

Prognostic significance of troponin level in 3121 patients presenting with atrial fibrillation (The NIHR Health Informatics Collaborative TROP-AF study)

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Background—Patients presenting with atrial fibrillation (AF) often undergo a blood test to measure troponin, but interpretation of the result is impeded by uncertainty about its clinical importance. We investigated the relationship between troponin level, coronary angiography, and all-cause mortality in real-world patients presenting with AF.

Methods and Results—We used National Institute of Health Research Health Informatics Collaborative data to identify patients admitted between 2010 and 2017 at 5 tertiary centers in the United Kingdom with a primary diagnosis of AF. Peak troponin results were scaled as multiples of the upper limit of normal. A total of 3121 patients were included in the analysis. Over a median follow-up of 1462 (interquartile range, 929–1975) days, there were 586 deaths (18.8%). The adjusted hazard ratio for mortality associated with a positive troponin (value above upper limit of normal) was 1.20 (95% CI, 1.01–1.43; $P < 0.05$). Higher troponin levels were associated with higher risk of mortality, reaching a maximum hazard ratio of 2.6 (95% CI, 1.9–3.4) at ≈ 250 multiples of the upper limit of normal. There was an exponential relationship between higher troponin levels and increased odds of coronary angiography. The mortality risk was 36% lower in patients undergoing coronary angiography than in those who did not (adjusted hazard ratio, 0.61; 95% CI, 0.42–0.89; $P = 0.01$).

Conclusions—Increased troponin was associated with increased risk of mortality in patients presenting with AF. The lower hazard ratio in patients undergoing invasive management raises the possibility that the clinical importance of troponin release in AF may be mediated by coronary artery disease, which may be responsive to revascularization. (*J Am Heart Assoc.* 2020;9:e013684. DOI: 10.1161/JAHA.119.013684.)

Key Words: angiography • atrial fibrillation • coronary artery disease • mortality • troponin

Patients presenting to the hospital with atrial fibrillation (AF), the most prevalent tachyarrhythmia,¹ often undergo measurement of cardiac biomarkers.^{2,3} In particular, troponin levels are measured, ostensibly, to diagnose an acute coronary

syndrome (ACS) manifesting as AF.⁴ However, interpretation of the result is hampered by uncertainty over the clinical importance of troponin levels in AF. The diagnostic and prognostic utility of troponin in ACS,⁵ and other cardiac presentations, such as heart

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Accompanying Data S1, Table S1, and Figures S1 through S3 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013684>

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Clinical Perspective

What Is New?

- Elevated troponin levels in patients presenting to the hospital with atrial fibrillation are associated with a high risk of mortality, with higher levels associated with worse prognosis.
- The risk of mortality associated with troponin increase was lower in patients who underwent coronary angiography than in those who did not undergo coronary angiography.

What Are the Clinical Implications?

- Even troponin elevations mildly above the upper limits of normal should be taken seriously in patients presenting with atrial fibrillation.
- Consideration should be given to investigate for underlying coronary artery disease in patients presenting with atrial fibrillation and an increased troponin level.

failure,⁶ is firmly established. However, these predictive relationships may not be observed in AF, where troponin release may be related to rapid ventricular response and the mechanical effects of fibrillation on the atria rather than coronary artery disease (CAD). Observational analysis of patients presenting with AF have identified associations between troponin level and clinically important outcomes, but these studies did not assess mortality. In clinical practice, small troponin increases in AF presentations are typically ignored and do not routinely prompt investigation for CAD.

The aims of our study were to explore the relationship between troponin level and mortality in patients presenting to the hospital with AF, to understand the pattern of referral for coronary angiography in relation to troponin level, and to determine the role of coronary angiography in the relationship between troponin and mortality in these patients.

Methods

The National Institute of Health Research Health Informatics Collaborative database consists of routinely collected electronic health record data from patients attending 5 large UK tertiary care centers with emergency departments (Imperial College Healthcare, University College Hospital, Oxford University Hospital, Kings College Hospital, and Guy's and St Thomas' Hospital) between 2010 (2008 for University College Hospital) and 2017. The data acquisition and analysis plan is found in Data S1. The National Institute of Health Research Health Informatics Collaborative study was registered at ClinicalTrials.gov, NCT03507309. This work used data provided by patients and collected by the National Health Service as part of their care and support. No verbal or written

informed consent from individual patients was required for data set generation. This study was approved by the London–South East Research Ethics Committee (16/HRA/3327).

Eligibility Criteria

We identified patients from the National Institute of Health Research Health Informatics Collaborative database who were admitted to the hospital with a primary diagnosis of AF and underwent at least one troponin measurement. Patients with a concomitant secondary diagnosis of AF were not eligible for inclusion in the study. Diagnoses were established from routinely recorded *International Classification of Diseases, Tenth Revision (ICD-10)*, discharge codes and were therefore established by the clinical team after inpatient investigations and management were complete. Patients meeting the eligibility criteria were followed up using routinely collected data, until death or censoring on April 1, 2017.

Troponin Level

All analyses on troponin were performed using the peak troponin level. For patients who had a single troponin measurement, the peak troponin was based on this measurement. In the remainder of the patients who had >1 troponin test in the same hospital episode of care, the peak troponin value was defined as the highest of all measurements. For patients with multiple episodes of care for which troponin was tested, the first episode of care was used.

In clinical practice, troponin levels are frequently dichotomized into “positive” (meaning >99th percentile of the upper limit of normal [ULN] for the troponin assay) or “negative.” Furthermore, troponin levels may have a progressive relationship with prognosis, too, but the shape of this relationship is not known across the full spectrum of values; and making the assumption of a linear relationship of mortality with troponin (or log troponin) may not be secure in our study participants.

For these reasons, we treated the data in 2 ways. First, we dichotomized the results as being either positive or negative. Second, we used troponin on a continuous scale by standardizing the many troponin assays, by scaling the results using the ratio of the observed troponin value divided by the ULN for that particular troponin assay.

Coronary Angiography and Revascularization

Patients undergoing coronary angiography, or revascularization with either percutaneous coronary intervention or coronary artery bypass grafting, during the follow-up period were identified. To account for outpatient procedures, patients were categorized as having angiography or intervention if performed within 3 months of the peak troponin level.

Follow-Up

Using a retrospective cohort study design, all patients were followed up until death or censoring on April 1, 2017. Life status was ascertained using routinely collected data on the National Health Service Spine Application, which was linked to the Office of National Statistics, and thereby to the national registry of deaths.

Statistical Analysis

Descriptive statistics are displayed as median (interquartile range) for continuous variables and number (percentage) for categorical variables. Comparisons of baseline characteristics between patients who did and did not undergo angiography were explored by Mann-Whitney *U* test or χ^2 test.

The relationship between dichotomous troponin level (above ULN or not), or continuous troponin, and all-cause mortality was performed using Cox proportional hazards regression modeling, using log transformation because of the positive skew of troponin values. The proportional hazard assumption was supported by a nonsignificant relationship between the Schoenfeld residuals and time. This test was not statistically significant for each of the covariates included in the Cox regression model.

Using Martingale residuals, nonlinearity was detected in the relationship between the log hazard and all continuous covariates (age, creatinine, hemoglobin, platelet count, white blood cell count, and troponin level). To model nonlinear relationships, we used restricted cubic splines for Cox regression and logistic regression analyses to calculate mortality hazard ratio and odds of angiography outcomes, respectively. Preliminary analyses suggested that 4 unforced knots should be used to model troponin level in the restricted cubic spline analyses. Splines were adjusted for demographic characteristics, hematological and biochemical blood results, cardiovascular risk factors, and comorbidities. Subgroup analyses were performed in angiography and no angiography subgroups. Kaplan-Meier survival curves were plotted according to angiography status.

$P < 0.05$ was considered significant. Statistical analyses were performed using the R 3.5.0 statistical package (the R Core Team, Vienna, Austria). Survival analyses were performed using the *Survminer* and *Survival* R packages.

Results

A total of 3121 patients admitted to the hospital with a primary diagnosis of AF, according to *ICD-10* discharge codes, underwent troponin measurement during the study period. Their baseline characteristics are displayed in Table 1. Mean age was 73 years (95% CI, 62–82 years), and 55.7% were men. Most of these

Table 1. Baseline Characteristics of Patients

Characteristics	Patients With Primary Presentation of AF (n=3121)
Demographic characteristics	
Age, y	73 (62–82)
Men	1738 (55.7)
Hematology and biochemistry results	
CRP, mg/dL (n=2796)	5.0 (2.0–14.9)
Creatinine, $\mu\text{mol/L}$ (n=3086)	82 (69–100)
Hemoglobin, g/dL (n=3075)	13.8 (12.5–15.0)
Platelet count, $\times 10^9/\text{L}$ (n=3071)	226 (187–274)
Troponin, xULN	0.5 (0.003–2.0)
White blood cell count, $\times 10^9/\text{L}$ (n=3075)	8.2 (6.6–10.2)
Cardiovascular risk factors	
Diabetes mellitus	355 (11.4)
Hypercholesterolemia	448 (14.4)
Hypertension	1062 (34.0)
Cardiovascular disease	
Aortic stenosis	53 (1.7)
Heart failure	302 (9.7)
Previous myocardial infarction	341 (10.9)
Other comorbidities	
Malignancy	207 (6.6)
Obstructive lung disease	146 (4.7)

Data represent median (interquartile range) or value (percentage). Numbers in parentheses indicate the number of patients who had data available for the relevant variable. AF indicates atrial fibrillation; CRP, C-reactive protein; xULN, 99th percentile of the upper limit of normal.

patients (60.4%) recorded a peak troponin level that was within the normal range (< 1 multiple of the ULN [xULN]) (Figure 1).

Relationship Between Troponin Level and Coronary Angiography

A total of 216 patients (6.9%) underwent coronary angiography, with 78 (36.1%) of these patients subsequently undergoing coronary revascularization by percutaneous coronary intervention (93.6%), coronary artery bypass grafting (2.6%), or both (3.8%). A total of 39 patients (1.2%) had a secondary diagnosis of ACS. Most coronary angiograms (89.8%; Figure 2A) and 43.6% of revascularization procedures (Figure 2B) occurred within 72 hours of the peak troponin level. The baseline characteristics of patients who did and did not undergo angiography are displayed in Table 2. The demographic and clinical factors associated with undergoing coronary angiography are shown in Figure S1 and Table S1.

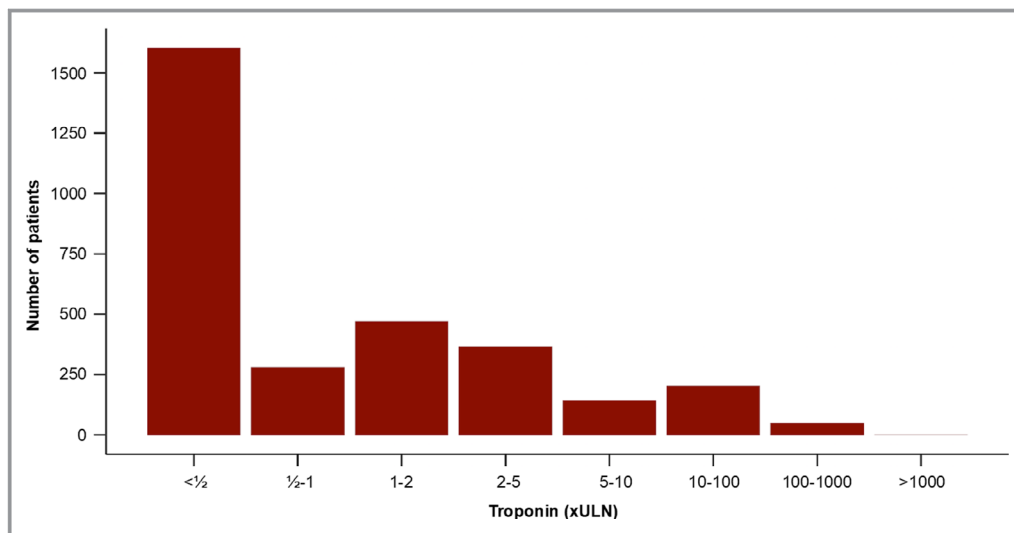


Figure 1. Bar chart of numbers of patients according to troponin level. xULN indicates 99th percentile of the upper limit of normal.

The relationship between troponin level and likelihood of undergoing coronary angiography was nonlinear (Figure 3B). At troponin levels less than the ULN, increasing troponin level was not associated with increasing likelihood of coronary angiography. Above the ULN, there was a direct relationship between troponin level and odds of angiography, with an exponential distribution at troponin levels >5 xULN. There was a direct relationship between odds ratio of undergoing coronary revascularization and troponin level (Figure S2). A patient with a peak troponin of 10 xULN was 2.7 times more likely to undergo coronary revascularization compared with a patient with a troponin level of 1.

Relationship Between Troponin Level and Mortality

Over a median follow-up of 48.1 (interquartile range, 30.5–64.9) months, there were 586 deaths (18.8%), with a 1-year mortality rate of 4.8%. The hazard ratio for mortality associated with a positive troponin result (value above ULN) was 1.20 (95% CI, 1.01–1.43; $P<0.05$) after adjustment for key demographic and baseline clinical factors. The relationship between continuous troponin level and mortality was demonstrated using restricted cubic spline Cox regression analysis, adjusted for the same demographic and baseline clinical factors (Figure 3A). Although troponin levels <1.3 xULN showed no significant relationship with hazard ratio, at higher troponin levels, a significant positive relationship was demonstrated.

Figure 3C and 3D shows the relationship between troponin level and mortality for patients presenting with AF who underwent coronary angiography (Figure 3C) and patients who did not (Figure 3D). Although there was no significant relationship between troponin level and mortality in patients

who underwent angiography (Figure 3C), a significant relationship was observed in patients who did not undergo angiography with troponin levels above the ULN (Figure 3D). Kaplan-Meier survival analysis demonstrated worse short-term survival in patients who did not undergo angiography ($P=0.02$; Figure 4A). This difference in mortality persisted at 4-year follow-up ($P=0.02$; Figure 4B). On multivariate Cox regression analysis, after adjustment for demographic and clinical factors, including troponin level, angiography was associated with a 39% reduction in mortality during follow-up (hazard ratio, 0.61; 95% CI, 0.42–0.89; $P=0.01$). For those patients who were referred for angiography, there was a nonsignificant trend toward revascularization being associated with a reduction in mortality during follow-up (hazard ratio, 0.36; 95% CI, 0.12–1.10; $P=0.07$). The relationship between troponin and mortality in patients who underwent angiography without revascularization and the relationship in those who did not undergo angiography are shown in Figure S3. This figure shows that increasing troponin was associated with increasing mortality risk in both groups but with wide CIs around the point estimates for unrevascularized patients who underwent angiography; it is not clear that there is a difference in the troponin-mortality relationship between these groups.

Discussion

This is the first study investigating the relationship between troponin level, coronary angiography, and mortality in patients admitted to the hospital with a primary diagnosis of AF. This is also the largest study to report the association between troponin level and all-cause mortality in this group.

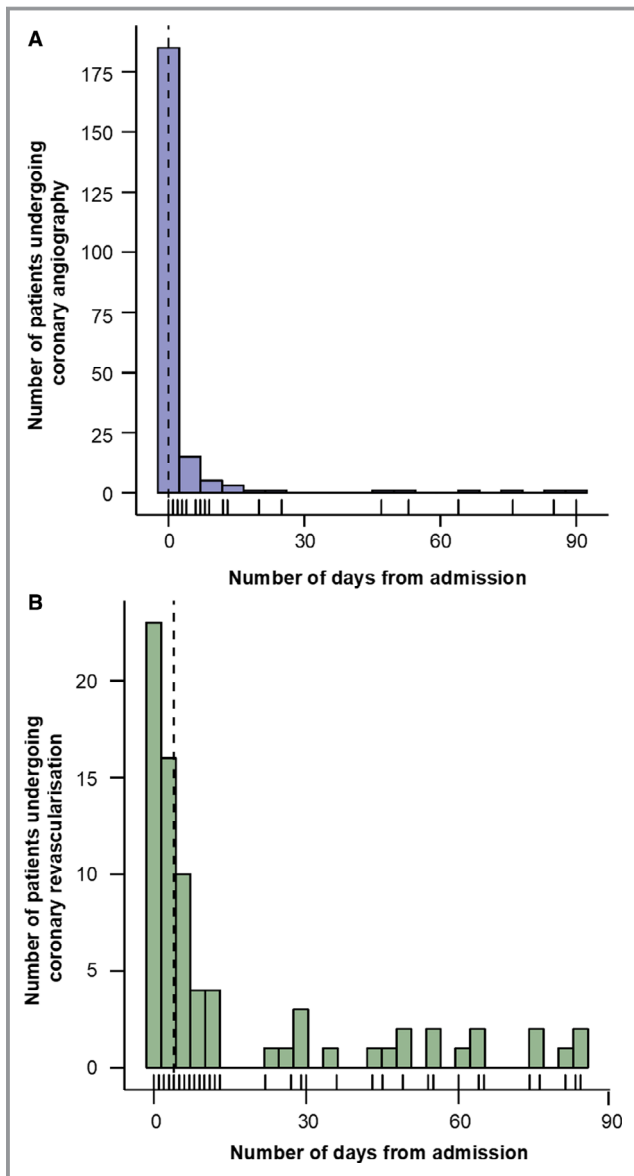


Figure 2. Histogram of numbers of patients undergoing coronary angiography (A) and revascularization (B) at different time points after measurement of peak troponin level at presentation.

Abnormal Troponin Levels Predict Mortality in AF

In 3121 patients presenting with AF, whose troponin was measured, there was a significant association between troponin levels (above the ULN) and higher mortality, even after adjusting for key demographic and clinical factors. Associations derived from dichotomizing continuous variables, such as troponin, can be driven by extreme values. However, even low-level troponin elevations above the normal range (1–10 xULN) were associated with higher mortality risk. Abnormal troponin levels, at any level, appear to have prognostic importance in AF; and higher troponin levels appear to confer worse prognosis.

Table 2. Baseline Characteristics of Patients Who Did and Did Not Undergo Angiography

Characteristics	Angiography (n=216)	No Angiography (n=2905)	P Value*
Demographic characteristics			
Age, y	73.5 (65.3–79.0)	73.0 (63.0–83.0)	0.47
Men	144 (66.7)	1594 (54.9)	0.001
Hematology and biochemistry results			
CRP, mg/dL	6.1 (2.03–16.5)	5.0 (1.9–14.8)	0.08
Creatinine, $\mu\text{mol/L}$	84.0 (73.3–100.8)	81.0 (69.0–100.0)	0.04
Hemoglobin, g/dL	13.9 (12.5–15.0)	13.8 (12.5–15.0)	0.78
Platelet count, $\times 10^9/\text{L}$	224 (182–270)	226 (187–275)	0.53
Troponin, xULN	1.4 (0.003–5.6)	0.5 (0.003–2.0)	<0.0001
White blood cell count, $\times 10^9/\text{L}$	8.5 (6.8–10.6)	8.2 (6.6–10.2)	0.21
Cardiovascular risk factors			
Diabetes mellitus	32 (14.8)	323 (11.1)	0.12
Hypercholesterolemia	41 (19.0)	407 (14.0)	0.06
Hypertension	74 (34.3)	988 (34.0)	0.94
Cardiovascular disease			
Aortic stenosis	8 (3.7)	45 (1.5)	0.03
Heart failure	27 (12.5)	275 (9.5)	0.15
Previous myocardial infarction	65 (30.1)	276 (9.5)	<0.0001
Other comorbidities			
Malignancy	7 (3.2)	200 (6.9)	0.03
Obstructive lung disease	12 (5.6)	134 (4.6)	0.50

Data represent median (interquartile range) or value (percentage). CRP indicates C-reactive protein; xULN, 99th percentile of the upper limit of normal.

*Comparison between angiography and no angiography groups using Mann-Whitney *U* test for continuous variables and χ^2 test for categorical variables.

Nonlinear Relationship Between Troponin and Mortality

The relationship between troponin level and adjusted hazard ratio for mortality in patients presenting with AF is nonlinear when considering the entire spectrum of troponin values, including detectable troponin within the normal range. Below the ULN of troponin, there does not appear to be any relationship between higher troponin levels and increased hazard ratio for mortality. A similar nonlinear pattern between troponin level and mortality has previously been observed in an unselected group of patients without ACS.⁷ Specifically, in our AF cohort, above the ULN there is a direct relationship between troponin level and mortality, reaching a hazard ratio

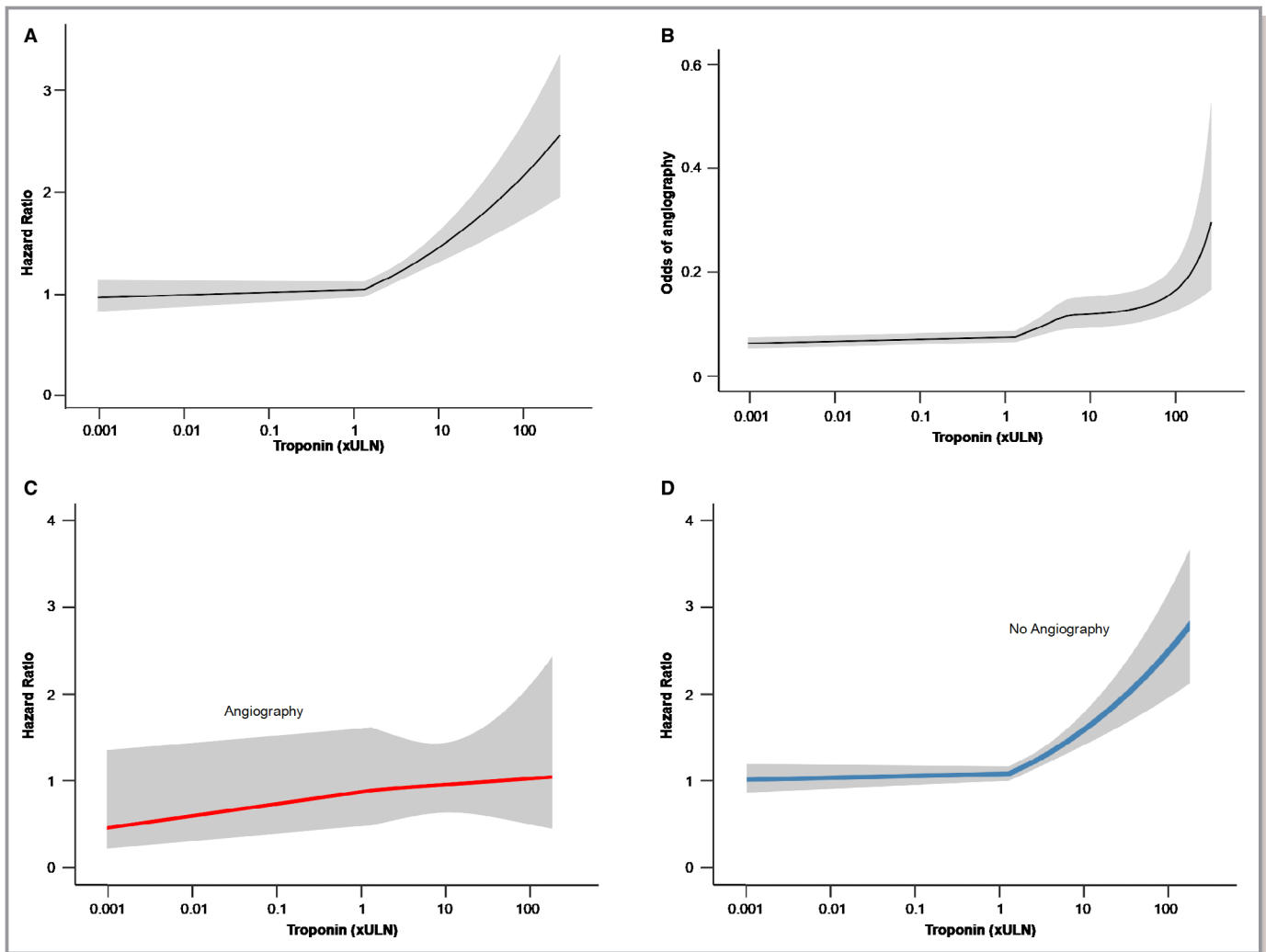


Figure 3. Multivariate restricted cubic spline modeling of association between troponin level and hazard ratio (A); association between troponin level and odds of coronary angiography (B); and association between troponin level and hazard ratio in angiography (C) and no angiography (D) subgroups. Data were adjusted for age, sex, CRP (C-reactive protein), creatinine, hemoglobin, platelet count, white blood cell count, diabetes mellitus, hypercholesterolemia, hypertension, aortic stenosis, heart failure, previous myocardial infarction, malignancy, and obstructive lung disease. The shaded area denotes the 95% CI.

of ≈ 2.6 at 263 xULN. The inflection near ULN may represent a genuine cutoff in the importance of troponin and supports the use of the 99th percentile in determining the “normal” range. Although this does not mean all patients presenting with AF should undergo invasive investigation, it does suggest that the troponin threshold for investigating for CAD may be lower than current practice.

Coronary Angiography Is Performed at Higher Troponin Levels

Coronary angiography was performed in <7% of patients presenting with AF who had troponin measured. Below the ULN for troponin, higher troponin levels were not associated with an increased likelihood of coronary angiography. Above

the ULN, there was an exponential relationship between troponin level and likelihood of coronary angiography. However, even at the highest troponin levels, less than half of patients underwent coronary angiography. This is consistent with typical clinical practice; small troponin increases in AF presentations are not deemed to be a useful marker of CAD by clinicians and even when troponin increases to high values, alternative explanations are often invoked. Other factors also influenced the likelihood of coronary angiography in this population: understandably, patients with malignancies were less likely to undergo coronary angiography and patients with prior infarcts were more likely to undergo coronary angiography. However, women were also less likely to undergo coronary angiography than men, despite other variances being accounted for in the multivariate analysis. This reflects

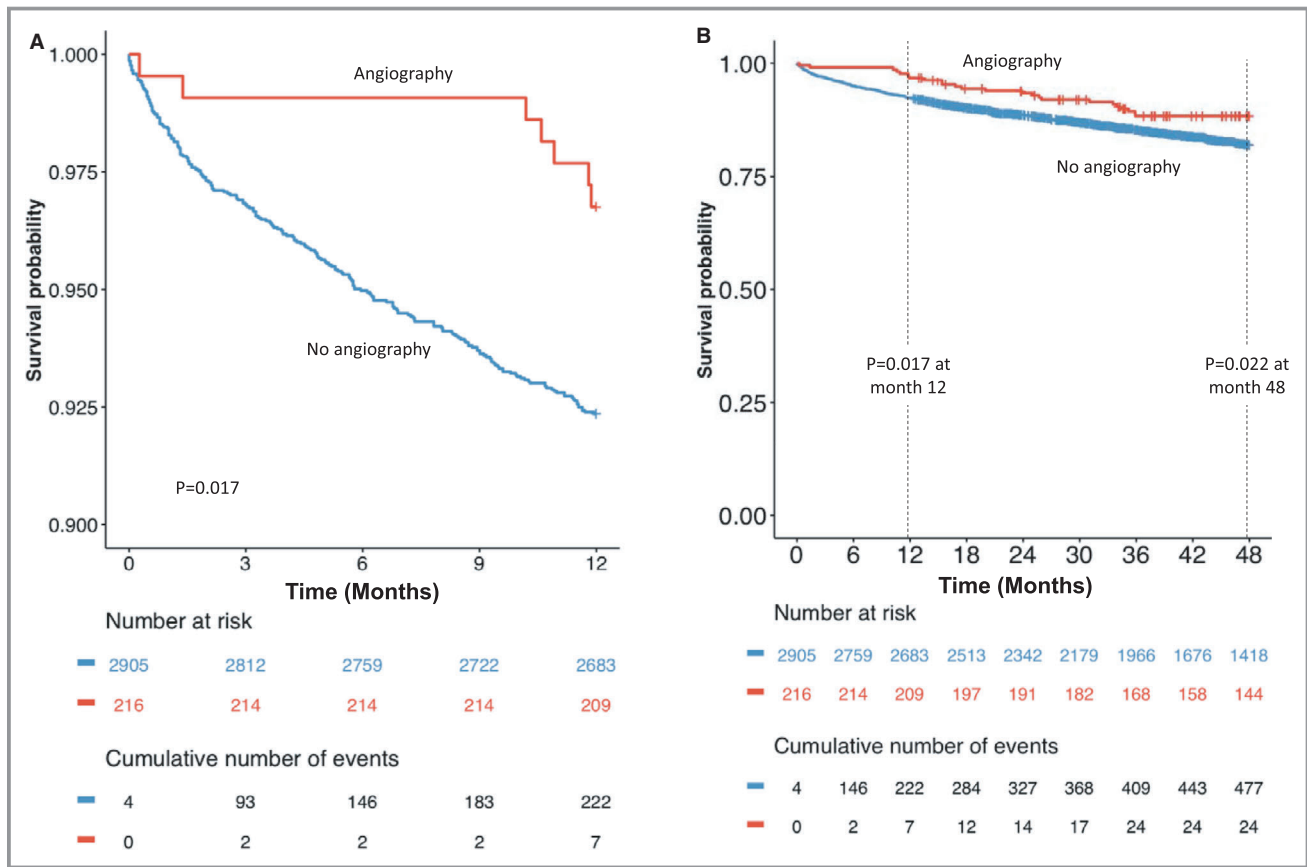


Figure 4. Kaplan-Meier survival curves according to angiography status over 12 months (A) and 48 months (B) of follow-up. Tick marks denote censored events. Survival curves compared using log-rank statistic.

a growing understanding that women with cardiac disease present, and are managed, in different ways to men, potentially to the detriment of women's health outcomes.

Coronary Angiography Alters the Troponin-Mortality Relationship

In patients who underwent coronary angiography, higher troponin levels above ULN were associated with higher mortality, but the relationship was weak, with a shallow gradient, and not statistically significant. In patients who did not undergo coronary angiography, there was a clear, direct relationship between higher troponin levels (above ULN) and higher risk of mortality. Coronary angiography appeared to be associated with a 36% reduction in mortality across the spectrum of troponin values. One possible explanation for this is that we may be selecting a relatively low-risk group of patients for coronary angiography compared with those we choose to treat medically. An alternative explanation is that invasive management may improve the prognosis of patients presenting with AF and abnormal troponin elevations, with

greater improvement at higher troponin levels. Coronary angiography at higher troponin levels is more likely to reveal clinically important CAD that is amenable to prognosis-improving treatment. Data on the rate of medical therapy for CAD were not available in this analysis, but coronary revascularization was performed in 36.1% of patients who underwent coronary angiography and there was a trend toward improved mortality with revascularization, although this did not reach statistical significance. The utility of routinely investigating for CAD in these patients requires testing in clinical trials.

Relationship With Existing Evidence

This is the largest study to assess the relationship between troponin and mortality in patients presenting to the hospital with AF. Other studies have assessed the effects on revascularization, stroke, cardiovascular death, and other clinically important outcomes. However, all such diagnoses, including fatal stroke and cardiovascular death, risk inaccuracy and bias to varying extents. All-cause mortality is the only

outcome where the diagnosis is free from such bias. Larger subanalyses of randomized controlled trials comparing direct oral anticoagulants with warfarin have assessed the relationship between troponin and mortality in patients with AF^{3,8} and found a significant correlation. However, this is an entirely different population of patients with a *background* of AF, rather than patients presenting to the hospital with a primary diagnosis of AF. In stable patients diagnosed with AF previously, increased troponin will inevitably be predictive of poor prognosis but troponin screening for patients in a stable phase of AF is rare and not a clinically relevant problem. How to interpret troponin increases in short-term presentations with AF is an extremely common clinical dilemma, which is addressed in this study.

Conti et al prospectively enrolled 3627 patients presenting with recent-onset (<48-hours) AF, but excluded patients with ACS, clinical instability, or severe comorbidity,⁴ and offered coronary angiography if the troponin level was elevated above the ULN. Troponin elevation (above the ULN) was associated with angiographic CAD, revascularization, and increased likelihood of adverse cardiovascular events, but mortality was not measured, and troponin was dichotomized at the ULN. We have shown that higher troponin levels are associated with a higher mortality risk, indicating that the magnitude of troponin increase as a continuous variable is important for decision making. Supporting our findings, Alghamry et al demonstrated, in a retrospective study of 200 patients, that troponin dichotomized at the ULN had poor ability to predict CAD, whereas peak troponin, analyzed continuously, did predict CAD.⁹ We did not find an association between higher levels of troponin below the ULN and increased mortality, despite a large number of patients analyzed at a long follow-up duration. A smaller study (n=330) suggested detectable troponin level below the ULN does predict mortality, but this may have been a chance finding as our study population for this group of patients was 4 times larger and found no association.¹⁰

Mechanisms of Troponin Release in AF

Troponin I and T bind to tropomyosin in the intracellular sarcomeric contraction complex, but they are also found in the cytosol.¹¹ In ACS, obstruction of epicardial coronary arteries results in myocyte necrosis, releasing troponin into the circulation, with larger infarcts both releasing more troponin and risking worse and more likely clinical sequelae, including death.⁵ The explanation for the relationship between troponin and mortality in ACS is, thus, clear, but troponin increases carry prognostic significance in several settings, such as heart failure, pulmonary embolism, and sepsis.⁶ The cause of circulating troponin in AF is particularly disputed, however, which is one reason for the relatively low importance

clinicians place on troponin leak in AF.¹¹ Type II myocardial infarction caused by ventricular myocyte death during rapidly conducted AF in the context of preexisting CAD is a putative mechanism. Although it is likely that this often plays a key role, as rate control can reduce troponin leak,¹² troponin release also occurs at normal ventricular rates. Furthermore, CAD identified is not always severe or physiologically significant, which makes treatment decisions, particularly the role of revascularization, uncertain. Although it is not known whether atrial myocytes themselves release troponin during fibrillation (regardless of ventricular rate), there is a large body of evidence for atrial scarring in AF,¹² suggesting this may be the case. However, acute atrial necrosis may only be the mechanism for new-onset AF as opposed to the first presentation of chronic AF. Patients with AF experience troponin increases in the short-term phase of stroke,¹³ implicating sympathetic activation as a cause for troponin release and a marker of mortality risk. AF as a manifestation of acute type I myocardial infarction, where there is spontaneous thrombotic occlusion of coronary arteries, is thought to occur rarely. This may be more common than diagnosed and would be another explanation of the link between troponin and mortality.

We cannot directly infer, from our analysis, a mechanism for troponin release nor the mechanism via which troponin increases are associated with worse prognosis, but our findings raise the possibility that the clinical importance of troponin release in AF may be mediated by CAD.

Limitations

Although this study benefits from having been conducted using real-world clinical data in a large number of patients from multiple centers, there are some limitations. This study was retrospective, with data extracted from electronic medical records and subject to the limitations of this approach, including difficulty in accounting for all potential confounding factors. Bias may be introduced because of inaccuracies in routine data collection. In routine clinical practice, patients with larger troponin increases are more likely to be given a primary diagnosis of ACS on discharge, even if their presentation was with AF, altering the overall risk status of the patients with AF as the primary diagnosis. The data set also includes only those patients who had a troponin measurement potentially altering the overall risk profile. Furthermore, the subtype of AF (paroxysmal or new onset) was not recorded, preventing analysis by chronicity of AF, and the role of stress testing was not available in the data set.

We could not directly infer mechanisms for the importance of troponin increases in AF. Routinely collected data from electronic health records lack resolution for fine details of clinical encounters. For this reason, we could not analyze the data for

the effect of troponin on cardiovascular outcomes and compare this with all-cause mortality. However, as previously discussed, all-cause mortality is the only outcome to be free from bias, which is of particular relevance in observational analyses.

Conclusions

Abnormally elevated troponin at any level is associated with increased risk of mortality in patients presenting with AF, and higher troponin levels confer worse prognosis. Coronary angiography is rarely performed unless AF is associated with large troponin increases, but when it is performed, it is associated with lower mortality. This raises the question of whether the prognostic significance of troponin could be mediated by CAD and may be responsive to revascularization. Clinical trials are warranted to clarify the role of investigating and treating CAD in patients presenting with AF with elevated troponin levels.

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Disclosures

None.

References

- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
- Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke*. 2010;41:2731–2738.
- Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Vinereanu D, Siegbahn A, Yusuf S. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a RELY substudy. *Circulation*. 2012;125:1605–1616.
- Conti A, Mariannini Y, Canuti E, Cerini G, De Bernardis N, Gigli C, Giampieri M, Viviani G, Poggioni C, Padeletti L. Role of masked coronary heart disease in patients with recent-onset atrial fibrillation and troponin elevations. *Eur J Emerg Med*. 2015;22:162–169.
- Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342–1349.
- Eggers KM, Lind L, Ahlström H, Bjerner T, Ebeling Barbier C, Larsson A, Venge P, Lindahl B. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. *Eur Heart J*. 2008;29:2252–2258.
- Kaura A, Panoulas V, Glampson B, Davies J, Mulla A, Woods K, Omigie J, Shah AD, Channon K, Weber JN, Thursz MR, Elliott P, Hemingway H, Williams B, Asselbergs F, O'Sullivan M, Lord G, Melikian N, Kharbada R, Shah AM, Perera D, Patel R, Francis DP, Mayet J. Mortality association of troponin level and age in over 250000 consecutive patients undergoing troponin measurement: cohort study across five UK acute centres (NIHR Health Informatics Collaborative TROP-RISK study). *BMJ*. 2019;367:l6055.
- Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Alexander JH, Atar D, Gersh BJ, Hanna M, Harjola VP, Horowitz JD. High-sensitivity troponin T and risk stratification in patients with atrial fibrillation during treatment with apixaban or warfarin. *J Am Coll Cardiol*. 2014;63:52–61.
- Alghamry A, Hanna J, Pelecanos A, Kyranis S, Khelgi V, O'Rourke P, Carroll O, Oxenford C, Rangaswamaiah S, Tan C. Predictors of significant coronary artery disease in atrial fibrillation: are cardiac troponins a useful measure. *Int J Cardiol*. 2016;223:744–749.
- van den Bos EJ, Constantinescu AA, van Domburg RT, Akin S, Jordaens LJ, Kofflard MJ. Minor elevations in troponin I are associated with mortality and adverse cardiac events in patients with atrial fibrillation. *Eur Heart J*. 2011;32:611–617.
- Costabel JP, Burgos LM, Trivi M. The significance of troponin elevation in atrial fibrillation. *J Atr Fibrillation*. 2017;9:1530.
- Ulimoen SR, Enger S, Norseth J, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Improved rate control reduces cardiac troponin T levels in permanent atrial fibrillation. *Clin Cardiol*. 2014;37:422–427.
- Lasek-Bal A, Gąsior Z, Kowalewska-Twardela T, Urbaneł T. New-onset atrial fibrillation in patients with elevated troponin I levels in the acute phase of stroke. *Int J Cardiol*. 2015;195:210–211.

Supplemental Material

Data S1.

NIHR Health Informatics Collaborative TROP-AF Study

DATA COLLECTION PLAN

Author: Amit Kaura
Approvers: Jamil Mayet
Date: 07/03/2017

Introduction

This document outlines the specifications and procedures for the NIHR Health Informatics Collaborative (NIHR HIC) Cardiovascular research database and defines the processes for the collection of the NIHR HIC Cardiovascular research data and onward sharing with researchers. The central research database is held within Imperial College Healthcare NHS Trust (ICHNT).

Data for all patients receiving a troponin test are collected locally at the following Trusts and submitted pseudonymously to ICHNT:

- Imperial College Healthcare NHS Trust
- University College London Hospitals NHS Foundation Trust
- Oxford University Hospitals NHS Foundation Trust
- Kings College Hospital NHS Foundation Trust
- Guys and St Thomas' Hospital NHS Foundation Trust

This document covers the processes for local collection of data at all sites. The main database and systems are hosted at ICHNT as the lead organisation for the Cardiovascular Theme.

NIHR HIC Cardiovascular Database Definitions

Local data store

Each Trust will have a local store of NIHR HIC Cardiovascular data; this collects their information in an identifiable form from clinical systems. The data will then be de-identified within the local NHS Trust. These de-identified data will be passed to the central research database.

Research database

The research database will contain only de-identified information. This database combines the data from each site (including ICHNT). The database will contain some secondary patient identifiers (e.g. date of procedure, date of death) which will not be made directly available to researchers. A further

anonymised view of the data will be prepared by ICHNT staff which will involve converting all dates to the number days since the first troponin test. This view of the data will contain only the variables necessary to complete the study rather than the full database.

Procedures for local data collection into local stores

Data will be collected automatically from primary clinical systems within each Trust. NHS staff will enter data into clinical systems during routine clinical care of patients, or data will be generated as a result of clinical tests. Data in the primary clinical systems will be processed in accordance with each Trusts clinical guidelines and subject to local quality and governance procedures. Data will be extracted automatically and validated processes for data extraction, transformation and loading (ETL) have been designed to import the data into the local secure data stores.

Access to local data stores

Access to identified data will be limited to those justified and approved by the local information governance teams and will always be NHS staff in accordance with the duty of confidentiality required by law. Anonymisation procedures will be automated after implementation.

Local data stores will be the only areas that hold any patient identifiers. De-identification is completed at this stage prior to passing data into any research databases and datasets.

De-identification

The data will be pseudonymised locally within each Trust; anonymisation processes will be automated and set up by NHS staff in accordance with:

- advice from local information governance procedures
- the HIC Standard Operating Procedure (SOP) for data sharing and anonymisation
- the Clinical Data transfer policy

The data items summarised in Table 1 will be anonymised. Anonymisation will be approved locally by information governance teams before data are sent externally to ICHNT. De-identified data are then shared in accordance with the overarching data sharing agreement.

Demographic	Anonymisation
Local Identifier	Provided if NHS number is missing
NHS Number	Use local pseudonymisation algorithm (key to be retained at source) Rename field to subject ID
Family Name	To be removed – LOCAL use
Given Name	To be removed – LOCAL use
Date of Birth	YYYY
Date of Death	DD-MM-YYYY

Table 1. Anonymisation of data elements

Each site will hold two versions of the database, one identifiable and one with de-identified, pseudonymised data. The de-identified version is for use in research and shared with the central research database at ICHNT. The identifiable database is held so that if necessary patients can be re-identified if it is of importance to re-contact the patient via their care team.

NHS numbers and hospital numbers are pseudonymised using locally approved procedures. Names are removed from the dataset and date of birth is transformed to year of birth. Date of death is shared, however, is converted in to relevant survival rates on provision of data to researchers. Researchers will never see the full date of death or be able to calculate it from other information (all dates are provided as delta for first troponin). The provision of date of death has been agreed by each of the information governance offices at each of the sites in the following de-identification and anonymisation protocol for the study:

- The exact date of death is required to evaluate mortality after diagnosis.
- Patients presenting with suspected acute coronary syndromes are likely to have a high frequency of cardiac events and a high short-term mortality rate. An accurate measure of death is therefore required to fully evaluate this.
- To redact the date of death to year only would misrepresent the survival of these patients, particularly for those who survive for less than one year. The clinical leads at our BRCs have underlined the importance of having the date in full for the study.

Data validity and quality

Prior to pseudonymisation within the clinical systems, NHS number, date of birth and patient names will be automatically checked to remove duplication of patients.

Samples of data will be clinically validated by members of the clinical team to ensure that the transformation process is correct and data are attributed to the correct patients prior to pseudonymisation. After clinical validation is complete, the data will be transformed to a standardised XML format and validated (Figure 1).

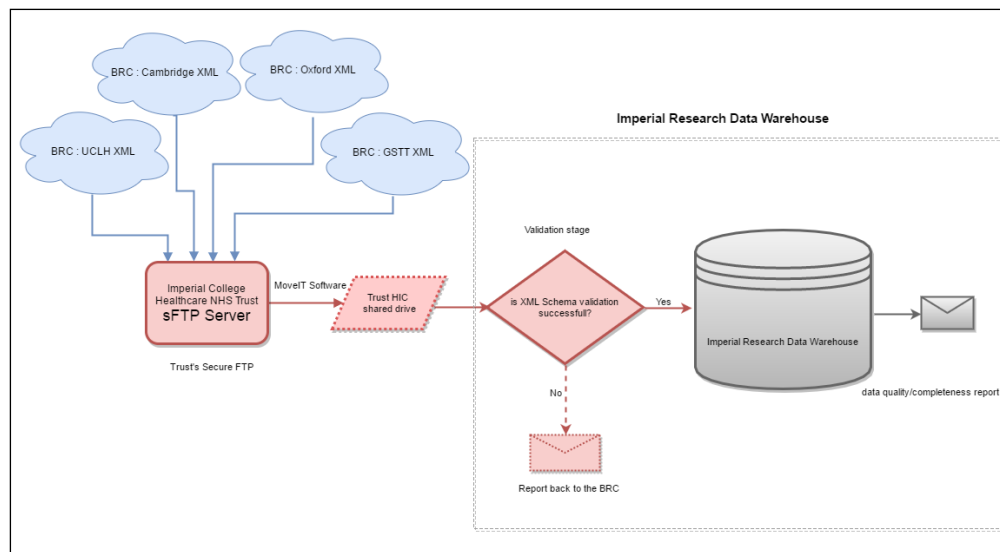


Figure 1. Data import and validation process.

Data sharing between Trusts

Data are shared in accordance with the SOP for data sharing. Data are encrypted in transit via sFTP on the N3 network (Figure 1). The sFTP is set up and hosted by ICHNT.

Procedures for secure research database

Data validity and quality

ICHNT validate the data to ensure that the structure, data items, units and data types are in accordance with the standardised data model. Data will be rejected if validation fails. On rejection, the files will be archived and the data manager will contact the data provider to review the submission and resend once corrected.

Once imported into the secure research database, data are subject to clinical validation by Cardiovascular clinical experts; these validations will be

completed by the clinical researchers using de-identified data. Data will be reviewed for data completeness, spread and actual data point values. If data appears invalid it will be rejected.

Data quality reports will be generated and provided to the research team and local data provider after each submission. These will be reviewed after each submission to ensure all areas are populated.

Research Database software

The database will be built using Microsoft SQL server 2014, Microsoft's principle database management system software. The installation of the software was carried out by certified technical consultants and tested by the Trust ICT team and data warehouse team in accordance with Trust ICT procedures and policies.

Database management

The database will be fully backed up on a daily basis. The back-ups are standardised for all Trust databases within the Trust data warehouse. Backups can be restored at any point by warehouse staff. Data are secondary copies from clinical systems; at any point the participating Trusts can re-extract the data from primary sources. Each site will submit data on a quarterly basis to the database. Data integrity checks will be completed to ensure correct structure is maintained and duplicates are not present.

Once entered on the system, data will not be changed. All access will be 'read only' except via exception, approved by the research Informatics Programme Manager and Clinical Leads group.

The database will be managed by the data manager (Ben Glampson) and developer (Abdul Mulla). Any database changes will be controlled by the research informatics Programme manager (Ben Glampson), and sanctioned by the NIHR HIC Cardiovascular scientific steering committee (chaired by Jamil Mayet). All staff are substantive NHS employees at ICHNT.

Data extracts taken for research will be stored within the data warehouse and retained for the period specified in the data request. All information pertinent to the request will be retained and tracked by the data manager.

DATA ACCESS FOR RESEARCH

Author: Amit Kaura
Approvers: Jamil Mayet
Date: 09/08/2018

TROP-AF STUDY dataset

All analyses for the TROP-AF STUDY will be completed on fully de-identified data. This includes further de-identification to remove dates.

A designated clinical researcher (Amit Kaura) froze a copy of the database on 1st April 2017, so a static dataset can be used for analysis. This will be retained separately from the live database to allow reproducible analyses.

The study dataset will comprise all patients who had a troponin measured at each of the five academic centres between 2010 (2008 for University College Hospital) and 2017.

Dates will be converted to delta dates, with date zero being the date of the first troponin test. All further dates will be provided as number of days from date zero. Age will be provided in years, at the time of the first troponin test.

Date of death will be converted to the number of days since date zero. All patients will be retrospectively followed up, using routinely collected data on the NHS Spine Application, Summary Care Record, until death or censoring on 1st April 2017.

Data elements

The database model includes 156 data points, grouped into demographics, emergency department attendance and inpatient episodes, biochemistry, diagnosis, angiography, revascularization, echocardiography and mortality. Diagnostic data will be based on International Statistical Classification of Diseases and Related Health Problems (ICD) discharge codes.

DATA ANALYSIS PLAN

Author: Amit Kaura

Approvers: Jamil Mayet / Darrel Francis

Date: 09/08/2018

Study population

The study dataset will include all patients who have had a troponin measured at each of the five academic centres between 2010 (2008 for University College Hospital) and 1st April 2017.

The study population will be focussing on those with a primary diagnosis of atrial fibrillation: ICD-10 code I48: Atrial fibrillation and flutter.

We will exclude all patients with a secondary diagnosis of atrial fibrillation.

Data variables

Troponin data

In clinical practice, troponin levels are frequently dichotomised into “positive” (meaning a result above the 99th percentile of the upper limit of normal (ULN)) or “negative”. Troponin levels may have a progressive relationship with prognosis, too, but the shape of this relationship is not known across the full spectrum of values and making the assumption of a linear relationship of mortality with troponin (or log troponin) may not be secure.

For these reasons, we will treat the data in two ways:

1. We will dichotomise the peak troponin level as being either positive or negative based on the ULN for each troponin assay. This makes no assumption of the shape of the relationship.
2. We will use troponin on a continuous scale by standardising the many troponin assays, by scaling the results using the ratio of the observed troponin value divided by the ULN for that particular troponin assay. For example, a patient with a troponin value of 96 using an assay which has an ULN of 40 would have a scaled result of $96/40 = 2.4$ xULN.

All analyses on troponin will be performed using the peak troponin level. For patients who have a single troponin measurement, the peak troponin will be based on this measurement. In the remainder of the patients who have more than one troponin test in the same hospital episode, the peak troponin value will be defined as the highest of all measurements.

Revascularisation status

Acute revascularisation will be defined as having PCI or CABG in the time window between 48 hours before and 3 months after the first troponin measurement. This will account for patients who had revascularisation, in particular PCI, as an emergency prior to their first troponin blood test and to capture revascularisation, in particular CABG, performed as an outpatient following their index admission.

Follow-up

- Using a retrospective cohort study design, all patients will be followed up until death or censoring on 1st April 2017.
- Life status will be ascertained using routinely collected data on the NHS Spine Application, which is linked to the Office of National Statistics, and thereby to the national registry of deaths.

Outcomes

Primary outcome

The primary outcome will be all-cause mortality. The nature of the data sources means that this is the outcome that will be available and it will be available with high fidelity.

Secondary outcomes

The secondary outcomes will be:

- Angiography
- Revascularisation (coronary artery bypass grafting CABG), percutaneous coronary intervention (PCI))

Statistical Methods

Baseline data

Baseline and demographic characteristics of patients with a primary presentation of atrial fibrillation will be summarised by standard descriptive summaries:

- means (standard deviation) for continuous variables which are normally distributed
- median (interquartile range) for continuous variables which are not normally distributed

- number (percentage) for categorical variables

These characteristics will also be described for patients who did and did not undergo coronary angiography.

Comparison between angiography and no angiography groups will be made using Mann-Whitney U test or unpaired t-test for continuous variables and Chi-square test for categorical variables.

Relationship between troponin level, coronary angiography and mortality

The relationship between dichotomous troponin level (above ULN or not), or continuous troponin, and all-cause mortality will be performed using multivariate Cox proportional hazards regression modelling.

The proportional hazard assumption will be tested, with a violation indicated by a significant relationship between Schoenfeld residuals of a covariate and time. If the proportional hazards assumption is violated, Cox regression analysis with time-dependent covariates will be used with follow-up time divided into time intervals within which the proportional hazard assumptions are met.

Furthermore, using Martingale residuals, if non-linearity is detected in the relationship between the log hazard and a continuous covariate, the non-linear relationship will be modelled using restricted cubic splines.

Splines will be adjusted for demographic characteristics, haematological and biochemical blood results, cardiovascular risk factors and comorbidities.

Subgroup analyses will be performed in angiography and no angiography subgroups. Kaplan-Meier survival curves will be plotted according to angiography status.

Statistical significance

All hypothesis tests will be 2-tailed. A p-value of <0.05 will be considered statistically significant. No correction will be implemented for multiple testing.

Statistical package

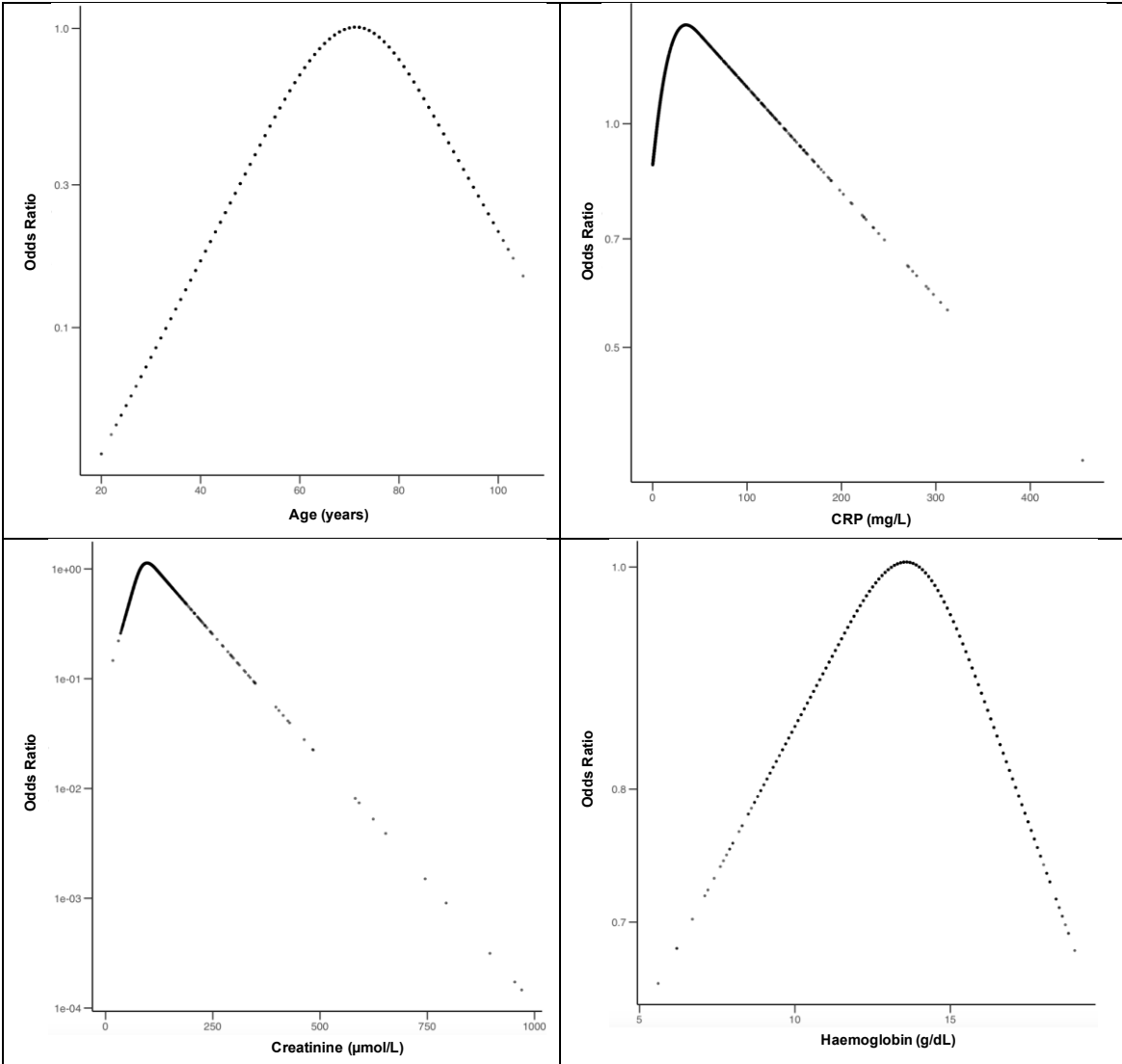
Statistical analyses will be performed using SPSS software version 24 (SPSS Inc., Chicago, Illinois, United States) or R 3.3.2 statistical package (the R Core Team, Vienna, Austria).

Table S1. Odds ratio of undergoing coronary angiography.

	Odds ratio (95% CI)	P-value
Male (vs female)	1.6 (1.2 – 2.1)	0.004
Diabetes mellitus	1.1 (0.7 – 1.7)	0.68
Hypercholesterolaemia	1.1 (0.8 – 1.7)	0.52
Hypertension	0.8 (0.6 – 1.2)	0.29
Aortic stenosis	2.1 (0.9 – 4.6)	0.07
Heart failure	1.1 (0.7 – 1.7)	0.67
Previous myocardial infarction	3.7 (2.6 – 5.2)	<0.0001
Malignancy	0.4 (0.2 – 0.9)	0.02
Obstructive lung disease	0.9 (0.5 – 1.6)	0.64
Positive troponin	1.5 (1.2 – 2.1)	0.003

Estimates compared to not having the disease, unless otherwise stated.

Figure S1. Odds ratio of undergoing coronary angiography.



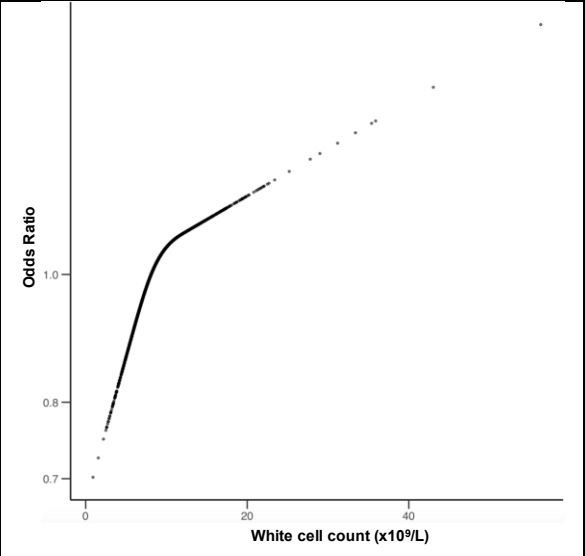
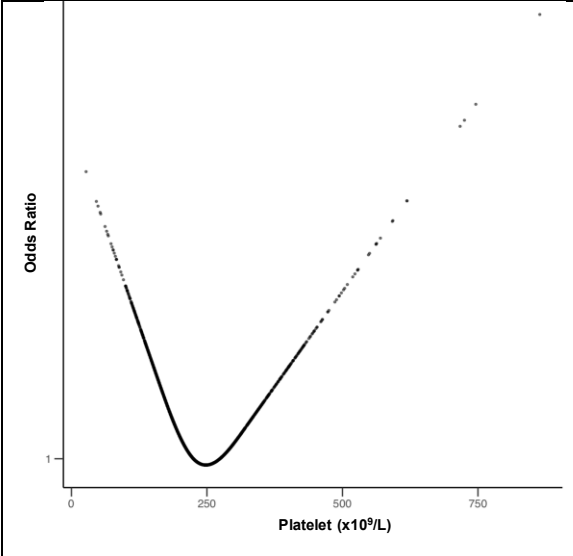
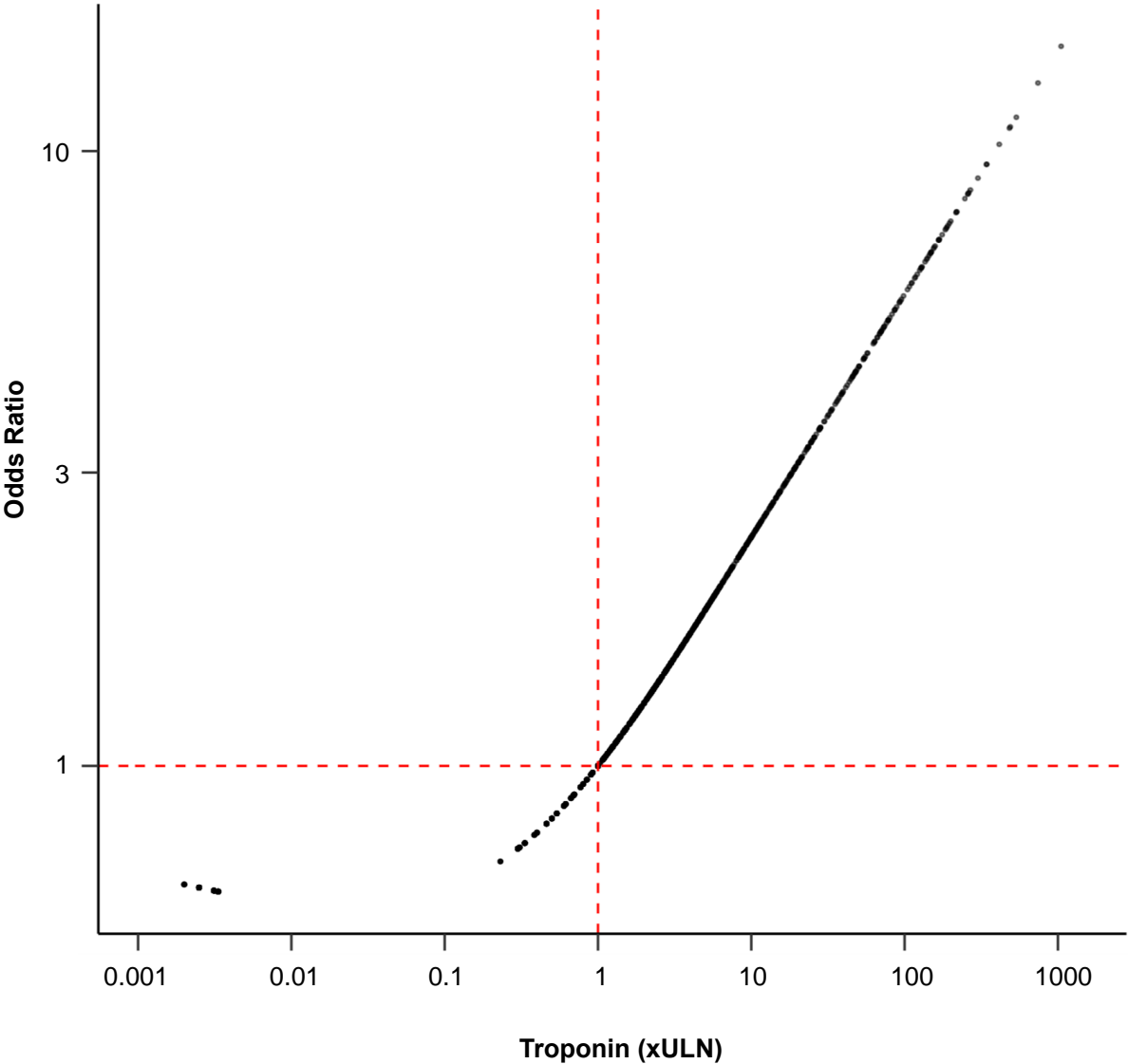
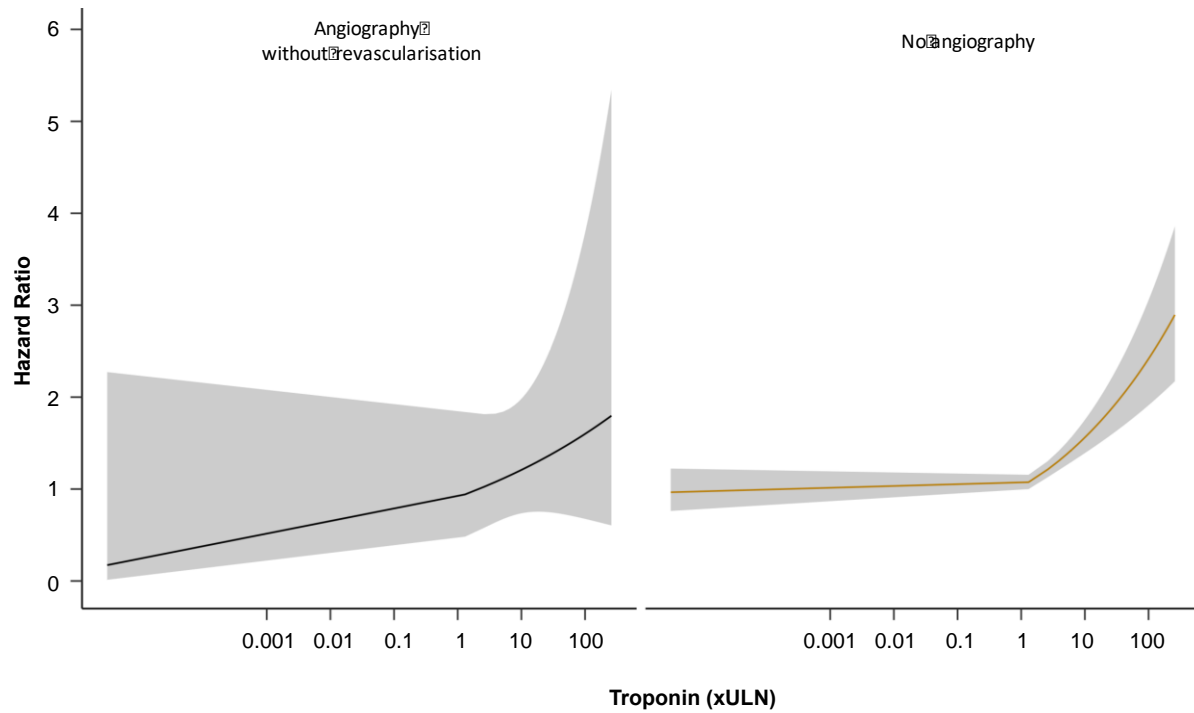


Figure S2. Odds ratio of undergoing coronary revascularisation according to troponin level.



The figure shows the odds ratios of undergoing coronary revascularisation according to troponin level, where the comparator troponin level value is of 1 xULN, which is marked with the red dotted lines. ULN, 99th percentile of the upper limit of normal.

Figure S3. Multivariate* restricted cubic spline modelling of association between troponin level and hazard ratio for patients who underwent angiography without revascularisation (left) and those who did not undergo angiography (right).



*adjustment for age, sex, C-reactive protein, creatinine, haemoglobin, platelet count, white cell count, diabetes mellitus, hypercholesterolaemia, hypertension, aortic stenosis, heart failure, previous myocardial infarction, malignancy and obstructive lung disease. The shaded area denotes the 95% confidence interval. 99th percentile of the upper limit of normal.