

Minor elevations in troponin I are associated with mortality and adverse cardiac events in patients with atrial fibrillation

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Aims

In patients with atrial fibrillation, minor troponin I elevation is regularly detected; however, the prognostic significance of this finding is unknown. We therefore sought to examine the prognostic value of elevated troponin I in patients with atrial fibrillation.

Methods and results

A prospective study was conducted analysing all consecutive patients admitted with atrial fibrillation in a 2-year period. Patients with an ST-elevation myocardial infarction (MI) were excluded. Minor troponin elevation was defined as a troponin I level between 0.15 and 0.65 ng/mL, which is still below the 99th percentile of the upper reference limit. A positive troponin I was defined as ≥ 0.65 ng/mL. Study outcomes were all-cause mortality (death), death and myocardial infarction (death/MI), or all major adverse cardiac events (MACE: death, MI, or revascularization). A total of 407 patients were eligible for inclusion. The median duration of follow-up was 688 days. A minor elevation occurred in 81 (20%) patients and 77 (19%) had a positive troponin I. In a multivariate model, minor troponin I elevation and a positive troponin I were independently associated with death [hazard ratio (HR): 2.36, 95% confidence interval (CI): 1.17–4.73 for minor elevation and HR: 3.77, 95% CI: 1.42–10.02 for positive troponin I]. Also, there was an independent correlation between the combined endpoints of death/MI and MACE and both a minor elevation and a positive troponin I.

Conclusion

Minor elevations in troponin I on hospital admission are associated with mortality and cardiac events in patients with atrial fibrillation and might be useful for risk stratification.

Keywords

Troponin I • Atrial fibrillation • Prognosis

Introduction

Cardiac troponins are sensitive and specific markers of cardiac injury. Therefore, the universal definition of myocardial infarction (MI) as defined in 2007 by the European Society of Cardiology relies on the elevation of troponin T or I above the 99th percentile of the upper reference limit (URL) of a control population.¹ However, even minor elevations in troponins below this limit have been shown to predict prognosis in acute coronary syndromes^{2,3} and a wide array of acute and chronic medical conditions such as sepsis,⁴ acute cerebral events,⁵ and stable heart failure,⁶ as

well as in apparently healthy persons.⁷ However, in patients admitted with atrial fibrillation, the significance of minor troponin elevations below the 99th percentile of the URL is so far unknown and their role in risk evaluation in this patient population remains to be identified. The identification of new prognostic markers is important since it has been shown that the presence of atrial fibrillation carries an adverse prognosis especially in heart failure patients.^{8,9} We hypothesized that subclinical cardiomyocyte damage demonstrated by minor elevations in troponin I is correlated with adverse events in patients with atrial fibrillation. Accordingly, we investigated whether circulating levels of troponin

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are associated with adverse events independently of other known risk factors in patients with atrial fibrillation on hospital admission.

Methods

Study population

This prospective study was conducted in the Albert Schweitzer Hospital, a large teaching hospital in the west of the Netherlands. All consecutive patients admitted to the cardiology ward or coronary care unit with atrial fibrillation on the admittance electrocardiogram (ECG) were screened for inclusion. Patients included in the study were admitted between 1 January 2005 till 31 December 2006. Exclusion criteria were: transfer from another hospital or from another ward inside the hospital, patients resuscitated after cardiac arrest, an ST-elevation MI (STEMI), or the unavailability of a serially measured cardiac troponin I or a troponin I measured at least 8 h after the start of complaints. Therefore, of the total of 452 patients screened, 16 were excluded because of an STEMI, 7 were lost to follow-up, 3 were resuscitated, and 19 patients did not have an appropriate troponin I measured, leaving 407 patients to include in the study.

Data collection

Baseline data included demographics, medical history (including a history of cardiac events, congestive heart failure, and revascularization procedures), and life-style information. Smoking was defined as actual smoking or a history of smoking. Diabetes mellitus was defined as reported physician diagnosis or the use of medication for diabetes. Hypertension was defined as reported physician diagnosis or the use of anti-hypertensive medication. Hypercholesterolaemia was defined as reported physician diagnosis or the use of cholesterol-lowering medication or a total cholesterol above 6.0 mmol/L on hospital admission. Known coronary artery disease was defined as a previous MI, coronary revascularization, or a coronary angiogram with any flow-limiting stenosis ($\geq 70\%$ diameter narrowing).

Symptoms of chest pain at presentation were recorded as described by the patient to the treating physician at admission. The quality and severity of these symptoms was not further specified due to the absence of standard definitions. The extent of ST-segment depression was measured in the leads with maximal depression at 80 ms after the QRS complex, with 0.5 mm or more ST depression in one or more leads considered ischaemia. To maximize the sensitivity of the ECG to detect ischaemia, we did not differentiate ST depression due to left ventricular hypertrophy from 'ischaemic-appearing' ST depression. A test for cardiac ischaemia was defined as any stress test or coronary angiogram conducted during hospitalization or at the outpatient clinic up to 6 months after the admission date. These were determined to be positive or negative for ischaemia by standard criteria applied by the clinical cardiologist interpreting the study.

Follow-up information was obtained from the hospital electronic medical record system or, when unavailable, by telephone interview. Follow-up began after the day of admittance and continued until 1 March 2008. All clinical records of both outpatient visits and hospital admissions were reviewed. For every encounter, all available information such as medical history, physical examination, laboratory tests, and ECG was reviewed. All-cause mortality was determined by chart review, telephone interviews, or by enquiry of the national death registry. Myocardial infarction was defined as described in the universal definition of MI expert consensus document.¹ Revascularization (REVASC) was defined as a coronary artery bypass grafting procedure or percutaneous coronary intervention.

Troponin I assay

For the determination of troponin I, serum was collected on hospital admission that was immediately processed using a standard assay (IMMULITE, DPC) according to the manufacturer's instructions. Analytical sensitivity and linearity of this assay was reported previously.¹⁰ Results are reported as ng/mL. The 99th percentile of the URL was calculated to be 0.65 ng/mL based on a sample of 100 healthy patients from the hospital adherence region. Therefore, a troponin I of 0.65 ng/mL or higher was defined as a positive troponin I, between 0.15 and 0.65 ng/mL as a minor elevation, and a level of ≤ 0.15 was defined as non-detectable. In 2006, in a small subset of patients, a higher level of ≤ 0.20 was used as the cut-off value because of an increase in test variance below this level. An imprecision of 7.8% coefficient of variation (CV) was found at 0.58 ng/mL.

Statistical analysis

The patient population was divided into three groups based on the maximal troponin I level measured at admission: (i) troponin I non-detectable, (ii) minor elevation in troponin I, or (iii) a positive troponin I. Baseline characteristics between categories of troponin I were compared by means of the χ^2 test for categorical variables. Continuous variables were compared by analysis of variance (ANOVA) with Bonferroni's *post hoc* correction. The study outcomes were all-cause mortality (death) or a combined endpoint of all-cause mortality and MI (death/MI), or all major adverse cardiac events (MACE: all-cause mortality, MI, or REVASC). Continuous variables are expressed as means \pm standard deviation except for troponin I levels (median). Dichotomous variables are expressed as percentages. Multivariate Cox proportional hazards models were used to determine the relationship between troponin I categories and death, MI, and REVASC as well as with the combined endpoints of death/MI and MACE. A similar analysis was performed with troponin I level as a continuous variable. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs). Adjustments were made for age, gender, history of coronary artery disease or congestive heart failure, smoking, hypertension, diabetes mellitus, hypercholesterolaemia, and creatinine level at admission. Kaplan–Meier plots were used to illustrate the timing of events. The three groups were compared with the log-rank test. A *P*-value of < 0.05 was considered significant (two-tailed). Statistical analysis was performed using SPSS version 16.0. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript written.

Results

Baseline data

Clinical characteristics by troponin I concentration at baseline are displayed in *Table 1*. Mean patient age at the time of hospital admission was 71 years. The median duration of follow-up was 688 days (range 3–1146 days). Of the 407 patients, 81 (20%) had a minor elevation in troponin I, with a median level of 0.31 ng/mL. Furthermore, 77 patients (19%) had a positive troponin I of ≥ 0.65 , with a median level of 3.41 ng/mL. Patients with elevated troponin I levels tended to be older than those with non-detectable troponin I, to have hypertension, a history of congestive heart failure, or coronary artery disease (*P* < 0.05 for trend and for comparison of elevated groups with the non-detectable group; *Table 1*). Furthermore,

Table 1 Characteristics of the study groups

	Troponin I			P-value for trend
	Non-detectable (n = 249)	Minor elevation (n = 81)	Positive (n = 77)	
Age (years)	67.6 ± 13.8	75.5 ± 10.4 ^a	77.9 ± 10.8 ^a	<0.001*
Men, n (%)	134 (54)	44 (54)	40 (52)	0.948
Hypertension, n (%)	124 (50)	59 (73) ^a	56 (73) ^a	<0.001
Diabetes, n (%)	46 (19)	23 (28)	23 (30) ^a	0.043
Smoker, n (%)	75 (31)	33 (43)	26 (36)	0.207
Hypercholesterolaemia, n (%)	92 (37)	28 (35)	22 (29)	0.402
Known CAD, n (%)	50 (20)	33 (41) ^a	31 (40) ^a	<0.001
Previous CHF, n (%)	21 (8)	17 (21) ^a	13 (17) ^a	0.005
Creatinine (µmol/L)	100.8 ± 35.7	111.9 ± 40.0	147.1 ± 104.5 ^{a,b}	<0.001*
History of AF, n (%)				0.663
Paroxysmal	83 (33)	27 (33)	22 (29)	
Persistent	6 (2)	1 (1)	2 (3)	
Permanent	31 (12)	16 (20)	10 (13)	

CAD, coronary artery disease; CHF, congestive heart failure; AF, atrial fibrillation.

*P for trend with ANOVA. Pairwise comparisons with Bonferroni's adjustment.

^aP < 0.05 vs. non-detectable troponin I.

^bP < 0.05 Positive troponin I vs. minor elevation in troponin I.

these patients were more likely to have diabetes mellitus ($P < 0.05$ for trend and for comparison of the positive group with the non-detectable group; *Table 1*). Creatinine was higher in the patients with elevated troponin I levels ($P < 0.05$ for trend and for comparison of the positive troponin group with others; *Table 1*).

Prognostic value of troponin I

In total, 102 of 407 patients (25%) in the total sample died and 117 patients (29%) experienced the combined endpoint of death and MI and 131 patients (32%) experienced any major adverse cardiac event. In the univariate analysis, minor troponin I elevation and positive troponin I were associated with death, death/MI, and MACE (*Table 2*), as well as the non-pre-specified endpoints of MI and REVASC. After adjustment for all baseline variables, minor troponin I elevation as well as a positive troponin I were independently correlated with death (HR: 2.35, 95% CI: 1.17–4.73 for minor elevation and HR: 3.77, 95% CI: 1.42–10.02 for positive troponin I; *Table 2*). There was an independent association between the combined endpoint of death/MI and both a minor elevation in troponin I and a positive troponin I (HR: 1.99, 95% CI: 1.05–3.80 for minor elevation and HR: 3.03, 95% CI: 1.24–7.37 for a positive troponin I; *Table 2*). Both a minor elevation in troponin I and a positive troponin I were independently associated with MACE (HR: 2.48, 95% CI: 1.33–4.63 for a minor elevation and HR: 5.60, 95% CI: 2.40–13.07 for a positive troponin I; *Table 2*). A similar pattern was observed for the absolute troponin I levels (after adjustment: HR: 1.03, 95% CI: 1.0–1.06 for death, HR: 1.15, 95% CI: 1.06–1.24 for death/MI, and HR: 1.05, 95% CI: 1.03–1.07 for MACE). The Kaplan–Meier plots for the three study endpoints by troponin I category at baseline are shown in *Figure 1*. Cumulative 3-year survival rates were 78% in the non-

detectable troponin I group, 62% in the minor elevation group, and 57% in the positive troponin I group (log-rank $P < 0.001$).

Cardiac ischaemia

Patients with an elevated troponin I were more likely to have chest pain on admission: 47 and 52% of the patients in the minor and positive troponin I groups had chest pain, respectively, vs. 37% of the patients in the non-detectable group ($P < 0.05$ for trend). Furthermore, they were more likely to have signs of ischaemia on the admission ECG as judged by ST-segment depression (25 and 52% of the patients in the minor and positive troponin I groups, respectively, vs. 18% in the non-detectable group; $P < 0.05$ for trend and for comparison of the positive troponin I group with the other groups). A subgroup analysis was performed in the patient population with and without chest pain and with and without ischaemic ST-segment depression. No significant interaction was found between troponin I category and these parameters. The results of this subgroup analysis are shown for the group with a minor elevation in troponin I in a forest plot (*Figure 2*).

Patients with an elevated troponin I were more likely to undergo a test for cardiac ischaemia (21 and 38% in the minor and positive groups, respectively, vs. 26% in the non-detectable group; $P < 0.05$ for trend and for all other comparisons between groups). Furthermore, ischaemia testing was more often positive in the elevated troponin I groups (53 and 61% in the minor and positive groups, respectively, vs. 16% in the non-detectable group; $P < 0.05$ for trend and for comparison with the non-detectable group). The percentage of coronary angiograms showing obstructive coronary artery disease was significantly higher in the elevated troponin I groups (64 and 75% in the minor and positive groups, respectively, vs. 24% in the non-detectable group; $P < 0.05$ for trend and for comparison with the non-detectable group).

Table 2 Unadjusted and adjusted hazard ratios for categories of troponin I elevation to predict all-cause mortality (death), all-cause mortality and myocardial infarction (death/MI), all major adverse cardiac events (MACE), myocardial infarction (MI), and revascularization (REVASC)

	Hazard ratio (95% CI)	
	Unadjusted	Adjusted ^a
Death		
Troponin I minor elevation	2.07 (1.29–3.34)	2.35 (1.17–4.73)
Troponin positive	2.74 (1.72–4.35)	3.77 (1.42–10.02)
Death/MI		
Troponin I minor elevation	2.19 (1.40–3.44)	1.99 (1.05–3.80)
Troponin positive	3.05 (1.98–4.68)	3.03 (1.24–7.37)
MACE		
Troponin I minor elevation	2.37 (1.53–3.67)	2.48 (1.33–4.63)
Troponin positive	4.45 (2.98–6.63)	5.60 (2.40–13.07)
MI		
Troponin I minor elevation	4.16 (1.40–12.37)	
Troponin positive	7.54 (2.78–20.41)	
REVASC		
Troponin I minor elevation	3.40 (1.10–10.54)	
Troponin positive	9.36 (3.59–24.45)	

CI, confidence interval.

^aAdjustments were made for age, gender, history of coronary artery disease, previous congestive heart failure, smoking, hypertension, diabetes mellitus, hypercholesterolaemia and creatinine level at admission.

Discussion

Primary observations

The main finding of the present study is the high prognostic value of circulating troponin I that was associated with mortality and major adverse cardiac events in patients with atrial fibrillation on hospital admission. Furthermore, even a minor elevation in troponin I below the 99th percentile of the URL was correlated with adverse events independently of other known risk factors. Thus, troponin I levels that thus far are considered clinically irrelevant for prognostic stratification in patients with atrial fibrillation appear to convey robust prognostic information.

In recent years, multiple studies have shown the significance of minor troponin elevations in multiple cardiac patient populations, such as acute coronary syndromes^{2,3} and heart failure.⁶ Furthermore, it appears that even troponin levels that are just above the detection limit significantly influence the risk for future cardiac events even in healthy patients.⁷ However, only one case report has described the elevation of troponin levels due to atrial fibrillation with a rapid ventricular response with a normal coronary angiogram.¹¹ A larger study assessed the cause of troponin release in patients who underwent coronary angiography without evidence for significant atherosclerosis: atrial fibrillation was only encountered in 1 out of the 21 patients.¹² To our

knowledge, only the present study has studied the significance of troponin rise in consecutive patients admitted with atrial fibrillation.

Potential mechanisms of troponin I release

Troponin I is a cardiac specific protein that is part of the contraction complex in the cardiomyocyte, although small levels can be found in the cytosol.¹³ Necrosis of cardiomyocytes due to a thrombotic acute coronary syndrome is the most common and well-known mechanism of troponin I release into the circulation. According to the universal definition of MI, this is termed a type I MI.¹ However, during atrial fibrillation, other reasons for cardiac troponin I release might be present. First, the fast ventricular response can cause demand ischaemia, despite normal coronary arteries. With significant troponin release, these would generally be defined as a type II MI (supply–demand mismatch). In this elderly study population with probably a high prevalence of obstructive coronary artery disease, demand ischaemia is probably an important mechanism. Although troponin I elevation due to supraventricular tachycardias other than atrial fibrillation has been most commonly described in the literature, the cases with atrial fibrillation present all had a fast ventricular response.^{11,12} In the present study, a fast ventricular response (>100/min) was present in 79% of the patients. Secondly, despite the greater demand, coronary flow has been shown to be reduced by alteration in coronary vascular resistance during atrial fibrillation both in animals models¹⁴ and in humans.¹⁵ Furthermore, coronary flow can be decreased by attenuated coronary vasodilatation on exercise.¹⁶ One of the mechanisms involved in the reduced ventricular perfusion during atrial fibrillation might be angiotensin II-induced oxidative stress.¹⁷ In the same study, it was shown that the AT-II blocker irbesartan was able to reduce troponin I rise in experimental atrial fibrillation. Also, this supply–demand mismatch might be present even without a fast ventricular rate.^{17,18} Thirdly, the co-existence of a fixed coronary artery stenosis can induce ischaemia during fast heart rates, as a history of significant coronary artery disease was documented in 28% of the patients. Furthermore, the limited number of coronary angiograms performed showed obstructive coronary artery disease more often in patients with elevated troponin I. Fourthly, another mechanism of troponin I release might be an increase in left ventricular wall strain due to the fast ventricular response and shorter diastolic filling times or due to a reduction in cardiac output and fluid retention, two conditions that can be exaggerated due to pre-existing heart failure. Notably, of the 407 patients, 141 had signs of left-sided heart failure on the admission chest X-ray (data not shown in the results) and 51 had a history of heart failure. Furthermore, it has been shown that troponin I degradation can occur due to proteolysis by elevated preload without signs of ischaemia.¹⁹ Also, elevated troponin I levels correlate with left ventricular wedge pressure in chronic heart failure patients.²⁰ A last mechanism of troponin I rise could be an acute thrombotic coronary event with pre-existing atrial fibrillation or atrial fibrillation caused by acute ischaemia. Although this possibility cannot be excluded, it has been described that atrial fibrillation secondary to an acute

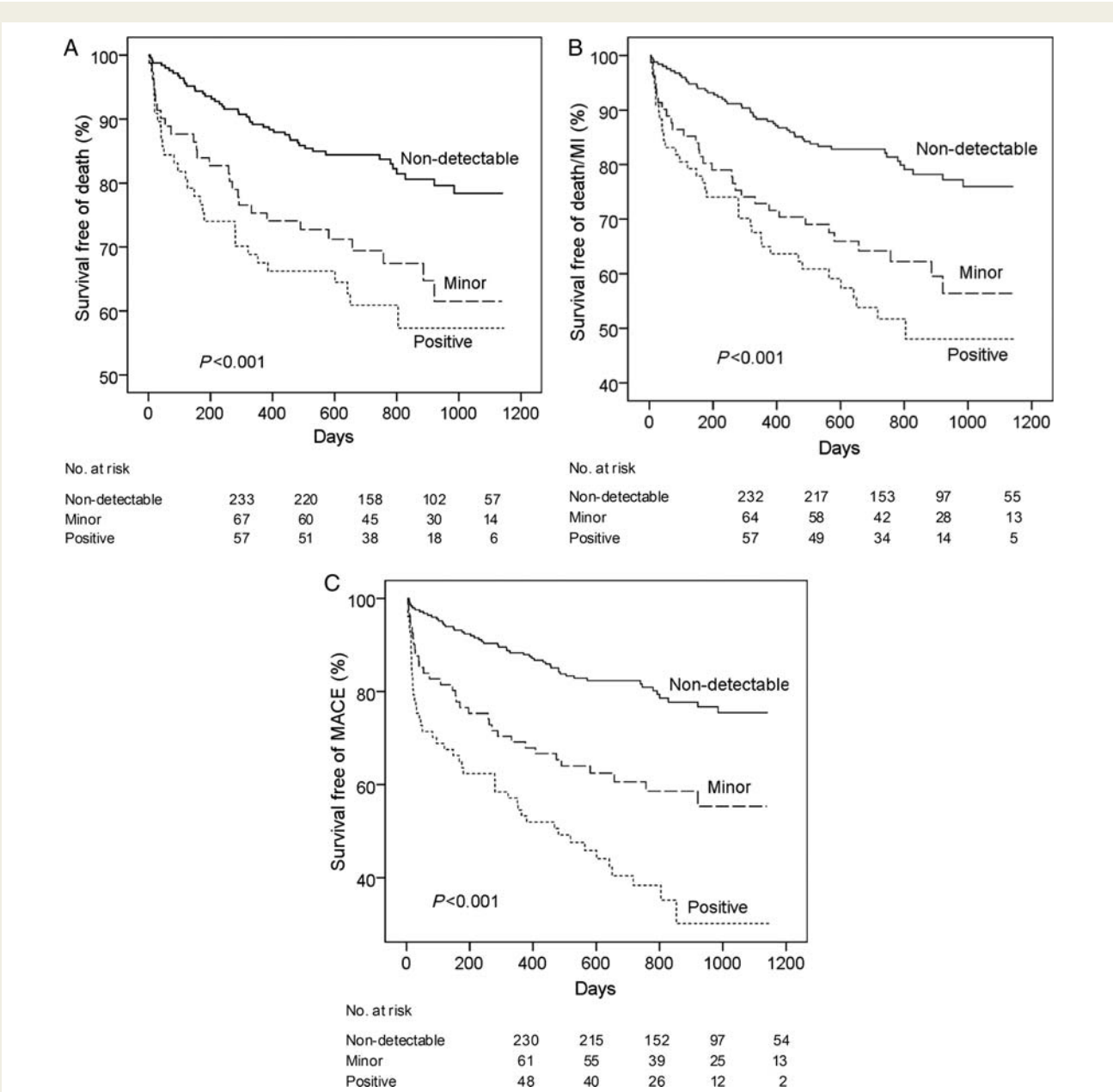


Figure 1 The Kaplan–Meier plots of survival free of death (A), death/myocardial infarction (B), or major adverse cardiac events (C) in relation to troponin I levels at baseline. Non-detectable indicates a maximal troponin I level below the detection limit; minor, a troponin I level between 0.15 and 0.65, which is still below the 99th percentile of the upper reference limit; positive, a troponin I level of 0.65 or higher. *P*-value by log-rank test.

MI is mostly due to an occlusion of the left circumflex artery leading to an STEMI, which were excluded from this study.²¹ Furthermore, in the subgroup analysis, no significant interaction was found between troponin I category and chest pain or ischaemic ST-segment depression. Finally, a history of coronary artery disease, definitely predisposing to an acute coronary syndrome, was not independently associated with adverse events. Other possible causes of troponin I rise are more speculative and include troponin I proteolysis due to the endothelial damage or the ensuing neurohumoral or inflammatory response.

Clinical implications

In routine daily practice, minor troponin elevation below the 99th percentile of the URL in patients with atrial fibrillation is attributed to the rapid or irregular ventricular response and does often not lead to additional diagnostic testing for cardiac ischaemia. In our population, only one-third of the patients with an elevated troponin I underwent a stress test and only 23% of these patients underwent coronary angiography. This clinical routine may be caused by the fact that other clinical signs of ischaemia such as chest pain or ST-segment depression also seem to lack value to predict obstructive coronary

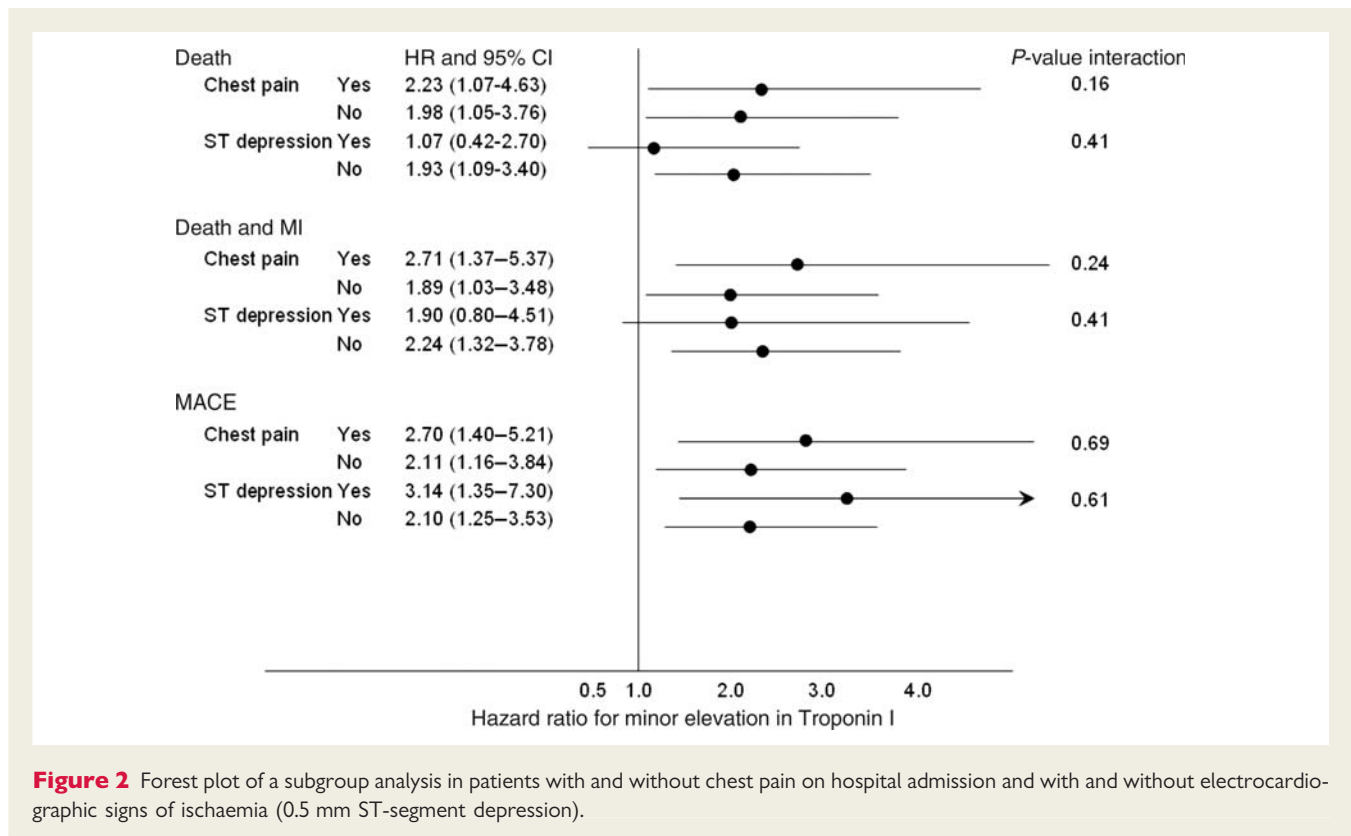


Figure 2 Forest plot of a subgroup analysis in patients with and without chest pain on hospital admission and with and without electrocardiographic signs of ischaemia (0.5 mm ST-segment depression).

artery disease in patients with atrial fibrillation. In patients presenting with chest pain and atrial fibrillation, significant coronary artery disease can be regularly excluded by coronary angiography.²² Furthermore, ST-segment depression consistent with ischaemia might be present without a clear correlation with obstructive coronary artery disease or an adverse prognosis.¹⁵ Finally, both chest pain and ECG signs of ischaemia may be present without a fast ventricular rate.^{18,23} The patients in this study did not undergo stress testing or coronary angiography routinely. Therefore, we do not know whether additional diagnostic testing would have had an additional value for finding obstructive coronary artery disease or lead to a different therapeutic strategy in patients with a minor elevation in troponin I. Finally, it should be taken into account that previous studies have shown a low positive predictive value of stress testing in atrial fibrillation patients.²⁴ This may hamper the predictive value of additional testing for the presence of significant coronary artery disease and decrease its possible role in determining the right therapeutic strategy. Future studies should resolve these issues.

This study shows that troponin I release might detect additional or ongoing myocardial damage, ultimately leading to deterioration in cardiac function in patients hospitalized for atrial fibrillation. Despite the unknown exact underlying pathophysiological mechanism, as discussed above, therapies aimed at reducing ventricular rate, wall stress, or microperfusion¹⁷ might be useful to improve prognosis in the future.

Study limitations

The study population consisted of patients admitted to the hospital, and therefore, results of this study cannot be extrapolated to patients with atrial fibrillation in different settings. Furthermore,

this patient population was very heterogeneous since all consecutive patients admitted with atrial fibrillation were included independently of the fact whether atrial fibrillation was the first admission diagnosis. Although each patient included had at least one troponin I measured 8 h after the start of complaints, serial troponins were not measured routinely to determine a 'rise and fall' in several patients, nor was a second marker present such as the CKmb isoform to determine a temporal pattern of cardiomyocyte damage. Another limitation is the small number of coronary angiographies, which hampers the definite exclusion of an acute coronary syndrome as a possible cause of troponin I rise. A final limitation of this study is the fact that the troponin I assay used in this study has less analytical sensitivity in comparison with other commercial troponin I assays.^{25,26} Furthermore, the detection threshold of the assay used is higher than most contemporary troponin I assays.^{25,26} To assess the accuracy of the assay as it was used in the present study and hospital adherence population, it was made sure that the analytical accuracy of the assay in this study had a 10% CV value below the 99th percentile of the URL. However, it is possible that troponin I values reported in this study to be below the 99th percentile of the URL are in fact above the 99th percentile of the URL with other assays. Therefore, the results of this study have to be interpreted with caution when extrapolating the results of this study to other troponin I assays.

Conclusions

Minor elevations in troponin I levels below the 99th percentile of the URL are associated with mortality and adverse cardiac events

independently of other known risk factors and might be useful for future risk stratification and to select appropriate medical or invasive interventions.

Conflict of interest: none declared.

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