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Journal of Atrial Fibrillation


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# Prognostic Value of Troponin in Patients With Atrial Fibrillation Admitted to an Emergency Department: Review and Meta-Analysis

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## Abstract

**Introduction:** Elevated levels of cardiac troponin (cTn) indicate underlying heart disease and isknown to predict adverse events in multiple conditions. Its role in atrial fibrillation (AF) in the acute setting is still not conclusive. We aimed to assess the prognostic value of c-Tn in patients with AF admitted to an emergency department (ED).

**Methods:** Systematic searches were conducted using PubMed and the Cochrane Library and the International Clinical Trials Registry Platform to identify studies from year 2009 to October 2019 reporting on the prognostic value ofcTn on all-cause mortality or major adverse cardiac events (MACE) in adult patients with AF in the ED. We pooled hazard ratio (HR) and 95% confidence interval (CI) using fixed and random effects models according the heterogeneity. We planned to conduct a sensitivity and subgroup analyses.

**Results:** Five studies involving 5750 patients were identified. The mean follow-up ranged from 12 to 35 months. An increase inmortality was observedin the elevated cTn group compared to the controls, HR=2.7 (95% CI 1.55-4.72), P for effect<0.001, I2=80%). For MACE, the pooled HR was 2.17 (95%CI 1.60-2.94), P for effect <0.001, I2=0%). In the subgroup analysis we found no significant difference in type of troponin used and study design.

**Conclusion:** The elevation of cardiac troponin was significantly associated with higher mortality and major adverse cardiac events in patients with AF admitted to an ED. In this setting the use of c-Tn could provide prognostic information.

## Introduction

Atrial fibrillation (AF) is the most common recurrent arrhythmia in clinical practice and represents an important cause of morbidity and mortality [1]. AF is associated with an increased occurrence of death [2], heart failure [3] and embolic phenomena, including stroke [4]. Its prevalence increases with patients' age, cardiovascular risk factors, coronary artery disease, structural heart disease and elevated cardiac filling pressures, among other phenomena [5-7].

Cardiac troponin is a highly sensitive and specific marker ofmyocardial damage [8]. Patients with elevated levels of troponin are considered to have an increased risk ofmajor cardiac events. As shown in multiple studies, minor troponin elevations result in prognostic outcomes in different cardiac patient populations, such as heart failure [9] acute coronary syndromes [10,11] and stable coronary artery disease [12].

## Key Words

Atrial fibrillation, Troponin, Myocardial infarction, Mortality

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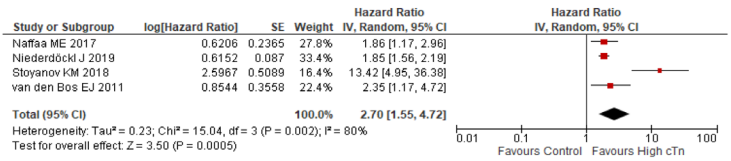
Troponin assays have improved over the past 10 years, and high-sensitivity troponins (hs-cTn) have been introduced in clinical practice since 2012. Hs-cTn assays reliably detect very low troponin levels in plasma, enabling early diagnosis; and present a much lower absolute coefficient of variation, accurately detecting small variations over time and differentiation of chronic and acute elevations. [13,14]. Hs-cTn have improved its prognostic value in almost every individual [15-16]

Increased cardiac troponin concentrations are common in patients with AF. The mechanisms causing cardiac troponin releasein this setting require further study, but are likely related to a myocardial oxygen supply–demand mismatch in the setting of tachyarrhythmia. In addition, AF patients often present associated chronic cardiac conditions that relate with elevated cTn[17].

It is already known that high levels of hs-cTn in patients with AF are linked to an adverse prognosis, based on secondary analyses of randomized controlled trials instable patients [18,19]. The prognostic value of troponin in patients with AF consultingto emergency departments has not been established conclusively.




**Central figure:** **Forest plot of the comparison of elevated c-Tn on mortality**

We conducted a systematic review and meta-analysis with the aim of assessing the prognostic value of troponin in patients with AF in the emergency department.

## Methods

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [20] in conducting and reporting this systematic review.

### Search methods for identification of studies

Systematic searches were conducted to identify studies using PubMed, the Cochrane Library and the International Clinical Trials Registry Platform.Those published from the year 2009 to October 2019onwards were included,using the terms: "atrial fibrillation", "troponin", "emergency department", "Emergency Service" or "Emergency department", and "mortality" or "death" as either keywords or MeSH headings.

We handsearched the reference list of all relevant publications (retrieved full texts of the key articles and identified reviews). We did not impose limits on eligibility related to the healthcare settings where the study took place, the language of publication and the number of participants in the included studies.

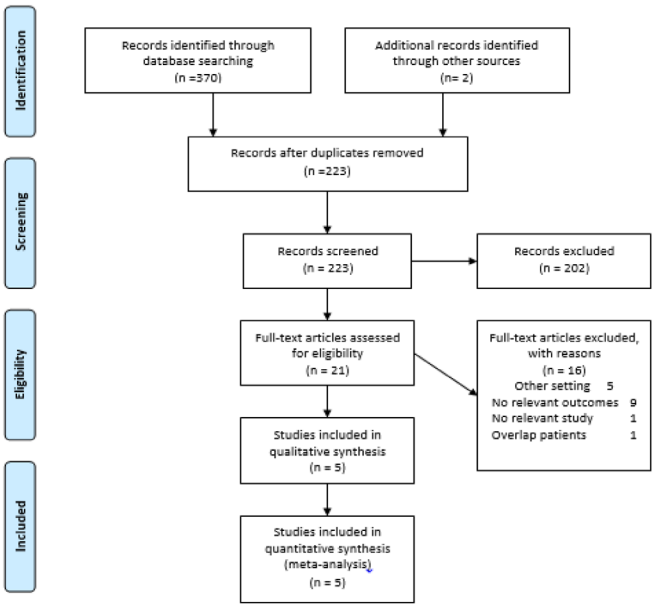



**Figure 1:** **PRISMA flow chart detailing the literature search process**

### Selection of studies for inclusion

Titles and abstracts were independently screened by tworeviewers (LMB and JPC) to identify potentially relevant articles. Discrepancies in judgment were resolved after discussion. Full-text articles were included in our analysis if they fulfilled the following:

a) prospective and retrospective studies with patients >18 years with AF presenting to an emergency department; b) Reported use of a Tn assay (T or I); c) all-cause mortality or major adverse cardiac events (MACEs) as outcomes during follow-up. d) follow-up duration time for at least 1 year. e) exclusion of patients with MI (NSTEMI and STEMI) as main diagnosis of index admission. f)reported statistical method of adjustment (Cox regression or multivariable logistic regression) for all-cause mortality or MACEs between patients with and without cardiac troponin elevation.

We excluded the following types of studies: Narrative or systematic reviews, case reports or case series, studies reported only in abstract form or in conference proceedings where the full text was not available, and studies not published in a peer-reviewed journal.

### Data extraction and management

Data extraction was performed independently by tworeviewers (LMB and JPC) and all disagreements were resolved through discussion or arbitration. Data extraction included first author, year of publication, region, study design, number of patients, study period, characteristics of the study population, type of troponin, outcome measures, time of follow-up and methodological quality items.

### Assessment of methodological quality

The Newcastle-Ottawa Scale was used to assess methodological strength in non-randomized studies [21]. A "star system" was developed, in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of observational studies. In this system, 9 stars represent the highest level and those studies that get 6 stars are of high quality.

We initially searched and evaluated unpublished and published study databases and conference proceedings.During the process of qualifying the studies for inclusion in this review, we faced substantial difficulty in obtaining full text publications or further details of studies published in an abstract form. This precluded a reliable assessment of eligibility and methodological quality, and we decided not to include these publication sources in this review.

### Sensitivity and subgroup analyses

In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove

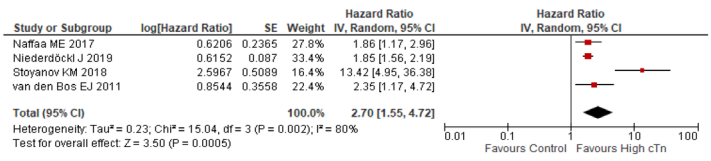



**Figure 2:** **Forest plot of the comparison of elevated c-Tn on mortality**

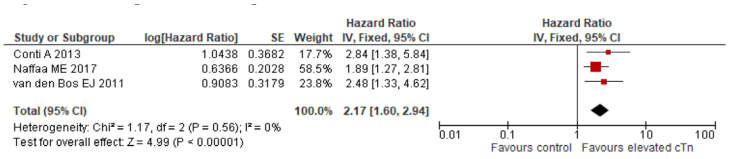



**Figure 3:** **Forest plot of the comparison of elevated c-Tn on MACE**

(leave-one-out) approach [22], to confirm that our findings were not driven by any single study and to explore heterogeneity [23].

We planned to conduct subgroup analyses to assess the impact of type of cardiac troponin measured, study design (prospective vs. retrospective), and type and time of onset of AF.

### Statistical analysis

We pooled hazard ratio (HR) and 95% confidence interval (CI) using fixed and random effects models according the heterogeneity. Heterogeneity among studies was quantified with the I2 metric, which is independent of the number of studies in a meta-analysis. I2>50% indicates significant heterogeneity between the studies [24]. Based on the test of heterogeneity, the pooled HR was calculated using the fixed-effects model when lacking of heterogeneity, while random-effects modeling was adopted when heterogeneity existed.

We converted median and range values to means and SDs according the actual suggested statistical method [25].

Publication bias was estimated in case we found more than 10 studies by the visual inspection of funnel plot. Egger's regression test was used to examine the asymmetry of the funnel plot [26].

All data from the included studies were extracted into Review Manager (RevMan 5.3) and Meta-Essentials 1.5. The screening process was performed with the reference manager Rayyan QCRI [27].

## Results

### Search results

Three hundred seventy-two studies were identified through a computerized literature search, among which 149 were duplicates and 202 were excluded after an initial review of titles and abstracts. The remaining 21 publications were reviewed in full-text and assessed against inclusion criteria. Finally, 5 were selected for the systematic review and meta-analysis [28-32].

The search and selection process is depicted in a PRISMA flow diagram (Figure 1)

### Risk of bias in included studies

Risk of bias evaluation according to NOS assessment tool for cohort studies is illustrated in supplementary Material Table S1.

### Study and patients characteristics

A total of fivestudies were included in the meta-analysis with 5750 patients. The majority of the studies were from Europe [28,29,31,32], and onefrom Israel [30]. All the included studies were observational, three of them had retrospective designs [29-31]. In the Conti et al [29]and Naffaa et al [30] studies was not informed whether the selection of patients was consecutive or unselected.

High-sensitivity assays were used to measure troponin T at presentation in two studies [31-32] and troponin I in the rest of them [28-30]. The definition of Positive Tn for statistical analysis was dissimilar across the different studies (supplementary Material Table S2). The most frequent statistical method of adjustment was by Coxregression in four studies [28,30-32], and multivariable logistic regression model in the other [29]. MACE outcome was evaluated in three of the included studies [28-30].The mean follow-up period was more than one year in all the included studies [28-32].

The mean age and incidence of classic cardiovascular factor in patients included were similar across studies (supplementary Material Table S3).

In two studies [28,31] the type of atrial fibrillation was described, which was paroxysmal in 29-30.9% of the cases In three studies the admission heart rate was reported, which had a similar average between them [29,30,32].

### Publication bias

It could not be performed given the low number of studies included.

### Effects of interventions

Four studies [28,30-32] reported on mortality, with a total of 4527 patients included. An increase inmortality was seen in the elevated cTn group compared to the controls, with a HR=2.7 (95%CI 1.55-4.72), P for effect<0.001, I2=80%. Pooled results from the random effect models are shown in Figure 2.

Three studies [28-30] reported the prognostic value of cTnina composite of outcomes. A total of 1629 patients were included. The pooled HR was 2.17 (95%CI 1.60-2.94), P for effect<0.001, I2=0%) for the elevated c-Tn group. Pooled results from the fixed effect models are shown in Figure 3.

### Sensitivity analysis

The strength of the pooled estimate was robust, and the heterogeneity did not significantly differ according to the characteristics of individual studies in the leave-one-out sensitivity analysis. Excluding Stoyanovet al study from the analysis, the overall effect was statistically significant(HR 1.87 95%CI 1.6-2.19; P<0.0001) but without statistical heterogeneity 0% (Figure 4).

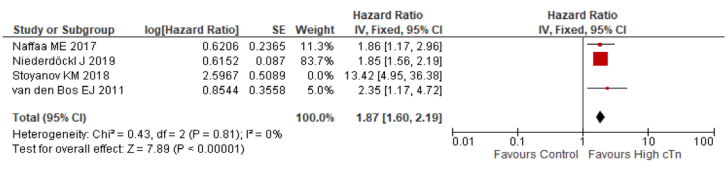



**Figure 4:** **Forest plot of the comparison of elevated c-Tn on MACE**

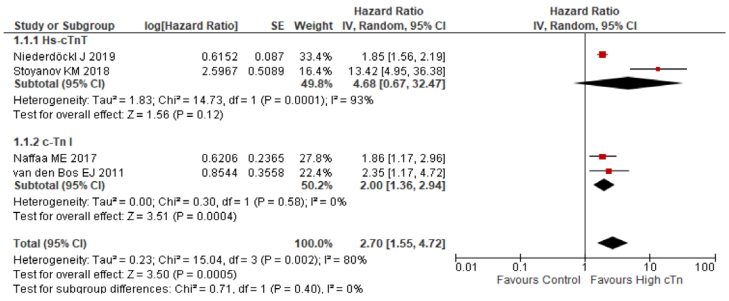



**Figure 5:** **Forest plot of the subgroup analysis on mortality: type of troponin**

## Subgroup analysis

### Type of troponin

In this subgroup analysis, we found no statistically significant differences according to the type of troponin used (Figure 5). We could not perform a subgroup analysis of type of troponin on MACE outcomes, because all the included studies used c-Tn I.

### Study design

For all-cause mortality and MACE outcomes, no differences were found between both subgroups (Figure 6 A and B).

The studies included in the analysis did not discriminate the outcomes according to the type or the time of AF onset.

## Discusion

This is the first meta-analysis to evaluate the prognostic value of troponin elevation in patients with AF admitted to an emergency department.

The main finding inour study is the high prognostic value of troponin,which was associated with an increased risk of all-cause mortality and MACE in this acute setting.

The mechanisms of elevated bloodstream troponin levels are multiple. Myocyte necrosis produces enzymatic degradation of the internal structures and sustained release of high amounts of troponin. However, as it has been previously mentioned, small amounts of Troponin T and Troponin I are free in the cytoplasm and exchange with those in the sarcomere.

It would be expected that if there is a quick release from this pool, troponin blood levels would fall with a rapid washout. The half-life of measurabecTnT and cTnI is about two hours. Rapid rise and fall within 24 h may therefore be consistent with a release from this pool and reversible myocyte damage rather than necrosis, where a time-dependent fall over a longer period (4 to 10 days) would be expected because of gradual degradation of myofibrils and release of the troponin complex [33].

Release fromthis cytoplasmaticpool would take place in situations in which cell membrane permeability has been altered, such as inflammation (as seen in myocarditis), and transient ischemia [34]. Another potential cause of troponin release could be associated with cellular liberationof proteolytic troponin degradation products, during which small fragments may pass through an unscathed cell membrane. This mechanism could justify troponin elevation in heart failure or tachyarrhythmias [34-36].

Data regarding the prognostic role of elevated cardiac troponin value in AF patients, inboth the short and long-term period, are scarce. Nowadays, there are limited recommendations about the use of cTn levels in the management of AF patients [37]. . The 2016 European consensus document suggests the evaluation of cardiac biomarkers (both cTn and/or brain natriuretic peptide) to improve the estimation of stroke and bleeding events (level of evidence IIb-B) without giving any suggestions about the possible prognostic role [38], similar to the 2014 American AF Clinical practice guidelines and its 2019 update [39-40]. The absence of strong recommendations in AF guidelines reflects that biomarkers have not been integrated into its routine management.

The prognostic value of elevated troponin levels in patients with AF and its mechanism can currently only be an area of speculation [18]. The underlying mechanisms for this independent relationship are probably multifactorial:aging and tissue vulnerability, myocardial necrosis and apoptosis, myocardial stress (e.g., due to increased or variable heart rates), myocardial dysfunction with variations in atrial and ventricular volume and pressure load, and episodes of myocardial ischemia (e.g., due to microembolism) [41-43]. However, even without a complete understanding of the underlying mechanisms, the firm evidence of the incremental prognostic value of hs-TnT for risk stratification and the availability of this test in almost every hospital worldwide should make it a very attractive tool to include as decision support for treatment selection in patients with AF [19].

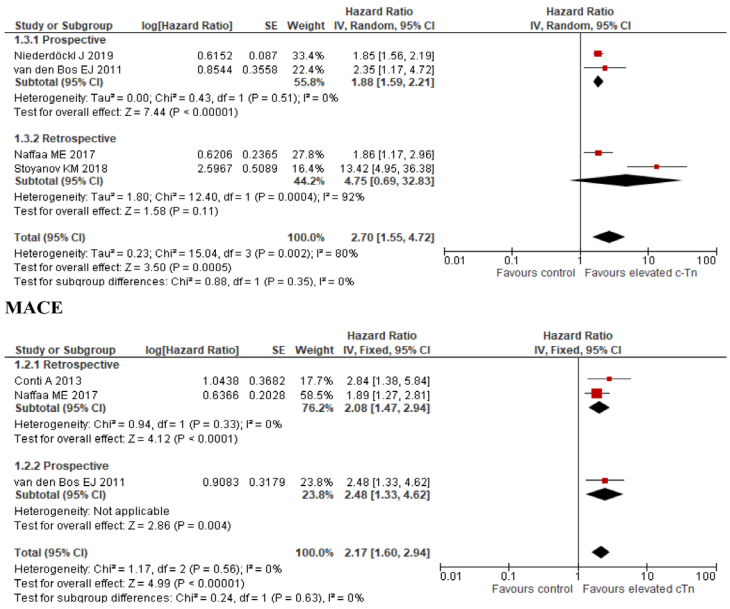



**Figure 6A&6B:** **Forest plot of the subgroup analysis on mortality and MACE: Design of study**

To our knowledge, there is only one published meta-analysis [44] that assessed the prognostic value of any troponin assay in patients with AF , and also included studies with patients in all types of settings. They observedthat elevated basal cardiac troponin level is independently associated with an increased risk of MACEs and all-cause mortality.

We consider that it is important to differentiate the prognostic impact of troponin in the acute context. Patients with acute AF presentation at the emergency department usuallypresent with a faster heart rate [45]. Several studies showed that elevated heart rate is one of the determinant factors forhigher c-Tn, and this phenomenondid not have a strong association with significant epicardial coronary artery disease [46–48]. Weobserved that, even in this context, elevated cardiac troponin is associated with an adverse prognosis.

The present meta-analysis should be interpreted within the context of its limitations. We present data of cohorts with retrospective data collection. We can also mention the high heterogeneity found in all-cause mortality outcomes. Nevertheless, during sensitivity analysis, we found that with the removal of the Stoyanov et al study the heterogeneity fell to 0%. The same was observed in the subgroup analysis,. This study included patients with different clinical characteristics than the other studies, with patients with higher values of troponin as they were more likely to present with acute myocardial infarction rather than secondary myocardial ischemia. Interestingly, MACE outcomes did not showed statistical heterogeneity, even though they were composed of different variables. One reason may be that they all included the same type of troponin and similar population characteristics. Other limitation is that we included studies with different troponin assays and different cut-off points. We could not perform a subgroup analysis with the type or time of onset of AF , since the data was not available. Finally, it was not possible to perform an analysis of publication bias since the number of included studies was less than ten.

In spite of these limitations, cardiac troponin may be useful in acute AF in the emergency department, providing prognostic information and the possibility of risk stratification.

Further research is needed to assess the prognosis of elevation and dynamic patterns of elevatedhs-cTn in patients with and without a history of coronary heart disease. A large prospective study needs to be initiated to address this issue,taking into consideration the type, rate and duration of AF.

## Conclusion

The elevation of cardiac troponin was significantly associated with higher mortality andmajor adverse cardiac events in patients with atrial fibrillation admitted to an emergency department. In this setting the use of cardiac troponin could provide prognostic information and potentially stratify the patients' risk.

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