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Review article

Cardiac troponin and adverse outcomes in atrial fibrillation: A meta-analysis

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ABSTRACT

Background: The prognostic value of cardiac troponin elevation in atrial fibrillation (AF) is unclear.
Objective: To investigate the association of cardiac troponin elevation with adverse outcomes in AF by conducting a meta-analysis.
Methods: We systematically searched the PubMed and Embase databases until April 2017 for studies assessing the association of cardiac troponin-T (cTnT) or troponin-I (cTnI) elevation with adverse outcomes in AF. The outcome measures were all-cause mortality and major adverse cardiac events (MACEs: death, stroke, myocardial infarction, pulmonary embolism, major bleeding, or revascularization).
Results: Six studies involving 22,697 AF patients were identified. Meta-analysis showed that AF with elevated cardiac troponin was independently associated with increased risk of all-cause mortality (HR 2.04; 95% CI 1.56–2.67) and MACEs (HR 1.93; 95% CI 1.61–2.30). Furthermore, the prognostic value of cardiac troponin elevation was consistently found irrespective of method determination, type of troponin measured, sample size, and study quality subgroup.
Conclusions: AF with cardiac troponin elevation was independently associated with increased risk of all-cause mortality and MACEs. Therefore, determination of troponin should be considered for risk stratification in AF.

1. Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia in clinical practice. The global age-adjusted prevalence of AF was 596 per 100,000 men and 373 per 100,000 women as estimated in the 2010 Global Burden of Disease Study [1]. Moreover, summary annual incidence of AF is 5.38 per 1000 person-year in Asian countries [2]. Approximately 3–5 million individuals suffer from AF in the United States [3]. In China, AF affects an estimated 3.9 million persons aged over 60 years [4]. AF has been recognized as an increasing global public health burden. Recent estimates from 104 eligible cohort studies indicated that patients with AF have a 46% and 2-fold greater risk of all-cause mortality and cardiovascular mortality [5]. Therefore, improving the prediction of death in patients with AF is needed.

Cardiac troponins are specific biomarkers of myocardial injury. Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) have been identified as the primary biomarkers for the early diagnosis of acute myocardial infarction [6] and risk stratification of acute coronary syndrome [7]. Moreover, abnormal troponin level has been identified as an independent predictor of AF in the general population [8], and patients with high troponin levels are faced with increased adverse outcomes [9]. However, individual studies on the association between cardiac troponin and poor outcomes have produced inconsistent results [10–17]. Furthermore, the strength of risk estimates vary significantly across the studies. To date, a quantitative assessment of published studies remains unavailable.

Obtaining all available studies could determine more robust estimates; thus, we conducted this meta-analysis of the available literature to evaluate the association between cardiac troponin elevation and adverse outcomes, which include all-cause mortality and major adverse cardiac events among patients with AF.

2. Methods

2.1. Literature search

We attempted to perform this meta-analysis according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology [18]. Two reviewers independently identified studies through searches of the PubMed and Embase databases until April 2017.The Medical Subject Headings terms and free keywords used to identify articles included “troponin” OR “cTnT” OR “cTni” AND “atrial fibrillation” OR “atrial tachycardia” AND “mortality” OR “death” OR “major adverse cardiac events”. To identify additional studies, further manual research

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was conducted using reference lists of included articles and relevant reviews. The literature searches were restricted in English-language.

2.2. Study selection

Studies that met the following pre-specified inclusion criteria were eligible: 1) studies enrolled patients with AF; 2) baseline serum level of cTnT or cTnI as exposure;3) all-cause mortality and major adverse cardiac events (MACEs) as end points; 4) follow-up duration > 12 month; and 5) reported multivariate-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality or MACEs between patients with and without cardiac troponin elevation. Studies were excluded if they were 1) combined cTnI and cTnT as exposure; 2) follow-up periods ≤ 12 month; and 3) not providing risk estimate based on abnormal troponin level.

2.3. Data extraction and quality assessment

For each included study, the baseline characteristics were extracted, including last name of the first author, publication year, study design, country of origin, study design, number of AF patients, sample size, gender, age, cut-off value of cardiac troponin, definition of MACEs, outcome measures, number of adverse events, length of follow-up, multivariate-adjusted risk estimate, and adjusted covariates in the statistical model. We applied the Newcastle Ottawa Scale (NOS) for the cohort studies to evaluate the methodological quality of the included studies [19]. Using this scale, the highest-quality study is 9 stars. Any disagreements in data extraction and quality assessment were settled by discussion.

2.4. Statistical analysis

All the statistical analyses were performed using STATA version 12.0 (Stata, College Station, TX). The pooled summary of cardiac troponin elevation with adverse outcomes was expressed as an HR with 95% CI. A summary HR > 1 indicated a worse prognosis in patients with elevated cardiac troponin. Heterogeneity of effect size across studies was tested using the I^2 statistic and Cochran's Q test. A random effect model was applied when significant heterogeneity was identified ($P < 0.10$ of the Cochran Q test or I^2 statistic ≥ 50%) across studies. Subgroup analyses were planned by the study design (prospective vs. retrospective), assay of troponin (conventional vs. high-sensitivity), type of cardiac troponin measured (cTnT vs. cTnI), sample size (≥ 1000 vs. < 1000), and NOS scores (≥ 6 stars vs. < 6 stars). Sensitivity analysis to investigate the impact of a single study on the overall risk estimate was conducted by removing one study in each turn. Publication bias test with a funnel plot was scheduled if > 10 studies were included.

3. Results

3.1. Search results and study characteristics

Fig. 1 shows the study selection process. Briefly, we initially identified 373 relevant articles through the electronic literature searches. A total of 332 of these articles were excluded after scanning titles or abstracts, leaving 41 potentially relevant articles for full-text assessment.

A total of 35 articles were further excluded because they did not satisfy our predefined inclusion criteria. Thus, 6 articles [10,13–17] were considered in the final meta-analysis. Table 1 summarizes the main characteristics of the included studies. The year of publication ranged from 2011 to 2017. Moreover, the 6 studies included 22,697 AF patients, with sample size ranging from 274 to 14,897 in the individual studies. Of these 6 observational studies, 4 [10,13–15] were a prospective designs and 2 [16,17] were retrospective designs. The length of follow-up ranged from 1.76 to 2.9 years. NOS scores for methodological quality of studies ranged from 6 to 8 stars, indicating moderate to good quality.

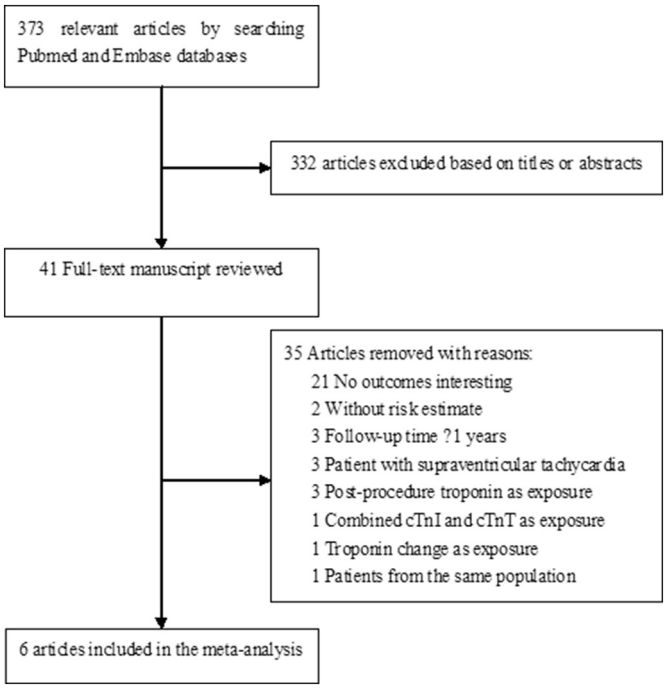

Fig. 1. Flow chart of studies selection process.

3.2. All-cause mortality

All the included studies used all-cause mortality as an outcome. As shown in Fig. 2, the pooled HR for all-cause mortality was 2.04 (95% CI 1.56–2.67) in AF patients with elevated cardiac troponin compared with those without elevation in a random effect model. Evidence of moderate heterogeneity (I^2 = 55.4%; p = 0.036) was observed across the studies. Sensitivity analysis by sequential removal of individual studies only slightly changed the pooled HR. Subgroup analyses showed generally consistent results of associations except for the retrospective subgroup (Table 2).

3.3. Major adverse cardiac events

Five studies [10,13–16] examined MACEs as an outcome. As shown in Fig. 3, no significant heterogeneity (I^2 = 0%; p = 0.582) was present among these 5 studies. Fixed-effect model meta-analysis showed that the pooled HR for MACEs was 1.93 (95% CI 1.61–2.30) in AF patients with elevated cardiac troponin compared with those without elevation. Sensitivity analysis did not change the statistical significance of the pooled HR (data not shown).

4. Discussion

This is the first meta-analysis to evaluate the prognostic value of cardiac troponin elevation in patients with AF. Our meta-analysis indicated that AF patients with elevated troponin levels are independently associated with an increased risk of all-cause mortality and MACEs. Moreover, AF patients with defective cardiac troponin exhibited approximately 2-fold higher risk of all-cause mortality and MACEs compared with those with undetectable controls. Measurement of cardiac troponin level may contribute to improved identification of patients that have an increased risk of adverse outcomes.

High-sensitivity cardiac troponin assays can detect very low levels of circulating troponin. With the development of high-sensitivity assays