Incidentally raised cardiac Troponin I (cTnI) has a worse prognosis in older patients compared to those with normal cTnI and patients with acute coronary syndrome: a cohort study

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Running title: Incidentally raised troponin I worsens prognosis

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Abstract:

BACKGROUND: Incidentally elevated cardiac troponin I (cTnI) levels are common in acutely unwell older patients. However, little is known about how this impacts on prognosis in these patients.

OBJECTIVE: We aimed to investigate whether incidentally elevated cTnI levels (group 1) are associated with poorer outcome when compared to age and sex-matched patients without an elevated cTnI (group 2), and patients diagnosed with acute coronary syndrome (ACS) (group 3).

METHODS: This prospective matched cohort study placed patients ≥75years admitted to a University teaching hospital into groups 1-3, based on cTnI result and underlying diagnosis. Outcomes were compared between the groups using mixed effect regression models and adjusted for renal function and C-Reactive Protein (CRP). All cause-mortality at discharge, 1-month and 3-months alongside length of hospital stay (LOS) were recorded.

RESULTS: In total, 315 patients were included with 105-patients in each of the 3 groups. The mean age was 84.8±5.5years with 41.9% male. All patients were followed-up to 3 months. The percentage all-cause mortality at discharge and LOS for groups 1, 2 and 3 was 12.4%, 3.8%, 8.6% and 11.2, 8.5, 7.7 days respectively. Group 1 had significantly increased mortality at 3 months (OR 2.80 (95% CI 1.12 - 6.96) p= 0.040) and LOS (OR 1.39 (95% CI 1.08 - 1.79) p= 0.008) compared to group 2 and did not differ significantly when compared to 3-month mortality (OR 2.39 (95% CI 0.91 - 6.29) p= 0.079) or LOS (OR 1.26 (95% CI 0.96 - 1.66) p= 0.097) in group 3.

CONCLUSION: There is a significant association between an incidental rise in cTnI with mortality and LOS in older patients. Further research is required to evaluate whether more systematic management of these patients would improve the prognosis.

Introduction

Cardiac troponins (cTnI) are highly sensitive and specific biomarkers for myocardial injury (1). Furthermore, in the patient who presents with an acute coronary syndrome (ACS), an elevated troponin is associated with a poorer prognosis (2). The prognosis of these patients in the absence of ACS is less certain, and in recent years there has been increasing interest in quantifying the prognostic value of cTnI in this setting. Examples of this emerging role for cTnI include recent work showing that the cTnI assay is a useful independent predictor of mortality in patients hospitalized with severe pneumonia (3), sepsis (4), and in prognosticating the risk of long-term cardiac outcomes following acute stroke (5).

The third universal definition of myocardial infarction (6) includes the category of type-2 myocardial infarction, which is considered secondary to an ischaemic imbalance. In older patients, elevated cTnI levels are often seen where neither ACS nor another condition known to be associated with elevated cTnI is present (7, 8). Equally, it is hard in these patients to demonstrate the presence of 'ischaemic imbalance' and hence define the rise in cTnI as a 'type 2' myocardial infarction. Given that in older patients the clinical presentation of ACS is often non-specific, greater reliance is placed upon the cTnI result by clinicians for diagnosis. What to do with this result is thus uncertain. Does this 'incidentally' raised troponin mean the patient should stay in hospital for longer as it may be of prognostic concern? Much of the research to date examining the prognostic value of elevated cTnI in the absence of ACS has focused on younger adults, and there remains a paucity of information on its prognostic impact in the older population (9, 10). Of the limited research investigating this in older people, it is clear that elevated cTnI level is associated with a poorer prognosis when compared to older people with ACS (11). However, it remains unclear whether this also translates into a poorer prognosis when compared to hospitalised older people with normal cTnI levels and to what extent this might affect all cause-mortality and length of hospital stay (LOS) in this group. We hypothesised that there is a significant association between an incidental rise in cTnI and prognosis in older patients.

We aimed to investigate how all-cause mortality at hospital discharge, one month and three months was affected by the presence of an incidentally raised cTnI level in older patients when compared to older patients without an elevated cTnI level and to older patients diagnosed with ACS. Secondly, we aimed to investigate how LOS varied between these three groups.

Methodology

This prospective observational matched cohort study investigated the prognosis of patients aged ≥75 years who attended the acute medical admissions unit (AMU) at a large University teaching hospital in the East of England (between April and June 2013).

Setting:

The hospital covers a tertiary catchment population of up to 822,500 people (of mainly Caucasian ethnicity). Ethical approval for this study was gained from the Berkshire National Research Ethics Service (NRES) (Research Ethics Committees (REC) reference: 12/LO/1744) and National Information Governance Board (NIGB) approval was gained from the Ethics and Confidentiality Committee, London.

Inclusion criteria:

All patients aged ≥75 years of age admitted to the AMU and who had a cTnI level measured ≥eight hours of symptom onset (for clinical reasons) were eligible for inclusion in this study. Patients were consecutively placed into 3 groups according to their cTnI result and underlying diagnosis. Patients in all 3 groups were matched by age (within 5 years) and week of admission. Patients who could not be matched were excluded. Patients with a cTnI level ≥0.04 mcg/L according to the local reference laboratory values (Beckman Coulter assay, Access Immunoassay System, Beckman Coulter Inc. Fullerton, CA) and with no known cause attributable were included in group 1. These patients were referred to as having 'incidentally' elevated cTnI and were formally defined according to the third universal definition of myocardial infarction as having Type 2: Myocardial infarction (12). Patients with a cTnI level of <0.04mcg/L were included in group 2 and patients with cTnI level ≥0.04 mcg/L and diagnosed with ACS (according to the third universal definition of myocardial infarction (12)) were included in group 3 (see Appendix 1).

Exclusion criteria:

Patients <75yrs of age were excluded from this study, as were any patients not admitted to the AMU or who did not have cTnI measured ≥eight hours of symptom onset. Patients meeting the inclusion criteria but who had an elevated cTnI attributed to a cause other than

ACS (as identified by the admitting clinical team) such as renal failure, pulmonary embolism, pericarditis, myocarditis, tachyarrhythmia, sepsis and critical illness were also excluded.

Sample size: The sample size was calculated with an expected in-hospital all-cause mortality rate of 15% in control and 30% in case groups based on the size of the expected effect from previous work (11). In order to have 80% power at 0.05 significance level, a minimum sample size of 95 patients per group was required for the primary outcome of in-hospital all-cause mortality.

Data collection

A list of admitted patients was obtained from a prospective registry of patients admitted to AMU on a weekly basis and any patient eligible for inclusion in the study had their hospital number recorded. Following this, each hospital number was entered into the hospital laboratory data system to check whether or not a cTnI level had been recorded. Two team members who were clinically qualified reviewed the clinical notes of each of the patients meeting the inclusion criteria and subsequently categorised them into one of the three groups based on clinical features, other investigation results and the diagnosis made by the admitting consultant (lead physician for the patient).

In addition to recording cTnI levels we also recorded age, sex, diagnosis, medical history, basic laboratory data, ECG findings, length of stay and whether or not the patient was alive at discharge, one month and three months. The primary outcome measure was all-cause mortality at hospital discharge, at one month and at three months, measured using the Patient Administration System (PAS) (13). The secondary outcome measure was length of hospital inpatient stay.

Statistical Analysis

Comparisons were made between patients in group 1 with sex and age (±5-years) matched patients in groups 2 and 3. Potential risk factors and outcomes were compared between the groups using mixed effect regression models, where the fixed effect was the group and the random effect was the matching pair. This accounted for the clustering of individuals by matched pair and makes the standard assumption of independence invalid. The potential risk factors were compared using a linear mixed effect model without any further adjustment. Mortality outcomes were analysed using a logistic mixed effect regression model and length

of stay by a linear mixed effect. Sensitivity analysis adjusted for a past medical history of cardiovascular heart disease (defined as the presence of, heart failure, hypertension, ischaemic heart disease, myocardial infarction, valvular heart disease or a permanent pace-maker). We also included adjustment for renal function (estimated Glomerular Filtration Rate, eGFR) and C-Reactive Protein (CRP) as continuous risk factors by including them as a linear predictor in the model.

Results

Patient Characteristics

In total, 315 patients (105 patients in each group) who met the eligibility criteria were included. The sample mean age was 84.8±5.5 years and 41.9% were men. The sample characteristics are shown in Table 1. At baseline, CRP was higher in group 1 compared to groups 2 and 3 (p = 0.0001). Although eGFR was lower in group 1 compared to groups 2 and 3 (p = 0.0085), the mean eGFR in all groups was within the criteria of Chronic Kidney Disease (CKD) stage 3. The total length of follow up was 3 months from the date of index admission for each patient. The overall all-cause mortality at hospital discharge was 8.3%, which rose to 10.8% by the end of 1 month and was 14.9% by the end of the 3 month period. The mean length of hospital stay was 9.1 days. No patients were lost to follow-up.

Association between cTnI group and all-cause mortality

Analysis of all-cause mortality between patients in group 1 and 2 demonstrated that those with an incidentally raised cTnI (group 1) were almost three times more likely to die at three months (OR: 2.81, (95% CI: 1.05 – 7.50, p= 0.04) compared to their counterparts in group 2, after adjustment for cardiovascular medical history, CRP and renal function. Group 1 also had a statistically significant increase in all-cause mortality whilst an inpatient (p= 0.027)) and at one month following discharge (p= 0.013) compared to group 2 in the unadjusted analysis. However, on adjustment for cardiovascular medical history, CRP and renal function, this difference became non-significant (p= 0.089 and p= 0.091 respectively) (table 2). Analysis of all-cause mortality between patients in group 1 and 3 revealed no statistically significant differences in all mortality time points in the adjusted model (table 3); at discharge (p= 0.585), at one month (p= 0.379), and at 3 months (p= 0.079). There were also no statistically significant differences in all mortality time points between groups 2 and 3; the corresponding p values were 0.16, 0.30 and 0.49 in the adjusted model.

Association between cTnI group and length of hospital stay (LOS)

Group 1 had a significantly prolonged LOS compared with group 2 (OR: 1.50, (95% CI: 1.11 - 2.03, p = 0.008)) when adjusted for cardiovascular medical history, CRP and renal function with almost three additional hospitalised inpatient days on average (Table 2). There were no statistically significant differences in LOS between group 2 and group 3 in the adjusted model (p= 0.08), or between group 1 and 3 (p= 0.097) (Table 3).

Discussion

Our findings show that older patients with incidentally elevated cTnI have a poorer prognosis than age-sex matched patients with cTnI <0.04mcg/L. Although the prognostic significance of cTnI has been previously documented (14), we present the first data focusing on the older population with or without elevated incidental cTnI compared to ACS patients and our results suggest a role for cTnI as a biomarker for adverse prognosis and longer hospital stay in this age group.

To date there has been little data on the ideal management of patients with incidentally elevated cTnI and there are no randomised controlled trials investigating strategies to improve both immediate and long-term mortality and other important outcomes such as LOS and quality of life. In particular, uncertainty continues to exist regarding whether there is benefit in optimising the cardiac medications of these patients and the exact role of angiotensin-converting enzyme inhibitors, beta-blockers, statins, nitrates, low-dose aspirin or other secondary prevention medication for incidentally raised cTnI (15, 16). The Third Universal Definition of Myocardial Infarction (6) introduced the type 2 MI in which the underlying pathophysiology is due to micronecrosis of cardiac myocytes precipitated by a primary imbalance in the myocardial blood supply to myocardial oxygen demand ratio. Studies of cardiac angiographic correlation in relation to Type 1 and 2 MI have shown that the majority of type 2 MIs do not have clear underlying coronary vessel disease (17). Thus, given that a raised troponin in itself is not a marker of ruptured plaque (type 1 MI) rather one of downstream micronecrosis, patients with an incidentally elevated cTnI do not necessarily need to proceed to coronary angiography with a view to revascularisation. However, in this older population (and indeed in younger ones), it is hard to prove the presence of 'ischaemic imbalance'. How does for instance a clinician make an assessment of coronary endothelial dysfunction in their 85 year old with an incidentally raised troponin? With the latest-generation high sensitivity troponin testing, knowing what to do with the increasing incidence of unexpected troponin positive test will be even harder (18).

Further ambiguity persists regarding the ideal environment for the care of these hospitalised patients and whether they should be managed by cardiologists, or by geriatricians/general physicians. We propose that these patients do not comfortably fit into any category under the third definition of MI. The exact role of cTnI may not be solely a diagnostic one but more

akin to that of an independent biomarker of general physiological frailty or co-morbidity severity (14). Whether it should be formally incorporated into existing prognostic scoring systems used in other conditions such pneumonia (19, 20), stroke (21, 22) and for acutely unwell older patients remains unknown (23). Such increases in troponin may however simply reflect underlying poor health that is not directly reflected in indices such as the Pre-morbid Rankin score, which measure disability and dependence. This is supported by the fact that although the Pre-morbid Rankin score was higher in Group 1, especially when compared with ACS patients in Group 3 (2.12 vs 1.69, p=0.0027), additional adjustment for it did not change our results (see online supplementary Tables 1 and 2).

In addition to the clear difference in all-cause mortality rates between patients with incidentally raised cTnI and age-sex matched patients with normal cTnI, the fiscal implications from prolonged LOS are also considerable. During the 3-month period of this study, 105 patients with incidentally raised cTnI stayed approximately three additional days in hospital compared to patients with normal cTnI. If extrapolated over a single year, we estimate that older patients with incidentally elevated cTnI may result in over £350,000 in additional costs from prolonged hospital stay (24). Given that these results are based on a single hospital with catchment population of <1.0 million population, the potential health economic impact in the UK and also globally is substantial. This emphasises the need for further work to better understand this disease entity and to address the uncertainties regarding its optimal management highlighted above.

Limitations:

As a hospital based study, troponin measurements were made after the presentation to hospital, which might have introduced some bias towards attenuation of effect size. Nonetheless, this random measurement error is less important as we were interested in discrete well characterised clinical syndromes rather than level of troponin I rise and outcome. With recent advances in high-sensitivity laboratory assays, more minute increases in cTnI levels can now be accurately measured, however, their exact significance continues to be the source of much interest (25). We were limited by the diagnostic accuracy of the cTnI assay available in our laboratory (≥0.04 mcg/L) at the time of study but evidence is emerging that in older patients, even very low levels of cTnI may be associated with a higher mortality (26). As a result, it is possible that there were patients with small incidental elevations in cTnI that were undetected but may have attenuated the differences among the groups.

We did not have detailed information on cardiac angiography results as the cases (group 1) are usually managed under general physicians or care of the elderly specialists who may not feel that interventional cardiology is warranted in these individual patients. Furthermore, we could not stratify our patients by type of ACS, which could have provided finer granularity of the real impact of incidental rise compared to specific ACS syndromes. All patients with a cTnI measured (for clinical reasons) were included in this study. Since we could not randomise which patients had cTnI measured, it is possible an element of selection bias was present within our cohort. This however will not have impacted on the internal relationship between exposure and outcome in the population of interest. We also noted lower mortality rates than those previously reported in the published literature upon which our sample size calculation was based [10]. This may be due to the fact that there have been many changes in service efficiency since these previous reports were published. As with any sample size calculation, it was based on the best available evidence for estimation and will, however, only further attenuate the results.

Conclusion

Incidental rises in cTnI levels are common amongst the older population presenting to hospital. This study has shown that there is a strong association between incidental rise in cTnI and poor prognosis in older patients. Further research is needed to explore whether more invasive investigation and/or treatment are indeed clinically effective and cost effective in managing older patients with an incidental rise in cTnI. This is particularly salient in the coming years when this older age-group will make up an increasing proportion of presentations to acute medical units.

Disclosures: No disclosures

Conflicts of interest: None

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Author Contributions: PKM conceived the study. GSM developed the study protocol and obtained ethical approval. KH and RS collected the data. JHBS was responsible for data linkage and ABC analysed the data. GSM drafted the paper and all authors contributed in the preparation of the manuscript. PKM is the guarantor.

Ethics: Ethical approval for this study was obtained from the South-Central research ethics committee (approval reference: 12/LO/1744) and National Information Governance Board (NIGB) approval was gained from the ethics and confidentiality committee, London.

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Supplementary material

Appendix 1. Figure 1:

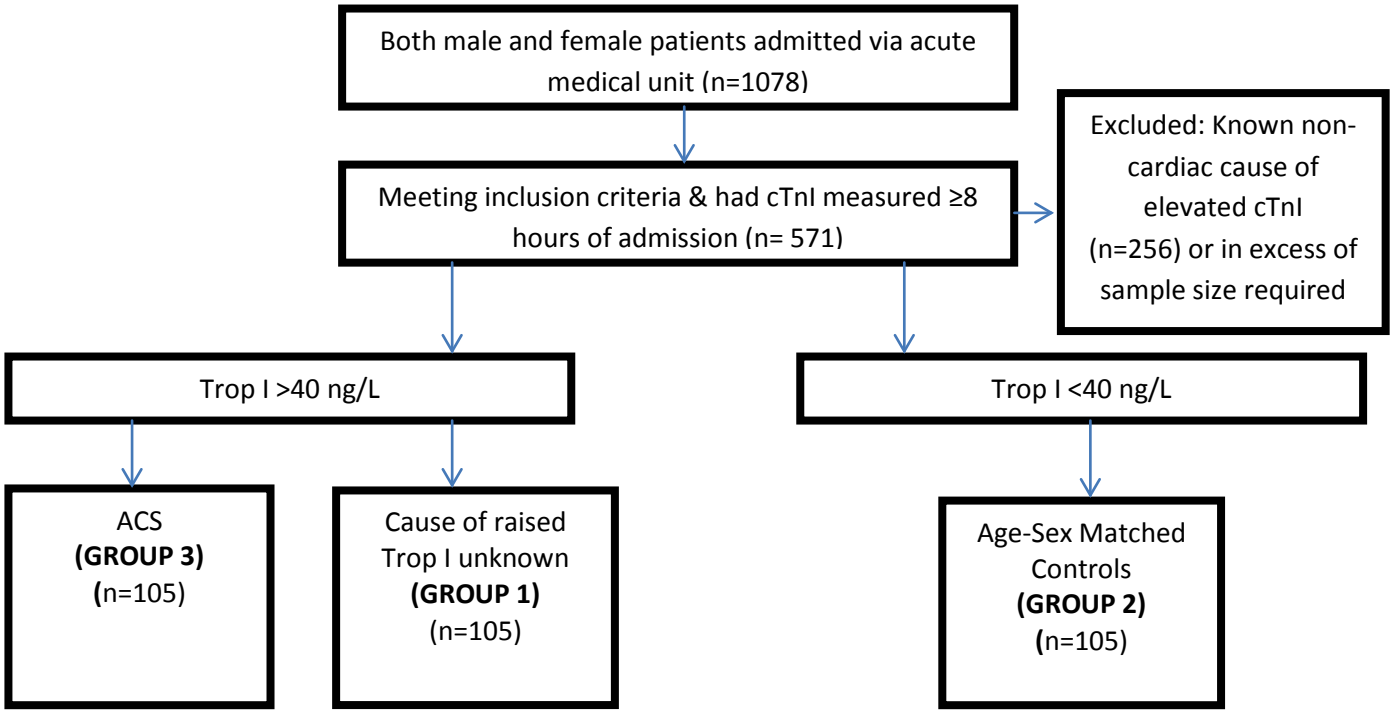

Table 1: Baseline characteristics of patients at time of admission.

		Group 1 (Incidentally raised cTnI)	Group 2 (Age-Sex Matched controls)	Group 3 (Patients with ACS)	*p*-value
		n=105	n=105	n=105	
Males		44 (41.9%)	44 (41.9%)	44 (41.9%)	NA*
Age (years)		86.0 (5.9)	85.4 (5.3)	83.0 (4.9)	NA*
Urea (mmol /l)		10.82 (7.01)	9.31 (5.9)	9.1 (4.84)	0.0748
Creatinine (μmol/l)		115.55 (53.97)	101.33 (44.82)	103.1 (50.12)	0.0762
eGFR (mL/min)		51.29 (19.20)	58.90 (21.09)	58.00 (18.61)	0.0204
WBC ($x10^9$/L)		11.02 (4.69)	9.87 (3.65)	10.39 (3.33)	0.1018
Neutrophils (x 10^9/L)		8.69 (4.38)	7.49 (3.46)	7.96 (3.2)	0.0673
Troponin (mcg/L)		0.41 (2.32)	NA[A]	4.38 (9.74)	<0.001[A]
Repeat troponin (mcg /L)		0.22 (0.20)	NA[A]	7.78 (13.70)	0.004[A]
CRP (mg/L)		78.44 (88.31)	43.02 (62.17)	33.68 (59.95)	<0.0001
Admitted from:	Home	79	89	92	<0.002
	Nursing Home	6	7	1	
	Other hospital	0	0	4	
	Residential home	20	9	8	
Mean number of co-morbidities per patient (SD)		3.57 (1.88)	3.16 (1.69)	3.23 (1.87)	0.2176
Mean Number of medications per patient		7.34 (3.77)	6.25 (4.13)	7.70 (4.51)	0.0002
Pre-morbid Rankin score		2.12 (0.96)	1.99 (1.00)	1.69 (0.88)	0.0027
Acute ischaemic changes on electrocardiograph		0	0	93	<0.001
Presenting with cardiac chest pain		12 (10.9)	19 (17.3)	79 (71.8)	<0.001
Number of individuals with at least one cardiovascular heart disease[1]		58 (55.24)	63 (60.00)	77 (73.33)	0.0205
Number of individuals with at least one coronary heart disease[2]		15 (14.29)	20 (19.05)	37 (35.24)	0.0012

*Age and sex were used as the matching criteria between groups 1-3 and so no significant differences were present. CRP: C-reactive protein, cTnI: cardiac troponin I, eGFR: Estimated Glomerular Filtration Rate, WBC: White Blood Count. [1]Cardiovascular heart disease defined as previous medical history including the presence of any of permanent pacemaker, heart failure, hypertension, ischaemic heart disease, myocardial infarction or valvular heart disease. [2]Coronary heart disease defined as previous medical history including the presence of either ischaemic heart disease or myocardial infarction. [3]Six participants with both IHD and MI. [A]*P*-value corresponds to comparison between group 1 and 3. Group 2 were age-sex matched controls that had normal cTnI levels (i.e. < 0.04mcg).

Table 2: Risk of all-cause death in patients with incidentally raised cardiac troponin I (cTnI) (group 1) compared to age-sex matched controls without raised cTnI (group 2).

	Group 1 (Incidentally raised cTnI) (n=105) n (%)	Group 2 (Age-Sex Matched controls) (n=105) n (%)	Unadjusted		Adjusted*	
			OR (95% CI) / Ratio of means (95% CI)	*p*-value	OR (95% CI) / Ratio of means (95% CI)	*p*-value
Death at discharge	13 (12.4)	4 (3.8)	5.49 (1.22, 24.75)	0.027	7.65 (0.73-79.66)	0.089
Length of stay	11.23 (12.79)	8.52 (10.32)	1.40 (1.07, 1.84)	0.016	1.50 (1.11-2.03)	0.008
Death at one month	18 (17.1)	6 (5.7)	3.41 (1.30, 8.98)	0.013	2.88 (0.85-9.79)	0.091
Death at 3 months	24 (22.9)	10 (9.5)	3.00 (1.28, 7.06)	0.012	2.81 (1.05-7.50)	0.040

* Adjusted for the presence of a past medical history of cardiovascular heart disease (defined as the presence of either heart failure, hypertension, ischaemic heart disease, myocardial infarction, valvular heart disease or a permanent pace-maker), renal function (estimated glomerular filtration rate) and C-reactive protein as continuous variables (see methods section).

Table 3: Risk of all-cause death in patients with incidentally raised cardiac troponin I (cTnI) (group 1) compared with patients diagnosed with acute coronary syndrome (ACS) (group 3).

	Group 1 (Incidentally raised Trop I) (n=105) n (%)	Group 3 (Patients with ACS) (n=105) n (%)	Unadjusted		Adjusted*	
			OR (95% CI) / Ratio of means (95% CI)	*p*-value	OR (95% CI) / Ratio of means (95% CI)	*p*-value
Death at discharge	13 (12.4)	9 (8.6)	1.51 (0.61,3.69)	0.37	1.39 (0.43-4.54)	0.585
Length of stay	11.23 (12.79)	7.68 (5.31)	1.13 (0.90,1.42)	0.294	1.26 (0.96-1.66)	0.097
Death at one month	18 (17.1)	10 (9.5)	1.97 (0.86,4.49)	0.109	1.77 (0.50-6.27)	0.379
Death at 3 months	24 (22.9)	13 (12.4)	2.10 (1.00,4.39)	0.049	2.39 (0.91-6.29)	0.079

* Adjusted for the presence of a past medical history of cardiovascular heart disease (defined as the presence of either heart failure, hypertension, ischaemic heart disease, myocardial infarction, valvular heart disease or a permanent pace-maker), renal function (estimated glomerular filtration rate) and C-reactive protein as continuous variables (see methods section).

Supplementary online Table 1: Risk of all-cause death in patients with incidentally raised cardiac troponin I (cTnI) (group 1) compared to age-sex matched controls without raised cTnI (group 2).

	Group 1 (Incidentally raised cTnI) (n=105) n (%)	Group 2 (Age-Sex Matched controls) (n=105) n (%)	Unadjusted		Adjusted*	
			OR (95% CI) / Ratio of means (95% CI)	*p*-value	OR (95% CI) / Ratio of means (95% CI)	*p*-value
Death at discharge	13 (12.4)	4 (3.8)	5.49 (1.22, 24.75)	0.027	18.03 (0.87,373.48)	0.061
Length of stay	11.23 (12.79)	8.52 (10.32)	1.40 (1.07, 1.84)	0.016	1.49 (1.11,2.02)	0.009
Death at one month	18 (17.1)	6 (5.7)	3.41 (1.30, 8.98)	0.013	7.72 (0.22,272.52)	0.261
Death at 3 months	24 (22.9)	10 (9.5)	3.00 (1.28, 7.06)	0.012	2.93 (1.00,8.55)	0.049

* Adjusted for the presence of a past medical history of cardiovascular heart disease (defined as the presence of either heart failure, hypertension, ischaemic heart disease, myocardial infarction, valvular heart disease or a permanent pace-maker), renal function (estimated glomerular filtration rate) and C-reactive protein as continuous variables (see methods section) and pre-morbid Rankin score.

Supplementary online Table 2: Risk of all-cause death in patients with incidentally raised cardiac troponin I (cTnI) (group 1) compared with patients diagnosed with acute coronary syndrome (ACS) (group 3).

	Group 1 (Incidentally raised Trop I) (n=105) n (%)	Group 3 (Patients with ACS) (n=105) n (%)	Unadjusted		Adjusted*	
			OR (95% CI) / Ratio of means (95% CI)	*p*-value	OR (95% CI) / Ratio of means (95% CI)	*p*-value
Death at discharge	13 (12.4)	9 (8.6)	1.51 (0.61,3.69)	0.37	1.04 (0.30,3.67)	0.951
Length of stay	11.23 (12.79)	7.68 (5.31)	1.13 (0.90,1.42)	0.294	1.28 (0.97,1.70)	0.08
Death at one month	18 (17.1)	10 (9.5)	1.97 (0.86,4.49)	0.109	1.01 (0.26,3.91)	0.987
Death at 3 months	24 (22.9)	13 (12.4)	2.10 (1.00,4.39)	0.049	1.78 (0.63,4.97)	0.274

* Adjusted for the presence of a past medical history of cardiovascular heart disease (defined as the presence of either heart failure, hypertension, ischaemic heart disease, myocardial infarction, valvular heart disease or a permanent pace-maker), renal function (estimated glomerular filtration rate) and C-reactive protein as continuous variables (see methods section) and pre-morbid Rankin score.