# Value of High-sensitivity C-reactive Protein Assays in Predicting Atrial Fibrillation Recurrence: a systematic review and meta-analysis

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# Value of High-sensitivity C-reactive Protein Assays in Predicting Atrial Fibrillation Recurrence: a systematic review and meta-analysis

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Abstract

Objectives: We performed a systematic review and meta-analysis of studies on high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are predictive of atrial fibrillation (AF) recurrence after cardioversion.

Design: Systematic review and meta-analysis.

Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of the reference lists in the retrieved articles from inception to April 2013.

Study eligibility criteria: This review selected observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. An hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring serum CRP to below 0.6 mg/dL.

Primary and secondary outcome measures: We summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic (HSROC) curves, and bivariate random effects models. Meta-regression analysis was performed to explore the source of heterogeneity.

Results: We included nine qualifying studies comprising a total of 347 patients with AF recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an independent predictor of AF recurrence after cardioversion (summary adjusted odds ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% Cl: 63% to 78%) and 72.0% (61% to 81%), respectively. Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence

(77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73% sensitivity, 71% specificity).

Conclusions: High-sensitivity CRP assays are moderately accurate in predicting AF recurrence after successful cardioversion. Different cutoffs should be applied to patients with short-term or long-term follow-up.

Strengths and limitations of this study

- This meta-analysis finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence.
- We reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy.
- A bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies.
- Results of sensitivity analysis did not show a significantly different overall predictive accuracy between long-term and short-term follow-up, however, a heterogeneity tended toward between-study variability.
- Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. An individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.

Keywords: atrial fibrillation, recurrence, cardioversion, C - reactive protein, meta-analysis

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, although the prevalence is highest among people of advanced age.[1,2] AF poses a significant economic burden, with a 66% increase in hospital admissions over the past two decades. It is estimated that the number of patients affected by AF is likely to grow 2.5 fold by the year 2050.[1-3] In addition, AF may lead to debilitating complications such as ischemic stroke and heart failure. Although ventricular rate control is an acceptable treatment strategy in many patients, some patients may remain symptomatic despite adequate rate controls. For this group of patients, cardioversion may be the treatment of choice. Electrical cardioversion can restore sinus rhythm effectively in most patients and can act with antiarrhythmic drugs synergistically to enhance the cardioversion success rate.[4] However, cardioversion is not the definite treatment. Approximately 50% of patients undergoing cardioversion usually present with recurrence of AF within three to six months of cardioversion despite ongoing antiarrhythmic treatment.[5] Left ventricular dysfunction, left atrial enlargement, arrhythmia duration, and history of hypertension are major risk factors for AF recurrence.[6] However, recent studies have indicated that inflammation, necrosis, and fibrosis play roles in the structural remodeling process of the atria, contributing to the perpetuation or recurrence of atrial fibrillation.

C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response to proinflammatory cytokines, notably interluekin-6, and other endogenous signals of innate immunity or tissue damage. CRP has recently been shown to be associated with cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is elevated in patients with AF.[7] However, 5 of the 6 studies included in that analysis used traditional automated immunonephelometric assays to

measure CRP. Unfortunately, those assays are insufficiently sensitive for measuring the low level of inflammation associated with AF. A newer enzyme immunoassay, namely high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL and may further enhance the predictability of AF recurrence.[8] Since 2006, several studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been published,[9-19] warranting a systemic and quantitative summary of current evidence on the accuracy of CRP in predicting AF recurrence after cardioversion.

## Methods

### Identification of Studies

General bibliographic databases (MEDLINE and EMBASE) were searched from inception to April 2013. The medical subject heading (MeSH) and text words for the term C -reactive protein were combined with the MeSH term "diagnosis of atrial fibrillation". The search was limited to human studies with no language restrictions. In addition to the electronic search, reference lists in all known reviews and primary studies were checked manually.

### Selection Criteria

This review focused on observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. The population of interest comprised patients with paroxysmal or persistent AF who underwent electric cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was defined as AF documented by ECG at any time after the cardioversion during the follow-up period. Generally, patients were instructed to return to the clinic if the symptoms such as palpitations, shortness of breath, or chest discomfort developed after cardioversion. We included studies using a cohort design or case-control design

with appropriate controls. Two reviewers independently assessed eligible articles for inclusion. Disagreements were initially resolved by consensus and using arbitration by a third reviewer if consensus could not be reached by the two reviewers. We extracted data from the included studies. Data collected include study design, participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of follow-up period, and recurrence of AF. One reviewer extracted the data and a second reviewer independently verified the correctness of the extracted data.

Quality Assessment

We assessed the methodological quality of the selected studies using a well-validated tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of Diagnostic Accuracy Studies, QUADAS).[20] The QUADAS instrument scrutinizes characteristics of study designs, population, index tests, and reference standards that may be associated with risk of bias. These features included the spectrum of patients, whether index tests and reference standards were evaluated and interpreted independently to avoid incorporation bias, and whether all patients underwent the same reference standards to avoid differential or partial verification bias.

Data Abstraction

One reviewer independently extracted the data and a second reviewer independently verified the data. Extracted data comprised the following: overall study characteristics (including the first author, country, language, and date of publication); patient characteristics (including age range and pre-existing atrial fibrillation); quantitative data required for construction of a 2 x 2 table (including number of participants, sensitivity, specificity, and recurrence case number); information

regarding the hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or semi-quantitative nature of the test); and study settings. In studies that reported multiple pairs of sensitivity and specificity data, we consistently used the data with the highest Youden index (sensitivity + specificity -1) and performed a sensitivity analysis at a later stage.

Quantitative Data Synthesis

We performed a meta-analysis of diagnostic test accuracy of CRP testing for the prediction of recurrent AF. When 2 × 2 tables contained 0 cells, we performed continuity correction by adding 0.5 to each cell. We calculated the pooled sensitivity and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate meta-analysis model.[21] Likelihood ratios were then translated to post-test probability by use of Fagan's plot. We constructed a hierarchical summary receiver operating characteristic (HSROC) curve that plots sensitivity versus specificity and calculated the area under the curve (AUROC).[22] We evaluated the degree of between-study heterogeneity by using the $I^2$ test.[23] To explore the clinical sources of heterogeneity, we defined the potential explanatory variables *a priori* and performed subgroup analysis to see if the accuracy estimates changed significantly across various subgroups. The presence and the effect of publication bias were examined using a combination of the Egger tests.[24] Statistical analyses were conducted using the statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably with the user-written "midas" and "metandi" programs. All statistical tests were two-sided and statistical significance was defined as a P value less than .05.

Search Results and Study Characteristics

The flow of inclusion and exclusion is summarized in Figure 1. Using our search criteria, we identified 784 studies, of which 352 were from PubMed and 432 were from EMBASE. A total of 752 citations were excluded based on pre-defined criteria. No additional citations were identified from the reference lists. A total of 32 articles were retrieved for full-text review, and 23 were excluded due to various reasons detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in predicting AF recurrence after cardioversion were finally included in the meta-analysis. The 9 studies included a total of 682 patients with AF after successful cardioversion, of which 347 (50.9%) developed recurrence.

Characteristics of included studies

Table 1 lists the study and population characteristics of the 9 patient populations. The mean age of patients in the included studies ranged from 55.1 years to 67.9 years and the mean follow-up period ranged from 30 days to 1 year. Seven studies included patients with persistent AF, while 2 studies included patients with paroxysmal AF. Seven studies used electric shock, one used circumferential pulmonary vein isolation, and the other used intravenous amiodarone as the primary method for cardioversion. A total of seven studies provided multivariate (adjusted) odds ratios to evaluate the independent predictive value of CRP levels. These studies generally adjusted for potential predictors of AF recurrence such as age, sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All studies showed that CRP was a significant independent predictor of AF recurrence. Associated adjusted ratios and adjusted variables are summarized in table 1.

Quality assessment

Results of the quality assessment of studies of diagnostic accuracy are summarized

in figure 2. All studies were prospective and enrolled consecutive outpatients with AF after cardioversion. Three studies had a short follow-up period (i.e. < X years). Although most of the studies did not indicate whether physicians were blinded to the index tests when diagnosing AF recurrence, the determination of AF recurrence was not affected by the knowledge of hs-CRP test results and risk of incorporation bias was minimal. None of the studies reported the undetermined results or withdrawals.

Diagnostic accuracy indices

Sensitivity, specificity, and diagnostic odds ratio

The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.5%). Table 2 shows the results of individual and combined sensitivity estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%), respectively. The pooled positive likelihood ratio was 2.57 and the negative likelihood ratio was 0.4, which can then be translated into a post-test probability of 73% for a positive hs-CRP test result and a post-test probability of 29% for a negative hs-CRP test result (Figure 2). The area under the ROC curve showed an acceptable overall accuracy (0.77, Figure 3). Figure 4 shows the forest plot of the ORs.

Subgroup analysis and meta-regression

In view of the potential influence of spectrum variability, we considered the duration of follow-up, mode of cardioversion, and type of AF in the study patients to be important. Hs-CRP test results generally had higher sensitivity and lower specificity in predicting long-term over short-term AF recurrence. Excluding two studies not using electric shock as the primary cardioversion method did not significantly alter

the predictive accuracy. Similarly, *focusing the study patients on persistent AF population* had similar results as compared with the main overall analysis. Exploratory meta-regression analysis did not find that any pre-specified covariate significantly changed the effect estimate.

## Discussion

This meta-analysis shows that elevated CRP levels are independently predictive of AF recurrence in patients with persistent or paroxysmal AF who have undergone successful cardioversion. This finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence. Despite the modest pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the high recurrence rate of AF observed in these included studies. A positive hs-CRP test result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months following cardioversion.

Previous studies have examined risk factors that predict AF recurrence. Traditional clinical risk factors for recurrence include history of multiple AF episodes, use of diuretic treatment, higher CHADS-2 (Congestive heart failure, history of Hypertension, Age≥75 years, Diabetes mellitus, and past history of Stroke or TIA doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C drugs, and digitalis.[25,26] Although each of these factors could predict AF recurrence with some accuracy, a quantitative combination of these predictors is not available, and the clinical utility of these variables remains questionable.

During the past decade, serum biomarkers have emerged as practical tools to help in the early identification of patients at high risk for various cardiac events. Elevation

of inflammatory markers is associated with sudden cardiac death in patients with heart failure or coronary artery disease, and onset of ventricular arrhythmia.[27-30] Of note, there is abundant evidence that elevated serum levels of CRP are associated with the genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in response to proinflammatory cytokine stimulation. Although the pathophysiology of AF remains elusive, there is pathophysiological evidence supporting the role of inflammation in the initiation, maintenance, and perpetuation of AF.[31] Clinically, AF is frequently associated with local inflammatory diseases such as myocarditis or pericarditis, and systemic inflammatory status, such as post-operative state and severe sepsis. Histologically, structural remodeling of the atria manifested by loss of myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.[32] Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial biopsy specimens from AF patients.[33] Activated inflammatory cells in conjunction with reactive oxygen species, cytokines, and growth factors, may ultimately lead to matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors, or glucocorticoids modulate the course of AF.[34]

In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator of new onset AF and AF recurrence after successful cardioversion.[29,30,35] BNP is also produced in response to atrial pressure and volume overload and there is evidence that BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed that the standardized mean difference in plasma BNP level between patients with non-recurrence and patients with recurrence was -1.35 (95%

confidence interval -2.17, -0.53).[36] Data on sensitivity and specificity in that study were not available. The comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus requires further analysis.

There are both strengths and limitations in our study. Considering the limitation of sensitivity and specificity in clinical interpretation, we reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy. The LRs indicate how much a given CRP testing result increases or decreases the probability of recurrence of AF. Post-test probabilities can be derived from pre-test probabilities and LRs, which are an important clinical parameter for major clinical decision making. Second, we used a bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies. Third, we performed sensitivity analysis by restricting analysis within two broad categories of follow-up duration. Results of sensitivity analysis did not show a significantly different overall predicative accuracy between long-term and short-term follow-up. Our study also had limitations. Overall, as assessed by the heterogeneity of dOR, the included studies evaluating CRP levels and AF recurrence strongly tended toward between-study variability (heterogeneity). Potential sources of between-study variability included differences in incidence of AF recurrence, different threshold values of CRP concentration used, and different duration for follow-up. Another limitation was the strategy we used to determine the optimal cutoff value. Most studies determined an optimal cutoff value to maximize both sensitivity and specificity. Although a single cutoff value is straightforward in clinical interpretation, it may make a marker neither sensitive nor specific enough to rule out or rule in an outcome of interest. A two cut-off value strategy, with one using a lower cutoff value to optimize the sensitivity (rule-out value) and the other

using a higher cutoff value to optimize the specificity (rule-in value), would make better use of the information that a biomarker with a continuous value could provide. Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. To make the best use of the biomarker information by adopting a two cutoff point strategy or a multi-cutoff point risk classification strategy, an individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.

Conclusions

Baseline CRP levels before cardioversion can independently predict AF recurrence after successful cardioversion. Given the high recurrence rate reported in most series, the modest positive likelihood ratio for hs-CRP assays still has high positive predictive value. Future studies should focus on the evaluation of two or multiple cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation algorithms should be considered.

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Table 1. Summary of the characteristics of the included studies

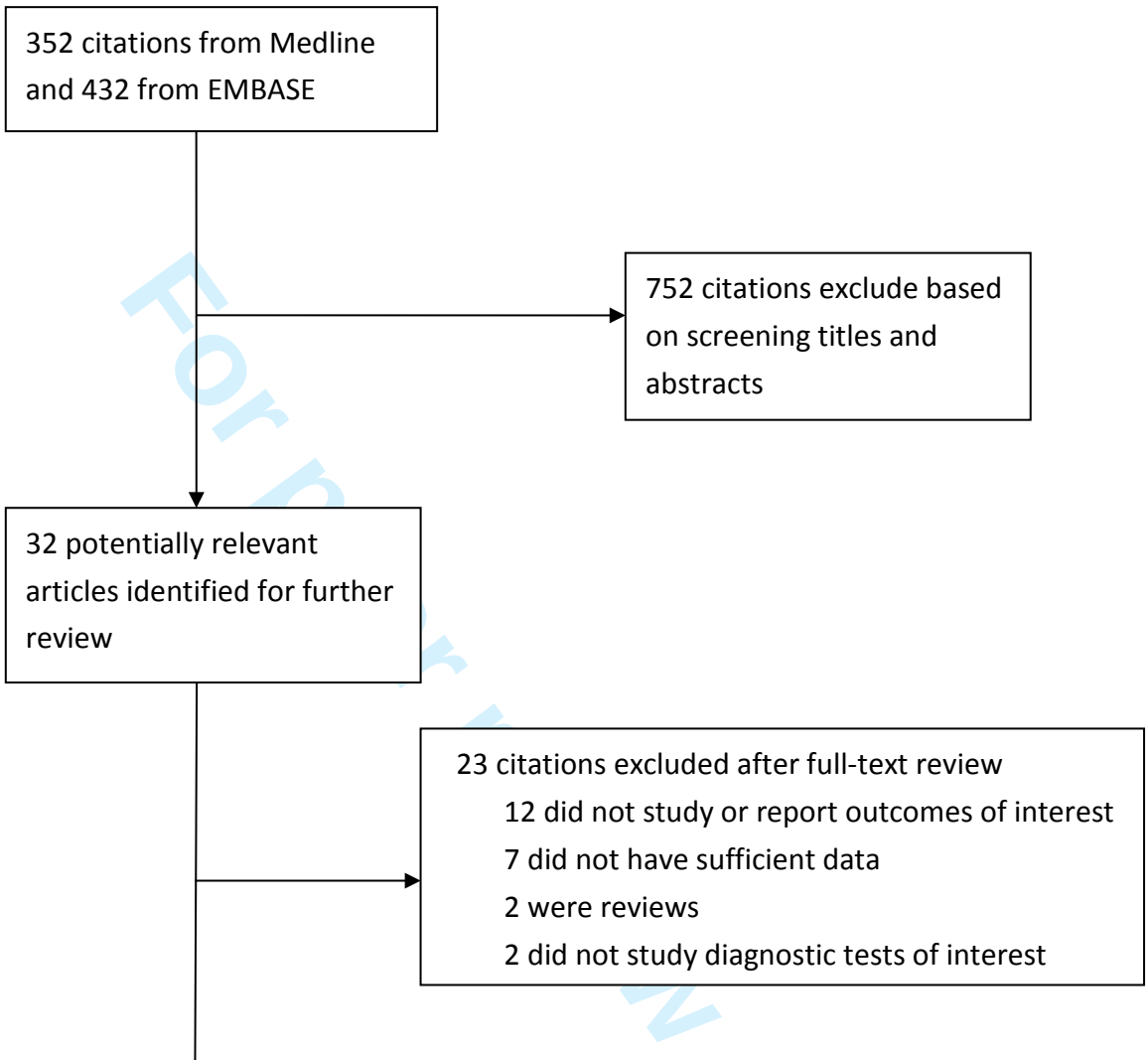
| Author, year, country | Mean Age | Prevalence (N) | Follow-up time | Cutoff (mg/l) | AF type | Cardioversion | Sensitivity, Specificity | Adjusted odd ratio | Adjusted variables |
|---|---|---|---|---|---|---|---|---|---|
| Wazni O, 2005,USA[1] | 67.3 | 0.68(111) | 76 days | 3.1 | Persistent AF | Electric | 59 %, 69 % | 2.0 (1.2-3.2) | Age, sex, duration of AF, coronary artery disease, hypertension, left ventricular hypertrophy, LAD |
| Zarauza J, 2006, Spain[2] | 62.7 | 0.43(37) | 30 days | 3.0 | Persistent AF | Electric | 81%, 67 % | 3.7 (1.3-10.8) | Sex, age, time, size of left atrium, history of hypertension, pharmacological treatment |
| Watanabe E, 2006, Japan[3] | 64 | 0.76(84) | 1 year | 0.6 | Persistent AF | Electric | 75%, 90% | 5.3 (2.5-11.5) | Sex, coronary artery disease, hypertension, smoking, diabetes, AF duration, LAD, and LVEF |
| Loricchio ML, 2007, Italy[4] | 67 | 0.52(102) | 1 year | 1.9 | Persistent AF | Electric | 87%, 37% | 5.0 (1.8-14.3) | Age, gender, EF, LAD , hypertension, diabetes, pharmacological treatment |
| Lombardi F, 2008, Italy[5] | 67 | 0.34(53) | 21 days | 3.6 | Persistent AF | Electric | 64%, 83% | 1.6 (1.0-2.5) | Age, LAD, LAA, LAAEV, NTproBNP level, history of AF, AF duration or pharmacological treatment |
| Henningsen KMA, 2009, Denmark[6] | 65 | 0.68(56) | 180 days | 3.0 | Persistent AF | Electric | 60%, 83% | NA | NA |
| Rizos I, 2010,Greece[7] | 67.9 | 0.64(61) | 1 year | 2.3 | Paroxysmal AF | Pharmacologic | 72%, 68% | 6.2 (2.2-17.6) | IL-6, age, gender, PAF history, LAD, EF, diabetes, smoking |
| Liu J, 2011,China[8] | 55.1 | 0.39(44) | 1 year | 1.9 | Paroxysmal AF | Electric ablation | 79%, 70 % | 5.1 (2.1–12.1) | Age, gender, type of AF, duration of AF, LAD, LVEF, plasma hsCRP concentration. |
| Barassi A, 2012,Italy[9] | 66.9 | 0.33(57) | 21 days | 3.0 | Persistent AF | Electric | 74%, 84 % | NA | NA |

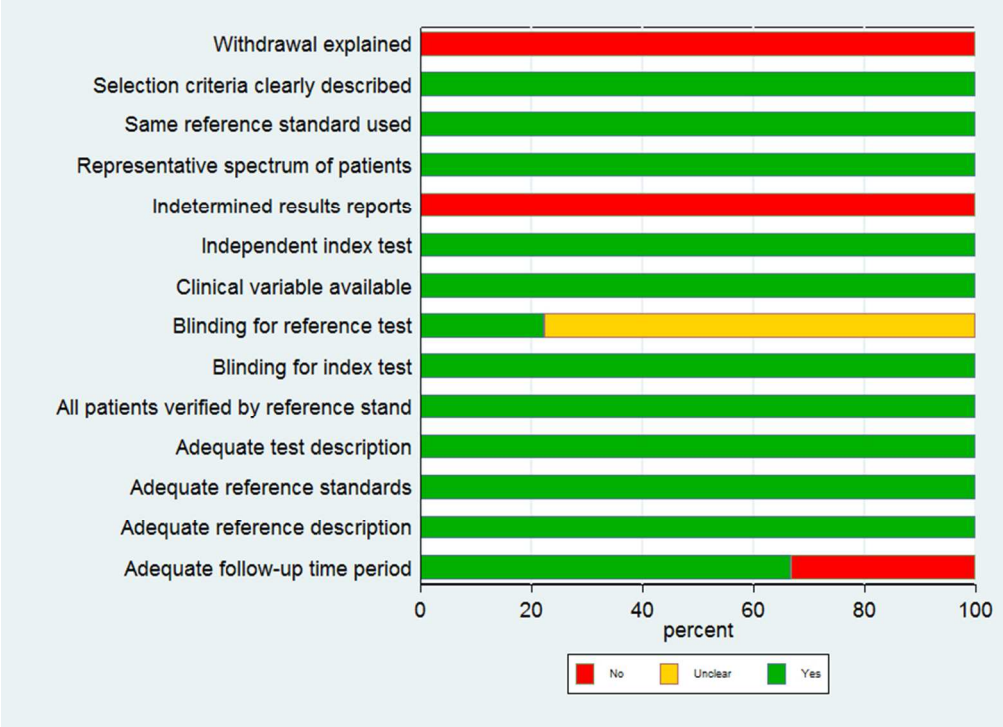
Abbreviations: HsCRP: High-sensitivity C-reactive protein NA: Not applicable ACE: angiotensin-converting enzyme;

Table 2. Summary of pooled diagnostic accuracy indices

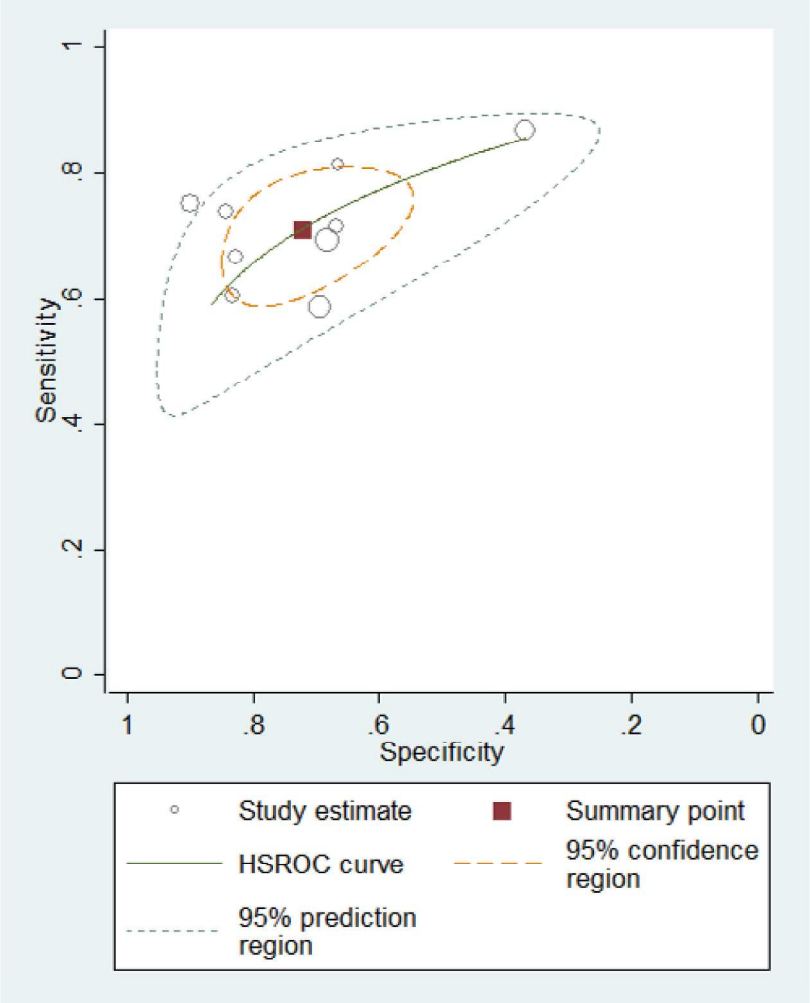
| Variables | Number of studies | Sensitivity (95% CI) | Specificity (95% CI) | Likelihood ratio+ | Likelihood ratio- | AUROC (95% CI) | $I^2$ (95% CI) | Diagnostic OR (95% CI) | Meta-regression P |
|---|---|---|---|---|---|---|---|---|---|
| Overall[1-9] | 9 | 0.71(0.63-0.78) | 0.72(0.61-0.81) | 2.57(1.86-3.55) | 0.40(0.32-0.50) | 0.77(0.73-0.81) | 14.6(0-56.6) | 5.91 (4.07-8.59) | -- |
| Follow time< 6 months[1,2,5,9] | 4 | 0.73(0.56-0.85) | 0.71(0.54-0.83) | 2.50(1.67-3.77) | 0.38(0.24-0.59) | 0.78(0.74-0.82) | 0.0(0.0-74.6) | 6.34(3.70- 10.85) | 0.759 |
| Follow time > one year[3,5-8] | 5 | 0.77(0.69-0.84) | 0.65(0.45-0.80) | 2.22(3.14-12.88) | 0.35(0.26-0.48) | 0.79(0.75-0.82) | 34.8(0.0-77.2) | 5.54(3.29-9.32) | 0.552 |
| Electric cardioversion[1-6,9] | 7 | 0.72(0.62-0.80) | 0.74(0.60-0.85) | 2.81(1.79-4.41) | 0.38(0.29-0.50) | 0.78(0.75-0.82) | 33.0(0.0-71.6) | 5.13(3.63- 7.25) | 0.611 |
| Persistent AF[1-6,9] | 7 | 0.70(0.61-0.78) | 0.71(0.59-0.80) | 2.40(1.77-3.25) | 0.42(0.33-0.53) | 0.76(0.72-0.80) | 22.3(0.0-64.2) | 5.70(3.77-8.62) | 0.899 |

Figure 1 Flow chart of study identification and inclusion

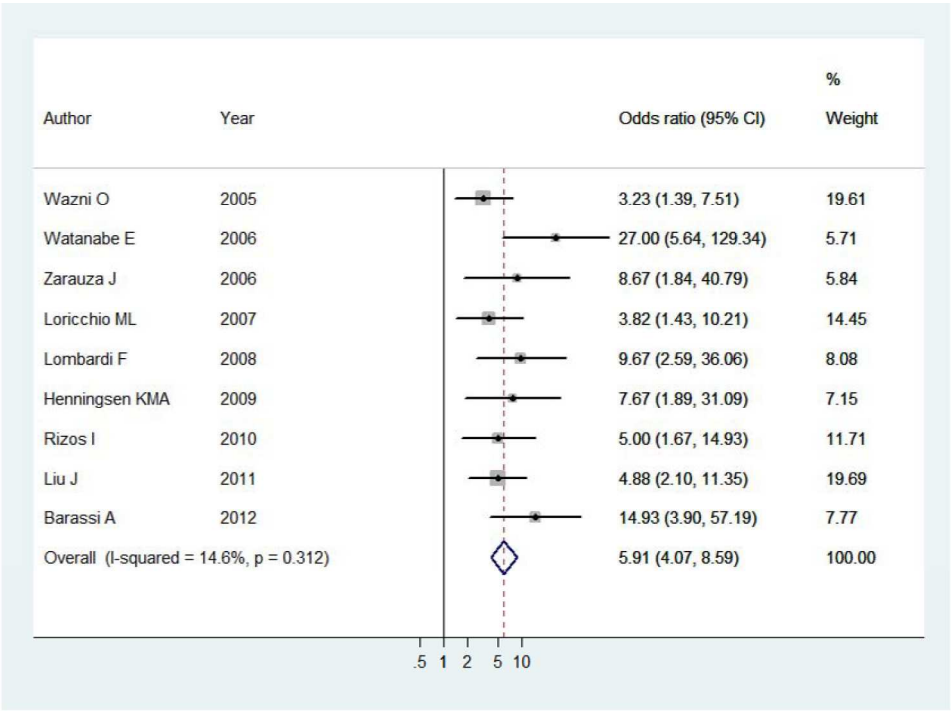





Results of the quality assessment of studies of diagnostic accuracy
302x219mm (72 x 72 DPI)




The summary ROC curve of hs-CRP
297x420mm (300 x 300 DPI)




The forest plot of the ORs
209x148mm (300 x 300 DPI)

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | X |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | X |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | X |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | X |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | X |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | X |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | X |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | X |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | X |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | X |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | X |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | X |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | X |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | X |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | X |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | X |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | X |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | X |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | X |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | X |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | X |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | X |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | X |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | X |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | X |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | X |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | X |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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# Value of High-sensitivity C-reactive Protein Assays in Predicting Atrial Fibrillation Recurrence: a systematic review and meta-analysis

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| | |

# Value of High-sensitivity C-reactive Protein Assays in Predicting Atrial Fibrillation Recurrence: a systematic review and meta-analysis

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Conflict of interest: None declared

Abstract

Objectives: We performed a systematic review and meta-analysis of studies on high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are predictive of atrial fibrillation (AF) recurrence after cardioversion.

Design: Systematic review and meta-analysis.

Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of the reference lists in the retrieved articles from inception to December 2013.

Study eligibility criteria: This review selected observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. An hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring serum CRP to below 0.6 mg/dL.

Primary and secondary outcome measures: We summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic (HSROC) curves, and bivariate random effects models. Meta-regression analysis was performed to explore the source of heterogeneity.

Results: We included nine qualifying studies comprising a total of 347 patients with AF recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an independent predictor of AF recurrence after cardioversion (summary adjusted odds ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% Cl: 63% to 78%) and 72.0% (61% to 81%), respectively. Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence

(77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73% sensitivity, 71% specificity).

Conclusions: High-sensitivity CRP assays are moderately accurate in predicting AF recurrence after successful cardioversion. Different cutoffs should be applied to short-term or long-term prediction of AF recurrence.

Strengths and limitations of this study

- This meta-analysis finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence.
- We reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy.
- A bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies, and occurring between the logit TPR and FPR.
- Results of sensitivity analysis did not show a significantly different overall predictive accuracy between long-term and short-term follow-up, however, a heterogeneity tended toward between-study variability.
- Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. An individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.

Keywords: atrial fibrillation, recurrence, cardioversion, C - reactive protein, meta-analysis

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, although the prevalence is highest among people of advanced age.[1,2] AF poses a significant economic burden, with a 66% increase in hospital admissions over the past two decades. It is estimated that the number of patients affected by AF is likely to grow 2.5 fold by the year 2050.[1-3] In addition, AF may lead to debilitating complications such as ischemic stroke and heart failure. Although ventricular rate control is an acceptable treatment strategy in many patients, some patients may remain symptomatic despite adequate rate controls. For this group of patients, cardioversion may be the treatment of choice. Electrical cardioversion can restore sinus rhythm effectively in most patients and can act with antiarrhythmic drugs synergistically to enhance the cardioversion success rate.[4] However, cardioversion is not the definite treatment. Approximately 50% of patients undergoing cardioversion usually present with recurrence of AF within three to six months of cardioversion despite ongoing antiarrhythmic treatment.[5] Left ventricular dysfunction, left atrial enlargement, arrhythmia duration, and history of hypertension are major risk factors for AF recurrence.[6] However, recent studies have indicated that inflammation, necrosis, and fibrosis play roles in the structural remodeling process of the atria, contributing to the perpetuation or recurrence of atrial fibrillation.

C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response to proinflammatory cytokines, notably interluekin-6, and other endogenous signals of innate immunity or tissue damage. CRP has recently been shown to be associated with cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is elevated in patients with AF.[7] However, 5 of the 6 studies included in that analysis

used traditional automated immunonephelometric assays to measure CRP. Unfortunately, those assays are insufficiently sensitive for measuring the low level of inflammation associated with AF. A newer enzyme immunoassay, namely high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL and may further enhance the predictability of AF recurrence.[8] Since 2006, several studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been published,[9-19] warranting a systemic and quantitative summary of current evidence on the accuracy of CRP in predicting AF recurrence after cardioversion.

## Methods

### Identification of Studies

General bibliographic databases (MEDLINE and EMBASE) were searched from inception to April 2013. The medical subject heading (MeSH) and text words for the term C -reactive protein were combined with the MeSH term "diagnosis of atrial fibrillation". The search was limited to human studies with no language restrictions. In addition to the electronic search, reference lists in all known reviews and primary studies were checked manually.

### Selection Criteria

This review focused on observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. The population of interest comprised patients with paroxysmal or persistent AF who underwent electric cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was defined as AF documented by ECG at any time after the cardioversion during the follow-up period. Generally, patients were instructed to return to the clinic if the symptoms such as palpitations, shortness of breath, or chest discomfort developed

after cardioversion. We included studies using a cohort design or case-control design with appropriate controls. Two reviewers independently assessed eligible articles for inclusion. Disagreements were initially resolved by consensus and using arbitration by a third reviewer if consensus could not be reached by the two reviewers. We extracted data from the included studies. Data collected include study design, participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of follow-up period, and recurrence of AF. One reviewer extracted the data and a second reviewer independently verified the correctness of the extracted data.

Quality Assessment

We assessed the methodological quality of the selected studies using a well-validated tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of Diagnostic Accuracy Studies, QUADAS).[20] The QUADAS instrument scrutinizes characteristics of study designs, population, index tests, and reference standards that may be associated with risk of bias. These features included the spectrum of patients, whether index tests and reference standards were evaluated and interpreted independently to avoid incorporation bias, and whether all patients underwent the same reference standards to avoid differential or partial verification bias.

Data Abstraction

One reviewer independently extracted the data and a second reviewer independently verified the data. Extracted data comprised the following: overall study characteristics (including the first author, country, language, and date of publication); patient characteristics (including age range and pre-existing atrial fibrillation); quantitative data required for construction of a 2 x 2 table (including number of participants, sensitivity, specificity, and recurrence case number); information regarding the

hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or semi-quantitative nature of the test); and study settings. In studies that reported multiple pairs of sensitivity and specificity data, we consistently used the data with the highest Youden index (sensitivity + specificity -1) and performed a sensitivity analysis at a later stage.

Quantitative Data Synthesis

We performed a meta-analysis of diagnostic test accuracy of CRP testing for the prediction of recurrent AF. When 2 × 2 tables contained 0 cells, we performed continuity correction by adding 0.5 to each cell. We calculated the pooled sensitivity and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate meta-analysis model.[21] Likelihood ratios were then translated to post-test probability by use of Fagan's plot. We constructed a hierarchical summary receiver operating characteristic (HSROC) curve that plots sensitivity versus specificity and calculated the area under the curve (AUROC).[22] We evaluated the degree of between-study heterogeneity by using the $I^2$ test.[23] To explore the clinical sources of heterogeneity, we defined the potential explanatory variables *a priori* and performed subgroup analysis to see if the accuracy estimates changed significantly across various subgroups. The presence and the effect of publication bias were examined using a combination of the Egger tests.[24] Statistical analyses were conducted using the statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably with the user-written "midas" and "metandi" programs. All statistical tests were two-sided and statistical significance was defined as a P value less than .05.

Search Results and Study Characteristics

The flow of inclusion and exclusion is summarized in Figure 1. Using our search criteria, we identified 784 studies, of which 352 were from PubMed and 432 were from EMBASE. A total of 752 citations were excluded based on pre-defined criteria. No additional citations were identified from the reference lists. A total of 32 articles were retrieved for full-text review, and 23 were excluded due to various reasons detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in predicting AF recurrence after cardioversion were finally included in the meta-analysis. The 9 studies included a total of 682 patients with AF after successful cardioversion, of which 347 (50.9%) developed recurrence.

Characteristics of included studies

Table 1 lists the study and population characteristics of the 9 patient populations even if we had additional 5 studies that don't have sufficient data for statistical analysis [25-29]. The mean age of patients in the included studies ranged from 55.1 years to 67.9 years and the mean follow-up period ranged from 30 days to 1 year. Seven studies included patients with persistent AF, while 2 studies included patients with paroxysmal AF. Seven studies used electric shock, one used circumferential pulmonary vein isolation (also known as electric ablation), and the other used intravenous amiodarone as the primary method for cardioversion. A total of seven studies provided multivariate (adjusted) odds ratios to evaluate the independent predictive value of CRP levels. These studies generally adjusted for potential predictors of AF recurrence such as age, sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All studies showed that CRP was a significant independent predictor of AF recurrence. Associated adjusted ratios and adjusted variables are summarized in table 1.

Quality assessment

Results of the quality assessment of studies of diagnostic accuracy are summarized in figure 2. All studies were prospective and enrolled consecutive outpatients with AF after cardioversion. Three studies had a short follow-up period (i.e. ≤0.5 or 1 year). Although most of the studies did not indicate whether physicians were blinded to the index tests when diagnosing AF recurrence, the determination of AF recurrence was not affected by the knowledge of hs-CRP test results and risk of incorporation bias was minimal. None of the studies reported the undetermined results or withdrawals.

Diagnostic accuracy indices

Sensitivity, specificity, and diagnostic odds ratio

The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.6%). Table 2 shows the results of individual and combined sensitivity estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%), respectively. We used the pooled prevalence of AF recurrence in this study as the pre-test probability. With a pooled positive likelihood ratio of 2.57 and a negative likelihood ratio of 0.4, the post-test probability for AF recurrence for a positive hs-CRP test result was 72% and a post-test probability for a negative hs-CRP test result was 29%. The area under the ROC curve showed an acceptable overall measurement of discrimination (0.77, Figure 3). Figure 4 shows the forest plot of the ORs.

Subgroup analysis and meta-regression

In view of the potential influence of spectrum variability, we considered the duration of follow-up, mode of cardioversion, and type of AF in the study patients to be important. Hs-CRP test results generally had higher sensitivity and lower specificity

in predicting long-term over short-term AF recurrence. Excluding two studies not using electric shock as the primary cardioversion method did not significantly alter the predictive accuracy. Similarly, *focusing the study patients on persistent AF population* had similar results as compared with the main overall analysis. Exploratory meta-regression analysis did not find that any pre-specified covariate significantly changed the effect estimate.

## Discussion

This meta-analysis shows that elevated CRP levels are independently predictive of AF recurrence in patients with persistent or paroxysmal AF who have undergone successful cardioversion. This finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence. Despite the modest pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the high recurrence rate of AF observed in these included studies. A positive hs-CRP test result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months following cardioversion.

Previous studies have examined risk factors that predict AF recurrence. Traditional clinical risk factors for recurrence include history of multiple AF episodes, use of diuretic treatment, higher CHADS-2 (Congestive heart failure, history of Hypertension, Age≥75 years, Diabetes mellitus, and past history of Stroke or TIA doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C drugs, and digitalis.[30,31] Although each of these factors could predict AF recurrence with some accuracy, a quantitative combination of these predictors is not available, and the clinical utility of these variables remains questionable. This also suggests that a multivariate prediction model should be developed for AF recurrence, and that

hsCRP should be a candidate for inclusion in the model.

During the past decade, serum biomarkers have emerged as practical tools to help in the early identification of patients at high risk for various cardiac events. Elevation of inflammatory markers is associated with sudden cardiac death in patients with heart failure or coronary artery disease, and onset of ventricular arrhythmia.[32-35] Of note, there is abundant evidence that elevated serum levels of CRP are associated with the genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in response to proinflammatory cytokine stimulation. Although the pathophysiology of AF remains elusive, there is pathophysiological evidence supporting the role of inflammation in the initiation, maintenance, and perpetuation of AF.[36] Clinically, AF is frequently associated with local inflammatory diseases such as myocarditis or pericarditis, and systemic inflammatory status, such as post-operative state and severe sepsis. Histologically, structural remodeling of the atria manifested by loss of myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.[37] Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial biopsy specimens from AF patients.[38] Activated inflammatory cells in conjunction with reactive oxygen species, cytokines, and growth factors, may ultimately lead to matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors, or glucocorticoids modulate the course of AF.[39]

In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator of new onset AF and AF recurrence after successful cardioversion.[34,35,40] BNP is also produced in response to atrial pressure and volume overload and there is evidence that

BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed that the standardized mean difference in plasma BNP level between patients with non-recurrence and patients with recurrence was -1.35 (95% confidence interval -2.17, -0.53).[41] Data on sensitivity and specificity in that study were not available. The comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus requires further analysis.

There are both strengths and limitations in our study. Considering the limitation of sensitivity and specificity in clinical interpretation, we reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy. The LRs indicate how much a given CRP testing result increases or decreases the probability of recurrence of AF. Post-test probabilities can be derived from pre-test probabilities and LRs, which are an important clinical parameter for major clinical decision making. Second, we used a bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies, and occurring between the logit TPR and FPR. Third, we performed sensitivity analysis by restricting analysis within two broad categories of follow-up duration. Results of sensitivity analysis did not show a significantly different overall predicative accuracy between long-term and short-term prediction of AF recurrence. Nonetheless, it is noteworthy that the sensitivity may be over estimated in our study under the hypothesis where the inflammation may be symptomatic since none of the studies provided withdrawal and undetermined results, and the ascertainment of AF was passive. This event further introduces the differential verification bias. Moreover, our meta-analysis is restricted to distinguish hsCRP levels above or below 0.6 mg/dL because the authors in only one of the studies claimed to possess such capability. Finally, due to the lack of individual data, it is hard to determine whether the area

under ROC (AUC) can be improved by the new assay either on overall or on individual studies. Overall, as assessed by the heterogeneity of dOR, the included studies evaluating CRP levels and AF recurrence strongly tended toward between-study variability (heterogeneity). Potential sources of between-study variability included differences in incidence of AF recurrence, different threshold values of CRP concentration used, and different duration for follow-up. Another limitation was the strategy we used to determine the optimal cutoff value. Most studies determined an optimal cutoff value to maximize both sensitivity and specificity. Although a single cutoff value is straightforward in clinical interpretation, it may make a marker neither sensitive nor specific enough to rule out or rule in an outcome of interest. A two cut-off value strategy, with one using a lower cutoff value to optimize the sensitivity (rule-out value) and the other using a higher cutoff value to optimize the specificity (rule-in value), would make better use of the information that a biomarker with a continuous value could provide. Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. To make the best use of the biomarker information by adopting a two cutoff point strategy or a multi-cutoff point risk classification strategy, an individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.

## Conclusions

Baseline CRP levels before cardioversion can independently predict AF recurrence after successful cardioversion. Given the high recurrence rate reported in most series, the modest positive likelihood ratio for hs-CRP assays still has high positive predictive value. Future studies should focus on the evaluation of two or multiple cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation

algorithms should be considered.

Acknowledgement

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Figure legends

Figure 1. **A simplified flow chart to identify and to include studies**. Amongst 752 citations in MEDLINE and EMBASE from inception to December 2013, a search limited to human studies using "C-reactive protein" and the MeSH term "diagnosis of atrial fibrillation" resulted in 32 potentially relevant articles for further review. After careful scrutinization on full text, 9 articles were left for meta-analysis.

Figure 2. **The quality assessment of diagnostic accuracy on studies**. A spectrum of features were analysed to avoid bias using a well-validated tool called Quality Assessment of Diagnostics Accuracy Studies (QUADAS). Percentage for each feature was independently evaluated among the studies. It is worthy of attention that none of the studies explained the withdrawal and reported indetermined results, likely to compromise the quality of diagnostic accuracy.

Figure 3. **The ROC curve of hs-CRP.** Our analysis suggests it is highly possible to predict atrial fibrillation using C-creative protein since the area under the curve generates a measurement of discrimination ~0.77. The overall sensitivity and specificity are relatively high. We have 5 out 9 studies that fall in the 95% CI region, while 8 out 9 in the 95% prediction region.

Figure 4. **The forest plot of the odds ratios (ORs)**. Our study indicates that hsCRP-positive patients are ~5.91 times more likely to develop a recurrence of atrial

fibrillation than hsCRP-negative patients are. The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.6%).

Table 1. Summary of the characteristics of the included studies

| Author, year, country | Mean Age | Prevalence (N) | Follow-up time | Cutoff (mg/l) | AF type | Cardioversion | Sensitivity, Specificity | Adjusted odd ratio | Adjusted variables |
|---|---|---|---|---|---|---|---|---|---|
| Wazni O, 2005,USA[16] | 67.3 | 0.68(111) | 76 days | 3.1 | Persistent AF | Electric | 59 %, 69 % | 2.0 (1.2-3.2) | Age, sex, duration of AF, coronary artery disease, hypertension, left ventricular hypertrophy, LAD |
| Zarauza J, 2006, Spain[19] | 62.7 | 0.43(37) | 30 days | 3.0 | Persistent AF | Electric | 81%, 67 % | 3.7 (1.3-10.8) | Sex, age, time, size of left atrium, history of hypertension, pharmacological treatment |
| Watanabe E, 2006, Japan[18] | 64 | 0.76(84) | 1 year | 0.6 | Persistent AF | Electric | 75%, 90% | 5.3 (2.5-11.5) | Sex, coronary artery disease, hypertension, smoking, diabetes, AF duration, LAD, and LVEF |
| Loricchio ML, 2007, Italy[15] | 67 | 0.52(102) | 1 year | 1.9 | Persistent AF | Electric | 87%, 37% | 5.0 (1.8-14.3) | Age, gender, EF, LAD , hypertension, diabetes, pharmacological treatment |
| Lombardi F, 2008, Italy[14] | 67 | 0.34(53) | 21 days | 3.6 | Persistent AF | Electric | 64%, 83% | 1.6 (1.0-2.5) | Age, LAD, LAA, LAAEV, NTproBNP level, history of AF, AF duration or pharmacological treatment |
| Henningsen KMA, 2009, Denmark[12] | 65 | 0.68(56) | 180 days | 3.0 | Persistent AF | Electric | 60%, 83% | 7.7 (1.9-31.1) * | NA |
| Rizos I, 2010,Greece[17] | 67.9 | 0.64(61) | 1 year | 2.3 | Paroxysmal AF | Pharmacologic | 72%, 68% | 6.2 (2.2-17.6) | IL-6, age, gender, PAF history, LAD, EF, diabetes, smoking |
| Liu J, 2011,China[13] | 55.1 | 0.39(44) | 1 year | 1.9 | Paroxysmal AF | Electric ablation | 79%, 70 % | 5.1 (2.1–12.1) | Age, gender, type of AF, duration of AF, LAD, LVEF, plasma hsCRP concentration. |
| Barassi A, 2012,Italy[10] | 66.9 | 0.33(57) | 21 days | 3.0 | Persistent AF | Electric | 74%, 84 % | 14.9 (3.9-57.2) * | NA |

Abbreviations: HsCRP: High-sensitivity C-reactive protein NA: Not applicable ACE: angiotensin-converting enzyme; *:crude effect estimate

Table 2. Summary of pooled diagnostic accuracy indices

| Variables | Number of studies | Sensitivity (95% CI) | Specificity (95% CI) | Likelihood ratio+ | Likelihood ratio- | AUROC (95% CI) | $I^2$ (95% CI) | Diagnostic OR (95% CI) | Meta-regression P | Egger's test P |
|---|---|---|---|---|---|---|---|---|---|---|
| Overall[10,12-19] | 9 | 0.71(0.63-0.78) | 0.72(0.61-0.81) | 2.57(1.86-3.55) | 0.40(0.32-0.50) | 0.77(0.73-0.81) | 14.6(0-56.6) | 5.91 (4.07-8.59) | -- | 0.566 |
| Follow time< 6 months[10,14,16,19] | 4 | 0.73(0.56-0.85) | 0.71(0.54-0.83) | 2.50(1.67-3.77) | 0.38(0.24-0.59) | 0.78(0.74-0.82) | 0.0(0.0-74.6) | 6.34(3.70- 10.85) | 0.759 | 0.345 |
| Follow time > one year[12-14,17,18] | 5 | 0.77(0.69-0.84) | 0.65(0.45-0.80) | 2.22(3.14-12.88) | 0.35(0.26-0.48) | 0.79(0.75-0.82) | 34.8(0.0-77.2) | 5.54(3.29-9.32) | 0.552 | 0.583 |
| Electric cardioversion[10,12, 14-16,18,19] | 7 | 0.72(0.62-0.80) | 0.74(0.60-0.85) | 2.81(1.79-4.41) | 0.38(0.29-0.50) | 0.78(0.75-0.82) | 33.0(0.0-71.6) | 5.13(3.63- 7.25) | 0.611 | 0.198 |
| Persistent AF[10,12,14-16,18,19] | 7 | 0.70(0.61-0.78) | 0.71(0.59-0.80) | 2.40(1.77-3.25) | 0.42(0.33-0.53) | 0.76(0.72-0.80) | 22.3(0.0-64.2) | 5.70(3.77-8.62) | 0.899 | 0.464 |

# Value of High-sensitivity C-reactive Protein Assays in Predicting Atrial Fibrillation Recurrence: a systematic review and meta-analysis

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Abstract

Objectives: We performed a systematic review and meta-analysis of studies on high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are predictive of atrial fibrillation (AF) recurrence after cardioversion.

Design: Systematic review and meta-analysis.

Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of the reference lists in the retrieved articles from inception to December 2013.

Study eligibility criteria: This review selected observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. An hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring serum CRP to below 0.6 mg/dL.

Primary and secondary outcome measures: We summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic (HSROC) curves, and bivariate random effects models. Meta-regression analysis was performed to explore the source of heterogeneity.

Results: We included nine qualifying studies comprising a total of 347 patients with AF recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an independent predictor of AF recurrence after cardioversion (summary adjusted odds ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% Cl: 63% to 78%) and 72.0% (61% to 81%), respectively. Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence

(77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73% sensitivity, 71% specificity).

Conclusions: High-sensitivity CRP assays are moderately accurate in predicting AF recurrence after successful cardioversion. Different cutoffs should be applied to ~~patients with~~ short-term or long-term ~~follow up~~prediction of AF recurrence.

Strengths and limitations of this study

- This meta-analysis finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence.
- We reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy.
- A bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies, and occurring between the logit TPR and FPR.
- Results of sensitivity analysis did not show a significantly different overall predictive accuracy between long-term and short-term follow-up, however, a heterogeneity tended toward between-study variability.
- Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. An individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.

Keywords: atrial fibrillation, recurrence, cardioversion, C - reactive protein, meta-analysis

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, although the prevalence is highest among people of advanced age.[1,2] AF poses a significant economic burden, with a 66% increase in hospital admissions over the past two decades. It is estimated that the number of patients affected by AF is likely to grow 2.5 fold by the year 2050.[1-3] In addition, AF may lead to debilitating complications such as ischemic stroke and heart failure. Although ventricular rate control is an acceptable treatment strategy in many patients, some patients may remain symptomatic despite adequate rate controls. For this group of patients, cardioversion may be the treatment of choice. Electrical cardioversion can restore sinus rhythm effectively in most patients and can act with antiarrhythmic drugs synergistically to enhance the cardioversion success rate.[4] However, cardioversion is not the definite treatment. Approximately 50% of patients undergoing cardioversion usually present with recurrence of AF within three to six months of cardioversion despite ongoing antiarrhythmic treatment.[5] Left ventricular dysfunction, left atrial enlargement, arrhythmia duration, and history of hypertension are major risk factors for AF recurrence.[6] However, recent studies have indicated that inflammation, necrosis, and fibrosis play roles in the structural remodeling process of the atria, contributing to the perpetuation or recurrence of atrial fibrillation.

C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response to proinflammatory cytokines, notably interluekin-6, and other endogenous signals of innate immunity or tissue damage. CRP has recently been shown to be associated with cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is elevated in patients with AF.[7] However, 5 of the 6 studies included in that analysis

used traditional automated immunonephelometric assays to measure CRP. Unfortunately, those assays are insufficiently sensitive for measuring the low level of inflammation associated with AF. A newer enzyme immunoassay, namely high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL and may further enhance the predictability of AF recurrence.[8] Since 2006, several studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been published,[9-19] warranting a systemic and quantitative summary of current evidence on the accuracy of CRP in predicting AF recurrence after cardioversion.

## Methods

### Identification of Studies

General bibliographic databases (MEDLINE and EMBASE) were searched from inception to April 2013. The medical subject heading (MeSH) and text words for the term C -reactive protein were combined with the MeSH term "diagnosis of atrial fibrillation". The search was limited to human studies with no language restrictions. In addition to the electronic search, reference lists in all known reviews and primary studies were checked manually.

### Selection Criteria

This review focused on observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. The population of interest comprised patients with paroxysmal or persistent AF who underwent electric cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was defined as AF documented by ECG at any time after the cardioversion during the follow-up period. Generally, patients were instructed to return to the clinic if the symptoms such as palpitations, shortness of breath, or chest discomfort developed

after cardioversion. We included studies using a cohort design or case-control design with appropriate controls. Two reviewers independently assessed eligible articles for inclusion. Disagreements were initially resolved by consensus and using arbitration by a third reviewer if consensus could not be reached by the two reviewers. We extracted data from the included studies. Data collected include study design, participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of follow-up period, and recurrence of AF. One reviewer extracted the data and a second reviewer independently verified the correctness of the extracted data.

Quality Assessment

We assessed the methodological quality of the selected studies using a well-validated tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of Diagnostic Accuracy Studies, QUADAS).[20] The QUADAS instrument scrutinizes characteristics of study designs, population, index tests, and reference standards that may be associated with risk of bias. These features included the spectrum of patients, whether index tests and reference standards were evaluated and interpreted independently to avoid incorporation bias, and whether all patients underwent the same reference standards to avoid differential or partial verification bias.

Data Abstraction

One reviewer independently extracted the data and a second reviewer independently verified the data. Extracted data comprised the following: overall study characteristics (including the first author, country, language, and date of publication); patient characteristics (including age range and pre-existing atrial fibrillation); quantitative data required for construction of a 2 x 2 table (including number of participants, sensitivity, specificity, and recurrence case number); information regarding the

hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or semi-quantitative nature of the test); and study settings. In studies that reported multiple pairs of sensitivity and specificity data, we consistently used the data with the highest Youden index (sensitivity + specificity -1) and performed a sensitivity analysis at a later stage.

Quantitative Data Synthesis

We performed a meta-analysis of diagnostic test accuracy of CRP testing for the prediction of recurrent AF. When 2 × 2 tables contained 0 cells, we performed continuity correction by adding 0.5 to each cell. We calculated the pooled sensitivity and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate meta-analysis model.[21] Likelihood ratios were then translated to post-test probability by use of Fagan's plot. We constructed a hierarchical summary receiver operating characteristic (HSROC) curve that plots sensitivity versus specificity and calculated the area under the curve (AUROC).[22] We evaluated the degree of between-study heterogeneity by using the $I^2$ test.[23] To explore the clinical sources of heterogeneity, we defined the potential explanatory variables *a priori* and performed subgroup analysis to see if the accuracy estimates changed significantly across various subgroups. The presence and the effect of publication bias were examined using a combination of the Egger tests.[24] Statistical analyses were conducted using the statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably with the user-written "midas" and "metandi" programs. All statistical tests were two-sided and statistical significance was defined as a P value less than .05.

Search Results and Study Characteristics

The flow of inclusion and exclusion is summarized in Figure 1. Using our search criteria, we identified 784 studies, of which 352 were from PubMed and 432 were from EMBASE. A total of 752 citations were excluded based on pre-defined criteria. No additional citations were identified from the reference lists. A total of 32 articles were retrieved for full-text review, and 23 were excluded due to various reasons detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in predicting AF recurrence after cardioversion were finally included in the meta-analysis. The 9 studies included a total of 682 patients with AF after successful cardioversion, of which 347 (50.9%) developed recurrence.

Characteristics of included studies

Table 1 lists the study and population characteristics of the 9 patient populations even if we had additional 5 studies that don't have sufficient data for statistical analysis [25-29]. The mean age of patients in the included studies ranged from 55.1 years to 67.9 years and the mean follow-up period ranged from 30 days to 1 year. Seven studies included patients with persistent AF, while 2 studies included patients with paroxysmal AF. Seven studies used electric shock, one used circumferential pulmonary vein isolation (also known as electric ablation), and the other used intravenous amiodarone as the primary method for cardioversion. A total of seven studies provided multivariate (adjusted) odds ratios to evaluate the independent predictive value of CRP levels. These studies generally adjusted for potential predictors of AF recurrence such as age, sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All studies showed that CRP was a significant independent predictor of AF recurrence. Associated adjusted ratios and adjusted variables are summarized in table 1.

Quality assessment

Results of the quality assessment of studies of diagnostic accuracy are summarized in figure 2. All studies were prospective and enrolled consecutive outpatients with AF after cardioversion. Three studies had a short follow-up period (i.e. ≤0.5 or 1 year). Although most of the studies did not indicate whether physicians were blinded to the index tests when diagnosing AF recurrence, the determination of AF recurrence was not affected by the knowledge of hs-CRP test results and risk of incorporation bias was minimal. None of the studies reported the undetermined results or withdrawals.

Diagnostic accuracy indices

Sensitivity, specificity, and diagnostic odds ratio

The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.6%). Table 2 shows the results of individual and combined sensitivity estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%), respectively. We used the pooled prevalence of AF recurrence in this study as the pre-test probability. With a pooled positive likelihood ratio of 2.57 and a negative likelihood ratio of 0.4, the post-test probability for AF recurrence for a positive hs-CRP test result was 72% and a post-test probability for a negative hs-CRP test result was 29%. The area under the ROC curve showed an acceptable overall measurement of discrimination (0.77, Figure 3). Figure 4 shows the forest plot of the ORs.

Subgroup analysis and meta-regression

In view of the potential influence of spectrum variability, we considered the duration of follow-up, mode of cardioversion, and type of AF in the study patients to be important. Hs-CRP test results generally had higher sensitivity and lower specificity

in predicting long-term over short-term AF recurrence. Excluding two studies not using electric shock as the primary cardioversion method did not significantly alter the predictive accuracy. Similarly, *focusing the study patients on persistent AF population* had similar results as compared with the main overall analysis. Exploratory meta-regression analysis did not find that any pre-specified covariate significantly changed the effect estimate.

## Discussion

This meta-analysis shows that elevated CRP levels are independently predictive of AF recurrence in patients with persistent or paroxysmal AF who have undergone successful cardioversion. This finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence. Despite the modest pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the high recurrence rate of AF observed in these included studies. A positive hs-CRP test result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months following cardioversion.

Previous studies have examined risk factors that predict AF recurrence. Traditional clinical risk factors for recurrence include history of multiple AF episodes, use of diuretic treatment, higher CHADS-2 (Congestive heart failure, history of Hypertension, Age≥75 years, Diabetes mellitus, and past history of Stroke or TIA doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C drugs, and digitalis.[30,31] Although each of these factors could predict AF recurrence with some accuracy, a quantitative combination of these predictors is not available, and the clinical utility of these variables remains questionable. This also suggests that a multivariate prediction model should be developed for AF recurrence, and that

hsCRP should be a candidate for inclusion in the model.

During the past decade, serum biomarkers have emerged as practical tools to help in the early identification of patients at high risk for various cardiac events. Elevation of inflammatory markers is associated with sudden cardiac death in patients with heart failure or coronary artery disease, and onset of ventricular arrhythmia.[32-35] Of note, there is abundant evidence that elevated serum levels of CRP are associated with the genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in response to proinflammatory cytokine stimulation. Although the pathophysiology of AF remains elusive, there is pathophysiological evidence supporting the role of inflammation in the initiation, maintenance, and perpetuation of AF.[36] Clinically, AF is frequently associated with local inflammatory diseases such as myocarditis or pericarditis, and systemic inflammatory status, such as post-operative state and severe sepsis. Histologically, structural remodeling of the atria manifested by loss of myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.[37] Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial biopsy specimens from AF patients.[38] Activated inflammatory cells in conjunction with reactive oxygen species, cytokines, and growth factors, may ultimately lead to matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors, or glucocorticoids modulate the course of AF.[39]

In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator of new onset AF and AF recurrence after successful cardioversion.[34,35,40] BNP is also produced in response to atrial pressure and volume overload and there is evidence that

BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed that the standardized mean difference in plasma BNP level between patients with non-recurrence and patients with recurrence was -1.35 (95% confidence interval -2.17, -0.53).[41] Data on sensitivity and specificity in that study were not available. The comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus requires further analysis.

There are both strengths and limitations in our study. Considering the limitation of sensitivity and specificity in clinical interpretation, we reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy. The LRs indicate how much a given CRP testing result increases or decreases the probability of recurrence of AF. Post-test probabilities can be derived from pre-test probabilities and LRs, which are an important clinical parameter for major clinical decision making. Second, we used a bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies, and occurring between the logit TPR and FPR. Third, we performed sensitivity analysis by restricting analysis within two broad categories of follow-up duration. Results of sensitivity analysis did not show a significantly different overall predicative accuracy between long-term and short-term ~~follow up~~prediction of AF recurrence. Nonetheless, it is noteworthy that the sensitivity may be over estimated in our study under the hypothesis where the inflammation may be symptomatic since none of the studies provided withdrawal and undetermined results, and the ascertainment of AF was passive. This event further introduces the differential verification bias. Moreover, our meta-analysis is restricted to distinguish hsCRP levels above or below 0.6 mg/dL because the authors in only one of the studies claimed to possess such capability. Finally, due to the lack of individual data, it is hard to determine whether the area

under ROC (AUC) can be improved by the new assay either on overall or on individual studies. Overall, as assessed by the heterogeneity of dOR, the included studies evaluating CRP levels and AF recurrence strongly tended toward between-study variability (heterogeneity). Potential sources of between-study variability included differences in incidence of AF recurrence, different threshold values of CRP concentration used, and different duration for follow-up. Another limitation was the strategy we used to determine the optimal cutoff value. Most studies determined an optimal cutoff value to maximize both sensitivity and specificity. Although a single cutoff value is straightforward in clinical interpretation, it may make a marker neither sensitive nor specific enough to rule out or rule in an outcome of interest. A two cut-off value strategy, with one using a lower cutoff value to optimize the sensitivity (rule-out value) and the other using a higher cutoff value to optimize the specificity (rule-in value), would make better use of the information that a biomarker with a continuous value could provide. Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. To make the best use of the biomarker information by adopting a two cutoff point strategy or a multi-cutoff point risk classification strategy, an individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.

## Conclusions

Baseline CRP levels before cardioversion can independently predict AF recurrence after successful cardioversion. Given the high recurrence rate reported in most series, the modest positive likelihood ratio for hs-CRP assays still has high positive predictive value. Future studies should focus on the evaluation of two or multiple cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation

algorithms should be considered.

Acknowledgement

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Figure legends

Figure 1. **A simplified flow chart to identify and to include studies**. Amongst 752 citations in MEDLINE and EMBASE from inception to December 2013, a search limited to human studies using "C-reactive protein" and the MeSH term "diagnosis of atrial fibrillation" resulted in 32 potentially relevant articles for further review. After careful scrutinization on full text, 9 articles were left for meta-analysis.

Figure 2. **The quality assessment of diagnostic accuracy on studies**. A spectrum of features were analysed to avoid bias using a well-validated tool called Quality Assessment of Diagnostics Accuracy Studies (QUADAS). Percentage for each feature was independently evaluated among the studies. It is worthy of attention that none of the studies explained the withdrawal and reported indetermined results, likely to compromise the quality of diagnostic accuracy.

Figure 3. **The ROC curve of hs-CRP.** Our analysis suggests it is highly possible to predict atrial fibrillation using C-creative protein since the area under the curve generates a measurement of discrimination ~0.77. The overall sensitivity and specificity are relatively high. We have 5 out 9 studies that fall in the 95% CI region, while 8 out 9 in the 95% prediction region.

Figure 4. **The forest plot of the odds ratios (ORs)**. Our study indicates that hsCRP-positive patients are ~5.91 times more likely to develop a recurrence of atrial

fibrillation than hsCRP-negative patients are. The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.6%).

Table 1. Summary of the characteristics of the included studies

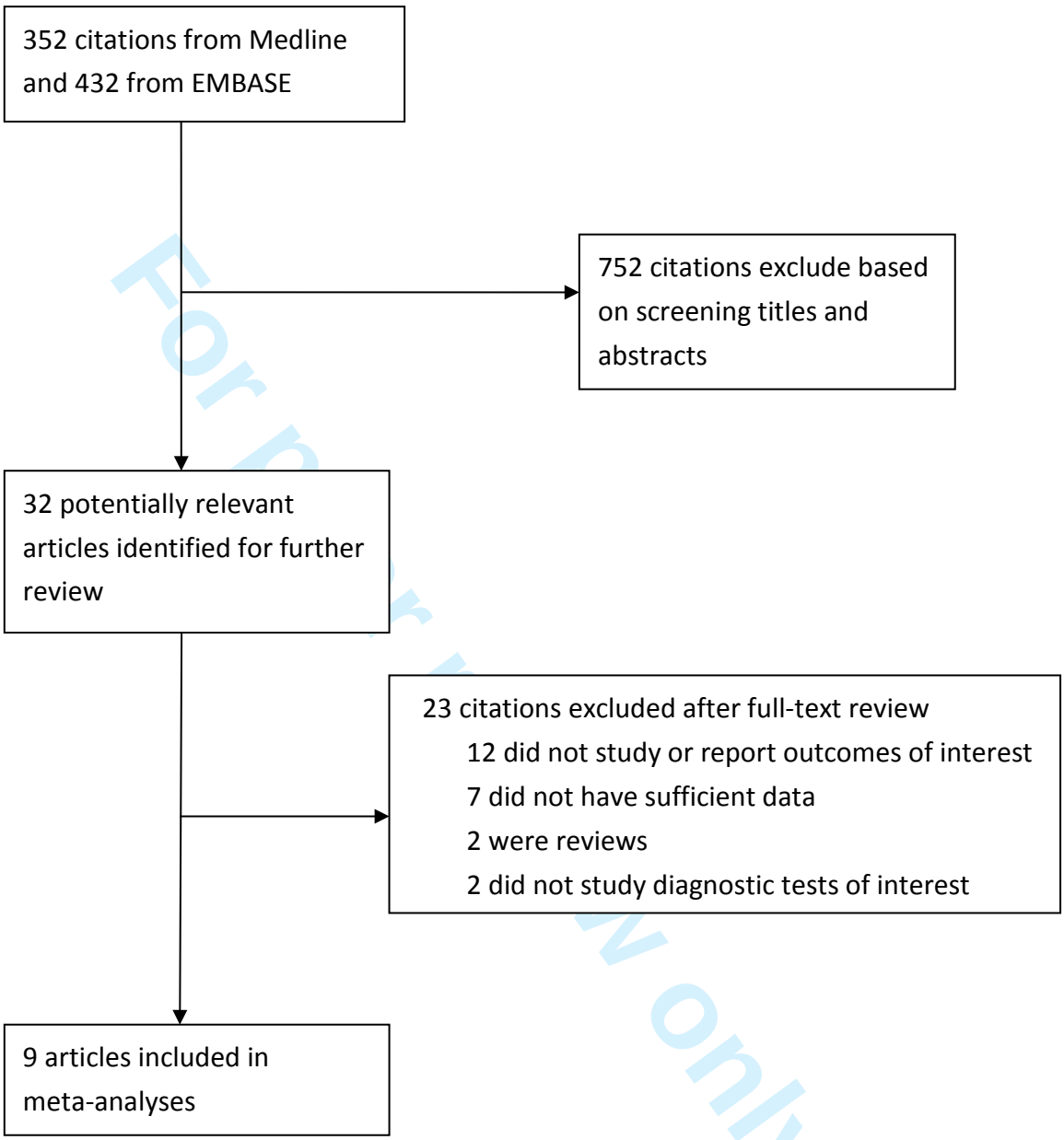
| Author, year, country | Mean Age | Prevalence (N) | Follow-up time | Cutoff (mg/l) | AF type | Cardioversion | Sensitivity, Specificity | Adjusted odd ratio | Adjusted variables |
|---|---|---|---|---|---|---|---|---|---|
| Wazni O, 2005,USA[16] | 67.3 | 0.68(111) | 76 days | 3.1 | Persistent AF | Electric | 59 %, 69 % | 2.0 (1.2-3.2) | Age, sex, duration of AF, coronary artery disease, hypertension, left ventricular hypertrophy, LAD |
| Zarauza J, 2006, Spain[19] | 62.7 | 0.43(37) | 30 days | 3.0 | Persistent AF | Electric | 81%, 67 % | 3.7 (1.3-10.8) | Sex, age, time, size of left atrium, history of hypertension, pharmacological treatment |
| Watanabe E, 2006, Japan[18] | 64 | 0.76(84) | 1 year | 0.6 | Persistent AF | Electric | 75%, 90% | 5.3 (2.5-11.5) | Sex, coronary artery disease, hypertension, smoking, diabetes, AF duration, LAD, and LVEF |
| Loricchio ML, 2007, Italy[15] | 67 | 0.52(102) | 1 year | 1.9 | Persistent AF | Electric | 87%, 37% | 5.0 (1.8-14.3) | Age, gender, EF, LAD , hypertension, diabetes, pharmacological treatment |
| Lombardi F, 2008, Italy[14] | 67 | 0.34(53) | 21 days | 3.6 | Persistent AF | Electric | 64%, 83% | 1.6 (1.0-2.5) | Age, LAD, LAA, LAAEV, NTproBNP level, history of AF, AF duration or pharmacological treatment |
| Henningsen KMA, 2009, Denmark[12] | 65 | 0.68(56) | 180 days | 3.0 | Persistent AF | Electric | 60%, 83% | 7.7 (1.9-31.1) * | NA |
| Rizos I, 2010,Greece[17] | 67.9 | 0.64(61) | 1 year | 2.3 | Paroxysmal AF | Pharmacologic | 72%, 68% | 6.2 (2.2-17.6) | IL-6, age, gender, PAF history, LAD, EF, diabetes, smoking |
| Liu J, 2011,China[13] | 55.1 | 0.39(44) | 1 year | 1.9 | Paroxysmal AF | Electric ablation | 79%, 70 % | 5.1 (2.1–12.1) | Age, gender, type of AF, duration of AF, LAD, LVEF, plasma hsCRP concentration. |
| Barassi A, 2012,Italy[10] | 66.9 | 0.33(57) | 21 days | 3.0 | Persistent AF | Electric | 74%, 84 % | 14.9 (3.9-57.2) * | NA |

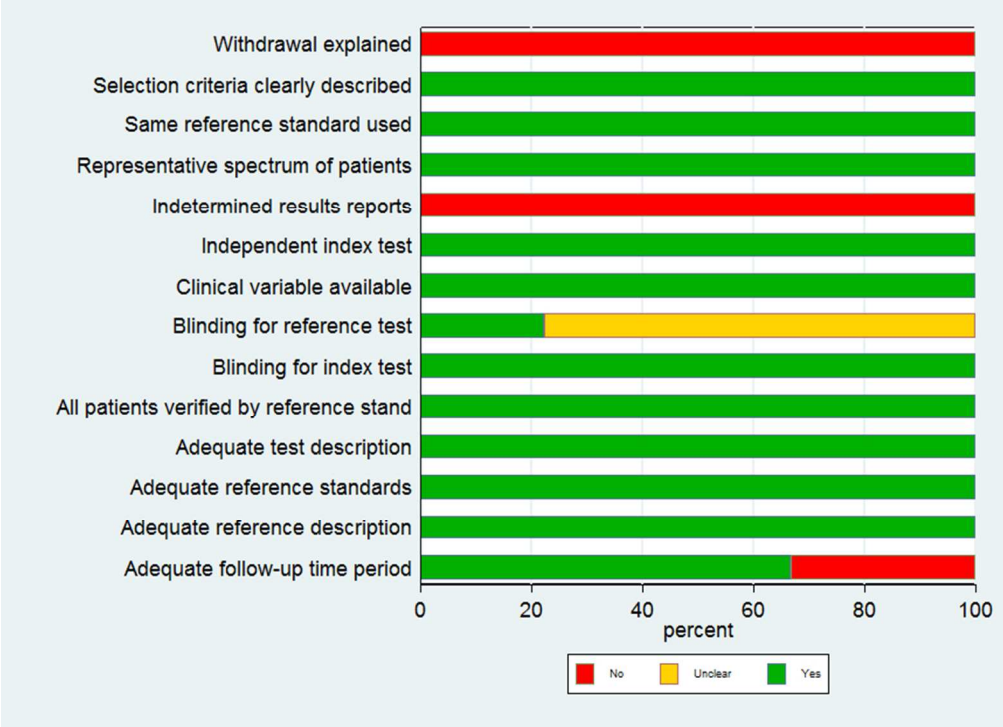
Abbreviations: HsCRP: High-sensitivity C-reactive protein NA: Not applicable ACE: angiotensin-converting enzyme; *:crude effect estimate

Table 2. Summary of pooled diagnostic accuracy indices

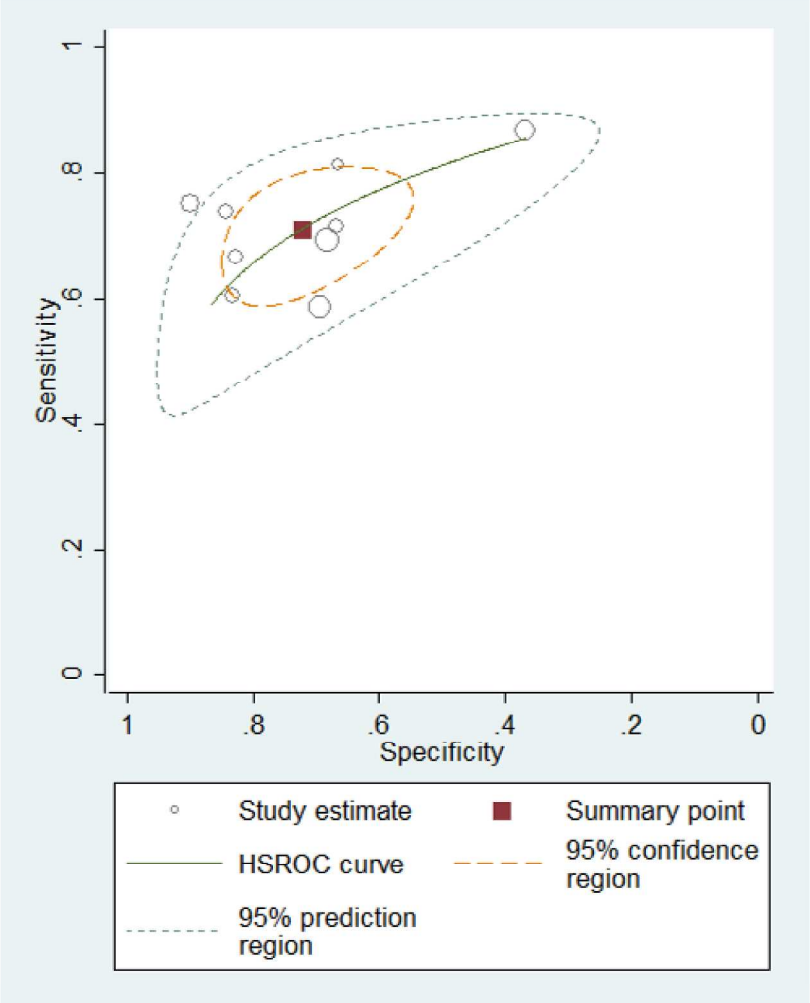
| Variables | Number of studies | Sensitivity (95% CI) | Specificity (95% CI) | Likelihood ratio+ | Likelihood ratio- | AUROC (95% CI) | $I^2$ (95% CI) | Diagnostic OR (95% CI) | Meta-regression P | Egger's test P |
|---|---|---|---|---|---|---|---|---|---|---|
| Overall[10,12-19] | 9 | 0.71(0.63-0.78) | 0.72(0.61-0.81) | 2.57(1.86-3.55) | 0.40(0.32-0.50) | 0.77(0.73-0.81) | 14.6(0-56.6) | 5.91 (4.07-8.59) | -- | 0.566 |
| Follow time< 6 months[10,14,16,19] | 4 | 0.73(0.56-0.85) | 0.71(0.54-0.83) | 2.50(1.67-3.77) | 0.38(0.24-0.59) | 0.78(0.74-0.82) | 0.0(0.0-74.6) | 6.34(3.70- 10.85) | 0.759 | 0.345 |
| Follow time > one year[12-14,17,18] | 5 | 0.77(0.69-0.84) | 0.65(0.45-0.80) | 2.22(3.14-12.88) | 0.35(0.26-0.48) | 0.79(0.75-0.82) | 34.8(0.0-77.2) | 5.54(3.29-9.32) | 0.552 | 0.583 |
| Electric cardioversion[10,12,14-16,18,19] | 7 | 0.72(0.62-0.80) | 0.74(0.60-0.85) | 2.81(1.79-4.41) | 0.38(0.29-0.50) | 0.78(0.75-0.82) | 33.0(0.0-71.6) | 5.13(3.63- 7.25) | 0.611 | 0.198 |
| Persistent AF[10,12,14-16,18,19] | 7 | 0.70(0.61-0.78) | 0.71(0.59-0.80) | 2.40(1.77-3.25) | 0.42(0.33-0.53) | 0.76(0.72-0.80) | 22.3(0.0-64.2) | 5.70(3.77-8.62) | 0.899 | 0.464 |

Figure 1 Flow chart of study identification and inclusion

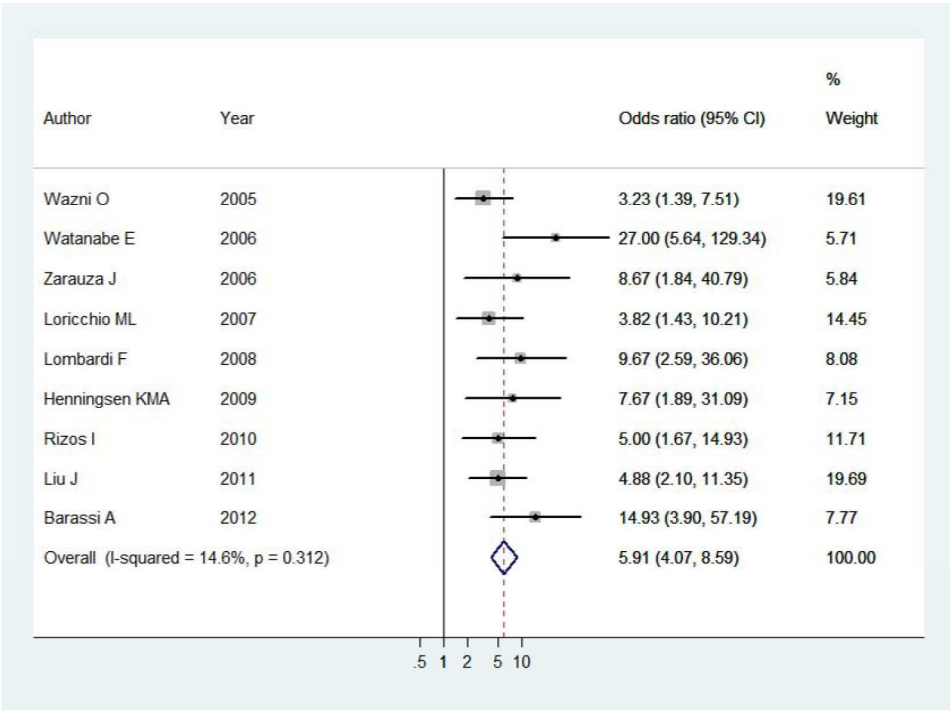





Results of the quality assessment of studies of diagnostic accuracy
302x219mm (72 x 72 DPI)




The summary ROC curve of hs-CRP
297x420mm (300 x 300 DPI)




The forest plot of the ORs
209x148mm (300 x 300 DPI)

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | P1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | P2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | P4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | P4-5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | P5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | P5-6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | P5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | P5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | P5-6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | P6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | P6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | P7 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | P6-7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | P7 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | P6-7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | P7 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | P8 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | P8, Table1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | P8,12-13 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | P9, Table1 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | P9, Table2, Fig3, Fig4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | P9,12-13 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | P9, Table2 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | P10-11 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | P12-13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | P13-14 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | P14 |

# PRISMA 2009 Checklist

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

# Value of High-sensitivity C-reactive Protein Assays in Predicting Atrial Fibrillation Recurrence: a systematic review and meta-analysis

| | |
|---|---|
| Journal: | *BMJ Open* |
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| Primary Subject Heading: | Cardiovascular medicine |
| Secondary Subject Heading: | Cardiovascular medicine |
| Keywords: | Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY, Hypertension < CARDIOLOGY, C - reactive protein, cardioversion, meta-analysis |
| | |

# Value of High-sensitivity C-reactive Protein Assays in Predicting Atrial Fibrillation Recurrence: a systematic review and meta-analysis

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Conflict of interest: None declared

Abstract

Objectives: We performed a systematic review and meta-analysis of studies on high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are predictive of atrial fibrillation (AF) recurrence after cardioversion.

Design: Systematic review and meta-analysis.

Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of the reference lists in the retrieved articles from inception to December 2013.

Study eligibility criteria: This review selected observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. An hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring serum CRP to below 0.6 mg/dL.

Primary and secondary outcome measures: We summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic (HSROC) curves, and bivariate random effects models. Meta-regression analysis was performed to explore the source of heterogeneity.

Results: We included nine qualifying studies comprising a total of 347 patients with AF recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an independent predictor of AF recurrence after cardioversion (summary adjusted odds ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% Cl: 63% to 78%) and 72.0% (61% to 81%), respectively. Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence

(77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73% sensitivity, 71% specificity).

Conclusions: High-sensitivity CRP assays are moderately accurate in predicting AF recurrence after successful cardioversion.

Strengths and limitations of this study

- This meta-analysis finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence.
- We reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy.
- A bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies, and occurring between the logit true positive rates (TPR) and false positive rates (FPR).
- Results of sensitivity analysis did not show a significantly different overall predictive accuracy between long-term and short-term follow-up, however, a heterogeneity tended toward between-study variability.
- Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays.

Keywords: atrial fibrillation, recurrence, cardioversion, C - reactive protein, meta-analysis

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, although the

prevalence is highest among people of advanced age.[1,2] AF poses a significant economic burden, with a 66% increase in hospital admissions over the past two decades. It is estimated that the number of patients affected by AF is likely to grow 2.5 fold by the year 2050.[1-3] In addition, AF may lead to debilitating complications such as ischemic stroke and heart failure. Although ventricular rate control is an acceptable treatment strategy in many patients, some patients may remain symptomatic despite adequate rate controls. For this group of patients, cardioversion may be the treatment of choice. Electrical cardioversion can restore sinus rhythm effectively in most patients and can act with antiarrhythmic drugs synergistically to enhance the cardioversion success rate.[4] However, cardioversion is not the definite treatment. Approximately 50% of patients undergoing cardioversion usually present with recurrence of AF within three to six months of cardioversion despite ongoing antiarrhythmic treatment.[5] Left ventricular dysfunction, left atrial enlargement, arrhythmia duration, and history of hypertension are major risk factors for AF recurrence.[6] However, recent studies have indicated that inflammation, necrosis, and fibrosis play roles in the structural remodeling process of the atria, contributing to the perpetuation or recurrence of atrial fibrillation.

C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response to proinflammatory cytokines, notably interluekin-6, and other endogenous signals of innate immunity or tissue damage. CRP has recently been shown to be associated with cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is elevated in patients with AF.[7] However, 5 of the 6 studies included in that analysis used traditional automated immunonephelometric assays to measure CRP. Unfortunately, those assays are insufficiently sensitive for measuring the low level of inflammation associated with AF. A newer enzyme immunoassay, namely

high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL and may further enhance the predictability of AF recurrence.[8] Since 2006, several studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been published,[9-19] warranting a systemic and quantitative summary of current evidence on the accuracy of CRP in predicting AF recurrence after cardioversion.

## Methods

### Identification of Studies

General bibliographic databases (MEDLINE and EMBASE) were searched from inception to April 2013. The medical subject heading (MeSH) and text words for the term C -reactive protein were combined with the MeSH term "diagnosis of atrial fibrillation". The search was limited to human studies with no language restrictions. In addition to the electronic search, reference lists in all known reviews and primary studies were checked manually.

### Selection Criteria

This review focused on observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. The population of interest comprised patients with paroxysmal or persistent AF who underwent electric cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was defined as AF documented by ECG at any time after the cardioversion during the follow-up period. Generally, patients were instructed to return to the clinic if the symptoms such as palpitations, shortness of breath, or chest discomfort developed after cardioversion. We included studies using a cohort design or case-control design with appropriate controls. Two reviewers independently assessed eligible articles for inclusion. Disagreements were initially resolved by consensus and using arbitration

by a third reviewer if consensus could not be reached by the two reviewers. We extracted data from the included studies. Data collected include study design, participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of follow-up period, and recurrence of AF. One reviewer extracted the data and a second reviewer independently verified the correctness of the extracted data.

Quality Assessment

We assessed the methodological quality of the selected studies using a well-validated tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of Diagnostic Accuracy Studies, QUADAS).[20] The QUADAS instrument scrutinizes characteristics of study designs, population, index tests, and reference standards that may be associated with risk of bias. These features included the spectrum of patients, whether index tests and reference standards were evaluated and interpreted independently to avoid incorporation bias, and whether all patients underwent the same reference standards to avoid differential or partial verification bias.

Data Abstraction

One reviewer independently extracted the data and a second reviewer independently verified the data. Extracted data comprised the following: overall study characteristics (including the first author, country, language, and date of publication); patient characteristics (including age range and pre-existing atrial fibrillation); quantitative data required for construction of a 2 x 2 table (including number of participants, sensitivity, specificity, and recurrence case number); information regarding the hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or semi-quantitative nature of the test); and study settings. In studies that reported multiple pairs of sensitivity and specificity data, we consistently used the data with

the highest Youden index (sensitivity + specificity -1) and performed a sensitivity analysis at a later stage.

Quantitative Data Synthesis

We performed a meta-analysis of diagnostic test accuracy of CRP testing for the prediction of recurrent AF. We calculated the pooled sensitivity and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate meta-analysis model.[21] Likelihood ratios were then translated to post-test probability by use of Fagan's plot. We constructed a hierarchical summary receiver operating characteristic (HSROC) curve that plots sensitivity versus specificity and calculated the area under the curve (AUROC).[22] We evaluated the degree of between-study heterogeneity by using the $I^2$ test.[23] To explore the clinical sources of heterogeneity, we defined the potential explanatory variables *a priori* and performed subgroup analysis to see if the accuracy estimates changed significantly across various subgroups. The presence and the effect of publication bias were examined using a combination of the Egger tests.[24] Statistical analyses were conducted using the statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably with the user-written "midas" and "metandi" programs. All statistical tests were two-sided and statistical significance was defined as a P value less than .05.

Search Results and Study Characteristics

The flow of inclusion and exclusion is summarized in Figure 1. Using our search criteria, we identified 784 studies, of which 352 were from PubMed and 432 were from EMBASE. A total of 752 citations were excluded based on pre-defined criteria. No additional citations were identified from the reference lists. A total of 32 articles

were retrieved for full-text review, and 23 were excluded due to various reasons detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in predicting AF recurrence after cardioversion were finally included in the meta-analysis. The 9 studies included a total of 682 patients with AF after successful cardioversion, of which 347 (50.9%) developed recurrence.

Characteristics of included studies

Table 1 lists the study and population characteristics of the 9 patient populations even if we had additional 5 studies that don't have sufficient data for statistical analysis [25-29]. The mean age of patients in the included studies ranged from 55.1 years to 67.9 years and the mean follow-up period ranged from 30 days to 1 year. Seven studies included patients with persistent AF, while 2 studies included patients with paroxysmal AF. Seven studies used electric shock, one used circumferential pulmonary vein isolation (also known as electric ablation), and the other used intravenous amiodarone as the primary method for cardioversion. A total of seven studies provided multivariate (adjusted) odds ratios to evaluate the independent predictive value of CRP levels. These studies generally adjusted for potential predictors of AF recurrence such as age, sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All studies showed that CRP was a significant independent predictor of AF recurrence. Associated adjusted ratios and adjusted variables are summarized in table 1.

Quality assessment

Results of the quality assessment of studies of diagnostic accuracy are summarized in figure 2. All studies were prospective and enrolled consecutive outpatients with AF after cardioversion. Three studies had a short follow-up period (i.e. ≤0.5 or 1 year). Although most of the studies did not indicate whether physicians were blinded to the

index tests when diagnosing AF recurrence, the determination of AF recurrence was not affected by the knowledge of hs-CRP test results and risk of incorporation bias was minimal. None of the studies reported the undetermined results or withdrawals.

Diagnostic accuracy indices

Sensitivity, specificity, and diagnostic odds ratio

The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.6%). Table 2 shows the results of individual and combined sensitivity estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%), respectively. The pooled prevalence of AF recurrence was 54% herein, and we used it as the pre-test probability. With a pooled positive likelihood ratio of 2.57 and a negative likelihood ratio of 0.4, the post-test probability for AF recurrence for a positive hs-CRP test result was 72% and a post-test probability for a negative hs-CRP test result was 29%. The area under the ROC curve showed an acceptable overall measurement of discrimination (0.77, Figure 3). Figure 4 shows the forest plot of the ORs.

Subgroup analysis and meta-regression

In view of the potential influence of spectrum variability, we considered the duration of follow-up, mode of cardioversion, and type of AF in the study patients to be important. Hs-CRP test results generally had higher sensitivity and lower specificity in predicting long-term over short-term AF recurrence. Excluding two studies not using electric shock as the primary cardioversion method did not significantly alter the predictive accuracy. Similarly, *focusing the study patients on persistent AF population* had similar results as compared with the main overall analysis.

Exploratory meta-regression analysis did not find that any pre-specified covariate significantly changed the effect estimate.

## Discussion

This meta-analysis shows that elevated CRP levels are independently predictive of AF recurrence in patients with persistent or paroxysmal AF who have undergone successful cardioversion. This finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence. Despite the modest pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the high recurrence rate of AF observed in these included studies. A positive hs-CRP test result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months following cardioversion.

Previous studies have examined risk factors that predict AF recurrence. Traditional clinical risk factors for recurrence include history of multiple AF episodes, use of diuretic treatment, higher CHADS-2 (Congestive heart failure, history of Hypertension, Age≥75 years, Diabetes mellitus, and past history of Stroke or TIA doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C drugs, and digitalis.[30,31] Although each of these factors could predict AF recurrence with some accuracy, a quantitative combination of these predictors is not available, and the clinical utility of these variables remains questionable. This also suggests that a multivariate prediction model should be developed for AF recurrence, and that hsCRP should be a candidate for inclusion in the model.

During the past decade, serum biomarkers have emerged as practical tools to help in the early identification of patients at high risk for various cardiac events. Elevation of

inflammatory markers is associated with sudden cardiac death in patients with heart failure or coronary artery disease, and onset of ventricular arrhythmia.[32-35] Of note, there is abundant evidence that elevated serum levels of CRP are associated with the genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in response to proinflammatory cytokine stimulation. Although the pathophysiology of AF remains elusive, there is pathophysiological evidence supporting the role of inflammation in the initiation, maintenance, and perpetuation of AF.[36] Clinically, AF is frequently associated with local inflammatory diseases such as myocarditis or pericarditis, and systemic inflammatory status, such as post-operative state and severe sepsis. Histologically, structural remodeling of the atria manifested by loss of myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.[37] Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial biopsy specimens from AF patients.[38] Activated inflammatory cells in conjunction with reactive oxygen species, cytokines, and growth factors, may ultimately lead to matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors, or glucocorticoids modulate the course of AF.[39]

In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator of new onset AF and AF recurrence after successful cardioversion.[34,35,40] BNP is also produced in response to atrial pressure and volume overload and there is evidence that BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed that the standardized mean difference in plasma BNP level between patients with non-recurrence and patients with recurrence was -1.35 (95% confidence interval -2.17, -0.53).[41] Data on sensitivity and specificity in that study were not available. The

comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus requires further analysis.

There are both strengths and limitations in our study. Considering the limitation of sensitivity and specificity in clinical interpretation, we reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy. The LRs indicate how much a given CRP testing result increases or decreases the probability of recurrence of AF. Post-test probabilities can be derived from pre-test probabilities and LRs, which are an important clinical parameter for major clinical decision making. Second, we used a bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies, and occurring between the logit TPR and FPR. Third, we performed sensitivity analysis by restricting analysis within two broad categories of follow-up duration. Results of sensitivity analysis did not show a significantly different overall predicative accuracy between long-term and short-term prediction of AF recurrence. Nonetheless, it is noteworthy that the sensitivity may be over estimated in our study under the hypothesis where the inflammation may be symptomatic since none of the studies provided withdrawal and undetermined results, and the ascertainment of AF was passive. This event further introduces the differential verification bias. Moreover, our meta-analysis is restricted to distinguish hsCRP levels above or below 0.6 mg/dL because the authors in only one of the studies claimed to possess such capability. Finally, due to the lack of individual data, it is hard to determine whether the area under ROC (AUC) can be improved by the new assay either on overall or on individual studies. In general, potential sources of between-study variability included differences in incidence of AF recurrence, different threshold values of CRP concentration used, and different duration for follow-up. Another limitation was the

strategy we used to determine the optimal cutoff value. Most studies determined an optimal cutoff value to maximize both sensitivity and specificity. Although a single cutoff value is straightforward in clinical interpretation, it may make a marker neither sensitive nor specific enough to rule out or rule in an outcome of interest. A two cut-off value strategy, with one using a lower cutoff value to optimize the sensitivity (rule-out value) and the other using a higher cutoff value to optimize the specificity (rule-in value), would make better use of the information that a biomarker with a continuous value could provide. Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. To make the best use of the biomarker information by adopting a two cutoff point strategy or a multi-cutoff point risk classification strategy, an individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.

Conclusions

Baseline CRP levels before cardioversion can independently predict AF recurrence after successful cardioversion. Given the high recurrence rate reported in most series, the modest positive likelihood ratio for hs-CRP assays still has high positive predictive value. Future studies should focus on the evaluation of two or multiple cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation algorithms should be considered.

Acknowledgement

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## Data sharing

The study results will be published in a peer-reviewed scientific journal. The extracted data will open to sharing upon request.

## Contributorship

C.H.Y.: study design, data management, statistics, first draft, final draft, and approval; S.H.L.: study design, scientific and statistic advisory, study monitoring, final draft, and approval; S.S.C.: statistics, final draft, and approval; M.C.L.; data collection, final draft, and approval; C.C.L.: design, scientific and statistic advisory, final draft, and approval.

## Competing Interest

None

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Figure legends

Figure 1. **A simplified flow chart to identify and to include studies**. Amongst 752 citations in MEDLINE and EMBASE from inception to December 2013, a search limited to human studies using "C-reactive protein" and the MeSH term "diagnosis of atrial fibrillation" resulted in 32 potentially relevant articles for further review. After careful scrutinization on full text, 9 articles were left for meta-analysis.

Figure 2. **The quality assessment of diagnostic accuracy on studies**. A spectrum of features were analysed to avoid bias using a well-validated tool called Quality Assessment of Diagnostics Accuracy Studies (QUADAS). Percentage for each feature was independently evaluated among the studies. It is worthy of attention that none of the studies explained the withdrawal and reported indetermined results, likely to compromise the quality of diagnostic accuracy.

Figure 3. **The ROC curve of hs-CRP.** Our analysis suggests it is highly possible to predict atrial fibrillation using C-creative protein since the area under the curve generates a measurement of discrimination ~0.77. The overall sensitivity and specificity are relatively high. We have 5 out 9 studies that fall in the 95% CI region, while 8 out 9 in the 95% prediction region.

Figure 4. **The forest plot of the odds ratios (ORs)**. Our study indicates that hsCRP-positive patients are ~5.91 times more likely to develop a recurrence of atrial

fibrillation than hsCRP-negative patients are. The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.6%).

Table 1. Summary of the characteristics of the included studies

| Author, year, country | Mean Age | Prevalence (N) | Follow-up time | Cutoff (mg/l) | AF type | Cardioversion | Sensitivity, Specificity | Adjusted odd ratio | Adjusted variables |
|---|---|---|---|---|---|---|---|---|---|
| Wazni O, 2005,USA[16] | 67.3 | 0.68(111) | 76 days | 3.1 | Persistent AF | Electric | 59 %, 69 % | 2.0 (1.2-3.2) | Age, sex, duration of AF, coronary artery disease, hypertension, left ventricular hypertrophy, LAD |
| Zarauza J, 2006, Spain[19] | 62.7 | 0.43(37) | 30 days | 3.0 | Persistent AF | Electric | 81%, 67 % | 3.7 (1.3-10.8) | Sex, age, time, size of left atrium, history of hypertension, pharmacological treatment |
| Watanabe E, 2006, Japan[18] | 64 | 0.76(84) | 1 year | 0.6 | Persistent AF | Electric | 75%, 90% | 5.3 (2.5-11.5) | Sex, coronary artery disease, hypertension, smoking, diabetes, AF duration, LAD, and LVEF |
| Loricchio ML, 2007, Italy[15] | 67 | 0.52(102) | 1 year | 1.9 | Persistent AF | Electric | 87%, 37% | 5.0 (1.8-14.3) | Age, gender, EF, LAD , hypertension, diabetes, pharmacological treatment |
| Lombardi F, 2008, Italy[14] | 67 | 0.34(53) | 21 days | 3.6 | Persistent AF | Electric | 64%, 83% | 1.6 (1.0-2.5) | Age, LAD, LAA, LAAEV, NTproBNP level, history of AF, AF duration or pharmacological treatment |
| Henningsen KMA, 2009, Denmark[12] | 65 | 0.68(56) | 180 days | 3.0 | Persistent AF | Electric | 60%, 83% | 7.7 (1.9-31.1) ＊ | NA |
| Rizos I, 2010,Greece[17] | 67.9 | 0.64(61) | 1 year | 2.3 | Paroxysmal AF | Pharmacologic | 72%, 68% | 6.2 (2.2-17.6) | IL-6, age, gender, PAF history, LAD, EF, diabetes, smoking |
| Liu J, 2011,China[13] | 55.1 | 0.39(44) | 1 year | 1.9 | Paroxysmal AF | Electric ablation | 79%, 70 % | 5.1 (2.1–12.1) | Age, gender, type of AF, duration of AF, LAD, LVEF, plasma hsCRP concentration. |
| Barassi A, 2012,Italy[10] | 66.9 | 0.33(57) | 21 days | 3.0 | Persistent AF | Electric | 74%, 84 % | 14.9 (3.9-57.2) ＊ | NA |

Abbreviations: HsCRP: High-sensitivity C-reactive protein NA: Not applicable ACE: angiotensin-converting enzyme; ＊:crude effect estimate

Table 2. Summary of pooled diagnostic accuracy indices

| Variables | Number of studies | Sensitivity (95% CI) | Specificity (95% CI) | Likelihood ratio+ | Likelihood ratio- | AUROC (95% CI) | $I^2$ (95% CI) | Diagnostic OR (95% CI) | Meta-regression P | Egger's test P |
|---|---|---|---|---|---|---|---|---|---|---|
| Overall[10,12-19] | 9 | 0.71(0.63-0.78) | 0.72(0.61-0.81) | 2.57(1.86-3.55) | 0.40(0.32-0.50) | 0.77(0.73-0.81) | 14.6(0-56.6) | 5.91 (4.07-8.59) | -- | 0.566 |
| Follow time< 6 months[10,14,16,19] | 4 | 0.73(0.56-0.85) | 0.71(0.54-0.83) | 2.50(1.67-3.77) | 0.38(0.24-0.59) | 0.78(0.74-0.82) | 0.0(0.0-74.6) | 6.34(3.70- 10.85) | 0.759 | 0.345 |
| Follow time > one year[12-14,17,18] | 5 | 0.77(0.69-0.84) | 0.65(0.45-0.80) | 2.22(3.14-12.88) | 0.35(0.26-0.48) | 0.79(0.75-0.82) | 34.8(0.0-77.2) | 5.54(3.29-9.32) | 0.552 | 0.583 |
| Electric cardioversion[10,12, 14-16,18,19] | 7 | 0.72(0.62-0.80) | 0.74(0.60-0.85) | 2.81(1.79-4.41) | 0.38(0.29-0.50) | 0.78(0.75-0.82) | 33.0(0.0-71.6) | 5.13(3.63- 7.25) | 0.611 | 0.198 |
| Persistent AF[10,12,14-16,18,19] | 7 | 0.70(0.61-0.78) | 0.71(0.59-0.80) | 2.40(1.77-3.25) | 0.42(0.33-0.53) | 0.76(0.72-0.80) | 22.3(0.0-64.2) | 5.70(3.77-8.62) | 0.899 | 0.464 |

# Value of High-sensitivity C-reactive Protein Assays in Predicting Atrial Fibrillation Recurrence: a systematic review and meta-analysis

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Abstract

Objectives: We performed a systematic review and meta-analysis of studies on high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are predictive of atrial fibrillation (AF) recurrence after cardioversion.

Design: Systematic review and meta-analysis.

Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of the reference lists in the retrieved articles from inception to December 2013.

Study eligibility criteria: This review selected observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. An hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring serum CRP to below 0.6 mg/dL.

Primary and secondary outcome measures: We summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic (HSROC) curves, and bivariate random effects models. Meta-regression analysis was performed to explore the source of heterogeneity.

Results: We included nine qualifying studies comprising a total of 347 patients with AF recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an independent predictor of AF recurrence after cardioversion (summary adjusted odds ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% Cl: 63% to 78%) and 72.0% (61% to 81%), respectively. Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence

(77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73% sensitivity, 71% specificity).

Conclusions: High-sensitivity CRP assays are moderately accurate in predicting AF recurrence after successful cardioversion. ~~Different cutoffs should be applied to patients with short-term or long-term follow-up~~prediction of AF recurrence~~.~~

Strengths and limitations of this study

- This meta-analysis finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence.
- We reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy.
- A bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies, and occurring between the logit true positive rates (TPR) and false positive rates (FPR).
- Results of sensitivity analysis did not show a significantly different overall predictive accuracy between long-term and short-term follow-up, however, a heterogeneity tended toward between-study variability.
- Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. ~~An individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.~~

Keywords: atrial fibrillation, recurrence, cardioversion, C - reactive protein, meta-analysis

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, although the prevalence is highest among people of advanced age.[1,2] AF poses a significant economic burden, with a 66% increase in hospital admissions over the past two decades. It is estimated that the number of patients affected by AF is likely to grow 2.5 fold by the year 2050.[1-3] In addition, AF may lead to debilitating complications such as ischemic stroke and heart failure. Although ventricular rate control is an acceptable treatment strategy in many patients, some patients may remain symptomatic despite adequate rate controls. For this group of patients, cardioversion may be the treatment of choice. Electrical cardioversion can restore sinus rhythm effectively in most patients and can act with antiarrhythmic drugs synergistically to enhance the cardioversion success rate.[4] However, cardioversion is not the definite treatment. Approximately 50% of patients undergoing cardioversion usually present with recurrence of AF within three to six months of cardioversion despite ongoing antiarrhythmic treatment.[5] Left ventricular dysfunction, left atrial enlargement, arrhythmia duration, and history of hypertension are major risk factors for AF recurrence.[6] However, recent studies have indicated that inflammation, necrosis, and fibrosis play roles in the structural remodeling process of the atria, contributing to the perpetuation or recurrence of atrial fibrillation.

C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response to proinflammatory cytokines, notably interluekin-6, and other endogenous signals of innate immunity or tissue damage. CRP has recently been shown to be associated with cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is elevated in patients with AF.[7] However, 5 of the 6 studies included in that analysis

used traditional automated immunonephelometric assays to measure CRP. Unfortunately, those assays are insufficiently sensitive for measuring the low level of inflammation associated with AF. A newer enzyme immunoassay, namely high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL and may further enhance the predictability of AF recurrence.[8] Since 2006, several studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been published,[9-19] warranting a systemic and quantitative summary of current evidence on the accuracy of CRP in predicting AF recurrence after cardioversion.

## Methods

### Identification of Studies

General bibliographic databases (MEDLINE and EMBASE) were searched from inception to April 2013. The medical subject heading (MeSH) and text words for the term C -reactive protein were combined with the MeSH term "diagnosis of atrial fibrillation". The search was limited to human studies with no language restrictions. In addition to the electronic search, reference lists in all known reviews and primary studies were checked manually.

### Selection Criteria

This review focused on observational studies in which the measurements of serum CRP were used to predict atrial fibrillation recurrence. The population of interest comprised patients with paroxysmal or persistent AF who underwent electric cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was defined as AF documented by ECG at any time after the cardioversion during the follow-up period. Generally, patients were instructed to return to the clinic if the symptoms such as palpitations, shortness of breath, or chest discomfort developed

after cardioversion. We included studies using a cohort design or case-control design with appropriate controls. Two reviewers independently assessed eligible articles for inclusion. Disagreements were initially resolved by consensus and using arbitration by a third reviewer if consensus could not be reached by the two reviewers. We extracted data from the included studies. Data collected include study design, participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of follow-up period, and recurrence of AF. One reviewer extracted the data and a second reviewer independently verified the correctness of the extracted data.

Quality Assessment

We assessed the methodological quality of the selected studies using a well-validated tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of Diagnostic Accuracy Studies, QUADAS).[20] The QUADAS instrument scrutinizes characteristics of study designs, population, index tests, and reference standards that may be associated with risk of bias. These features included the spectrum of patients, whether index tests and reference standards were evaluated and interpreted independently to avoid incorporation bias, and whether all patients underwent the same reference standards to avoid differential or partial verification bias.

Data Abstraction

One reviewer independently extracted the data and a second reviewer independently verified the data. Extracted data comprised the following: overall study characteristics (including the first author, country, language, and date of publication); patient characteristics (including age range and pre-existing atrial fibrillation); quantitative data required for construction of a 2 x 2 table (including number of participants, sensitivity, specificity, and recurrence case number); information regarding the

hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or semi-quantitative nature of the test); and study settings. In studies that reported multiple pairs of sensitivity and specificity data, we consistently used the data with the highest Youden index (sensitivity + specificity -1) and performed a sensitivity analysis at a later stage.

Quantitative Data Synthesis

We performed a meta-analysis of diagnostic test accuracy of CRP testing for the prediction of recurrent AF. ~~When 2 × 2 tables contained 0 cells, we performed continuity correction by adding 0.5 to each cell.~~ We calculated the pooled sensitivity and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate meta-analysis model.[21] Likelihood ratios were then translated to post-test probability by use of Fagan's plot. We constructed a hierarchical summary receiver operating characteristic (HSROC) curve that plots sensitivity versus specificity and calculated the area under the curve (AUROC).[22] We evaluated the degree of between-study heterogeneity by using the $I^2$ test.[23] To explore the clinical sources of heterogeneity, we defined the potential explanatory variables *a priori* and performed subgroup analysis to see if the accuracy estimates changed significantly across various subgroups. The presence and the effect of publication bias were examined using a combination of the Egger tests.[24] Statistical analyses were conducted using the statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably with the user-written "midas" and "metandi" programs. All statistical tests were two-sided and statistical significance was defined as a P value less than .05.

Search Results and Study Characteristics

The flow of inclusion and exclusion is summarized in Figure 1. Using our search criteria, we identified 784 studies, of which 352 were from PubMed and 432 were from EMBASE. A total of 752 citations were excluded based on pre-defined criteria. No additional citations were identified from the reference lists. A total of 32 articles were retrieved for full-text review, and 23 were excluded due to various reasons detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in predicting AF recurrence after cardioversion were finally included in the meta-analysis. The 9 studies included a total of 682 patients with AF after successful cardioversion, of which 347 (50.9%) developed recurrence.

Characteristics of included studies

Table 1 lists the study and population characteristics of the 9 patient populations even if we had additional 5 studies that don't have sufficient data for statistical analysis [25-29]. The mean age of patients in the included studies ranged from 55.1 years to 67.9 years and the mean follow-up period ranged from 30 days to 1 year. Seven studies included patients with persistent AF, while 2 studies included patients with paroxysmal AF. Seven studies used electric shock, one used circumferential pulmonary vein isolation (also known as electric ablation), and the other used intravenous amiodarone as the primary method for cardioversion. A total of seven studies provided multivariate (adjusted) odds ratios to evaluate the independent predictive value of CRP levels. These studies generally adjusted for potential predictors of AF recurrence such as age, sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All studies showed that CRP was a significant independent predictor of AF recurrence. Associated adjusted ratios and adjusted variables are summarized in table 1.

Quality assessment

Results of the quality assessment of studies of diagnostic accuracy are summarized in figure 2. All studies were prospective and enrolled consecutive outpatients with AF after cardioversion. Three studies had a short follow-up period (i.e. ≤0.5 or 1 year). Although most of the studies did not indicate whether physicians were blinded to the index tests when diagnosing AF recurrence, the determination of AF recurrence was not affected by the knowledge of hs-CRP test results and risk of incorporation bias was minimal. None of the studies reported the undetermined results or withdrawals.

Diagnostic accuracy indices

Sensitivity, specificity, and diagnostic odds ratio

The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.6%). Table 2 shows the results of individual and combined sensitivity estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%), respectively. The pooled prevalence of AF recurrence was 54% herein, and w~~W~~e used ~~the pooled prevalence of AF recurrence in this study~~it as the pre-test probability. With a pooled positive likelihood ratio of 2.57 and a negative likelihood ratio of 0.4, the post-test probability for AF recurrence for a positive hs-CRP test result was 72% and a post-test probability for a negative hs-CRP test result was 29%. The area under the ROC curve showed an acceptable overall measurement of discrimination (0.77, Figure 3). Figure 4 shows the forest plot of the ORs.

Subgroup analysis and meta-regression

In view of the potential influence of spectrum variability, we considered the duration of follow-up, mode of cardioversion, and type of AF in the study patients to be important. Hs-CRP test results generally had higher sensitivity and lower specificity

in predicting long-term over short-term AF recurrence. Excluding two studies not using electric shock as the primary cardioversion method did not significantly alter the predictive accuracy. Similarly, *focusing the study patients on persistent AF population* had similar results as compared with the main overall analysis. Exploratory meta-regression analysis did not find that any pre-specified covariate significantly changed the effect estimate.

## Discussion

This meta-analysis shows that elevated CRP levels are independently predictive of AF recurrence in patients with persistent or paroxysmal AF who have undergone successful cardioversion. This finding supports that measurement of CRP levels before cardioversion can aid in the prediction of AF recurrence. Despite the modest pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the high recurrence rate of AF observed in these included studies. A positive hs-CRP test result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months following cardioversion.

Previous studies have examined risk factors that predict AF recurrence. Traditional clinical risk factors for recurrence include history of multiple AF episodes, use of diuretic treatment, higher CHADS-2 (Congestive heart failure, history of Hypertension, Age≥75 years, Diabetes mellitus, and past history of Stroke or TIA doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C drugs, and digitalis.[30,31] Although each of these factors could predict AF recurrence with some accuracy, a quantitative combination of these predictors is not available, and the clinical utility of these variables remains questionable. This also suggests that a multivariate prediction model should be developed for AF recurrence, and that

hsCRP should be a candidate for inclusion in the model.

During the past decade, serum biomarkers have emerged as practical tools to help in the early identification of patients at high risk for various cardiac events. Elevation of inflammatory markers is associated with sudden cardiac death in patients with heart failure or coronary artery disease, and onset of ventricular arrhythmia.[32-35] Of note, there is abundant evidence that elevated serum levels of CRP are associated with the genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in response to proinflammatory cytokine stimulation. Although the pathophysiology of AF remains elusive, there is pathophysiological evidence supporting the role of inflammation in the initiation, maintenance, and perpetuation of AF.[36] Clinically, AF is frequently associated with local inflammatory diseases such as myocarditis or pericarditis, and systemic inflammatory status, such as post-operative state and severe sepsis. Histologically, structural remodeling of the atria manifested by loss of myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.[37] Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial biopsy specimens from AF patients.[38] Activated inflammatory cells in conjunction with reactive oxygen species, cytokines, and growth factors, may ultimately lead to matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors, or glucocorticoids modulate the course of AF.[39]

In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator of new onset AF and AF recurrence after successful cardioversion.[34,35,40] BNP is also produced in response to atrial pressure and volume overload and there is evidence that

BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed that the standardized mean difference in plasma BNP level between patients with non-recurrence and patients with recurrence was -1.35 (95% confidence interval -2.17, -0.53).[41] Data on sensitivity and specificity in that study were not available. The comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus requires further analysis.

There are both strengths and limitations in our study. Considering the limitation of sensitivity and specificity in clinical interpretation, we reported summary likelihood ratios (LRs) as an ancillary measure of predictive accuracy. The LRs indicate how much a given CRP testing result increases or decreases the probability of recurrence of AF. Post-test probabilities can be derived from pre-test probabilities and LRs, which are an important clinical parameter for major clinical decision making. Second, we used a bivariate random effect model to account for the inherent negative correlation arising from different cutoff values used in different studies, and occurring between the logit TPR and FPR. Third, we performed sensitivity analysis by restricting analysis within two broad categories of follow-up duration. Results of sensitivity analysis did not show a significantly different overall predicative accuracy between long-term and short-term ~~follow up~~prediction of AF recurrence. Nonetheless, it is noteworthy that the sensitivity may be over estimated in our study under the hypothesis where the inflammation may be symptomatic since none of the studies provided withdrawal and undetermined results, and the ascertainment of AF was passive. This event further introduces the differential verification bias. Moreover, our meta-analysis is restricted to distinguish hsCRP levels above or below 0.6 mg/dL because the authors in only one of the studies claimed to possess such capability. Finally, due to the lack of individual data, it is hard to determine whether the area

under ROC (AUC) can be improved by the new assay either on overall or on individual studies. In general, ~~Overall, as assessed by the heterogeneity of dOR, the included studies evaluating CRP levels and AF recurrence strongly tended toward between-study variability (heterogeneity). p~~Potential sources of between-study variability included differences in incidence of AF recurrence, different threshold values of CRP concentration used, and different duration for follow-up. Another limitation was the strategy we used to determine the optimal cutoff value. Most studies determined an optimal cutoff value to maximize both sensitivity and specificity. Although a single cutoff value is straightforward in clinical interpretation, it may make a marker neither sensitive nor specific enough to rule out or rule in an outcome of interest. A two cut-off value strategy, with one using a lower cutoff value to optimize the sensitivity (rule-out value) and the other using a higher cutoff value to optimize the specificity (rule-in value), would make better use of the information that a biomarker with a continuous value could provide. Current summary estimates based on the one cutoff point may thus have under-evaluated the clinical usefulness of hs-CRP assays. To make the best use of the biomarker information by adopting a two cutoff point strategy or a multi-cutoff point risk classification strategy, an individual data meta-analysis would be needed to overcome the limitations of this aggregated data meta-analysis.

Conclusions

Baseline CRP levels before cardioversion can independently predict AF recurrence after successful cardioversion. Given the high recurrence rate reported in most series, the modest positive likelihood ratio for hs-CRP assays still has high positive predictive value. Future studies should focus on the evaluation of two or multiple cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation

algorithms should be considered.

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Figure legends

Figure 1. **A simplified flow chart to identify and to include studies**. Amongst 752 citations in MEDLINE and EMBASE from inception to December 2013, a search limited to human studies using "C-reactive protein" and the MeSH term "diagnosis of atrial fibrillation" resulted in 32 potentially relevant articles for further review. After careful scrutinization on full text, 9 articles were left for meta-analysis.

Figure 2. **The quality assessment of diagnostic accuracy on studies**. A spectrum of features were analysed to avoid bias using a well-validated tool called Quality Assessment of Diagnostics Accuracy Studies (QUADAS). Percentage for each feature was independently evaluated among the studies. It is worthy of attention that none of the studies explained the withdrawal and reported indetermined results, likely to compromise the quality of diagnostic accuracy.

Figure 3. **The ROC curve of hs-CRP.** Our analysis suggests it is highly possible to predict atrial fibrillation using C-creative protein since the area under the curve generates a measurement of discrimination ~0.77. The overall sensitivity and specificity are relatively high. We have 5 out 9 studies that fall in the 95% CI region, while 8 out 9 in the 95% prediction region.

Figure 4. **The forest plot of the odds ratios (ORs)**. Our study indicates that hsCRP-positive patients are ~5.91 times more likely to develop a recurrence of atrial

fibrillation than hsCRP-negative patients are. The estimated sensitivity and specificity were relatively consistent across studies ($I^2$=14.6%).

Table 1. Summary of the characteristics of the included studies

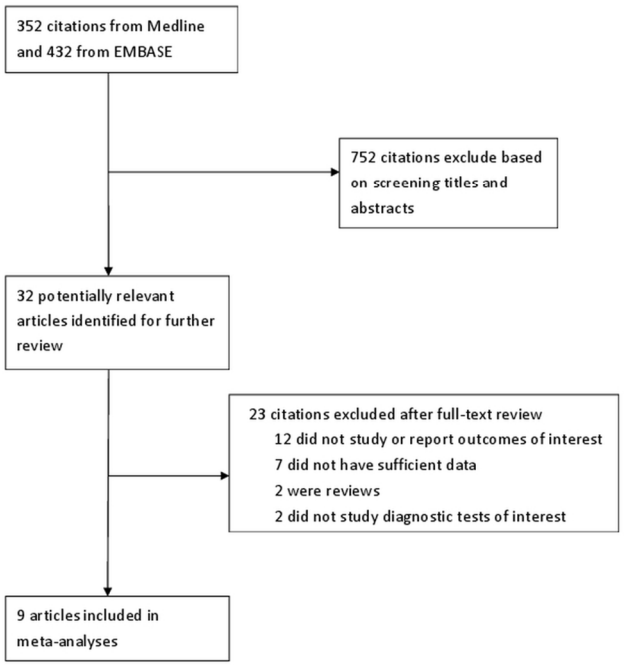
| Author, year, country | Mean Age | Prevalence (N) | Follow-up time | Cutoff (mg/l) | AF type | Cardioversion | Sensitivity, Specificity | Adjusted odd ratio | Adjusted variables |
|---|---|---|---|---|---|---|---|---|---|
| Wazni O, 2005,USA[16] | 67.3 | 0.68(111) | 76 days | 3.1 | Persistent AF | Electric | 59 %, 69 % | 2.0 (1.2-3.2) | Age, sex, duration of AF, coronary artery disease, hypertension, left ventricular hypertrophy, LAD |
| Zarauza J, 2006, Spain[19] | 62.7 | 0.43(37) | 30 days | 3.0 | Persistent AF | Electric | 81%, 67 % | 3.7 (1.3-10.8) | Sex, age, time, size of left atrium, history of hypertension, pharmacological treatment |
| Watanabe E, 2006, Japan[18] | 64 | 0.76(84) | 1 year | 0.6 | Persistent AF | Electric | 75%, 90% | 5.3 (2.5-11.5) | Sex, coronary artery disease, hypertension, smoking, diabetes, AF duration, LAD, and LVEF |
| Loricchio ML, 2007, Italy[15] | 67 | 0.52(102) | 1 year | 1.9 | Persistent AF | Electric | 87%, 37% | 5.0 (1.8-14.3) | Age, gender, EF, LAD , hypertension, diabetes, pharmacological treatment |
| Lombardi F, 2008, Italy[14] | 67 | 0.34(53) | 21 days | 3.6 | Persistent AF | Electric | 64%, 83% | 1.6 (1.0-2.5) | Age, LAD, LAA, LAAEV, NTproBNP level, history of AF, AF duration or pharmacological treatment |
| Henningsen KMA, 2009, Denmark[12] | 65 | 0.68(56) | 180 days | 3.0 | Persistent AF | Electric | 60%, 83% | 7.7 (1.9-31.1) * | NA |
| Rizos I, 2010,Greece[17] | 67.9 | 0.64(61) | 1 year | 2.3 | Paroxysmal AF | Pharmacologic | 72%, 68% | 6.2 (2.2-17.6) | IL-6, age, gender, PAF history, LAD, EF, diabetes, smoking |
| Liu J, 2011,China[13] | 55.1 | 0.39(44) | 1 year | 1.9 | Paroxysmal AF | Electric ablation | 79%, 70 % | 5.1 (2.1–12.1) | Age, gender, type of AF, duration of AF, LAD, LVEF, plasma hsCRP concentration. |
| Barassi A, 2012,Italy[10] | 66.9 | 0.33(57) | 21 days | 3.0 | Persistent AF | Electric | 74%, 84 % | 14.9 (3.9-57.2) * | NA |

Abbreviations: HsCRP: High-sensitivity C-reactive protein NA: Not applicable ACE: angiotensin-converting enzyme; *:crude effect estimate

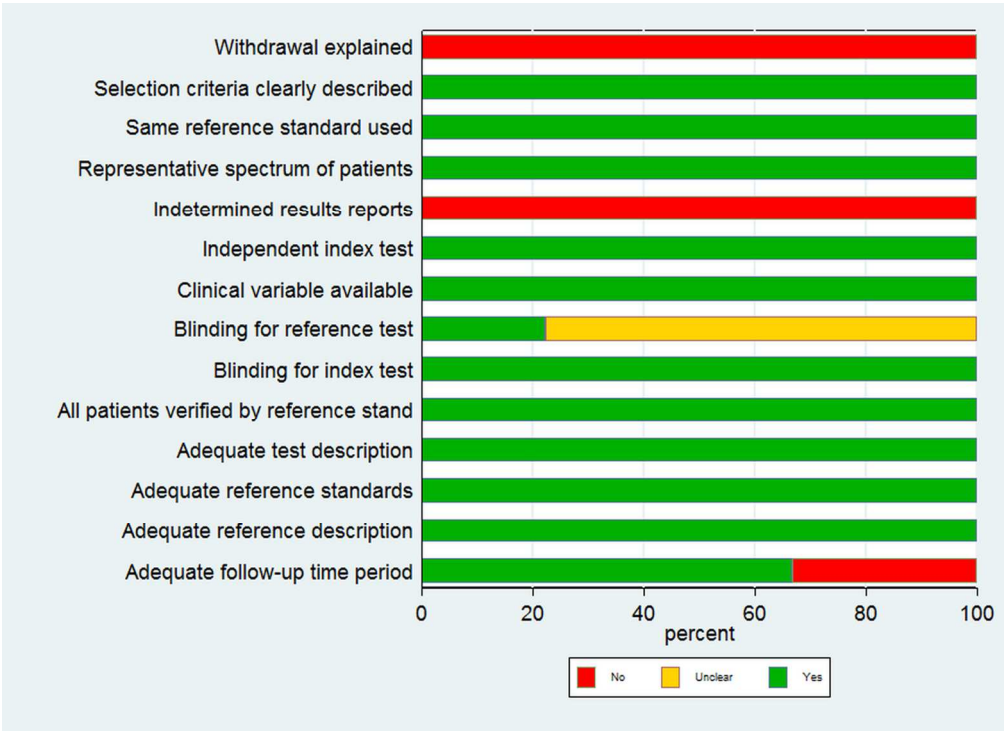
Table 2. Summary of pooled diagnostic accuracy indices

| Variables | Number of studies | Sensitivity (95% CI) | Specificity (95% CI) | Likelihood ratio+ | Likelihood ratio- | AUROC (95% CI) | $I^2$ (95% CI) | Diagnostic OR (95% CI) | Meta-regression P | Egger's test P |
|---|---|---|---|---|---|---|---|---|---|---|
| Overall[10,12-19] | 9 | 0.71(0.63-0.78) | 0.72(0.61-0.81) | 2.57(1.86-3.55) | 0.40(0.32-0.50) | 0.77(0.73-0.81) | 14.6(0-56.6) | 5.91 (4.07-8.59) | -- | 0.566 |
| Follow time< 6 months[10,14,16,19] | 4 | 0.73(0.56-0.85) | 0.71(0.54-0.83) | 2.50(1.67-3.77) | 0.38(0.24-0.59) | 0.78(0.74-0.82) | 0.0(0.0-74.6) | 6.34(3.70- 10.85) | 0.759 | 0.345 |
| Follow time > one year[12-14,17,18] | 5 | 0.77(0.69-0.84) | 0.65(0.45-0.80) | 2.22(3.14-12.88) | 0.35(0.26-0.48) | 0.79(0.75-0.82) | 34.8(0.0-77.2) | 5.54(3.29-9.32) | 0.552 | 0.583 |
| Electric cardioversion[10,12,14-16,18,19] | 7 | 0.72(0.62-0.80) | 0.74(0.60-0.85) | 2.81(1.79-4.41) | 0.38(0.29-0.50) | 0.78(0.75-0.82) | 33.0(0.0-71.6) | 5.13(3.63- 7.25) | 0.611 | 0.198 |
| Persistent AF[10,12,14-16,18,19] | 7 | 0.70(0.61-0.78) | 0.71(0.59-0.80) | 2.40(1.77-3.25) | 0.42(0.33-0.53) | 0.76(0.72-0.80) | 22.3(0.0-64.2) | 5.70(3.77-8.62) | 0.899 | 0.464 |

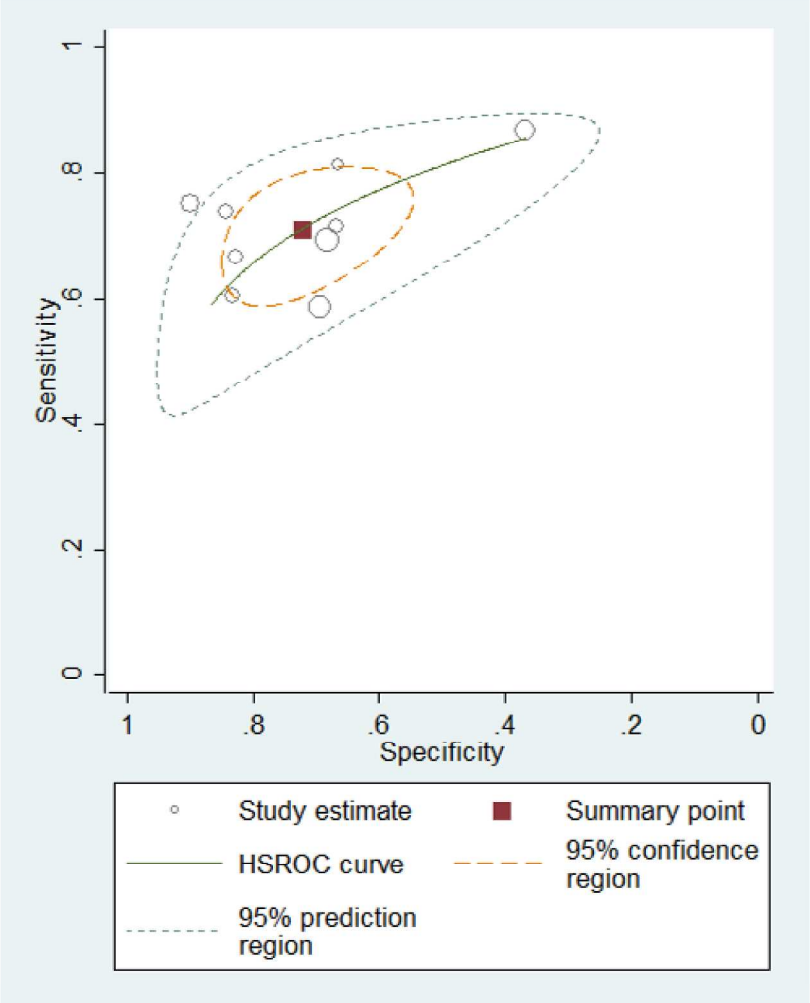
Figure 1 Flow chart of study identification and inclusion



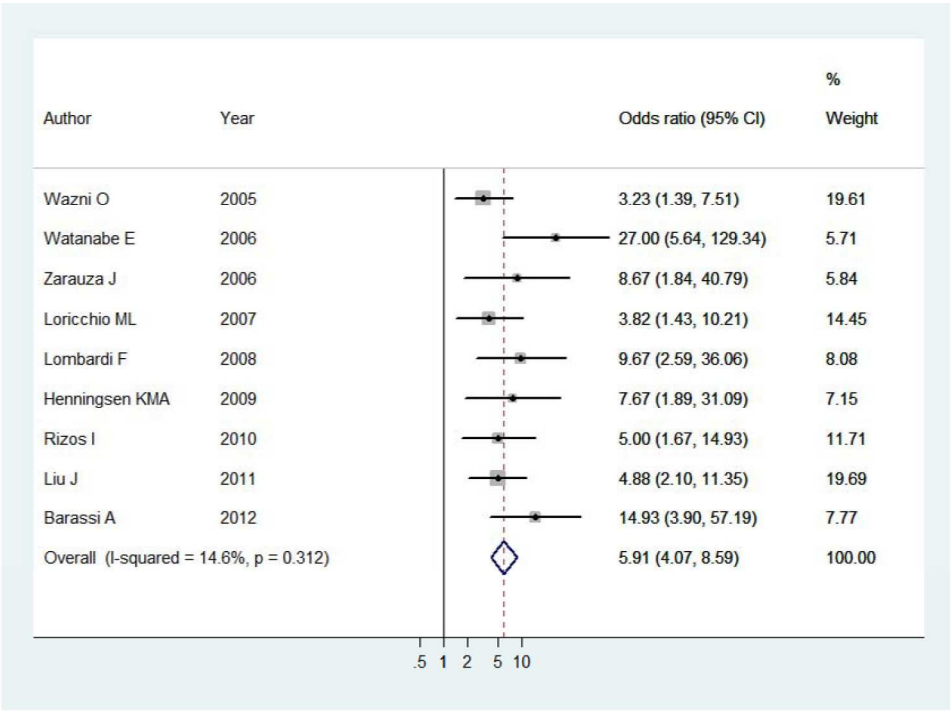

Flow chart of study identification and inclusion
90x127mm (300 x 300 DPI)




Results of the quality assessment of studies of diagnostic accuracy
123x90mm (300 x 300 DPI)




The summary ROC curve of hs-CRP
297x420mm (300 x 300 DPI)




The forest plot of the ORs
209x148mm (300 x 300 DPI)

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | P1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | P2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | P4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | P4-5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | P5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | P5-6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | P5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | P5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | P5-6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | P6-7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | P6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | P7 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | P6-7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | P7 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | P6-7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | P7 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | P8 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | P8, Table1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | P8,12-13 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | P9, Table1 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | P9, Table2, Fig3, Fig4 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | P9,12-13 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | P9, Table2 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | P10-11 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | P12-13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | P13-14 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | P14 |

# PRISMA 2009 Checklist

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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