplasty procedures.

Seventeen patients (34%) with ambulatory ischaemia experienced adverse events compared with 12 patients (26%) with no ischaemia. Kaplan-Meier actuarial analysis of cumulative survival (Figure 7.4) revealed no significant difference in event-free survival between patients with and without ischaemia (66% vs 72%, p = NS). Slightly more patients with ambulatory ischaemia experienced the combined end points of death or myocardial infarction compared to patients with no ischaemia (14% vs 9%), but again this difference was not statistically significant.

Survival was also compared in relation to duration of ischaemia. Eight of 26 (31%) patients with more than 60 minutes of ischaemia during 24 hours of ambulatory monitoring experienced events compared with 21 of 67 (31%) patients with ischaemia

less than 60 minutes or no ischaemia. Overall event-free survival in both groups was identical (69%).

	STD (n=50)	No STD (n=46)
mean age (yr)	59.4 (9.2)	55.5 (10.3)*
male (%)	68	65
cigarette smokers (%)	28	37
hypertension (%)	52	48
serum cholesterol mg/dl	290 (54)	275 (50)
diabetes (%)	8	9
Symptoms		
frequency ≥ once daily (%)	36	33
duration < one month (%)	44	46
Exercise		
STD ≥ 1mm (%)	87	38 †
duration (min)	6.3 (2.5)	7.1 (2.8)
rate pressure product ($x10^3$)	27.7 (5.8)	29 (5.8)

STD = ST segment depression
value in parenthesis is standard deviation
* $p = 0.05$ † $p < 0.001$

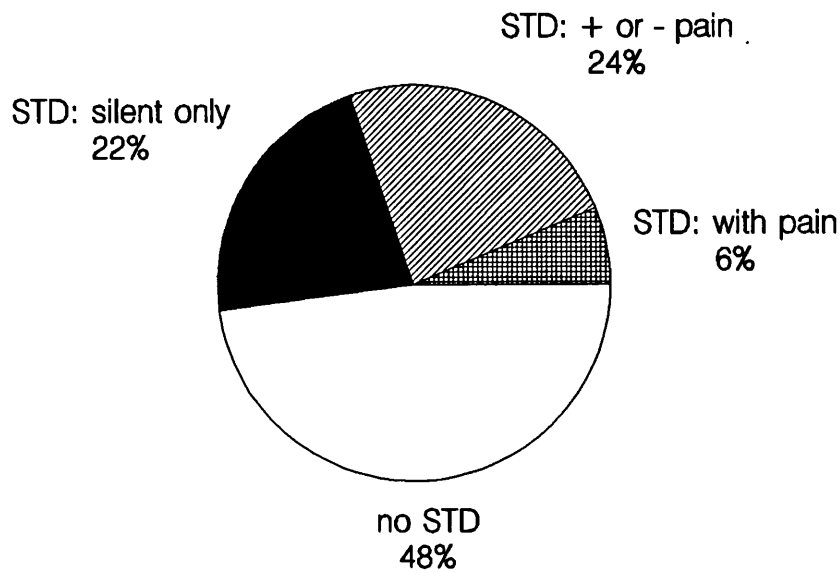
Table 7.1 Baseline clinical characteristics of angina patients with and without ambulatory ischaemia.

Univariate	STD (n=34)	No STD (n=30)	p value
mean age in years	60.3	54.4	0.02
serum cholesterol mg/dl	294	255	0.004
exercise STD ≥ 1mm (%)	84	38	<0.001

Multivariate	Relative Risk (95% CI)	p value
serum cholesterol	1.9 (1.0, 3.4)	0.02
exercise STD	6.6 (1.8, 24.1)	0.003

STD = ST segment depression ≥ 1mm

Table 7.2 Associations of ambulatory ischaemia in men by univariate and multivariate analyses.



n = 96 patients

Figure 7.1 Nature of ischaemic ST segment depression (STD) in new patients with angina pectoris in the general population.

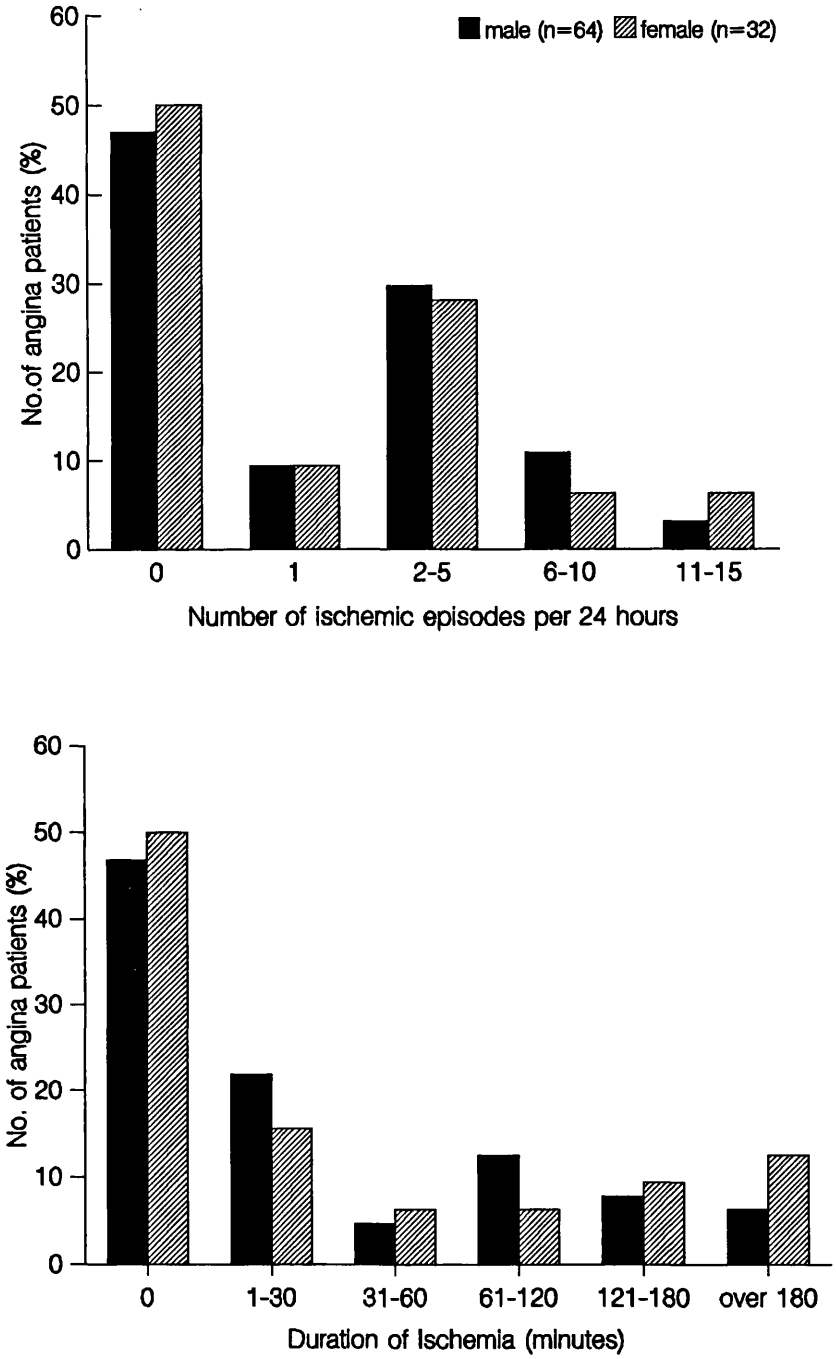
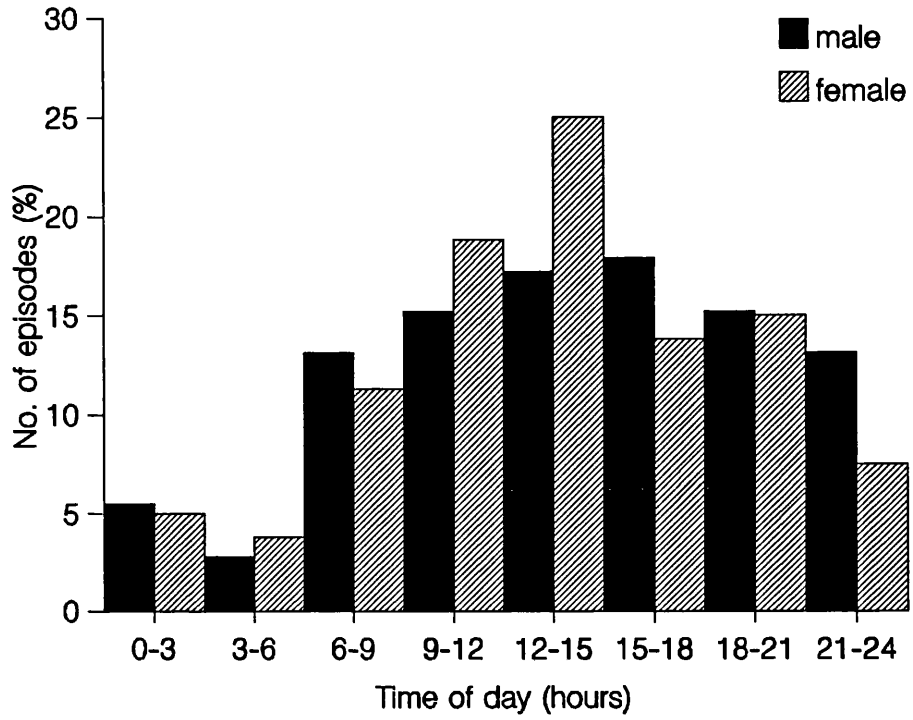


Figure 7.2 Number of ischaemic episodes (top) and duration of ischaemia (bottom) recorded by 24 hour ambulatory electrocardiographic monitoring in men and women presenting with angina pectoris in the general population.



n = 225 episodes

Figure 7.3 **Circadian distribution of ischaemic episodes in men and women with angina.**

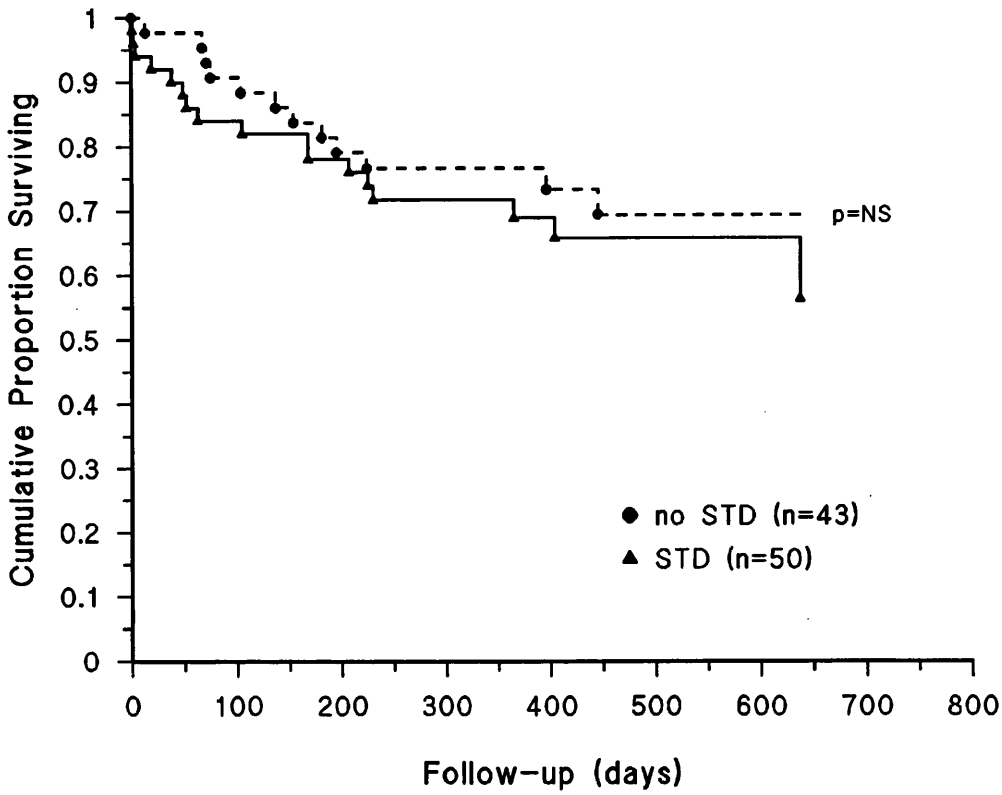


Figure 7.4 Kaplan-Meier survival curves comparing cumulative proportion of angina patients surviving without cardiac events (death, non-fatal myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) during mean follow-up of 15.8 months for 50 patients with ischaemia and 46 patients without ischaemia as detected by ambulatory electrocardiographic monitoring (STD = ST segment depression).

CHAPTER 8

DISCUSSION

8.1 Introduction

The majority of patients with angina pectoris are managed in the community yet since the advent of revascularisation there is very little contemporary information about the incidence, characteristics and natural history of this disease in the population. One of the reasons for the paucity of data is difficulty in obtaining access to angina patients in the population. Patients referred to hospital outpatient clinics are 'survivors' who are not representative of the broad spectrum of clinically manifest disease.

A further difficulty lies in the lack of a standard definition for the disease. There is an important distinction between angina defined by a questionnaire and clinical angina. Angina pectoris is a clinical syndrome where the diagnosis is made by a physician based on the patients reported symptom complex. An individual who responds positively to questions about chest discomfort in a questionnaire may not report any symptoms to his/her physician. Likewise, patients who report symptoms of typical angina to their physician may not satisfy the Rose questionnaire criteria for angina. Subjects with questionnaire positive angina may therefore not have the same characteristics as patients with clinical angina. This is supported by Rose's (1978) observation that patients who present to their doctor seem to have prognostically more important disease compared with those who do not. A physician diagnosis of angina thus has a higher sensitivity for cardiac mortality (Kannel, 1972) compared with a questionnaire diagnosis of angina (Bulpitt, 1990). In this study therefore, the diagnosis of angina pectoris was made when the history reported to the physician matched the criteria of an anatomically (Weiner, 1979) and prognostically (Murabito, 1990) validated definition.

This is the first study to investigate the clinical incidence and prognosis of angina since the advent of revascularisation. General practitioners' perceptions of current angina management are discussed, followed by an appraisal of incidence and short-term prognosis of angina in the population.

One of the principal aims of this study was to investigate the clinical significance of ambulatory electrocardiographic monitoring in a representative sample of unselected incident angina patients. This is discussed in section 8.5.

8.2 Management of Angina Pectoris in the Community

The questionnaire survey (section 2.2) revealed striking differences in opinion among

a representative sample of general practitioners about the significance of symptom characteristics, the usefulness of exercise testing and the benefits of revascularisation for patients with angina. The majority of general practitioners appear to refer at most only a quarter of their patients with angina pectoris to a hospital physician, and only up to a tenth of all patients to a cardiologist at the regional centre. The findings suggest that unless symptoms are severe, investigation of patients with angina to determine suitability for revascularisation assumes a low priority. Whilst this is a survey of self reported referral practices without a formal audit of angina management in the surgeries, these findings are consistent with those of a cross-sectional survey which showed that of patients receiving medical treatment for angina from their general practitioner, only 19% had attended a hospital medical clinic during a six month study period, 7% had had an exercise test, and 4% a coronary angiogram (Cannon, 1988).

Although symptoms of angina, both frequency and duration, are considered important by the majority of general practitioners in deciding when to refer a patient for investigation, over half do not think these are a reliable guide to severity of underlying coronary artery disease. This suggests the main reason for referring patients with angina is to improve symptom control rather than to determine the presence and significance of coronary artery disease, or to stratify for risk of future cardiac events. A referral policy based on symptoms may not be justified because symptoms are in general a poor guide to disease severity and long term prognosis (Hultgren, 1984). Furthermore the increased risk of cardiac events, particularly sudden death (Kannel, 1972), may depend on physiological significance of coronary artery disease rather than the severity of angiographic stenoses or symptoms alone. (Epstein, 1989). Therefore the presentation of angina, regardless of severity, would justify an exercise test to detect physiologically significant disease (Wilson, 1991), and age should not be a bar to investigation and revascularisation (RCP, 1991).

Over half of the general practitioners surveyed thought an exercise test was unnecessary for the majority of new patients with angina, or that it was required only in selected patients. By contrast, in a questionnaire survey of family physicians in the USA (response rate of only 34%) about exercise testing in patients with angina (Hartz, 1989) 81% of the 265 physicians questioned said a non-invasive stress test should be ordered as part of the initial management plan for a patient with angina. However less

than 40% accepted any given strategy for using the test result to make a decision about referring a patient to a cardiologist. These physicians seemed to know when to order the test, but were uncertain as to why they were ordering it and disagreed on how the test results should be used.

Although availability of exercise testing for general practitioners could be facilitated by offering open access to hospital facilities (Sulke, 1991), this survey emphasises the need for caution because most general practitioners are not exposed to this investigation routinely, and are therefore not confident at correctly interpreting the result. An exercise testing facility without the back up of a physician with cardiological experience to make management decisions would therefore be of limited value, and may be harmful to patients.

The survey revealed divided opinion among general practitioners about whether or not there is scientific evidence for the benefits of revascularisation. About a fifth did not know that coronary angioplasty relieves symptoms, and a similar proportion thought prolongation of survival following coronary angioplasty has been scientifically demonstrated although this is not the case (Nwasokwa, 1991). Likewise, about a fifth did not know whether coronary artery bypass surgery prolonged survival, and a further fifth considered such an operation to be of no value in relation to survival despite evidence to the contrary (Nwasokwa, 1991). These differences in the perception of trial results inevitably produce variation between general practitioners in the management of angina in the community, and are further compounded by disagreement among specialists about the appropriateness of coronary intervention (Brook, 1988). The lack of awareness among general practitioners of the benefits of coronary intervention and a low referral rate for investigation may, in part, be responsible for the low rate of revascularisation procedures per million population in the United Kingdom (Hubner, 1992; Unger, 1992).

Whilst there was a high response rate to this survey, a fifth of general practitioners did not participate and the practice of these non-responders is not known. Amongst the responders no distinction was made by year of graduation, possession of postgraduate diplomas or degrees, or whether the practice was fundholding or not, although these factors could influence the reported responses. If the respondents differ from a national sample of general practitioners they are likely to be less heterogenous, and therefore the variation in management of angina among other practitioners is likely

to be at least as great as that found in this survey.

With the wide range of treatments now available to relieve symptoms, improve quality of life and prolong survival in selected patients with angina, the general practitioner has to choose patients for cardiological evaluation. This survey found that even though this disease has significant short term morbidity and mortality (Section 5.3), only a minority of patients with angina are reportedly referred to a general physician for investigation, and fewer still to a cardiologist. General practitioners expressed divergent and contradictory opinions about exercise testing and the scientific evidence for coronary angioplasty and coronary artery bypass surgery. These data provide a compelling basis for developing guidelines for the management of angina presenting in general practice in order to optimise the selection of those patients who are most likely to benefit from coronary intervention.

8.3 Incidence and Prognosis of Angina Pectoris

One of the aims of this study was to determine incidence and outcome of clinically manifest angina pectoris representative of the disease in the general population. Therefore, like the Framingham study (Kannel, 1972), the diagnosis of angina was based on a clinical history which is highly predictive of underlying coronary artery disease especially in men (Weiner, 1979), and which is prognostically validated by its independent association in both men and women with a three-fold increased risk of a non fatal or fatal cardiac event within two years of diagnosis (Murabito, 1990). Whilst the incidence of angina may be underestimated by missing those patients who do not report their symptoms to the general practitioner, those who do tend to be the ones with prognostically important disease (Rose, 1978). As general practitioners agreed to refer all new patients to the chest pain clinic, this study provides a useful estimate of the clinical incidence and prognosis of this disease based on a representative sample of unselected patients presenting with angina in the general population.

The crude incidence rate of angina in the present study is lower than previously reported (Table 1.2) and whilst differences between countries, patient populations, periods of study and methods make direct comparisons difficult, it is consistent with the 27% decline in incidence of angina in 50-59 year old men in the Framingham cohort between 1950 and 1970 (Sytkowski, 1990). The rate reported by

Fry based on 25 years of follow-up in a single south-east London general practice reflects an older population in which 56% of angina patients were over 60 years old at the time of diagnosis (Fry, 1976).

Incidence of angina increased in both sexes above the age of 50. The rate of increase diminished in women above this age, but in men the sharp rise continued such that 61-70 year old men had a four-fold higher incidence compared with 41-50 year old men and an almost three-fold higher incidence compared with women of the same age. In the present study the crude incidence rate of angina in women was about half that of men, consistent with the experience of Framingham women who over 26 years encountered half the coronary heart disease morbidity as men (Lerner, 1986). Biennial incidence rates for all cause morbidity from coronary heart disease in Framingham were also higher in men than in women, and in both sexes above 55 years of age. But in women, the incidence of angina continued to increase in old age and was higher than in men above the age of 75. The reason for a higher incidence of coronary heart disease in women after menopause and the associated less favourable outcome compared to men is unclear, but the economic implications and need for further research in women are increasingly appreciated (Manolio, 1993).

The prognosis of patients who present to a general practitioner with exertional chest pain is not benign. About 10% in this study experienced myocardial infarction or death within one year of initial diagnosis. Some have classified new onset angina as 'unstable' implying the need for urgent treatment (Braunwald, 1989). However such a classification is of little practical value to a general practitioner to whom patients who ultimately follow a chronic stable course actually present with 'new onset' exertional chest pain. Extrapolating our data to the United Kingdom suggests that well over 2,000 patients present each year to general practitioners with exertional chest pain a few months prior to experiencing their first non-fatal or fatal myocardial infarction. Although the rates of myocardial infarction and death in men in the current study are similar to rates reported in a community study of men with unstable angina from selected general practices in Edinburgh (Duncan, 1976), they could underestimate the national rate for several reasons. Firstly, elective revascularisation in almost a fifth of patients may have averted an adverse outcome in a proportion of these patients. Secondly, as in a previous study (Fulton, 1972), it is possible some patients with chest pain did not present to their general practitioner or were not

referred to the clinic for assessment, but subsequently experienced a cardiac event. The likelihood of this occurring is small because the general practitioners agreed to refer all patients and the provision of an open access chest pain service where such patients could be seen within 24 hours of presentation made referrals to any other part of the medical service unlikely. Lastly, because of known regional variation in incidence of coronary heart disease (Garg, 1992) and a lower standardised mortality ratio in the south-west (OPCS, 1991), incidence and mortality of angina in other parts of the United Kingdom are likely to be higher.

Like previous studies of angina in the population in which spontaneous remission of chest pain occurred in 14-39% of patients (Fry, 1976; Duncan, 1976; Kannel, 1978), spontaneous remission of symptoms occurred in 11% of patients in this study, and with concomitant medical therapy in a further 19%. The reason for disappearance of symptoms without medication in this small proportion of patients is unclear. Angina is a clinical syndrome and therefore it is difficult to be certain whether remission is part of the natural history of the disease or was related to an 'incorrect' initial diagnosis (Kannel, 1978).

The combined event rate for myocardial infarction and cardiac death in the current study was higher than the rate of cardiac events in patients with effort related angina admitted to a district general hospital (Murphy, 1992). In their prospective survey of admissions in whom cardiac enzymes had been measured, Murphy et al excluded patients with a confirmed myocardial infarction, and divided the remaining 141 patients with angina into three categories: effort angina diagnosed by a modified Rose questionnaire, patients with confirmed prior infarction and those admitted with ST-T changes in association with chest pain. In contrast to the present study in which 4 deaths and 8 myocardial infarctions were recorded within one year among 110 patients with angina who were ambulant, none of the 35 patients with effort angina in that study experienced such events during the first 4 months after admission, and only 2 events (6%) were recorded in the group after 3 years. Although a hospital study based on 'survivors' partly explains the low event rate, their results also underline the poor sensitivity of a Rose chest pain questionnaire diagnosis of angina for cardiac mortality. A diagnosis of angina based on a history elicited by a physician in the Framingham study (Kannel, 1972), as used in the present study, had a higher sensitivity for cardiac mortality than the Rose questionnaire which was used in the

Whitehall study (Bulpitt, 1990).

Revascularisation rates in the current study and in the study by Murphy et al reveal striking differences in attitudes to coronary intervention amongst cardiologists in the United Kingdom. Compared to 18% of the community based ambulant cohort of patients with typical angina in the current study who underwent coronary angioplasty or coronary artery bypass grafting within one year of first presentation, in the study by Murphy et al (1992), only 12% (17 of 141) of patients with unstable angina had undergone revascularisation 3 years after initial hospital admission. Of 67 patients in whom chest pain on admission was associated with resting ST-T changes, 6 (9%) patients had undergone revascularisation within 3 years for persistent symptoms despite medical treatment, while 4 (6%) sustained a non fatal myocardial infarction and 18 (27%) patients died. Their data suggests that patients with unstable angina admitted to a 'district' hospital were managed more conservatively with regards coronary intervention procedures than outpatients with stable angina assessed by regional centre cardiologists in the present study.

This is the first survey of the incidence and short-term prognosis of angina pectoris since the advent of improved medical therapy and coronary revascularisation procedures. A major strength is its representativeness of clinically incident angina pectoris in the general population. Current incidence rates confirm the persisting sex differential in coronary heart disease. The apparent decline in incidence is consistent with the falling mortality from coronary heart disease.

8.4 Exercise Testing

Increasing reliance has been placed on non invasive tests to predict which patients with angina are at increased risk of future adverse cardiac events. Can exercise testing be used to refine the way in which patients are referred for bypass surgery? Studies evaluating the prognostic value of exercise variables have differed in their conclusions.

Non randomised studies of patients undergoing coronary angiography analysed on an 'intention to treat' basis suggest that survival varies according to stage of exercise attained and presence of ST segment changes (McNeer, 1978; Weiner, 1986). By contrast, in a prospective study of 838 patients following first myocardial infarction, the severity of angiographic disease, but not exercise induced ST segment changes, was predictive of future cardiac events (Ngo, 1990). Randomised studies

comparing medical versus surgical treatment in patients with angiographic coronary artery disease also very in their results. While both the Veterans Administration (Peduzzi, 1986) and the European Coronary Surgery Study (Varnouskas, 1988) suggested that patients who develop ST segment depression at low workloads benefit from bypass surgery, in the Coronary Artery Surgery Study (Ryan, 1985), neither the degree of ST segment depression nor stage of exercise predicted benefit from surgery.

An important limitation inherent in most reports is 'work up bias', when the result of an exercise test influences the chance to be entered into the study (Philbrick, 1982). The majority of studies include patients referred for cardiac catheterisation and are subject to this bias which is a source of considerable variance in the results, but which cannot be quantified (Detrano, 1989). In a study of 588 male veterans who were selected for coronary arteriography, exercise induced ST segment depression did not emerge as an independent predictor of infarct-free survival. However, when patients referred to the same institution who were not selected for cardiac catheterisation were studied, exercise workload and ST segment depression emerged as independent risk predictors of subsequent events (Brown, 1992). The authors concluded that work up bias was the likely explanation of the failure of exercise induced ST segment depression to be consistently chosen as a risk predictor (Morrow, 1993).

The current study avoided referred bias by including consecutively referred new patients with typical angina from a randomly selected general population sample. The Framingham study which is the only other population based study of men and women with angina did not investigate the value of exercise testing.

While it was not a primary objective of this study, the study design provided a unique opportunity to prospectively investigate the prognostic value of exercise testing in a broad spectrum of new population based angina patients. The prevalence of a low workload positive exercise test among new angina patients was high at 29%. Clinical characteristics, and in particular the severity of angina symptoms did not identify patients likely to have marked exercise ischaemia at low workloads. More importantly, the frequency and duration of angina did not predict cardiac events.

Decreasing age and male gender were independently associated with increased risk of a cardiac event. This is likely to reflect the higher probability of revascularisation procedures in younger men.

A total exercise duration ≤ 6 minutes, but not exercise induced ST segment depression, was independently associated with reduced event free survival from all events ie PTCA, CABG, myocardial infarction or death. It was also independently associated with more than a three-fold increased risk of experiencing the objective end-points of myocardial infarction and death. This study demonstrated that risk stratification of new patients can be simply based on total exercise workload attained. Exercise ischaemia was a poor predictor of cardiac risk. This is likely to be due to its poor specificity for prognostically important coronary artery disease especially in women. The results of this study of a representative sample of angina patients should be confirmed by a larger study with adequate statistical power.

8.5 Ambulatory Myocardial Ischaemia

Patient selection is critical to all scientific clinical investigations because it determines the generalisability of results. Previous studies of ambulatory electrocardiographic monitoring have included a variable number of patients with prior myocardial infarction (Rocco, 1988; Deedwania, 1990; Yeung, 1991; Mulcahy, 1992; Quyyumi, 1993) or revascularisation (Rocco, 1988; Yeung, 1991; Mulcahy, 1992), are based on predominantly male patients (Tzivoni, 1989; Deedwania, 1990) with a low workload positive exercise test (Rocco, 1988; Tzivoni, 1989; Yeung, 1991; Deedwania, 1990) or angiographically proven coronary artery disease (Tzivoni, 1989; Quyyumi, 1993), and have all recruited patients referred to a specialist centre. With an increasing number of selection criteria, the spectrum of patients included becomes narrower, and the term 'consecutive patients' has no meaning when the population from which they are drawn is not known. To avoid these sources of bias, the present study was designed to investigate the frequency and prognosis of ambulatory ischaemia in a representative sample of new patients with angina from the general population typical of those who present in clinical practice. None of the patients had previously diagnosed coronary heart disease, and entry was not limited to patients with exercise induced ischaemia at low workloads or proven angiographic coronary artery stenoses.

8.5.1 Prevalence and Characteristics

Ischaemia during daily living activities was detected in half of all patients in this general population sample in whom angina pectoris was the first manifestation of coronary heart disease. There was no difference in the extent or duration of ischaemia

between the sexes. Prevalence of ambulatory ischaemia in women in the present study was 50% compared with only 22% in a recently reported cohort of 121 women with coronary artery disease who underwent 48 hours of ambulatory monitoring (Thadani, 1992). The lower prevalence in that study may be due to the inclusion of only selected women with mild or no symptoms, some of whom may have had a previous myocardial infarction (Pepine, 1991), whereas the present study was representative of all women in the general population up to the age of 70 years presenting with angina pectoris. Compared with asymptomatic controls, women with angina had a significantly higher prevalence of ischaemic ST segment depression during daily living which cannot therefore be regarded as all 'false-positive' even if the prevalence of significant coronary artery stenoses may be lower than in men with ischaemia (Welch, 1975). The pathophysiological mechanism responsible for ST segment depression in women with angina may be different from that in men (Maseri, 1991).

Ambulatory ST segment depression was detected in 9% of 'healthy' asymptomatic individuals drawn from the general population. This may reflect underlying asymptomatic coronary artery disease as all were above the age of 55 years and at a higher risk for future cardiac events (Hedblad, 1989; Fleg, 1992). Reported frequency of ischaemic ST segment changes in selected healthy individuals ranges from 2% in hospital workers (Deanfield, 1984) to 30% in volunteer policemen (Armstrong, 1982). In the only other study of population based healthy subjects (Kohli, 1988), the reported prevalence of 12% was similar to the present study.

In this study, as in others (Mulcahy, 1988), the majority of ambulatory ischaemic episodes detected in patients with angina were not accompanied by chest pain. However the distribution of silent ischaemia was uneven and over half (56%) of all silent ischaemic episodes were detected in just 14% of the total study population. This is consistent with a study of 150 selected patients with clinically significant coronary artery disease in which over 50% of silent ischaemic episodes during 48 hours of monitoring were concentrated in only 7% of patients (Mulcahy, 1988).

There were large differences between new angina patients in the number of transient ischaemic episodes and in the duration of ischaemia recorded over a 24 hour period. This inherent variability of ambulatory ischaemia, which has been quantified in patients with chronic stable angina (Nabel, 1987), emphasises the need for caution when interpreting data regarding therapeutic anti-ischaemic effects particularly if

criteria to take account of this variability are not used (Redl, 1990).

A circadian variation in the frequency of transient ischaemic episodes was evident in both men and women. A primary peak in the afternoon rather than in the morning hours in the current study is similar to observations in patients taking beta blockers (Deedwania, 1990), but is at variance with patients monitored off treatment in whom the primary peak of ischaemic episodes appeared to be in the morning hours (Hausman, 1990). While these differences could arise from the intrinsic variability of ambulatory ischaemia, they might also be due to influence of environmental factors which can modify the circadian pattern of heart rate change (Mulcahy, 1990). Thus patients with established chronic stable angina may modify their daily activity pattern to avoid peaks in daytime stress whereas the early afternoon peak in new patients in the present study probably reflects continuing occupational stress. The latter explanation is supported by a similar primary afternoon peak in the number of episodes of ST segment depression in the asymptomatic control population. The significance of the peaks in ambulatory ischaemic activity in relation to coronary events remains speculative because neither a direct causal relationship, nor a modification of outcome by medical intervention, has been demonstrated.

The relationship between the major cardiovascular risk factors and ischaemic activity during daily living in patients with angina was also investigated. In men, an elevated serum cholesterol level was positively associated with the presence of ambulatory ischaemic activity independent of age and baseline clinical characteristics. A similar relationship was not evident in women. This may be because women in the current study were of a predominantly post menopausal age group. Although incidence of coronary heart disease and prevalence of angiographic coronary artery stenoses are both positively associated with total cholesterol in women under 50, this relationship has not been demonstrated in older women (Kannel, 1971; Vliestra, 1980), and there is no association between serum cholesterol and risk of sudden death (Cupples, 1992). Furthermore, in women, ST segment depression and normal coronary arteries can be associated with other factors such as hormonal status (Morise, 1992) and may not represent prognostically important ischaemia. In contrast the independent association of raised cholesterol levels with ischaemic activity in men might underlie an important pathophysiological basis because cholesterol level is independently associated in men of all ages up to seventy years with both the short and

long-term increased risk of sudden unexpected death (Cupples, 1992). While the association with raised cholesterol levels might reflect increased ischaemic activity due to more extensive coronary artery disease, other mechanisms associated with hypercholesterolaemia, such as endothelial dysfunction (Vita, 1990), increased hypercoagulability (Hunt, 1990) and enhanced platelet activity (Badimon, 1991) may be involved.

8.5.2 Ambulatory ischaemia and prognosis

In this study of patients presenting for the first time with angina pectoris in the general population, there was no statistically significant difference in event-free survival between those with and without ambulatory ischaemia. Ambulatory ischaemia remained prognostically unimportant even after women were excluded from the analysis. The findings of previous reports are contradictory. Ambulatory ischaemia predicts adverse coronary events in some selected patients with stable coronary disease (Rocco, 1988; Tzivoni, 1989; Deedwania, 19980; Yeung, 1991), but not in others (Mulcahy, 1992; Quyyumi, 1993). Deedwania and Carbajal showed an independent association of silent ischaemia with cardiac mortality in patients receiving medical treatment for angina (Deedwania, 1990), but unlike the current study of entirely new patients, the duration of symptoms in their study population of men with low workload positive exercise tests ranged from 2 - 42 years. By contrast, ambulatory ischaemia was found to be of no prognostic significance in 172 patients with stable angina selected non-consecutively from two centres (Mulcahy, 1992). In that study, the combined event rate for myocardial infarction and death was in fact two-fold higher in patients with no detectable ischaemia on ambulatory monitoring compared to those with ischaemia. A similar trend towards an increased event rate in patients without ischaemia was also found in a recent study by Quyyumi et al in asymptomatic or mildly symptomatic patients with coronary artery disease (Quyyumi, 1993). They used multiple criteria based on coronary angiography and exercise testing to select 116 'low risk' patients, but as selection was based on coronary anatomy determined a mean of 2 years prior to enrolment, they could not include patients who had experienced an adverse event in the interim period, nor allow for any change in coronary anatomy during the 2 years following initial angiography. Furthermore their method of defining 'low risk' using coronary anatomy and radionuclide ventriculography may not be entirely appropriate because in 5 of 6 patients, the most

significant lesion at baseline angiography was not in the vessel that was totally occluded at the time of a subsequent acute clinical event, and the infarcted region in four of five patients did not show ischaemic dysfunction at the time of baseline radionuclide ventriculography (Quyyumi, 1993).

When patient selection is based on positive exercise tests at low workloads, the prognostic importance of ambulatory monitoring may be exaggerated because exercise induced ischaemia at low workloads not only predicts the presence of ambulatory ischaemia (Panza, 1991) but is also independently associated with an adverse outcome (Weiner, 1984). In such studies, patients with a high probability of having ischaemia recorded on ambulatory monitoring are therefore also the ones most likely to experience a cardiac event. It is therefore not surprising that in studies which based patient selection on a positive exercise test, ambulatory ischaemia appeared to have prognostic value (Rocco, 1988; Tzivoni, 1989; Deedwania, 1990), but in those which did not (Mulcahy, 1992; Quyyumi, 1993), including the current study, ambulatory ischaemia did not discriminate patients with an adverse outcome. Exercise-induced ischaemia probably results predominantly from increased demand across fixed, narrow lumen, flow-limiting stenoses associated with severe coronary atheroma, whereas ischaemic episodes during ambulatory monitoring may also occur at rest, and at lower levels of exercise, due to vasoconstriction and a reduction in coronary flow reserve associated with milder coronary artery disease (Cohn, 1992). Thus ischaemia in patients with low workload exercise tests which is mainly 'demand' related may be prognostically important, but ambulatory ischaemic ST segment depression which also occurs at rest due to altered vasomotor tone and vasoconstriction may have less prognostic importance.

In common with previous studies assessing the prognostic importance of ambulatory ischaemia (Rocco, 1988; Tzivoni, 1989; Deedwania, 1990; Yeung, 1991; Mulcahy, 1992; Quyyumi, 1993), in which the number of stable angina patients enroled ranged from 56 (Tzivoni, 1989) to 172 (Mulcahy, 1992), the number of patients in this study was small; therefore all studies lack adequate statistical power. The 95% confidence interval for the observed difference in event rates of 6% between patients with and without ambulatory ischaemia in this study is -13% to +25%. So a much larger study would be required to detect with confidence, a clinically important difference of say 15%. A longer duration of follow up may also reveal a statistically

significant difference in survival, but the prognostic value of ambulatory monitoring in predicting the objective end points of myocardial infarction and death diminishes over time (Yeung, 1991), and therefore it is likely that any difference in survival between patients with and without ischaemia would diminish.

As discussed earlier, the use of an exercise test to select patients for coronary angiography could have increased the chances of an association between ambulatory ischaemia and revascularisation procedures. This would have resulted in a higher event rate in patients with ambulatory ischaemia. Therefore this bias, if anything, strengthens the conclusion of this study in relation to the lack of prognostic importance of ambulatory ischaemia.

In order to evaluate the importance of ambulatory ischaemia in new patients with typical angina representative of those seen in clinical practice, cardiac catheterisation was not required for entry to the study, and therefore some patients may not have significant coronary artery stenosis. However comparisons with asymptomatic controls, especially in women, puts the reported prevalence of ischaemia in patients with angina into perspective.

In men, an association between ambulatory ischaemia and sudden cardiac death might be expected in view of the independent association of serum cholesterol level with each of these factors, but no conclusions can be drawn about this relationship from the present study because of the very small number of cardiac deaths. While a much larger study with sufficient end-points could address this important question, ambulatory electrocardiography is an insensitive marker of ischaemia related to a single vessel territory (Romeral, 1992) and is unlikely to have predictive value for sudden death if it is associated with a predominance of single vessel coronary artery disease (Drory, 1991).

8.6 Conclusions

In summary, the annual clinical incidence of angina pectoris in the United Kingdom is estimated at 22,570 patients (95% CI 17,840, 27,030). Of these, 9,370 men (95% CI 7,760, 11,450) and 4,250 women (95% CI 2,890, 5,330) can expect to have ischaemia ($\geq$ 1mm ST segment depression) on exercise testing.

However in the generality of new patients with angina pectoris, exercise induced ischaemia appears to have no prognostic value. Furthermore, the severity of angina is a poor predictor of subsequent prognosis. On the other hand, a total exercise duration of $\leq$ 6 minutes on the Bruce protocol treadmill test is independently associated with an increased risk of subsequent cardiac events.

Transient ischaemic episodes on ambulatory electrocardiographic monitoring occur in over half of patients presenting for the first time with typical angina pectoris in the general population. The pathophysiological basis of ischaemia may be different between the sexes, and in men, ischaemic activity during daily living is independently and positively associated with serum cholesterol. Ambulatory ST segment monitoring does not identify a subgroup at increased risk of death, myocardial infarction or future revascularisation. Therefore for the generality of patients presenting with angina pectoris, it is of no value in prognostic risk stratification and its use in routine clinical practice is not recommended.

The prognosis of incident angina is not benign. About 10% of new patients experience myocardial infarction or death within one year of presentation.

General practitioners' knowledge about the prognostic value of angina symptoms, exercise testing and revascularisation shows a striking variation. The majority of patients with angina are reportedly not referred for cardiological investigation by their general practitioners.

8.7 Implications for Future Research

Non invasive tests used for risk stratification of patients with angina pectoris should be evaluated in a broad spectrum of unselected patients representative of the generality of disease encountered in clinical practice. Extrapolation of results from studies of selected patients referred to tertiary cardiac centres is inappropriate and can be misleading. At present the question of which non invasive investigation is optimum for prognostic risk stratification remains open.

The severity of angina is an unreliable guide to subsequent prognosis. General practitioners would therefore be justified in referring all patients for further investigation. If this were to happen, then with current incidence rates, existing invasive and non invasive cardiological services in the United Kingdom would be overwhelmed. Further efforts should be directed at increasing general practitioners' access to cardiological investigation, possibly through open access services. The important question of whether early cardiological assessment and revascularisation improve clinical outcome should be scientifically addressed in a randomised controlled trial.

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APPENDICES

APPENDIX 1

Chest Pain Service : Angina Questionnaire For Office Use

Q.No. |__|__|__|__|__|
1 - 5

(Please tick (✓) appropriate box)

1. In a patient with stable angina do you consider symptom characteristics in terms of frequency and duration a reliable guide to the severity of underlying coronary artery disease?

	Yes	No	Don't know	
(i) Frequency	|__|	|__|	|__|	|__| 6
(ii) Duration	|__|	|__|	|__|	|__| 7

2. For patients presenting for the first time with stable angina, and with no history of CHD, an exercise test is

a) unnecessary in the majority of patients |__| |__| 8

b) required in selected patients only |__| |__| 9
please specify.....
.....

c) necessary in the majority of patients |__| |__| 10

3. Please rate the usefulness of an exercise test for each of the following indications:

	1 Almost never useful	2 Some-times useful	3 frequently useful	4 Almost always useful	5 Don't know	
Screening asympto-matic patients for CHD	|__|	|__|	|__|	|__|	|__|	|__| 11
For correct diagnosis of angina	|__|	|__|	|__|	|__|	|__|	|__| 12
For assessing prognosis of angina	|__|	|__|	|__|	|__|	|__|	|__| 13
For selecting patients with angina for coronary angio-graphy	|__|	|__|	|__|	|__|	|__|	|__| 14
For reassurance	|__|	|__|	|__|	|__|	|__|	|__| 15
For arrhythmia assessment	|__|	|__|	|__|	|__|	|__|	|__| 16

.....

4. How confident are you at correctly interpreting

For Office Use

	Almost never confident	Sometimes confident	Usually confident	Always confident	
a) a resting ECG for signs of ischaemia and infarction:	|__|	|__|	|__|	|__|	|__| 17
b) an exercise test result:	|__|	|__|	|__|	|__|	|__| 18

5. In your opinion, for stable angina patients, is there scientific evidence to show that:

	Yes	No	Don't Know	
(i) PTCA (Coronary angioplasty)				
(a) relieves symptoms	|__|	|__|	|__|	|__| 19
(b) prolongs survival	|__|	|__|	|__|	|__| 20

If yes, for which age group?

	a) Symptom relief	b) Prolong Survival	
Up to 65 years	|__|	|__|	|__| 21
Over 65 years	|__|	|__|	|__| 22
All ages	|__|	|__|	|__| 23
Other Specify.....	|__|	|__|	|__| 24

	Yes	No	Don't know	
(ii) CABG (Coronary artery bypass surgery)				
(a) relieve symptoms	|__|	|__|	|__|	|__| 25
(b) prolongs survival	|__|	|__|	|__|	|__| 26

If yes, for which age group?

	a) Symptom Relief	b) Prolong Survival	
Up to 65 years	|__|	|__|	|__| 27
Over 65 years	|__|	|__|	|__| 28
All ages	|__|	|__|	|__| 29
Other Specify.....	|__|	|__|	|__| 30

.....

6. How important do you consider each of the following criteria when deciding to refer patients presenting for the first time with angina for assessment by a hospital Cardiologist?

For Office Use

	1 Very Important	2 Of moderate importance	3 Of little importance	4 Of no importance		
Age	|__|	|__|	|__|	|__|	|__|	31
Sex	|__|	|__|	|__|	|__|	|__|	32
Family history of CHD	|__|	|__|	|__|	|__|	|__|	33
Presence of Hypertension	|__|	|__|	|__|	|__|	|__|	34
Diabetes	|__|	|__|	|__|	|__|	|__|	35
Cholesterol level	|__|	|__|	|__|	|__|	|__|	36
Smoking status	|__|	|__|	|__|	|__|	|__|	37
Duration of symptoms	|__|	|__|	|__|	|__|	|__|	38
Frequency of symptoms	|__|	|__|	|__|	|__|	|__|	39
Amount of exertion required to produce symptoms	|__|	|__|	|__|	|__|	|__|	40
Symptoms at rest (as well as on exertion)	|__|	|__|	|__|	|__|	|__|	41
Normal resting ECG	|__|	|__|	|__|	|__|	|__|	42
ECG evidence of ischaemia	|__|	|__|	|__|	|__|	|__|	43
ECG evidence of myocardial infarction	|__|	|__|	|__|	|__|	|__|	44

Other: please specify:..... \|__\| 45

Would you refer all patients with angina for hospital assessment irrespective of above criteria.

Yes \|__\|

No \|__\| \|__\| 46

.....

7. What proportion of your stable angina patients are

For Office Use

	None	Up to 10%	Up to 25%	Up to 50%	Up to 75%	All	
Referred to a general hospital physician	|__|	|__|	|__|	|__|	|__|	|__|	|__| 47
Referred directly to a Cardiologist at the regional centre.	|__|	|__|	|__|	|__|	|__|	|__|	|__| 48

8. At present, when you refer a patient presenting for the first time with suspected angina to a hospital Out Patient Clinic for consideration of an exercise test, in your estimate how long does it take from the date of referral to the time that the investigation results and management plan are made available to you?

..... \|__\|__\|__\|
49 - 51

9. If an open access clinic providing a complete initial cardiological assessment (including exercise testing and advice on recommended management by a Registrar) was available to you for referral of new suspected angina patients would your referral rate of such patients to a hospital consultant physician's out patient clinic

a) stay the same \|__\| \|__\| 52

b) decrease \|__\| \|__\| 53

c) increase \|__\| \|__\| 54

Would you utilise such a clinic?

Yes \|__\| \|__\| 55

No \|__\|

==========

ANY OTHER COMMENTS:

.....

.....

.....

.....

.....

APPENDIX 2a

Angina Study : GP Coding

Surgery	Practice Code	GP Code	G.P.s
Blackthorn Surgery	001	01	Goodison S.F.
73 Station Road		02	Wilson D.
Netley Abbey		03	Laing H.C.
Southampton		04	Steer J.M.
SO3 5AE		05	Lennon A
Tel. 453110		06	Thomson M
Prac.Mgr. Mrs. Jean Hay			
The Surgery	002	01	Blount A.
112 Shirley Road		02	Davidson S.I
Southampton SO1 3FS		03	Brooke M.J.
Tel. 221964			
Prac.Mgr. Mrs. Jean Parker			
The Green Park Surgery		04	Barnes R.C.
22 Wimpson Lane		05	Simpson R.L.
Southampton SO1 4QF		06	Simpson Rosalind M.
Tel. 774853			
Prac.Mgr. Mrs. Marion Nelson			
The Medical Centre	003	01	Gordon A.D.
Hythe		02	Cunliffe J.
Southampton SO4 5ZB		03	Davidson K.
Tel. 845955			
Off.Mgr. Mr. A.E. Lord			
Blackfield Medical Centre		04	Gregory.P
Blackfield		05	Vincent S.
Southampton SO4 1XA		06	Greaves F.
Tel. 899119		07	Rial S.
Prac.Mgr. Mrs. S. Augustus			

Surgery	Practice Code	GP Code	GP.s
1 Shirley Avenue	004	01	Gilbert M.
Shirley		02	Knight A.O.C.
Southampton		03	Stringfellow M
SO9 2UP		04	Pringle J.
Tel. 771356			
1 Cheviot Road,		05	Murphy C
Millbrook,		06	Kelpie A.
Southampton SO1 4AH		07	Patten T.
Tel. 773174		08	Tiller G (R)(p/t)
Prac.Mgr. Mrs. J. Hunt			
68 Alma Road	005	01	Lee R.D.
Portswood		02	Woodbine G.
Southampton		03	Yardley D.N.
SO9 4TR		04	Lawrence I.
Tel. 551555		05	Ord-Hume G.
		06	Westensee W.
Prac.Mgr. Mr. Tom Shaw			
The Medical Centre	006	01	Husband P.
Hythe		02	Bolt S.A.
Southampton		03	Radcliffe M.J.
SO4 5ZB		04	Newton D.J.
Tel. 845955		05	Hill-Cousins S.T.
Prac.Mgr. Mrs. Julia Pegg			
The Surgery			Husband P.
Old Malthouse			Bolt S.A.
Main Rd.			Radcliffe, M.J.
Marchwood,			Newton D.J.
Southampton SO4 4UZ.			Hill-Cousins S.T.
Tel. 871233			

Surgery	Practice Code	GP Code	GP.s
Testvale Surgery	007	01	Crawford V.
12 Salisbury Road		02	Dracass J.
Totton		03	Hunter S.
Southampton		04	Entwisle I.
SO4 3PY		05	Zardis M.
Tel. 866990		06	Whitfield S. (T)
Prac.Mgr. Mrs. Linda Millard			
4 Chessel Avenue	008	01	Nicholls M.J.
Bitterne		02	Plumptre A.M.
Southampton		03	Bradberry S.W.
SO9 3LJ		04	Fisher. M.S.
Tel. 447777		05	Maclean J.K.
		06	Shaw K.I.
		07	Bute K.J.
Prac.Mgr. Mrs. Angela Tipper			
Lordshill Health Centre	009	01	Mansbridge.B.J.
Lordshill District Centre		02	Billington T.R.M.
Lordshill		03	Bainbridge B.M.
Southampton		04	Fung P.J.
SO1 8HY		05	Barnfield M.
Tel. 738144		06	Gray B.
		07	Watson T. (R)
			Teddels S. (T)
Prac.Mgr. Mrs. J. Gingell			
Shirley Health Centre	010	01	Mansfield J.E.
Grove Road		02	Nightingale J.H.
Shirley		03	Walton R.J.
Southampton		04	May P.G.R.
SO9 3ZA		05	Short P.M.
Tel. 783611		06	Clouter C.A.
		07	Donnelly P. (T)
		08	Vyas D. (T)
Gen.Mgr. Mrs. Brenda Sawyer			

Surgery	Practice Code	GP Code	GP.s
Group Practice Centre	011	01	Trickett A.C.H.
Victor Street		02	Johnson W.J.
Shirley		03	Hutchin A.K.M.
Southampton		04	Varney P.R.
SO9 5HL		05	Pitt I.
Tel. 774781		06	Stephens C.R.
		07	Glasspool J.A.
		08	Graham J.
Prac.Mgr. Mrs. Norma York			
Bath Lodge Practice	012	01	Gray P.J.
Bitterne Health Centre		02	Hayes N.R.
Commercial Street		03	Rolles T.F.
Bitterne		04	Paynton D.J.
Southampton		05	McKay A.
SO9 2DA		06	Davidson P.H.
Tel. 442111		07	Godwin D.S.
			Ayoub S.A. (T)
Prac. Mgr. Mrs. D. Parsons			
Forest Gate Surgery	013	01	Leftley P.
Hazel Farm Road		02	Bramley K.W.
Totton		03	Parry K.T.
Southampton		04	Newman C.J.
SO4 3WU		05	Ayres C.M.
Tel. 663839		06	Detsios C.
Prac.Mgr. Mrs. N. Head			
The Medical Centre	014	01	Hamilton A.C.E.
Hythe		02	Bedford B.
Southampton		03	Pitts J.R.
SO4 5ZB		04	Campbell D.R.
Tel. 845955		05	Allen A.P.
		06	Whitby M.E.
Blackfield Medical Centre		07	Varney A.D.
Hampton Lane		08	Hoegan R. (T)
Blackfield		09	Ellis J. (T)
Southampton SO4 1XA.			Hoegan (T)
Administrator Mrs. S. Augustus			

Surgery	Practice Code	GP Code	GP.s
The Surgery	015	01	Waddington G.E.
6 Stoneham Lane		02	Fitzpatrick W.J.
Swaythling		03	Harman A.N.
Southampton		04	Lloyd C.N.
SO9 4NB		05	Cunningham L.M.
Tel. 555776		06	Hubbard M. (T)
Prac.Mgr. Mrs. P. Watkins			
The Health Centre	016	01	Munro M.R.
Testwood Lane		02	Wood T.A.
Totton		03	Stobbs I.P.
Southampton		04	Darch M.H.
SO4 3AP		05	Boyd U.B.
Tel. 865051		06	Godfrey S.
Prac.Mgr. Mrs. J. Atkinson			
St Mary's Surgery	017	01	Coleman G.P.
James Street		02	Munro W.P.
Southampton		03	Percy D.B.
SO1 1PJ		04	Prichard P.
Tel. 333778		05	Booth K.
		06	Buis C.(T)
		07	Barnes K. (T)
Prac.Mgr. Mrs. Barbara Avery			

Practice Populations by Age and Sex

APPENDIX 2b

Prac No.	≤ 30		31 - 40		41 - 50		51 - 60		61 - 70		> 70		TOTAL
	M	F	M	F	M	F	M	F	M	F	M	F	
001	1,664	1,696	639	613	602	534	407	370	343	383	404	675	8,330
002	1,331	1,408	481	460	399	333	505	276	393	465	237	407	6,695
003	2,892	2,748	997	990	974	953	671	639	602	644	412	596	13,118
004													12,422
005	2,191	2,043	711	521	681	530	528	445	454	478	537	915	10,034
006	2,001	2,348	799	812	666	660	501	517	385	412	356	478	9,935
007	2,175	2,080	733	704	680	666	558	570	470	479	375	525	10,015
008	3,342	3,161	1,108	905	1,027	1,022	775	741	633	760	558	912	14,944
009	2,768	2,627	820	933	694	688	345	356	320	420	290	526	10,787
010	2,295	2,332	836	712	636	550	435	384	430	476	500	806	10,392
011	3,556	3565	1,107	1,076	1,172	1,153	942	937	835	948	751	1,284	17,326
012	2,895	2,881	1,025	945	843	803	682	751	701	768	557	816	13,667
013	2,646	2,548	1,048	896	900	812	682	666	620	615	460	729	12,622
014	2,783	2,652	825	923	962	845	737	810	730	758	481	707	13,213
015	1,708	2,025	481	518	373	517	373	455	367	503	380	613	8,313
016													11,180
017	1,939	1,904	680	519	572	386	466	347	476	359	450	586	8,684

Invitation to Healthy Controls **APPENDIX 3**

Date

Dear

I am writing to ask if you could help with a special research project on Heart Disease. Your name has been chosen completely at random and you are one of several people who are being approached in this way.

You will have a complete heart check, including a recording of your heart (ECG) and a short fitness test on a treadmill whilst your heart is being monitored, so wear casual clothes and comfortable walking shoes. A blood sample will be taken to measure your cholesterol level. Your visit to the hospital will take approximately 1-2 hours.

In the hope that you will help we have reserved a personal appointment for you at the Non-Invasive Cardiology Department

on at

A map is attached and you are advised to allow sufficient time for parking.

This service is supported by your family doctor and I hope you will make use of it. You will benefit from a full heart check-up, whilst at the same time, making an important contribution to medical research.

Please **complete and post back** the enclosed reply slip in the pre-paid envelope provided as soon as possible.

If the appointment is not convenient please contact Mrs. Linda Truscott on the above telephone number, extension 2842, so that we can offer you an alternative.

Yours sincerely,

Dr M M Gandhi
Clinical Research Fellow

Att.

APPENDIX 4

CHEST PAIN SERVICE

Monday to Friday 9 am - 1 pm

REFERRAL FORM FOR NEW PATIENTS WITH CHEST PAIN

Date _____

To: Non-Invasive Cardiology
Outpatients Department
Royal South Hants Hospital
Graham Road
Southampton
SO9 4PE
Tel: 634288 Ext: 2842/2961

Referring Doctor

_____

_____

_____

Patient Name _____

Address: _____

_____

_____

_____

Current Medication: _____

_____

_____

_____

PLEASE COMPLETE AND SIGN THE CHEST X-RAY REQUEST CARD ATTACHED TO THIS FORM

Signed:_____

APPENDIX 5

Consent Form

Name .....

I agree to undergo a heart check which will involve the following:

(i) An interview and physical examination by a Doctor.

(ii) Giving of a blood sample.

(iii) An exercise test on a treadmill which will be medically supervised and has no greater risk than a vigorous walk uphill.

(iv) A 24 hour tape recording of the heart beat using a light portable tape.

I understand the main results will be sent to my General Practitioner and also used for medical research.

Signature ..... Date .....

APPENDIX 6

CHEST PAIN SERVICE

QUESTIONNAIRE

Please answer the questions in this record as far as you are able **by ringing the appropriate answer.**

If you have any questions or problems do not hesitate to ask the staff.

All the information recorded in this personal health record will be treated as **strictly confidential.** The results, which you will be told about at the end of the examination, will be used for research into coronary heart disease but only in the form of general statistics from which it will be impossible to identify you as an individual.

A report of the examination and any further tests will be sent to your general practitioner.

Thank you for your co-operation in this study.

CHEST PAIN SERVICE

Study Number |__|__|__|__|__|__|

Practice Code |__|__|__|

General Practitioner |__|__|

Please write your name and address in full.

NAME .....

ADDRESS .....

.....

.....

POSTCODE .....

TEL.NO. Home .....

Work .....

DATE .....

Your General Practitioner's name:.....

Section Number	|__|__| 1- 2
Study Number	|__|__|__|__|__|__| 3- 7
Practice Code	|__|__|__| 8-10
General Practitioner	|__|__|11-12

I would be grateful for some personal information first

(Please circle the appropriate answer or write in space provided)

1. What is your date of birth? \|__\|__\|__\|__\|__\|__\|13-18

   .....

2. What is your sex?

   Male Female \|__\| 19

3. What is your country of origin?

   England

   Other \|__\| 20

   If other please specify:-
   (e.g. Rep. of Ireland, Indian, Afro Caribbean, etc)

   .....

4. What is your marital status?

   Single Married Widowed

   Separated Other \|__\| 21

5. For how many years have you lived in this area?

   .....years \|__\|__\|22-23

6. What kind of work have you done for the longest period of your life?

   Please give the name of the job and describe what you do or did as fully as possible.

   .....

   .....

   .....

7. What business or industry is or was this in? |__| 24

   .....

8. For how many years have you done or did you do this work?

   .....years |__|__|25-26

For Married Women

9. What kind of work has your husband done for the longest period of his life?

   Please give the name of the job and describe what he does or did as fully as possible.

   .....

   .....

   .....

10. What business or industry is or was this in? |__| 27

    .....

11. For how many years has he or did he do this kind of work?

    .....years |__|__|28-29

Section |__|__| 1- 2

Study |__|__|__|__|__| 3- 7

I would like to ask you about your medical history

(Please circle the appropriate answer or write in the space provided)

12. Have you ever been told by a doctor that you have, or have had, any of the following:-

(a) Heart trouble	Yes	No	|__| 8
(b) Rheumatic fever	Yes	No	|__| 9
(c) Angina	Yes	No	|__| 10
(d) Heart attack	Yes	No	|__| 11
(e) Coronary thrombosis	Yes	No	|__| 12
(f) Myocardial infarction	Yes	No	|__| 13

If YES, please specify

.....

(g) High blood pressure	Yes	No	|__| 14
(h) Stroke	Yes	No	|__| 15
(i) Diabetes	Yes	No	|__| 16
(j) Hardening of the arteries in the legs	Yes	No	|__| 17
(k) Hiatus hernia	Yes	No	|__| 18
(l) Gallstones/gallbladder disease	Yes	No	|__| 19
(m) Peptic (stomach or duodenal) ulcer	Yes	No	|__| 20

13. Are you on any regular medical treatment at present from a doctor for any condition?

Yes No |__| 21

If 'YES' please list:

Name of Medication	Condition	
1.....	.....	|__|__|22-23
2.....	.....	|__|__|24-25
3.....	.....	|__|__|26-27
4.....	.....	|__|__|28-29
5.....	.....	|__|__|30-31
6.....	.....	|__|__|32-33
7.....	.....	|__|__|34-35
8.....	.....	|__|__|36-37
9.....	.....	|__|__|38-39

14. Do you get pain or discomfort in your chest?

Yes No |__| 40

15. How long does/did the discomfort last?

.....Hours .....Minutes .....Seconds

Not applicable |__|__|__|__|__|__|41-46

16. Do you get it when you walk uphill or hurry?

Yes No

I never hurry or walk uphill |__| 47

17. Do you get it when you walk at an ordinary pace on the level?

Yes No |__| 48

18. What do you do if you get it while walking?

Stop or slow down	Carry on	|__| 49

19. If you stand still, what happens to it?

Relieved	Not relieved	|__| 50

20. How soon?

10 minutes	More than 10 minutes	|__| 51

21. What was/is the nature of the pain or discomfort?

Stabbing	|__| 52
Dull ache	|__| 53
Burning	|__| 54
Tight	|__| 55

22. Please indicate the site of the pain

Sternum (upper or middle)	|__| 56
Sternum (lower)	|__| 57
Left anterior chest	|__| 58
Left arm	|__| 59
Other	|__| 60

23. Did/do you feel it anywhere else?

Yes No |__| 61

If YES, please describe where

.....

.....

24. Have you ever experienced chest pain or discomfort during sexual intercourse?

Yes

No

Not Applicable |__| 62

If YES, has this occurred:

Once or twice only

Frequently

Not applicable |__| 63

25. Have you ever had a severe pain across the front of your chest lasting for half an hour or more?

Yes No |__| 64

26. Do you suffer from indigestion?

Yes No |__| 65

27 Do you consider yourself to be under "stress"?

Yes No |__| 66

If YES, please describe why

.....

.....

.....

Section |__|__| 1- 2

Study No. |__|__|__|__|__|__| 3- 7

Family History

(Please circle the appropriate answer or write in the space provided)

28. Is there a family history of heart disease?

Yes No |__| 8

If YES, please detail

Relation-ship(incl sex)	Age when heart disease developed	Diagnosis	Alive or dead includ-ing age at death

.....

.....

.....

..... |__|__| 9-10

29. Has anyone in your family ever had diabetes? (Sugar disease)?

Yes No |__| 11

If YES, which of your relatives (eg brother, cousin, parent)?

.....

..... |__| 12

30. Has anyone in your family ever had high blood pressure?

Yes No |__| 13

If YES, which of your relatives (eg brother, cousin, parent)?

.....

..... |__| 14

31. For Women Only

Have you ever had:-

a) The contraceptive pill	Yes	No	|__| 15
b) Hormone replacement therapy (HRT)	Yes	No	|__| 16
c) A hysterectomy	Yes	No	|__| 17
d) An oophorectomy (ovaries removed)	Yes	No	|__| 18

I would like to ask some questions about smoking

(Please circle the appropriate answer or write in the space provided)

32. Do you smoke?

Yes No \|__\| 19

If NO, proceed to question 37

33. What do you usually smoke?

Cigarettes	Yes	No	|__| 20
Pipe	Yes	No	|__| 21
Cigars	Yes	No	|__| 22

34. How many do you usually smoke?

Cigarettes per day	.....	|__|__|23-24
Ozs of tobacco per day	.....	|__|__|__|25-27
Cigars per week	.....	|__|__|28-29

35. What brand do you usually smoke?

..... \|__\| 30

36. For how many years have you smoked during your life? \|__\|__\|31-32

.....years

Proceed to question 42.

37. Have you ever smoked regularly since you left school?

Yes No |__| 33

If NO, proceed to question 42

38. What did you usually smoke?

Cigarettes	Yes	No	|__| 34
Pipe	Yes	No	|__| 35
Cigars	Yes	No	|__| 36

39. How many did you usually smoke?

Cigarettes per day	.....	|__|__|37-38
Ozs of tobacco per week	.....	|__|__|__|39-41
Cigars per week	.....	|__|__|42-43

40. For how many years did you smoke?

..... years |__|__|44-45

41. How long is it since you finally gave up smoking?

..... months/years |__|__|46-47

I would like to ask you about your drinking habits

(Please circle the appropriate answer or write in the space provided)

42. Do you drink alcohol?

Yes No |__| 48

If NO, proceed to question 46

43. Think carefully back over the last seven days. Please tell me exactly what alcoholic drinks you have consumed on each day during the past week.

For each day I would like to know:-

i) the number of pints of beer, lager, shandy, cider, stout etc.

ii) the number of single glasses of whisky, vodka, gin, rum etc.

iii)the number of single glasses of Martini, port, sherry, wine etc.

that you have drunk. Try to remember where you were and who you were with on each day. This may help you remember what you have had to drink.

	Pints of Beer etc	Single glasses spirits	Single glasses wine etc.
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Number of units per week |__|__|__|49-51

44. Would you say that last week was fairly typical of what you usually have to drink in a week?

Yes No |__| 52

45. If last week was <u>not</u> typical, would you normally drink more or less in a week?

More Less |__| 53

46. Have you ever drunk alcohol?

Yes No |__| 54

Thank you for completing the questionnaire.

APPENDIX 7

EXAMINATION RECORD

HISTORY

Date:.....

Name:.....

Age:.....

Study Number:.....

Section |__|__| 1- 2

Study Number |__|__|__|__|__|__| 3- 7

1. Classification

Typical angina	= 1	Myocardial infarction	= 5	|__| 8
Non-cardiac pain	= 2	Unstable angina	= 6		
Possible angina	= 3	Exclusion	= 7		
Atypical pain ?cause	= 4				

2. Clinical examination

Weight (kg) |__|__|__|.|__| 9-12

Height (m) |__|.|__|__| 13-15

Body mass index (calculated) |__|__|.|__| 16-18

3. Blood pressure Systolic |__|__|__| 19-21

Diastolic |__|__|__| 22-24

Heart Rate |__|__|__| 25-27

Rhythm |__| 28

4. Stigmata of hyperlipidaemia

Arcus	Yes = 1	No = 2	|__| 29
Xanthelasmata	Yes = 1	No = 2	|__| 30
Xanthomata	Yes = 1	No = 2	|__| 31

Investigations

5. Resting ECG recorded Yes = 1 No = 2 |__| 32

If NO, specify reason:.....

Rate /min |__|__|__| 33-35

Rhythm |__| 36

PR |__|__| 37-38

Axis |__|__|__| 39-41

QTc |__|__| 42-43

ST-T change Yes = 1 No = 2 |__| 44

6. Exercise ECG tests Yes = 1 No = 2 |__| 45

If NO specify reason:.....

7. 24h ambulatory ECG Yes = 1 No = 2 |__| 46

If NO specify reason:.....

8. Chest X-Ray Yes = 1 No = 2 |__| 47

Findings:.....

.....

.....

9. Serum cholesterol Yes = 1 No = 2 |__| 48

10. Random blood glucose Yes = 1 No = 2 |__| 49

11. Biochemistry Yes = 1 No = 2 |__| 50

12. FBC Yes = 1 No = 2 |__| 51

13. Other ..... Yes = 1 No = 2 |__| 52

14. Date seen |__|__|__|__|__|__| 53-58

EXAMINATION RECORD (CONTROL)

HISTORY

Date:.....

Name:.....

Age:.....

Study Number:.....

Section |__|__| 1- 2

Study Number |__|__|__|__|__| 3- 7

1. Classification

Suitable control	= 1	Exclusion: mitral valve prolapse	= 5
History of angina (undiagnosed previously)	= 2	Exclusion: LVH with ST changes	= 6
Exclusion: known PMH of CHD	= 3	Exclusion: Other criteria	= 7
Exclusion: Left bundle branch block	= 4		

|__| 8

2. Clinical examination

Weight (kg) |__|__|__|.|__| 9-12

Height (m) |__|.|__|__| 13-15

Body mass index (calculated) |__|__|.|__| 16-18

3. Blood pressure Systolic |__|__|__| 19-21

Diastolic |__|__|__| 22-24

Heart Rate |__|__|__| 25-27

Rhythm |__| 28

4. Stigmata of hyperlipidaemia

Arcus	Yes = 1	No = 2	|__| 29
Xanthelasmata	Yes = 1	No = 2	|__| 30
Xanthomata	Yes = 1	No = 2	|__| 31

Investigations

5.	Resting ECG recorded	Yes = 1	No = 2	|__| 32
	If NO, specify reason:.....			
	Rate /min			|__|__|__| 33-35
	Rhythm			|__| 36
	PR			|__|__| 37-38
	Axis			|__|__|__| 39-41
	QTc			|__|__| 42-43
	ST-T change	Yes = 1	No = 2	|__| 44
6.	Exercise ECG tests	Yes = 1	No = 2	|__| 45
	If NO specify reason:.....			
7.	24h ambulatory ECG	Yes = 1	No = 2	|__| 46
	If NO specify reason:.....			
8.	Chest X-Ray	Yes = 1	No = 2	|__| 47
	Findings:.....			
	.....			
	.....			
9.	Serum cholesterol	Yes = 1	No = 2	|__| 48
10.	Random blood glucose	Yes = 1	No = 2	|__| 49
11.	Biochemistry	Yes = 1	No = 2	|__| 50
12.	FBC	Yes = 1	No = 2	|__| 51
13.	Other	Yes = 1	No = 2	|__| 52
14.	Date seen			|__|__|__|__|__|__| 53-58

Angina Study : Cholesterol, Glucose, symptom duration, management.

Study Number |__|__|__|__|__| 1- 5

1. Serum Cholesterol |__|__|.|__| 6- 8

2. Plasma Glucose |__|__|.|__| 9-11

3. Duration of Symptoms (days) |__|__|__|__|12-15

4. Medical treatment initiated for angina (long acting nitrates, calcium antagonist and/or beta blocker)
   1 = Yes
   2 = No |__| 16

5. Antihypertensive medication (new) prescribed
   1 = Yes
   2 = No |__| 17

6. Frequency |__| 18

7. Which antianginal? |__| 19

File number (where different from Study Number):.....

Codes Re : Cholesterol, Glucose, symptom duration, management

No.	Box numbers	Code
	1- 5	Study Number
1.	6- 8	Random serum cholesterol (mmol/L) 99.9 = not available
2.	9-11	Random plasma glucose (mmol/L) 99.9 = not available
3.	12-15	Number of days (prior to date of clinical attendance) since symptoms first started.
4.	16	0 = Not applicable 1 = Yes 2 = No 3 = Hospital admission due to myocardial infarction prior to exercise test. 4 = Hospital admission for another reason prior to exercise test.
5.	17	1 = Yes 2 = No
6.	18	1 = more than once a day 2 = Once daily 3 = 4 - 6 times a week 4 = Up to 2 - 3 times a week 5 = Once a week 6 = Less than once a week 7 = Single episode only

7.	19	1 = Beta blocker
		2 = Calcium antagonist
		3 = Long acting nitrate
		4 = Any combination

APPENDIX 8

Angina Study : Resting Electrocardiograph

Section Number |_0|_1|1-2

Study Number |__|__|__|__|__|__|3-7

Date of ECG |__|__|__|__|__|__|8-13

1. Q and QS patterns

   Anterolateral site (I, aVL, V6) |__|__|__|14-16

   Inferior site (II, III, aVF) |__|__|__|17-19

   Anterior (V1 V2 V3 V4 V5) |__|__|__|20-22

2. QRS Axis

   See Coding Sheets |__|__|23-24

3. ST segment depression

   Anterolateral (I, aVL, V6) |__|__|__|25-27

   Inferior (II, III aVF) |__|__|__|28-30

   Anterior (V1 V2 V3 V4 V5) |__|__|__|31-33

4. T wave items

   Anterolateral (I, aVL, V6) |__|__|34-35

   Inferior (II, III aVF) |__|__|36-37

   Anterior (V2 V3 V4 V5) |__|__|38-39

5. A-V Conduction defect |__|__|__|40-42

   Specify.....

   PR interval |__|43

6. Ventricular conduction defect |__|__|__|44-46

   Specify.....

7. Heart Rate |__|__|__|47-49

   Arrhythmias |__|__|__|50-52

   Specify.....

8. ST segment elevation: Anterolateral (I, aVL, V6) |__|__|53-54

Inferior (II, III aVF) |__|__|55-56

Anterior (V1 V2 V3 V4 V5) |__|__|57-58

9. Miscellaneous |__|__|__|59-61

Angina Study : Resting Electrocardiograph Codes

Question	Box numbers	Coding
	1- 2	01 = Section Number
	3- 7	Study Number
	8-13	Date of ECG
1. Q.QS patterns	14-16	anterolateral (I, aVL, V6)
	17-19	inferior (II, III, aVF)
	20-22	anterior (V1 V2 V3 V4 V5)
		000 = No Q wave present
		When Q wave present in any lead(s) refer to summary of 'Minnesota Code 1982' and choose from Code 111 through 136 for each set of 3 boxes.
2. QRS axis	23-24	20 = Normal axis -29° through +89° 21 = Left -30° through -90° 22 = Right +120° through -150° 23 = Right Optional +90° through +119°
		DO NOT CODE IN PRESENCE OF: 91 = Low QRS amplitude (see Code 9-1, page 129) LBBB or RBBB 00 = Not codable.
3. ST depression (STD)	25-27	Anterolateral (I, aVL, V6)
	28-30	Inferior (II, III, aVF)
	31-33	Anterior (V1 V2 V3 V4 V5)
		000 = No horizontal/downward sloping STD
		For horizontal/downward sloping STD:
		411 = ≥ 2.0 mm 412 = ≥ 1.0 mm but < 2.0 mm 420 = ≥ 0.5 mm and < 1.0 mm
		(Select boxes appropriate to lead(s))
		999 = Not codable. (eg in presence of bundle branch block).

4. T wave	34-35	Anterolateral (I, aVL, V6)
	36-37	Inferior (II, III, aVF)
	38-39	Anterior(V2 V3 V4 V5)
		00 = No T wave changes.
		(Read full codes on page 126)
		51 = T negative ≥ 5.0 mm 52 = T negative or diphasic ≥ 1.0 mm but < 5.0 mm 53 = T flat, negative or diphasic < 1.0 mm
		99 = Not codable (in presence of WPW or bundle branch blocks)
5. AV Conduction	40-42	Select from Codes 610 through 680 (page 127 Minnesota Code Summary) 000 = No AV conduction abnormality
	43	PR interval 1 = < 0.12 2 = 0.12 - 0.20 3 = 0.21 - 0.22 4 = > 0.22
6. Ventricular Conduction	44-46	711 = Complete LBBB 712 = Intermittent LBBB 721 = Complete RBBB 722 = Intermittent RBBB 730 = Incomplete RBBB 740 = Intraventricular block 750 = R-R1 with R1 ≤ R 760 = Incomplete LBBB
7. Heart Rate	47-49	Heart Rate (beats/min) (Page 127 Minnesota Code Summary)
Arrhythmias	50-52	See page 128, Minnesota Code Summary Selected examples of codes:
		812 = Frequent ventricular premature beats 831 = Atrial fibrillation (persistent) 832 = Atrial flutter (persistent) 870 = Sinus tachycardia (> 100/min) 880 = Sinus bradycardia (< 50/min)
		000 = No codable arrhythmia

8. ST elevation	53-54	Anterolateral (I, aVL, V6)
	55-56	Inferior (II, III aVF)
		92 = ST elevation ≥ 1.0 mm in any lead
	57-58	Anterior (V1 V2 V3 V4 V5)
		92 = ≥ 1.0 mm in V5 or ≥ 2.0 mm in any of V1 V2 V3 V4
9. Miscellaneous	59-61	See page 129 Minnesota Code Summary Example 981 = technical problems which interfere with coding. 983 = LVH on voltage criteria, no ST changes.

APPENDIX 9

Angina Study: Exercise Test Results

PART I

Section Number |_0|_1| 1 - 2

Study Number |__|__|__|__|__| 3 - 7

Date of test |__|__|__|__|__|__| 8 - 13

1. Blood Pressure/Heart Rate Response:

	Systolic	Diastolic	HR
Resting	|__|__|__| 14-16	|__|__|__| 29-31	|__|__|__| 44-46
Peak exercise	|__|__|__| 17-19	|__|__|__| 32-34	|__|__|__| 47-49
Immediate recovery	|__|__|__| 20-22	|__|__|__| 35-37	|__|__|__| 50-52
End recovery	|__|__|__| 23-25	|__|__|__| 38-40	|__|__|__| 53-55
Maximum recorded (up to and including immediate recovery)	|__|__|__| 26-28	|__|__|__| 41-43	

BP response
1 = Normal
2 = Hypotension (≥ 20 mmHg fall)
3 = Hypertensive (> 210 and/or > 110)
4 = Other
5 = Not applicable
|__| 56

PART II

Section Number |_0|_2| 1 - 2

Study Number |__|__|__|__|__| 3 - 7

2. **ST segment changes**

Hyperventilation/postural changes 1 = Yes 2 = No |__| 8

If yes:
1 = T wave changes
2 = ST depression
3 = Other (specify .....)
|__| 9

ST depression (modified Minnesota code)

anterolateral (I, aVL, V6)	|__|__|.|__|10-12
maximum (mm)	|__|.|__|13-14
inferior (posterior) (II,III,aVF)	|__|__|.|__|15-17
maximum (mm)	|__|.|__|18-19
anterior (V1-5)	|__|__|.|__|20-22
maximum (mm)	|__|.|__|23-24

ST elevation |__|__|.|__|25-27

3. Arrhythmias |__|__|.|__|28-30

Specify type..... |__| 31

4. Ventricular Conduction Specify..... |__|__|.|__|32-34

5. A-V conduction Specify..... |__|__|.|__|35-37

6. Total exercise duration (minutes:seconds) |__|__|.|__|__|38-41

7. Recovery time for ECG to return to baseline |__|__|.|__|__|42-45

8. Symptoms:

Chest pain during exercise 1 = yes 2 = no |__| 46

Time start |__| |__|__|.|__|__|47-51

Time stop |__| |__|__|.|__|__|52-56

(0 prior to time signifies during exercise)
1 prior to time signifies during recovery)

9. Reason for stopping test (see codes) |__|__|57-58

Specify.....

10. On regular medication? 1 = yes 2 = No |__| 59
(betablocker, calcium antagonist, long acting nitrates)

If yes, medications stopped: |__| 60
0 = not applicable
1 = less than 24 hours prior to test
2 = 24-47 hours prior to test
3 = 48 or more hours prior to test
4 = Not stopped

Study number.....

Angina Study: Exercise Test Codes

PART I

Q.	Box No.	Code
	1 - 2	01 = Section Number
	3 - 7	Study number
	8 - 13	Date of test
1. BP		Systolic blood pressure
	14 - 16	resting
	17 - 19	peak exercise
	20 - 22	immediate recovery
	23 - 25	end recovery
	26 - 28	maximum recorded
		Diastolic blood pressure
	29 - 31	resting
	32 - 34	peak exercise
	35 - 37	immediate recovery
	38 - 40	end recovery
	41 - 43	maximum recorded
		Heart rate
	44 - 46	resting
	47 - 49	peak exercise
	50 - 52	immediate recovery
	53 - 55	end recovery
		999 = missing
	56	BP response: 1 = Normal 2 = Hypotension (fall in systolic **and/or** diastolic BP of ≥20mmHg) 3 = Hypertensive (rise in systolic BP > 210 **and/or** diastolic BP >110 mmHg) 4 = Other 5 = Not applicable 9 = Incomplete data missing

PART II

	1 - 2	Section number (02)	
	3 - 7	Study No.	
2. ST changes	8	1 = Yes 2 = No	
	9	1 = T wave changes 2 = ST depression 3 = Other	
		Leads	ST code
ST depression, etc.	10 - 12	Anterolateral I, aVL or V6	(codes 11.1 - 11.9 apply to Box. Nos 10-12, 15-17 and/or 20-22)
	15 - 17	Inferior II, III or aVF	11.1 = ST-J depression **≥1.0mm horizontal or downward sloping** and any one of these leads
	20 - 22	Anterior V1-5	11.4 = ST-J depression ≥1.0mm **upward sloping,** in one of these leads.
			11.5 = ST-J depression **≥1.0mm** horizontal or downward sloping **from baseline coded ST depression.**
			11.6 = Post exercise decrease in horizontal/downward sloping ST-J depression coded at rest, or change to upward sloping ST depression.
			11.7 = No change from resting coded ST item.
			11.8 = Change from any coded ST item at rest to no reportable ST item post exercise.
			11.9 = Questionable ST depression post exercise due to technical considerations.
			00.0 = **No codable post exercise ST items.**

		Maximum measured (mm) **horizontal/planar** ST depression (J+60 msec)
		0.0 = None/Not applicable
	13 - 14	in anterolateral (I, aVL or V6) leads.
	18 - 19	in inferior (II, III or aVF) leads.
	23 - 24	in anterior (V1 2 3 4 or V 5) leads.
ST elevation	25 - 27	16.1 = Change from no coded ST elevation at rest to ST segment elevation ≥1.0mm in any lead.
3. Arrhythmias	28 - 30	15.1 = change from no coded arrhythmia at rest to any reportable arrhythmia post exercise.
		00.0 = No arrhythmia
Type	31	1 = frequent (10% or more of recorded complexes) ventricular premature beats
		2 = frequent atrial/functional premature beats
		3 = Supraventricular tachycardia (persistent)
		4 = Ventricular tachycardia (persistent)
		5 = Intermittent VT : three or more ventricular premature beats at a rate ≥ 100
		6 = Atrial fibrillation (persistent)
		7 = Atrial flutter (persistent)
		8 = Other
		0 = No arrhythmia
4. Ventricular conduction		Change from no coded ventricular conduction item at rest to :
	32 - 34	14.1 = complete left bundle branch block 14.2 = complete right bundle branch block 14.3 = incomplete right bundle branch block 88.8 = Other 00.0 = No change

5. A V Conduction		Change from no coded AV conduction item at rest to:
	35-37	13.1 = Complete (third degree)A-V block 13.2 = Partial (second degree) A-V block 13.3 = first degree A-V block (PR ≥ 0.22) 13.8 = Other 00.0 = No change in A-V conduction
6.	38 - 41	Total exercise duration
	38 - 39	minutes
	40 - 41	seconds
7.	42 -45	Recovery time for ECG to return to baseline
	42 - 43	minutes
	44 - 45	seconds
8. Chest pain	46	1 = Yes 2 = No
Start	47 - 51	(where > 1 episode, longest recorded)
	47	0 = indicates time period up to peak exercise 1 = indicates time period into recovery
	48 - 49	minutes
	50 - 51	seconds
Stop	52 - 56	
	52	0 = indicates time period up to peak exercise 1 = indicates time period into recovery
	53 - 54	minutes
	55 - 56	seconds
		999.99 = data missing
		000.00 = not applicable

9. Reason stopped

57 - 58

01 = Leg fatigue

02 = General fatigue

03 = Chest pain

04 = Shortness of breath (dyspnoea, 'SOB')

05 = Chest pain and dyspnoea

06 = Dyspnoea due to COAD

07 = ST changes

08 = Intermittent claudication

09 = Hypotension (with or without symptoms)

10 = Dizziness with no drop in BP.

11 = Increasing ventricular ectopic activity

12 = Arrhythmia (other than '11')

13 = Disability e.g. OA knees

14 = Other

10. On regular medication
(betablocker, calcium antagonist and/or long acting nitrates)

59

1 = Yes
2 = No

60

If 'yes' medications stopped:

0 = not applicable
1 = less than 24 hours prior to test
2 = 24-47 hours prior to test
3 = 48 or more hours prior to test
4 = Not stopped

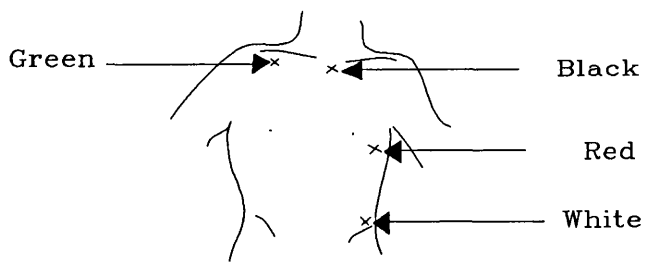
APPENDIX 10

CHEST PAIN STUDY

TAPE HOOK-UP PROTOCOL

Patient undressed to waist; hip bone exposed on left side.

All hair to be shaved off following positions:-



Skin abrasion with gauze and electrode jelly until red (warn patient - may hurt!).

Wipe with swab and let dry.

Attach electrodes as above (check for adequate R-wave height in V5 on resting ECG; if necessary, use exploring electrode to find best position for red electrode).

After forming 'stress loop' on wire, each electrode to be secured with ample tape.

Tracker Tape

Check 24 hour tape clock reads correct time.

Insert battery.

Insert cassette (TDK D90) - Engage head.

Press Calibrate button once - clock will flash until calibrated (Calibration **before** electrodes attached to patient).

Secure tape.

Press 'Event' button then patient carries out following manoeuvres, each approx. 30 seconds:

Lies flat

Stands upright

Bends to left

Bends to right

Hyperventilates

Press 'Event' button again. **Time at end of manoeuvres to be written down in patient's diary.**

To give to patient:

a) Diary with explanation.

b) Instruction leaflet.

Information for Patients about 24 Hour Tape Monitoring

This tape will record the electrical activity of your heart over one day. It is important that you carry on with **ALL** your usual daily activities and not restrict yourself in any way.

If you experience any chest pain or discomfort (or heaviness in the arms) press the 'Event' button demonstrated to you earlier. At the same time, make a note of the time of onset of pain in the diary provided.

If this is more than once a day, the same procedure should be carried out on each occasion.

The time any spray or tablet is used under the tongue must also be noted.

Please record times of any:

(i) strenuous activities.

(ii) time of main meal

(iii) driving/cycling

(iv) long walks

(v) bowel movement

Thank you for your co-operation.

APPENDIX 11

Angina Study: 24 hour tape results

PART I

Study No	Line No	Time Begin	End	ST change CM5	CM2	Heart Rate Pre	Onset	During	Chest Pain
1-4	0 1 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	0 2 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	0 3 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	0 4 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	0 5 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	0 6 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	0 7 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	0 8 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	0 9 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	1 0 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	1 1 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	1 2 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	1 3 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	1 4 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30
1-4	1 5 (5-6)	7-10	11-14	15-17	18-20	21-23	24-26	27-29	30

PART II

Section Number |_0|_1| 1 - 2

Study Number |__|__|__|__| 3 - 6

Recording date |__|__|__|__|__|__| 7 -12

1. Trend printout

Episodes ≥ 1 mm ST depression on trend:

Episode Number		Time of max.STD:		mm STD	
|_0|_1|	13 - 14	|__|__|__|__|	15 - 18	|__|.|__|	19 - 20
|_0|_2|	21 - 22	|__|__|__|__|	23 - 26	|__|.|__|	27 - 28
|_0|_3|	29 - 30	|__|__|__|__|	31 - 34	|__|.|__|	35 - 36
|_0|_4|	37 - 38	|__|__|__|__|	39 - 42	|__|.|__|	43 - 44
|_0|_5|	45 - 46	|__|__|__|__|	47 - 50	|__|.|__|	51 - 52
|_0|_6|	53 - 54	|__|__|__|__|	55 - 58	|__|.|__|	59 - 60
|_0|_7|	61 - 62	|__|__|__|__|	63 - 66	|__|.|__|	67 - 68
|_0|_8|	69 - 70	|__|__|__|__|	71 - 74	|__|.|__|	75 - 76

Section Number |_0|_2| 1 - 2

Study Number |__|__|__|__| 3 - 6

|_0|_9|	7 - 8	|__|__|__|__|	9 - 12	|__|.|__|	13 - 14
|_1|_0|	15 - 16	|__|__|__|__|	17 - 20	|__|.|__|	21 - 22
|_1|_1|	23 - 24	|__|__|__|__|	25 - 28	|__|.|__|	29 - 30
|_1|_2|	31 - 32	|__|__|__|__|	33 - 36	|__|.|__|	37 - 38
|_1|_3|	39 - 40	|__|__|__|__|	41 - 44	|__|.|__|	45 - 46
|_1|_4|	47 - 48	|__|__|__|__|	49 - 52	|__|.|__|	53 - 54
|_1|_5|	55 - 56	|__|__|__|__|	57 - 60	|__|.|__|	61 - 62

Specify reason trend incorrect:.....

.....

2. Duration of record |__|__|.|__|__|63-66

3. Any significant arrhythmia 1 = Yes 2 = No |__| 67

Type: 1 = Ventricular tachycardia |__|__|68-69

2 = Supraventricular tachycardia

3 = Atrial fibrillation

4 = Idioventricular rhythm

5 = Frequent ventricular ectopics

6 = Frequent supraventricular ectopics

7 = L B B B

8 = Two or more types

9 = A - V conduction abnormality

00 = Not applicable

11 = Other: specify.....

If arrhythmia :

Number of consecutive beats (if < 60s) |__|__|__|70-72

If > 60 seconds, total duration in minutes |__|__|__|73-76

000 = Not applicable

Associated with symptoms? 1 = Yes 2 = No 3 = Sometimes 0 = Not applicable |__| 77

4. Baseline ST elevation (≥ 1mm) at night > 30 minutes. 1 = Yes 2 = No |__| 78

Section Number |_0|_3| 1-2

Study Number |__|__|__|__| 3-6

5. Medication: Any regular beta blockers, calcium antagonists or nitrates (excluding sublingual)

1 = Yes
2 = No |__| 7

Type: 1 = Beta blocker |__| 8

2 = calcium antagonist

3 = regular nitrate

4 = Combination

0 = Not applicable

If yes, medication stopped prior to recording for:

1 = ≥ 24 hr |__| 9

2 = ≥ 48 hr

3 = Not stopped

0 = Not applicable

6. Postural/hyperventilation ST changes |__| 10

0 = None

1 = T wave inversion

2 = ST depression

3 = ST elevation

4 = Other

7. Technical suitability: 1 = Yes |__| 11

2 = No (for reason other than '3')

3 = No, Baseline instability affecting analysis

If no, specify: .....

Angina Study : Coding for 24 Hour Tape Results

PART I

Box number	Code
1- 4	Study Number
5- 6	Line Number
7-10	Start time of episode in hours and minutes (24 hour clock)
11-14	End of episode time (24 hour clock)
15-17	mm ST depression from baseline in lead CM5 to one decimal place ('9' in box 15 indicates ST elevation from baseline) 00.0 = No ST change
18-20	mm ST depression from baseline in lead CM2 to one decimal place ('9' in box 18 indicates ST elevation) 00.0 = No ST change 99.9 = Not recorded/technically unsuitable
21-23	Heart rate preceeding onset of episode (within 30 minutes) 999 = Not recorded/technically unsuitable
24-26	Heart rate at onset of episode
27-29	Heart rate during episode 000 = Not recorded
30	1 = Anginal chest discomfort 2 = No chest discomfort
7-30	Blank boxes = No episodes 9 999 = missing data 9999

Angina Study : Coding for 24 Hour Tape Results (Cont'd)

PART II

No.	Box number	Code
	1- 2	Section number = 01
	3- 6	Study number
	7-12	Date of recording
1.	13-14	
	21-22	
	29-30	
	37-38	= Trend episode number
	45-46	
	53-54	
	61-62	
	69-70	
	15-18	
	23-26	
	31-34	
	39-42	
	47-50	= Time of max.STD (hours, minutes)
	55-58	9999 = No trend printout
	63-66	8888 = Trend unreliable due to 'aberrants'/wavy base
	71-74	
	19-20	
	27-28	
	35-36	= mmSTD in trend
	43-44	0.0 = Not applicable
	51-52	
	59-60	
	67-68	
	75-76	
	(15-76	Blank boxes = no trend episodes)

Section 2	1- 2	Section number = 02
	3- 6	Study number
	7- 8	
	15-16	
	23-24	= Trend episode number
	31-32	
	39-40	
	47-48	
	55-56	
	9-12	
	17-20	
	25-28	= Time of max.STD (hours, minutes)
	33-36	9999 = No trend printout
	41-44	8888 = Trend unreliable due to 'aberrants'/wavy base
	49-52	
	57-60	
	13-14	
	21-22	
	29-30	= mmSTD in trend
	37-38	0.0 = not applicable
	45-46	
	53-54	
	61-62	
	(9-62	Blank boxes = No trend episodes)
2. Duration of record	63-66	63-64 = hours 65-66 = minutes
3. Arrhythmias	67	1 = Yes 2 = No

	68-69	1 = Ventricular tachycardia
		2 = Supraventricular tachycardia
		3 = Atrial fibrillation
		4 = Idioventricular rhythm
		5 = Frequent ventricular ectopics
		6 = Frequent supraventricular ectopics
		7 = Left bundle branch block
		8 = Two or more types
		9 = A-V conduction abnormality
		00 = Not applicable
		11 = Other
	70-72	No. of consecutive beats (if < 60s)
	73-76	Total duration in minutes (if > 60s)
		000 = Not applicable
Symptoms	77	1 = Yes
		2 = No
		3 = Sometimes
		0 = Not applicable
4. Baseline ST elevation	78	1 = Yes
		2 = No
		0 = Not applicable

Section 3

	1- 2	Section Number
	3- 6	Study Number
5. Medication	7	1 = Yes
		2 = No
	8	1 = Beta blocker
		2 = calcium antagonist
		3 = regular nitrate
		4 = combination
		0 = Not applicable

	9	Medication stopped prior recording for 1 = ≥ 24 hr 2 = ≥ 48 hr 3 = Not stopped 0 = Not applicable
6. Postural/hyper-ventilation	10	0 = none 1 = T wave inversion 2 = ST depression 3 = ST elevation 4 = Other
7. Technical suitability	11	1 = Yes 2 = No (for reason other than '3') 3 = No, Baseline instablity affecting analysis

Follow-up Questionnaire **APPENDIX 12**

PLEASE ANSWER BY PUTTING A TICK (✓) IN THE APPROPRIATE BOX AND BY WRITING IN THE SPACES PROVIDED

FOR OFFICE USE

No. |__|__|__|__| 1- 4

|__|__|__|__| 5- 8

|__|__|__|__|__|__| 9-14

|__|__|__|__|__|__| 15-21

1. Since your visit to the Chest Pain Clinic **are you now under the care of:**

	Yes	No		
(1) Your General Practitioner alone	|__|	|__|	|__|	22
or				
(2) Your General Practitioner and a hospital specialist	|__|	|__|	|__|	23

2. Since your visit to the Chest Pain Clinic **do you still get chest pain?**

Yes |__| No |__| |__| 24

3. Since your visit to the Chest Pain Clinic **have you attended any hospital outpatient clinic about your heart?**

Yes |__| No |__| |__| 25

If 'No' , please go to Question 4.

If 'Yes' , please state:

Name of Hospital _____ |__| 26

Name of Consultant _____ |__|__| 27-28

What were the main diagnoses:

(i) _____ |__| 29

(ii) _____ |__| 30

(iii) _____ |__| 31

4. Since your visit to the Chest Pain Clinic **have you been admitted to hospital with heart problems?**

Yes |__| No |__| |__| 32

If 'No', please go to Question 5.

If 'Yes', please give the following information for **your most recent** hospital admission:

Name of Hospital _____ |__| 33

Name of Consultant _____ |__|__| 34-35

Date of admission Day..... Month..... Year .....|__|__|__|__|__|__| 36-41

What were the main diagnoses?

(i) _____ |__| 42

(ii) _____ |__| 43

(iii) _____ |__| 44

5. Since your visit to the Chest Pain Clinic **have you had a Cardiac Catheter test? (Coronary angiography)**

Yes |__| No |__| |__| 45

If 'No', please go to Question 6.

If 'Yes':

Date of test Day..... Month ..... Year..... |__|__|__|__|__|__| 46-51

Name of Hospital _____ |__| 52

Name of Consultant _____ |__|__| 53-54

What was the result of your test?

_____ |__| 55

_____

6. Since your visit to the Chest Pain Clinic **has your GP or a hospital specialist prescribed treatment for any of the following?**

	Yes	No		
(1) High blood pressure	|__|	|__|	|__|	56
(2) High blood cholesterol	|__|	|__|	|__|	57
(3) Diabetes	|__|	|__|	|__|	58

7. Since your visit to the Chest Pain Clinic **have you had any of the following?**

Section \|_2\| 1

No. \|__\|__\|__\|__\|__\| 2- 5

	Yes	No	If 'Yes' please state Date:	Consultant:		
(1) Unstable Angina	|__|	|__|	_____	_____	|__|	6
					|__|__|	7- 8
					|__|__|__|__|__|__|	9-14
(2) Heart attack (myocardial infarction)	|__|	|__|	_____	_____	|__|	15
					|__|__|	16-17
					|__|__|__|__|__|__|	18-23
(3) Balloon angioplasty (PTCA)	|__|	|__|	_____	_____	|__|	24
					|__|__|	25-26
					|__|__|__|__|__|__|	27-32
(4) Coronary Bypass Surgery (CABG)	|__|	|__|	_____	_____	|__|	33
					|__|__|	34-35
					|__|__|__|__|__|__|	36-41

8. **Please list the names of any drugs (including tablets or spray under the tongue) you are <u>now</u> taking:**

Name of Medication:

1. _____ |__|__| 42-43
2. _____ |__|__| 44-45
3. _____ |__|__| 46-47
4. _____ |__|__| 48-49
5. _____ |__|__| 50-51
6. _____ |__|__| 52-53
7. _____ |__|__| 54-55
8. _____ |__|__| 56-57
9. _____ |__|__| 58-59
10. _____ |__|__| 60-61

9. Please state your Hospital number (if known, for example from your Outpatient appointment card)

.....

10. Name of current General Practitioner_____

Surgery Address _____

_____

_____

_____

11. Today's Date _____

THANK YOU VERY MUCH FOR YOUR TIME AND EFFORT IN COMPLETING THIS QUESTIONNNAIRE.

PLEASE RETURN IT IN THE STAMPED ADDRESSED ENVELOPE SUPPLIED.