Selection bias in the management of unstable angina

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ABSTRACT - Objectives: To examine the criteria for selecting patients presenting with unstable angina for cardiac catheterisation and to assess the extent to which these criteria successfully incorporate high risk groups.

Methods and results: This was a prospective cohort study of 517 patients admitted with unstable angina with 12 months follow-up; 139 patients (26.9%) had cardiac catheterisation 32 days or longer after presentation. The odds of early catheterisation were increased by regional ST segment depression on the presenting ECG (odds ratio (OR) 1.70, 95% confidence intervals (CI) 1.01–2.87) and ongoing ischaemic chest pain more than 12 hours after admission (OR 9.72, CI 6.10–15.49), and reduced by age over 65 years (OR 0.56, 95% CI 0.35–0.90) and heart failure (OR 0.26, CI 0.11–0.64). The 12-month rates of myocardial infarction (MI) or death were 8.6% and 17.7% (p = 0.01) in patients who were and were not referred for early cardiac catheterisation, respectively. Survival analysis showed that the odds of MI and death in the first 12 months were increased substantially by heart failure (OR 2.82, 95% CI 1.53–5.20) and age over 65 (OR 1.91, 95% CI 1.13–3.23).

Conclusion: Selection for early cardiac catheterisation in this unstable angina population was largely ischaemia-driven, based on ongoing chest pain and ST segment depression. This policy was associated with a low event rate in the ischaemic group, but it failed to target elderly patients and those with heart failure who were at greatest risk of MI and death during the first year.

Anti-ischaemic and anti-thrombotic drugs provide the mainstay of treatment of unstable angina. They are usually effective in controlling symptoms and protecting against progression to myocardial infarction (MI). Uncontrolled ischaemia in unstable angina identifies a group at risk of future events1–3, which has led to calls for an ischaemia-driven approach to invasive management although whether this reduces risk is not clear4. Studies currently in progress may help resolve this question but, in the absence of clear information on which to base catheterisation decisions, many centres will continue to take a pragmatic view and favour selection of patients in whom ongoing ischaemic symptoms prohibit discharge from hospital.

The present study has examined the management pathway and outcome in a large group of patients with unstable angina, paying particular attention to documenting the criteria used clinically for selecting patients for cardiac catheterisation and the extent to which these criteria successfully incorporate high risk groups.

Methods

Patients

We prospectively identified 553 consecutive patients with an admission diagnosis of Braunwald class 3B unstable angina (cardiac chest pain at rest within the preceding 48 hours that was not attributable to non-cardiac causes5) between January 1995 and December 1997. None fulfilled ST or enzymatic criteria for MI based on serial ECGs and creatine kinase analyses during the first 36 hours5. The 517 (93.5%) of the 553 patients who suffered a hard event (MI or died) during the next 12 months, or completed 365 days of event free follow up, comprised the study group.

Setting

The study was undertaken at an inner city district general hospital without on-site cardiac catheterisation facilities. All patients requiring coronary angiography were studied at The London Chest Hospital.

Data collection

Demographic, clinical and ECG data were collected prospectively by a cardiologist and stored on a purpose-built electronic database. Treatment with aspirin, heparin and anti-anginal drugs was recorded. Patients in whom chest pain failed to settle within 12 hours of admission despite medical treatment, or in whom recurrent episodes of chest pain occurred after that time, were recorded as having 'ongoing chest pain'. The first ECG recorded on arrival in the Accident and Emergency department was defined as the 'admission ECG'. Regional ST depression (≥1 mm planar or downsloping) or T wave inversion was recorded if present in at least one standard or two or more contiguous chest leads. The subsequent development or resolution of these changes on later ECG recordings were defined as 'labile' ST or T wave changes. Heart failure was diagnosed in patients

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requiring diuretic therapy who had radiological signs of interstitial or alveolar pulmonary oedema, or symptoms of breathlessness accompanied by basal crepitations and/or a third heart sound. Diabetes was recorded in patients on insulin, oral hypoglycaemic drugs or dietary restriction. Hypertension was recorded in patients taking antihypertensive drugs. Current smokers were classified as smokers, while ex-smokers and non-smokers were grouped as non-smokers for the purpose of this study.

Follow-up

The purpose of the follow-up was to define time to cardiac catheterisation, MI and death during the first 12 months after admission. The patients were flagged by the Office for National Statistics to obtain follow-up mortality data. Information about non-fatal MI in patients known to be alive at 12 months, not already available from outpatient follow-up or hospital readmission, was obtained through postal questionnaires backed up by telephone inquiry for non-responders.

Statistical analysis

Survival curves were generated by the Kaplan-Meier method, and survival probabilities expressed as percentages with 95% confidence intervals (CI). Subgroups were compared using the log rank test. Comparison of discrete variables was by chi-squared analysis and continuous variables by the Mann-Whitney U-test. In order to evaluate their independent influence, variables believed to be of clinical or biological relevance were entered into a logistic regression analysis with cardiac catheterisation or hard events as the dependent variable. Improvements in model fit were based on comparison of likelihood ratios. Odds ratios (OR) are quoted together with 95% CIs.

Results

Early cardiac catheterisation (Tables 1 and 2)

Of the 517 unstable angina patients, 271 (52.5%) had cardiac catheterisation a median of 32 days (interquartile range 8–143) after presentation; 141 patients (27%) later underwent coronary angioplasty (n = 71) or coronary bypass surgery (n = 70). The 139 patients (26.9%) who had ‘early’ cardiac catheterisation (≤32 days after presentation) were younger and more likely to have regional ST segment depression than those in whom cardiac catheterisation was delayed or not performed. More significant were the increased frequency of ongoing chest pain more than 12 hours after admission and the reduced frequency of heart failure (and use of beta-blockers) in patients referred for early cardiac catheterisation. Multivariate analysis confirmed independent association of ischaemic variables with early cardiac catheterisation, particularly regional ST segment depression and ongoing chest pain, which increased the odds of referral by 70% and over 900%, respectively. Conversely, advanced age and heart failure reduced the odds of early cardiac catheterisation by less than 40% and 75%, respectively. The 12-month rates of MI or death were 8.6% in patients who were referred for early cardiac catheterisation and 17.7% (p = 0.01) in those who were not, reducing to 4.3% and 11.4% (p = 0.02) when analysis was confined to events occurring after 32 days.

Predischarge stress testing (Table 3)

Of the 508 patients who survived to leave hospital, 133 (26.2%) had a predischarge stress test. Multivariate analysis showed that a normal presenting ECG increased the odds of having a stress test by 74%. In patients aged over 65 the odds of having a stress test were reduced by 45% compared with patients below 65. Heart failure and ongoing chest pain also reduced the odds of a predischarge stress test by 70% and 47%, respectively. Of the 43 patients with inducible exertional ischaemia, 12 (27.9%) were referred for cardiac catheterisation within 32 days of admission, compared with five of 90 patients (5.6%) without inducible ischaemia (p = 0.0003).

Outcome (Table 4 and Fig 1)

Kaplan-Meier estimates of survival at 30 days, six months and one year were 96.5% (CI 94.9–98.1%), 91.3% (CI 88.8–93.7%) and 88.1% (CI 85.4–90.9%), respectively. Infarct-free survival was lower, falling to 84.7% (CI 81.6–87.8%) at one year. Subgroup analyses showed that outcome was substantially worse for patients with heart failure and those aged over 65, in whom infarct-free survival at one year was only 77.6% (CI 70.8–84.3%) and 79.4% (CI 74.3–84.4%), respectively. Outcome also tended to be worse in patients with ongoing chest pain and regional ST depression on the presenting ECG. Multivariate analysis (Table 5) confirmed that the odds of MI and death

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**Key Points**

- The likelihood of early cardiac catheterisation is increased by regional ST depression on the 12 lead ECG and by ongoing ischaemic chest pain more than 12 hours after admission.
- Age over 65 and the presence of heart failure substantially reduces the likelihood of early angiography and pre-discharge exercise testing.
- 12 month event rates are highest for those patients aged >65 and those with heart failure.
- Selecting patients for early angiography using an ischaemia driven policy is associated with a low event rate in the ischaemic group but fails to target the elderly and those in heart failure who are at the greatest risk.
in the first 12 months were increased nearly three times by heart failure, by 91% in patients aged over 65, and by 74% in patients with ongoing chest pain.

Discussion

This prospective analysis of management pathways in unstable angina has shown that decisions to refer for early cardiac catheterisation were driven largely by symptomatic or ECG evidence of ongoing myocardial ischaemia. This ischaemia-driven approach accorded in principle with local guidelines and resulted in early catheterisation rates closely similar to those reported from other UK centres, although lower than US rates. Paradoxically, however, patients with heart failure and those aged over 65 who were at greatest risk of MI and death in the first 12 months were those least likely to be selected for invasive management.

The medical management of unstable angina is aimed at relieving chest pain and protecting against recurrent ischaemic events, particularly MI and death. In the present study, neither of these aims was fully achieved by conventional treatment strategies. Thus, in common with previous investigators, we found that many patients remained unstable after hospital admission with ongoing ischaemic chest pain, whilst 15.3% went on to have MI or died in the first 12 months despite treatment with aspirin and heparin in nearly every case. Recognition of the inadequacies of conventional treatment strategies has stimulated debate about the role of interventional management. There is general agreement that ongoing ischaemic symptoms can usually be corrected by revascularisation and, as in many other units in this country, this was the major predictor of early referral for cardiac catheterisation in the present study. ECG evidence of ischaemia was also independently predictive of early referral, in accordance with recent recommendations for an ischaemia-driven approach to interventional management. Based largely on these ischaemic criteria, a quarter of our patients with unstable angina were referred for early cardiac catheterisation with a view to later revascularisation.

Application of this ischaemia-driven approach to patient selection for cardiac catheterisation satisfies the important
requirement to control symptoms in patients not responding to medical treatment. It may also identify a group at heightened risk of future events, although there is no clear evidence that an interventional strategy reduces the risk. Registry data in the Organisation to Assess Strategies for Ischaemic Syndromes (OASIS), for example, found that higher rates of invasive investigation and revascularisation were not associated with a better prognosis in terms of MI and death. Thus, while patients in our study who underwent early catheterisation had significantly lower event rates during the first year, this cannot necessarily be attributed to the intervention because selection bias provides an alternative and equally plausible explanation.

The importance of selection bias as an explanation for the better prognosis in the patients who had early cardiac catheterisation is emphasised by the finding that advanced age and heart failure were both independently associated with a conservative management strategy. Yet, as others have reported\textsuperscript{12,13}, these factors were closely associated with MI and death during the first year, the association being independent of ongoing symptomatic or ECG ischaemia. We have previously reported a tendency for elderly patients with acute MI to receive less aggressive management, and the data in the present study show that the same may apply to patients with unstable angina\textsuperscript{14}. Of course, this may be appropriate in individual cases, but systematic bias against the elderly will ensure that any benefits that may be attributable to the invasive management of unstable angina are obscured by the exclusion of this high risk group. Exclusion of patients with heart failure is likely to have a similar effect; they too are at high risk, yet represent a group for whom revascularisation may be associated with prognostic benefit, particularly when multivessel disease is present\textsuperscript{15}.

Predischarge stress testing has been recommended for risk stratification in unstable angina but, although an ischaemic response at low workload has been associated with an increased risk\textsuperscript{16}, the positive predictive value of an

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**Table 4. Event-free survival analysis for (1) all-cause mortality and (2) all-cause mortality and acute myocardial infarction (MI).**

| Survival | 30 days | 6 months | 1 year |
|----------|---------|----------|--------|
| %        | CI      | %        | CI     |
| 1 Survival (all cause) | 96.5 | 94.9−98.1 | 91.3 | 88.8−93.7 | 88.1 | 85.4−90.9 |
| 2 Survival without acute MI | 94.2 | 92.2−96.2 | 88.0 | 85.2−90.8 | 84.7 | 81.6−87.8 |

CI = confidence interval

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**Fig 1.** Kaplan-Meier survival curves in unstable angina showing the effects of (a) heart failure (lvf), (b) age, (c) ongoing chest pain, and (d) regional ST depression (presenting ECG) on survival without myocardial infarction during the first 12 months.
Table 5. Multivariate predictors of death and non-fatal myocardial infarction during first 12 months after admission (494 complete data sets).

|                        | Odds ratio | 95% CI      | p value |
|------------------------|------------|-------------|---------|
| Age group (years):<65  | 1          |             |         |
| Age group (years):>65  | 1.91       | 1.13-3.23   | 0.02    |
| Male sex               | 1.27       | 0.73-2.20   | NS      |
| Presenting ECG: ST depression | 1.27 | 0.73-2.20 | NS      |
| Ongoing chest pain     | 1.74       | 1.03-2.93   | 0.04    |
| (>12 h after admission) |            |             |         |
| Heart failure          | 2.82       | 1.53-5.20   | 0.009   |

CI = confidence interval

abnormal test is low; by analogy with post-infarction stress testing, this must limit its clinical value. It continues to be recommended, however, in patients at indeterminate risk, probably accounting for the observation that a normal ECG was the major baseline variable independently associated with a predischarge stress test in the present study. Only about a quarter of our patients underwent a stress test, those with inducible ischaemia being significantly more likely to have early cardiac catheterisation in accordance with ischaemia-driven recommendations. Patients with ongoing chest pain more than 12 hours after admission were significantly less likely to have a stress test, presumably because they were identified as a high risk group and many were already preselected for early cardiac catheterisation. Stress testing was also less likely in patients who were old or had heart failure. While in some cases this may have reflected an inability to exercise, it again emphasises the tendency for these high risk groups to receive less aggressive management.

This study has identified criteria used for selecting patients with unstable angina for interventional management. The data show that selection was largely ischaemia-driven and resulted in a catheterisation rate closely similar to that reported from other UK centres. It is clear, however, that an ischaemia-driven policy will not impact significantly on prognosis unless it successfully incorporates elderly patients and patients with heart failure who are at greatest risk during the first 12 months. This would require a change in prevailing attitudes, which in many centres will continue to be shaped by considerations of symptomatic status with preference given to younger patients and those without heart failure in whom revascularisation procedures carry a lower risk. The data emphasise the need to include elderly patients and patients with heart failure in trials of interventional management in unstable angina if the potential benefits are to be properly tested. The recently published Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC) II study, comparing invasive with non-invasive treatment in unstable angina, found a reduction in mortality at six months in those assigned to invasive management. The benefits were seen in all patient groups, with divergence of the survival curves occurring two weeks after admission. However, the median time to catheterisation in our cohort of patients was 32 days, whereas in FRISC II the patients assigned to the intervention arm were catheterised (and revascularised where appropriate) within 10 days. Limited resources make the implementation of such early intervention unrealistic for all patients presenting with unstable angina and ST depression and/or raised cardiac enzymes. In such a climate, this strategy may continue to be denied to those at greatest risk. Even in the FRISC II study, 282 patients out of an eligible 3,048 were excluded because of advanced age.

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