Managing high-risk patients with acute coronary syndromes: the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK)

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ABSTRACT – A study was carried out to find out whether more intense treatment (both medical and revascularisation) is targeted towards higher-risk patients with acute coronary syndromes. A prospective UK registry of patients admitted with non-ST elevation acute coronary syndromes was established to examine practice patterns and clinical outcomes with respect to the risk profile of the patients. Clinically important high-risk subgroups included the elderly, diabetics, those with heart failure and those with ST depression or bundle branch block on the presenting ECG. Elderly patients were less likely to receive evidence-based treatments, including beta blockers, statins and revascularisation. Diabetics received more revascularisation procedures but the overall revascularisation rate was low. Heart failure patients received less evidence-based treatment, with the exception of angiotensin-converting enzyme (ACE) inhibitors. Heparin was used less frequently in those with a normal ECG, although rates of revascularisation were not different when compared with those with ECG abnormalities. The conclusions of the study were that groups of patients with particularly high event rates are readily identified by their clinical characteristics, but use of evidence-based treatments and invasive investigations do not appear to be targeted towards those at greatest risk. Risk stratification and the appropriate application of treatments for patients with acute coronary syndromes need to be reviewed in the clinical setting.

KEY WORDS: acute coronary syndromes, clinical outcomes, epidemiology, prospective registry, risk stratification, unstable angina

Acute coronary syndromes (ACS) include a spectrum of disease severity ranging from acute myocardial infarction (MI) with ST elevation to unstable angina. For these groups of patients, accepted treatments include aspirin,[1] heparin,[2] and beta blockers,[3] as well as conventional anti-anginal treatments. Despite these treatments, patients with ACS remain at high risk of further ischaemic events that lead to death, new MI and recurrent angina. Newer treatment strategies such as low molecular weight heparin,[4–7] more aggressive antiplatelet inhibition with glycoprotein IIb/IIIa inhibitors[8–10] and clopidogrel,[11] and early revascularisation[12–14] may offer better outcomes for patients with ACS.

We established the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) to determine characteristics, practice patterns, outcomes and important markers of risk of patients with ACS without ST elevation admitted to a wide range of UK hospitals. From the main PRAIS-UK analyses we identified patient groups at higher risk, including the elderly, those with heart failure, diabetes, or ST depression on the ECG. These high-risk patients, according to recent guidelines,[15,16] are most likely to benefit from more intensive management. We identified the higher-risk patients in PRAIS-UK in order to determine whether they received more intensive treatment.

Methods

PRAIS-UK was a prospective observational cohort registry of patients admitted to UK hospitals with ACS. The methods used have been published.[17] In brief, 56 hospitals participated and each was asked to collect data on 20 consecutive eligible patients, irrespective of admission location or consultant team. Each patient was followed for six months after their index hospital admission. Patients with a clinical diagnosis of ACS without ST elevation (unstable angina or suspected non-Q wave MI) were eligible if they were admitted to the hospital either through A&E or directly to the wards. A typical history of cardiac chest pain was required together with either ECG abnormalities consistent with myocardial ischaemia or a history of pre-existing evidence of coronary artery disease (eg prior MI, prior revascularisation). The exclusion criteria were ST elevation >1 mm in two or more contiguous leads on the ECG or planned or actual treatment with thrombolytic therapy on admission. The study had ethical

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approval from the Multicentre and Local Research Ethics Committee and patients provided informed consent prior to entry.

Major outcomes recorded included death, new MI, refractory angina and readmission with unstable angina. The definition of new MI required at least two of the following:

- new severe cardiac chest pain
- creatinine kinase (CK) or other cardiac enzyme rise to twice the upper limit normal
- new ECG changes (either prolonged ST elevation or new Q waves).

Refractory angina was defined as new cardiac chest pain in hospital with associated ECG changes consistent with ischaemia lasting at least five minutes despite optimal medical therapy (including intravenous nitrates) and leading to either thrombolysis for threatened MI, insertion of an intra-aortic balloon pump or revascularisation within seven days of its onset. A multivariate analysis was performed to identify patient groups at high risk for death or MI.

Statistical analysis

Comparison of proportions was made using the Chi-squared test. Multiple logistic regression was used to determine whether prognostic variables were still statistically significant when corrected for other variables that were significantly associated with adverse outcomes on the univariate analysis. The ECG categories were:

1 = normal

2 = ST depression or bundle branch block

3 = T wave inversion or non-specific ST segment abnormalities.

Results

A total of 1,046 patients were entered into the registry from 56 participating centres between 23 May 1998 and 3 February 1999. Data at six months were available for 1,031 (99%) of the patients.

Baseline characteristics (overall group)

Mean age at presentation was 66 ± 12 years, 61% were male, 16% had diabetes, 37% treated hypertension, 23% were current smokers, 48% had had a prior MI and 23% prior revascularisation (either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG)). The clinical diagnosis at admission was unstable angina in 95% and MI without ST elevation in 5%. Based on cardiac enzyme elevation at hospital admission, 13.9% had MI associated with admission symptoms.

Rates of major adverse outcomes (overall group)

Rates of death were 1.5% and 7.4% in hospital and at six months respectively, and rates of MI were 3.9% and 7.3% respectively. For the composite of death or new, non-fatal MI, the rates were 5.0% and 12.2%. For the combination of death, MI, refractory angina or readmission for unstable angina, rates of events were 7.6% and 30.0% respectively.

Multivariate analysis

A multivariate logistic regression model was performed to identify patient groups at high risk for death or MI. Age, ECG changes and a prior history of heart failure were independent predictors of an adverse outcome (death or new MI). For age, compared with those aged <60, odds ratio (OR) for this outcome was 3.5 for those >70 years (95% confidence interval (CI) 2.03–5.87, p <0.001), and 2.2 for those aged 60–70 (95% CI 1.21–3.94, p = 0.03). Compared with those admitted with a normal ECG, OR for ST depression or left lumber branch block (LBBB) was 5.02 (95% CI 1.66–15.12, p = 0.004) and for other ECG changes 3.2 (95% CI 1.11–8.97, p <0.03). Prior heart failure conferred an OR of 1.88 (95% CI 1.14–3.12, p = 0.01) compared with those with no such history. A history of diabetes was not an independent predictor of outcome in our study (OR 1.56, 95% CI 0.95–2.56, p = 0.08).

Outcomes in key high-risk subgroups

Outcomes are summarised in Table 1. Rates of adverse events were substantially higher in the elderly, in those with a history of heart failure and in those with abnormal ECGs on admission (particularly those with ST depression or bundle branch block). Diabetes was included as other studies have indicated its importance and it may act as a marker for patients with a higher risk profile.

Management of key high-risk subgroups

The elderly (Table 2)

We compared characteristics in patients >70 (n = 420, 40%) with those aged 60–70 (n = 283, 27%) and <60 (n = 343, 33%). In each of these groups, the proportion of males was 49%, 67% and 70% respectively (p <0.001). Rates of adverse events increased sharply with increasing age. All treatments were used less frequently in elderly patients, with large differences observed in the use of statins and beta blockers. In-hospital

Key Points

Rates of death or new myocardial infarction for acute coronary syndromes without ST elevation are high

High-risk groups are easily recognised, but in the UK their management is no more aggressive than for those at low risk

Use of evidence-based medical therapies is low in the UK

Rates of revascularisation are low and these procedures are not targeted to high-risk patients

stress testing was performed in a relatively small proportion of the elderly. After six months, both angiography and angioplasty had been performed in a lower proportion of the elderly, although this did not appear to be the case for CABG.

Diabetes (Table 3)

At baseline, 170 (16.3%) of patients had a history of diabetes. There were no differences in age or gender. Patients with diabetes had more hypertension (49% versus 35%, $p < 0.001$), more prior MI (58% versus 46%, $p = 0.004$) and more ST depression or bundle branch block on the admission ECG (41% versus 27%, $p = 0.001$). Angiography was performed in 31% for those with diabetes compared with 26% for those without ($p = 0.03$). Death was more frequent in diabetic patients (12% versus 7%, $p = 0.01$) as was the composite of death or myocardial infarction (17% versus 11%, $p = 0.05$). For patients with diabetes, the rate of angiography was 28.2% compared to 23.0% for those without ($p = 0.14$) and rates of revascularisation were 19.1% and 13.8% respectively ($p = 0.12$). In a multivariate analysis, there was no significant association of diabetes with an adverse clinical trend (odds ratio for diabetes versus no diabetes 1.56, 95% CI 0.95–2.56, $p = 0.08$).

Prior heart failure (Table 4)

From the original sample, 139 (13.3%) had a prior history of heart failure and 907 (86.7%) did not. Mean age for those with and without heart failure was 72.8 ± 9.7 years and 64.7 ± 11.8 years respectively ($p < 0.001$). More patients with prior heart failure had diabetes (26% versus 15%, $p = 0.001$) and prior MI (68% versus 46%, $p < 0.001$). More patients with prior heart failure had ST depression or bundle branch block on the admission ECG (46% versus 27%, $p < 0.001$). Fewer patients with prior heart failure were treated with aspirin in hospital. At six months, use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 antagonists were more frequent in patients with prior heart failure. At six months, the rates of death, death or new myocardial infarction, and death, new refractory angina or readmission for unstable angina were substantially higher in those with a prior history of heart failure. Rates of angiography were also lower, although there was no significant difference in revascularisation.

ST depression or bundle branch block on the admission ECG (Table 5)

We compared data in those with ST depression or bundle branch block on the admission ECG (n = 304, 29%) with those with 'other' changes (T wave inversion, Q waves etc) (n = 576, 55%) and those with a normal ECG (n =166, 16%). In each of these groups, the proportion aged over 70 was 54%, 37% and 27% ($p < 0.001$) respectively. The proportions with diabetes were 23%, 14% and 13% ($p = 0.001$), with hypertension 41%, 37% and 31% ($p = 0.08$) and with a prior history of MI 43%, 54% and 39% ($p < 0.001$).

Table 1. Major outcomes in high-risk subgroups.

Death	Death/MI (%)	Death/MI/ (%)	RFA/UA (%)
Age			
Under 60	1.8	5.5	30.0
60–70	6.7	12.4	34.3
Over 70	12.4*	18.5*	38.7**
History of diabetes			
Present	12.1	16.5	34.2
Absent	6.6**	11.1**	28.9***
History of heart failure			
Present	19.3	22.0	42.8
Absent	5.6*	10.5*	27.8*
Admission ECG			
ST depression/BBB	14.8	22.4	44.1
Other	4.9	9.2	30.9
Normal	1.8*	6.0*	29.5*

Statistical comparisons made across groups *p <0.001; **p <0.05; ***p = NS. BBB = bundle branch block ; MI = myocardial infarction; RFA = refractory angina; UA = unstable angina.

Table 2. Management of elderly patients.

	Age >70 (n = 420) (%)	Age 60–70 (n = 283) (%)	Age <60 (n = 343) (%)	p
In-hospital treatment				
Aspirin	83.6	87.3	90.4	0.021
LMWH	41.2	44.9	46.1	0.366
IV UFH	30.0	37.1	35.6	0.102
Either LMWH or IV UFH	72.7	79.5	79.6	0.036
Treatment at 6 months				
Aspirin *	78.9	85.3	83.5	0.080
Beta blockers**	34.7	42.3	52.0	<0.001
Statins*	34.5	50.6	57.9	<0.001
In-hospital investigation				
Angiography	7.1	10.3	13.1	0.023
PTCA	1.7	3.9	5.8	0.009
CABG	1.9	2.1	1.8	0.945
Stress test	6.9	11.7	21.3	<0.001
Investigation at 6 months				
Angiography***	13.0	22.8	25.6	<0.001
PTCA***	1.8	7.1	7.2	0.001
CABG***	5.4	6.7	5.1	0.662

p values are given for any difference across the groups. *n = 976; **n = 975; ***n = 992.
Tables 2–5: CABG = coronary artery bypass graft; LMWH = low molecular weight heparin; PTCA = percutaneous transluminal coronary angioplasty; UFH = unfractionalised heparin.

At six months, death, death or new MI, and death, new MI, refractory angina or readmission for unstable angina were more frequent in those without a normal ECG on admission, and, in particular, in those with ST depression or bundle branch block. After six months, there were no significant differences in the use of beta blockers or statins. There were no significant differences between ECG groups in the use of angiography or PTCA, although CABG was performed more frequently in those with ECG abnormalities.

Discussion

In our study, the majority of the patients enrolled were known to have coronary artery disease. Adverse events were frequent with the composite of death, new MI, refractory angina or re-admission for unstable angina occurring in about one-third of patients after six months. Easily defined subgroups including the elderly are at substantially higher risk of adverse events, particularly death or new MI. Despite this, those at highest risk are not necessarily more likely to receive treatments known to be of benefit. This is particularly true of the elderly, with lower use of heparin, aspirin, statins and beta-blockers. The elderly and those with prior heart failure also undergo angiography less frequently and are less likely to be revascularised. Those with heart failure were more likely to be treated with ACE inhibitors than those without; however, over 40% of this group did not receive them. Although those with easily defined changes such as ST depression or bundle branch block are readily identifiable and at substantially higher risk of adverse events, the rates of angiography are not significantly different.

Two recent registries of patients with acute coronary syndromes with and without ST elevation describe the variation in management and outcomes. In a report from the GRACE Registry of over 11,000 patients with a diagnosis of an acute coronary syndrome worldwide,[18] 38% had a final diagnosis of unstable angina and 25% of non-ST elevation MI. Use of aspirin was above 90% across all diagnoses, hospital types and geographical regions. Use of beta blockers and statins was lower in non-teaching hospitals and centres without catheterisation laboratories. Not surprisingly, use of percutaneous coronary intervention was higher in hospitals with a catheterisation laboratory.

The Euro Heart Survey of Acute Coronary Syndromes also showed variation in management but no gross differences in outcome[19] (see Table 6).

A large study involving over 24,000 patients in primary care in the UK demonstrated ample scope for improving secondary prevention for those known to have a coronary heart disease. Only around half were receiving aspirin, less than a quarter beta blockers and less than one in five statins. Many patients had no record of lipid measurement and the overall numbers of patients

Table 3. Management of diabetic patients.

	With diabetes (n = 170) (%)	No diabetes (n = 876) (%)	*p*
In-hospital treatment			
Aspirin	81.2	87.9	0.018
LMWH	38.8	44.8	0.15
IV UFH	38.2	32.9	0.18
Either LMWH or IV UFH	68.2	72.7	0.23
Treatment at 6 months			
Aspirin	78.7	79.3	0.23
Beta blockers	36.6	43.7	0.10
Statins	45.8	46.9	0.79
In-hospital investigation			
Angiography	15.3	8.9	0.01
PTCA	7.1	3.0	0.009
CABG	2.4	1.8	0.65
Stress test	4.7	14.5	<0.001
Investigation at 6 months			
Angiography	17.7	20.3	0.43
PTCA	3.8	5.3	0.44
CABG	8.9	5.0	0.06

Table 4. Management of patients admitted with prior history of heart failure (HF).

	With prior HF (n= 139) (%)	No prior HF (n= 907) (%)	*p*
In-hospital treatment			
Aspirin	78.4	88.1	0.002
LMWH	36.7	44.9	0.07
IV UFH	33.1	33.9	0.86
Either LMWH or IV UFH	64.8	73.1	0.04
Treatment at 6 months			
Aspirin	72.8	82.2	0.008
Beta blockers	17.4	46.1	<0.001
Statins	35.5	48.3	0.008
ACE inhibitors	58.7	28.2	<0.001
A2 antagonists	10.7	2.8	<0.001
In-hospital investigation			
Angiography	7.2	10.4	0.25
PTCA	2.9	3.8	0.61
CABG	0.7	2.1	0.27
Stress test	4.3	14.2	0.001
Investigation at 6 months			
Angiography	11.9	21.0	0.02
PTCA	3.2	5.3	0.31
CABG	4.8	5.8	0.65

ACE = angiotensin-converting enzyme.

with coronary disease were low, suggesting that significant numbers of patients with established disease were not recorded as such on practice databases. Both of these factors suggest that the estimates for levels of treatment may be low.[20]

Updates of clinical guidelines for the management of patients with ACS without ST elevation were presented for the ACC/AHA guidelines[21] in March 2002 and for the ESC guidelines in September 2002.[22] Both guidelines incorporated data from the CURE study[11] and recommended the use of the combination of aspirin and clopidogrel for all patients with ACS without ST elevation. Both guidelines emphasise that for patients with an established diagnosis of ACS, the management strategy to be selected depends on the risk of progression to death or MI, with high-risk patients progressing to angiography. Therefore, markers of myocardial damage such as troponins have a key role in risk stratification. Any detectable elevation of cardiac troponin is associated with an increased risk of death or MI. Clinical guidelines recommended that patients at high risk should start intravenous GP IIb/IIIa inhibitors and undergo angiography. In those patients with coronary artery lesions suitable for revascularisation, PCI or CABG, when appropriate, should be performed.

It seems easy to identify high-risk subgroups (those with diabetes, prior history of heart failure, the elderly) who may benefit from more aggressive treatment strategies. It may be that the addition of other risk stratification tools, which were measured infrequently in our cohort, such as troponin measurement[23–25] and stress testing,[26] may add useful information that clearly identifies a low-risk group. The reliable identification of such a group would allow their early discharge and may allow more resources to be used for those at highest risk. In addition, the use of specialised chest pain units may allow more appropriate risk stratification.[27] Improved methods of risk stratification by increasing rates of troponin measurement and of exercise testing should be adopted in order to allow improvements in the targeting of treatments towards those at highest risk such as the TIMI risk score.[28] In particular, revascularisation and the use of agents such as clopidogrel and the glycoprotein IIb/IIIa

Table 5. Management of patients by ECG.

	ST depression/ BBB (n = 304) (%)	Other‡ (n = 576) (%)	Normal (n = 166) (%)	*p*
In-hospital treatment				
Aspirin	82.6	88.5	88.5	0.035
LMWH	43.4	44.1	43.4	0.975
IV UFH	37.2	33.7	27.7	0.116
Either LMWH or IV UFH	79.3	78.0	68.7	0.022
Treatment at 6 months				
Aspirin*	78.3	83.2	85.2	0.126
Beta blockers**	38.2	45.8	38.9	0.071
Statins*	44.6	49.0	42.6	0.254
In-hospital investigation				
Angiography	12.8	10.2	3.6	0.006
PTCA	3.6	4.0	2.4	0.630
CABG	2.6	1.7	1.2	0.502
Stress test	9.5	13.0	18.7	0.018
Investigation at 6 months				
Angiography***	18.3	20.1	21.6	0.675
PTCA***	4.4	5.2	5.6	0.829
CABG***	8.8	5.0	2.5	0.015

p values are given for any difference across the groups.
‡Other = ECG changes including Q waves, T wave insertion.
*n = 976; **n = 975; ***n = 992.

Table 6. Comparison of treatment received by registry populations of patients with coronary heart disease.

	GRACE[18]		Euro Heart[19]	Brady *et al*[20]
Patient population	**11,543 patients admitted with ACS (world-wide)***		**10,484 patients admitted with ACS (Europe)***	**24,431 stable patients with established coronary heart disease from UK GP practices**
	UA (n = 4,393)	**NSTEMI (n = 2,893)**		
Aspirin	75%	91%	85%	50%
Beta blockers	75%	78%	76%	21%
Statins		47%	53%	
LMWH	46%	51%	81%**	
UFH	48%	61%		

ACS = acute coronary syndrome; UA = unstable angina; NSTEMI = non-ST elevation myocardial infarction; LMWH = low molecular weight heparin; UFH = unfractionated heparin.
*medication at time of discharge
**Either LMWH or UFH.

ACRONYMS

ACC/AHA	American College of Cardiology/American Heart Association
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
ESC	European Society of Cardiology
GRACE	Global Registry of Acute Coronary Events

receptor antagonists should be considered more frequently in those groups of patients at highest risk for adverse events. The UK has some of the highest rates of coronary artery disease in the world and there are concerns that revascularisation rates may be inappropriately low.

These data demonstrate that some patients with readily identified characteristics are at high risk but that their treatment is sub-optimal. Additional risk stratification techniques such as the more extensive use of troponin, C-reactive protein or stress testing are likely to add useful information. Clinicians need to be aware that high-risk groups are likely to benefit more from evidence-based treatments. Further studies are needed to determine current practice patterns and outcomes, whether evidence-based treatments are being used and to refine our risk stratification methods.

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