



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004418
Article Type:	Research
Date Submitted by the Author:	07-Nov-2013
Complete List of Authors:	Yo, Chia-Hung; Far Eastern Memorial Hospital, Department of Emergency Medicine Lee, Si-Huei; Taipei Veteran General Hospital, Department of Rehabilitation and Physical Medicine Chang, Shy-Shin; Chang Gung Memorial Hospital, Department of Family Medicine Lee, Chien-Hung; Medical Wisdom Consultants, Lee, Chien-Chang; National Taiwan University Hospital Yunlin Branch, Department of Emergency Medicine
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY, Hypertension < CARDIOLOGY, C - reactive protein, cardioversion, meta-analysis

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

<sup>1</sup>Chia-Hung Yo MD, <sup>2</sup>Si-Huei Lee MD <sup>3,4</sup>Shy-Shin Chang MD, <sup>5</sup>Matthew  
Chien-Hung Lee PhD, JD, <sup>4,5</sup>Chien-Chang Lee MD, MSc

<sup>1</sup>Department of Emergency Medicine, Far Eastern Memorial Hospital, New Taipei  
City, Taiwan.

<sup>2</sup>Department of Rehabilitation and Physical Medicine, Taipei Veteran  
General Hospital, Taipei, Taiwan

<sup>3</sup>Department of Family Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

<sup>4</sup>Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung  
University, Taoyuan, Taiwan.

<sup>5</sup>Medical Wisdom Consultants, Houston, USA

<sup>4</sup>Department of Epidemiology, Harvard School of Public Health, Boston, USA.

<sup>5</sup>Department of Emergency Medicine, National Taiwan University Hospital Yunlin  
Branch, Douliou, Taiwan

Address correspondence to

Chien-Chang Lee MD, MSc

Email: clee100@gmail.com

Postal Address: No 579 Sec 2 Yunlin Road, Douliou, Yunlin County 640, Taiwan

Telephone: +886-5-532-3911 ext. 2326

Fax: +886-2322-3150

Word count: 2535

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 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% CI: 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.<sup>1,2</sup> 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.<sup>1-3</sup> 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.<sup>4</sup> 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.<sup>5</sup> Left ventricular dysfunction, left atrial enlargement, arrhythmia duration, and history of hypertension are major risk factors for AF recurrence.<sup>6</sup> 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 interleukin-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.<sup>7</sup> However, 5 of the 6 studies included in that analysis used traditional automated immunonephelometric assays to

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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.<sup>8</sup> Since 2006, several studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been published,<sup>9-19</sup> 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

1  
2  
3  
4 with appropriate controls. Two reviewers independently assessed eligible articles for  
5  
6 inclusion. Disagreements were initially resolved by consensus and using arbitration  
7  
8 by a third reviewer if consensus could not be reached by the two reviewers. We  
9  
10 extracted data from the included studies. Data collected include study design,  
11  
12 participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of  
13  
14 follow-up period, and recurrence of AF. One reviewer extracted the data and a  
15  
16 second reviewer independently verified the correctness of the extracted data.  
17  
18  
19

### 20 21 Quality Assessment

22  
23 We assessed the methodological quality of the selected studies using a  
24  
25 well-validated tool for assessment of quality of diagnostic accuracy studies (Quality  
26  
27 Assessment of Diagnostic Accuracy Studies, QUADAS).<sup>20</sup> The QUADAS  
28  
29 instrument scrutinizes characteristics of study designs, population, index tests, and  
30  
31 reference standards that may be associated with risk of bias. These features included  
32  
33 the spectrum of patients, whether index tests and reference standards were evaluated  
34  
35 and interpreted independently to avoid incorporation bias, and whether all patients  
36  
37 underwent the same reference standards to avoid differential or partial verification  
38  
39 bias.  
40  
41  
42  
43  
44

### 45 Data Abstraction

46  
47 One reviewer independently extracted the data and a second reviewer independently  
48  
49 verified the data. Extracted data comprised the following: overall study  
50  
51 characteristics (including the first author, country, language, and date of publication);  
52  
53 patient characteristics (including age range and pre-existing atrial fibrillation);  
54  
55 quantitative data required for construction of a 2 x 2 table (including number of  
56  
57 participants, sensitivity, specificity, and recurrence case number); information  
58  
59  
60

1  
2  
3 regarding the hs-CRP assay (including brand name of the test kit, cutoff levels, and  
4 quantitative or semi-quantitative nature of the test); and study settings. In studies  
5 that reported multiple pairs of sensitivity and specificity data, we consistently used  
6 the data with the highest Youden index (sensitivity + specificity - 1) and performed a  
7 sensitivity analysis at a later stage.  
8  
9

### 16 Quantitative Data Synthesis

17  
18 We performed a meta-analysis of diagnostic test accuracy of CRP testing for the  
19 prediction of recurrent AF. When  $2 \times 2$  tables contained 0 cells, we performed  
20 continuity correction by adding 0.5 to each cell. We calculated the pooled sensitivity  
21 and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio  
22 of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate  
23 meta-analysis model.<sup>21</sup> Likelihood ratios were then translated to post-test probability  
24 by use of Fagan's plot. We constructed a hierarchical summary receiver operating  
25 characteristic (HSROC) curve that plots sensitivity versus specificity and calculated  
26 the area under the curve (AUROC).<sup>22</sup> We evaluated the degree of between-study  
27 heterogeneity by using the  $I^2$  test.<sup>23</sup> To explore the clinical sources of heterogeneity,  
28 we defined the potential explanatory variables *a priori* and performed subgroup  
29 analysis to see if the accuracy estimates changed significantly across various  
30 subgroups. The presence and the effect of publication bias were examined using a  
31 combination of the Egger tests.<sup>24</sup> Statistical analyses were conducted using the  
32 statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably  
33 with the user-written "midas" and "metandi" programs. All statistical tests were  
34 two-sided and statistical significance was defined as a P value less than .05.  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

### 58 Search Results and Study Characteristics



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

1  
2  
3  
4 in figure 2. All studies were prospective and enrolled consecutive outpatients with  
5  
6 AF after cardioversion. Three studies had a short follow-up period (i.e. < X years).  
7  
8 Although most of the studies did not indicate whether physicians were blinded to the  
9  
10 index tests when diagnosing AF recurrence, the determination of AF recurrence was  
11  
12 not affected by the knowledge of hs-CRP test results and risk of incorporation bias  
13  
14 was minimal. None of the studies reported the undetermined results or withdrawals.  
15  
16

### 17 18 19 Diagnostic accuracy indices

#### 20 21 Sensitivity, specificity, and diagnostic odds ratio

22  
23 The estimated sensitivity and specificity were relatively consistent across studies  
24  
25 ( $I^2=14.5\%$ ). Table 2 shows the results of individual and combined sensitivity  
26  
27 estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP  
28  
29 was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%),  
30  
31 respectively. The pooled positive likelihood ratio was 2.57 and the negative  
32  
33 likelihood ratio was 0.4, which can then be translated into a post-test probability of  
34  
35 73% for a positive hs-CRP test result and a post-test probability of 29% for a  
36  
37 negative hs-CRP test result (Figure 2). The area under the ROC curve showed an  
38  
39 acceptable overall accuracy (0.77, Figure 3). Figure 4 shows the forest plot of the  
40  
41 ORs.  
42  
43  
44  
45

#### 46 47 Subgroup analysis and meta-regression

48  
49 In view of the potential influence of spectrum variability, we considered the duration  
50  
51 of follow-up, mode of cardioversion, and type of AF in the study patients to be  
52  
53 important. Hs-CRP test results generally had higher sensitivity and lower specificity  
54  
55 in predicting long-term over short-term AF recurrence. Excluding two studies not  
56  
57 using electric shock as the primary cardioversion method did not significantly alter  
58  
59

1  
2  
3 the predictive accuracy. Similarly, *focusing the study patients on persistent AF*  
4  
5  
6 *population* had similar results as compared with the main overall analysis.

7  
8 Exploratory meta-regression analysis did not find that any pre-specified covariate  
9  
10 significantly changed the effect estimate.

## 11 12 13 Discussion

14  
15 This meta-analysis shows that elevated CRP levels are independently predictive of  
16  
17 AF recurrence in patients with persistent or paroxysmal AF who have undergone  
18  
19 successful cardioversion. This finding supports that measurement of CRP levels  
20  
21 before cardioversion can aid in the prediction of AF recurrence. Despite the modest  
22  
23 pooled sensitivity and specificity, the rule-in diagnostic value was still high, given  
24  
25 the high recurrence rate of AF observed in these included studies. A positive hs-CRP  
26  
27 test result at baseline can predict a 73% chance of AF recurrence in the 6 to 12  
28  
29 months following cardioversion.  
30  
31  
32  
33  
34  
35

36 Previous studies have examined risk factors that predict AF recurrence. Traditional  
37  
38 clinical risk factors for recurrence include history of multiple AF episodes, use of  
39  
40 diuretic treatment, higher CHADS-2 (Congestive heart failure, history of  
41  
42 Hypertension, Age $\geq$ 75 years, Diabetes mellitus, and past history of Stroke or TIA  
43  
44 doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C  
45  
46 drugs, and digitalis.<sup>25,26</sup> Although each of these factors could predict AF recurrence  
47  
48 with some accuracy, a quantitative combination of these predictors is not available,  
49  
50 and the clinical utility of these variables remains questionable.  
51  
52  
53  
54

55 During the past decade, serum biomarkers have emerged as practical tools to help in  
56  
57 the early identification of patients at high risk for various cardiac events. Elevation  
58  
59  
60

1  
2  
3 of inflammatory markers is associated with sudden cardiac death in patients with  
4 heart failure or coronary artery disease, and onset of ventricular arrhythmia.<sup>27-30</sup> Of  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

of inflammatory markers is associated with sudden cardiac death in patients with heart failure or coronary artery disease, and onset of ventricular arrhythmia.<sup>27-30</sup> 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.<sup>31</sup> 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.<sup>32</sup> Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial biopsy specimens from AF patients.<sup>33</sup> 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.<sup>34</sup>

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.<sup>29,30,35</sup> 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%

1  
2  
3 confidence interval -2.17, -0.53).<sup>36</sup> Data on sensitivity and specificity in that study  
4  
5 were not available. The comparative accuracy between BNP and hs-CRP in  
6  
7 predicting AF recurrence thus requires further analysis.  
8  
9

10  
11 There are both strengths and limitations in our study. Considering the limitation of  
12  
13 sensitivity and specificity in clinical interpretation, we reported summary likelihood  
14  
15 ratios (LRs) as an ancillary measure of predictive accuracy. The LRs indicate how  
16  
17 much a given CRP testing result increases or decreases the probability of recurrence  
18  
19 of AF. Post-test probabilities can be derived from pre-test probabilities and LRs,  
20  
21 which are an important clinical parameter for major clinical decision making.  
22  
23 Second, we used a bivariate random effect model to account for the inherent  
24  
25 negative correlation arising from different cutoff values used in different studies.  
26  
27 Third, we performed sensitivity analysis by restricting analysis within two broad  
28  
29 categories of follow-up duration. Results of sensitivity analysis did not show a  
30  
31 significantly different overall predictive accuracy between long-term and  
32  
33 short-term follow-up. Our study also had limitations. Overall, as assessed by the  
34  
35 heterogeneity of dOR, the included studies evaluating CRP levels and AF recurrence  
36  
37 strongly tended toward between-study variability (heterogeneity). Potential sources  
38  
39 of between-study variability included differences in incidence of AF recurrence,  
40  
41 different threshold values of CRP concentration used, and different duration for  
42  
43 follow-up. Another limitation was the strategy we used to determine the optimal  
44  
45 cutoff value. Most studies determined an optimal cutoff value to maximize both  
46  
47 sensitivity and specificity. Although a single cutoff value is straightforward in  
48  
49 clinical interpretation, it may make a marker neither sensitive nor specific enough to  
50  
51 rule out or rule in an outcome of interest. A two cut-off value strategy, with one  
52  
53 using a lower cutoff value to optimize the sensitivity (rule-out value) and the other  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 using a higher cutoff value to optimize the specificity (rule-in value), would make  
4 better use of the information that a biomarker with a continuous value could provide.  
5  
6 Current summary estimates based on the one cutoff point may thus have  
7  
8 under-evaluated the clinical usefulness of hs-CRP assays. To make the best use of  
9  
10 the biomarker information by adopting a two cutoff point strategy or a multi-cutoff  
11  
12 point risk classification strategy, an individual data meta-analysis would be needed  
13  
14 to overcome the limitations of this aggregated data meta-analysis.  
15  
16  
17  
18  
19

## 20 21 Conclusions

22  
23 Baseline CRP levels before cardioversion can independently predict AF recurrence  
24  
25 after successful cardioversion. Given the high recurrence rate reported in most series,  
26  
27 the modest positive likelihood ratio for hs-CRP assays still has high positive  
28  
29 predictive value. Future studies should focus on the evaluation of two or multiple  
30  
31 cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation  
32  
33 algorithms should be considered.  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## References

1. Fabbri G, Maggioni AP. A review of the epidemiological profile of patients with atrial fibrillation and heart failure. *Expert review of cardiovascular therapy*. Sep 2012;10(9):1133-1140.
2. Menezes AR, Lavie CJ, DiNicolantonio JJ, et al. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. *Mayo Clinic proceedings. Mayo Clinic*. Apr 2013;88(4):394-409.
3. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. May 7 2013;61(18):1935-1944.
4. Manlucu J, Brancato S, Lane C, Kazemian P, Michaud GF. Contemporary approaches to persistent atrial fibrillation. *Expert review of cardiovascular therapy*. Nov 2012;10(11):1421-1435.
5. Disertori M, Lombardi F, Barlera S, et al. Clinical characteristics of patients with asymptomatic recurrences of atrial fibrillation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. *American heart journal*. Aug 2011;162(2):382-389.
6. Letsas KP, Weber R, Burkle G, et al. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Feb 2009;11(2):158-163.
7. Liu T, Li L, Korantzopoulos P, Goudevenos JA, Li G. Meta-analysis of association between C-reactive protein and immediate success of electrical cardioversion in persistent atrial fibrillation. *The American journal of cardiology*. Jun 15 2008;101(12):1749-1752.
8. Roberts WL, Sedrick R, Moulton L, Spencer A, Rifai N. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. *Clinical chemistry*. Apr 2000;46(4):461-468.
9. Celebi OO, Celebi S, Canbay A, Ergun G, Aydogdu S, Diker E. The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion. *Cardiology*. 2011;118(3):168-174.



10. Barassi A, Pezzilli R, Morselli-Labate AM, et al. Serum amyloid a and C-reactive protein independently predict the recurrences of atrial fibrillation after cardioversion in patients with preserved left ventricular function. *The Canadian journal of cardiology*. Sep-Oct 2012;28(5):537-541.
11. Hatzinikolaou-Kotsakou E, Tziakas D, Hotidis A, et al. Relation of C-reactive protein to the first onset and the recurrence rate in lone atrial fibrillation. *The American journal of cardiology*. Mar 1 2006;97(5):659-661.
12. Henningsen KM, Therkelsen SK, Bruunsgaard H, Krabbe KS, Pedersen BK, Svendsen JH. Prognostic impact of hs-CRP and IL-6 in patients with persistent atrial fibrillation treated with electrical cardioversion. *Scandinavian journal of clinical and laboratory investigation*. 2009;69(3):425-432.
13. Liu J, Fang PH, Dibs S, Hou Y, Li XF, Zhang S. High-sensitivity C-reactive protein as a predictor of atrial fibrillation recurrence after primary circumferential pulmonary vein isolation. *Pacing and clinical electrophysiology : PACE*. Apr 2011;34(4):398-406.
14. Lombardi F, Tundo F, Belletti S, Mantero A, Melzi D'eril G V. C-reactive protein but not atrial dysfunction predicts recurrences of atrial fibrillation after cardioversion in patients with preserved left ventricular function. *Journal of cardiovascular medicine (Hagerstown, Md.)*. Jun 2008;9(6):581-588.
15. Loricchio ML, Cianfrocca C, Pasceri V, et al. Relation of C-reactive protein to long-term risk of recurrence of atrial fibrillation after electrical cardioversion. *The American journal of cardiology*. May 15 2007;99(10):1421-1424.
16. Wazni O, Martin DO, Marrouche NF, et al. C reactive protein concentration and recurrence of atrial fibrillation after electrical cardioversion. *Heart (British Cardiac Society)*. Oct 2005;91(10):1303-1305.
17. Rizos I, Rigopoulos AG, Kalogeropoulos AS, et al. Hypertension and paroxysmal atrial fibrillation: a novel predictive role of high sensitivity C-reactive protein in cardioversion and long-term recurrence. *Journal of human hypertension*. Jul 2010;24(7):447-457.
18. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity C-reactive protein is predictive of successful cardioversion for atrial fibrillation and maintenance of sinus rhythm after conversion. *International journal of cardiology*. Apr 14 2006;108(3):346-353.
19. Zarauza J, Rodriguez Lera MJ, Farinas Alvarez C, et al. [Relationship between C-reactive protein level and early recurrence of atrial fibrillation after electrical cardioversion]. *Revista espanola de cardiologia*. Feb 2006;59(2):125-129.
20. Leeftang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of



- diagnostic test accuracy. *Annals of internal medicine*. Dec 16 2008;149(12):889-897.
21. Arends LR, Hamza TH, van Houwelingen JC, Heijnenbrok-Kal MH, Hunink MG, Stijnen T. Bivariate random effects meta-analysis of ROC curves. *Medical decision making : an international journal of the Society for Medical Decision Making*. Sep-Oct 2008;28(5):621-638.
  22. Harbord RM, Whiting P, Sterne JA, et al. An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary. *Journal of clinical epidemiology*. Nov 2008;61(11):1095-1103.
  23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed.)*. Sep 6 2003;327(7414):557-560.
  24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed.)*. Sep 13 1997;315(7109):629-634.
  25. Komatsu T, Sato Y, Ozawa M, et al. Relationship between CHADS2 score and efficacy of antiarrhythmic drug therapy in patients with paroxysmal atrial fibrillation. *Circulation journal : official journal of the Japanese Circulation Society*. Feb 25 2013;77(3):639-645.
  26. Letsas KP, Efremidis M, Giannopoulos G, et al. CHADS2 and CHA2DS2-VASc scores as predictors of left atrial ablation outcomes for paroxysmal atrial fibrillation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Jun 28 2013.
  27. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation*. Jun 4 2002;105(22):2595-2599.
  28. Parekh RS, Plantinga LC, Kao WH, et al. The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney international*. Nov 2008;74(10):1335-1342.
  29. Streitner F, Kuschyk J, Veltmann C, et al. Role of proinflammatory markers and NT-proBNP in patients with an implantable cardioverter-defibrillator and an electrical storm. *Cytokine*. Sep 2009;47(3):166-172.
  30. Korngold EC, Januzzi JL, Jr., Gantzer ML, Moorthy MV, Cook NR, Albert CM. Amino-terminal pro-B-type natriuretic peptide and high-sensitivity C-reactive protein as predictors of sudden cardiac death among women. *Circulation*. Jun 9 2009;119(22):2868-2876.
  31. Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation

- 1  
2  
3 of atrial fibrillation. *European heart journal*. Oct 2005;26(20):2083-2092.  
4  
5 32. Allesie M, Ausma J, Schotten U. Electrical, contractile and structural  
6 remodeling during atrial fibrillation. *Cardiovascular research*. May  
7 2002;54(2):230-246.  
8  
9 33. Van Wagoner DR. Oxidative Stress and Inflammation in Atrial Fibrillation:  
10 Role in Pathogenesis and Potential as a Therapeutic Target. *Journal of*  
11 *Cardiovascular Pharmacology*. 2008;52(4):306-313  
12 310.1097/FJC.1090b1013e31817f39398.  
13  
14 34. Moro C, Hernandez-Madrid A, Matia R. Non-antiarrhythmic drugs to prevent  
15 atrial fibrillation. *American journal of cardiovascular drugs : drugs, devices,*  
16 *and other interventions*. 2010;10(3):165-173.  
17  
18 35. den Uijl DW, Delgado V, Tops LF, et al. Natriuretic peptide levels predict  
19 recurrence of atrial fibrillation after radiofrequency catheter ablation.  
20 *American heart journal*. Jan 2011;161(1):197-203.  
21  
22 36. Tang Y, Yang H, Qiu J. Relationship between brain natriuretic peptide and  
23 recurrence of atrial fibrillation after successful electrical cardioversion: a  
24 meta-analysis. *The Journal of international medical research*.  
25 2011;39(5):1618-1624.  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1. Summary of the characteristics of the included studies

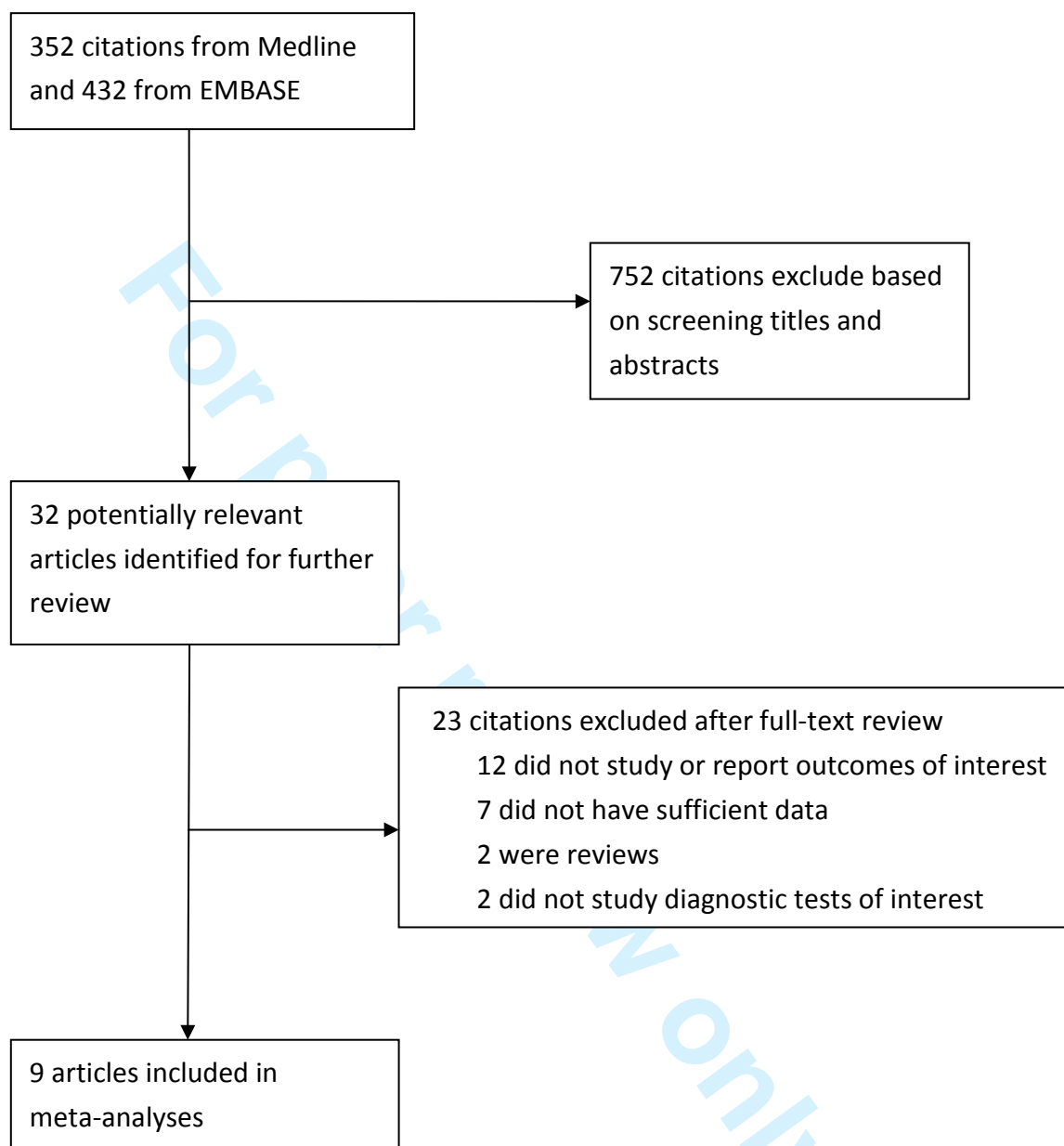
Author, year, country	Mean Age	Prevalence (N)	Follow-up time	Cutoff (mg/l)	AF type	Cardioversion	Sensitivity, Specificity	Adjusted odd ratio	Adjusted variables
Wazni O, 2005, USA <sup>1</sup>	67.3	0.68(111)	76 days	3.1	Persistent AF	Electric	59 %, 69 %	2.0 (1.2-3.2)	Age, sex, duration of AF, coronary artery disease, hypertension, left ventricular hypertrophy, LAD
Zarauza J, 2006, Spain <sup>2</sup>	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 <sup>3</sup>	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 <sup>4</sup>	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 <sup>5</sup>	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 <sup>6</sup>	65	0.68(56)	180 days	3.0	Persistent AF	Electric	60%, 83%	NA	NA
Rizos I, 2010, Greece <sup>7</sup>	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 <sup>8</sup>	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 <sup>9</sup>	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;

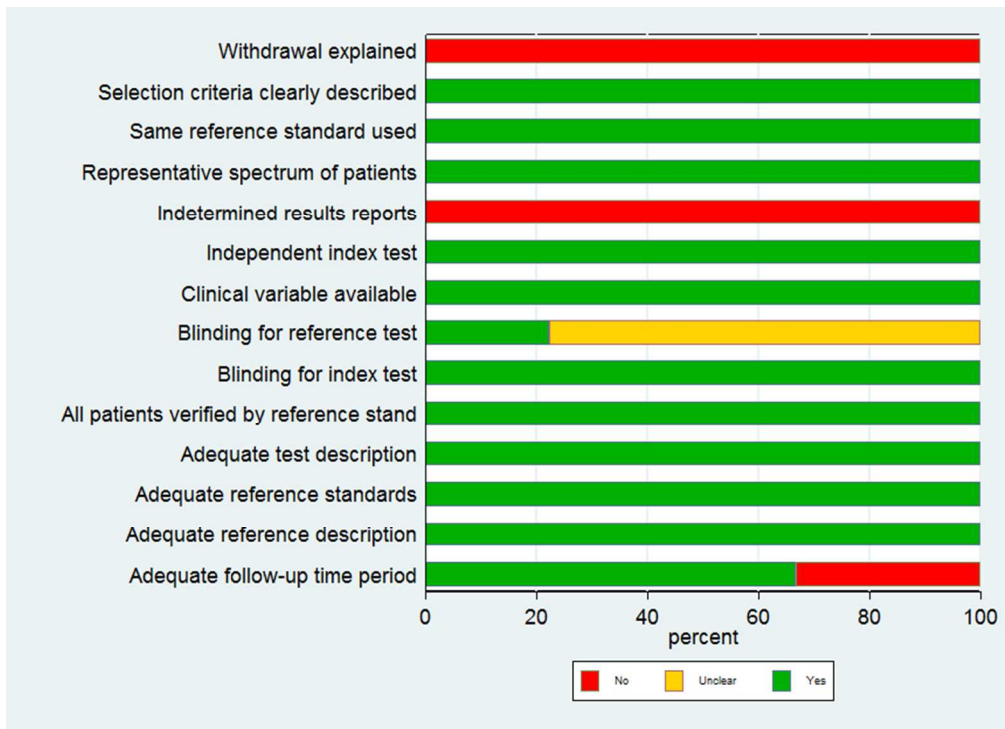
Table 2. Summary of pooled diagnostic accuracy indices

Variables	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio+	Likelihood ratio-	AUROC (95% CI)	I <sup>2</sup> (95% CI)	Diagnostic OR (95% CI)	Meta-regression P
Overall <sup>1-9</sup>	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 <sup>1,2,5,9</sup>	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 <sup>3,5-8</sup>	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 <sup>1-6,9</sup>	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 <sup>1-6,9</sup>	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

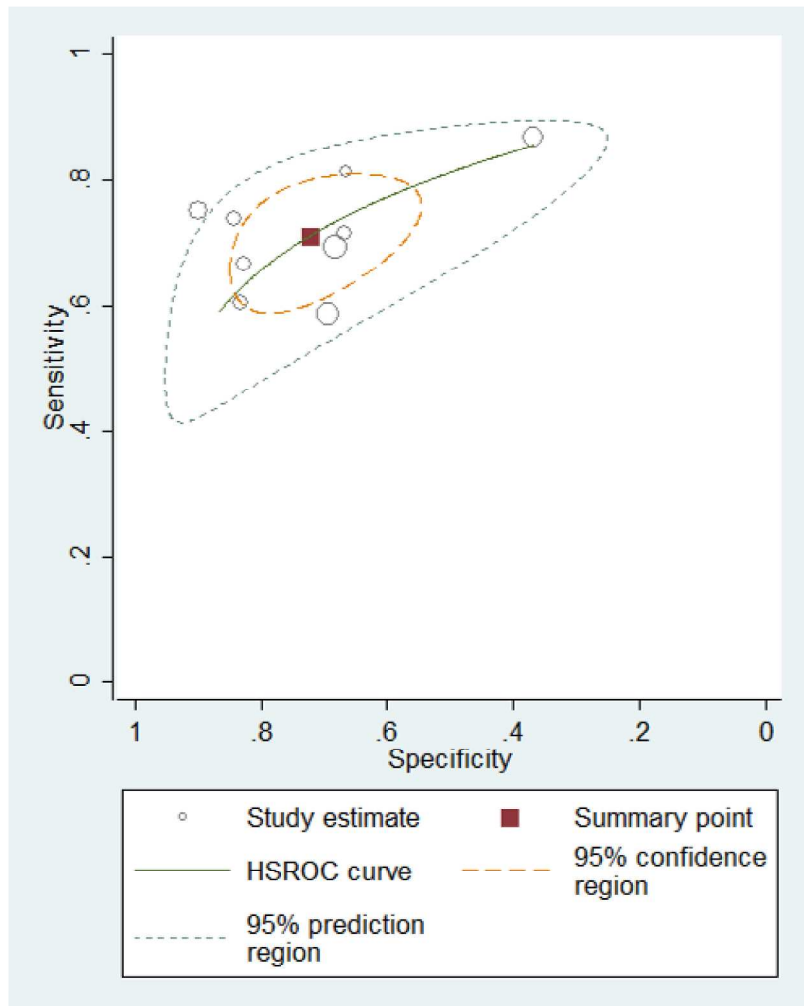


1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



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

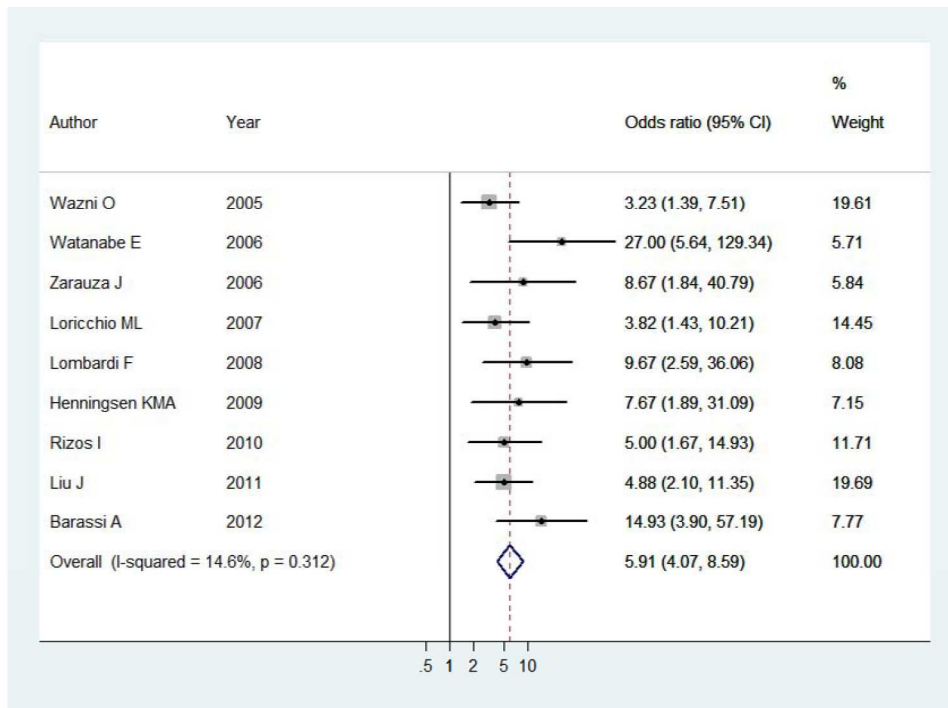
View only



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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



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

view only





# PRISMA 2009 Checklist

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	X
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>



## PRISMA 2009 Checklist

Page 1 of 2

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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Page 2 of 2

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004418.R1
Article Type:	Research
Date Submitted by the Author:	14-Jan-2014
Complete List of Authors:	Yo, Chia-Hung; Far Eastern Memorial Hospital, Department of Emergency Medicine Lee, Si-Huei; Taipei Veteran General Hospital, Department of Rehabilitation and Physical Medicine Chang, Shy-Shin; Chang Gung Memorial Hospital, Department of Family Medicine Lee, Chien-Hung; Medical Wisdom Consultants, Lee, Chien-Chang; National Taiwan University Hospital Yunlin Branch, Department of Emergency Medicine
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY, Hypertension < CARDIOLOGY, C - reactive protein, cardioversion, meta-analysis

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

3  
4 <sup>1</sup>Chia-Hung Yo MD, <sup>2</sup>Si-Huei Lee MD <sup>3,4</sup>Shy-Shin Chang MD, <sup>5</sup>Matthew  
5 Chien-Hung Lee PhD, JD, <sup>6,7</sup>Chien-Chang Lee MD, MSc

6  
7 <sup>1</sup>Department of Emergency Medicine, Far Eastern Memorial Hospital, New Taipei  
8 City, Taiwan.

9 <sup>2</sup>Department of Rehabilitation and Physical Medicine, Taipei Veteran  
10 General Hospital, Taipei, Taiwan

11 <sup>3</sup>Department of Family Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

12 <sup>4</sup>Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung  
13 University, Taoyuan, Taiwan.

14 <sup>5</sup>Medical Wisdom Consultants, Houston, USA

15 <sup>6</sup>Department of Epidemiology, Harvard School of Public Health, Boston, USA.

16 <sup>7</sup>Department of Emergency Medicine, National Taiwan University Hospital Yunlin  
17 Branch, Douliou, Taiwan

18 Address correspondence to

19 Chien-Chang Lee MD, MSc

20 Email: clee100@gmail.com

21 Postal Address: No 579 Sec 2 Yunlin Road, Douliou, Yunlin County 640, Taiwan

22 Telephone: +886-5-532-3911 ext. 2326

23 Fax: +886-2322-3150

24 Word count: 2535

25 Conflict of interest: None declared

1  
2  
3  
4 26 Abstract

5 27 Objectives: We performed a systematic review and meta-analysis of studies on  
6  
7  
8 28 high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are  
9  
10 29 predictive of atrial fibrillation (AF) recurrence after cardioversion.  
11  
12 30

13  
14 31 Design: Systematic review and meta-analysis.  
15  
16 32

17  
18  
19 33 Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of  
20  
21 34 the reference lists in the retrieved articles from inception to December 2013.  
22  
23 35

24  
25 36 Study eligibility criteria: This review selected observational studies in which the  
26  
27 37 measurements of serum CRP were used to predict atrial fibrillation recurrence. An  
28  
29 38 hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring  
30  
31 39 serum CRP to below 0.6 mg/dL.  
32  
33

34 40  
35  
36 41 Primary and secondary outcome measures: We summarized test performance  
37  
38 42 characteristics with the use of forest plots, hierarchical summary receiver operating  
39  
40 43 characteristic (HSROC) curves, and bivariate random effects models. Meta-regression  
41  
42 44 analysis was performed to explore the source of heterogeneity.  
43  
44 45

45  
46 46 Results: We included nine qualifying studies comprising a total of 347 patients with AF  
47  
48 47 recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an  
49  
50 48 independent predictor of AF recurrence after cardioversion (summary adjusted odds  
51  
52 49 ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for  
53  
54 50 hs-CRP was 71.0% (95% CI: 63% to 78%) and 72.0% (61% to 81%), respectively.  
55  
56 51

57  
58 51 Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence  
59  
60

52 (77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73%  
53 sensitivity, 71% specificity).

54

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

58

59 Strengths and limitations of this study

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

74

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

77

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
6078  
79 Introduction

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

98  
99 C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response  
100 to proinflammatory cytokines, notably interleukin-6, and other endogenous signals of  
101 innate immunity or tissue damage. CRP has recently been shown to be associated with  
102 cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is  
103 elevated in patients with AF.<sup>7</sup> However, 5 of the 6 studies included in that analysis

1  
2  
3  
4 104 used traditional automated immunonephelometric assays to measure CRP.  
5  
6 105 Unfortunately, those assays are insufficiently sensitive for measuring the low level of  
7  
8 106 inflammation associated with AF. A newer enzyme immunoassay, namely  
9  
10 107 high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL  
11  
12 108 and may further enhance the predictability of AF recurrence.<sup>8</sup> Since 2006, several  
13  
14 109 studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been  
15  
16 110 published,<sup>9-19</sup> warranting a systemic and quantitative summary of current evidence on  
17  
18 111 the accuracy of CRP in predicting AF recurrence after cardioversion.  
19  
20  
21 112

## 22 23 113 Methods

### 24 25 114 Identification of Studies

26  
27 115 General bibliographic databases (MEDLINE and EMBASE) were searched from  
28  
29 116 inception to April 2013. The medical subject heading (MeSH) and text words for the  
30  
31 117 term C -reactive protein were combined with the MeSH term “diagnosis of atrial  
32  
33 118 fibrillation”. The search was limited to human studies with no language restrictions.  
34  
35 119 In addition to the electronic search, reference lists in all known reviews and primary  
36  
37 120 studies were checked manually.  
38  
39  
40 121

### 41 42 122 Selection Criteria

43  
44 123 This review focused on observational studies in which the measurements of serum  
45  
46 124 CRP were used to predict atrial fibrillation recurrence. The population of interest  
47  
48 125 comprised patients with paroxysmal or persistent AF who underwent electric  
49  
50 126 cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was  
51  
52 127 defined as AF documented by ECG at any time after the cardioversion during the  
53  
54 128 follow-up period. Generally, patients were instructed to return to the clinic if the  
55  
56 129 symptoms such as palpitations, shortness of breath, or chest discomfort developed  
57  
58  
59  
60



1  
2  
3  
4 130 after cardioversion. We included studies using a cohort design or case-control design  
5  
6 131 with appropriate controls. Two reviewers independently assessed eligible articles for  
7  
8 132 inclusion. Disagreements were initially resolved by consensus and using arbitration  
9  
10 133 by a third reviewer if consensus could not be reached by the two reviewers. We  
11  
12 134 extracted data from the included studies. Data collected include study design,  
13  
14 135 participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of  
15  
16 136 follow-up period, and recurrence of AF. One reviewer extracted the data and a second  
17  
18 137 reviewer independently verified the correctness of the extracted data.  
19  
20  
21 138

### 22 23 139 Quality Assessment

24  
25 140 We assessed the methodological quality of the selected studies using a well-validated  
26  
27 141 tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of  
28  
29 142 Diagnostic Accuracy Studies, QUADAS).<sup>20</sup> The QUADAS instrument scrutinizes  
30  
31 143 characteristics of study designs, population, index tests, and reference standards that  
32  
33 144 may be associated with risk of bias. These features included the spectrum of patients,  
34  
35 145 whether index tests and reference standards were evaluated and interpreted  
36  
37 146 independently to avoid incorporation bias, and whether all patients underwent the  
38  
39 147 same reference standards to avoid differential or partial verification bias.  
40  
41  
42 148

### 43 44 45 149 Data Abstraction

46  
47 150 One reviewer independently extracted the data and a second reviewer independently  
48  
49 151 verified the data. Extracted data comprised the following: overall study characteristics  
50  
51 152 (including the first author, country, language, and date of publication); patient  
52  
53 153 characteristics (including age range and pre-existing atrial fibrillation); quantitative  
54  
55 154 data required for construction of a 2 x 2 table (including number of participants,  
56  
57 155 sensitivity, specificity, and recurrence case number); information regarding the  
58  
59  
60

1  
2  
3  
4 156 hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or  
5  
6 157 semi-quantitative nature of the test); and study settings. In studies that reported  
7  
8 158 multiple pairs of sensitivity and specificity data, we consistently used the data with  
9  
10 159 the highest Youden index (sensitivity + specificity - 1) and performed a sensitivity  
11  
12 160 analysis at a later stage.

13  
14 161

### 15 162 Quantitative Data Synthesis

16 163 We performed a meta-analysis of diagnostic test accuracy of CRP testing for the  
17  
18 164 prediction of recurrent AF. When  $2 \times 2$  tables contained 0 cells, we performed  
19  
20 165 continuity correction by adding 0.5 to each cell. We calculated the pooled sensitivity  
21  
22 166 and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio  
23  
24 167 of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate  
25  
26 168 meta-analysis model.<sup>21</sup> Likelihood ratios were then translated to post-test probability  
27  
28 169 by use of Fagan's plot. We constructed a hierarchical summary receiver operating  
29  
30 170 characteristic (HSROC) curve that plots sensitivity versus specificity and calculated  
31  
32 171 the area under the curve (AUROC).<sup>22</sup> We evaluated the degree of between-study  
33  
34 172 heterogeneity by using the  $I^2$  test.<sup>23</sup> To explore the clinical sources of heterogeneity,  
35  
36 173 we defined the potential explanatory variables *a priori* and performed subgroup  
37  
38 174 analysis to see if the accuracy estimates changed significantly across various  
39  
40 175 subgroups. The presence and the effect of publication bias were examined using a  
41  
42 176 combination of the Egger tests.<sup>24</sup> Statistical analyses were conducted using the  
43  
44 177 statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably  
45  
46 178 with the user-written "midas" and "metandi" programs. All statistical tests were  
47  
48 179 two-sided and statistical significance was defined as a P value less than .05.  
49  
50  
51  
52  
53  
54  
55  
56  
57

58 180

### 59 181 Search Results and Study Characteristics

1  
2  
3  
4 182 The flow of inclusion and exclusion is summarized in Figure 1. Using our search  
5  
6 183 criteria, we identified 784 studies, of which 352 were from PubMed and 432 were  
7  
8 184 from EMBASE. A total of 752 citations were excluded based on pre-defined criteria.  
9  
10 185 No additional citations were identified from the reference lists. A total of 32 articles  
11  
12 186 were retrieved for full-text review, and 23 were excluded due to various reasons  
13  
14 187 detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in  
15  
16 188 predicting AF recurrence after cardioversion were finally included in the  
17  
18 189 meta-analysis. The 9 studies included a total of 682 patients with AF after successful  
19  
20 190 cardioversion, of which 347 (50.9%) developed recurrence.  
21  
22  
23  
24

#### 25 192 Characteristics of included studies

26  
27 193 Table 1 lists the study and population characteristics of the 9 patient populations even  
28  
29 194 if we had additional 5 studies that don't have sufficient data for statistical analysis<sup>25-29</sup>.  
30  
31 195 The mean age of patients in the included studies ranged from 55.1 years to 67.9 years  
32  
33 196 and the mean follow-up period ranged from 30 days to 1 year. Seven studies included  
34  
35 197 patients with persistent AF, while 2 studies included patients with paroxysmal AF.  
36  
37 198 Seven studies used electric shock, one used circumferential pulmonary vein isolation  
38  
39 199 (also known as electric ablation), and the other used intravenous amiodarone as the  
40  
41 200 primary method for cardioversion. A total of seven studies provided multivariate  
42  
43 201 (adjusted) odds ratios to evaluate the independent predictive value of CRP levels.  
44  
45 202 These studies generally adjusted for potential predictors of AF recurrence such as age,  
46  
47 203 sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All  
48  
49 204 studies showed that CRP was a significant independent predictor of AF recurrence.  
50  
51 205 Associated adjusted ratios and adjusted variables are summarized in table 1.  
52  
53  
54  
55

#### 56 206 57 207 Quality assessment

1  
2  
3 208 Results of the quality assessment of studies of diagnostic accuracy are summarized in  
4  
5 209 figure 2. All studies were prospective and enrolled consecutive outpatients with AF  
6  
7 210 after cardioversion. Three studies had a short follow-up period (i.e.  $\leq 0.5$  or 1 year).  
8  
9 211 Although most of the studies did not indicate whether physicians were blinded to the  
10  
11 212 index tests when diagnosing AF recurrence, the determination of AF recurrence was  
12  
13 213 not affected by the knowledge of hs-CRP test results and risk of incorporation bias  
14  
15 214 was minimal. None of the studies reported the undetermined results or withdrawals.  
16  
17 215

## 216 Diagnostic accuracy indices

### 217 Sensitivity, specificity, and diagnostic odds ratio

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

229

### 230 Subgroup analysis and meta-regression

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

1  
2  
3  
4 234 in predicting long-term over short-term AF recurrence. Excluding two studies not  
5  
6 235 using electric shock as the primary cardioversion method did not significantly alter  
7  
8 236 the predictive accuracy. Similarly, *focusing the study patients on persistent AF*  
9  
10 237 *population* had similar results as compared with the main overall analysis.  
11  
12 238 Exploratory meta-regression analysis did not find that any pre-specified covariate  
13  
14 239 significantly changed the effect estimate.  
15  
16  
17 240

## 18 241 Discussion

20 242 This meta-analysis shows that elevated CRP levels are independently predictive of AF  
21  
22 243 recurrence in patients with persistent or paroxysmal AF who have undergone  
23  
24 244 successful cardioversion. This finding supports that measurement of CRP levels  
25  
26 245 before cardioversion can aid in the prediction of AF recurrence. Despite the modest  
27  
28 246 pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the  
29  
30 247 high recurrence rate of AF observed in these included studies. A positive hs-CRP test  
31  
32 248 result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months  
33  
34 249 following cardioversion.  
35  
36  
37 250

38  
39  
40 251 Previous studies have examined risk factors that predict AF recurrence. Traditional  
41  
42 252 clinical risk factors for recurrence include history of multiple AF episodes, use of  
43  
44 253 diuretic treatment, higher CHADS-2 (Congestive heart failure, history of  
45  
46 254 Hypertension, Age $\geq$ 75 years, Diabetes mellitus, and past history of Stroke or TIA  
47  
48 255 doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C  
49  
50 256 drugs, and digitalis.<sup>30,31</sup> Although each of these factors could predict AF recurrence  
51  
52 257 with some accuracy, a quantitative combination of these predictors is not available,  
53  
54 258 and the clinical utility of these variables remains questionable. This also suggests that  
55  
56 259 a multivariate prediction model should be developed for AF recurrence, and that  
57  
58  
59  
60

1  
2  
3 260 hsCRP should be a candidate for inclusion in the model.  
4  
5 261  
6  
7 262 During the past decade, serum biomarkers have emerged as practical tools to help in  
8  
9 263 the early identification of patients at high risk for various cardiac events. Elevation of  
10  
11 264 inflammatory markers is associated with sudden cardiac death in patients with heart  
12  
13 265 failure or coronary artery disease, and onset of ventricular arrhythmia.<sup>32-35</sup> Of note,  
14  
15 266 there is abundant evidence that elevated serum levels of CRP are associated with the  
16  
17 267 genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical  
18  
19 268 inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in  
20  
21 269 response to proinflammatory cytokine stimulation. Although the pathophysiology of  
22  
23 270 AF remains elusive, there is pathophysiological evidence supporting the role of  
24  
25 271 inflammation in the initiation, maintenance, and perpetuation of AF.<sup>36</sup> Clinically, AF  
26  
27 272 is frequently associated with local inflammatory diseases such as myocarditis or  
28  
29 273 pericarditis, and systemic inflammatory status, such as post-operative state and severe  
30  
31 274 sepsis. Histologically, structural remodeling of the atria manifested by loss of  
32  
33 275 myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.<sup>37</sup>  
34  
35 276 Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial  
36  
37 277 biopsy specimens from AF patients.<sup>38</sup> Activated inflammatory cells in conjunction  
38  
39 278 with reactive oxygen species, cytokines, and growth factors, may ultimately lead to  
40  
41 279 matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of  
42  
43 280 immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors,  
44  
45 281 or glucocorticoids modulate the course of AF.<sup>39</sup>  
46  
47 282  
48  
49 283 In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator  
50  
51 284 of new onset AF and AF recurrence after successful cardioversion.<sup>34,35,40</sup> BNP is also  
52  
53 285 produced in response to atrial pressure and volume overload and there is evidence that  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 286 BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed  
5  
6 287 that the standardized mean difference in plasma BNP level between patients with  
7  
8 288 non-recurrence and patients with recurrence was -1.35 (95% confidence interval -2.17,  
9  
10 289 -0.53).<sup>41</sup> Data on sensitivity and specificity in that study were not available. The  
11  
12 290 comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus  
13  
14 291 requires further analysis.  
15

16  
17 292

18 293 There are both strengths and limitations in our study. Considering the limitation of  
19  
20 294 sensitivity and specificity in clinical interpretation, we reported summary likelihood  
21  
22 295 ratios (LRs) as an ancillary measure of predictive accuracy. The LR indicates how  
23  
24 296 much a given CRP testing result increases or decreases the probability of recurrence  
25  
26 297 of AF. Post-test probabilities can be derived from pre-test probabilities and LR,  
27  
28 298 which are an important clinical parameter for major clinical decision making. Second,  
29  
30 299 we used a bivariate random effect model to account for the inherent negative  
31  
32 300 correlation arising from different cutoff values used in different studies, and occurring  
33  
34 301 between the logit TPR and FPR. Third, we performed sensitivity analysis by  
35  
36 302 restricting analysis within two broad categories of follow-up duration. Results of  
37  
38 303 sensitivity analysis did not show a significantly different overall predictive accuracy  
39  
40 304 between long-term and short-term prediction of AF recurrence. Nonetheless, it is  
41  
42 305 noteworthy that the sensitivity may be over estimated in our study under the  
43  
44 306 hypothesis where the inflammation may be symptomatic since none of the studies  
45  
46 307 provided withdrawal and undetermined results, and the ascertainment of AF was  
47  
48 308 passive. This event further introduces the differential verification bias. Moreover, our  
49  
50 309 meta-analysis is restricted to distinguish hsCRP levels above or below 0.6 mg/dL  
51  
52 310 because the authors in only one of the studies claimed to possess such capability.  
53  
54 311 Finally, due to the lack of individual data, it is hard to determine whether the area  
55  
56  
57  
58  
59  
60



1  
2  
3  
4 312 under ROC (AUC) can be improved by the new assay either on overall or on  
5  
6 313 individual studies. Overall, as assessed by the heterogeneity of dOR, the included  
7  
8 314 studies evaluating CRP levels and AF recurrence strongly tended toward  
9  
10 315 between-study variability (heterogeneity). Potential sources of between-study  
11  
12 316 variability included differences in incidence of AF recurrence, different threshold  
13  
14 317 values of CRP concentration used, and different duration for follow-up. Another  
15  
16 318 limitation was the strategy we used to determine the optimal cutoff value. Most  
17  
18 319 studies determined an optimal cutoff value to maximize both sensitivity and  
19  
20 320 specificity. Although a single cutoff value is straightforward in clinical interpretation,  
21  
22 321 it may make a marker neither sensitive nor specific enough to rule out or rule in an  
23  
24 322 outcome of interest. A two cut-off value strategy, with one using a lower cutoff value  
25  
26 323 to optimize the sensitivity (rule-out value) and the other using a higher cutoff value to  
27  
28 324 optimize the specificity (rule-in value), would make better use of the information that  
29  
30 325 a biomarker with a continuous value could provide. Current summary estimates based  
31  
32 326 on the one cutoff point may thus have under-evaluated the clinical usefulness of  
33  
34 327 hs-CRP assays. To make the best use of the biomarker information by adopting a two  
35  
36 328 cutoff point strategy or a multi-cutoff point risk classification strategy, an individual  
37  
38 329 data meta-analysis would be needed to overcome the limitations of this aggregated  
39  
40 330 data meta-analysis.

41  
42  
43  
44 331

## 45 332 Conclusions

46  
47 333 Baseline CRP levels before cardioversion can independently predict AF recurrence  
48  
49 334 after successful cardioversion. Given the high recurrence rate reported in most series,  
50  
51 335 the modest positive likelihood ratio for hs-CRP assays still has high positive  
52  
53 336 predictive value. Future studies should focus on the evaluation of two or multiple  
54  
55 337 cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation



1  
2  
3  
4 338 algorithms should be considered.  
5  
6 339  
7  
8 340  
9

10 341 Acknowledgement

11 342 This study was supported by grants of Far Eastern Memorial Hospital, Taiwan  
12  
13  
14 343 (FEMH-2013\_D\_036)  
15

16 344  
17  
18  
19 345  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## References

1. Fabbri G, Maggioni AP. A review of the epidemiological profile of patients with atrial fibrillation and heart failure. *Expert review of cardiovascular therapy*. Sep 2012;10(9):1133-1140.
2. Menezes AR, Lavie CJ, DiNicolantonio JJ, et al. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. *Mayo Clinic proceedings. Mayo Clinic*. Apr 2013;88(4):394-409.
3. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. May 7 2013;61(18):1935-1944.
4. Manlucu J, Brancato S, Lane C, Kazemian P, Michaud GF. Contemporary approaches to persistent atrial fibrillation. *Expert review of cardiovascular therapy*. Nov 2012;10(11):1421-1435.
5. Disertori M, Lombardi F, Barlera S, et al. Clinical characteristics of patients with asymptomatic recurrences of atrial fibrillation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. *American heart journal*. Aug 2011;162(2):382-389.
6. Letsas KP, Weber R, Burkle G, et al. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Feb 2009;11(2):158-163.
7. Liu T, Li L, Korantzopoulos P, Goudevenos JA, Li G. Meta-analysis of association between C-reactive protein and immediate success of electrical cardioversion in persistent atrial fibrillation. *The American journal of cardiology*. Jun 15 2008;101(12):1749-1752.
8. Roberts WL, Sedrick R, Moulton L, Spencer A, Rifai N. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. *Clinical chemistry*. Apr 2000;46(4):461-468.
9. Celebi OO, Celebi S, Canbay A, Ergun G, Aydogdu S, Diker E. The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion. *Cardiology*. 2011;118(3):168-174.
10. Barassi A, Pezzilli R, Morselli-Labate AM, et al. Serum amyloid a and C-reactive protein independently predict the recurrences of atrial fibrillation

- 1  
2  
3 after cardioversion in patients with preserved left ventricular function. *The*  
4 *Canadian journal of cardiology*. Sep-Oct 2012;28(5):537-541.
- 5  
6 11. Hatzinikolaou-Kotsakou E, Tziakas D, Hotidis A, et al. Relation of C-reactive  
7 protein to the first onset and the recurrence rate in lone atrial fibrillation. *The*  
8 *American journal of cardiology*. Mar 1 2006;97(5):659-661.
- 9  
10 12. Henningsen KM, Therkelsen SK, Bruunsgaard H, Krabbe KS, Pedersen BK,  
11 Svendsen JH. Prognostic impact of hs-CRP and IL-6 in patients with persistent  
12 atrial fibrillation treated with electrical cardioversion. *Scandinavian journal of*  
13 *clinical and laboratory investigation*. 2009;69(3):425-432.
- 14  
15 13. Liu J, Fang PH, Dibs S, Hou Y, Li XF, Zhang S. High-sensitivity C-reactive  
16 protein as a predictor of atrial fibrillation recurrence after primary  
17 circumferential pulmonary vein isolation. *Pacing and clinical*  
18 *electrophysiology : PACE*. Apr 2011;34(4):398-406.
- 19  
20 14. Lombardi F, Tundo F, Belletti S, Mantero A, Melzi D'eril G V. C-reactive  
21 protein but not atrial dysfunction predicts recurrences of atrial fibrillation after  
22 cardioversion in patients with preserved left ventricular function. *Journal of*  
23 *cardiovascular medicine (Hagerstown, Md.)*. Jun 2008;9(6):581-588.
- 24  
25 15. Loricchio ML, Cianfrocca C, Pasceri V, et al. Relation of C-reactive protein to  
26 long-term risk of recurrence of atrial fibrillation after electrical cardioversion.  
27 *The American journal of cardiology*. May 15 2007;99(10):1421-1424.
- 28  
29 16. Wazni O, Martin DO, Marrouche NF, et al. C reactive protein concentration and  
30 recurrence of atrial fibrillation after electrical cardioversion. *Heart (British*  
31 *Cardiac Society)*. Oct 2005;91(10):1303-1305.
- 32  
33 17. Rizos I, Rigopoulos AG, Kalogeropoulos AS, et al. Hypertension and  
34 paroxysmal atrial fibrillation: a novel predictive role of high sensitivity  
35 C-reactive protein in cardioversion and long-term recurrence. *Journal of human*  
36 *hypertension*. Jul 2010;24(7):447-457.
- 37  
38 18. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity  
39 C-reactive protein is predictive of successful cardioversion for atrial fibrillation  
40 and maintenance of sinus rhythm after conversion. *International journal of*  
41 *cardiology*. Apr 14 2006;108(3):346-353.
- 42  
43 19. Zarauza J, Rodriguez Lera MJ, Farinas Alvarez C, et al. [Relationship between  
44 C-reactive protein level and early recurrence of atrial fibrillation after electrical  
45 cardioversion]. *Revista espanola de cardiologia*. Feb 2006;59(2):125-129.
- 46  
47 20. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of  
48 diagnostic test accuracy. *Annals of internal medicine*. Dec 16  
49 2008;149(12):889-897.
- 50  
51 21. Arends LR, Hamza TH, van Houwelingen JC, Heijenbrok-Kal MH, Hunink MG,  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 Stijnen T. Bivariate random effects meta-analysis of ROC curves. *Medical*  
4 *decision making : an international journal of the Society for Medical Decision*  
5 *Making*. Sep-Oct 2008;28(5):621-638.
- 6  
7 22. Harbord RM, Whiting P, Sterne JA, et al. An empirical comparison of methods  
8 for meta-analysis of diagnostic accuracy showed hierarchical models are  
9 necessary. *Journal of clinical epidemiology*. Nov 2008;61(11):1095-1103.
- 10  
11 23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in  
12 meta-analyses. *BMJ (Clinical research ed.)*. Sep 6 2003;327(7414):557-560.
- 13  
14 24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis  
15 detected by a simple, graphical test. *BMJ (Clinical research ed.)*. Sep 13  
16 1997;315(7109):629-634.
- 17  
18 25. Buob A, Jung J, Siaplaouras S, Neuberger HR, Mewis C. Discordant regulation  
19 of CRP and NT-proBNP plasma levels after electrical cardioversion of  
20 persistent atrial fibrillation. *Pacing and clinical electrophysiology : PACE*. Jun  
21 2006;29(6):559-563.
- 22  
23 26. Cosgrave J, Foley JB, Bahadur K, Bennett K, Crean P, Walsh MJ. Inflammatory  
24 markers are not associated with outcomes following elective external  
25 cardioversion. *International journal of cardiology*. Jun 28  
26 2006;110(3):373-377.
- 27  
28 27. Ellinor PT, Low A, Patton KK, Shea MA, MacRae CA. C-Reactive protein in  
29 lone atrial fibrillation. *The American journal of cardiology*. May 1  
30 2006;97(9):1346-1350.
- 31  
32 28. Korantzopoulos P, Kolettis TM, Kountouris E, Siogas K, Goudevenos JA.  
33 Variation of inflammatory indexes after electrical cardioversion of persistent  
34 atrial fibrillation. Is there an association with early recurrence rates?  
35 *International journal of clinical practice*. Aug 2005;59(8):881-885.
- 36  
37 29. Psychari SN, Chatzopoulos D, Iliodromitis EK, Apostolou TS, Kremastinos DT.  
38 C-reactive protein, interleukin 6, and N-terminal pro-brain natriuretic peptide  
39 following cardioversion of atrial fibrillation: is there a role of biomarkers in  
40 arrhythmia recurrence? *Angiology*. May 2011;62(4):310-316.
- 41  
42 30. Komatsu T, Sato Y, Ozawa M, et al. Relationship between CHADS2 score and  
43 efficacy of antiarrhythmic drug therapy in patients with paroxysmal atrial  
44 fibrillation. *Circulation journal : official journal of the Japanese Circulation*  
45 *Society*. Feb 25 2013;77(3):639-645.
- 46  
47 31. Letsas KP, Efremidis M, Giannopoulos G, et al. CHADS2 and CHA2DS2-VASc  
48 scores as predictors of left atrial ablation outcomes for paroxysmal atrial  
49 fibrillation. *Europace : European pacing, arrhythmias, and cardiac*  
50 *electrophysiology : journal of the working groups on cardiac pacing,*  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Jun 28 2013.
32. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation*. Jun 4 2002;105(22):2595-2599.
33. Parekh RS, Plantinga LC, Kao WH, et al. The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney international*. Nov 2008;74(10):1335-1342.
34. Streitner F, Kuschyk J, Veltmann C, et al. Role of proinflammatory markers and NT-proBNP in patients with an implantable cardioverter-defibrillator and an electrical storm. *Cytokine*. Sep 2009;47(3):166-172.
35. Korngold EC, Januzzi JL, Jr., Gantzer ML, Moorthy MV, Cook NR, Albert CM. Amino-terminal pro-B-type natriuretic peptide and high-sensitivity C-reactive protein as predictors of sudden cardiac death among women. *Circulation*. Jun 9 2009;119(22):2868-2876.
36. Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *European heart journal*. Oct 2005;26(20):2083-2092.
37. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovascular research*. May 2002;54(2):230-246.
38. Van Wagoner DR. Oxidative Stress and Inflammation in Atrial Fibrillation: Role in Pathogenesis and Potential as a Therapeutic Target. *Journal of Cardiovascular Pharmacology*. 2008;52(4):306-313  
310.1097/FJC.1090b1013e31817f39398.
39. Moro C, Hernandez-Madrid A, Matia R. Non-antiarrhythmic drugs to prevent atrial fibrillation. *American journal of cardiovascular drugs : drugs, devices, and other interventions*. 2010;10(3):165-173.
40. den Uijl DW, Delgado V, Tops LF, et al. Natriuretic peptide levels predict recurrence of atrial fibrillation after radiofrequency catheter ablation. *American heart journal*. Jan 2011;161(1):197-203.
41. Tang Y, Yang H, Qiu J. Relationship between brain natriuretic peptide and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. *The Journal of international medical research*. 2011;39(5):1618-1624.

1  
2  
3  
4 Figure legends  
5  
6

7 Figure 1. **A simplified flow chart to identify and to include studies.** Amongst 752  
8  
9 citations in MEDLINE and EMBASE from inception to December 2013, a search  
10  
11 limited to human studies using “C-reactive protein” and the MeSH term “diagnosis of  
12  
13 atrial fibrillation” resulted in 32 potentially relevant articles for further review. After  
14  
15 careful scrutinization on full text, 9 articles were left for meta-analysis.  
16  
17

18  
19  
20  
21 Figure 2. **The quality assessment of diagnostic accuracy on studies.** A spectrum of  
22  
23 features were analysed to avoid bias using a well-validated tool called Quality  
24  
25 Assessment of Diagnostics Accuracy Studies (QUADAS). Percentage for each feature  
26  
27 was independently evaluated among the studies. It is worthy of attention that none of  
28  
29 the studies explained the withdrawal and reported indetermined results, likely to  
30  
31 compromise the quality of diagnostic accuracy.  
32  
33  
34  
35  
36

37  
38  
39 Figure 3. **The ROC curve of hs-CRP.** Our analysis suggests it is highly possible to  
40  
41 predict atrial fibrillation using C-reative protein since the area under the curve  
42  
43 generates a measurement of discrimination ~0.77. The overall sensitivity and  
44  
45 specificity are relatively high. We have 5 out 9 studies that fall in the 95% CI region,  
46  
47  
48 while 8 out 9 in the 95% prediction region.  
49  
50  
51

52  
53 Figure 4. **The forest plot of the odds ratios (ORs).** Our study indicates that  
54  
55 hsCRP-positive patients are ~5.91 times more likely to develop a **recurrence** of **atrial**  
56  
57  
58  
59  
60

1  
2  
3  
4 fibrillation than hsCRP-negative patients are. The estimated sensitivity and specificity  
5  
6  
7 were relatively consistent across studies ( $I^2=14.6\%$ ).  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



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 <sup>16</sup>	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 <sup>19</sup>	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 <sup>18</sup>	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 <sup>15</sup>	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 <sup>14</sup>	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 <sup>12</sup>	65	0.68(56)	180 days	3.0	Persistent AF	Electric	60%, 83%	7.7 (1.9-31.1) *	NA
Rizos I, 2010, Greece <sup>17</sup>	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 <sup>13</sup>	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 <sup>10</sup>	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 <sup>2</sup> (95% CI)	Diagnostic OR (95% CI)	Meta-regression P	Egger's test P
Overall <sup>10,12-19</sup>	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 <sup>10,14,16,19</sup>	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 <sup>12-14,17,18</sup>	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 <sup>10,12,14-16,18,19</sup>	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 <sup>10,12,14-16,18,19</sup>	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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

3  
4 <sup>1</sup>Chia-Hung Yo MD, <sup>2</sup>Si-Huei Lee MD <sup>3,4</sup>Shy-Shin Chang MD, <sup>5</sup>Matthew  
5 Chien-Hung Lee PhD, JD, <sup>6,7,5</sup>Chien-Chang Lee MD, MSc

6  
7 <sup>1</sup>Department of Emergency Medicine, Far Eastern Memorial Hospital, New Taipei  
8 City, Taiwan.

9 <sup>2</sup>Department of Rehabilitation and Physical Medicine, Taipei Veteran  
10 General Hospital, Taipei, Taiwan

11 <sup>3</sup>Department of Family Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

12 <sup>4</sup>Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung  
13 University, Taoyuan, Taiwan.

14 <sup>5</sup>Medical Wisdom Consultants, Houston, USA

15 <sup>6,4</sup>Department of Epidemiology, Harvard School of Public Health, Boston, USA.

16 <sup>7,5</sup>Department of Emergency Medicine, National Taiwan University Hospital Yunlin  
17 Branch, Douliou, Taiwan

18 Address correspondence to

19 Chien-Chang Lee MD, MSc

20 Email: clee100@gmail.com

21 Postal Address: No 579 Sec 2 Yunlin Road, Douliou, Yunlin County 640, Taiwan

22 Telephone: +886-5-532-3911 ext. 2326

23 Fax: +886-2322-3150

24 Word count: 2535

25 Conflict of interest: None declared

1  
2  
3  
4 26 Abstract

5 27 Objectives: We performed a systematic review and meta-analysis of studies on  
6  
7  
8 28 high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are  
9  
10 29 predictive of atrial fibrillation (AF) recurrence after cardioversion.  
11  
12 30

13  
14 31 Design: Systematic review and meta-analysis.  
15  
16 32

17  
18  
19 33 Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of  
20  
21 34 the reference lists in the retrieved articles from inception to December 2013.  
22  
23 35

24  
25 36 Study eligibility criteria: This review selected observational studies in which the  
26  
27 37 measurements of serum CRP were used to predict atrial fibrillation recurrence. An  
28  
29 38 hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring  
30  
31 39 serum CRP to below 0.6 mg/dL.  
32  
33 40

34  
35  
36 41 Primary and secondary outcome measures: We summarized test performance  
37  
38 42 characteristics with the use of forest plots, hierarchical summary receiver operating  
39  
40 43 characteristic (HSROC) curves, and bivariate random effects models. Meta-regression  
41  
42 44 analysis was performed to explore the source of heterogeneity.  
43  
44 45

45  
46 46 Results: We included nine qualifying studies comprising a total of 347 patients with AF  
47  
48 47 recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an  
49  
50 48 independent predictor of AF recurrence after cardioversion (summary adjusted odds  
51  
52 49 ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for  
53  
54 50 hs-CRP was 71.0% (95% CI: 63% to 78%) and 72.0% (61% to 81%), respectively.  
55  
56 51

57  
58 51 Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence  
59  
60

52 (77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73%  
53 sensitivity, 71% specificity).

54

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

58

59 Strengths and limitations of this study

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

74

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

77

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
6078  
79 Introduction

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

98  
99 C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response  
100 to proinflammatory cytokines, notably interleukin-6, and other endogenous signals of  
101 innate immunity or tissue damage. CRP has recently been shown to be associated with  
102 cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is  
103 elevated in patients with AF.<sup>7</sup> However, 5 of the 6 studies included in that analysis

1  
2  
3  
4 104 used traditional automated immunonephelometric assays to measure CRP.  
5  
6 105 Unfortunately, those assays are insufficiently sensitive for measuring the low level of  
7  
8 106 inflammation associated with AF. A newer enzyme immunoassay, namely  
9  
10 107 high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL  
11  
12 108 and may further enhance the predictability of AF recurrence.<sup>8</sup> Since 2006, several  
13  
14 109 studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been  
15  
16 110 published,<sup>9-19</sup> warranting a systemic and quantitative summary of current evidence on  
17  
18 111 the accuracy of CRP in predicting AF recurrence after cardioversion.  
19  
20  
21 112

## 22 23 113 Methods

### 24 114 Identification of Studies

25  
26 115 General bibliographic databases (MEDLINE and EMBASE) were searched from  
27  
28 116 inception to April 2013. The medical subject heading (MeSH) and text words for the  
29  
30 117 term C -reactive protein were combined with the MeSH term “diagnosis of atrial  
31  
32 118 fibrillation”. The search was limited to human studies with no language restrictions.  
33  
34  
35 119 In addition to the electronic search, reference lists in all known reviews and primary  
36  
37 120 studies were checked manually.  
38  
39  
40 121

### 41 42 122 Selection Criteria

43  
44 123 This review focused on observational studies in which the measurements of serum  
45  
46 124 CRP were used to predict atrial fibrillation recurrence. The population of interest  
47  
48 125 comprised patients with paroxysmal or persistent AF who underwent electric  
49  
50 126 cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was  
51  
52 127 defined as AF documented by ECG at any time after the cardioversion during the  
53  
54 128 follow-up period. Generally, patients were instructed to return to the clinic if the  
55  
56 129 symptoms such as palpitations, shortness of breath, or chest discomfort developed  
57  
58  
59  
60

1  
2  
3  
4 130 after cardioversion. We included studies using a cohort design or case-control design  
5  
6 131 with appropriate controls. Two reviewers independently assessed eligible articles for  
7  
8 132 inclusion. Disagreements were initially resolved by consensus and using arbitration  
9  
10 133 by a third reviewer if consensus could not be reached by the two reviewers. We  
11  
12 134 extracted data from the included studies. Data collected include study design,  
13  
14 135 participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of  
15  
16 136 follow-up period, and recurrence of AF. One reviewer extracted the data and a second  
17  
18 137 reviewer independently verified the correctness of the extracted data.  
19  
20  
21 138

### 22 23 139 Quality Assessment

24  
25 140 We assessed the methodological quality of the selected studies using a well-validated  
26  
27 141 tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of  
28  
29 142 Diagnostic Accuracy Studies, QUADAS).<sup>20</sup> The QUADAS instrument scrutinizes  
30  
31 143 characteristics of study designs, population, index tests, and reference standards that  
32  
33 144 may be associated with risk of bias. These features included the spectrum of patients,  
34  
35 145 whether index tests and reference standards were evaluated and interpreted  
36  
37 146 independently to avoid incorporation bias, and whether all patients underwent the  
38  
39 147 same reference standards to avoid differential or partial verification bias.  
40  
41  
42 148

### 43 44 45 149 Data Abstraction

46  
47 150 One reviewer independently extracted the data and a second reviewer independently  
48  
49 151 verified the data. Extracted data comprised the following: overall study characteristics  
50  
51 152 (including the first author, country, language, and date of publication); patient  
52  
53 153 characteristics (including age range and pre-existing atrial fibrillation); quantitative  
54  
55 154 data required for construction of a 2 x 2 table (including number of participants,  
56  
57 155 sensitivity, specificity, and recurrence case number); information regarding the  
58  
59  
60

1  
2  
3  
4 156 hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or  
5  
6 157 semi-quantitative nature of the test); and study settings. In studies that reported  
7  
8 158 multiple pairs of sensitivity and specificity data, we consistently used the data with  
9  
10 159 the highest Youden index (sensitivity + specificity - 1) and performed a sensitivity  
11  
12 160 analysis at a later stage.

13  
14 161

### 15 162 Quantitative Data Synthesis

16 163 We performed a meta-analysis of diagnostic test accuracy of CRP testing for the  
17  
18 164 prediction of recurrent AF. When  $2 \times 2$  tables contained 0 cells, we performed  
19  
20 165 continuity correction by adding 0.5 to each cell. We calculated the pooled sensitivity  
21  
22 166 and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio  
23  
24 167 of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate  
25  
26 168 meta-analysis model.<sup>21</sup> Likelihood ratios were then translated to post-test probability  
27  
28 169 by use of Fagan's plot. We constructed a hierarchical summary receiver operating  
29  
30 170 characteristic (HSROC) curve that plots sensitivity versus specificity and calculated  
31  
32 171 the area under the curve (AUROC).<sup>22</sup> We evaluated the degree of between-study  
33  
34 172 heterogeneity by using the  $I^2$  test.<sup>23</sup> To explore the clinical sources of heterogeneity,  
35  
36 173 we defined the potential explanatory variables *a priori* and performed subgroup  
37  
38 174 analysis to see if the accuracy estimates changed significantly across various  
39  
40 175 subgroups. The presence and the effect of publication bias were examined using a  
41  
42 176 combination of the Egger tests.<sup>24</sup> Statistical analyses were conducted using the  
43  
44 177 statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably  
45  
46 178 with the user-written "midas" and "metandi" programs. All statistical tests were  
47  
48 179 two-sided and statistical significance was defined as a P value less than .05.  
49  
50  
51  
52  
53  
54  
55  
56  
57

58 180

### 59 181 Search Results and Study Characteristics



1  
2  
3  
4 182 The flow of inclusion and exclusion is summarized in Figure 1. Using our search  
5  
6 183 criteria, we identified 784 studies, of which 352 were from PubMed and 432 were  
7  
8 184 from EMBASE. A total of 752 citations were excluded based on pre-defined criteria.  
9  
10 185 No additional citations were identified from the reference lists. A total of 32 articles  
11  
12 186 were retrieved for full-text review, and 23 were excluded due to various reasons  
13  
14 187 detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in  
15  
16 188 predicting AF recurrence after cardioversion were finally included in the  
17  
18 189 meta-analysis. The 9 studies included a total of 682 patients with AF after successful  
19  
20 190 cardioversion, of which 347 (50.9%) developed recurrence.  
21  
22  
23  
24

#### 25 192 Characteristics of included studies

26  
27 193 Table 1 lists the study and population characteristics of the 9 patient populations even  
28  
29 194 if we had additional 5 studies that don't have sufficient data for statistical analysis<sup>25-29</sup>.

30  
31  
32 195 The mean age of patients in the included studies ranged from 55.1 years to 67.9 years  
33  
34 196 and the mean follow-up period ranged from 30 days to 1 year. Seven studies included  
35  
36 197 patients with persistent AF, while 2 studies included patients with paroxysmal AF.

37  
38 198 Seven studies used electric shock, one used circumferential pulmonary vein isolation  
39  
40 199 (also known as electric ablation), and the other used intravenous amiodarone as the  
41  
42 200 primary method for cardioversion. A total of seven studies provided multivariate  
43  
44 201 (adjusted) odds ratios to evaluate the independent predictive value of CRP levels.

45  
46  
47 202 These studies generally adjusted for potential predictors of AF recurrence such as age,  
48  
49 203 sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All  
50  
51 204 studies showed that CRP was a significant independent predictor of AF recurrence.

52  
53 205 Associated adjusted ratios and adjusted variables are summarized in table 1.  
54  
55  
56  
57

#### 58 207 Quality assessment

1  
2  
3 208 Results of the quality assessment of studies of diagnostic accuracy are summarized in  
4  
5 209 figure 2. All studies were prospective and enrolled consecutive outpatients with AF  
6  
7 210 after cardioversion. Three studies had a short follow-up period (i.e. ≤0.5 or 1 year).  
8  
9  
10 211 Although most of the studies did not indicate whether physicians were blinded to the  
11  
12 212 index tests when diagnosing AF recurrence, the determination of AF recurrence was  
13  
14 213 not affected by the knowledge of hs-CRP test results and risk of incorporation bias  
15  
16 214 was minimal. None of the studies reported the undetermined results or withdrawals.  
17  
18  
19 215

20  
21 216 Diagnostic accuracy indices

22  
23 217 Sensitivity, specificity, and diagnostic odds ratio

24  
25 218 The estimated sensitivity and specificity were relatively consistent across studies

26  
27 219 ( $I^2=14.6\%$ ). Table 2 shows the results of individual and combined sensitivity

28  
29 220 estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP

30  
31 221 was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%),

32  
33 222 respectively. We used the pooled prevalence of AF recurrence in this study as the

34  
35 223 pre-test probability. With a pooled positive likelihood ratio of 2.57 and a negative

36  
37 224 likelihood ratio of 0.4, the post-test probability for AF recurrence for a positive

38  
39 225 hs-CRP test result was 72% and a post-test probability for a negative hs-CRP test

40  
41 226 result was 29%. The area under the ROC curve showed an acceptable overall

42  
43 227 measurement of discrimination (0.77, Figure 3). Figure 4 shows the forest plot of the

44  
45 228 ORs.

46  
47  
48  
49 229

50  
51 230 Subgroup analysis and meta-regression

52  
53 231 In view of the potential influence of spectrum variability, we considered the duration

54  
55 232 of follow-up, mode of cardioversion, and type of AF in the study patients to be

56  
57 233 important. Hs-CRP test results generally had higher sensitivity and lower specificity

1  
2  
3  
4 234 in predicting long-term over short-term AF recurrence. Excluding two studies not  
5  
6 235 using electric shock as the primary cardioversion method did not significantly alter  
7  
8 236 the predictive accuracy. Similarly, *focusing the study patients on persistent AF*  
9  
10 237 *population* had similar results as compared with the main overall analysis.  
11  
12 238 Exploratory meta-regression analysis did not find that any pre-specified covariate  
13  
14 239 significantly changed the effect estimate.  
15  
16  
17 240

## 18 241 Discussion

20 242 This meta-analysis shows that elevated CRP levels are independently predictive of AF  
21  
22 243 recurrence in patients with persistent or paroxysmal AF who have undergone  
23  
24 244 successful cardioversion. This finding supports that measurement of CRP levels  
25  
26 245 before cardioversion can aid in the prediction of AF recurrence. Despite the modest  
27  
28 246 pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the  
29  
30 247 high recurrence rate of AF observed in these included studies. A positive hs-CRP test  
31  
32 248 result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months  
33  
34 249 following cardioversion.  
35  
36  
37 250

38  
39  
40 251 Previous studies have examined risk factors that predict AF recurrence. Traditional  
41  
42 252 clinical risk factors for recurrence include history of multiple AF episodes, use of  
43  
44 253 diuretic treatment, higher CHADS-2 (Congestive heart failure, history of  
45  
46 254 Hypertension, Age $\geq$ 75 years, Diabetes mellitus, and past history of Stroke or TIA  
47  
48 255 doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C  
49  
50 256 drugs, and digitalis.<sup>30,31</sup> Although each of these factors could predict AF recurrence  
51  
52 257 with some accuracy, a quantitative combination of these predictors is not available,  
53  
54  
55 258 and the clinical utility of these variables remains questionable. This also suggests that  
56  
57  
58 259 a multivariate prediction model should be developed for AF recurrence, and that  
59  
60

1  
2  
3  
4 260 hsCRP should be a candidate for inclusion in the model.  
5  
6 261

7  
8 262 During the past decade, serum biomarkers have emerged as practical tools to help in  
9  
10 263 the early identification of patients at high risk for various cardiac events. Elevation of  
11  
12 264 inflammatory markers is associated with sudden cardiac death in patients with heart  
13  
14 265 failure or coronary artery disease, and onset of ventricular arrhythmia.<sup>32-35</sup> Of note,  
15  
16 266 there is abundant evidence that elevated serum levels of CRP are associated with the  
17  
18 267 genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical  
19  
20 268 inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in  
21  
22 269 response to proinflammatory cytokine stimulation. Although the pathophysiology of  
23  
24 270 AF remains elusive, there is pathophysiological evidence supporting the role of  
25  
26 271 inflammation in the initiation, maintenance, and perpetuation of AF.<sup>36</sup> Clinically, AF  
27  
28 272 is frequently associated with local inflammatory diseases such as myocarditis or  
29  
30 273 pericarditis, and systemic inflammatory status, such as post-operative state and severe  
31  
32 274 sepsis. Histologically, structural remodeling of the atria manifested by loss of  
33  
34 275 myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.<sup>37</sup>  
35  
36 276 Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial  
37  
38 277 biopsy specimens from AF patients.<sup>38</sup> Activated inflammatory cells in conjunction  
39  
40 278 with reactive oxygen species, cytokines, and growth factors, may ultimately lead to  
41  
42 279 matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of  
43  
44 280 immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors,  
45  
46 281 or glucocorticoids modulate the course of AF.<sup>39</sup>  
47  
48  
49  
50  
51  
52

53 283 In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator  
54  
55 284 of new onset AF and AF recurrence after successful cardioversion.<sup>34,35,40</sup> BNP is also  
56  
57 285 produced in response to atrial pressure and volume overload and there is evidence that  
58  
59  
60

1  
2  
3  
4 286 BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed  
5  
6 287 that the standardized mean difference in plasma BNP level between patients with  
7  
8 288 non-recurrence and patients with recurrence was -1.35 (95% confidence interval -2.17,  
9  
10 289 -0.53).<sup>41</sup> Data on sensitivity and specificity in that study were not available. The  
11  
12 290 comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus  
13  
14 291 requires further analysis.  
15

16  
17 292

18  
19 293 There are both strengths and limitations in our study. Considering the limitation of  
20  
21 294 sensitivity and specificity in clinical interpretation, we reported summary likelihood  
22  
23 295 ratios (LRs) as an ancillary measure of predictive accuracy. The LR indicates how  
24  
25 296 much a given CRP testing result increases or decreases the probability of recurrence  
26  
27 297 of AF. Post-test probabilities can be derived from pre-test probabilities and LR,  
28  
29 298 which are an important clinical parameter for major clinical decision making. Second,  
30  
31 299 we used a bivariate random effect model to account for the inherent negative  
32  
33 300 correlation arising from different cutoff values used in different studies, and occurring  
34  
35 301 between the logit TPR and FPR. Third, we performed sensitivity analysis by  
36  
37 302 restricting analysis within two broad categories of follow-up duration. Results of  
38  
39 303 sensitivity analysis did not show a significantly different overall predictive accuracy  
40  
41 304 between long-term and short-term ~~follow-up~~ prediction of AF recurrence. Nonetheless,  
42  
43 305 it is noteworthy that the sensitivity may be over estimated in our study under the  
44  
45 306 hypothesis where the inflammation may be symptomatic since none of the studies  
46  
47 307 provided withdrawal and undetermined results, and the ascertainment of AF was  
48  
49 308 passive. This event further introduces the differential verification bias. Moreover, our  
50  
51 309 meta-analysis is restricted to distinguish hsCRP levels above or below 0.6 mg/dL  
52  
53 310 because the authors in only one of the studies claimed to possess such capability.  
54  
55 311 Finally, due to the lack of individual data, it is hard to determine whether the area  
56  
57  
58  
59  
60

1  
2  
3  
4 312 under ROC (AUC) can be improved by the new assay either on overall or on  
5  
6 313 individual studies. Overall, as assessed by the heterogeneity of dOR, the included  
7  
8 314 studies evaluating CRP levels and AF recurrence strongly tended toward  
9  
10 315 between-study variability (heterogeneity). Potential sources of between-study  
11  
12 316 variability included differences in incidence of AF recurrence, different threshold  
13  
14 317 values of CRP concentration used, and different duration for follow-up. Another  
15  
16 318 limitation was the strategy we used to determine the optimal cutoff value. Most  
17  
18 319 studies determined an optimal cutoff value to maximize both sensitivity and  
19  
20 320 specificity. Although a single cutoff value is straightforward in clinical interpretation,  
21  
22 321 it may make a marker neither sensitive nor specific enough to rule out or rule in an  
23  
24 322 outcome of interest. A two cut-off value strategy, with one using a lower cutoff value  
25  
26 323 to optimize the sensitivity (rule-out value) and the other using a higher cutoff value to  
27  
28 324 optimize the specificity (rule-in value), would make better use of the information that  
29  
30 325 a biomarker with a continuous value could provide. Current summary estimates based  
31  
32 326 on the one cutoff point may thus have under-evaluated the clinical usefulness of  
33  
34 327 hs-CRP assays. To make the best use of the biomarker information by adopting a two  
35  
36 328 cutoff point strategy or a multi-cutoff point risk classification strategy, an individual  
37  
38 329 data meta-analysis would be needed to overcome the limitations of this aggregated  
39  
40 330 data meta-analysis.

41 331

## 42 332 Conclusions

43 333 Baseline CRP levels before cardioversion can independently predict AF recurrence  
44  
45 334 after successful cardioversion. Given the high recurrence rate reported in most series,  
46  
47 335 the modest positive likelihood ratio for hs-CRP assays still has high positive  
48  
49 336 predictive value. Future studies should focus on the evaluation of two or multiple  
50  
51 337 cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation

1  
2  
3  
4 338 algorithms should be considered.  
5  
6 339  
7  
8 340  
9

10 341 Acknowledgement

11 342 This study was supported by grants of Far Eastern Memorial Hospital, Taiwan  
12  
13  
14 343 (FEMH-2013\_D\_036)  
15

16 344  
17  
18  
19 345  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## References

1. Fabbri G, Maggioni AP. A review of the epidemiological profile of patients with atrial fibrillation and heart failure. *Expert review of cardiovascular therapy*. Sep 2012;10(9):1133-1140.
2. Menezes AR, Lavie CJ, DiNicolantonio JJ, et al. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. *Mayo Clinic proceedings. Mayo Clinic*. Apr 2013;88(4):394-409.
3. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. May 7 2013;61(18):1935-1944.
4. Manlucu J, Brancato S, Lane C, Kazemian P, Michaud GF. Contemporary approaches to persistent atrial fibrillation. *Expert review of cardiovascular therapy*. Nov 2012;10(11):1421-1435.
5. Disertori M, Lombardi F, Barlera S, et al. Clinical characteristics of patients with asymptomatic recurrences of atrial fibrillation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. *American heart journal*. Aug 2011;162(2):382-389.
6. Letsas KP, Weber R, Burkle G, et al. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Feb 2009;11(2):158-163.
7. Liu T, Li L, Korantzopoulos P, Goudevenos JA, Li G. Meta-analysis of association between C-reactive protein and immediate success of electrical cardioversion in persistent atrial fibrillation. *The American journal of cardiology*. Jun 15 2008;101(12):1749-1752.
8. Roberts WL, Sedrick R, Moulton L, Spencer A, Rifai N. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. *Clinical chemistry*. Apr 2000;46(4):461-468.
9. Celebi OO, Celebi S, Canbay A, Ergun G, Aydogdu S, Diker E. The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion. *Cardiology*. 2011;118(3):168-174.
10. Barassi A, Pezzilli R, Morselli-Labate AM, et al. Serum amyloid a and C-reactive protein independently predict the recurrences of atrial fibrillation



- 1  
2  
3 after cardioversion in patients with preserved left ventricular function. *The*  
4 *Canadian journal of cardiology*. Sep-Oct 2012;28(5):537-541.
- 5  
6 11. Hatzinikolaou-Kotsakou E, Tziakas D, Hotidis A, et al. Relation of C-reactive  
7 protein to the first onset and the recurrence rate in lone atrial fibrillation. *The*  
8 *American journal of cardiology*. Mar 1 2006;97(5):659-661.
- 9  
10 12. Henningsen KM, Therkelsen SK, Bruunsgaard H, Krabbe KS, Pedersen BK,  
11 Svendsen JH. Prognostic impact of hs-CRP and IL-6 in patients with persistent  
12 atrial fibrillation treated with electrical cardioversion. *Scandinavian journal of*  
13 *clinical and laboratory investigation*. 2009;69(3):425-432.
- 14  
15 13. Liu J, Fang PH, Dibs S, Hou Y, Li XF, Zhang S. High-sensitivity C-reactive  
16 protein as a predictor of atrial fibrillation recurrence after primary  
17 circumferential pulmonary vein isolation. *Pacing and clinical*  
18 *electrophysiology : PACE*. Apr 2011;34(4):398-406.
- 19  
20 14. Lombardi F, Tundo F, Belletti S, Mantero A, Melzi D'eril G V. C-reactive  
21 protein but not atrial dysfunction predicts recurrences of atrial fibrillation after  
22 cardioversion in patients with preserved left ventricular function. *Journal of*  
23 *cardiovascular medicine (Hagerstown, Md.)*. Jun 2008;9(6):581-588.
- 24  
25 15. Loricchio ML, Cianfrocca C, Pasceri V, et al. Relation of C-reactive protein to  
26 long-term risk of recurrence of atrial fibrillation after electrical cardioversion.  
27 *The American journal of cardiology*. May 15 2007;99(10):1421-1424.
- 28  
29 16. Wazni O, Martin DO, Marrouche NF, et al. C reactive protein concentration and  
30 recurrence of atrial fibrillation after electrical cardioversion. *Heart (British*  
31 *Cardiac Society)*. Oct 2005;91(10):1303-1305.
- 32  
33 17. Rizos I, Rigopoulos AG, Kalogeropoulos AS, et al. Hypertension and  
34 paroxysmal atrial fibrillation: a novel predictive role of high sensitivity  
35 C-reactive protein in cardioversion and long-term recurrence. *Journal of human*  
36 *hypertension*. Jul 2010;24(7):447-457.
- 37  
38 18. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity  
39 C-reactive protein is predictive of successful cardioversion for atrial fibrillation  
40 and maintenance of sinus rhythm after conversion. *International journal of*  
41 *cardiology*. Apr 14 2006;108(3):346-353.
- 42  
43 19. Zarauza J, Rodriguez Lera MJ, Farinas Alvarez C, et al. [Relationship between  
44 C-reactive protein level and early recurrence of atrial fibrillation after electrical  
45 cardioversion]. *Revista espanola de cardiologia*. Feb 2006;59(2):125-129.
- 46  
47 20. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of  
48 diagnostic test accuracy. *Annals of internal medicine*. Dec 16  
49 2008;149(12):889-897.
- 50  
51 21. Arends LR, Hamza TH, van Houwelingen JC, Heijenbrok-Kal MH, Hunink MG,  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 Stijnen T. Bivariate random effects meta-analysis of ROC curves. *Medical*  
4 *decision making : an international journal of the Society for Medical Decision*  
5 *Making*. Sep-Oct 2008;28(5):621-638.
- 6  
7 22. Harbord RM, Whiting P, Sterne JA, et al. An empirical comparison of methods  
8 for meta-analysis of diagnostic accuracy showed hierarchical models are  
9 necessary. *Journal of clinical epidemiology*. Nov 2008;61(11):1095-1103.
- 10  
11 23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in  
12 meta-analyses. *BMJ (Clinical research ed.)*. Sep 6 2003;327(7414):557-560.
- 13  
14 24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis  
15 detected by a simple, graphical test. *BMJ (Clinical research ed.)*. Sep 13  
16 1997;315(7109):629-634.
- 17  
18 25. Buob A, Jung J, Siaplaouras S, Neuberger HR, Mewis C. Discordant regulation  
19 of CRP and NT-proBNP plasma levels after electrical cardioversion of  
20 persistent atrial fibrillation. *Pacing and clinical electrophysiology : PACE*. Jun  
21 2006;29(6):559-563.
- 22  
23 26. Cosgrave J, Foley JB, Bahadur K, Bennett K, Crean P, Walsh MJ. Inflammatory  
24 markers are not associated with outcomes following elective external  
25 cardioversion. *International journal of cardiology*. Jun 28  
26 2006;110(3):373-377.
- 27  
28 27. Ellinor PT, Low A, Patton KK, Shea MA, MacRae CA. C-Reactive protein in  
29 lone atrial fibrillation. *The American journal of cardiology*. May 1  
30 2006;97(9):1346-1350.
- 31  
32 28. Korantzopoulos P, Kolettis TM, Kountouris E, Siogas K, Goudevenos JA.  
33 Variation of inflammatory indexes after electrical cardioversion of persistent  
34 atrial fibrillation. Is there an association with early recurrence rates?  
35 *International journal of clinical practice*. Aug 2005;59(8):881-885.
- 36  
37 29. Psychari SN, Chatzopoulos D, Iliodromitis EK, Apostolou TS, Kremastinos DT.  
38 C-reactive protein, interleukin 6, and N-terminal pro-brain natriuretic peptide  
39 following cardioversion of atrial fibrillation: is there a role of biomarkers in  
40 arrhythmia recurrence? *Angiology*. May 2011;62(4):310-316.
- 41  
42 30. Komatsu T, Sato Y, Ozawa M, et al. Relationship between CHADS2 score and  
43 efficacy of antiarrhythmic drug therapy in patients with paroxysmal atrial  
44 fibrillation. *Circulation journal : official journal of the Japanese Circulation*  
45 *Society*. Feb 25 2013;77(3):639-645.
- 46  
47 31. Letsas KP, Efremidis M, Giannopoulos G, et al. CHADS2 and CHA2DS2-VASc  
48 scores as predictors of left atrial ablation outcomes for paroxysmal atrial  
49 fibrillation. *Europace : European pacing, arrhythmias, and cardiac*  
50 *electrophysiology : journal of the working groups on cardiac pacing,*  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Jun 28 2013.
32. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation*. Jun 4 2002;105(22):2595-2599.
33. Parekh RS, Plantinga LC, Kao WH, et al. The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney international*. Nov 2008;74(10):1335-1342.
34. Streitner F, Kuschik J, Veltmann C, et al. Role of proinflammatory markers and NT-proBNP in patients with an implantable cardioverter-defibrillator and an electrical storm. *Cytokine*. Sep 2009;47(3):166-172.
35. Korngold EC, Januzzi JL, Jr., Gantzer ML, Moorthy MV, Cook NR, Albert CM. Amino-terminal pro-B-type natriuretic peptide and high-sensitivity C-reactive protein as predictors of sudden cardiac death among women. *Circulation*. Jun 9 2009;119(22):2868-2876.
36. Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *European heart journal*. Oct 2005;26(20):2083-2092.
37. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovascular research*. May 2002;54(2):230-246.
38. Van Wagoner DR. Oxidative Stress and Inflammation in Atrial Fibrillation: Role in Pathogenesis and Potential as a Therapeutic Target. *Journal of Cardiovascular Pharmacology*. 2008;52(4):306-313  
310.1097/FJC.1090b1013e31817f39398.
39. Moro C, Hernandez-Madrid A, Matia R. Non-antiarrhythmic drugs to prevent atrial fibrillation. *American journal of cardiovascular drugs : drugs, devices, and other interventions*. 2010;10(3):165-173.
40. den Uijl DW, Delgado V, Tops LF, et al. Natriuretic peptide levels predict recurrence of atrial fibrillation after radiofrequency catheter ablation. *American heart journal*. Jan 2011;161(1):197-203.
41. Tang Y, Yang H, Qiu J. Relationship between brain natriuretic peptide and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. *The Journal of international medical research*. 2011;39(5):1618-1624.

1  
2  
3  
4 Figure legends  
5  
6

7 Figure 1. A simplified flow chart to identify and to include studies. Amongst 752  
8  
9  
10 citations in MEDLINE and EMBASE from inception to December 2013, a search  
11  
12 limited to human studies using “C-reactive protein” and the MeSH term “diagnosis of  
13 atrial fibrillation” resulted in 32 potentially relevant articles for further review. After  
14 careful scrutinization on full text, 9 articles were left for meta-analysis.  
15  
16  
17  
18  
19

20  
21 Figure 2. The quality assessment of diagnostic accuracy on studies. A spectrum of  
22 features were analysed to avoid bias using a well-validated tool called Quality  
23 Assessment of Diagnostics Accuracy Studies (QUADAS). Percentage for each feature  
24 was independently evaluated among the studies. It is worthy of attention that none of  
25 the studies explained the withdrawal and reported indetermined results, likely to  
26 compromise the quality of diagnostic accuracy.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38

39 Figure 3. The ROC curve of hs-CRP. Our analysis suggests it is highly possible to  
40 predict atrial fibrillation using C-reative protein since the area under the curve  
41 generates a measurement of discrimination ~0.77. The overall sensitivity and  
42 specificity are relatively high. We have 5 out 9 studies that fall in the 95% CI region,  
43 while 8 out 9 in the 95% prediction region.  
44  
45  
46  
47  
48  
49  
50  
51  
52

53 Figure 4. The forest plot of the odds ratios (ORs). Our study indicates that  
54 hsCRP-positive patients are ~5.91 times more likely to develop a recurrence of atrial  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 fibrillation than hsCRP-negative patients are. The estimated sensitivity and specificity  
5  
6  
7 were relatively consistent across studies ( $I^2=14.6\%$ ).  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

Table 1. Summary of the characteristics of the included studies

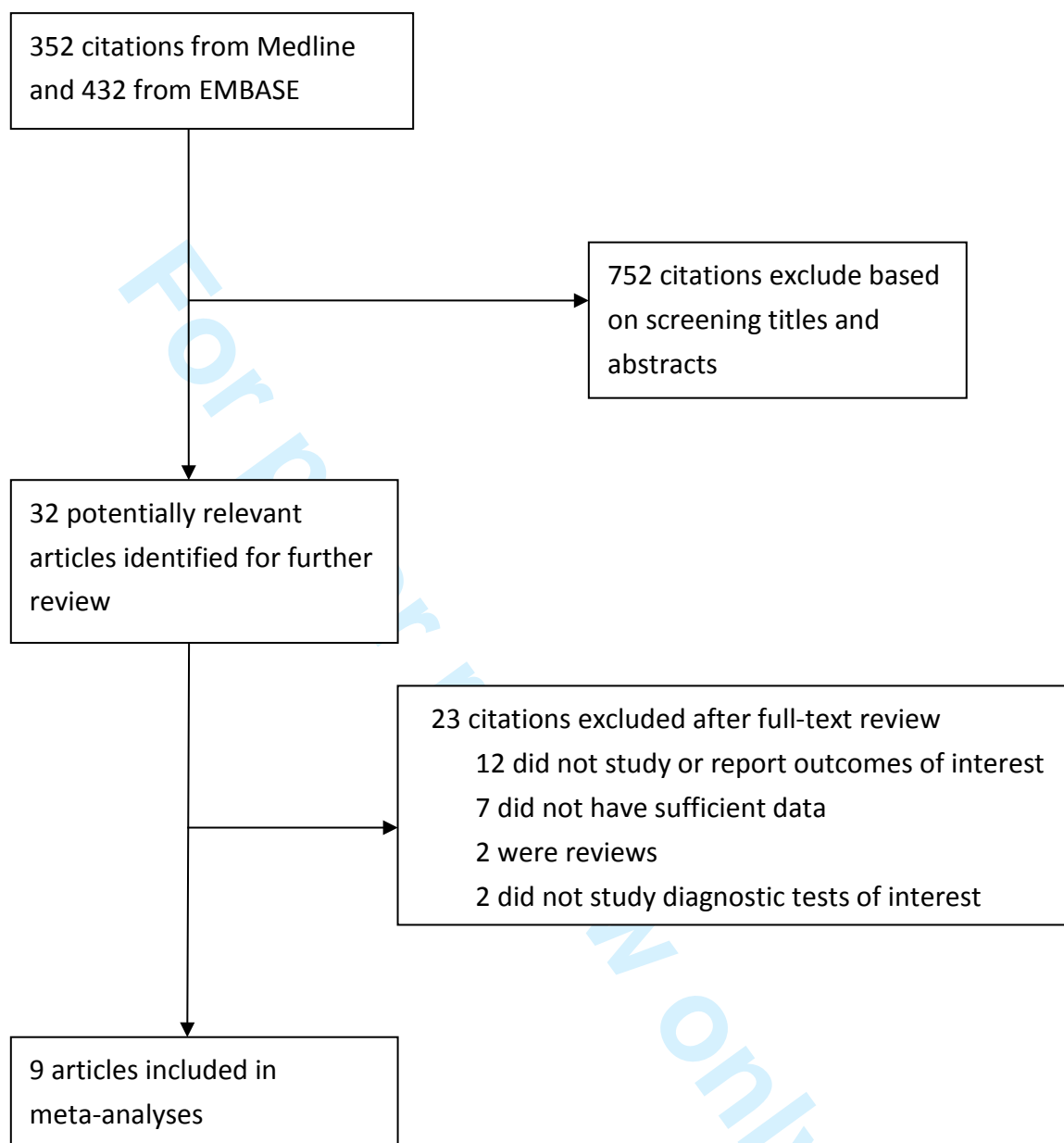
Author, year, country	Mean Age	Prevalence (N)	Follow-up time	Cutoff (mg/l)	AF type	Cardioversion	Sensitivity, Specificity	Adjusted odd ratio	Adjusted variables
Wazni O, 2005,USA <sup>16</sup>	67.3	0.68(111)	76 days	3.1	Persistent AF	Electric	59 %, 69 %	2.0 (1.2-3.2)	Age, sex, duration of AF, coronary artery disease, hypertension, left ventricular hypertrophy, LAD
Zarauza J, 2006, Spain <sup>19</sup>	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 <sup>18</sup>	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 <sup>15</sup>	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 <sup>14</sup>	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 <sup>12</sup>	65	0.68(56)	180 days	3.0	Persistent AF	Electric	60%, 83%	7.7 (1.9-31.1) *	NA
Rizos I, 2010,Greece <sup>17</sup>	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 <sup>13</sup>	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 <sup>10</sup>	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

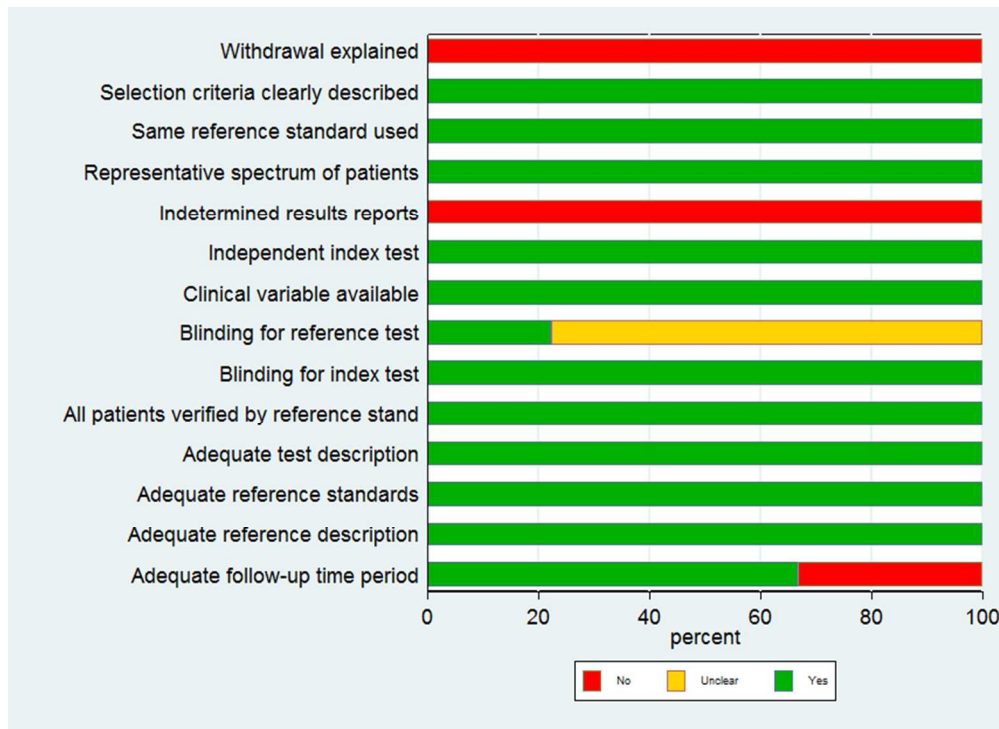
Table 2. Summary of pooled diagnostic accuracy indices

Variables	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio+	Likelihood ratio-	AUROC (95% CI)	I <sup>2</sup> (95% CI)	Diagnostic OR (95% CI)	Meta-regression P	Egger's test P
Overall <sup>10,12-19</sup>	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 <sup>10,14,16,19</sup>	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 <sup>12-14,17,18</sup>	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 <sup>10,12,14-16,18,19</sup>	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 <sup>10,12,14-16,18,19</sup>	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





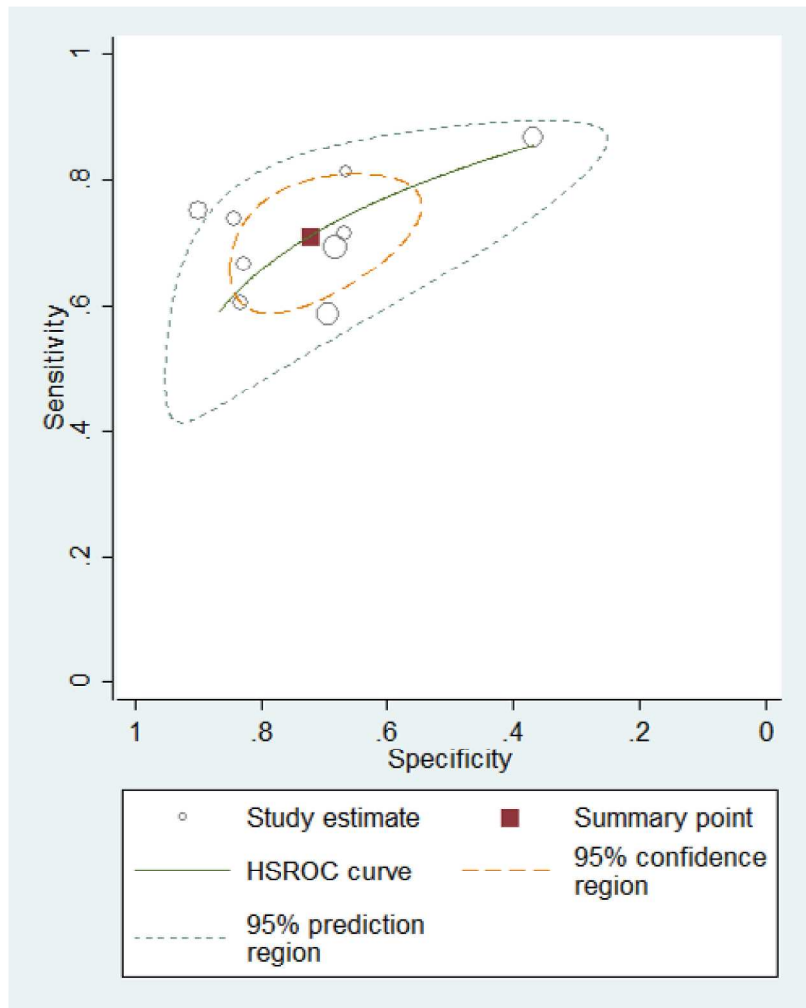


Results of the quality assessment of studies of diagnostic accuracy  
302x219mm (72 x 72 DPI)

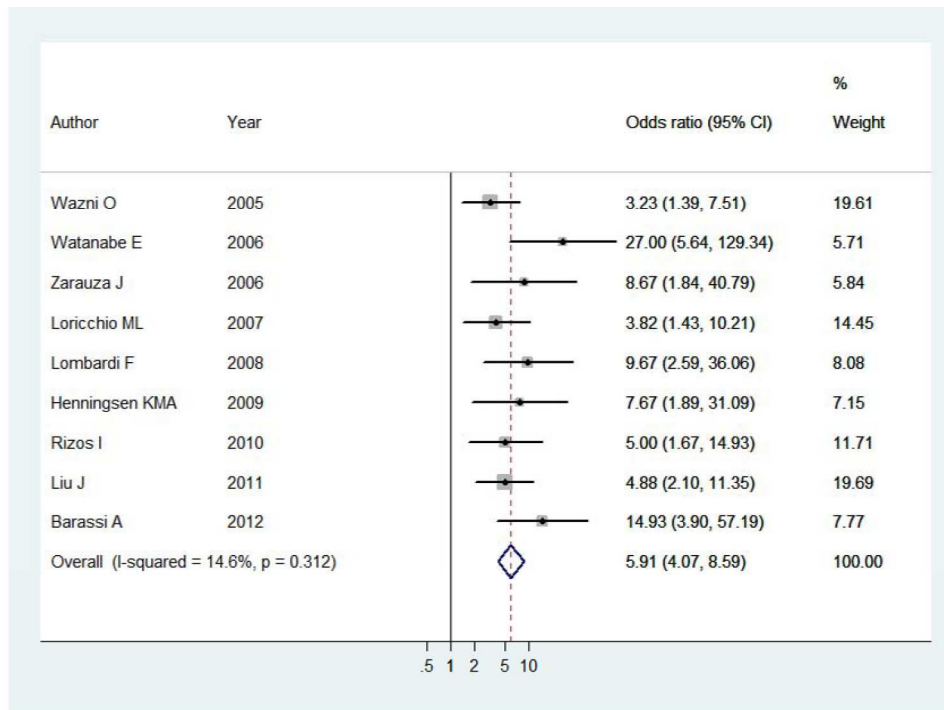
View only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



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



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

view only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



# PRISMA 2009 Checklist

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>



# PRISMA 2009 Checklist

Page 1 of 2

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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>



# PRISMA 2009 Checklist

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

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](http://www.prisma-statement.org).

Page 2 of 2

For peer review only

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004418.R2
Article Type:	Research
Date Submitted by the Author:	29-Jan-2014
Complete List of Authors:	Yo, Chia-Hung; Far Eastern Memorial Hospital, Department of Emergency Medicine Lee, Si-Huei; Taipei Veteran General Hospital, Department of Rehabilitation and Physical Medicine Chang, Shy-Shin; Chang Gung Memorial Hospital, Department of Family Medicine Lee, Chien-Hung; Medical Wisdom Consultants, Lee, Chien-Chang; National Taiwan University Hospital Yunlin Branch, Department of Emergency Medicine
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY, Hypertension < CARDIOLOGY, C - reactive protein, cardioversion, meta-analysis

SCHOLARONE™  
Manuscripts



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

3  
4 <sup>1</sup>Chia-Hung Yo MD, <sup>2</sup>Si-Huei Lee MD <sup>3,4</sup>Shy-Shin Chang MD, <sup>5</sup>Matthew  
5 Chien-Hung Lee PhD, JD, <sup>6,7</sup>Chien-Chang Lee MD, MSc

6  
7 <sup>1</sup>Department of Emergency Medicine, Far Eastern Memorial Hospital, New Taipei  
8 City, Taiwan.

9 <sup>2</sup>Department of Rehabilitation and Physical Medicine, Taipei Veteran  
10 General Hospital, Taipei, Taiwan

11 <sup>3</sup>Department of Family Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

12 <sup>4</sup>Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung  
13 University, Taoyuan, Taiwan.

14 <sup>5</sup>Medical Wisdom Consultants, Houston, USA

15 <sup>6</sup>Department of Epidemiology, Harvard School of Public Health, Boston, USA.

16 <sup>7</sup>Department of Emergency Medicine, National Taiwan University Hospital Yunlin  
17 Branch, Douliou, Taiwan

18 Address correspondence to

19 Chien-Chang Lee MD, MSc

20 Email: clee100@gmail.com

21 Postal Address: No 579 Sec 2 Yunlin Road, Douliou, Yunlin County 640, Taiwan

22 Telephone: +886-5-532-3911 ext. 2326

23 Fax: +886-2322-3150

24 Word count: 2535

25 Conflict of interest: None declared

1  
2  
3  
4 26 Abstract

5 27 Objectives: We performed a systematic review and meta-analysis of studies on  
6  
7  
8 28 high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are  
9  
10 29 predictive of atrial fibrillation (AF) recurrence after cardioversion.  
11  
12 30

13  
14 31 Design: Systematic review and meta-analysis.  
15  
16 32

17  
18  
19 33 Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of  
20  
21 34 the reference lists in the retrieved articles from inception to December 2013.  
22  
23 35

24  
25 36 Study eligibility criteria: This review selected observational studies in which the  
26  
27 37 measurements of serum CRP were used to predict atrial fibrillation recurrence. An  
28  
29 38 hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring  
30  
31 39 serum CRP to below 0.6 mg/dL.  
32  
33 40

34  
35  
36 41 Primary and secondary outcome measures: We summarized test performance  
37  
38 42 characteristics with the use of forest plots, hierarchical summary receiver operating  
39  
40 43 characteristic (HSROC) curves, and bivariate random effects models. Meta-regression  
41  
42 44 analysis was performed to explore the source of heterogeneity.  
43  
44 45

45  
46 46 Results: We included nine qualifying studies comprising a total of 347 patients with AF  
47  
48 47 recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an  
49  
50 48 independent predictor of AF recurrence after cardioversion (summary adjusted odds  
51  
52 49 ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for  
53  
54 50 hs-CRP was 71.0% (95% CI: 63% to 78%) and 72.0% (61% to 81%), respectively.  
55  
56 51

57  
58 51 Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence  
59  
60

1  
2  
3  
4 52 (77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73%  
5  
6 53 sensitivity, 71% specificity).  
7  
8  
9

10 55 Conclusions: High-sensitivity CRP assays are moderately accurate in predicting AF  
11  
12 56 recurrence after successful cardioversion.  
13  
14  
15

16  
17 58 Strengths and limitations of this study

- 18  
19 59 • This meta-analysis finding supports that measurement of CRP levels before  
20  
21 60 cardioversion can aid in the prediction of AF recurrence.  
22  
23 61 • We reported summary likelihood ratios (LRs) as an ancillary measure of predictive  
24  
25 62 accuracy.  
26  
27 63 • A bivariate random effect model to account for the inherent negative correlation  
28  
29 64 arising from different cutoff values used in different studies, and occurring  
30  
31 65 between the logit true positive rates (TPR) and false positive rates (FPR).  
32  
33 66 • Results of sensitivity analysis did not show a significantly different overall  
34  
35 67 predictive accuracy between long-term and short-term follow-up, however, a  
36  
37 68 heterogeneity tended toward between-study variability.  
38  
39 69 • Current summary estimates based on the one cutoff point may thus have  
40  
41 70 under-evaluated the clinical usefulness of hs-CRP assays.  
42  
43  
44  
45  
46

47 72 Keywords: atrial fibrillation, recurrence, cardioversion, C - reactive protein,  
48  
49 73 meta-analysis  
50  
51  
52  
53  
54

55  
56 76 Introduction

57  
58 77 Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, although the  
59  
60

1  
2  
3 78 prevalence is highest among people of advanced age.<sup>1,2</sup> AF poses a significant  
4  
5 79 economic burden, with a 66% increase in hospital admissions over the past two decades.  
6  
7  
8 80 It is estimated that the number of patients affected by AF is likely to grow 2.5 fold by  
9  
10 81 the year 2050.<sup>1-3</sup> In addition, AF may lead to debilitating complications such as  
11  
12 82 ischemic stroke and heart failure. Although ventricular rate control is an acceptable  
13  
14 83 treatment strategy in many patients, some patients may remain symptomatic despite  
15  
16 84 adequate rate controls. For this group of patients, cardioversion may be the treatment of  
17  
18 85 choice. Electrical cardioversion can restore sinus rhythm effectively in most patients  
19  
20 86 and can act with antiarrhythmic drugs synergistically to enhance the cardioversion  
21  
22 87 success rate.<sup>4</sup> However, cardioversion is not the definite treatment. Approximately 50%  
23  
24 88 of patients undergoing cardioversion usually present with recurrence of AF within three  
25  
26 89 to six months of cardioversion despite ongoing antiarrhythmic treatment.<sup>5</sup> Left  
27  
28 90 ventricular dysfunction, left atrial enlargement, arrhythmia duration, and history of  
29  
30 91 hypertension are major risk factors for AF recurrence.<sup>6</sup> However, recent studies have  
31  
32 92 indicated that inflammation, necrosis, and fibrosis play roles in the structural  
33  
34 93 remodeling process of the atria, contributing to the perpetuation or recurrence of atrial  
35  
36 94 fibrillation.  
37  
38  
39 95  
40  
41  
42 96 C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response  
43  
44 97 to proinflammatory cytokines, notably interleukin-6, and other endogenous signals of  
45  
46 98 innate immunity or tissue damage. CRP has recently been shown to be associated with  
47  
48 99 cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is  
49  
50 100 elevated in patients with AF.<sup>7</sup> However, 5 of the 6 studies included in that analysis  
51  
52 101 used traditional automated immunonephelometric assays to measure CRP.  
53  
54  
55 102 Unfortunately, those assays are insufficiently sensitive for measuring the low level of  
56  
57 103 inflammation associated with AF. A newer enzyme immunoassay, namely  
58  
59  
60

1  
2  
3  
4 104 high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL  
5  
6 105 and may further enhance the predictability of AF recurrence.<sup>8</sup> Since 2006, several  
7  
8 106 studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been  
9  
10 107 published,<sup>9-19</sup> warranting a systemic and quantitative summary of current evidence on  
11  
12 108 the accuracy of CRP in predicting AF recurrence after cardioversion.  
13

14 109

15  
16  
17 110 Methods18  
19 111 Identification of Studies

20  
21 112 General bibliographic databases (MEDLINE and EMBASE) were searched from  
22  
23 113 inception to April 2013. The medical subject heading (MeSH) and text words for the  
24  
25 114 term C -reactive protein were combined with the MeSH term “diagnosis of atrial  
26  
27 115 fibrillation”. The search was limited to human studies with no language restrictions.  
28  
29 116 In addition to the electronic search, reference lists in all known reviews and primary  
30  
31 117 studies were checked manually.  
32

33 118

34  
35  
36 119 Selection Criteria

37  
38 120 This review focused on observational studies in which the measurements of serum  
39  
40 121 CRP were used to predict atrial fibrillation recurrence. The population of interest  
41  
42 122 comprised patients with paroxysmal or persistent AF who underwent electric  
43  
44 123 cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was  
45  
46 124 defined as AF documented by ECG at any time after the cardioversion during the  
47  
48 125 follow-up period. Generally, patients were instructed to return to the clinic if the  
49  
50 126 symptoms such as palpitations, shortness of breath, or chest discomfort developed  
51  
52 127 after cardioversion. We included studies using a cohort design or case-control design  
53  
54 128 with appropriate controls. Two reviewers independently assessed eligible articles for  
55  
56 129 inclusion. Disagreements were initially resolved by consensus and using arbitration  
57  
58  
59  
60

1  
2  
3  
4 130 by a third reviewer if consensus could not be reached by the two reviewers. We  
5  
6 131 extracted data from the included studies. Data collected include study design,  
7  
8 132 participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of  
9  
10 133 follow-up period, and recurrence of AF. One reviewer extracted the data and a second  
11  
12 134 reviewer independently verified the correctness of the extracted data.  
13

14  
15 135

### 16 136 Quality Assessment

17  
18 137 We assessed the methodological quality of the selected studies using a well-validated  
19  
20 138 tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of  
21  
22 139 Diagnostic Accuracy Studies, QUADAS).<sup>20</sup> The QUADAS instrument scrutinizes  
23  
24 140 characteristics of study designs, population, index tests, and reference standards that  
25  
26 141 may be associated with risk of bias. These features included the spectrum of patients,  
27  
28 142 whether index tests and reference standards were evaluated and interpreted  
29  
30 143 independently to avoid incorporation bias, and whether all patients underwent the  
31  
32 144 same reference standards to avoid differential or partial verification bias.  
33

34  
35 145

### 36 146 Data Abstraction

37  
38 147 One reviewer independently extracted the data and a second reviewer independently  
39  
40 148 verified the data. Extracted data comprised the following: overall study characteristics  
41  
42 149 (including the first author, country, language, and date of publication); patient  
43  
44 150 characteristics (including age range and pre-existing atrial fibrillation); quantitative  
45  
46 151 data required for construction of a 2 x 2 table (including number of participants,  
47  
48 152 sensitivity, specificity, and recurrence case number); information regarding the  
49  
50 153 hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or  
51  
52 154 semi-quantitative nature of the test); and study settings. In studies that reported  
53  
54 155 multiple pairs of sensitivity and specificity data, we consistently used the data with  
55  
56  
57  
58  
59  
60

1  
2  
3 156 the highest Youden index (sensitivity + specificity -1) and performed a sensitivity  
4  
5 157 analysis at a later stage.  
6  
7  
8 158

#### 9 10 159 Quantitative Data Synthesis

11  
12 160 We performed a meta-analysis of diagnostic test accuracy of CRP testing for the  
13  
14 161 prediction of recurrent AF. We calculated the pooled sensitivity and specificity,  
15  
16 162 positive and negative likelihood ratios, and the diagnostic odds ratio of CRP, along  
17  
18 163 with the respective 95% confidence intervals (CIs), using a bivariate meta-analysis  
19  
20 164 model.<sup>21</sup> Likelihood ratios were then translated to post-test probability by use of  
21  
22 165 Fagan's plot. We constructed a hierarchical summary receiver operating characteristic  
23  
24 166 (HSROC) curve that plots sensitivity versus specificity and calculated the area under  
25  
26 167 the curve (AUROC).<sup>22</sup> We evaluated the degree of between-study heterogeneity by  
27  
28 168 using the  $I^2$  test.<sup>23</sup> To explore the clinical sources of heterogeneity, we defined the  
29  
30 169 potential explanatory variables *a priori* and performed subgroup analysis to see if the  
31  
32 170 accuracy estimates changed significantly across various subgroups. The presence and  
33  
34 171 the effect of publication bias were examined using a combination of the Egger tests.<sup>24</sup>  
35  
36 172 Statistical analyses were conducted using the statistical package STATA (Version 11.0,  
37  
38 173 Stata Corp, College Station, TX), notably with the user-written "midas" and  
39  
40 174 "metandi" programs. All statistical tests were two-sided and statistical significance  
41  
42 175 was defined as a P value less than .05.  
43  
44  
45  
46  
47  
48

#### 49 177 Search Results and Study Characteristics

50  
51 178 The flow of inclusion and exclusion is summarized in Figure 1. Using our search  
52  
53 179 criteria, we identified 784 studies, of which 352 were from PubMed and 432 were  
54  
55 180 from EMBASE. A total of 752 citations were excluded based on pre-defined criteria.  
56  
57 181 No additional citations were identified from the reference lists. A total of 32 articles



1  
2  
3  
4 182 were retrieved for full-text review, and 23 were excluded due to various reasons  
5  
6 183 detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in  
7  
8 184 predicting AF recurrence after cardioversion were finally included in the  
9  
10 185 meta-analysis. The 9 studies included a total of 682 patients with AF after successful  
11  
12 186 cardioversion, of which 347 (50.9%) developed recurrence.  
13

14  
15 187

#### 16 17 188 Characteristics of included studies

18  
19 189 Table 1 lists the study and population characteristics of the 9 patient populations even  
20  
21 190 if we had additional 5 studies that don't have sufficient data for statistical analysis<sup>25-29</sup>.

22  
23 191 The mean age of patients in the included studies ranged from 55.1 years to 67.9 years  
24  
25 192 and the mean follow-up period ranged from 30 days to 1 year. Seven studies included  
26  
27 193 patients with persistent AF, while 2 studies included patients with paroxysmal AF.

28  
29 194 Seven studies used electric shock, one used circumferential pulmonary vein isolation  
30  
31 195 (also known as electric ablation), and the other used intravenous amiodarone as the  
32  
33 196 primary method for cardioversion. A total of seven studies provided multivariate  
34  
35 197 (adjusted) odds ratios to evaluate the independent predictive value of CRP levels.

36  
37 198 These studies generally adjusted for potential predictors of AF recurrence such as age,  
38  
39 199 sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All  
40  
41 200 studies showed that CRP was a significant independent predictor of AF recurrence.

42  
43 201 Associated adjusted ratios and adjusted variables are summarized in table 1.  
44

45  
46 202

#### 47 48 203 Quality assessment

49  
50 204 Results of the quality assessment of studies of diagnostic accuracy are summarized in  
51  
52 205 figure 2. All studies were prospective and enrolled consecutive outpatients with AF  
53  
54 206 after cardioversion. Three studies had a short follow-up period (i.e.  $\leq 0.5$  or 1 year).

55  
56 207 Although most of the studies did not indicate whether physicians were blinded to the

1  
2  
3 208 index tests when diagnosing AF recurrence, the determination of AF recurrence was  
4  
5 209 not affected by the knowledge of hs-CRP test results and risk of incorporation bias  
6  
7  
8 210 was minimal. None of the studies reported the undetermined results or withdrawals.  
9

10 211

11  
12 212 Diagnostic accuracy indices

13  
14 213 Sensitivity, specificity, and diagnostic odds ratio

15  
16 214 The estimated sensitivity and specificity were relatively consistent across studies

17  
18 215 ( $I^2=14.6\%$ ). Table 2 shows the results of individual and combined sensitivity

19  
20 216 estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP

21  
22 217 was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%),

23  
24 218 respectively. The pooled prevalence of AF recurrence was 54% herein, and we used it

25  
26 219 as the pre-test probability. With a pooled positive likelihood ratio of 2.57 and a

27  
28 220 negative likelihood ratio of 0.4, the post-test probability for AF recurrence for a

29  
30 221 positive hs-CRP test result was 72% and a post-test probability for a negative hs-CRP

31  
32 222 test result was 29%. The area under the ROC curve showed an acceptable overall

33  
34 223 measurement of discrimination (0.77, Figure 3). Figure 4 shows the forest plot of the

35  
36 224 ORs.

37  
38 225

39  
40 226 Subgroup analysis and meta-regression

41  
42 227 In view of the potential influence of spectrum variability, we considered the duration

43  
44 228 of follow-up, mode of cardioversion, and type of AF in the study patients to be

45  
46 229 important. Hs-CRP test results generally had higher sensitivity and lower specificity

47  
48 230 in predicting long-term over short-term AF recurrence. Excluding two studies not

49  
50 231 using electric shock as the primary cardioversion method did not significantly alter

51  
52 232 the predictive accuracy. Similarly, *focusing the study patients on persistent AF*

53  
54 233 *population* had similar results as compared with the main overall analysis.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 234 Exploratory meta-regression analysis did not find that any pre-specified covariate  
5  
6 235 significantly changed the effect estimate.  
7

8 236

9  
10 237 Discussion

11  
12 238 This meta-analysis shows that elevated CRP levels are independently predictive of AF  
13  
14 239 recurrence in patients with persistent or paroxysmal AF who have undergone  
15  
16 240 successful cardioversion. This finding supports that measurement of CRP levels  
17  
18 241 before cardioversion can aid in the prediction of AF recurrence. Despite the modest  
19  
20 242 pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the  
21  
22 243 high recurrence rate of AF observed in these included studies. A positive hs-CRP test  
23  
24 244 result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months  
25  
26 245 following cardioversion.  
27  
28

29  
30 246

31  
32 247 Previous studies have examined risk factors that predict AF recurrence. Traditional  
33  
34 248 clinical risk factors for recurrence include history of multiple AF episodes, use of  
35  
36 249 diuretic treatment, higher CHADS-2 (Congestive heart failure, history of  
37  
38 250 Hypertension, Age $\geq$ 75 years, Diabetes mellitus, and past history of Stroke or TIA  
39  
40 251 doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C  
41  
42 252 drugs, and digitalis.<sup>30,31</sup> Although each of these factors could predict AF recurrence  
43  
44 253 with some accuracy, a quantitative combination of these predictors is not available,  
45  
46 254 and the clinical utility of these variables remains questionable. This also suggests that  
47  
48 255 a multivariate prediction model should be developed for AF recurrence, and that  
49  
50 256 hsCRP should be a candidate for inclusion in the model.  
51

52  
53 257

54  
55  
56 258 During the past decade, serum biomarkers have emerged as practical tools to help in  
57  
58 259 the early identification of patients at high risk for various cardiac events. Elevation of

1  
2  
3  
4 260 inflammatory markers is associated with sudden cardiac death in patients with heart  
5  
6 261 failure or coronary artery disease, and onset of ventricular arrhythmia.<sup>32-35</sup> Of note,  
7  
8 262 there is abundant evidence that elevated serum levels of CRP are associated with the  
9  
10 263 genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical  
11  
12 264 inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in  
13  
14 265 response to proinflammatory cytokine stimulation. Although the pathophysiology of  
15  
16 266 AF remains elusive, there is pathophysiological evidence supporting the role of  
17  
18 267 inflammation in the initiation, maintenance, and perpetuation of AF.<sup>36</sup> Clinically, AF  
19  
20 268 is frequently associated with local inflammatory diseases such as myocarditis or  
21  
22 269 pericarditis, and systemic inflammatory status, such as post-operative state and severe  
23  
24 270 sepsis. Histologically, structural remodeling of the atria manifested by loss of  
25  
26 271 myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.<sup>37</sup>  
27  
28  
29 272 Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial  
30  
31 273 biopsy specimens from AF patients.<sup>38</sup> Activated inflammatory cells in conjunction  
32  
33 274 with reactive oxygen species, cytokines, and growth factors, may ultimately lead to  
34  
35 275 matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of  
36  
37 276 immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors,  
38  
39 277 or glucocorticoids modulate the course of AF.<sup>39</sup>  
40  
41  
42 278  
43  
44 279 In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator  
45  
46 280 of new onset AF and AF recurrence after successful cardioversion.<sup>34,35,40</sup> BNP is also  
47  
48 281 produced in response to atrial pressure and volume overload and there is evidence that  
49  
50 282 BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed  
51  
52 283 that the standardized mean difference in plasma BNP level between patients with  
53  
54 284 non-recurrence and patients with recurrence was -1.35 (95% confidence interval -2.17,  
55  
56 285 -0.53).<sup>41</sup> Data on sensitivity and specificity in that study were not available. The

1  
2  
3  
4 286 comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus  
5  
6 287 requires further analysis.  
7  
8 288  
9  
10 289 There are both strengths and limitations in our study. Considering the limitation of  
11  
12 290 sensitivity and specificity in clinical interpretation, we reported summary likelihood  
13  
14 291 ratios (LRs) as an ancillary measure of predictive accuracy. The LR<sub>s</sub> indicate how  
15  
16 292 much a given CRP testing result increases or decreases the probability of recurrence  
17  
18 293 of AF. Post-test probabilities can be derived from pre-test probabilities and LR<sub>s</sub>,  
19  
20 294 which are an important clinical parameter for major clinical decision making. Second,  
21  
22 295 we used a bivariate random effect model to account for the inherent negative  
23  
24 296 correlation arising from different cutoff values used in different studies, and occurring  
25  
26 297 between the logit TPR and FPR. Third, we performed sensitivity analysis by  
27  
28 298 restricting analysis within two broad categories of follow-up duration. Results of  
29  
30 299 sensitivity analysis did not show a significantly different overall predictive accuracy  
31  
32 300 between long-term and short-term prediction of AF recurrence. Nonetheless, it is  
33  
34 301 noteworthy that the sensitivity may be over estimated in our study under the  
35  
36 302 hypothesis where the inflammation may be symptomatic since none of the studies  
37  
38 303 provided withdrawal and undetermined results, and the ascertainment of AF was  
39  
40 304 passive. This event further introduces the differential verification bias. Moreover, our  
41  
42 305 meta-analysis is restricted to distinguish hsCRP levels above or below 0.6 mg/dL  
43  
44 306 because the authors in only one of the studies claimed to possess such capability.  
45  
46 307 Finally, due to the lack of individual data, it is hard to determine whether the area  
47  
48 308 under ROC (AUC) can be improved by the new assay either on overall or on  
49  
50 309 individual studies. In general, potential sources of between-study variability included  
51  
52 310 differences in incidence of AF recurrence, different threshold values of CRP  
53  
54 311 concentration used, and different duration for follow-up. Another limitation was the  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 312 strategy we used to determine the optimal cutoff value. Most studies determined an  
5  
6 313 optimal cutoff value to maximize both sensitivity and specificity. Although a single  
7  
8 314 cutoff value is straightforward in clinical interpretation, it may make a marker neither  
9  
10 315 sensitive nor specific enough to rule out or rule in an outcome of interest. A two  
11  
12 316 cut-off value strategy, with one using a lower cutoff value to optimize the sensitivity  
13  
14 317 (rule-out value) and the other using a higher cutoff value to optimize the specificity  
15  
16 318 (rule-in value), would make better use of the information that a biomarker with a  
17  
18 319 continuous value could provide. Current summary estimates based on the one cutoff  
19  
20 320 point may thus have under-evaluated the clinical usefulness of hs-CRP assays. To  
21  
22 321 make the best use of the biomarker information by adopting a two cutoff point  
23  
24 322 strategy or a multi-cutoff point risk classification strategy, an individual data  
25  
26 323 meta-analysis would be needed to overcome the limitations of this aggregated data  
27  
28 324 meta-analysis.  
29  
30  
31  
32  
33

## 326 Conclusions

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

333

334

335

336

337

1  
2  
3 338 Acknowledgement  
4

5 339 This study was supported by grants of Far Eastern Memorial Hospital, Taiwan  
6

7  
8 340 (FEMH-2013\_D\_036)  
9

10 341

11  
12 342 **Data sharing**  
13

14 343 The study results will be published in a peer-reviewed scientific journal. The  
15

16 344 extracted data will open to sharing upon request.  
17

18  
19 345

20  
21 346 **Contributorship**  
22

23 347

24  
25 348 C.H.Y.: study design, data management, statistics, first draft, final draft, and  
26

27 349 approval; S.H.L.: study design, scientific and statistic advisory, study monitoring,  
28

29 350 final draft, and approval; S.S.C.: statistics, final draft, and approval; M.C.L.; data  
30

31 351 collection, final draft, and approval; C.C.L.: design, scientific and statistic advisory,  
32

33 352 final draft, and approval.  
34

35  
36 353  
37

38 354  
39

40 355 **Competing Interest**  
41

42 356 None  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## References

1. Fabbri G, Maggioni AP. A review of the epidemiological profile of patients with atrial fibrillation and heart failure. *Expert review of cardiovascular therapy*. Sep 2012;10(9):1133-1140.
2. Menezes AR, Lavie CJ, DiNicolantonio JJ, et al. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. *Mayo Clinic proceedings. Mayo Clinic*. Apr 2013;88(4):394-409.
3. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. May 7 2013;61(18):1935-1944.
4. Manlucu J, Brancato S, Lane C, et al. Contemporary approaches to persistent atrial fibrillation. *Expert review of cardiovascular therapy*. Nov 2012;10(11):1421-1435.
5. Disertori M, Lombardi F, Barlera S, et al. Clinical characteristics of patients with asymptomatic recurrences of atrial fibrillation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. *American heart journal*. Aug 2011;162(2):382-389.
6. Letsas KP, Weber R, Burkle G, et al. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Feb 2009;11(2):158-163.
7. Liu T, Li L, Korantzopoulos P, Goudevenos JA, et al. Meta-analysis of association between C-reactive protein and immediate success of electrical cardioversion in persistent atrial fibrillation. *The American journal of cardiology*. Jun 15 2008;101(12):1749-1752.
8. Roberts WL, Sedrick R, Moulton L, et al. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. *Clinical chemistry*. Apr 2000;46(4):461-468.
9. Celebi OO, Celebi S, Canbay A, et al. The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion. *Cardiology*. 2011;118(3):168-174.
10. Barassi A, Pezzilli R, Morselli-Labate AM, et al. Serum amyloid a and C-reactive protein independently predict the recurrences of atrial fibrillation

- 1  
2  
3 after cardioversion in patients with preserved left ventricular function. *The*  
4 *Canadian journal of cardiology*. Sep-Oct 2012;28(5):537-541.
- 5  
6 11. Hatzinikolaou-Kotsakou E, Tziakas D, Hotidis A, et al. Relation of C-reactive  
7 protein to the first onset and the recurrence rate in lone atrial fibrillation. *The*  
8 *American journal of cardiology*. Mar 1 2006;97(5):659-661.
- 9  
10 12. Henningsen KM, Therkelsen SK, Bruunsgaard H, et al. Prognostic impact of  
11 hs-CRP and IL-6 in patients with persistent atrial fibrillation treated with  
12 electrical cardioversion. *Scandinavian journal of clinical and laboratory*  
13 *investigation*. 2009;69(3):425-432.
- 14  
15 13. Liu J, Fang PH, Dibs S, et al. High-sensitivity C-reactive protein as a predictor  
16 of atrial fibrillation recurrence after primary circumferential pulmonary vein  
17 isolation. *Pacing and clinical electrophysiology : PACE*. Apr  
18 2011;34(4):398-406.
- 19  
20 14. Lombardi F, Tundo F, Belletti S, et al. C-reactive protein but not atrial  
21 dysfunction predicts recurrences of atrial fibrillation after cardioversion in  
22 patients with preserved left ventricular function. *Journal of cardiovascular*  
23 *medicine (Hagerstown, Md.)*. Jun 2008;9(6):581-588.
- 24  
25 15. Loricchio ML, Cianfrocca C, Pasceri V, et al. Relation of C-reactive protein to  
26 long-term risk of recurrence of atrial fibrillation after electrical cardioversion.  
27 *The American journal of cardiology*. May 15 2007;99(10):1421-1424.
- 28  
29 16. Wazni O, Martin DO, Marrouche NF, et al. C reactive protein concentration and  
30 recurrence of atrial fibrillation after electrical cardioversion. *Heart (British*  
31 *Cardiac Society)*. Oct 2005;91(10):1303-1305.
- 32  
33 17. Rizos I, Rigopoulos AG, Kalogeropoulos AS, et al. Hypertension and  
34 paroxysmal atrial fibrillation: a novel predictive role of high sensitivity  
35 C-reactive protein in cardioversion and long-term recurrence. *Journal of human*  
36 *hypertension*. Jul 2010;24(7):447-457.
- 37  
38 18. Watanabe E, Arakawa T, Uchiyama T, et al. High-sensitivity C-reactive protein  
39 is predictive of successful cardioversion for atrial fibrillation and maintenance  
40 of sinus rhythm after conversion. *International journal of cardiology*. Apr 14  
41 2006;108(3):346-353.
- 42  
43 19. Zarauza J, Rodriguez Lera MJ, Farinas Alvarez C, et al. [Relationship between  
44 C-reactive protein level and early recurrence of atrial fibrillation after electrical  
45 cardioversion]. *Revista espanola de cardiologia*. Feb 2006;59(2):125-129.
- 46  
47 20. Leeflang MM, Deeks JJ, Gatsonis C, et al. Systematic reviews of diagnostic test  
48 accuracy. *Annals of internal medicine*. Dec 16 2008;149(12):889-897.
- 49  
50 21. Arends LR, Hamza TH, van Houwelingen JC, et al. Bivariate random effects  
51 meta-analysis of ROC curves. *Medical decision making : an international*  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 *journal of the Society for Medical Decision Making*. Sep-Oct  
4 2008;28(5):621-638.
- 5  
6 22. Harbord RM, Whiting P, Sterne JA, et al. An empirical comparison of methods  
7 for meta-analysis of diagnostic accuracy showed hierarchical models are  
8 necessary. *Journal of clinical epidemiology*. Nov 2008;61(11):1095-1103.
- 9  
10 23. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in  
11 meta-analyses. *BMJ (Clinical research ed.)*. Sep 6 2003;327(7414):557-560.
- 12  
13 24. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by  
14 a simple, graphical test. *BMJ (Clinical research ed.)*. Sep 13  
15 1997;315(7109):629-634.
- 16  
17 25. Buob A, Jung J, Siaplaouras S, et al. Discordant regulation of CRP and  
18 NT-proBNP plasma levels after electrical cardioversion of persistent atrial  
19 fibrillation. *Pacing and clinical electrophysiology : PACE*. Jun  
20 2006;29(6):559-563.
- 21  
22 26. Cosgrave J, Foley JB, Bahadur K, et al. Inflammatory markers are not associated  
23 with outcomes following elective external cardioversion. *International journal  
24 of cardiology*. Jun 28 2006;110(3):373-377.
- 25  
26 27. Ellinor PT, Low A, Patton KK, et al. C-Reactive protein in lone atrial fibrillation.  
27 *The American journal of cardiology*. May 1 2006;97(9):1346-1350.
- 28  
29 28. Korantzopoulos P, Kolettis TM, Kountouris E, et al. Variation of inflammatory  
30 indexes after electrical cardioversion of persistent atrial fibrillation. Is there an  
31 association with early recurrence rates? *International journal of clinical  
32 practice*. Aug 2005;59(8):881-885.
- 33  
34 29. Psychari SN, Chatzopoulos D, Iliodromitis EK, et al. C-reactive protein,  
35 interleukin 6, and N-terminal pro-brain natriuretic peptide following  
36 cardioversion of atrial fibrillation: is there a role of biomarkers in arrhythmia  
37 recurrence? *Angiology*. May 2011;62(4):310-316.
- 38  
39 30. Komatsu T, Sato Y, Ozawa M, et al. Relationship between CHADS2 score and  
40 efficacy of antiarrhythmic drug therapy in patients with paroxysmal atrial  
41 fibrillation. *Circulation journal : official journal of the Japanese Circulation  
42 Society*. Feb 25 2013;77(3):639-645.
- 43  
44 31. Letsas KP, Efremidis M, Giannopoulos G, et al. CHADS2 and CHA2DS2-VASc  
45 scores as predictors of left atrial ablation outcomes for paroxysmal atrial  
46 fibrillation. *Europace : European pacing, arrhythmias, and cardiac  
47 electrophysiology : journal of the working groups on cardiac pacing,  
48 arrhythmias, and cardiac cellular electrophysiology of the European Society of  
49 Cardiology*. Jun 28 2013.
- 50  
51 32. Albert CM, Ma J, Rifai N, et al. Prospective study of C-reactive protein,  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 homocysteine, and plasma lipid levels as predictors of sudden cardiac death.  
4 *Circulation*. Jun 4 2002;105(22):2595-2599.  
5  
6 33. Parekh RS, Plantinga LC, Kao WH, et al. The association of sudden cardiac  
7 death with inflammation and other traditional risk factors. *Kidney international*.  
8 Nov 2008;74(10):1335-1342.  
9  
10 34. Streitner F, Kuschyk J, Veltmann C, et al. Role of proinflammatory markers and  
11 NT-proBNP in patients with an implantable cardioverter-defibrillator and an  
12 electrical storm. *Cytokine*. Sep 2009;47(3):166-172.  
13  
14 35. Korngold EC, Januzzi JL, Jr., Gantzer ML, et al. Amino-terminal pro-B-type  
15 natriuretic peptide and high-sensitivity C-reactive protein as predictors of  
16 sudden cardiac death among women. *Circulation*. Jun 9  
17 2009;119(22):2868-2876.  
18  
19 36. Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of  
20 atrial fibrillation. *European heart journal*. Oct 2005;26(20):2083-2092.  
21  
22 37. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural  
23 remodeling during atrial fibrillation. *Cardiovascular research*. May  
24 2002;54(2):230-246.  
25  
26 38. Van Wagoner DR. Oxidative Stress and Inflammation in Atrial Fibrillation:  
27 Role in Pathogenesis and Potential as a Therapeutic Target. *Journal of*  
28 *Cardiovascular Pharmacology*. 2008;52(4):306-313  
29 310.1097/FJC.1090b1013e31817f39398.  
30  
31 39. Moro C, Hernandez-Madrid A, Matia R. Non-antiarrhythmic drugs to prevent  
32 atrial fibrillation. *American journal of cardiovascular drugs : drugs, devices,*  
33 *and other interventions*. 2010;10(3):165-173.  
34  
35 40. den Uijl DW, Delgado V, Tops LF, et al. Natriuretic peptide levels predict  
36 recurrence of atrial fibrillation after radiofrequency catheter ablation. *American*  
37 *heart journal*. Jan 2011;161(1):197-203.  
38  
39 41. Tang Y, Yang H, Qiu J. Relationship between brain natriuretic peptide and  
40 recurrence of atrial fibrillation after successful electrical cardioversion: a  
41 meta-analysis. *The Journal of international medical research*.  
42 2011;39(5):1618-1624.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 Figure legends  
5  
6

7 Figure 1. **A simplified flow chart to identify and to include studies.** Amongst 752  
8  
9 citations in MEDLINE and EMBASE from inception to December 2013, a search  
10  
11 limited to human studies using “C-reactive protein” and the MeSH term “diagnosis of  
12  
13 atrial fibrillation” resulted in 32 potentially relevant articles for further review. After  
14  
15 careful scrutinization on full text, 9 articles were left for meta-analysis.  
16  
17

18  
19  
20  
21 Figure 2. **The quality assessment of diagnostic accuracy on studies.** A spectrum of  
22  
23 features were analysed to avoid bias using a well-validated tool called Quality  
24  
25 Assessment of Diagnostics Accuracy Studies (QUADAS). Percentage for each feature  
26  
27 was independently evaluated among the studies. It is worthy of attention that none of  
28  
29 the studies explained the withdrawal and reported indetermined results, likely to  
30  
31 compromise the quality of diagnostic accuracy.  
32  
33  
34  
35  
36  
37

38  
39 Figure 3. **The ROC curve of hs-CRP.** Our analysis suggests it is highly possible to  
40  
41 predict atrial fibrillation using C-reative protein since the area under the curve  
42  
43 generates a measurement of discrimination  $\sim 0.77$ . The overall sensitivity and  
44  
45 specificity are relatively high. We have 5 out 9 studies that fall in the 95% CI region,  
46  
47  
48 while 8 out 9 in the 95% prediction region.  
49  
50  
51

52  
53 Figure 4. **The forest plot of the odds ratios (ORs).** Our study indicates that  
54  
55  
56  
57  
58  
59  
60  
hsCRP-positive patients are  $\sim 5.91$  times more likely to develop a recurrence of atrial

1  
2  
3  
4 fibrillation than hsCRP-negative patients are. The estimated sensitivity and specificity  
5  
6  
7 were relatively consistent across studies ( $I^2=14.6\%$ ).  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

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 <sup>16</sup>	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 <sup>19</sup>	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 <sup>18</sup>	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 <sup>15</sup>	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 <sup>14</sup>	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 <sup>12</sup>	65	0.68(56)	180 days	3.0	Persistent AF	Electric	60%, 83%	7.7 (1.9-31.1) *	NA
Rizos I, 2010, Greece <sup>17</sup>	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 <sup>13</sup>	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 <sup>10</sup>	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 <sup>2</sup> (95% CI)	Diagnostic OR (95% CI)	Meta-regression P	Egger's test P
Overall <sup>10,12-19</sup>	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 <sup>10,14,16,19</sup>	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 <sup>12-14,17,18</sup>	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 <sup>10,12,14-16,18,19</sup>	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 <sup>10,12,14-16,18,19</sup>	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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

3  
4 <sup>1</sup>Chia-Hung Yo MD, <sup>2</sup>Si-Huei Lee MD <sup>3,4</sup>Shy-Shin Chang MD, <sup>5</sup>Matthew  
5 Chien-Hung Lee PhD, JD, <sup>6,7,5</sup>Chien-Chang Lee MD, MSc

6  
7 <sup>1</sup>Department of Emergency Medicine, Far Eastern Memorial Hospital, New Taipei  
8 City, Taiwan.

9 <sup>2</sup>Department of Rehabilitation and Physical Medicine, Taipei Veteran  
10 General Hospital, Taipei, Taiwan

11 <sup>3</sup>Department of Family Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

12 <sup>4</sup>Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung  
13 University, Taoyuan, Taiwan.

14 <sup>5</sup>Medical Wisdom Consultants, Houston, USA

15 <sup>6,4</sup>Department of Epidemiology, Harvard School of Public Health, Boston, USA.

16 <sup>7,5</sup>Department of Emergency Medicine, National Taiwan University Hospital Yunlin  
17 Branch, Douliou, Taiwan

18 Address correspondence to

19 Chien-Chang Lee MD, MSc

20 Email: clee100@gmail.com

21 Postal Address: No 579 Sec 2 Yunlin Road, Douliou, Yunlin County 640, Taiwan

22 Telephone: +886-5-532-3911 ext. 2326

23 Fax: +886-2322-3150

24 Word count: 2535

25 Conflict of interest: None declared

1  
2  
3  
4 26 Abstract

5 27 Objectives: We performed a systematic review and meta-analysis of studies on  
6  
7  
8 28 high-sensitivity C-reactive protein (hs-CRP) assays to see whether these tests are  
9  
10 29 predictive of atrial fibrillation (AF) recurrence after cardioversion.  
11  
12 30

13  
14 31 Design: Systematic review and meta-analysis.  
15  
16 32

17  
18  
19 33 Data sources: PubMed, EMBASE, and Cochrane databases as well as a hand search of  
20  
21 34 the reference lists in the retrieved articles from inception to December 2013.  
22  
23 35

24  
25 36 Study eligibility criteria: This review selected observational studies in which the  
26  
27 37 measurements of serum CRP were used to predict atrial fibrillation recurrence. An  
28  
29 38 hs-CRP assay was defined as any c-reactive protein (CRP) test capable of measuring  
30  
31 39 serum CRP to below 0.6 mg/dL.  
32  
33 40

34  
35  
36 41 Primary and secondary outcome measures: We summarized test performance  
37  
38 42 characteristics with the use of forest plots, hierarchical summary receiver operating  
39  
40 43 characteristic (HSROC) curves, and bivariate random effects models. Meta-regression  
41  
42 44 analysis was performed to explore the source of heterogeneity.  
43  
44 45

45  
46 46 Results: We included nine qualifying studies comprising a total of 347 patients with AF  
47  
48 47 recurrence and 335 controls. A CRP level higher than the optimal cutoff point was an  
49  
50 48 independent predictor of AF recurrence after cardioversion (summary adjusted odds  
51  
52 49 ratio: 3.33; 95%CI: 2.10-5.28). The estimated pooled sensitivity and specificity for  
53  
54 50 hs-CRP was 71.0% (95% CI: 63% to 78%) and 72.0% (61% to 81%), respectively.  
55  
56 51

57  
58 51 Most studies used a CRP cutoff point of 1.9 mg/l to predict long-term AF recurrence  
59  
60

52 (77% sensitivity, 65% specificity), and 3 mg/l to predict short-term AF recurrence (73%  
53 sensitivity, 71% specificity).

54

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

58

59 Strengths and limitations of this study

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

74

75 Keywords: atrial fibrillation, recurrence, cardioversion, C - reactive protein,

76 meta-analysis

77

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
6078  
79 Introduction

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

98  
99 C-reactive protein (CRP) is an acute-phase reactant whose levels increase in response  
100 to proinflammatory cytokines, notably interleukin-6, and other endogenous signals of  
101 innate immunity or tissue damage. CRP has recently been shown to be associated with  
102 cardiovascular risk and AF recurrence. A previous meta-analysis revealed that CRP is  
103 elevated in patients with AF.<sup>7</sup> However, 5 of the 6 studies included in that analysis

1  
2  
3  
4 104 used traditional automated immunonephelometric assays to measure CRP.  
5  
6 105 Unfortunately, those assays are insufficiently sensitive for measuring the low level of  
7  
8 106 inflammation associated with AF. A newer enzyme immunoassay, namely  
9  
10 107 high-sensitivity CRP (hs-CRP), is capable of measuring serum CRP below 0.6 mg/dL  
11  
12 108 and may further enhance the predictability of AF recurrence.<sup>8</sup> Since 2006, several  
13  
14 109 studies evaluating the accuracy of hs-CRP in predicting AF recurrence have been  
15  
16 110 published,<sup>9-19</sup> warranting a systemic and quantitative summary of current evidence on  
17  
18 111 the accuracy of CRP in predicting AF recurrence after cardioversion.  
19  
20  
21 112

## 22 23 113 Methods

### 24 114 Identification of Studies

25  
26 115 General bibliographic databases (MEDLINE and EMBASE) were searched from  
27  
28 116 inception to April 2013. The medical subject heading (MeSH) and text words for the  
29  
30 117 term C -reactive protein were combined with the MeSH term “diagnosis of atrial  
31  
32 118 fibrillation”. The search was limited to human studies with no language restrictions.  
33  
34  
35 119 In addition to the electronic search, reference lists in all known reviews and primary  
36  
37 120 studies were checked manually.  
38  
39  
40 121

### 41 42 122 Selection Criteria

43  
44 123 This review focused on observational studies in which the measurements of serum  
45  
46 124 CRP were used to predict atrial fibrillation recurrence. The population of interest  
47  
48 125 comprised patients with paroxysmal or persistent AF who underwent electric  
49  
50 126 cardioversion, ablation therapy, or pharmacological cardioversion. AF recurrence was  
51  
52 127 defined as AF documented by ECG at any time after the cardioversion during the  
53  
54 128 follow-up period. Generally, patients were instructed to return to the clinic if the  
55  
56 129 symptoms such as palpitations, shortness of breath, or chest discomfort developed  
57  
58  
59  
60

1  
2  
3  
4 130 after cardioversion. We included studies using a cohort design or case-control design  
5  
6 131 with appropriate controls. Two reviewers independently assessed eligible articles for  
7  
8 132 inclusion. Disagreements were initially resolved by consensus and using arbitration  
9  
10 133 by a third reviewer if consensus could not be reached by the two reviewers. We  
11  
12 134 extracted data from the included studies. Data collected include study design,  
13  
14 135 participants, country, period of recruitment, hs-CRP assay, cutoff-points, length of  
15  
16 136 follow-up period, and recurrence of AF. One reviewer extracted the data and a second  
17  
18 137 reviewer independently verified the correctness of the extracted data.  
19  
20  
21 138

### 22 23 139 Quality Assessment

24  
25 140 We assessed the methodological quality of the selected studies using a well-validated  
26  
27 141 tool for assessment of quality of diagnostic accuracy studies (Quality Assessment of  
28  
29 142 Diagnostic Accuracy Studies, QUADAS).<sup>20</sup> The QUADAS instrument scrutinizes  
30  
31 143 characteristics of study designs, population, index tests, and reference standards that  
32  
33 144 may be associated with risk of bias. These features included the spectrum of patients,  
34  
35 145 whether index tests and reference standards were evaluated and interpreted  
36  
37 146 independently to avoid incorporation bias, and whether all patients underwent the  
38  
39 147 same reference standards to avoid differential or partial verification bias.  
40  
41  
42 148

### 43 44 45 149 Data Abstraction

46  
47 150 One reviewer independently extracted the data and a second reviewer independently  
48  
49 151 verified the data. Extracted data comprised the following: overall study characteristics  
50  
51 152 (including the first author, country, language, and date of publication); patient  
52  
53 153 characteristics (including age range and pre-existing atrial fibrillation); quantitative  
54  
55 154 data required for construction of a 2 x 2 table (including number of participants,  
56  
57 155 sensitivity, specificity, and recurrence case number); information regarding the  
58  
59  
60

1  
2  
3  
4 156 hs-CRP assay (including brand name of the test kit, cutoff levels, and quantitative or  
5  
6 157 semi-quantitative nature of the test); and study settings. In studies that reported  
7  
8 158 multiple pairs of sensitivity and specificity data, we consistently used the data with  
9  
10 159 the highest Youden index (sensitivity + specificity - 1) and performed a sensitivity  
11  
12 160 analysis at a later stage.

13  
14 161

#### 15 162 Quantitative Data Synthesis

16 163 We performed a meta-analysis of diagnostic test accuracy of CRP testing for the  
17  
18 164 prediction of recurrent AF. ~~When 2 × 2 tables contained 0 cells, we performed~~  
19  
20  
21  
22  
23 165 ~~continuity correction by adding 0.5 to each cell.~~ We calculated the pooled sensitivity  
24  
25 166 and specificity, positive and negative likelihood ratios, and the diagnostic odds ratio  
26  
27 167 of CRP, along with the respective 95% confidence intervals (CIs), using a bivariate  
28  
29 168 meta-analysis model.<sup>21</sup> Likelihood ratios were then translated to post-test probability  
30  
31 169 by use of Fagan's plot. We constructed a hierarchical summary receiver operating  
32  
33 170 characteristic (HSROC) curve that plots sensitivity versus specificity and calculated  
34  
35 171 the area under the curve (AUROC).<sup>22</sup> We evaluated the degree of between-study  
36  
37 172 heterogeneity by using the I<sup>2</sup> test.<sup>23</sup> To explore the clinical sources of heterogeneity,  
38  
39 173 we defined the potential explanatory variables *a priori* and performed subgroup  
40  
41 174 analysis to see if the accuracy estimates changed significantly across various  
42  
43 175 subgroups. The presence and the effect of publication bias were examined using a  
44  
45 176 combination of the Egger tests.<sup>24</sup> Statistical analyses were conducted using the  
46  
47 177 statistical package STATA (Version 11.0, Stata Corp, College Station, TX), notably  
48  
49 178 with the user-written "midas" and "metandi" programs. All statistical tests were  
50  
51 179 two-sided and statistical significance was defined as a P value less than .05.  
52  
53  
54  
55

56 180

#### 57 181 Search Results and Study Characteristics



1  
2  
3  
4 182 The flow of inclusion and exclusion is summarized in Figure 1. Using our search  
5  
6 183 criteria, we identified 784 studies, of which 352 were from PubMed and 432 were  
7  
8 184 from EMBASE. A total of 752 citations were excluded based on pre-defined criteria.  
9  
10 185 No additional citations were identified from the reference lists. A total of 32 articles  
11  
12 186 were retrieved for full-text review, and 23 were excluded due to various reasons  
13  
14 187 detailed in Figure 1. A total of 9 studies that evaluated the accuracy of hs-CRP tests in  
15  
16 188 predicting AF recurrence after cardioversion were finally included in the  
17  
18 189 meta-analysis. The 9 studies included a total of 682 patients with AF after successful  
19  
20 190 cardioversion, of which 347 (50.9%) developed recurrence.  
21  
22  
23  
24

#### 25 192 Characteristics of included studies

26  
27 193 Table 1 lists the study and population characteristics of the 9 patient populations even  
28  
29 194 if we had additional 5 studies that don't have sufficient data for statistical analysis<sup>25-29</sup>.

30  
31  
32 195 The mean age of patients in the included studies ranged from 55.1 years to 67.9 years  
33  
34 196 and the mean follow-up period ranged from 30 days to 1 year. Seven studies included  
35  
36 197 patients with persistent AF, while 2 studies included patients with paroxysmal AF.

37  
38 198 Seven studies used electric shock, one used circumferential pulmonary vein isolation  
39  
40 199 (also known as electric ablation), and the other used intravenous amiodarone as the  
41  
42 200 primary method for cardioversion. A total of seven studies provided multivariate  
43  
44 201 (adjusted) odds ratios to evaluate the independent predictive value of CRP levels.

45  
46  
47 202 These studies generally adjusted for potential predictors of AF recurrence such as age,  
48  
49 203 sex, use of anti-arrhythmic agents, and heart structural and functional parameters. All  
50  
51 204 studies showed that CRP was a significant independent predictor of AF recurrence.

52  
53 205 Associated adjusted ratios and adjusted variables are summarized in table 1.  
54  
55  
56  
57

#### 58 207 Quality assessment

1  
2  
3  
4 208 Results of the quality assessment of studies of diagnostic accuracy are summarized in  
5  
6 209 figure 2. All studies were prospective and enrolled consecutive outpatients with AF  
7  
8 210 after cardioversion. Three studies had a short follow-up period (i.e. ≤0.5 or 1 year).  
9  
10 211 Although most of the studies did not indicate whether physicians were blinded to the  
11  
12 212 index tests when diagnosing AF recurrence, the determination of AF recurrence was  
13  
14 213 not affected by the knowledge of hs-CRP test results and risk of incorporation bias  
15  
16 214 was minimal. None of the studies reported the undetermined results or withdrawals.  
17  
18  
19

20  
21 216 Diagnostic accuracy indices

22  
23 217 Sensitivity, specificity, and diagnostic odds ratio

24  
25 218 The estimated sensitivity and specificity were relatively consistent across studies

26  
27 219 ( $I^2=14.6\%$ ). Table 2 shows the results of individual and combined sensitivity

28  
29 220 estimates for the tests. The estimated pooled sensitivity and specificity for hs-CRP

30  
31 221 was 71.0% (95% confidence interval 63% to 78%) and 72.0% (61% to 81%),

32  
33 222 respectively. The pooled prevalence of AF recurrence was 54% herein, and we used

34  
35 223 the pooled prevalence of AF recurrence in this study as the pre-test probability. With

36  
37 224 a pooled positive likelihood ratio of 2.57 and a negative likelihood ratio of 0.4, the

38  
39 225 post-test probability for AF recurrence for a positive hs-CRP test result was 72% and a

40  
41 226 post-test probability for a negative hs-CRP test result was 29%. The area under the

42  
43 227 ROC curve showed an acceptable overall measurement of discrimination (0.77,

44  
45 228 Figure 3). Figure 4 shows the forest plot of the ORs.  
46  
47  
48

49 229

50  
51 230 Subgroup analysis and meta-regression

52  
53 231 In view of the potential influence of spectrum variability, we considered the duration

54  
55 232 of follow-up, mode of cardioversion, and type of AF in the study patients to be

56  
57 233 important. Hs-CRP test results generally had higher sensitivity and lower specificity

1  
2  
3  
4 234 in predicting long-term over short-term AF recurrence. Excluding two studies not  
5  
6 235 using electric shock as the primary cardioversion method did not significantly alter  
7  
8 236 the predictive accuracy. Similarly, *focusing the study patients on persistent AF*  
9  
10 237 *population* had similar results as compared with the main overall analysis.  
11  
12 238 Exploratory meta-regression analysis did not find that any pre-specified covariate  
13  
14 239 significantly changed the effect estimate.  
15  
16  
17 240

## 18 241 Discussion

20 242 This meta-analysis shows that elevated CRP levels are independently predictive of AF  
21  
22 243 recurrence in patients with persistent or paroxysmal AF who have undergone  
23  
24 244 successful cardioversion. This finding supports that measurement of CRP levels  
25  
26 245 before cardioversion can aid in the prediction of AF recurrence. Despite the modest  
27  
28 246 pooled sensitivity and specificity, the rule-in diagnostic value was still high, given the  
29  
30 247 high recurrence rate of AF observed in these included studies. A positive hs-CRP test  
31  
32 248 result at baseline can predict a 73% chance of AF recurrence in the 6 to 12 months  
33  
34 249 following cardioversion.  
35  
36 250

37  
38  
39  
40 251 Previous studies have examined risk factors that predict AF recurrence. Traditional  
41  
42 252 clinical risk factors for recurrence include history of multiple AF episodes, use of  
43  
44 253 diuretic treatment, higher CHADS-2 (Congestive heart failure, history of  
45  
46 254 Hypertension, Age $\geq$ 75 years, Diabetes mellitus, and past history of Stroke or TIA  
47  
48 255 doubled) index score, frequent use of amiodarone, calcium-channel blockers, and 1C  
49  
50 256 drugs, and digitalis.<sup>30,31</sup> Although each of these factors could predict AF recurrence  
51  
52 257 with some accuracy, a quantitative combination of these predictors is not available,  
53  
54 258 and the clinical utility of these variables remains questionable. This also suggests that  
55  
56 259 a multivariate prediction model should be developed for AF recurrence, and that  
57  
58  
59  
60

1  
2  
3  
4 260 hsCRP should be a candidate for inclusion in the model.  
5  
6 261

7  
8 262 During the past decade, serum biomarkers have emerged as practical tools to help in  
9  
10 263 the early identification of patients at high risk for various cardiac events. Elevation of  
11  
12 264 inflammatory markers is associated with sudden cardiac death in patients with heart  
13  
14 265 failure or coronary artery disease, and onset of ventricular arrhythmia.<sup>32-35</sup> Of note,  
15  
16 266 there is abundant evidence that elevated serum levels of CRP are associated with the  
17  
18 267 genesis and perpetuation of atrial fibrillation. CRP is the most commonly used clinical  
19  
20 268 inflammatory biomarker. It is mainly produced in liver and by inflammatory cells in  
21  
22 269 response to proinflammatory cytokine stimulation. Although the pathophysiology of  
23  
24 270 AF remains elusive, there is pathophysiological evidence supporting the role of  
25  
26 271 inflammation in the initiation, maintenance, and perpetuation of AF.<sup>36</sup> Clinically, AF  
27  
28 272 is frequently associated with local inflammatory diseases such as myocarditis or  
29  
30 273 pericarditis, and systemic inflammatory status, such as post-operative state and severe  
31  
32 274 sepsis. Histologically, structural remodeling of the atria manifested by loss of  
33  
34 275 myocardium and increased atrial fibrosis is a hallmark of atrial fibrillation.<sup>37</sup>  
35  
36 276 Inflammatory cell infiltrates and oxidative damage have been demonstrated in atrial  
37  
38 277 biopsy specimens from AF patients.<sup>38</sup> Activated inflammatory cells in conjunction  
39  
40 278 with reactive oxygen species, cytokines, and growth factors, may ultimately lead to  
41  
42 279 matrix deposition with atrial fibrosis. Recent evidence also shows that the uses of  
43  
44 280 immune-modulating agents such as statins, angiotensin-converting enzyme inhibitors,  
45  
46 281 or glucocorticoids modulate the course of AF.<sup>39</sup>  
47  
48  
49  
50  
51

52  
53 283 In addition to CRP, b-type natriuretic peptide (BNP) has been shown to be an indicator  
54  
55 284 of new onset AF and AF recurrence after successful cardioversion.<sup>34,35,40</sup> BNP is also  
56  
57 285 produced in response to atrial pressure and volume overload and there is evidence that  
58  
59  
60

1  
2  
3  
4 286 BNP is secreted by the atrium in patients with AF. A previous meta-analysis showed  
5  
6 287 that the standardized mean difference in plasma BNP level between patients with  
7  
8 288 non-recurrence and patients with recurrence was -1.35 (95% confidence interval -2.17,  
9  
10 289 -0.53).<sup>41</sup> Data on sensitivity and specificity in that study were not available. The  
11  
12 290 comparative accuracy between BNP and hs-CRP in predicting AF recurrence thus  
13  
14 291 requires further analysis.  
15

16  
17 292

18  
19 293 There are both strengths and limitations in our study. Considering the limitation of  
20  
21 294 sensitivity and specificity in clinical interpretation, we reported summary likelihood  
22  
23 295 ratios (LRs) as an ancillary measure of predictive accuracy. The LR indicates how  
24  
25 296 much a given CRP testing result increases or decreases the probability of recurrence  
26  
27 297 of AF. Post-test probabilities can be derived from pre-test probabilities and LR,  
28  
29 298 which are an important clinical parameter for major clinical decision making. Second,  
30  
31 299 we used a bivariate random effect model to account for the inherent negative  
32  
33 300 correlation arising from different cutoff values used in different studies, and occurring  
34  
35 301 between the logit TPR and FPR. Third, we performed sensitivity analysis by  
36  
37 302 restricting analysis within two broad categories of follow-up duration. Results of  
38  
39 303 sensitivity analysis did not show a significantly different overall predictive accuracy  
40  
41 304 between long-term and short-term ~~follow-up~~ prediction of AF recurrence. Nonetheless,  
42  
43 305 it is noteworthy that the sensitivity may be over estimated in our study under the  
44  
45 306 hypothesis where the inflammation may be symptomatic since none of the studies  
46  
47 307 provided withdrawal and undetermined results, and the ascertainment of AF was  
48  
49 308 passive. This event further introduces the differential verification bias. Moreover, our  
50  
51 309 meta-analysis is restricted to distinguish hsCRP levels above or below 0.6 mg/dL  
52  
53 310 because the authors in only one of the studies claimed to possess such capability.  
54  
55 311 Finally, due to the lack of individual data, it is hard to determine whether the area  
56  
57  
58  
59  
60

1  
2  
3  
4 312 under ROC (AUC) can be improved by the new assay either on overall or on  
5  
6 313 individual studies. In general, Overall, as assessed by the heterogeneity of dOR, the  
7  
8 314 included studies evaluating CRP levels and AF recurrence strongly tended toward  
9  
10 315 between study variability (heterogeneity). Potential sources of between-study  
11  
12 316 variability included differences in incidence of AF recurrence, different threshold  
13  
14 317 values of CRP concentration used, and different duration for follow-up. Another  
15  
16 318 limitation was the strategy we used to determine the optimal cutoff value. Most  
17  
18 319 studies determined an optimal cutoff value to maximize both sensitivity and  
19  
20 320 specificity. Although a single cutoff value is straightforward in clinical interpretation,  
21  
22 321 it may make a marker neither sensitive nor specific enough to rule out or rule in an  
23  
24 322 outcome of interest. A two cut-off value strategy, with one using a lower cutoff value  
25  
26 323 to optimize the sensitivity (rule-out value) and the other using a higher cutoff value to  
27  
28 324 optimize the specificity (rule-in value), would make better use of the information that  
29  
30 325 a biomarker with a continuous value could provide. Current summary estimates based  
31  
32 326 on the one cutoff point may thus have under-evaluated the clinical usefulness of  
33  
34 327 hs-CRP assays. To make the best use of the biomarker information by adopting a two  
35  
36 328 cutoff point strategy or a multi-cutoff point risk classification strategy, an individual  
37  
38 329 data meta-analysis would be needed to overcome the limitations of this aggregated  
39  
40 330 data meta-analysis.

41 331

## 42 332 Conclusions

43 333 Baseline CRP levels before cardioversion can independently predict AF recurrence  
44  
45 334 after successful cardioversion. Given the high recurrence rate reported in most series,  
46  
47 335 the modest positive likelihood ratio for hs-CRP assays still has high positive  
48  
49 336 predictive value. Future studies should focus on the evaluation of two or multiple  
50  
51 337 cutoff points. In the interim, their inclusion in existing pre-cardioversion evaluation

1  
2  
3  
4 338 algorithms should be considered.  
5  
6 339  
7  
8 340  
9

10 341 Acknowledgement

11 342 This study was supported by grants of Far Eastern Memorial Hospital, Taiwan  
12  
13  
14 343 (FEMH-2013\_D\_036)  
15

16 344  
17  
18  
19 345  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## References

1. Fabbri G, Maggioni AP. A review of the epidemiological profile of patients with atrial fibrillation and heart failure. *Expert review of cardiovascular therapy*. Sep 2012;10(9):1133-1140.
2. Menezes AR, Lavie CJ, DiNicolantonio JJ, et al. Atrial fibrillation in the 21st century: a current understanding of risk factors and primary prevention strategies. *Mayo Clinic proceedings. Mayo Clinic*. Apr 2013;88(4):394-409.
3. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. May 7 2013;61(18):1935-1944.
4. Manlucu J, Brancato S, Lane C, Kazemian P, Michaud GF. Contemporary approaches to persistent atrial fibrillation. *Expert review of cardiovascular therapy*. Nov 2012;10(11):1421-1435.
5. Disertori M, Lombardi F, Barlera S, et al. Clinical characteristics of patients with asymptomatic recurrences of atrial fibrillation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. *American heart journal*. Aug 2011;162(2):382-389.
6. Letsas KP, Weber R, Burkle G, et al. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Feb 2009;11(2):158-163.
7. Liu T, Li L, Korantzopoulos P, Goudevenos JA, Li G. Meta-analysis of association between C-reactive protein and immediate success of electrical cardioversion in persistent atrial fibrillation. *The American journal of cardiology*. Jun 15 2008;101(12):1749-1752.
8. Roberts WL, Sedrick R, Moulton L, Spencer A, Rifai N. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. *Clinical chemistry*. Apr 2000;46(4):461-468.
9. Celebi OO, Celebi S, Canbay A, Ergun G, Aydogdu S, Diker E. The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion. *Cardiology*. 2011;118(3):168-174.
10. Barassi A, Pezzilli R, Morselli-Labate AM, et al. Serum amyloid a and C-reactive protein independently predict the recurrences of atrial fibrillation

- 1  
2  
3 after cardioversion in patients with preserved left ventricular function. *The*  
4 *Canadian journal of cardiology*. Sep-Oct 2012;28(5):537-541.
- 5  
6 11. Hatzinikolaou-Kotsakou E, Tziakas D, Hotidis A, et al. Relation of C-reactive  
7 protein to the first onset and the recurrence rate in lone atrial fibrillation. *The*  
8 *American journal of cardiology*. Mar 1 2006;97(5):659-661.
- 9  
10 12. Henningsen KM, Therkelsen SK, Bruunsgaard H, Krabbe KS, Pedersen BK,  
11 Svendsen JH. Prognostic impact of hs-CRP and IL-6 in patients with persistent  
12 atrial fibrillation treated with electrical cardioversion. *Scandinavian journal of*  
13 *clinical and laboratory investigation*. 2009;69(3):425-432.
- 14  
15 13. Liu J, Fang PH, Dibs S, Hou Y, Li XF, Zhang S. High-sensitivity C-reactive  
16 protein as a predictor of atrial fibrillation recurrence after primary  
17 circumferential pulmonary vein isolation. *Pacing and clinical*  
18 *electrophysiology : PACE*. Apr 2011;34(4):398-406.
- 19  
20 14. Lombardi F, Tundo F, Belletti S, Mantero A, Melzi D'eril G V. C-reactive  
21 protein but not atrial dysfunction predicts recurrences of atrial fibrillation after  
22 cardioversion in patients with preserved left ventricular function. *Journal of*  
23 *cardiovascular medicine (Hagerstown, Md.)*. Jun 2008;9(6):581-588.
- 24  
25 15. Loricchio ML, Cianfrocca C, Pasceri V, et al. Relation of C-reactive protein to  
26 long-term risk of recurrence of atrial fibrillation after electrical cardioversion.  
27 *The American journal of cardiology*. May 15 2007;99(10):1421-1424.
- 28  
29 16. Wazni O, Martin DO, Marrouche NF, et al. C reactive protein concentration and  
30 recurrence of atrial fibrillation after electrical cardioversion. *Heart (British*  
31 *Cardiac Society)*. Oct 2005;91(10):1303-1305.
- 32  
33 17. Rizos I, Rigopoulos AG, Kalogeropoulos AS, et al. Hypertension and  
34 paroxysmal atrial fibrillation: a novel predictive role of high sensitivity  
35 C-reactive protein in cardioversion and long-term recurrence. *Journal of human*  
36 *hypertension*. Jul 2010;24(7):447-457.
- 37  
38 18. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity  
39 C-reactive protein is predictive of successful cardioversion for atrial fibrillation  
40 and maintenance of sinus rhythm after conversion. *International journal of*  
41 *cardiology*. Apr 14 2006;108(3):346-353.
- 42  
43 19. Zarauza J, Rodriguez Lera MJ, Farinas Alvarez C, et al. [Relationship between  
44 C-reactive protein level and early recurrence of atrial fibrillation after electrical  
45 cardioversion]. *Revista espanola de cardiologia*. Feb 2006;59(2):125-129.
- 46  
47 20. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of  
48 diagnostic test accuracy. *Annals of internal medicine*. Dec 16  
49 2008;149(12):889-897.
- 50  
51 21. Arends LR, Hamza TH, van Houwelingen JC, Heijenbrok-Kal MH, Hunink MG,  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 Stijnen T. Bivariate random effects meta-analysis of ROC curves. *Medical*  
4 *decision making : an international journal of the Society for Medical Decision*  
5 *Making*. Sep-Oct 2008;28(5):621-638.
- 6  
7 22. Harbord RM, Whiting P, Sterne JA, et al. An empirical comparison of methods  
8 for meta-analysis of diagnostic accuracy showed hierarchical models are  
9 necessary. *Journal of clinical epidemiology*. Nov 2008;61(11):1095-1103.
- 10  
11 23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in  
12 meta-analyses. *BMJ (Clinical research ed.)*. Sep 6 2003;327(7414):557-560.
- 13  
14 24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis  
15 detected by a simple, graphical test. *BMJ (Clinical research ed.)*. Sep 13  
16 1997;315(7109):629-634.
- 17  
18 25. Buob A, Jung J, Siaplaouras S, Neuberger HR, Mewis C. Discordant regulation  
19 of CRP and NT-proBNP plasma levels after electrical cardioversion of  
20 persistent atrial fibrillation. *Pacing and clinical electrophysiology : PACE*. Jun  
21 2006;29(6):559-563.
- 22  
23 26. Cosgrave J, Foley JB, Bahadur K, Bennett K, Crean P, Walsh MJ. Inflammatory  
24 markers are not associated with outcomes following elective external  
25 cardioversion. *International journal of cardiology*. Jun 28  
26 2006;110(3):373-377.
- 27  
28 27. Ellinor PT, Low A, Patton KK, Shea MA, MacRae CA. C-Reactive protein in  
29 lone atrial fibrillation. *The American journal of cardiology*. May 1  
30 2006;97(9):1346-1350.
- 31  
32 28. Korantzopoulos P, Kolettis TM, Kountouris E, Siogas K, Goudevenos JA.  
33 Variation of inflammatory indexes after electrical cardioversion of persistent  
34 atrial fibrillation. Is there an association with early recurrence rates?  
35 *International journal of clinical practice*. Aug 2005;59(8):881-885.
- 36  
37 29. Psychari SN, Chatzopoulos D, Iliodromitis EK, Apostolou TS, Kremastinos DT.  
38 C-reactive protein, interleukin 6, and N-terminal pro-brain natriuretic peptide  
39 following cardioversion of atrial fibrillation: is there a role of biomarkers in  
40 arrhythmia recurrence? *Angiology*. May 2011;62(4):310-316.
- 41  
42 30. Komatsu T, Sato Y, Ozawa M, et al. Relationship between CHADS2 score and  
43 efficacy of antiarrhythmic drug therapy in patients with paroxysmal atrial  
44 fibrillation. *Circulation journal : official journal of the Japanese Circulation*  
45 *Society*. Feb 25 2013;77(3):639-645.
- 46  
47 31. Letsas KP, Efremidis M, Giannopoulos G, et al. CHADS2 and CHA2DS2-VASc  
48 scores as predictors of left atrial ablation outcomes for paroxysmal atrial  
49 fibrillation. *Europace : European pacing, arrhythmias, and cardiac*  
50 *electrophysiology : journal of the working groups on cardiac pacing,*  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Jun 28 2013.
32. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation*. Jun 4 2002;105(22):2595-2599.
33. Parekh RS, Plantinga LC, Kao WH, et al. The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney international*. Nov 2008;74(10):1335-1342.
34. Streitner F, Kuschik J, Veltmann C, et al. Role of proinflammatory markers and NT-proBNP in patients with an implantable cardioverter-defibrillator and an electrical storm. *Cytokine*. Sep 2009;47(3):166-172.
35. Korngold EC, Januzzi JL, Jr., Gantzer ML, Moorthy MV, Cook NR, Albert CM. Amino-terminal pro-B-type natriuretic peptide and high-sensitivity C-reactive protein as predictors of sudden cardiac death among women. *Circulation*. Jun 9 2009;119(22):2868-2876.
36. Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *European heart journal*. Oct 2005;26(20):2083-2092.
37. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovascular research*. May 2002;54(2):230-246.
38. Van Wagoner DR. Oxidative Stress and Inflammation in Atrial Fibrillation: Role in Pathogenesis and Potential as a Therapeutic Target. *Journal of Cardiovascular Pharmacology*. 2008;52(4):306-313  
310.1097/FJC.1090b1013e31817f39398.
39. Moro C, Hernandez-Madrid A, Matia R. Non-antiarrhythmic drugs to prevent atrial fibrillation. *American journal of cardiovascular drugs : drugs, devices, and other interventions*. 2010;10(3):165-173.
40. den Uijl DW, Delgado V, Tops LF, et al. Natriuretic peptide levels predict recurrence of atrial fibrillation after radiofrequency catheter ablation. *American heart journal*. Jan 2011;161(1):197-203.
41. Tang Y, Yang H, Qiu J. Relationship between brain natriuretic peptide and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. *The Journal of international medical research*. 2011;39(5):1618-1624.

1  
2  
3  
4 Figure legends

5  
6  
7 Figure 1. A simplified flow chart to identify and to include studies. Amongst 752  
8  
9  
10 citations in MEDLINE and EMBASE from inception to December 2013, a search  
11  
12 limited to human studies using “C-reactive protein” and the MeSH term “diagnosis of  
13 atrial fibrillation” resulted in 32 potentially relevant articles for further review. After  
14  
15 careful scrutinization on full text, 9 articles were left for meta-analysis.

16  
17  
18  
19  
20  
21 Figure 2. The quality assessment of diagnostic accuracy on studies. A spectrum of  
22 features were analysed to avoid bias using a well-validated tool called Quality  
23  
24 Assessment of Diagnostics Accuracy Studies (QUADAS). Percentage for each feature  
25  
26 was independently evaluated among the studies. It is worthy of attention that none of  
27  
28 the studies explained the withdrawal and reported indetermined results, likely to  
29  
30 compromise the quality of diagnostic accuracy.

31  
32  
33  
34  
35  
36  
37  
38  
39 Figure 3. The ROC curve of hs-CRP. Our analysis suggests it is highly possible to  
40  
41 predict atrial fibrillation using C-reative protein since the area under the curve  
42  
43 generates a measurement of discrimination ~0.77. The overall sensitivity and  
44  
45 specificity are relatively high. We have 5 out 9 studies that fall in the 95% CI region,  
46  
47 while 8 out 9 in the 95% prediction region.

48  
49  
50  
51  
52  
53 Figure 4. The forest plot of the odds ratios (ORs). Our study indicates that  
54  
55 hsCRP-positive patients are ~5.91 times more likely to develop a recurrence of atrial  
56  
57

1  
2  
3  
4 fibrillation than hsCRP-negative patients are. The estimated sensitivity and specificity  
5  
6  
7 were relatively consistent across studies ( $I^2=14.6\%$ ).  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

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 <sup>16</sup>	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 <sup>19</sup>	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 <sup>18</sup>	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 <sup>15</sup>	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 <sup>14</sup>	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 <sup>12</sup>	65	0.68(56)	180 days	3.0	Persistent AF	Electric	60%, 83%	7.7 (1.9-31.1) *	NA
Rizos I, 2010,Greece <sup>17</sup>	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 <sup>13</sup>	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 <sup>10</sup>	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

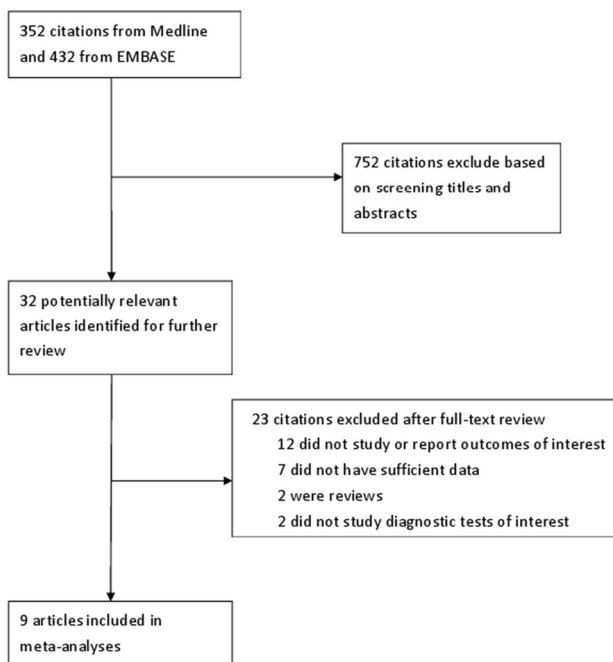


Table 2. Summary of pooled diagnostic accuracy indices

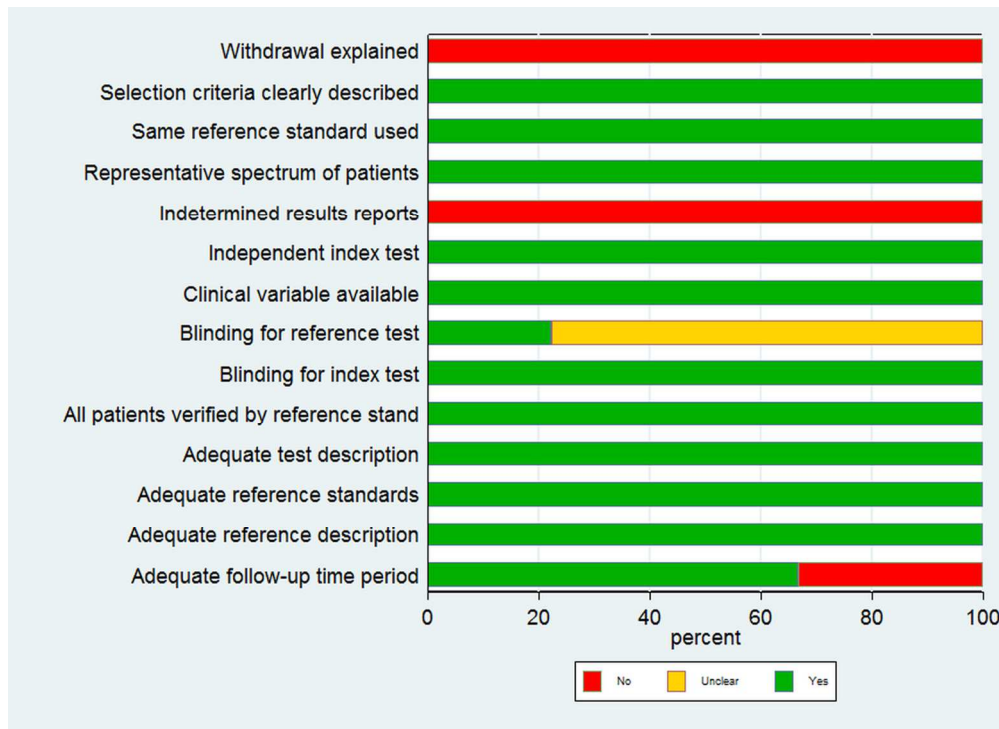
Variables	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio+	Likelihood ratio-	AUROC (95% CI)	I <sup>2</sup> (95% CI)	Diagnostic OR (95% CI)	Meta-regression P	Egger's test P
Overall <sup>10,12-19</sup>	9	0.71(0.63-0.78)	0.72(0.61-0.81)	2.57(1.86-3.55)	0.40(0.32-0.50)	0.77(0.73-0.81)	14.6(0-56.6)	5.91 (4.07-8.59)	--	0.566
Follow time < 6 months <sup>10,14,16,19</sup>	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 <sup>12-14,17,18</sup>	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 <sup>10,12,14-16,18,19</sup>	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 <sup>10,12,14-16,18,19</sup>	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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 1 Flow chart of study identification and inclusion



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

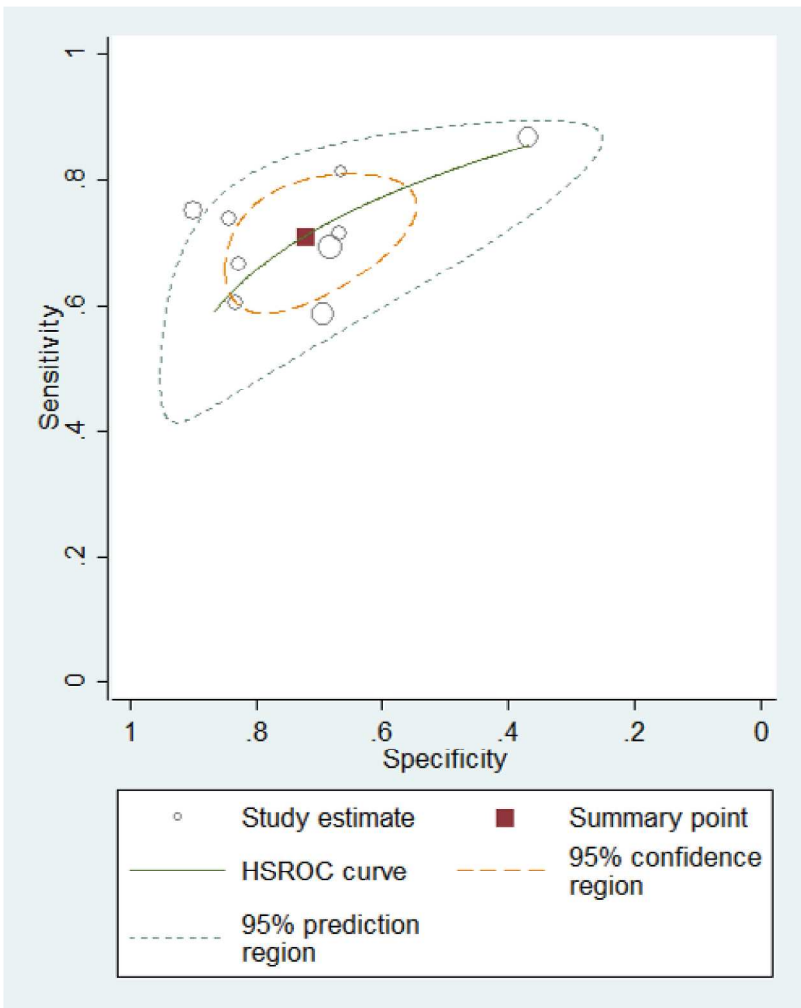


Results of the quality assessment of studies of diagnostic accuracy  
123x90mm (300 x 300 DPI)

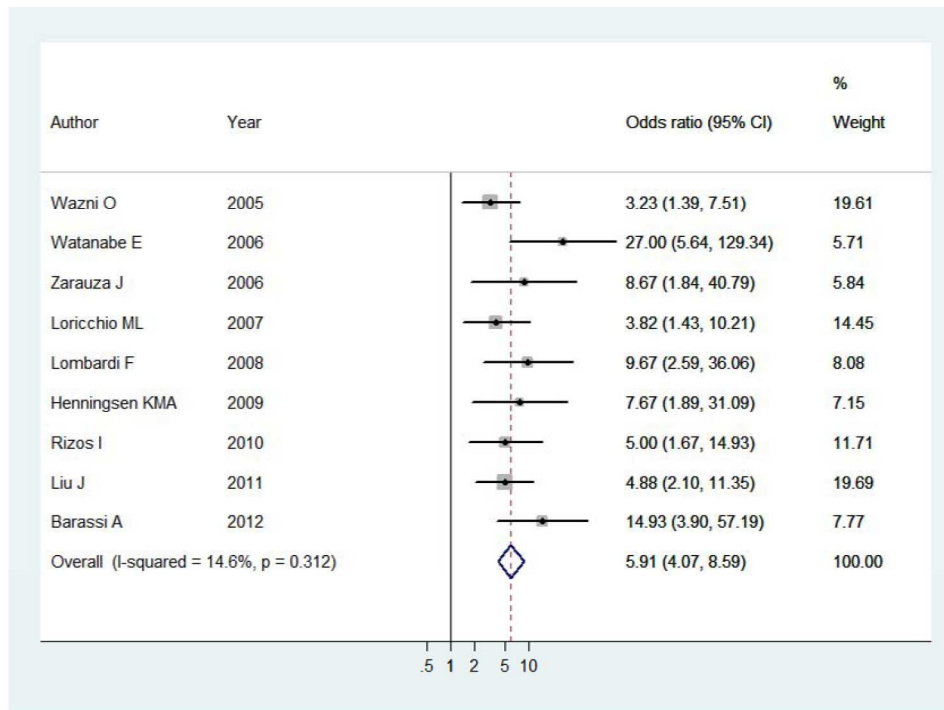
View only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



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



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

view only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



# PRISMA 2009 Checklist

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>



# PRISMA 2009 Checklist

Page 1 of 2

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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>





# PRISMA 2009 Checklist

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

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](http://www.prisma-statement.org).

Page 2 of 2

For peer review only

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>