Risk of death, MI and patterns of care delivered in non-ST elevation ACS patients with intermediate elevations in cardiac troponin T: a UK DGH experience

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Abstract

Prior studies have suggested a gradation in clinical risk with increasing elevations of cardiac troponins in patients with non-ST elevation acute coronary syndromes (ACS). We hypothesised that patients with cardiac troponin-T (cTnT) between 0.01-0.1 µg/L might be perceived as a low-risk group and consequently receive less active medical treatment.

Data were drawn from a UK district general hospital ACS registry between 2001 and 2002, and from the Office of National Statistics. A total of 255 patients were found to have had a non-ST elevation ACS with a cTnT rise between 0.01-0.10 µg/L.

Minor elevations in cTnT below 0.1 µg/L were found to be associated with a 20.1% risk of cardiovascular death or myocardial infarction (MI) at six months, with no ascending grade of risk from the lowest to the highest quintile. The use of statins (48.6%), angiotensin-converting enzyme (ACE) inhibitors (46.7%) and combined antiplatelet treatment (7.5%) was low, as was the use of angiography (8.2%) and stress testing (8.2%). In patients not undergoing early angiography, non-use of statins and ACE inhibitors was associated with twice the risk of death or MI (p=0.02). In a multivariate analysis, ST segment depression and non-use of ACE inhibitors were significant markers of risk.

Patients with non-ST elevation ACS and a cTnT between 0.01–0.1 ug/L are a universally high-risk group with no gradation of risk throughout this range. In a representative UK district general hospital (DGH), use of cardioprotective medication and cardiovascular assessment is low. An increased use of statins, ACE inhibitors and antiplatelet drugs, together with early angiography might improve prognosis in this group.

Key words: troponin T, cardiovascular risk, district general hospital, audit, secondary prevention.

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Introduction

Patients with non-ST elevation acute coronary syndromes (ACS) are at increased risk of death and reinfarction following the index admission.[1] These patients form a heterogeneous group, however, and attempts have been made to risk-stratify them by risk scores that use clinical and laboratory markers.[2] Among the various laboratory markers used, cardiac-specific troponin T (cTnT) has emerged as a powerful marker of risk.[3] Typically, patients with cTnT > 0.1 µg/L are considered at high risk, although recent studies suggest that even minor elevations of cTnT are associated with increased cardiovascular (CV) risk.[4,5]

Whilst clinicians are uniformly in agreement regarding the CV risk associated with a cTnT > 0.1 µg/L, the management of patients with cTnT between 0.01–0.1 µg/L remains a grey area in many non-specialist centres. The clinical uncertainty, and the perception that patients with cTnT between 0.01–0.1 µg/L are at a lower risk, might then translate into less aggressive medical treatment and an increased risk of CV events. Our primary hypothesis was to determine whether patients with cTnT between 0.01–0.1 µg/L at presentation were at low CV risk in a 'real world setting', and in doing so also to determine the use of cardioprotective medication and use of stress testing and coronary angiography in this subgroup. A secondary aim was to determine if

Table 1. Baseline characteristics of patients with cTnT between 0.01–0.1 µg/L. Values are shown as absolute numbers with percentages in parentheses

Variable	Whole group (n=255)
Males	143 (56.1%)
Diabetes	41 (17.9%)
Smokers	56 (25.1%)
Hypertension	75 (32.9%)
Hyperlipidaemia	56 (31.8%)
Early angiography (< 1 week)	7 (2.7%)
Angiography within six months	21 (8.2%)
Stress testing within six months	21 (8.2%)
Aspirin	151 (59.2%)
Clopidogrel + aspirin	19 (7.5%)
Unfractionated heparin	87 (51.5%)
Low molecular weight heparin	26 (10.2%)
Statin	124 (48.6%)
ACE inhibitors	119 (46.7%)
Beta blockers	94 (36.9%)
Admitted to CCU	61 (23.9%)
Under cardiologist care	64 (25.1%)

Key: ACE = angiotensin-converting enzyme; CCU = coronary care unit

there was a gradation in CV risk within the 0.01–0.1 µg/L cTnT range. In order to evaluate this we carried out an observational prospective study in a UK district general hospital over one year.

Methods

Between 01/05/2001 and 30/04/2002 all patients admitted to Doncaster Royal Infirmary with chest pain were reviewed by Specialist Nurse Practitioners. Patients considered to have typical cardiac ischaemic pain at rest were recorded on a central database. Cardiac TnT was routinely measured at 12 hours after the onset of pain using a Roche 10/10 analyser, with a coefficient of variation of 5.4% between 0.01–0.1 µg/L. Patients with cTnT between 0.01–0.1 µg/L were considered for this analysis. Clinical demographic data were obtained from our database and case notes.

Patients were managed by two cardiologists and eight general physicians with other specialist interests. Use of urgent cardiac catheterisation at the regional centre was noted, as was use of routine diagnostic angiography at our centre. Use of exercise and pharmacological stress testing was obtained from departmental records. Readmission data were recorded from case notes and six-month mortality data were obtained from the Office of National Statistics.

Statistical analysis

All continuous variables are reported as mean ± standard deviation. Analyses were carried out using SPSS statistical package.

Table 2. The six-month rate of cardiovascular death and non-fatal MI in patients not undergoing early angiography, and the effects of secondary prevention with statins and ACE inhibitors. The combined use of statins and ACE inhibitors resulted in a 50% reduction in end points, compared with neither (p=0.02)

Use of ACE inhibitor and statin treatment	Six-month combined CV death/MI end point	95% confidence intervals	
		Lower	Upper
Neither	27%	18%	36%
ACE inhibitor only	19%	6%	32%
Statin only	16%	3%	28%
Statin and ACE inhibitor	14%	7%	21%

Key: CV = cardiovascular; MI = myocardial infarction; ACE = angiotensin-converting enzyme

For the univariate analyses, the student's t-test and chi-squared test were used to analyse parametric and categorical data, respectively, as appropriate. For the multivariate analyses, logistic regression was used.

Results

Baseline characteristics

The total number of patients admitted with non-ST elevation ACS with a cTnT > 0.01 µg/L was 592: of these, 255 patients (43%) had a cTnT between 0.01–0.1 µg/L and were included in this analysis. The demographic characteristics for the 0.01–0.1 µg/L group as a whole are shown in table 1.

Secondary prevention and cardiovascular investigations

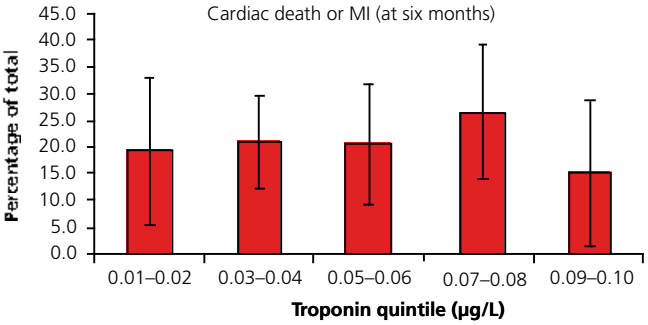
The use of secondary cardioprotective medication and cardiovascular investigations is also shown in table 1. Statins, ACE inhibitors and beta blockers were used in 48.6%, 46.7% and 36.9%, respectively of eligible patients. Aspirin and clopidogrel were used in 59.2% and 13%, respectively, with 7.5% of patients taking both. Low molecular weight heparin use was 10.2%. Cardiac catheterisation was performed in 8.2% (within six months) and stress testing also in 8.2% (within six months). Early coronary angiography (< 1 week) was performed in 2.7% of patients.

In an analysis confined to patients not undergoing early angiography, the event rates by use of statin and ACE inhibitor treatment group are shown in table 2. The lower event rate (14%) in patients taking both drugs compared to that in the group taking either (27%) was statistically significant (p=0.02).

cTnT and clinical outcomes

There were 32 cardiovascular deaths (12.6%) and 19 non-fatal myocardial infarctions (MIs) (7.5%) at six months. A composite end point of death or non-fatal MI occurred in 20.1% of patients at six months. The percentage of patients with a combined clin-

Figure 1. Cardiovascular death and recurrent MI for each quintile of the cTnT range between 0.01–0.1 µg/L



Results are represented as rates with 95% confidence intervals
p=non-significant between quintiles

ical end point for each cTnT quintile is shown in figure 1. There was no significant gradation of risk between the lowest and the highest quintile.

Predictors of death and MI at six months

Table 3 shows the univariate analysis of predictors of cardiovascular death or MI at six months. Only ECG changes (ST depression and T wave inversion) at admission (p=0.0003) and age (p=0.036) predicted an adverse event although several variables such as lack of an early aggressive strategy (p=0.068) showed a trend towards increased risk.

Multivariate analysis (table 4) was restricted to the most significant variables from the univariate analysis. ST depression conferred a 5- and 7-fold increased risk of events at six months compared to those with T wave changes and 'other ECG', respectively. The only other significant predictor (after stepwise removal of non-significant variables) was ACE inhibitor therapy, which reduced risk by more than half. It is likely that the predictive effect of some variables on risk is not evident due to difficulties in demonstrating statistical significance from relatively small datasets.

Discussion

It is now accepted that the cardiac-specific troponins predict clinical risk in ACS.[1] Despite this evidence, considerable heterogeneity remains in the management of patients with an elevated cTnT. This is particularly apparent for minor elevations below the European Society of Cardiology (American College of Cardiology) (ESC/ACC) cutoff for MI, possibly because many of these cases are not accompanied by significant ECG changes or have otherwise low-risk features.[6] Our data show that a minor elevation of cTnT in the context of an ACS is not a benign condition and is associated with a significant six-month mortality and morbidity (20.1%). This is comparable to data from the Fragmin during Instability in Coronary artery disease (FRISC) and the Global Use of Strategies To open Occluded coronary arteries

Table 3. Univariate predictors of cardiovascular death and MI at six months in patients with a cTnT between 0.01–0.1 µg/L. The presence of ST segment or T wave changes (p=0.0003) and increasing age (p=0.036) were significant predictors of events at six months

Variable	p value
ECG changes at presentation	0.0003
Age	0.036
Early angiography	0.068
Beta blocker therapy	0.070
Statin therapy	0.084
Smoking	0.087
ACE inhibitor therapy	0.091
Aspirin therapy	0.117
Diabetes	0.172
TIMI score	0.174
Low molecular weight heparin	0.175
Unfractionated heparin	0.206
Gender	0.283
Cardiologist vs. non-cardiologist	0.312
Previous MI	0.314
Clopidogrel therapy	0.605
Hypertension	0.706
Troponin	0.787
Peak CK	0.865

Only presenting ECG (ST segment depression/T wave inversion) and age predicted clinical events at six months

Key: ACE = angiotensin-converting enzyme; MI = myocardial infarction; CK = creatine kinase; cTnT = cardiac-specific troponin T

II (GUSTO II) studies in patients with non-ST elevation ACS with cTnT > 0.1 µg/L and ST elevation MI, respectively.[4,7]

At the time of this study the evidence base for the use of secondary prevention strategies such as beta blockers and ACE inhibitors in patients with coronary artery disease already existed. The evidence for the use of statins in ACS has been enhanced by the recent PRavastatin or atOrVastatin Evaluation and Infection Therapy-Thrombolysis in myocardial infarction (PROVE IT) study, although this had not been published at the time of the work reported here.[8,9] Unfortunately, the use of drugs was low in this patient group (statins 49% and ACE inhibitors 47%). Strikingly, in patients not undergoing early diagnostic angiography (< 1 week) the non-use of statins and ACE inhibitors was associated with a doubling of risk of death or MI at six months. These data reinforce the need for secondary prevention agents (aspirin/statin and ACE inhibitors) in all patients, whether they are revascularised or not. These data suggest that in centres without the facility for early angiography the prescription of statins and ACE inhibitors in eligible patients is even more important at discharge. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study showed that dual antiplatelet therapy significantly

Table 4. Multivariate analysis of the nine strongest predictors of clinical events at six months. The absence of ST segment depression was associated with a reduction in clinical risk (odds ratio 0.219 for any ECG change, and 0.134 for T wave inversion versus ST depression)

Variable	OR (95% CI)	p value
Other ECG compared to ST depression	0.219 (0.09–0.532)	0.001
T wave changes compared to ST depression	0.134 (0.043–0.422)	0.001
Not on ACE inhibitor therapy *	1.998 (0.899–4.488)	0.094
Conservative strategy	4.686 (0.580–37.834)	0.147
Age	1.028 (0.990–1.067)	0.154
Not on beta blockers	0.731 (0.327–1.635)	0.446
Smoker	1.342 (0.516–3.492)	1.342
Not on aspirin	1.258 (0.587–2.697)	0.555
Not on statin	1.164 (0.500–2.710)	0.725

*After stepwise removal of least significant predictors, 'not on ACE inhibitor therapy' also achieved significance (in addition to ECG changes), with odds ratio 2.232, 95% CI 1.133–4.398, p=0.02

Key: ACE = angiotensin-converting enzyme; OR = odds ratio

reduced cardiovascular events.[10] However, the use of combined antiplatelet treatment with clopidogrel and aspirin was low (7.5%) in our study.

The reasons behind the under-use of appropriate secondary prevention medication and both invasive and non-invasive cardiovascular investigations are unclear and warrant further research. This under-use may result from the perception that these patients are a low-risk group in the absence of ongoing symptoms or other high-risk features. Our data clearly show that within the cTnT range of 0.01–0.1 µg/L there is no safe threshold that identifies a low-risk group, and that the group as a whole should be considered at high risk and should receive appropriate treatment regardless of the absolute value of their cTnT. The only marker that conferred additional prognostic information amongst this cohort was the presence of ST segment deviation on the presenting ECG. This is an important observation. In the current era of high throughput medicine there is a desire for a numerical test that helps us to triage and treat patients. Our data show some of the pitfalls of relying simply on 'numbers alone' and suggest that some of the more traditional tests in cardiology, such as the baseline ECG and exercise testing, still have a valuable role to play.[11,12]

The event rates observed in our study are greater than those in the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) registry.[13] The rate of death or non-fatal MI in PRAIS-UK was 12% (95% CI 10–14%) whereas it was 20% (95% CI 15–25%) in our study. This may reflect slight differences in the population and study criteria. The patients in our study were older, with a mean age of 73 years, compared to a mean of 66 years in PRAIS-UK. The proportion of male subjects and incidence of risk factors were similar in both studies. One important point of differentiation between this analysis and PRAIS-UK is that we studied patients with ischaemic chest pain and a detectable cTnT (ECG changes were not required); by contrast, ECG changes (and not cTnT) were a prerequisite in PRAIS-UK, which will have included both cTnT-positive and -negative patients. The higher event rate in our analysis may, therefore, reflect differences in the predictive power between these two independent prognostic markers when risk-stratifying ACS patients. The use of secondary cardioprotective medication and invasive testing appears similar between these two studies performed some four years apart, suggesting that no significant changes have occurred between 1998 and 2002 in the routine management of ACS in the UK district hospital setting. On the basis of these two cohorts, we propose that the six-month mortality data on ACS patients should be fed back to each UK hospital. The fact that a sizeable proportion of ACS patients perish during this timeframe is undoubtedly unrecognised by most clinicians in charge.

Morrow *et al.* demonstrated a benefit from early invasive management in patients with even minor elevations of cTnT and cTnI.[5] The transfer times for stabilised ACS patients to our regional cardiac centre is one week, on average. This represents a considerable increase in the hospital stay in busy UK district general hospitals, already under pressure from lengthy bed stays. In a stretched healthcare system where resources are often rationed to those most at need, ACS patients with minor cTnT elevations may be considered less of a priority. Our data clearly show that these patients are in fact at similar risk to 'higher risk' patients in many clinical trials of non-ST elevation ACS as well as STEMI.[4,7] These patients should therefore be considered for early angiography.

The principal finding from this survey was that ACS patients with minor elevations of cTnT have a 20.1% risk of death or MI at six months. This result supports a recent study reporting equally high rates of death/MI among ACS patients with cTnT < 0.1 µg/L.[14] The risk could be reduced by an increase in use of both secondary prevention medication and invasive and non-invasive testing.

The majority of patients were under the care of non-cardiologists during their admission. The present study was not powered to demonstrate a difference in outcomes between patients managed by cardiologists and those managed by generalists. In a recent report from the Myocardial Infarction National Audit Program (MINAP), which is coordinated by the Royal College of Physicians, Birkhead has confirmed that the great majority (67%) of patients admitted to hospital in England with an ACS are

Key messages

- Minor elevations in cardiac-specific troponin T were found to be associated with a 20% risk of cardiovascular death or MI at six months
- There was no gradation in risk for patients between the lowest quintile (0.01–0.02 µg/L) and the highest (0.09–0.10 µg/L)
- The use of statins, ACE inhibitors and combined antiplatelet treatment was low, as was the use of angiography and stress testing

supervised by non-cardiologists. This results in significant differences in patient management in the acute phase and in mortality.[15]

The results from the MINAP registry suggest that consideration should be given to all patients admitted with an ACS being reviewed by a cardiologist during their hospital stay. This has clear implications for increased provision of resources, both personnel and equipment. It is anticipated that these outcomes will be monitored and reported to individual institutions and as national data for England and Wales, and will cover all patients admitted with an ACS rather than just those with an ST-elevation myocardial infarction.

Conclusions

ACS patients with minor elevations of cTnT have a 20% risk of death or MI at six months. This risk could potentially be reduced by an increase in secondary prevention medication and a greater use of invasive and non-invasive testing, which may require a greater expenditure from cardiology budgets and additional staff in the UK.

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Conflict of interest

KKR has received research grants from Pfizer, Bristol-Myers Squibb and Sanofi-Aventis. The other co-authors have no conflicts to declare.

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