ABSTRACT

Aim: To compare prognosis for patients with a diagnosis of angina alone to patients postacute myocardial infarction (AMI) and/or revascularisation and/or angina.

Design: Community-based retrospective cohort study.

Setting: A random selection of 37 Irish general practices.

Participants: 1,609 adults with ischaemic heart disease (IHD) identified in 2000/1.

Intervention: Medical records searches and postal questionnaires in 2000/1 and 2005/6.

Outcome measures: Primary: all-cause and IHD-related mortality. Secondary: acute myocardial infarction (AMI), cardiac artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA); physical and mental health status as measured by SF36 and SF12; process of care measurements and behavioural risk factor outcomes.

Results: Compared with patients with previous AMI and/or revascularisation, patients with angina alone had slightly lower risks of all-cause and IHD-related death; however, although hazard ratios of 0.73 (95% CI 0.55 to 0.98) and 0.65 (95% CI 0.44 to 0.98), respectively, were significant at the p<0.05 level, they were not significant at the p<0.01 level currently suggested as appropriate in observational research. Proportional hazards models identified no statistically significant differences in adjusted risks of subsequent AMI, CABG or PTCA between patients with angina-alone and those with other IHD. Over the 4.5-year follow-up, physical functioning was consistently lower among those with angina alone, and the extent to which physical functioning was increasingly impaired was slightly greater.

Conclusions: Prognosis to death or cardiac outcomes for patients with angina-alone was similar to those with previous AMI and/or revascularisation, while health status was poorer. The clinical importance of angina should not be underestimated in primary care. Further descriptive research is needed among representative community cohorts of people with angina.

The personal, clinical and societal burden of ischaemic heart disease (IHD) and the importance of its secondary prevention are well established. Yet, while the prognostic significance of previous acute myocardial infarction (AMI) is widely recognised, the position of angina pectoris in the IHD spectrum is less well understood. Angina is increasingly being diagnosed in primary care, and the growing elderly population is likely to result in an increased prevalence in the community. A recent systematic review highlighted that the primary care angina population has received relatively little attention from researchers. There is some evidence that a degree of inequity may exist in the provision of secondary preventive care to those with angina alone compared with those with other manifestations of IHD.

Underestimation of the importance of angina has been fuelled both by the success of revascularisation in providing symptomatic relief in the short term and by the results of recent trials of medical treatments which appear to reduce adverse outcomes to normal levels. In truth, the prognosis of angina in the community is largely unknown: an association between survival benefit and revascularisation has not been demonstrated, while evidence on the effectiveness of medical management was established by trials in largely white male populations identified in secondary or tertiary care settings and may not be generalisable to the Primary Care population.

Understanding the prognosis of angina is of importance to clinicians working in primary care. Yet, relatively few prognostic studies have been conducted in primary care populations, and of those that have, most are old, small and of poor quality, leading authors to comment that the prognosis of angina in primary care remains a key question. And descriptions of prognosis derived from populations identified in secondary or tertiary care settings may not be appropriate: the effect of patient selection for referral to secondary care means that these populations may typically have more serious disease or may be referred at an early and more acute stage of their illness when their prognosis is at its worst.

Large epidemiological studies in primary care settings with carefully defined and measured start- and end-points are needed in order to address this issue. Several factors have been identified which have serious implications for the current understanding of angina: the lack of studies in unselected populations; the lack of studies with longitudinal data on patients from early- to late-stage disease; varying standards for defining and reporting the various conditions which come under the term “stable angina”; lack of data on a full spectrum of possible outcomes such as AMI, CABG, PTCA and functional status as opposed to simply mortality. We present data on a large 5-year follow-up cohort study of an unselected primary care population with a comprehensive array of outcomes.
METHODS

CoHeart study

The CoHeart study was a 5-year follow-up of a cohort of 1609 people with IHD in 37 general practices in the west and northwest of Ireland. Data were collected from a search of general practice medical records and patient questionnaire at baseline and follow-up. Practices were randomised and stratified for rural or urban location and for single-handed or partnership status (four rural and 12 urban partnerships, eight rural and 13 urban single-handed). The cohort was established in 2000–2001 and presented a valuable opportunity to conduct a follow-up study of the secondary prevention of IHD among a representative community cohort. General practitioners were asked to identify all patients with established IHD in their care. IHD was defined as a history of previous AMI, angina pectoris, CABG or PTCA. A diagnosis of angina only was based on records maintained in general practice, which included hospital and practice-based diagnostic investigations. Previous research has shown the accuracy of data recorded in general practice to be high. Analysis of all our patients with angina showed that angiography was recorded for 37.4%, stress electrocardiography (ECG) for 52.2% and resting ECG for 89.7%. Diagnostic categories in angina were therefore pragmatic and reflected primary care clinical decision-making. The baseline patient questionnaire was more onerous than that used at follow-up because of its focus on attitudes to medication and healthcare, and consequently patients were excluded from participation if they were over 80 years of age, affected by serious comorbidity or considered by their GP to be terminally ill. Mortality data were collected at follow-up and confirmed by the use of death certificates through the Irish Central Register Office. Retrospective data on demographics, process of care, medication, health-related behaviour, risk factors and morbidity were collected from a chart search conducted by specifically trained research nurses at baseline and again at follow-up. At both baseline and follow-up, patient questionnaires were sent to participants seeking information on health status (using the SF36 and SF12 questionnaire) and health-related lifestyle. The cohort study is reported in accordance with the recommendations of the STROBE guidelines for the reporting of observational research.

Diagnostic categories

Underestimation of the clinical importance of angina, lack of prognostic research among the primary care angina population and inequity in service provision and investigation between those with angina alone versus those with other or additional manifestations of IHD have been referred to by other researchers (Delaney E, Campbell NC. Coronary deaths have been identified as a list of conditions coded by Information and Statistics Division, Scotland, personal correspondence 27 June 2006). Our aim was to consider whether a diagnosis of angina aloneconfers a more benign prognosis than “more serious” IHD. Therefore, the cohort was divided into two subgroups: those who had “angina alone” at baseline and those who had “other IHD.” This latter group included those with a history of previous AMI and/or revascularisation and those who had angina as well as previous AMI and/or revascularisation.

Data sources, measurement and statistical analysis

Main outcome measures were all-cause and IHD mortality. IHD death was defined as deaths where IHD or cardiovascular disease (AMI, acute IHD, chronic IHD, coronary atherosclerosis, left ventricular heart failure, congestive heart failure, unstable angina pectoris, ischaemic heart disease and complications, stable or unstable angina, ischaemic cardiomyopathy) (Delaney E, Campbell NC. Coronary deaths have been identified as a list of conditions coded by Information and Statistics Division, Scotland, personal correspondence 27 June 2006) was included as either a primary or contributing factor on the death certificate, but not if included only as a coexisting morbidity. Secondary outcomes were AMI, PTCA and/or CABG since baseline and health status. Health status was measured using the SF36 questionnaire at baseline and SF12 at follow-up. This change in instruments was due to a need for consistency with a concurrent IHD study at follow-up. Studies have indicated that there exists very considerable compatibility between SF36 and SF12, especially if the key scores to be considered are the two summary measures, the Physical Component Summary (PCS) and Mental Component Summary (MCS) scales. Dichotomous health status outcome variables were created which recorded either stable or increased PCS and MCS scores (indicating stable or improving physical or mental health status respectively) or reduced scores (indicating reduced status).

Independent variables included in analysis were age (in years), sex, rurality (whether the practice was in a rural or urban area), deprivation, coexisting diabetes (type I or II) and prescription of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or statins. Reliable data on aspirin use were judged not to be available because of the low cost of the drug and the consequent tendency to self-medicate rather than pay or attend surgery for prescriptions. Demographic and clinical data were extracted from GP records. Deprivation was measured by eligibility or ineligibility for free General Medical Services (GMS) within the Irish health system—at the time of the follow-up study just under 40% of the population in the area in which the study was based were GMS-eligible, representing the least affluent members of society.

Data analysis was performed using SPSS 14.0 for Windows. The Student t test was used to compare the distribution of continuous variables between angina-only and AMI and/or revascularisation subgroups. χ² tests compared the distribution of dichotomous categorical variables. Multiple logistic regression was used to consider the predictive effect of angina-only status, adjusted for confounding by other variables, in relation to dichotomous outcome variables. Kaplan–Meier and logrank tests and Cox proportional hazards modelling were employed to compare survival between angina-only and AMI and/or revascularisation subgroups, controlling for covariates including gender, age, rurality, GMS eligibility, diabetes, prescription of beta blockers, ACE inhibitors or lipid-lowering drugs at baseline. Time was measured from the patient’s date of baseline data collection to the time of outcome event. In all analyses, a value of p ≤ 0.01 was selected to denote significance. This is in line with recent recommendations and practice in observational research, in which the effect of unmeasured variables is not countered by the effect of randomisation.

Ethical approval for the study

Ethical approval for both baseline and follow-up studies was granted by the Irish College of General Practitioners.

RESULTS

Cohort

Figure 1 illustrates the study process. At baseline data collection in 2000/1, 1609 eligible patients were identified for inclusion,
3.16% (95% CI 2.86 to 3.62) of the total practice population. At follow-up in 2005/6, charts were located and searched for 1592 (98.9%). The average length of follow-up was 4.5 years. Patient questionnaires were returned by 68.7% at baseline and 69.0% at follow-up, which is acceptable in an elderly population in Primary Care. At baseline, the cohort (n = 1609) was 65.4% (n = 1053) male; at follow-up 65.7% male (n = 909). The mean age of men was 64.6 years (SD 8.98) at baseline, 69.1 (SD 8.99) at follow-up. The mean age of women was 68.2 (SD 8.92) at baseline, 72.6 (SD 9.05) at follow-up. The cohort was 100% white.

Diagnostic categories
At baseline 38.3% of patients (n = 616) developed angina alone, while 61.7% had other IHD. At follow-up, these figures were 38.7% (n = 535) and 61.3% (n = 849) respectively. Demographic and other data relating to the two subgroups are presented in table 1.

At both baseline and follow-up those with angina alone were more likely to be female and slightly older. A date of first IHD diagnosis was sought at baseline and identified for 99.6% of the cohort (n = 1603). The time in years between first IHD diagnosis and baseline data collection was calculated. Those with angina alone were likely to have been diagnosed more recently than those with other IHD. At baseline, univariate analysis and multiple logistic regression (controlling for demographic risk factors, diabetes and prescribing covariates) considered whether angina-only diagnostic status affected the likelihood of appropriate secondary preventive measures and identified significant negative associations between angina-only diagnostic status and prescription of ACE inhibitors and lipid-lowering drugs, OR 0.63 (0.47 to 0.86) and OR 0.55 (0.43 to 0.71), respectively. At follow-up, a similar analysis by multiple logistic regression identified no significant associations (table 2).

Survival: angina alone versus other IHD
Primary outcomes
Cox proportional hazards models were fitted to calculate the predictive value of angina-only status for all-cause death and IHD death controlling for gender, age, rurality, GMS eligibility, diabetes, prescription of beta blockers, ACE inhibitors or lipid-lowering drugs at baseline. The results are summarised in table 3. Compared with those patients who had other IHD, patients with angina alone had a reduced risk of all-cause death and IHD-related death, with hazard ratios of 0.73 (95% CI 0.55 to 0.98) and 0.65 (0.44 to 0.98), respectively. Although statistically significant at the p < 0.05 level (p = 0.035 and 0.038, respectively), these differences were not significant at the p < 0.01 level suggested as appropriate for observational research.13

Secondary outcomes
Results of Cox proportional hazards analysis for AMI, CABG and PTCA are summarised in table 4. No significant difference was detected between those patients with other IHD and those with angina alone in terms of any of these outcomes. Nor did angina-only status appear to confer any benefit in terms of health status as measured by the SF12 questionnaire: no significant association was determined in logistic regression analysis between angina-only status and stable or improved SF12 PCS and MCS scores.

Health status data were available at both baseline and follow-up for 724 of the cohort. Analysis at follow-up revealed no significant differences between questionnaire respondents and non-respondents. The mean (SD) PCS and MCS scores for those with angina alone and with other IHD are presented in table 5. The Student t test suggested that a diagnosis of angina alone was associated with significantly worse Physical Component Summary scores than was other IHD at both baseline and follow-up, with a slightly larger decrease in physical functioning over 4.5 years. No significant difference was detected between those with angina alone and those with other IHD in terms of Mental Component Summary scores and changes over 4.5 year were slight. Logistic regression, controlling for gender, age, deprivation, rurality, diabetes and prescribing, identified only one baseline variable as being significantly associated with improved or worsened PCS or MCS scores at follow-up: baseline prescription of beta blockers was positively associated with improved PCS at follow-up, OR 1.51 (1.11 to 2.00). No significant difference was identified between prescribing of beta blockers to those with angina alone or with other IHD at baseline or follow-up (tables 1, 2).

DISCUSSION
Main findings
Recent commentators have questioned unproven perceptions that current treatments for angina confer upon patients with
angina alone a more benign prognosis than those with “more dramatic” ischaemic heart disease and have suggested that observational research in Primary Care may shed some much needed light on the area. This study recorded a wide range of data among a large representative Primary Care cohort and was able to compare those with angina alone with those with other IHD. Whereas previous research has indicated that risk of all-cause or IHD death is increased twofold or threefold among those with previous AMI, this study among a representative, elderly Primary Care IHD population identified differences in prognosis which are much less striking. Controlling for baseline demographic, comorbidity and process of care factors, the differences in survival to IHD or all-cause death between patients with angina alone and those with other IHD were barely significant at the conventional 0.05 level and non-significant at the 0.01 level.

The implications must be considered of applying the same 0.05 (5%) measure of significance in observational research as has come to be accepted in experimental research. Observational research does not benefit from the added validity that randomisation can bestow, and it has been argued that more rigorous standards of statistical significance should there be applied to observational research, with a significance level of 0.01 and more robust risk ratios of effect outcome to enable to be applied to observational research, with a significance level of 0.01 and more robust risk ratios of effect outcome to natural outcome being suggested as appropriate. This more rigorous significance level of 0.01 has been adopted in other recent IHD research. For other IHD events, health status and process of care at follow-up, no significant differences were identified. Our findings support recent research which has similarly identified a poor prognosis for patients with incident angina, none with a history of AMI, who had been referred to rapid-access chest-pain clinics.

Strengths and limitations

In the reporting of cohort studies, the acknowledgement of limitations and the identification of possible sources of confounding are of great importance. The highly selected nature of populations included in trials has been identified as a problem affecting the evidence base for prognosis in angina, and a strength of this study is that it represents in so far as was practical or appropriate an entire primary care IHD population from 57 general practices. Practices were asked to identify every patient with IHD, and individuals were only excluded from the baseline cross-sectional study if they were deemed too elderly or ill to complete that study. The 3.16% identified practice prevalence and the profile of the study population in terms of gender and age are broadly in line with other UK and Irish prevalence studies, and suggests that the case-finding strategy adopted was effective. Ascertainment bias is a potential confounder in this study of patients with IHD because those with angina only may be more likely to remain unidentified by general practitioners than those with previous AMI, CABG or PTCA. As a result of the potential absence from the cohort of those with less symptomatic angina alone or those who delay help-seeking, it is possible that the likelihood of serious outcomes in the angina-only group has

<table>
<thead>
<tr>
<th>Variable</th>
<th>Angina only</th>
<th>Other ischaemic heart disease</th>
<th>( \chi^2 ) or t value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M), baseline</td>
<td>49.5%</td>
<td>75.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (M), follow-up</td>
<td>48.6%</td>
<td>78.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, baseline</td>
<td>67.2 (9.01)</td>
<td>65.0 (9.09)</td>
<td>4.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age, follow-up</td>
<td>70.8 (9.22)</td>
<td>68.7 (9.08)</td>
<td>4.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rural location, baseline</td>
<td>21.1%</td>
<td>23.6%</td>
<td>1.32</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, baseline</td>
<td>11.5%</td>
<td>10.9%</td>
<td>0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Years since diagnosis, baseline</td>
<td>5.6 (5.3)</td>
<td>7.1 (6.1)</td>
<td>4.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Beta blockers, baseline</td>
<td>46.5%</td>
<td>46.2%</td>
<td>0.017</td>
<td>NS</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors, baseline</td>
<td>19.7%</td>
<td>27.8%</td>
<td>13.34</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lipid-lowering drugs, baseline</td>
<td>36.9%</td>
<td>53.5%</td>
<td>41.30</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 2 Predictive effect of baseline angina-only status (controlling for covariates*) in relation to process of care and clinical/behavioural risk-factor-dependent variables at baseline and follow-up—summary of multiple regression analyses

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Adjusted odds ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At baseline</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>1.11 (0.86 to 1.43)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>0.63 (0.47 to 0.86)†</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>0.55 (0.43 to 0.71)†</td>
</tr>
<tr>
<td>Last blood pressure &lt;140/90</td>
<td>0.94 (0.57 to 0.97)</td>
</tr>
<tr>
<td>Cholesterol &lt; 5.0</td>
<td>1.06 (0.82 to 1.38)</td>
</tr>
<tr>
<td>Adequate exercise</td>
<td>0.74 (0.52 to 1.05)</td>
</tr>
<tr>
<td>Low-fat diet</td>
<td>0.90 (0.66 to 1.23)</td>
</tr>
<tr>
<td>High-fibre diet</td>
<td>0.93 (0.68 to 1.27)</td>
</tr>
</tbody>
</table>

*Controlling for gender, age, deprivation, rurality, baseline prescription of beta blockers, angiotensin-converting enzyme inhibitors, lipid-lowering drugs, diabetes, total cholesterol and blood pressure within guidelines at baseline.
†p < 0.01.
been overestimated. On the other hand, one way in which a prevalent cohort differs from an incident cohort is that it may not include patients whose IHD was short-lived and terminal: estimates of survival may therefore be more optimistic than would be the case if such patients were included. A limitation in our study is the absence of any measurement of the severity of disease in individuals. Likewise, the variable diagnostic standards for angina are a limitation, although this reflects clinical reality in primary care where clinicians must manage the broad spectrum of conditions which are referred to as angina. The data for this study were collected from medical records in general practice or self-reported by participants, which may have introduced information bias. However, previous research has shown the accuracy of data recorded in general practice to be very high.9,10,21 And while the accuracy of self-reported patient data can be questioned, consistency between baseline and follow-up questionnaire data suggests either an encouraging degree of honesty in patient responses or a very consistent degree of duplicity.

The comparison of two SF health status questionnaires may have presented a limitation, yet very considerable compatibility between the PCS and MCS scales of the SF36 and SF12 has been established in previous research.22 An alternative strategy would be the use of raw baseline SF-36 data to synthesise SF-12 scores for comparison with follow-up data. This strategy was tested for a portion of the data, and synthesised mean and summary baseline SF-12 scores were virtually identical to mean and summarised SF-36 scores, so it was decided that a direct comparison of SF-36 baseline and SF-12 follow-up data was acceptable.

Losses to follow-up are a potentially crucial source of information bias in a cohort study. Ethical approval for the research, which recognised the value of the opportunity to generate prognostic data in a large community-based cohort in an important clinical area, enabled the collection of medical-record data from patients who did not return a questionnaire or who had moved from the practice. The risk of information bias resulting from losses to follow-up (of 1.2%) was thus minimised.

Our study in the context of previous research

The current study recorded data on a wider range of outcomes than has often been the case previously.7 Thus, it was possible to consider survival and prognosis in terms of not only all-cause or IHD-related death, but also subsequent AMI, CABG and PTCA, health status and secondary prevention treatments.

Previously published research has indicated a reduced risk of mortality in IHD patients with a diagnosis of "angina alone" compared with post-AMI and post-revascularisation patients.22–25 For example, compared with men with no IHD, Rosengren reported the risk of IHD death in men with an initial diagnosis of angina, as determined by proportional hazards modelling, to be 2.60 (2.04 to 3.31) and with previous AMI to be 6.67 (5.29 to 8.39); the risk of all-cause death in these groups was reported as 1.63 (1.38 to 1.83) and 3.20 (2.67 to 3.83), respectively. However, in the current study—controlling for gender, age, rurality, GMS eligibility, diabetes and prescription of beta blockers, ACE inhibitors or lipid-lowering drugs at baseline, and accepting a significance level of 0.01—reduced risk of both all-cause and IHD-related deaths associated with angina-only status was not significant. Significance levels were not reported by Rosengren, but the confidence intervals for risk of mortality are clearly more robust than those identified in our analysis.

Neither was any significant difference in survival to AMI, CABG or PTCA or change in physical or mental health status identified between the angina only subgroup and the AMI and/or revascularisation subgroup. Comparison with previous research is not simple, however, not only because of the paucity of published research among primary-care angina populations, but also because the reported analysis has often concentrated on prognostic differences by gender rather than diagnostic status, or because the populations featured have differed: Rosengren’s study included only men, and these had a much younger baseline age (51–59 years). There is a paucity of data relating to functional health status in people with angina in primary care. It is of interest, therefore, to note that mean physical functioning as measured by the SF36 and SF12 questionnaires was consistently lower among those with angina alone and that over the 4.5-year follow-up period, the extent to which mean physical functioning became increasingly impaired was slightly larger.

Our study would appear to support concerns recently expressed that the importance of angina—the most common initial manifestation of ischaemic heart disease—has been increasingly misunderstood as a result of recent large trials which have demonstrated the effectiveness of medical
Other ischaemic heart disease 449 49.20 10.80 49.76 12.10
Angina only 275 48.75 11.04 0.59 48.62 10.30 0.19

Mental Component Summary score
Other ischaemic heart disease 449 42.00 8.95 40.31 11.21

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