Prognostic value of troponins in acute coronary syndrome depends upon patient age

Phyo Kyaw Myint MD[1], Chun Shing Kwok MBBS[1,2], Max O Bachmann PhD[3], Susan Stirling MSc[3], Lee Shepstone PhD[3], M Justin S Zaman PhD[4]

1. School of Medicine & Dentistry, University of Aberdeen, Foresterhill, Aberdeen, UK.

2. Cardiovascular Institute, University of Manchester, Manchester, UK

3. Norwich Research Park Cardiovascular Research Group, Norwich, UK

4. Department of Medicine, James Paget University Hospital, Gorleston, UK

Correspondence to:

Phyo Kyaw Myint

Room 4:013

Polwarth Building

School of Medicine & Dentistry,

Division of Applied Health Sciences,

Foresterhill, University of Aberdeen,

Aberdeen, AB25 2ZD

UK

Tel: +44 (0) 1224 437957

Fax: +44 (0) 1603 286428

Mail to:phyo.myint@abdn.ac.uk

Keywords: acute coronary syndrome, age, cardiac troponin, mortality, oldest old, prognosis

Word count: 3,000

Abstract

Objective: This study aims to determine if the prognostic significance of troponins in acute coronary syndrome in predicting mortality varies by age, and if so, to what extent when other prognostic indicators are considered.

Methods: We analysed Myocardial Ischemia National Audit Project registry data collected between January 2006 and December 2010 and followed up this cohort for all-cause mortality until August 2011. Relationships between peak troponin levels (types I and T) and time to death in different age groups, and between age and time to death at different troponin levels were investigated using multiple variable adjusted Cox regression models.

Results: Of the 322,617 patients with acute coronary syndromes included, a third (n=106,365, 33%) died during 695,334 person-years of follow-up. Within each troponin category, older age was associated with a higher mortality even in those with a troponin <0.01 ng/ml for both troponin types (HR ~10-12 in ≥85 years cf. HR of 1.0 in <65 years). The relative potency of an elevated troponin to predict an adverse outcome compared to a low troponin attenuated with increased age (for troponin I ≥15.0 compared to troponin I <0.01 in age <65, adjusted HR 2.41 (95% confidence interval (CI) 1.80-3.24); age ≥85 HR 2.01 (1.62-2.52)). Similar but less consistent results were observed with troponin T elevation at the higher levels.

Conclusion: Clinicians should interpret the prognostic value of troponin taking into account the patient's age.

Key questions

What is already known about the subject?

- The prognostic significance of cardiac troponin is well documented but little research has focused on whether this varies with age.

What does this study add?

- We found the risk of mortality in older patients were very high compared to the younger patients even among patients with the lowest troponin levels.
- The magnitude of risk of mortality with similarly high troponin levels tended to decrease in older age group compared to younger age group.

How might this impact clinical practice?

- Clinicians should interpret the prognostic value of troponins taking into account of the patient's age.

Introduction

Cardiac troponins are both sensitive and specific markers of myocardial cell damage and have prognostic significance in acute coronary syndrome, with higher levels predicting worse outcomes.[1,2] Recent evidence suggests that levels of troponin I as low as 0.012-0.049 ng/ml carry a significant risk of recurrent myocardial infarction or death compared to a troponin I level of <0.012.[3] However, it is not known whether troponins have equal or more or less prognostic value in patients aged 65-84 years compared to those who are older (85+ years) and those who are younger(<65 years years).

Understanding the prognostic significance of troponins in older patients is important as there is a rapidly ageing population in developed world societies yet most clinical trials exclude patients with very old age. Acute coronary syndrome (ACS) is also more prevalent in older age and recent work by our group[4,5] and others[3] suggest that even a minimal rise in troponin may be associated with worse outcomes in older patients. Therefore it is likely that a troponin rise in older age may have a different prognostic value compared to those who are younger and may vary even within the older age spectrum.

Therefore, we aimed to address two related research questions: (1) does the prognostic significance of troponins in ACS in predicting mortality vary by age, and if so, (2) to what extent, when other prognostic indicators such as age, sex, co-morbidities, treatment receipt and site and level of care are also considered?

Methods

Study design and population

This was a cohort study of all patients aged 18 years or over in the United Kingdom Myocardial Ischemia National Audit Project (MINAP) database admitted to all 230 NHS hospital trusts in England and Wales between January 2006 and December 2010 who had a confirmed diagnosis of an acute coronary syndrome. For the purposes of this study, eligibility criteria were defined as any ACS as determined by the medical teams at time of discharge, including ST-segment elevation myocardial infarction (STEMI) and other acute coronary syndromes (non-ST elevation myocardial infarction (Non-STEMI), troponin negative ACS, threatened and unconfirmed myocardial infarction). The outcome was all-cause mortality outcome at follow up of up to August 2011. We deliberately excluded entries to MINAP prior to 2006 as the use of primary percutaneous coronary intervention in the UK was less than 10% before 2006.[6] Mortality was ascertained through linkage with the Office of National Statistics.[7]

Data collection

The MINAP dataset is contributed to by all 230 NHS trusts in England and Wales and uses a standardised data format that allows examination of pre-hospital and in-hospital care of all acute coronary syndromes, and is a part of the NHS data dictionary.[8] The development and initial findings of MINAP have been previously reported.[9,10] The dataset was collected by nurses and clinical audit staff and contains 123 fields.[11] The subset of variables included and description of variables are described in Data Supplement 1. We used the cut offs of <65 year, 65-74 years, 75-84 years and ≥85 years as age groups. Furthermore, we defined participants who were <65 years as young, participants who were 65-74 years as younger elderly, 75-84 years as older elderly and ≥85 as oldest old.

Statistical methods

We investigated associations between troponin levels, age group and other prognostic variables using Spearman correlation test for continuous variables, Cuzick non-parametric test for trend for binary variables and chi square test for other categorical variables. We estimated the independent effects of prognostic variables on time to death using Cox proportional hazards models. To assess the proportionality of hazards between age or troponin subgroups, postestimation complementary log log plots were constructed. These produced parallel lines for the different subgroups, confirming that hazards were proportional for the primary explanatory variables. Statistical tests of proportional hazards could be misleading, given the very large sample. All analyses were performed using Stata statistical software (Version 10.1, StatCorp, USA).

Missing values of variables other than troponin measurements were imputed using multiple imputation by chained equation method in STATA, assuming that data were missing at random.[12.13] In fact, previous imputation analyses on the MINAP dataset[14] have not significantly altered effect sizes and imply that missing data in MINAP is at random whilst work by others has also shown that the level of missing data does not alter regional standardised mortality ratios.[15]

Troponin I and T levels were used in the imputations, but for the statistical analyses patients with missing troponin levels were excluded from the respective analyses. We analysed 10 imputed datasets, with point estimates and standard errors calculated using Rubin's rules.[16] Analysis of baseline characteristics of participants was restricted to the complete data only but the Cox regression analyses presented results of the imputed data.

Analysis was stratified by the type of troponin measured (I and T) and age group (<65, 65-74, 75-84 and ≥85 years). For each troponin type, we re-categorised six categories (troponin specific) based on pre-specified cut off points. The cut off points for troponin I were <0.01, 0.01-0.049, 0.05-0.49, 0.5-2.49, 2.5-14.99 and ≥15.0. For troponin T the cut off points were <0.01, 0.01-0.049, 0.05-0.099, 0.1-0.49, 0.5-1.79 and ≥1.8). These cut off points represent respective percentile values equivalent to each other; the troponin I cut off points were predetermined first based on clinically meaningful cut off points at lower levels and then 25^{th}, 50^{th} and 75^{th} centile values and the equivalent troponin T values were determined based on similar percentile values.

The explanatory variables in the Cox models were troponin I or T levels, age group, sex, BMI, current smokers, family history of heart disease, STEMI or non-STEMI (any ACS other than STEMI as defined in this study), co-morbidities (hypertension, diabetes, MI, angina, stroke, heart failure, chronic renal failure, peripheral vascular disease), previous PCI, previous CABG, serum cholesterol, serum glucose, troponin group, medications prior to admission (aspirin, ACEi, beta-blocker, statin, clopidogrel), speciality of consultant in charge at the time of admission and admission ward. All of these variables were independently associated with time to death in the full models. We adjusted for medications that patients had been taking on admission because there were potential confounders that could affect survival. However, we did not include in the multivariate model medications that were started after the admission because there could have been a causal relationship between admission and subsequent death or survival.

We additionally tested whether age modified the effect of troponin and vice versa by adding age-troponin interaction variables to the Cox models, assessing statistical significance using Wald chi-squared tests. Hazard ratios for troponin within each age stratum and for age within each troponin stratum were estimated using linear combinations of terms after each regression.

Results

A total of 424,848 patient records were available in the MINAP registry over 5 years (2006-2010). After exclusion of patients with missing troponin and mortality data and those with a final diagnosis of non-ACS chest pain (e.g. pericarditis), the study cohort consisted of 322,617 participants. Peak troponin I and T were measured in 186,988 participants and 135,629 participants respectively. The mean age of the entire cohort was 70.0 (SD14.0) years and 208,343 participants (65%) were men. The mean follow up was just over 2.0 years (789±564 days; 695,334 person-years; median follow up 706 days (inter quartile range 308-1227 days).

The characteristics of the study sample by peak troponin specific group stratified by different age groups are shown in Table 1. There were a decreasing proportion of men, current smokers and participants with a positive family history of heart disease with older age groups. In all age groups, the most common known co-morbidities were hypertension and hyperlipidaemia, the former more common with older age, the latter less common. Older age was significantly associated with prevalence of prior cardiovascular disease and chronic renal failure. Prior PCI was most prevalent in participants from the youngest age group whilst prior CABG was most prevalent in those aged 65-84 years. With regards to peak troponin levels, lower levels of peak troponins were observed with older age. Except for aspirin, all other cardiac medication specific to ACS were used significantly less frequently in older age groups. Younger patients were more likely to be treated by a cardiologist and admitted to a coronary care unit. The proportion of patients with a confirmed diagnosis of STEMI decreased with age. The characteristics of the study sample stratified by peak troponin categories are shown in Supplementary Table 1. A total of 106,365 patients (33%) died during the follow-up. The crude mortality of oldest old (≥85 years) was very high compared

to those <65 years; >60% vs. 7-8% during the overall follow-up (Supplementary Figure 1). Mortality at 1-year were 44.5% and 4.6%, respectively. Comparing this to expected mortality of the same age categories of general population in the UK (data source: Office of National Statistics. Death registration by single year of age http://www.ons.gov.uk/ons/rel/vsob1/death-registrations-by-single-year-of-age/united-kingdom-2011/index.html) confirms the disproportionate incremental increase with older age (see Supplementary Figure 2).

The hazard ratios for mortality in older age groups compared to the youngest age group, stratified by troponins levels, are shown in Table 2 and Figure 1. Within each troponin category, older age was associated with a higher mortality and whilst adjusting for all potential confounders attenuated the higher risk of death with increased age, the results remained highly significant statistically. Even in the lowest category level of troponins I and T (<0.01 ng/ml), older patients had very high mortality compared to younger patients (HRs for oldest old age group (≥85 years) compared to young age group (<65 years; reference hazard ratio of 1.00) showed adjusted HRs 11.70 and 9.24 respectively for troponin I and T). The age-troponin interaction term was statistically significant for both troponin I and troponin T models (P<0.0001).

The hazards ratios of mortality associated with troponin levels stratified by age are shown in Table 3 and Figure 2. Higher troponin levels were associated with increasing risk of mortality in all age groups. However, the relative potency of an elevated troponin to predict an adverse outcome compared to a low troponin attenuated with increased age (for troponin I ≥15.0 compared to troponin I <0.01 in age <65, adjusted HR 2.41 (95% confidence interval (CI) 1.80-3.24); age ≥85 HR 2.01 (1.62-2.52)). A similar attenuation was observed for

troponin T up to troponin levels of 0.1; however at levels higher than 0.1, the relative potency of troponin to predict an adverse outcome did not attenuate with increased age.

Secondary sensitivity analyses by additionally adjusting for discharge medications and reperfusion strategies in the model did not alter the results (data not shown).

Discussion

Our results showed that in any age group, higher troponin levels were associated with increasing risk of mortality. We found very high mortality rates in older patients even at the lowest troponin values. There was an attenuation of the prognostic value of troponins in older age. Thus, the prognostic value of troponins depends on patient age in acute coronary syndrome.

The very high mortality rates in older patients even at the lowest troponin values usually regarded as normal (<0.04) may be partly explained by frailty and other unknown confounders; there may also be differences in care delivered for older patients with ACS as with increasing age, we found cardiac medication specific to ACS were used significantly less frequently in older age groups. Our observations show that older patients are less likely to be managed by cardiologists, less likely to be managed in coronary care units, intensive care units and cardiac wards. Other studies have also found that older patients were more likely to receive medical treatments[17] and are less likely to receive evidence-based treatments, including myocardial revascularisation therapy.[18] Therefore, the higher mortality we report in the older patient with ACS might be associated with poor physiological reserve, frailty and increased co-morbidity but equally may be driven by lesser receipt of evidence-based treatments and the fact they tend to be managed with a more conservative strategy compared to younger patients.

Due to uncertainties around the benefits of the invasive interventions, despite their higher risk of adverse clinical outcomes following ACS, older patients may often be managed with more conservative strategies compared to younger patients.[19] Although, there is evidence to suggest that adherence to guideline-recommended therapy is associated with a

decrease in mortality, [20] the management of ACS in older age is challenging. It is well documented that older patients are more likely to present atypically (e.g. with dyspnoea rather than chest pain) compared to younger patients with ACS[21] and it has been suggested that there are high misdiagnosis rates and inappropriate discharge rates for ACS particularly in older populations.[22,23]. Our study is limited to those who were entered into the MINAP registry and this might have introduced some selection bias and thus the estimated hazard risks in the oldest old might have been underestimated.

We found interestingly that even with the lowest troponin levels in ACS, the risk of death in older patients was very high (even higher than the other troponin groups) compared to younger counterparts. The exact reason for this is unclear. A recent cohort study suggests that lowering the troponin I threshold using the lowest percentile as cut off point would identify more patients with acute coronary syndrome who are at risk of recurrent myocardial infarction and death.[3] It is possible that patients with lowest troponin had myocardial damage but because the peak troponin value was not very high they were not adequately investigated and treated. However, we adjusted for a large number of potential confounders.

We have previously found that "incidental rises in troponin" in older patients in the absence of evidence of ACS (STEMI or NSTEMI) and any other known causes of troponin elevation predicted outcomes comparable to those of someone having had an ACS.[5] We postulated that the minimal rise in cardiac troponins in such circumstances may be related to myocardial necrosis and perhaps served as a prognostic marker indicating cardiac frailty in older patients with general illness other than an ACS. Studies suggest that even mild transient elevations of troponin levels are associated with increased mortality and major cardiovascular events in the general population.[24,25] It has been suggested that microvascular coronary artery disease in congestive heart failure, diabetes and chronic kidney disease may cause

troponin elevations. In heart failure, left ventricular strain, decreased subendothelial perfusion, endothelial dysfunction and apoptosis may cause troponin rises and microvascular disease are known to occur in diabetes and chronic kidney disease.[25] In addition, older people may not have as high a troponin rise as in younger people despite having a similar extent of cardiac damage because age related physiological changes in cardiac myocytes may influence the response to injury.

For the first time, we report the attenuation of the prognostic value of troponins in older age. It is possible that this attenuation may be apparent due to very high baseline risk in older patients even in the troponin values which fell within normal reference range. The other plausible reason behind this is that with increasing age, the global risk factor profile worsens and thus these competing risks may attenuate the prognostic significance of troponins in older age. Clinicians should be aware that troponin values in isolation do not provide the whole prognostic outlook of the patient.

Our study has several strengths. First, we analysed a large sample which captures sufficient variations of patients in all ages and troponin levels. As the MINAP data is based on all NHS trusts in England and Wales, the findings are representative of UK and Western populations in general. Secondly, we were able to adjust for individual prognostic factors and a variety of potential confounding factors which may affect mortality outcome. We were also able to consider both troponins I and T separately, and have shown similar results in both allowing us more confidence in the validity of these findings. Furthermore, we included patients since 2006 only to allow comparison to contemporary standards of management of ACS.

Study limitations

Our study has some limitations. First, most patients had some prognostic data missing, which we replaced using multiple imputation and meant we were unable to undertake a complete dataset analysis. The primary outcome was all-cause mortality and we were unable to determine if the cause of death was related to a cardiac pathology. Although we have adjusted for several potential confounders, there remains the possibility of residual confounding. Whilst we were able to take into account whether the initial care was delivered by a cardiologist or non-cardiologist, we could not establish if the subsequent care may have involved a cardiologist. One other limitation was that we did not have information on reperfusion therapy for patients. However, previously analyses within MINAP have reported that receipt of evidence-based cardiac medications post ACS is less in older age groups, [26] and we expect that our cohort will be similar to other cohorts in literature where it has been reported that younger patients are more likely to receive reperfusion therapy [27]. Another limitation was that we do not have information on time to therapy as we expect that delay in presentation may be associated with delayed treatment and worse outcomes. However chest pain in older person is usually associated with a heart attack compared to a younger person and we have no reason to believe age would have influenced the health seeking behaviour particularly with regard to chest pain.

Future studies

Future studies should evaluate the prognostic value of re-defining the cut off points for troponins based on the patient's age. Furthermore, randomised trials should examine whether targeted assessments and interventions would improve the outcome in patients in older age with ACS including those with minimal troponin rise regardless of the clinical diagnosis. These future randomised studies should also consider the feasibility, clinical and

cost effectiveness of individually tailored specialised management of ACS in older age, who currently remain at high risk following ACS but have concomitantly less specialist cardiology input.

Conclusions

In conclusion, we have shown that the prognostic significance of troponin in ACS attenuates with increased age and that older age is associated with a worse prognosis compared to younger counterparts given the same level of troponin rise, even at very low levels of troponin. Therefore, the age of the patient should be taken into consideration when assessing the prognosis of a patient given a raised troponin value for prognostication in ACS based on this evidence.

Contributorship statement:

Phyo Kyaw Myint and M Justin S Zaman planned the study. Chun Shing Kwok, Max O Bachmann and Susan Stirling analysed the data. All authors contributed to the interpretation of the findings and reporting of the work. Phyo Kyaw Myint is responsible for the overall content as the guarantor.

Funding:

This work was undertaken by the research team led by Phyo Kyaw Myint and M Justin S Zaman and funded by the Sir Halley Stewart Trust. The views expressed within this article are those of authors' and not necessarily those of the Trust.

Competing interests:

The authors have no conflicts of interest to declare.

Acknowledgements:

We would like to thank our funder, The Sir Halley Stewart Trust, for the funding support and the MINAP Academic Steering Committee for their approval to conduct the project.

References

1. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;**335**:1342-9.
2. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. N Engl J Med 1996;**335**:1333-41.
3. Mills NL, Lee KK, McAllister DA, et al. Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction: cohort study. BMJ 2012;**344**:e1533.
4. Myint PK, Al-Jawad M, Chacko SM, Chu GS, Vowler SL, May HM. Prevalence, characteristics and outcomes of people aged 65 years and over with an incidental rise in cardiac troponin I. An observational prospective cohort study. Cardiology 2008;**110**:62-7.
5. Zaman MJ, Vrotsou K, Chu GS, May HM, Myint PK. A high incidental rise in cardiac troponin I carries a higher mortality risk in older patients than in those with a diagnosed acute coronary syndrome. Age Ageing 2011;**40**:122-5.
6. West RM, Cattle BA, Bouyssie M, et al. Impact of hospital proportion and volume on primary percutaneous coronary intervention performance in England and Wales. Eur Heart J. 2011;**32**:706-11
7. Herrett E, Smeeth L, Walker L, Weston C, and on behalf of the MINAP Academic Group. The Myocardial Ischaemia National Audit Project (MINAP). Heart 2010; **96**:1264-67.
8. Myocardial Ischaemia National Audit Project (MINAP). Available at: http://www.hqip.org.uk/myocardial-ischaemia-national-audit-project-minap/. Accessed July 8, 2013.

9. Birkhead JS, Pearson M, Norris RM, Rickards AF, Georgiou A. The national audit of myocardial infarction: a new development in the audit process. Journal of Clinical Excellence 2002;4:379-85.
10. Birkhead JS, Walker L, Pearson M, Weston CM, Cunningham AD, Rickards AF. Improving care for patients with acute coronary syndromes: initial results from the national audit of myocardial infarction project (MINAP). Heart 2004;**90**:1004-9.
11. MINAP steering group. Myocardial Ischaemia National Audit Project [MINAP] How the NHS cares for patients with heart attacks. Ninth Public Report 2010. Available at: http://www.rcplondon.ac.uk/sites/default/files/minap-public-report-sept-2010.pdf. Accessed July 8, 2013.
12. Royston P. Multiple imputation of missing values. The Stata Journal 2004;**4**: 227-241.
13. Royston P. Multiple imputation of missing values: update of ice. The Stata Journal 2005;**5**:527-536.
14. Zaman MJ, Philipson P, Chen R, et al. South Asians and coronary disease: is there discordance between effects on incidence and prognosis? Heart. 2013;**99**:729-36.
15. Gale CP, Cattle BA, Moore J, Dawe H, Greenwood DC, West RM. Impact of missing data on standardised mortality ratios for acute myocardial infarction: evidence from the Myocardial Ischaemia National Audit Project (MINAP) 2004-7. Heart. 2011;**97**:1926-31.
16. Rubin D. Multiple Imputation for Nonresponse in Surveys. New York: Wiley, 1987.
17. Rosengren A, Wallentin L, Simoons M, et al. Age, clinical presentation, and outcome of acute coronary syndrome in the Euroheart acute coronary syndrome survey. Eur Heart J 2005;**27**:789-95.
18. Carro A, Kaski JC. Myocardial infarction in the Elderly. Aging Dis 2011;**2**:116-137.

19. Carro A, Bastiaenen R, Kaska JC. Age related issues in reperfusion of myocardial infarction. Cardiovasc Drugs Ther 2011;**25**:139-48.
20. Skolnick AH, Alexander KP, Chen AY, et al. Characteristic, management and outcomes of 5,557 patients aged ≥90 years with acute coronary syndromes. J Am Coll Cardiol 2007;**49**:1790-7.
21. Woon VC, Lim KH. Acute Myocardial Infarction in the Elderly – The Differences Compared with the Young. Singapore Med J 2003;**44**:414-418.
22. Hung CL, Jia-Yin C, Yeh, HI, Change WH. Atypical chest pain in the elderly: prevalence, possible mechanisms and prognosis. Int J Gerotology 2010;**4**:1-8.
23. Rich MW. Epidemiology, clinical features, and prognosis of acute myocardial infarction in the elderly. Am J Geriatr Cardiol 2006;**15**:7-11.
24. Gudmundsson GS, Kahn SE, Moran JF. Association of mild transient troponin I levels with increased mortality and major cardiovascular events in the general patient population. Arch Path Lab Med 2005;**129**:474-80.
25. Wallace TW, Abdullah SM, Drazner MH, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;**113**:1958-65.
26. Zaman MJ, Stirling S, Shepstone L, Ryding A, Flather M, Bachmann M, Myint PK. Eur Heart J 2014; doi: 10.1093.
27. Lievesley N. Ageism and age discrimination in secondary health care in the United Kingdom. A review from the literature carried out on behalf of the Department of Health. Centre for Policy on Ageing, 2009.

Table and Figure legends

Table 1: Troponin assay specific baseline characteristics of 322,617 men and women of the MINAP acute coronary syndrome cohort (2006-2011) according to age category by different troponin assays

Table 2: Troponin specific unadjusted and adjusted hazards ratios and their corresponding 95% confidence intervals for the risk of mortality for people in the older age groups compared to the people in the youngest age group (<65 years) within troponin strata

Table 3: Unadjusted and adjusted hazards ratios and their corresponding 95% confidence intervals for mortality for higher troponin level categories compared to the lowest level of troponin (<0.01 ng/ml) within the same age strata

Supplementary Table 1: Troponin assay specific baseline characteristics of 322,617 men and women of the MINAP acute coronary syndrome cohort (2006-2011) according to different troponin categories

Supplementary Table 2: Comparison of baseline characteristics of the included and excluded cohort

Figure 1: Adjusted hazards ratios (95% confidence intervals) of mortality according to various age groups within troponin strata

Figure 2: Adjusted hazard ratios (95% confidence intervals) of mortality according to various levels of peak troponin categories within age strata

Supplementary Figure 1: Crude mortality rates (95% confidence intervals) at follow up (August 2011) in different age groups by peak troponin categories

Supplementary Figure 2: Crude mortality rates (95% confidence intervals) compared to expected mortality of similar age categories at follow up (August 2011) for the oldest and youngest age groups by peak troponin categories

Data Supplement 1: MINAP description of variables in analysis and definitions of variables

Table 1: Troponin assay specific baseline characteristics of 322,617 men and women of the MINAP acute coronary syndrome cohort (2006-2011) according to age category by different troponin assays

Variable*	**Troponin I cohort (n=186,988)**					**Troponin T cohort (n=135,629)**				
Age group (years)	<65 (n=65,761)	65-74 (n=44,564)	75-84 (n=49,611)	≥85 (n=27,052)	P value‡	<65 (n=47,123)	65-74 (n=31,527)	75-84 (n=36,163)	≥85 (n=20,816)	P-value†
Men	51,292 (78)	29,831 (67)	27,762 (56)	11,576 (43)	<0.0001	36,984 (79)	21,272 (68)	20,475 (57)	9,151 (44)	<0.0001
BMI (kg/m^2)	29 (6)	28 (6)	26 (5)	24 (5)	<0.0001	29 (6)	28 (5)	26 (5)	25 (5)	<0.0001
Current smokers	29,413 (47)	9,362 (22)	5,134 (11)	1,191 (5)	<0.0001	22,359 (49)	7,125 (24)	4,027 (12)	977 (5)	<0.0001
IMD score	23 (16)	21 (15)	20 (15)	19 (14)	<0.0001	27 (17)	25 (17)	23 (16)	22 (15)	<0.0001
Family history of heart disease	26,881 (47)	11,499 (32)	7,945 (21)	2,218 (11)	<0.0001	19,105 (49)	8,216 (35)	6,087 (24)	1,915 (15)	<0.0001
Prior co-morbidities										
Hyperlipidemia	23,196 (37)	17,366 (41)	16,805 (36)	6,231 (25)	<0.0001	15,022 (35)	11,501 (40)	11,593 (35)	4,822 (26)	<0.0001
Hypertension	26,122 (41)	23,823 (55)	28,673 (60)	14,763 (57)	<0.0001	17,792 (40)	16,029 (54)	20,214 (59)	11,138 (57)	<0.0001
Diabetes	10,444 (16)	10,908 (25)	12,119 (25)	4,629 (18)	<0.0001	7,054 (15)	7,603 (25)	8,510 (24)	3,556 (18)	<0.0001
MI	12,631 (20)	12,916 (30)	16,876 (35)	9,284 (35)	<0.0001	8,331 (19)	8,413 (28)	11,781 (34)	6,842 (35)	<0.0001
Angina	13,149 (21)	14,803 (35)	19,868 (42)	11,090 (43)	<0.0001	9,422 (21)	10,103 (34)	14,382 (42)	8,570 (44)	<0.0001
Heart failure	1,116 (2)	2,160 (5)	4,327 (9)	3,463 (13)	<0.0001	849 (2)	1,600 (5)	3,289 (10)	2,679 (14)	<0.0001
Stroke	2,235 (4)	3,860 (9)	6,149 (13)	3,823 (15)	<0.0001	1,645 (4)	2,738 (9)	4,567 (14)	3,025 (16)	<0.0001
Chronic renal failure	1,262 (2)	2,155 (5)	4,140 (9)	2,742 (11)	<0.0001	1,000 (2)	1,515 (5)	2,911 (9)	1,999 (10)	<0.0001
PVD	1,756 (3)	2,378 (6)	2,874 (6)	1,207 (5)	<0.0001	1,319 (3)	1,755 (6)	2,334 (7)	994 (5)	<0.0001
Prior interventions										
PCI	7,530 (12)	5,671 (13)	4,666 (10)	1,088 (4)	<0.0001	5,042 (12)	3,585 (12)	3,012 (9)	729 (4)	<0.0001
CABG	2,926 (5)	4,456 (10)	4,588 (10)	948 (4)	<0.0001	1,892 (4)	2,922 (10)	3,124 (9)	712 (4)	<0.0001
Biochemical results										
Troponin (ng/ml)	16.8 (27.3)	14.1 (24.5)	12.7 (23.1)	11.8 (21.9)	<0.0001	3.11 (13.23)	2.91 (13.26)	2.77 (12.64)	2.79 (14.10)	<0.0001

Cholesterol (mmol/L)	5.2 (1.6)	4.6 (1.5)	4.3 (1.5)	4.2 (1.6)	<0.0001	5.2 (1.6)	4.6 (1.6)	4.3 (1.6)	4.1 (1.7)	<0.0001
Glucose (mmol/L)	7.9 (4.6)	8.4 (4.7)	8.5 (4.6)	8.4 (4.5)	<0.0001	8.1 (5.4)	8.6 (5.5)	8.7 (5.4)	8.4 (4.6)	<0.0001
Admission medications										
ACE inhibitor	17,689 (30)	16,642 (42)	20,199 (46)	10,098 (41)	<0.0001	12,550 (30)	11,517 (41)	14,619 (45)	7,734 (41)	<0.0001
Beta blocker	14,745 (25)	13,331 (34)	16,107 (36)	8,350 (34)	<0.0001	10,760 (26)	9,142 (33)	11,644 (36)	6,557 (35)	<0.0001
Statin	21,869 (36)	20,911 (52)	24,429 (54)	10,940 (44)	<0.0001	15,875 (37)	14,711 (51)	17,801 (54)	8,452 (44)	<0.0001
Clopidogrel	5,279 (15)	4,365 (19)	4,997 (19)	2,446 (18)	<0.0001	5,020 (18)	3,698 (20)	4,565 (21)	2,419 (20)	<0.0001
Aspirin	36,256 (55)	26,241 (59)	28,556 (58)	14,674 (54)	0.414	26,282 (56)	18,607 (59)	20,973 (58)	11,568 (56)	0.109
Management, setting and diagnosis										
Cardiologist as lead consultant	34,088 (53)	20,480 (47)	18,570 (38)	7,086 (27)	<0.0001	26,091 (56)	15,557 (50)	14,899 (42)	6,767 (33)	<0.0001
Admission ward										
CCU	36,448 (60)	21,426 (51)	19,830 (43)	8,373 (34)	<0.0001	30,521 (67)	17,932 (60)	17,474 (53)	7,872 (43)	<0.0001
ITU	959 (2)	775 (2)	636 (1)	150 (1)		778 (2)	538 (2)	487 (1)	119 (1)	
Cardiac ward	5,544 (9)	3,979 (9)	4,254 (9)	2,038 (8)		2,948 (7)	2,236 (8)	2,505 (8)	1,384 (8)	
Other	19,262 (31)	15,773 (38)	21,150 (46)	13,748 (57)		11,102 (24)	9,077 (30)	12,626 (38)	8,763 (48)	
Diagnosis										
STEMI	27,022 (41)	13,706 (31)	11,972 (24)	5,328 (20)	<0.0001	22,054 (47)	11,361 (36)	10,206 (28)	4,716 (23)	<0.0001
ACS but not STEMI	38,739 (59)	30,858 (69)	37,639 (76)	21,724 (80)		25,069 (53)	20,166 (64)	25,957 (72)	16,100 (77)	
Outcome										
Death at follow up	4,398 (7)	8,793 (20)	18,991 (38)	16,181 (60)	<0.0001	3,593 (8)	6,818 (22)	15,394 (43)	13,367 (64)	<0.0001

* Results reported as mean (SD) for continuous variables and n (%) for categorical variables. † Spearman correlation test for continuous variables, Chi square test for admission ward, Cuzick non-parametric test for trend for binary variables were used. BMI = body mass index; IMD = index of multiple deprivation; MI= myocardial infarction; PVD= peripheral vascular disease; PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, CCU = coronary care unit, ITU = intensive care unit, STEMI = ST elevation myocardial infarction, ACS = acute coronary syndrome

Table 2: Troponin specific unadjusted and adjusted hazards ratios and their corresponding 95% confidence intervals for the risk of mortality for people in the older age groups compared to the people in the youngest age group (<65 years) within troponin strata

Troponin I (n=185,510)							
Age group	**Unadjusted hazards ratio (95% CI)**						
	<0.01	0.01-0.049	0.05-0.49	0.5-2.49	2.5-14.99	≥15.0	All troponin I levels
<65	1.00	1.00	1.00	1.00	1.00	1.00	1.00
65-74	3.49 (2.46-4.97)	2.74 (2.14-3.52)	3.18 (2.92-3.46)	3.17 (2.92-3.45)	3.31 (3.09-3.56)	3.26 (3.05-3.49)	3.23 (3.11-3.35)
75-84	7.28 (5.20-10.19)	5.42 (4.30-6.84)	6.63 (6.14-7.16)	6.78 (6.29-7.31)	7.60 (7.13-8.11)	7.78 (7.32-8.27)	7.25 (7.01-7.49)
≥85	19.45 (13.56-27.91)	13.07 (10.07-16.95)	12.56 (11.62-13.58)	13.55 (12.56-14.62)	14.36 (13.45-15.32)	15.82 (14.86-16.84)	14.29 (13.81-14.79)
	Adjusted hazards ratio (95% CI)*						
<65	1.00	1.00	1.00	1.00	1.00	1.00	1.00
65-74	2.90 (2.04-4.13)	2.25 (1.76-2.89)	2.50 (2.30-2.72)	2.46 (2.27-2.68)	2.64 (2.46-2.84)	2.72 (2.54-2.91)	2.61 (2.51-2.71)
75-84	5.32 (3.79-7.46)	3.91 (3.10-4.93)	4.43 (4.10-4.79)	4.51 (4.18-4.88)	5.18 (4.84-5.54)	5.50 (5.16-5.87)	4.97 (4.78-5.16)
≥85	11.70 (8.14-16.81)	8.20 (6.31-10.65)	7.34 (6.76-7.97)	8.19 (7.55-8.87)	8.63 (8.04-9.26)	9.77 (9.12-10.46)	8.59 (8.22-8.97)
Troponin T (n=134,547)							
Age group	**Unadjusted hazards ratio (95% CI)**						
	<0.01	0.01-0.049	0.05-0.099	0.1-0.49	0.5-1.79	≥1.8	All troponin T levels
<65	1.00	1.00	1.00	1.00	1.00	1.00	1.00

65-74	2.58 (2.16-3.09)	2.87 (2.35-3.50)	2.75 (2.34-3.23)	3.24 (3.02-3.49)	3.20 (2.95-3.48)	3.09 (2.86-3.35)	3.13 (3.00-3.26)
75-84	6.27 (5.33-7.38)	6.05 (5.06-7.23)	6.03 (5.22-6.97)	6.97 (6.52-7.45)	7.67 (7.11-8.27)	7.43 (6.92-7.97)	7.24 (6.98-7.52)
≥85	11.84 (9.90-14.17)	10.35 (8.63-12.41)	11.12 (9.63-12.85)	12.89 (12.05-13.78)	14.86 (13.77-16.04)	15.67 (14.57-16.85)	13.96 (13.44-14.49)
	Adjusted hazards ratio (95% CI)*						
<65	1.00	1.00	1.00	1.00	1.00	1.00	1.00
65-74	2.19 (1.83-2.63)	2.26 (1.86-2.76)	2.17 (1.85-2.55)	2.55 (2.36-2.74)	2.52 (2.32-2.75)	2.55 (2.36-2.76)	2.50 (2.39-2.61)
75-84	4.74 (4.02-5.60)	4.03 (3.37-4.82)	3.96 (3.43-4.58)	4.64 (4.33-4.97)	5.08 (4.70-5.49)	5.19 (4.83-5.58)	4.83 (4.63-5.04)
≥85	9.24 (7.69-11.11)	6.20 (5.15-7.45)	6.60 (5.69-7.66)	7.69 (7.16-8.26)	8.82 (8.12-9.58)	9.48 (8.78-10.25)	8.27 (7.89-8.66)

* adjusted for age group, sex, body mass index, current smokers, family history of heart disease, STEMI or non-STEMI, co-morbidities (hypertension, diabetes, MI, angina, stroke, heart failure, chronic renal failure, peripheral vascular disease), previous PCI, previous CABG, serum cholesterol, serum glucose, troponin group, admission medications (aspirin, ACEi, beta-blocker, statin, clopidogrel), admission consultant, admission ward.

Table 3: Unadjusted and adjusted hazards ratios and their corresponding 95% confidence intervals for mortality for higher troponin level categories compared to the lowest level of troponin (<0.01 ng/ml) within the same age strata

Troponin I (n=185,510)	**Unadjusted hazards ratio (95% CI)**				
	<65	65-74	75-84	≥85	All troponin I levels
<0.01	1.00	1.00	1.00	1.00	1.00
0.01-0.049	1.13 (0.79-1.60)	0.88 (0.69-1.14)	0.84 (0.68-1.04)	0.76 (0.58-1.00)	0.92 (0.81-1.05)
0.05-0.49	1.89 (1.40-2.55)	1.72 (1.40-2.12)	1.72 (1.45-2.05)	1.22 (0.98-1.52)	2.20 (1.98-2.45)
0.5-2.49	2.16 (1.61-2.91)	1.96 (1.59-2.41)	2.01 (1.69-2.39)	1.59 (1.26-2.02)	2.68 (2.41-2.98)
2.5-14.99	2.14 (1.59-2.87)	2.03 (1.65-2.49)	2.23 (1.88-2.66)	1.58 (1.27-1.96)	2.72 (2.44-3.02)
≥15.0	2.10 (1.56-2.81)	1.96 (1.59-2.40)	2.24 (1.88-2.67)	1.71 (1.37-2.12)	2.33 (2.09-2.59)
	Adjusted hazards ratio (95% CI)*				
<0.01	1.00	1.00	1.00	1.00	1.00
0.01-0.049	1.23 (0.86-1.74)	0.95 (0.74-1.23)	0.90 (0.73-1.12)	0.86 (0.65-1.13)	0.94 (0.83-1.07)
0.05-0.49	1.95 (1.45-1.63)	1.69 (1.37-2.08)	1.63 (1.36-1.94)	1.23 (0.98-1.53)	1.56 (1.40-1.73)
0.5-2.49	2.22 (1.65-2.99)	1.89 (1.53-2.33)	1.89 (1.58-2.25)	1.64 (1.29-2.08)	1.85 (1.66-2.06)
2.5-14.99	2.26 (1.69-3.04)	2.06 (1.68-2.54)	2.21 (1.85-2.63)	1.67 (1.34-2.08)	2.05 (1.84-2.28)
≥15.0	2.41 (1.80-3.24)	2.27 (1.84-2.79)	2.50 (2.09-2.98)	2.01 (1.62-2.52)	2.34 (2.10-2.61)
Troponin T (n=134,547)	**Unadjusted hazards ratio (95% CI)**				
	<65	65-74	75-84	≥85	All troponin T levels

<0.01	1.00	1.00	1.00	1.00	1.00
0.01-0.049	1.77 (1.43-2.19)	1.97 (1.67-2.32)	1.71 (1.52-1.92)	1.55 (1.34-1.78)	2.32 (2.15-2.49)
0.05-0.099	2.08 (1.72-2.52)	2.22 (1.91-2.57)	2.00 (1.80-2.23)	1.96 (1.72-2.23)	2.81 (2.63-3.01)
0.1-0.49	1.95 (1.68-2.27)	2.45 (2.17-2.77)	2.17 (1.98-2.38)	2.45 (2.10-2.85)	2.98 (2.81-3.15)
0.5-1.79	1.80 (1.55-2.10)	2.24 (1.97-2.54)	2.20 (2.00-2.42)	2.26 (2.00-2.55)	2.78 (2.62-2.95)
≥1.80	1.87 (1.62-2.18)	2.25 (1.99-2.56)	2.22 (2.02-2.45)	2.49 (2.20-2.81)	2.47 (2.33-2.62)
	Adjusted hazards ratio (95% CI)*				
<0.01	1.00	1.00	1.00	1.00	1.00
0.01-0.049	1.78 (1.44-2.20)	1.83 (1.56-2.16)	1.51 (1.34-1.70)	1.19 (1.03-1.38)	1.49 (1.39-1.61)
0.05-0.099	2.04 (1.69-2.47)	2.02 (1.74-2.34)	1.71 (1.53-1.90)	1.46 (1.27-1.67)	1.73 (1.61-1.85)
0.1-0.49	1.92 (1.65-2.23)	2.23 (1.97-2.52)	1.88 (1.71-2.06)	1.83 (1.56-2.14)	1.88 (1.77-1.99)
0.5-1.79	1.91 (1.64-2.22)	2.19 (1.93-2.49)	2.04 (1.85-2.25)	1.82 (1.60-2.06)	2.03 (1.91-2.16)
≥1.80	2.19 (1.88-2.54)	2.54 (2.24-2.89)	2.39 (2.17-2.64)	2.24 (1.97-2.55)	2.40 (2.26-2.55)

* adjusted for age group, sex, body mass index, current smokers, family history of heart disease, STEMI or non-STEMI, comorbidities (hypertension, diabetes, MI, angina, stroke, heart failure, chronic renal failure, peripheral vascular disease), previous PCI, previous CABG, serum cholesterol, serum glucose, troponin group, admission medications (aspirin, ACEi, beta-blocker, statin, clopidogrel), admission consultant, admission ward.

Supplementary Table 1: Troponin assay specific baseline characteristics of 322,617 men and women of the MINAP acute coronary syndrome cohort (2006-2011) according to different troponin categories

Variables†	**Troponin I cohort (n=186,988)**							**Troponin T cohort (n=135,629)**						
	<0.01 (n=2,948)	0.01-0.049 (n=6,006)	0.05-0.49 (n=40,730)	0.5-2.49 (n=38,353)	2.5-14.99 (n=49,616)	≥15 (n=49,335)	P-value‡	<0.01 (n=9,661)	0.01-0.049 (n=6,929)	0.05-0.099 (n=9,371)	0.1-0.49 (n=43,395)	0.5-1.79 (n=32,720)	≥1.8 (n=33,553)	P-value‡
Age group (years)							<0.0001							<0.0001
<65	1,402 (48)	2,654 (44)	13,340 (33)	11,851 (31)	20,166 (41)	22,262 (40)		4,550 (47)	2,139 (31)	2,849 (30)	13,181 (30)	11,001 (34)	13,403 (40)	
65-74.9	802 (27)	1,640 (27)	9,919 (24)	9,006 (23)	11,552 (23)	12,884 (23)		2,521 (26)	1,647 (24)	2,152 (23)	9,940 (23)	7,504 (23)	7,763 (23)	
75-84.9	575 (20)	1,362 (23)	11,211 (28)	10,975 (29)	11,718 (24)	13,329 (24)		1,879 (19)	2,010 (29)	2,623 (28)	12,479 (29)	8,961 (27)	8,211 (24)	
≥85	169 (6)	350 (6)	6,260 (15)	6,521 (17)	5,899 (12)	6,790 (12)		711 (7)	1,133 (16)	1,747 (19)	7,795 (18)	5,254 (16)	4,176 (12)	
Male gender	1,905 (65)	3,965 (66)	24,841 (61)	22,929 (60)	31,760 (64)	35,061 (71)	<0.0001	6,288 (65)	4,458 (64)	5,909 (63)	26,657 (62)	20,950 (64)	23,620 (71)	<0.0001
BMI (kg/m^2)	28 (6)	28 (6)	28 (6)	27 (6)	27 (6)	27 (6)	<0.0001	28 (6)	28 (6)	28 (6)	27 (6)	27 (6)	27 (5)	<0.0001
Current smoker	608 (22)	1,193 (21)	8,054 (21)	8,275 (23)	11,797 (26)	15,173 (33)	<0.0001	2,238 (24)	1,422 (22)	1,970 (23)	9,750 (24)	8,476 (28)	10,632 (34)	<0.0001
Index of multiple deprivation score	28 (6)	28 (6)	28 (6)	27 (6)	27 (6)	27 (6)	<0.0001	26 (17)	26 (17)	24 (16)	25 (17)	24 (17)	24 (17)	<0.0001
Family history of heart disease	1,043 (42)	2,040 (45)	10,297 (31)	9,197 (30)	12,403 (31)	13,563 (33)	<0.0001	3,165 (42)	1,676 (33)	2,341 (35)	10,707 (34)	8,377 (35)	9,057 (35)	0.917
Prior comorbidities														
Hyperlipidaemia	1,393 (49)	2,726 (49)	15,014 (39)	12,961 (36)	16,332 (35)	15,172 (33)	<0.0001	4,392 (48)	2,689 (41)	3,213 (37)	14,106 (36)	9,439 (32)	9,099 (30)	<0.0001
Hypertension	1,612 (56)	3,312 (58)	21,974 (56)	19,736 (53)	24,682 (52)	22,065 (47)	<0.0001	5,158 (55)	3,715 (56)	4,781 (54)	21,942 (53)	15,183 (49)	14,394 (46)	<0.0001

Diabetes	604 (21)	1,271 (22)	9,333 (23)	8,530 (23)	10,220 (21)	8,142 (17)	<0.0001	1,982 (21)	1,675 (25)	2,191 (24)	9,436 (22)	6,189 (20)	5,250 (16)	<0.0001
MI	1,092 (38)	2,394 (41)	14,059 (36)	11,613 (31)	13,313 (28)	9,236 (19)	<0.0001	3,516 (37)	2,468 (37)	3,012 (34)	12,808 (31)	7,796 (25)	5,767 (18)	<0.0001
Angina	1,353 (47)	3,121 (54)	16,298 (42)	13,069 (35)	14,695 (31)	10,374 (22)	<0.0001	4,928 (52)	3,063 (46)	3,636 (41)	14,903 (37)	9,195 (30)	6,752 (22)	<0.0001
Heart failure	124 (4)	233 (5)	3,085 (8)	2,715 (8)	3,067 (7)	1,842 (4)	<0.0001	341 (4)	606 (9)	816 (9)	3,480 (8)	1,867 (6)	1,307 (4)	<0.0001
Stroke	199 (7)	380 (7)	3,906 (10)	3,683 (10)	4,477 (10)	3,422 (7)	<0.0001	755 (8)	735 (11)	947 (11)	4,359 (11)	2,769 (9)	2,410 (8)	<0.0001
Chronic renal failure	99 (3)	160 (3)	2,462 (6)	2,451 (7)	2,990 (6)	2,137 (5)	<0.0001	210 (2)	369 (6)	616 (7)	2,940 (7)	1,753 (6)	1,537 (5)	<0.0001
Peripheral vascular disease	106 (3)	201 (4)	1,803 (5)	1,885 (5)	2,392 (5)	1,828 (4)	<0.0001	369 (4)	418 (6)	505 (6)	2,317 (6)	1,507 (5)	1,286 (4)	<0.0001
Prior interventions														
PCI	675 (24)	1,352 (24)	5,678 (15)	3,830 (10)	4,205 (9)	3,215 (7)	<0.0001	2,151 (23)	976 (15)	1,051 (12)	3,886 (10)	2,254 (8)	2,050 (7)	<0.0001
CABG	300 (11)	711 (13)	3,832 (10)	2,921 (8)	3,185 (7)	1,969 (4)	<0.0001	1,162 (12)	654 (10)	788 (9)	3,198 (8)	1,741 (6)	1,107 (4)	<0.0001
Biochemical results														
Serum cholesterol (mmol/L)	3.9 (2.1)	4.6 (1.3)	4.5 (1.6)	4.6 (1.6)	4.7 (1.6)	4.9 (1.5)	<0.0001	4.4 (1.8)	4.5 (1.6)	4.5 (1.7)	4.6 (1.7)	4.7 (1.6)	4.9 (1.5)	<0.0001
Serum glucose (mmol/L)	7.5 (5.0)	7.2 (3.6)	7.8 (4.2)	8.2 (4.5)	8.4 (4.8)	8.7 (4.8)	<0.0001	7.2 (3.7)	7.7 (4.3)	8.1 (5.1)	8.4 (5.7)	8.6 (5.6)	8.9 (5.3)	<0.0001
Admission medications														
ACE inhibitor	1,175 (48)	2,455 (49)	16,387 (45)	14,213 (41)	17,070 (38)	13,328 (30)	<0.0001	4,237 (46)	3,113 (49)	3,672 (43)	16,099 (41)	10,407 (36)	8,892 (30)	<0.0001
Beta blocker	1,198 (49)	2,414 (48)	13,495 (37)	11,184 (33)	13,322 (30)	10,920 (25)	<0.0001	4,014 (44)	2,443 (38)	2,866 (34)	12,776 (33)	8,576 (30)	7,428 (25)	<0.0001
Statin	1,593 (65)	3,447 (65)	20,137 (54)	17,215 (49)	20,054 (44)	15,703 (35)	<0.0001	5,701 (62)	3,726 (57)	4,453 (51)	19,545 (49)	12,665 (43)	10,749 (35)	<0.0001
Clopidogrel	387 (26)	808 (28)	4,301 (23)	3,632 (18)	4,462 (16)	3,497 (13)	<0.0001	1,830 (26)	850 (23)	981 (20)	5,590 (22)	3,641 (19)	2,810 (15)	<0.0001
Aspirin	1,673 (57)	3,969 (66)	22,421 (55)	20,265 (53)	27,192 (55)	30,207 (61)	<0.0001	6,151 (64)	4,240 (61)	5,257 (56)	23,331 (54)	18,007 (55)	20,444 (61)	<0.0001
Management, setting and diagnosis														

Cardiologist as lead consultant	1,074 (37)	3,133 (53)	14,908 (37)	13,523 (36)	20,284 (41)	27,302 (56)	<0.0001	4,702 (49)	3,714 (54)	5,681 (62)	25,636 (60)	17,136 (53)	13,302 (40)	<0.0001
Admission ward							<0.0001							<0.0001
CCU	1,079 (39)	2,190 (39)	13,987 (37)	13,579 (38)	22,628 (49)	32,614 (69)		5,361 (58)	2,956 (48)	3,638 (43)	18,506 (47)	18,095 (59)	25,243 (78)	
ITU	13(<1)	7 (<1)	254 (1)	487 (1)	783 (2)	976 (2)		34 (<1)	29 (<1)	85 (1)	547 (1)	571 (2)	656 (2)	
Cardiac ward	570 (21)	441 (8)	4,218 (11)	3,604 (10)	3,996 (9)	2,986 (6)		638 (7)	603 (10)	928 (11)	3,700 (9)	2,005 (7)	1,199 (4)	
Other	1,075 (39)	3,023 (53)	18,957 (51)	17,639 (50)	18,818 (41)	10,421 (22)		3,241 (35)	2,633 (42)	3,788 (45)	16,794 (42)	9,898 (32)	5,214 (16)	
Diagnosis														
STEMI	537 (18)	621 (10)	4,646 (11)	5,987 (16)	14,021 (28)	32,216 (65)	<0.0001	1,833 (19)	986 (14)	1,374 (15)	7,854 (18)	12,148 (37)	24,142 (72)	<0.0001
ACS but not STEMI	2,411 (82)	5,385 (90)	36,084 (89)	32,366 (84)	35,595 (72)	17,119 (65)		7,828 (81)	5,943 (86)	7,997 (85)	35,541 (82)	20,572 (63)	24,142 (72)	
Discharge medications														
ACE inhibitor	1,632 (72)	3,589 (73)	24,859 (70)	23,792 (71)	31,663 (73)	33,914 (77)	<0.0001	5,748 (69)	4,243 (68)	5,447 (66)	26,197 (69)	20,648 (72)	22,853 (77)	<0.0001
Beta blocker	1,772 (72)	3,783 (72)	24,159 (67)	22,705 (67)	30,327 (69)	32,459 (74)	<0.0001	5,782 (68)	3,992 (63)	5,199 (62)	24,955 (65)	19,759 (69)	21,603 (72)	0.008
Statin	2,182 (87)	4,664 (87)	29,881 (82)	27,717 (82)	36,078 (82)	37,097 (84)	<0.0001	7,556 (86)	5,064 (80)	6,618 (78)	31,101 (80)	23,714 (82)	25,137 (84)	<0.0001
Clopidogrel	853 (73)	1,745 (67)	13,127 (75)	14,246 (79)	19,698 (80)	19,691 (80)	<0.0001	3,611 (58)	2,095 (64)	3,134 (68)	17,342 (72)	13,476 (73)	13,316 (74)	<0.0001
Aspirin	2,127 (84)	4,570 (85)	29,577 (81)	27,518 (80)	25,835 (81)	36,790 (83)	0.280	7,426 (84)	5,033 (78)	6,586 (77)	30,937 (79)	23,607 (81)	25,034 (83)	0.049
Outcome														
Death at follow up	367 (12)	680 (11)	9,611 (24)	10,896 (28)	14,378 (29)	12,431 (25)	0.586	1,330 (14)	1,746 (25)	2,780 (30)	14,052 (32)	10,117 (31)	9,147 (27)	<0.0001

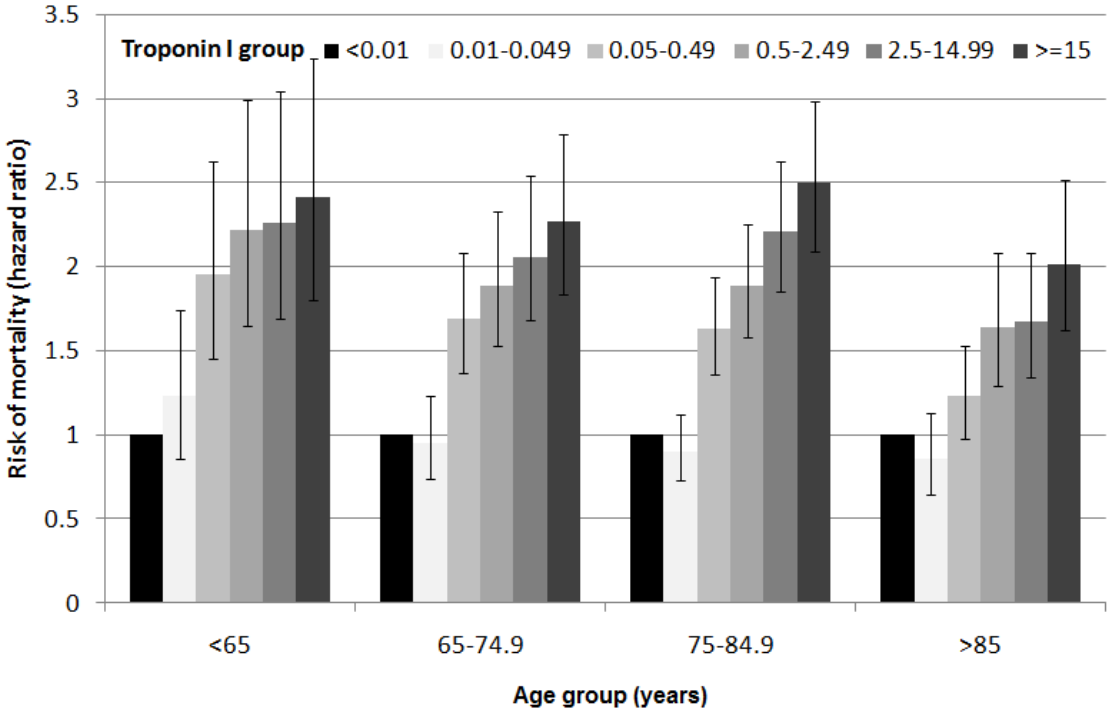
†Results reported as mean (SD) for continuous variables and n (%) for categorical variables. ‡ Spearman correlation test for continuous variables and age group, Chi square test for Admission ward and Cuzick non-parametric test for trend for binary variables

Supplementary Table 2: Comparison of baseline characteristics of the included and excluded cohort

Variables and associations with missing troponin I	Odds ratio (95% CI)	p-value
Age	0.9989731 (0.9984244-0.9995221)	<0.001
Sex	1.043736 (1.028532-1.059165)	<0.001
Prior MI	0.9011443 (0.8858318-0.9167216)	<0.001
Prior PCI	1.006812 (0.9828668-1.031341)	0.580
Prior CABG	0.9471632 (0.9205756-0.9745187)	<0.001
Diabetes	0.9706904 (0.9539319-0.9877433)	0.001
Hypertension	0.9254187 (0.9125855-0.9384322)	<0.001
Current smoker	0.9133879 (0.8983817-0.9286448)	<0.001

Variables and associations with missing troponin T	Odds ratio (95% CI)	p-value
Age	0.9961729 (0.9956016-0.9967446)	<0.001
Sex	0.9989445 (0.9838167-1.014305)	0.892
Prior MI	1.006932 (0.9891724-1.02501)	0.447
Prior PCI	1.036507 (1.010787-1.062881)	0.005
Prior CABG	0.9469983 (0.9195531-0.9752626)	<0.001
Diabetes	0.9837969 (0.9661617-1.001754)	0.077
Hypertension	1.025531 (1.010734-1.040545)	0.001
Current smoker	1.049961 (1.03199-1.068244)	<0.001

Figure 1: Adjusted hazards ratios (95% confidence intervals) of mortality according to various age groups within troponin strata



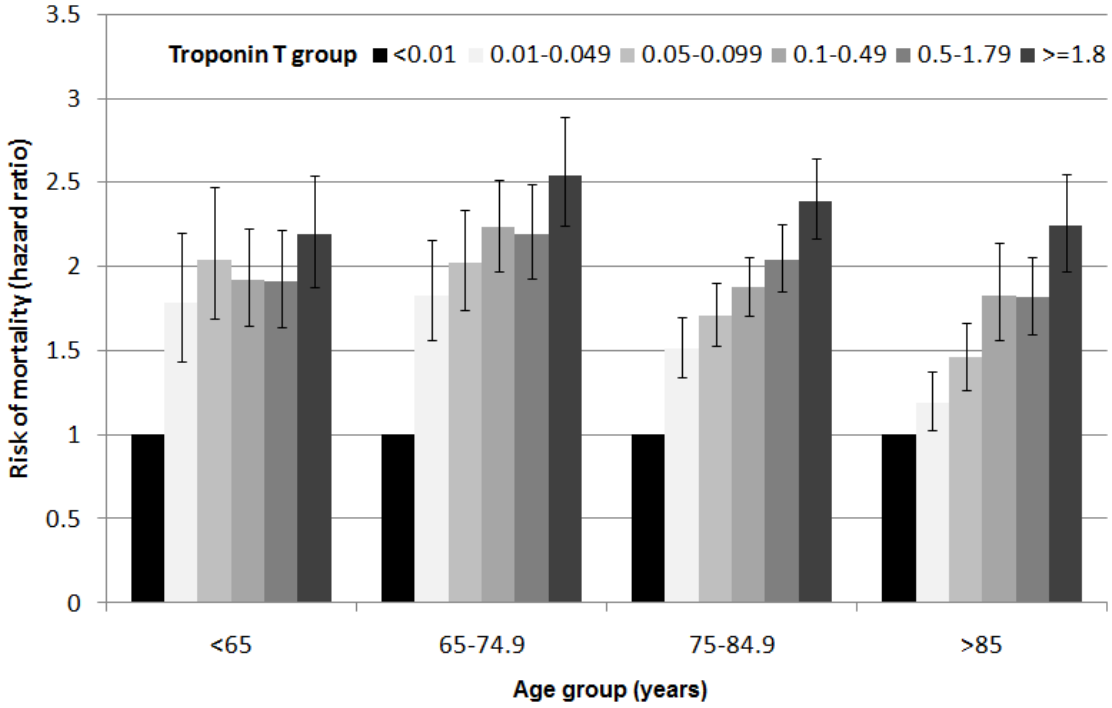
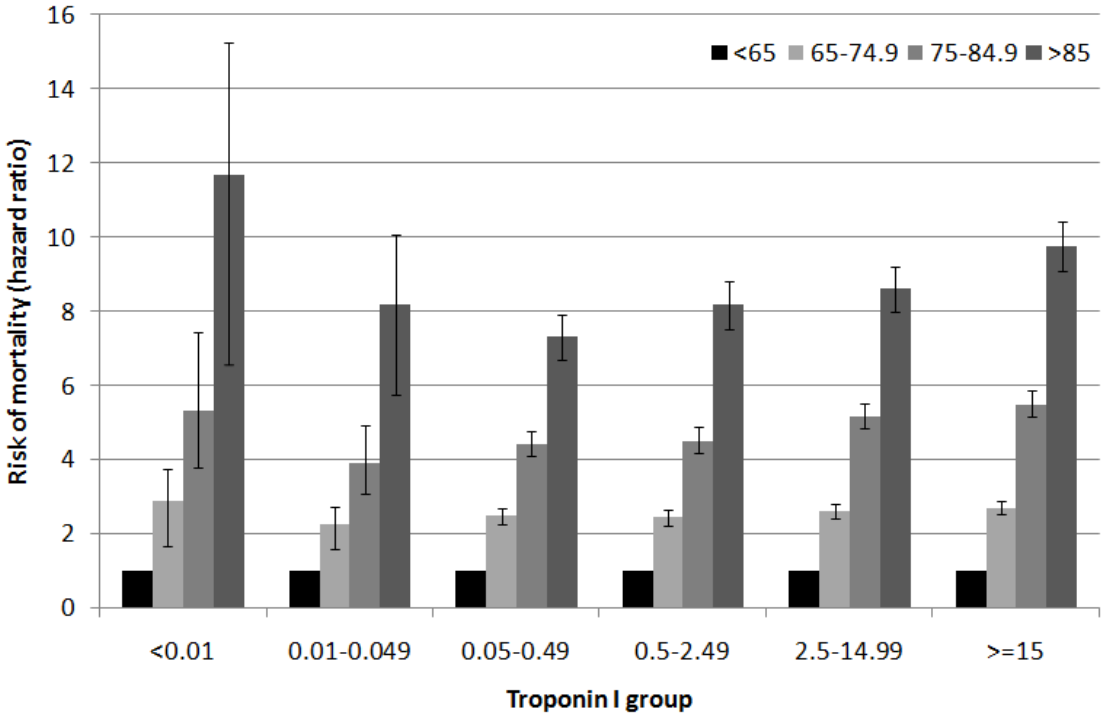
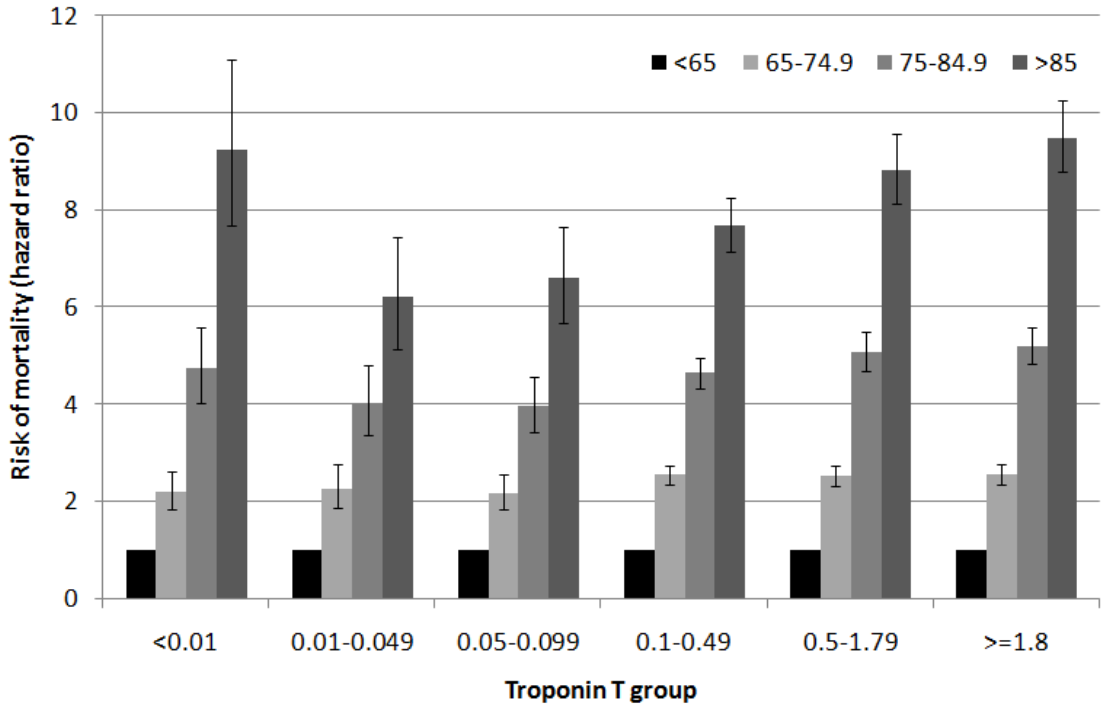
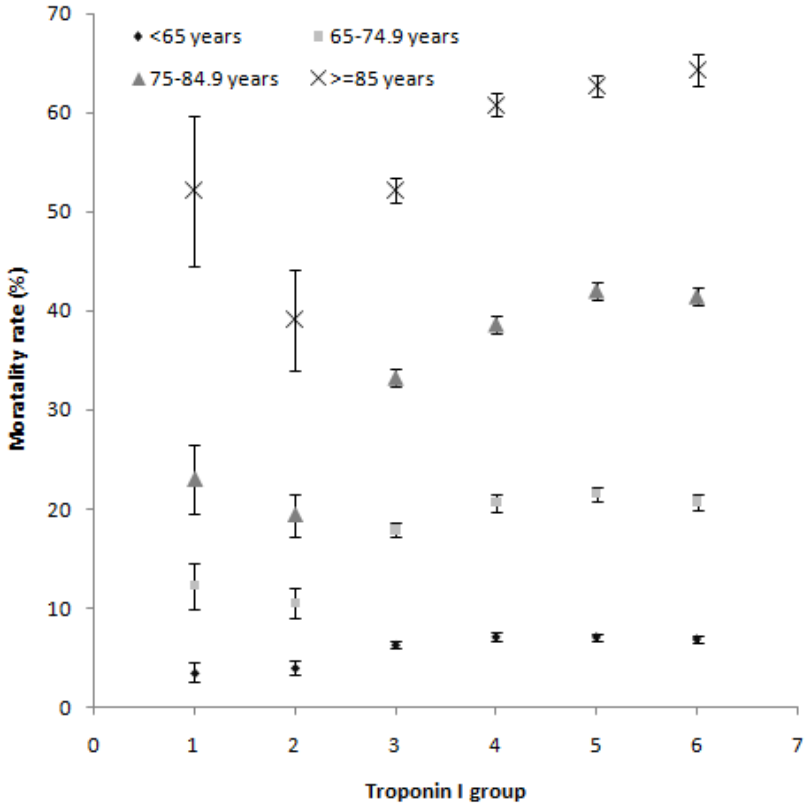


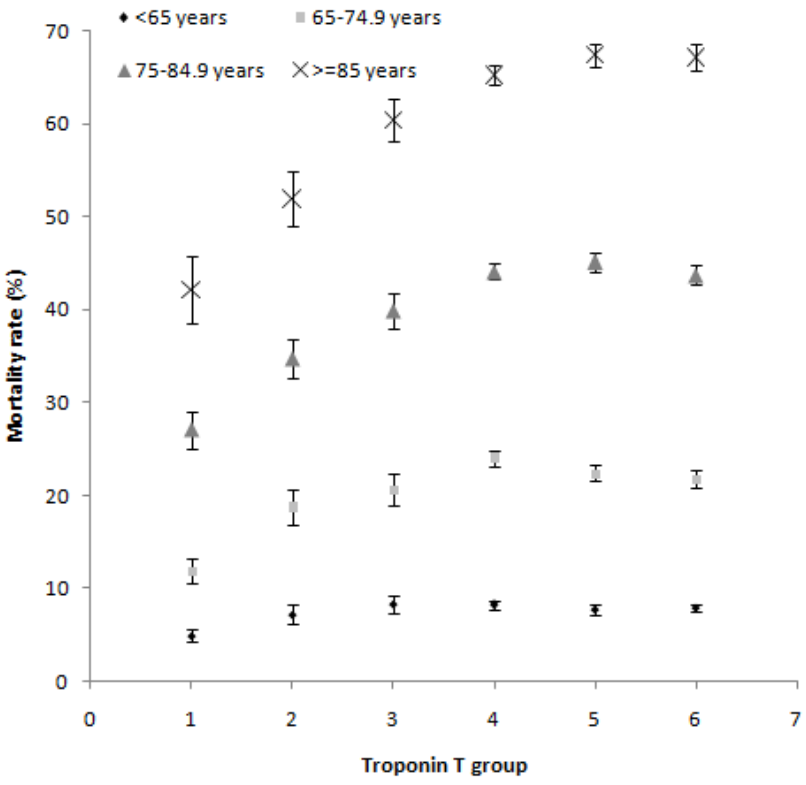
Figure 2: Adjusted hazard ratios (95% confidence intervals) of mortality according to various levels of peak troponin categories within age strata



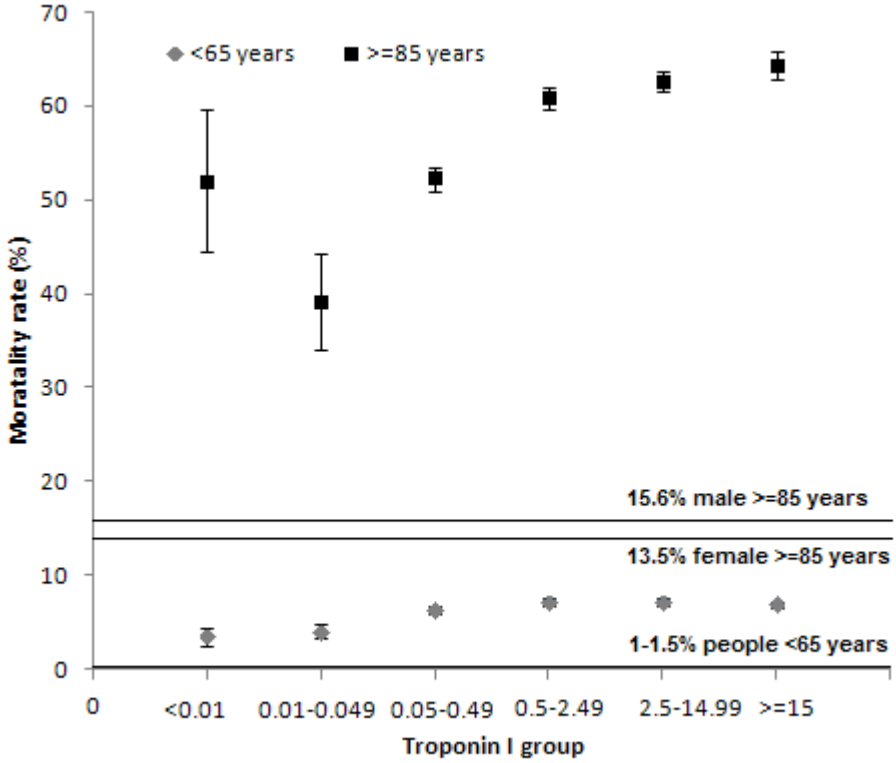


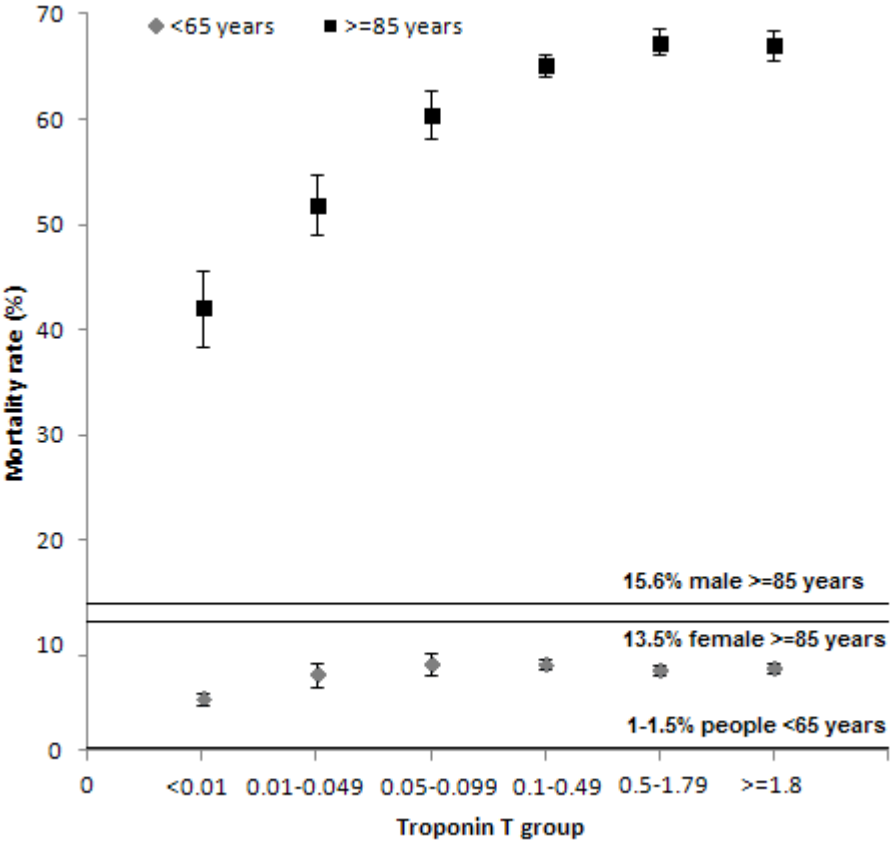
Supplementary Figure 1: Crude mortality rates (95% confidence intervals) at follow up (August 2011) in different age groups by peak troponin categories





Supplementary Figure 2: Crude mortality rates (95% confidence intervals) compared to expected mortality of similar age categories at follow up (August 2011) for the oldest and youngest age groups by peak troponin categories





Data Supplement 1: MINAP definitions of variables

Variable	Definition
Chronic renal failure	Creatinine chronically >200 micromol/L
Cerebrovascular disease	A history of cerebrovascular ischaemia. To include transient cerebral ischaemic episodes as well as events with deficit lasting >24 hours.
Peripheral vascular disease	The presence of peripheral vascular disease, either presently symptomatic or previously treated by intervention or surgery. Includes known renovascular disease and aortic aneurysm.
Chronic obstructive pulmonary disease	Any form of obstructive airways disease.
Congestive cardiac failure	A previously validated diagnosis of heart failure on any therapeutic regime.
Smoking	Ex-smoker or current smoker
Known diabetes mellitus	Diabetic with any of dietary control, receiving insulin or oral medication.
Hypertension	A patient already receiving treatment (drug, dietary or lifestyle) for hypertension or with recorded BP > 140/90 on at least two occasions prior to admission.

The MINAP dataset and definitions are freely accessible at:
http://www.ucl.ac.uk/nicor/audits/minap/dataset