

# The natural history of prevalent ischaemic heart disease in middle-aged men

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**Objective** To describe the long-term outcome of different forms of symptomatic and asymptomatic ischaemic heart disease in middle-aged men.

**Methods** 7735 men aged 40–59, randomly selected from 24 general practices in Britain were classified into one of seven ischaemic heart disease groups according to a questionnaire and electrocardiogram (ECG): I=diagnosed myocardial infarction; II=unrecognized myocardial infarction; III=diagnosed angina; IV=angina symptoms; V=possible myocardial infarction symptoms; VI=ECG ischaemia or possible myocardial infarction; VII=no evidence of ischaemic heart disease. The association of disease group with a range of fatal and non-fatal outcomes during 15 years of follow-up was assessed.

**Results** At baseline 25% of men had evidence of ischaemic heart disease (groups I–VI). Risks of major ischaemic heart disease events, total and cardiovascular mortality, stroke, and major cardiovascular events tended to increase strongly from group VII to I. Diagnosed myocardial infarction was associated with a much poorer prognosis than all other groups (including unrecognized infarction) for all cardiovascular outcomes other than stroke. The relative risk associated with ischaemic heart disease at baseline declined dramatically over time. However, men with myocardial infarction who survived event-free for 10 years continued to experience a high excess risk in the subsequent 5 years, in

contrast to event-free survivors of angina and other ischaemic heart disease. Adjusted to an average age of 50, the percentage of men surviving for 15 years free of a new major cardiovascular event was 44 for diagnosed myocardial infarction, 52 for unrecognized myocardial infarction, 66 for diagnosed angina, 68 for angina symptoms, 73 for possible myocardial infarction symptoms, 73 for ECG ischaemia, and 79 for no ischaemic heart disease. Comparison of outcome between prevalent and incident myocardial infarction illustrated the improved prognosis of men surviving the initial years after their event.

**Conclusions** Differing manifestations of prevalent ischaemic heart disease are associated with widely differing outcome, and the majority of middle-aged men in the community who have evidence of ischaemic heart disease short of myocardial infarction survive for 15 years without heart attack or stroke. The excess risk associated with myocardial infarction appears more persistent than that associated with angina and other ischaemic heart disease, remaining high even after 10 years of event-free survival.

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**Key Words:** ischaemic heart disease, chest pain, questionnaire, resting electrocardiogram, natural history, prediction.

## Introduction

A complete understanding of the natural history of ischaemic heart disease requires study not only of acute

presentations of disease, but also of prevalent disease in the community. Studies based exclusively on hospital patients<sup>[1–5]</sup>, or those seeking medical care due to new symptoms<sup>[6]</sup>, have the advantage of obtaining incident cases on which detailed clinical and investigative information can be collected, but their disadvantage is that these patients may represent the tip of the clinical iceberg. Evidence of ischaemic heart disease is common in middle-aged men<sup>[7,8]</sup>, and not all men will be referred to a hospital physician<sup>[9]</sup>, or even be known to their general practitioner as suffering from

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heart disease<sup>[10]</sup>. Population studies, examining the natural history of both symptomatic and asymptomatic ischaemic heart disease in large samples of subjects<sup>[11–14]</sup>, are also essential for an understanding of the long-term outcome of the whole spectrum of disease present in the population.

Knowledge of prognosis for different forms of disease is necessary for appropriate management. Risk stratification based on absolute level of coronary risk is increasingly emphasized as an aid to priority setting for both primary and secondary prevention of ischaemic heart disease<sup>[15–17]</sup>. For groups at high risk, intervention strategies are justified as their benefits tend to be greater than any associated risks. Scoring systems and risk tables developed to help practitioners estimate an individual's coronary risk<sup>[18–22]</sup> have tended to focus on men and women free of ischaemic heart disease, treating those with clinically overt disease as a relatively homogeneous high risk group. In fact this group has highly variable coronary risk, dependent on the extent and severity of disease in addition to patterns of risk factors.

This paper aims to describe comprehensively the natural history of differing manifestations of prevalent ischaemic heart disease ascertained by questionnaire and resting electrocardiogram among middle-aged men in the British Regional Heart Study. Whilst previous population studies have focused on total and coronary heart disease mortality as end-points, this study aims to present a more complete picture of the long-term relative and absolute risk of fatal and non-fatal outcomes associated with varying forms of ischaemic heart disease in middle-aged men. A separate report will examine the influence of risk factors on outcome in men with ischaemic heart disease.

## Methods

The British Regional Heart Study is a prospective study of 7735 men, aged 40–59 years at entry (1978–80), who were randomly selected from the age–sex registers of one general practice in each of 24 British towns. The criteria for selecting the towns, the general practices and the subjects have been reported<sup>[23]</sup>. In brief, the 24 towns were taken from those with populations of 50 000–100 000 (1971 census). They covered the full range of mortality from cardiovascular disease and included all major geographic regions. The general practice in each town was required to have a social class distribution representative of that town. The baseline examination included a questionnaire administered by research nurses (Q1) and a three-lead resting electrocardiogram (ECG). The average response rate was 78%.

### *Evidence of ischaemic heart disease at baseline*

#### *Electrocardiogram*

Definitions of electrocardiographic abnormalities and their relationships to the Minnesota Code have been

described<sup>[24]</sup>. Subjects were classified into mutually exclusive electrocardiographic categories: definite myocardial infarction, possible myocardial infarction, definite ischaemia, possible ischaemia or no ischaemia.

#### *Diagnosed ischaemic heart disease*

The administered questionnaire inquired whether each subject had ever been told by a doctor that they had (i) a heart attack (myocardial infarction, coronary thrombosis) and (ii) angina<sup>[10]</sup>.

#### *Symptoms of ischaemic heart disease*

The administered questionnaire included the WHO (Rose) chest pain questionnaire (with minor modifications)<sup>[8]</sup>. Angina symptoms were defined as chest pain brought on either by walking uphill or hurrying, or by walking at an ordinary pace on the level, regardless of whether pain fulfilled additional criteria<sup>[8,25]</sup>. A history of possible myocardial infarction symptoms was defined as severe chest pain lasting half an hour or more, situated in the sternum or left anterior chest<sup>[8]</sup>.

### *Baseline ischaemic heart disease categories*

Each man was classified into one of seven mutually exclusive categories according to evidence of ischaemic heart disease at baseline.

I *Diagnosed myocardial infarction*: subject report of a doctor-diagnosis of myocardial infarction.

II *Unrecognized myocardial infarction*: unequivocal ECG evidence of myocardial infarction but no subject report of diagnosed myocardial infarction.

III *Diagnosed angina*: subject report of a doctor-diagnosis of angina, but no doctor-diagnosis or unequivocal ECG evidence of myocardial infarction.

IV *Angina symptoms*: angina symptoms on chest pain questionnaire, but no doctor-diagnosis of ischaemic heart disease or unequivocal ECG evidence of myocardial infarction.

V *Possible myocardial infarction symptoms*: history of possible myocardial infarction symptoms on chest pain questionnaire, but no angina symptoms and no doctor-diagnosis of ischaemic heart disease or unequivocal ECG evidence of myocardial infarction.

VI *ECG ischaemia or possible myocardial infarction*: ECG evidence of possible or definite ischaemia short of a definite myocardial infarction, but no symptoms of angina or possible myocardial infarction and no doctor-diagnosis of ischaemic heart disease.

VII *No evidence of ischaemic heart disease*: no diagnosis, ECG evidence or symptoms of ischaemic heart disease.

### *Five-year questionnaire*

A further questionnaire (Q5) was sent to all surviving men in 1983–1985, 5 years after their initial examination. The men were again asked about ischaemic heart disease

**Table 1 Risk of a major ischaemic heart disease event for specific periods of follow-up by ischaemic heart disease classification at baseline**

IHD group	0–15 years (n/N) <sup>§</sup> (983/7711)				0–5 years (300/7715)	5–10 years (350/7258)	10–15 years (333/6648)
	N	Mean age	Prevalence %	Event rate*	HR <sup>#</sup> (95% CI)	HR <sup>#</sup> (95% CI)	HR <sup>#</sup> (95% CI)
I Diagnosed MI	292	53.8	3.8	47.0	5.6 (4.6, 6.8)	6.8 (4.9, 9.2)	4.6 (3.2, 6.7)
II Unrecognized MI	135	52.3	1.7	24.6	3.1 (2.3, 4.4)	3.3 (1.8, 5.9)	4.2 (2.6, 6.9)
III Diagnosed angina	123	53.7	1.6	21.1	2.5 (1.7, 3.6)	3.5 (2.0, 6.2)	1.2 (0.5, 3.0)
IV Angina symptoms	349	51.6	4.5	14.4	1.9 (1.5, 2.4)	2.4 (1.5, 3.7)	1.5 (0.9, 2.4)
V Possible MI symptoms	360	50.5	4.7	10.5	1.4 (1.1, 1.9)	2.0 (1.3, 3.3)	0.8 (0.5, 1.6)
VI ECG ischaemia/possible MI	680	50.8	8.8	11.2	1.5 (1.2, 1.9)	1.7 (1.1, 2.5)	1.3 (0.9, 1.9)
VII No evidence IHD	5776	49.8	74.9	7.1	1.0	1.0	1.0
Total	7715	50.2	100	9.5			

IHD=ischaemic heart disease; MI=myocardial infarction.

\*Major IHD event rate/1000/year.

<sup>#</sup>Hazard ratio, adjusted for age.

<sup>§</sup>Number of events/Total number of subjects for analysis.

diagnoses and chest pain, using identical questions to those in the baseline administered questionnaire, with the exception of the question on severe chest pain. This now asked: 'Have you ever had a severe pain across the front of your chest lasting for half an hour or more?' rather than asking the subject to indicate the specific site of pain.

### Follow-up for cardiovascular events

By 31 December 1995, 99% of the 7735 men initially examined in 1978–1980 had been followed up for 15 years. The established tagging procedure carried out by the National Health Service Central Registers in Southport and Edinburgh was used for notification of deaths, with date and cause from the death certificate. Cause of death was established in all but four cases: these men were excluded from cause-specific analyses where necessary. Information on non-fatal cardiovascular events (myocardial infarction, stroke, coronary artery bypass graft [CABG], coronary angioplasty [PTCA]) was obtained from biennial reviews of each subject's general practice records (including hospital correspondence)<sup>[26]</sup>. A non-fatal myocardial infarction was required to be associated with at least two of the following features at the time of event: severe prolonged chest pain, electrocardiographic evidence of myocardial infarction and cardiac enzyme abnormalities, with survival for at least 28 days<sup>[27]</sup>. A non-fatal stroke was defined as acute symptoms of cerebral dysfunction of vascular origin, lasting 24 h or more. A major ischaemic heart disease event was defined as an ischaemic heart disease death (ICD 410–414) or a non-fatal myocardial infarction. A major cardiovascular event was defined as a cardiovascular death ICD (401–459) or a non-fatal stroke or myocardial infarction.

### Statistical methods

Event rates were calculated using person-years of follow-up and are expressed as number of events/1000/year. Cox proportional hazards survival analysis with adjustment for age (as a continuous variable) was used to assess the effect of ischaemic heart disease group on each outcome considered; results are presented as hazard ratios (relative risks) with 95% confidence intervals (CI). Each end-point was defined as the first event of that type occurring after baseline for each subject. Subjects who died during follow-up of causes not included in the end-point of interest had their survival time censored at their date of death. For the small proportion of events with incomplete dates, a missing day was set to 15 (about 7% of events) and a missing month to 6 (less than 1% of events). A time dependent variable [ $\log(\text{time}) \times \text{IHD group}$ ] was used to test whether the hazard ratio associated with evidence of ischaemic heart disease at baseline changed over time. Cumulative survival proportions were calculated using the Kaplan–Meier technique; age-adjusted proportions were calculated using direct standardization (with four 5-year age bands) to the baseline age structure of the entire sample<sup>[28]</sup> (average age 50.2 years).

### Results

Of the 7735 men, 20 could not be assigned to an ischaemic heart disease classification, due to missing data for the baseline questionnaire or electrocardiogram. Of the remaining 7715 men, 1940 (25.1%) were classified in groups I to VI as having evidence of ischaemic heart disease at baseline, with 427 (5.5%) having experienced a definite myocardial infarction (Table 1). The majority (103; 76.3%) of the 135 men with

unrecognized myocardial infarction (group II) had no other indication of ischaemic heart disease (no angina diagnosis, no symptoms of angina or possible myocardial infarction). Men with doctor-diagnosed disease were older on average than those with other manifestations of ischaemic heart disease.

### *Major ischaemic heart disease events*

Table 1 shows major ischaemic heart disease event rates and age-adjusted hazard ratios for 15 years of follow-up by baseline classification. All indications of ischaemic heart disease at baseline significantly increased risk of a major ischaemic heart disease event. Diagnosed myocardial infarction (group I) was associated with considerably poorer outcome than all other groups, with unrecognized myocardial infarction (group II) having a prognosis more similar to that of diagnosed angina (group III). Men without definite infarction or diagnosed disease (groups IV–VI) were at lower risk. Overall, 41% of first events during follow-up were fatal within 28 days. Case fatality was increased among men with evidence of ischaemic heart disease at baseline compared to those without (in whom the rate was 35%), but was highest among men with myocardial infarction and diagnosed angina at baseline (groups I, II, III), in whom 54–60% of new events were fatal.

### *Persistence of ischaemic heart disease risk*

Hazard ratios were examined separately for three 5-year periods of follow-up (Table 1). Each analysis was based on men who had survived free of a major ischaemic heart disease event up to that point in the follow-up. The risk associated with evidence of ischaemic heart disease at baseline diminished considerably as follow-up increased. The hazard ratio comparing any evidence of ischaemic heart disease (groups I to VI) with no evidence of disease (group VII) showed a highly significant decrease over the 15-year period (likelihood ratio chi-squared = 11.05  $P < 0.001$ ) when a [log(time)  $\times$  ischaemic heart disease group] interaction term was included in the model. This reduction in relative risk over time was particularly striking for men with ischaemic heart disease short of myocardial infarction, although a statistical test assessing whether the hazard ratio associated with groups I and II combined showed a greater change over time than that for groups III to VI combined was not significant. However, a marked separation between men with and without myocardial infarction was apparent in estimates of relative risk in the last 5-year period of follow-up. Men with myocardial infarction at baseline who survived event-free for 10 years were more than four times as likely as men without ischaemic heart disease to experience a new event in the next 5 years, whereas men with lesser ischaemic heart disease at baseline who survived event free for 10 years experi-

enced minimal excess risk subsequently. Age adjusted hazard ratios (95% CI) from years 10–15 were 4.4 (3.2, 6.1) for groups I and II combined, compared to 1.2 (0.9, 1.6) for groups III to VI combined.

Because of the inadequacy of a proportional hazards model in summarizing relative risks over the entire follow-up period, remaining rates and hazard ratios presented in this paper are based on 10 years of follow-up, although some descriptive statistics are also presented for 15 years of follow-up. Ten-year major ischaemic heart disease event rates and relative hazards are presented in Table 2.

### *Effect of angina among men with myocardial infarction*

Angina (either diagnosed or angina symptoms) was present in 175 (59.9%) men with diagnosed myocardial infarction (group I), but only in 22 (16.3%) of men with unrecognized infarction (group II). In group I, the age-adjusted hazard ratio of a major ischaemic heart disease event over 10 years was 4.6 for men without angina compared to 7.1 for those with angina. In group II, the corresponding relative hazards were 2.6 and 3.0. Overall, among all men with myocardial infarction (groups I and II combined), the additional increase in risk associated with angina was 1.8 (1.3, 2.6).

### *Effect of ischaemia and possible myocardial infarction among men with angina*

ECG ischaemia at rest (including ECG possible myocardial infarction) was present in 29 (23.6%) men with diagnosed angina (group III), and 63 (18.1%) men with angina symptoms (group IV). The presence of ECG ischaemia at rest increased risk substantially; the hazard ratio rose from 2.3 to 5.8 in group III, and from 1.9 to 2.9 in group IV. Among all men with angina (groups III and IV combined) the additional increase in risk associated with ECG ischaemia was 1.9 (1.1, 3.1). A history of possible myocardial infarction symptoms (present in 35.0% of men with diagnosed angina and 13.8% of men with angina symptoms) had a weaker effect, increasing the hazard ratio from 2.9 to 3.4 in group III and from 1.9 to 3.1 in group IV [additional increase of 1.5 (0.9, 2.6) for groups III and IV combined].

### *Stroke and all cause mortality*

The relationship between baseline ischaemic heart disease group and 10-year risk of stroke and all cause mortality is shown in Table 2. All indications of ischaemic heart disease increased the risk of stroke (fatal and non-fatal combined) compared to group VII. Although there was a significant trend of increasing stroke risk from groups VII to I, the gradient in risk was less

Table 2 Ten year risk of different outcomes by ischaemic heart disease classification at baseline

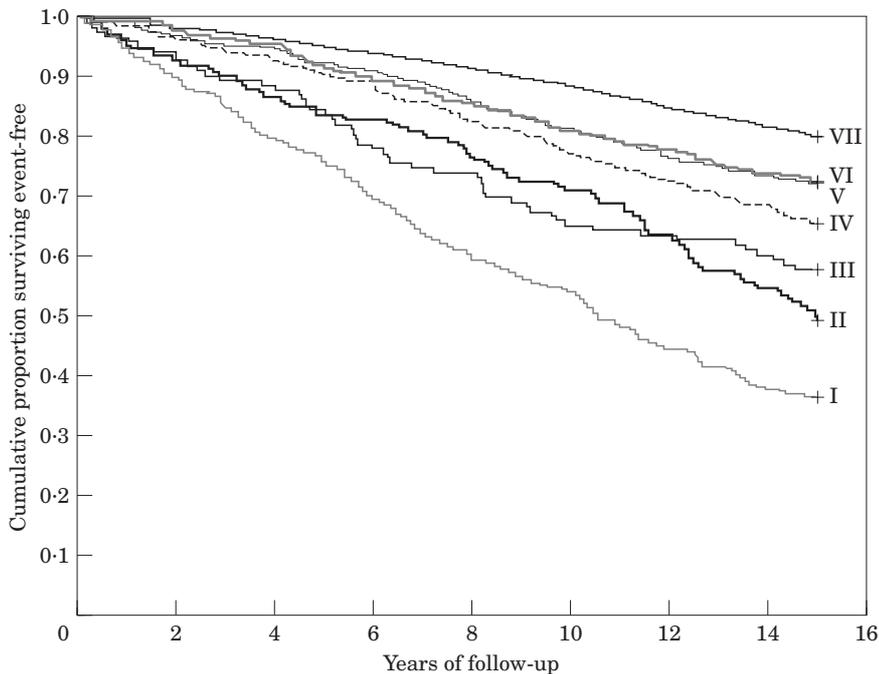
IHD group	Major IHD event (n/N) <sup>§</sup> (650/7714)		Stroke (164/7714)		Total mortality (745/7715)		CVD mortality (381/7714)		Non-CVD mortality (363/7714)	
	Event rate*	HR# (95% CI)	Event rate*	HR# (95%CI)	Event rate*	HR# (95% CI)	Event rate*	HR# (95% CI)	Event rate*	HR# (95% CI)
I Diagnosed MI	47.0	6.0 (4.8, 7.5)	5.8	2.5 (1.4, 4.4)	37.9	3.7 (3.0, 4.7)	7.3 (5.5, 9.6)	1.2 (0.7, 1.9)		
II Unrecognized MI	18.9	2.7 (1.7, 4.1)	6.9	3.5 (1.7, 7.3)	25.3	2.9 (2.0, 4.2)	4.4 (2.7, 7.1)	1.8 (1.0, 3.3)		
III Diagnosed angina	24.2	3.1 (2.0, 4.6)	5.6	2.5 (1.1, 5.6)	30.3	3.0 (2.1, 4.2)	4.3 (2.7, 6.9)	2.0 (1.1, 3.5)		
IV Angina symptoms	14.2	2.1 (1.5, 2.8)	5.0	2.6 (1.5, 4.4)	16.8	2.0 (1.5, 2.6)	2.6 (1.8, 3.8)	1.5 (1.0, 2.3)		
V Possible MI symptoms	11.6	1.8 (1.3, 2.5)	3.5	2.1 (1.1, 3.8)	10.4	1.4 (1.0, 1.9)	1.5 (0.9, 2.4)	1.3 (0.8, 2.0)		
VI ECG ischaemia/possible MI	11.0	1.7 (1.3, 2.2)	2.7	1.5 (0.9, 2.5)	13.5	1.7 (1.3, 2.1)	2.3 (1.7, 3.2)	1.3 (0.9, 1.8)		
VII No evidence IHD	6.2	1.0	1.6	1.0	7.3	1.0	1.0	1.0		

CVD = cardiovascular disease. For other abbreviations, see Table 1.

\*Event rate/1000/year.

#Hazard ratio, adjusted for age.

§Number of events/Total number of subjects for analysis.



**Figure 1** Kaplan–Meier cumulative probability of surviving free of a myocardial infarction or stroke by ischaemic heart disease classification at baseline. I=diagnosed MI; II=unrecognized MI; III=diagnosed angina; IV=angina symptoms; V=possible myocardial infarction symptoms; VI=ECG ischaemic or possible myocardial infarction; VII=no IHD.

marked than that for the other outcomes. Baseline ischaemic heart disease status showed a stronger relationship with cardiovascular mortality than with ischaemic heart disease events, due both to the increased risk of stroke and the increased likelihood of a fatal event among men with evidence of ischaemic heart disease. Cardiovascular deaths accounted for 82, 63 and 61% of total deaths in groups I, II and III respectively, 45–55% in groups IV–VI, and 42% in group VII. Evidence of ischaemic heart disease at baseline also tended to be associated with a small to moderate increase (up to twofold) in non-cardiovascular mortality, but there was no clear pattern across the groups. The majority of men in every group survived for 15 years: age-adjusted survival proportions ranged from 59% in group I to 86% in group VII.

### *Event-free survival*

Figure 1 shows the Kaplan–Meier cumulative probabilities of survival free of a major cardiovascular event by baseline ischaemic heart disease group. Crude percentages surviving free of myocardial infarction or stroke for 15 years ranged from 37% in group I to 80% in group VII. The corresponding percentages adjusted to an average age of 50 were 44, 52, 66, 68, 73, 73, and 79 in groups I to VII respectively. Standard errors for these age-adjusted event-free survival percentages were 5% or

lower, other than for groups II and III, for which standard errors were 7% and 9% respectively.

### *Coronary revascularization*

During the 15 years of follow-up, 168 (2.2%) men had either a CABG or a PTCA. A coronary revascularization procedure occurred most frequently among men with diagnosed angina at baseline: 12.4% (31/251) of all men with diagnosed angina, and 17.6% (21/119) of men with diagnosed angina *and* diagnosed myocardial infarction at baseline underwent revascularization. Among those with other manifestations of ischaemic heart disease at baseline, revascularization rates were 4% or lower. The age-adjusted percentages for 15 years survival free of myocardial infarction, stroke or coronary revascularization were 39, 50, 60, 67, 71, 73, and 79 for groups I to VII respectively.

### *Influence of age at baseline*

Table 3 shows risk estimates for two age-specific subgroups. The ischaemic heart disease classification has been condensed into three groups (all myocardial infarction, other ischaemic heart disease, and no ischaemic heart disease) in order to have sufficient numbers for meaningful analysis. Although the event rates associated

**Table 3** Age-specific rates and survival percentages by baseline ischaemic heart disease group

	N	Prevalence (%)	Age-adjusted HR <sup>#</sup> major IHD event	Major event rates (SE)/1000/year <sup>#</sup>		% Surviving free of major CVD event*	
				IHD events	CVD events	10 years	15 years
40–49 years							
All MI (groups I and II)	103	2.8	5.1 (3.1, 8.2)	22.5 (5.0)	23.7 (5.2)	77	54
Other IHD (groups III–VI)	629	16.9	2.0 (1.4, 2.8)	8.3 (1.2)	9.9 (1.3)	88	82
No IHD (group VII)	2995	80.4	1	4.0 (0.4)	4.8 (0.4)	93	88
50–59 years							
All MI (groups I and II)	324	8.1	4.9 (3.9, 6.1)	42.6 (4.1)	50.5 (4.5)	54	36
Other IHD (groups III–VI)	883	22.1	1.9 (1.5, 2.3)	16.5 (1.5)	22.4 (1.7)	73	61
No IHD (group VII)	2781	69.7	1	8.8 (0.6)	11.5 (0.7)	83	72

SE=standard error.

For other abbreviations, see Table 1.

<sup>#</sup>Based on 10 years follow-up.

\*Survival free of heart attack or stroke.

**Table 4** Ten year major ischaemic heart disease event rates by evidence of ischaemic heart disease on questionnaire (Q) at Q1 and Q5: men aged 45–59 years only

	N	Prevalence (%)	Mean age	Major IHD event rate*	Age-adjusted HR (95% CI)
Q1 (1978–80)					
Diagnosed MI	258	4.5	54.4	49.6	5.5 (4.4, 7.0)
Diagnosed angina	116	2.0	54.2	26.1	2.9 (1.9, 4.3)
Angina symptoms	295	5.1	53.1	17.0	2.0 (1.5, 2.7)
Possible MI symptoms	292	5.1	52.4	13.7	1.7 (1.2, 2.3)
No IHD on Q	4813	83.4	52.3	8.2	1.0
Total	5774	100	52.5	10.8	
Q5 (1983–85)					
Diagnosed MI	252	4.9	54.6	42.8	5.4 (4.2, 6.9)
Diagnosed angina	117	2.3	54.7	31.3	3.9 (2.6, 5.7)
Angina symptoms	257	5.0	53.4	15.0	2.0 (1.4, 2.9)
Possible MI symptoms	180	3.5	52.6	10.3	1.4 (0.9, 2.3)
No IHD on Q	4333	84.3	52.5	7.2	1.0
Total	5139	100	52.7	9.5	

For abbreviations, see Table 1.

\*Event rate/1000/year.

with ischaemic heart disease at baseline were halved in younger men, the relative increases in risk associated both with myocardial infarction, and with other ischaemic heart disease were very similar in the two age groups. The impact of stroke on event rates was evident only in the older age group, as stroke was very rare in younger men. Fifteen-year survival free of heart attack or stroke fell below 50% only among men aged 50–59 with myocardial infarction at baseline. The persistence of excess risk associated with myocardial infarction at baseline which has been described for the whole sample was apparent in both age groups.

#### *Outcome for ischaemic heart disease groups defined at the 5-year questionnaire*

Ischaemic heart disease groups were also defined from the 5-year questionnaire (Q5), in order to compare the

10 year outcome for these groups with the 10 year outcome for the baseline classification (Q1). As there was no ECG at Q5, the ECG categories (II and VI) were removed, with the other five groups remaining in the same hierarchical order. The comparison was restricted to men aged 45–59 at the time of each questionnaire, to give identical age distributions. Table 4 shows the similarity of 10 year ischaemic heart disease event rates and hazard ratios between the two classifications.

#### *Diagnosed myocardial infarction and angina: outcome from time of diagnosis*

As the biennial GP record reviews provided information on new diagnosed cardiovascular events from the time the study started, we were also able to compare the outcome of prevalent diagnosed myocardial infarction with the outcome of incident myocardial infarction for

28-day survivors. There were 198 confirmed non-fatal myocardial infarctions which occurred among the study subjects in the first 5-year period after the baseline examination. The subsequent prognosis for these 198 men from the date of infarction was much poorer than that for the 292 men with self-reported prevalent diagnosed infarction at baseline (group I). Five-year death rates (95% CI) were 23.2% (17.3, 29.1) and 13.4% (9.5, 17.3) for incident and prevalent infarction respectively, and 5 year rates of re-infarction (fatal or non-fatal) were 26.8% (20.6, 32.9) and 19.5% (15.0, 24.1). A similar comparison was made for angina. In this case, outcome for the 157 men with diagnosed angina (but without a history of myocardial infarction) ascertained from record reviews in the 5 years after baseline, was quite similar to outcome for the 123 men with prevalent diagnosed angina at baseline (group III). The 5-year death rates were 10.8% (6.0, 15.7) and 10.6% (5.1, 16.0) for 'incident' and prevalent angina respectively, and the corresponding 5-year infarction rates were 14.6% (9.1, 20.2) and 10.6% (5.1, 16.0). The mean age of incident and prevalent cases differed only by 1 year for both myocardial infarction and angina.

## Discussion

This paper has examined the long-term outcome of differing manifestations of pre-existing ischaemic heart disease ascertained by questionnaire and electrocardiogram in a representative sample of middle-aged British men. The relative and absolute risks of cardiovascular events and death which are associated with various manifestations of disease have been presented. Ischaemic heart disease outcome for the baseline classification has been compared with outcome for the classification defined 5 years later, and differences in outcome between prevalent and incident disease have been considered. A separate report will focus on the influence of risk factors on prognosis among men with different forms of ischaemic heart disease.

### *Validity of diagnostic categories*

It is a limitation of this study that subject reported ischaemic heart disease diagnoses were not confirmed at baseline. However subsequent validation studies for diagnosed angina and myocardial infarction have shown substantial agreement between subject report and medical record<sup>[29,30]</sup>. Nevertheless, some underestimation of event rates in groups I and III is possible. Of the 292 men reporting doctor-diagnosed myocardial infarction in this study (group I), 88% had either a history of typical symptoms or unequivocal ECG evidence of infarction at baseline. Of all 252 men reporting diagnosed angina (from groups I to III) just under half (49%) were recorded to be taking nitrates at baseline, and 75% reported exertional chest pain at that time. It is also

possible that group II (unrecognized myocardial infarction) may include some cases of unreported but diagnosed myocardial infarction. However of these 135 men, only 19 (14%) reported previous severe chest pain, with 77 (57%) reporting no chest pain symptoms of any description, suggesting that the vast majority had atypical symptoms or 'silent' infarction. Evidence of the validity of our definition for angina symptoms on questionnaire (any exertional chest pain) has been presented previously from this<sup>[25,31]</sup> and other<sup>[32,33]</sup> studies; use of a definition requiring additional WHO criteria gave lower prevalence but very similar risk estimates. The similarity of the results from the administered and postal questionnaires gives evidence of the reproducibility of risk estimates associated with questionnaire ischaemic heart disease groups, as any changes in long-term prognosis of prevalent ischaemic heart disease over this 5-year period due to secular trends are likely to have been small.

Although several different orderings of diagnostic categories are possible, the current grouping was used in order to place those with irreversible myocardial damage first in the hierarchy. In this way the two angina groups were free of men with evidence of definite myocardial infarction, but contained men with evidence of possible infarction (from either symptoms or ECG.) This ensures comparability with other studies which have tended to exclude only men with definite myocardial infarction from angina cohorts.

### *Prevalent and incident ischaemic heart disease*

By defining categories of ischaemic heart disease at the baseline examination, this study is concerned with prevalent ischaemic heart disease, which may have been present for a number of years. Clearly, the men in this study with pre-existing myocardial infarction had survived the initial and most hazardous period of their illness, and their rates of death and re-infarction will be considerably lower than rates measured from the time of event or for 28 day survivors. It is more difficult to study the natural history of angina from the time of onset due to the less acute nature of the condition: people experiencing exertional chest pain may not seek medical help immediately, if at all. Differences in results from 'incident' and 'prevalent' studies are considered further below. Information from both types of studies is necessary for an overall picture of the natural history of disease.

### *Clinically recognized myocardial infarction*

There is extensive literature on prognosis after myocardial infarction. Many studies are based on hospital case series<sup>[2-5]</sup>, but several have attempted to include all cases occurring in the community<sup>[12,34,35]</sup>. Comparison is made difficult by the differing age inclusion criteria, but

most studies excluded elderly men or provided age-specific rates. Mortality in the first month is reported from community studies to be up to 40%<sup>[12,34,35]</sup>. For those surviving 28 days, community-based studies and studies based on hospital discharges show strong agreement, giving estimates for 5-year mortality of around 30%<sup>[2,4,5,12,34–36]</sup> for men up to 60 or 70 years of age. A meta-analysis based on studies prior to 1980 concluded that, in contrast to in-hospital mortality, this estimate of 5 year mortality had not changed greatly over time.<sup>[36]</sup> More recent studies, however, have shown improvements in longer-term survival after myocardial infarction.<sup>[37,38]</sup> Our study gave an estimate of 23% for the 5-year death rate of 28-day survivors of myocardial infarction for events which occurred between 1978 and 1985. For those surviving the first few years, after myocardial infarction the outlook improves again<sup>[4]</sup>. The Reykjavik Study<sup>[14]</sup> reported 5 and 10-year CHD death rates of about 11 and 22%, for 129 men with a history of definite symptomatic infarction (conforming to WHO criteria) and age-standardization of rates to a mean age of 50.7. These results are similar to our study, for which 5 and 10-year CHD death rates (standardized to a mean age of 50.2) were 7.7 and 20.0% for men reporting prevalent diagnosed myocardial infarction, and 5 and 10 year total death rates were 11.6 and 26.8%. Many studies have shown that although absolute mortality increases with age among men with myocardial infarction, relative mortality does not, and we also found this to be the case.

### Angina

The earliest studies which aimed to identify all new angina cases arising in the population (rather than using hospital cases series) for long-term follow-up were Framingham<sup>[11]</sup> and the Health Insurance Plan Study<sup>[6]</sup> (HIP), although the HIP only included subjects seeking medical care. Results from these two studies were similar: middle-aged men with uncomplicated angina (no history of myocardial infarction) defined by structured clinical interview had a 5-year death rate of 15–20% and an infarction rate of 4–5% per year; a prognosis found to be similar to that of myocardial infarction. This is a much poorer outlook than suggested by our study and by two other more recent population studies of prevalent cases: the Gothenburg based study<sup>[13]</sup> and the Reykjavik<sup>[14]</sup> study, both of which used combinations of the WHO (Rose) questionnaire and clinical assessment to ascertain angina. In these studies, men with uncomplicated angina experienced 15–20% mortality in 10 years, the infarction rate was 1.8% per year (Gothenburg study), and the presence of myocardial infarction had a profound effect on event rates. Results for our study were almost identical: an 19% 10-year death rate and an infarction rate of 1.7% per year for men with uncomplicated angina (groups III and IV combined) of a similar mean age (about 52 years). The large differences in estimated survival between these three studies on the one hand and the earlier Framingham and HIP studies on

the other may reflect a change in angina prognosis over 20 years, but is also likely to be due to more exclusive selection criteria, older average age, and attempt to monitor prognosis from a time closer to the onset of symptoms in the earlier studies. In our study, no major difference in outcome was apparent between prevalent and 'incident' diagnosed angina cases. However for 'incident' cases, follow-up started from the date on which angina was documented in the medical records, rather than the date on which symptoms started or the subject sought medical help.

### Unrecognized myocardial infarction

Many studies have reported a relatively high prevalence of myocardial infarction discovered on ECG for which there is no corresponding clinical history or typical symptoms. Occurrence of 'unrecognized' infarction is likely always to be underestimated, as electrocardiographic changes can disappear with time. In common with other studies, we found that one third of infarctions were unrecognized (range 20–40% from previous studies<sup>[14,39–42]</sup>), about half of those appeared to be 'silent'<sup>[39,40]</sup> and angina was much less common among men with unrecognized compared to recognized infarction<sup>[39,43]</sup>. All studies have shown that men with unrecognized infarction have substantially increased coronary risk. However, studies disagree regarding the prognosis of unrecognized compared to recognized infarction. The Framingham<sup>[39,41]</sup> and Honolulu<sup>[42]</sup> studies (using serial comparison of ECGs to identify unrecognized infarction) and the Reykjavik study<sup>[14,43]</sup> (using a single ECG assessment) reported an outlook for men with unrecognized infarction at least as poor as that of men with recognized infarction. Our results were similar to the Israeli Heart Attack Study<sup>[40]</sup>, which found a better prognosis for men with unrecognized compared to recognized infarction. As the early mortality from myocardial infarction is so substantial, and as the event date for an unrecognized infarction is not known, differences between study results may reflect different 'starting points' from which outcome is monitored for two infarction groups. In agreement with other studies<sup>[44]</sup>, we found 'silent' ischaemic changes short of definite infarction (group VI) to be associated with moderately increased risk, particularly of cardiovascular mortality.

### Persistence of risk

Some attenuation of relative risk as follow-up lengthens is usual for many factors, due to individuals changing status over time, measurement error and selective mortality. For the ischaemic heart disease classification, this attenuation was considerable. However, the persistence into the last 5 years of follow-up of greatly increased risk for men with myocardial infarction compared those without ischaemic heart disease was evident in both

younger and older men. Although survivors of myocardial infarction do experience a decline in relative risk over time, and interventions can certainly improve prognosis for this group, these data suggest that a high excess risk persists in the long-term, even for those who remain event free for many years after their initial attack. This appears consistent with the permanent myocardial damage sustained by those who have suffered a definite infarction.

### *Risk stratification among men with evidence of ischaemic heart disease*

With major event rates among middle-aged men with evidence of ischaemic heart disease on questionnaire and ECG estimated to range from less than 1% to over 5% per year, reliance should not be placed on crude classifications in prevention guidelines. The two groups with the highest short-term risk (I and III) — which differ in risk by a factor of two — are known to their doctors. However middle-aged men with unrecognized myocardial infarction are also at high long-term risk. The prevalence of this condition may not be considered high enough to justify population screening, but the event rates of 2–3% per year found in this study, and the higher rates found in other studies, suggest that this group would benefit from secondary prevention<sup>[15]</sup>, although no intervention trials have been conducted specifically to examine this. Several studies have concluded that men who already have adverse risk profiles should have frequent ECG monitoring<sup>[39,41–43]</sup>.

Recommendations for the use of chest pain questionnaires to identify men with symptoms for investigation and prevention<sup>[33]</sup> can be misleading when based on risk estimates which ignore pre-existing diagnosis of ischaemic heart disease. In this study, once this diagnosed subgroup were excluded, the remainder of middle-aged men with ischaemic heart disease symptoms on questionnaire had ischaemic heart disease event rates of less than 2% per year, reaching 2% only if the combination of angina and possible infarction symptoms were present. It is also important to note the strong influence that age will exert if ischaemic heart disease management policy is based on estimates of absolute coronary risk. Even among middle-aged men in this study, ten-year ischaemic heart disease event rates for those with any evidence of ischaemic heart disease (groups I–VI) ranged from 6.0/1000/year for men aged 40–44 to 26.5/1000/year for men aged 55–59. Haq *et al.*<sup>[21]</sup> reported that men aged under 52 who are free of vascular disease are unlikely to reach coronary death risks of more than 1.5% per year irrespective of risk factors; this may also hold true for men of this age with evidence of vascular disease short of definite myocardial infarction.

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