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C-Reactive Protein and the risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis.

Venkata M Alla MD[a], Senthil Thambidorai MD[a], Kishlay Anand MD, MS[a], Aryan N Mooss MD[a], Richard Baltaro MD b, Syed M Mohiuddin MD[a] .

[a] Division of Cardiology, Department of Medicine, Creighton University, Omaha, Nebraska. [b] Department of Pathology, Creighton University, Omaha, Nebraska.

Abstract

There is increasing evidence linking C-reactive protein (CRP) and atrial fibrillation (AF). Despite the abundance of literature, confusion exists regarding this association because of inconsistent results. MEDLINE and Cochrane Controlled Trials Register databases were carefully searched through July, 2009 combining the following terms "C-reactive protein" and "atrial fibrillation". Reference lists of selected articles and reviews were also screened to identify additional relevant studies. Of the 129 studies initially identified, 8 studies with 7507 subjects (719 with AF) were included in the meta-analysis. Analysis yielded a relative risk of 1.63 (1.43, 1.86) for occurrence of AF when CRP level was above a cut off of 3-3.5 mg/l. When 3 studies with data on a higher cut off of 4.5-5.0 mg/l were analyzed separately, the relative risk was 4.03 (3.1, 5.25). Our study suggests that elevated CRP is associated with increased risk for AF. The risk appears incremental with higher CRP levels conferring proportionately increased risk. There is an urgent need for further large scale, well designed prospective studies to assess the relationship between CRP and AF.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in everyday clinical practice and affects approximately 0.9% of the general population.[1] It is associated with significant cardiovascular morbidity and mortality and also has an adverse impact on the quality of life.[2] The prevalence of AF increases with increasing age. With the demographic curve leaning towards the elderly, the burden imposed by this disease on healthcare systems across the western world is expected to increase significantly.[3] It is therefore imperative to devise new ways to prevent, detect and treat this condition. There is growing evidence linking inflammation to a variety of cardiovascular diseases. C-reactive protein (CRP) is an excellent marker of inflammation and has been linked to the pathogenesis and prognosis in patients with coronary artery disease, congestive heart failure, AF, myocarditis and aortic valve disease.[4] The increasing body of evidence linking CRP and AF has opened a new door of opportunity in our understanding of AF and will potentially lead to new ways of managing this common problem. The association between CRP and AF has been demonstrated in various settings and has been previously reviewed.[5] The aim of this study is to systematically review published data on the association between CRP and AF and study the strength of this association. We used a meta-analytic approach to estimate the relative risk of AF associated with elevated CRP.

Corresponding Address : Venkata M Alla, 3006, Webster Street, Omaha, NE- 68131. USA.

Methods

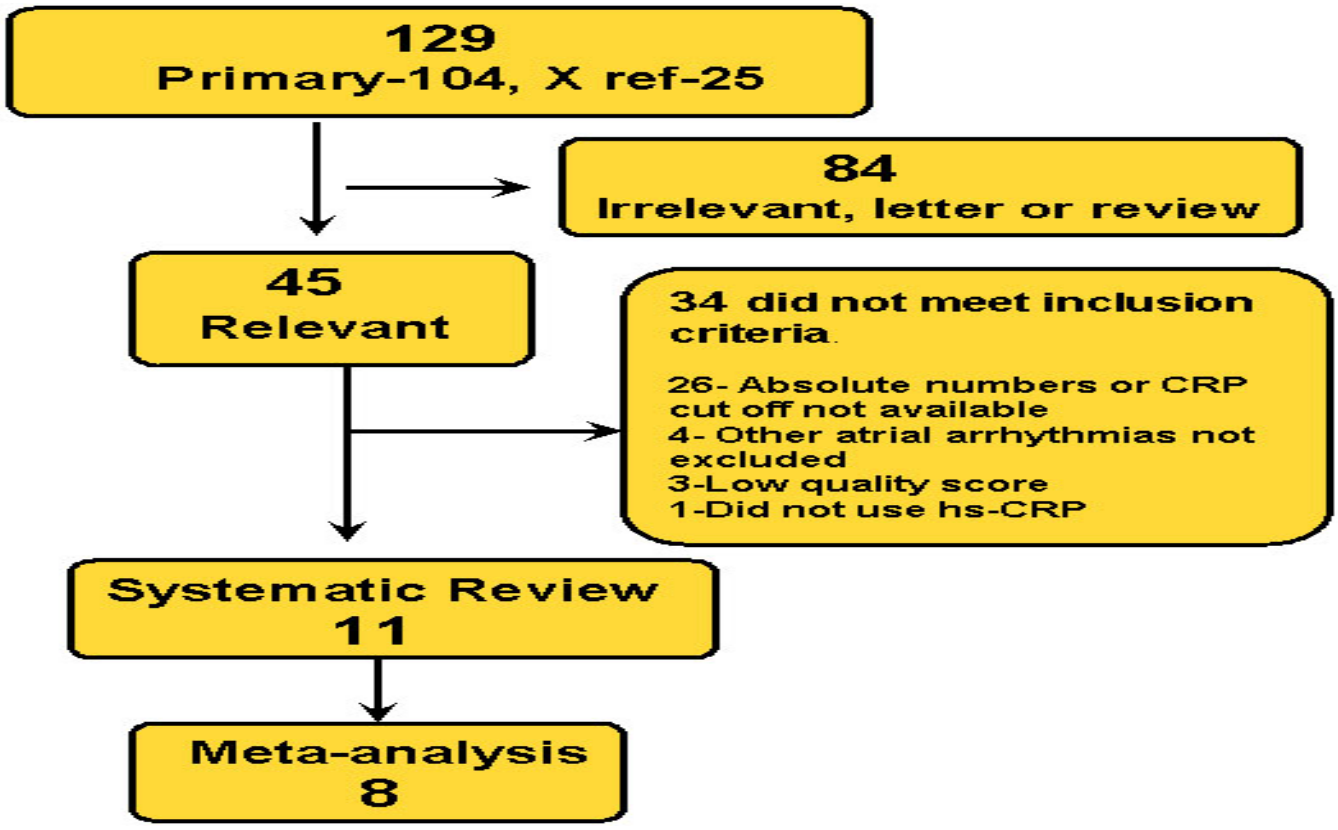
Literature Search

MEDLINE and Cochrane Controlled Trials Register databases were carefully searched through July, 2009 combining the following terms "C-reactive protein" and "Atrial Fibrillation". One of the authors (V.A) screened the studies for potential inclusion. Reference lists of the identified reports, reviews and letters were also screened to include potentially relevant studies. Studies were selected for further review after letters, reviews and irrelevant articles were excluded from the search results [flow sheet in Figure 1]. The manuscripts of the short listed studies were then separately reviewed by two of the authors (V.A, S.T) for inclusion in the systematic review. Studies which fulfilled the following criteria were included for systematic review. 1. Availability of baseline CRP levels. 2. Availability of duration of follow up 3. Exclusion of atrial arrhythmias other than AF. 4. AF diagnosed by a physician based on EKG or telemetry strip, or by coded diagnosis of AF (ICD-9) on discharge records. 5. Availability of the absolute number of subjects with AF in the high and low CRP groups, and CRP cut offs. 6. CRP measurement using high sensitive assay. 7. Quality score ≥ 7. The quality of the selected studies was assessed using the Newcastle-Ottawa quality assessment scale.[6] Discrepancies were resolved by consensus after review by the third author (K.A). If more than one study from the same authors fulfilled the inclusion criteria, the larger of the two was included in the review so as to avoid duplication of data sets.

Data Extraction

Using a standardized data extraction form the two authors extracted the following data from each of the eligible studies: first author, citation, year of publication, study population, study design, ascertainment of AF, method of CRP assay, baseline CRP distribution, CRP cut off, number of subjects in the high and low CRP groups, incidence or prevalence of AF in the high and low CRP groups, relative risk for AF based on CRP level, adjusted covariates and brief results. A CRP value of 3mg/l was empirically chosen for stratification into high and low CRP groups based on the AHA statement on CRP and increased risk of cardiovascular dis-

Figure 1: Flow diagram of study identification and selection



ease.[7] From among the studies selected for systematic review, those in which high and low CRP groups could be stratified into a combinable format (CRP cut off close to 3 mg/l) were included in the final meta-analysis. Letters were mailed to the authors regarding the above details when the same were not available in the manuscript.

Statistical Analysis

The absolute number of subjects who developed AF in the high and low CRP groups, and the total number of subjects in each group were obtained for each individual study and the pooled data was used to obtain the cumulative relative risk. Meta-analysis was performed adhering to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[8] Analyses were conducted based on intention to treat principle. Each study was considered as a single stratum. We obtained the pooled relative risks with 95% confidence interval (CI) for development of AF using the random effects model of Der Simonian and Laird.[9] Random effects model was preferred over fixed effects model because of the significant heterogeneity between the included trials. We used inverse-variance weighting to calculate random effects summary estimates, and used the Q test to test for heterogeneity of study results. We performed an influence analysis and assessed the influence of individual studies on the summary effect estimate. A funnel plot was also done to look for any publication bias in the studies. All statistical analyses were performed using Stata 9.0 (Stata Corporation, College Station, TX).

Results

The literature search yielded 129 potentially relevant studies. 84 of these were excluded after scrutiny of the abstract because they were letters, replies, reviews or irrelevant. Manuscripts of the

Table 1 Characteristics of the studies selected for Systematic Review

Author / year	Study group	N	Type of AF/ Ascertainment	CRP assay	Cut offs	RR (CI)	Qual. score
Aviles 2003	Random Patients from Medicare > 65 yrs.	5806	Prevalent AF / EKG or discharge diagnosis	ELISA	3.4 mg/l	1.31 (1.08-1.58)	9
Bernard Lo 2005	Patients of stable angina undergoing CABG.	152	Post CABG AF/ EKG or Telemetry.	Immunonephelometry	3.0 mg/l	3.3 (1.4-7.6)	8
Dernellis J. 2006 §	Healthy subjects in sinus rhythm.	1011	Incident AF/ EKG or Holter.	Immuno turbidometry	4.85 mg/l	1.1 (1.0-1.4)	9
Hogue 2006 §	Women > 55 years undergoing open heart surgery.	130	Post Cardiac surgery AF/ EKG or Telemetry.	Immuno nephelometry	19.2 mg/l	-	7
Kotsakaou. 2006 ¶	1st paroxysm of Lone AF.	125	Recurrent AF/ EKG	Immunoassay	4.9 mg/l	1.15 (1.04-1.24)	8
Loricchio 2007	Cardioverted patients of Persistent AF	102	Post cardioversion AF/ EKG, Holter	Immunoturbidometry	1.9 mg/l	4.98 (1.75-14.26)	9
Watanabe 2006 ¶	Persistent AF successfully cardioverted	84	Post cardioversion AF/ EKG or Holter.	Latex nephelometry	0.6 mg/l	5.3 (2.46-115)	7
Wazni 2005	Cardioverted patients of Persistent AF	111	Post cardioversion AF/ EKG	Immunonephelometry	3.09 mg/l	2.0 (1.2-3.2)	8
Zarauza J 2006	Cardioverted patients of Persistent AF	37	Post cardioversion AF/ EKG	ELISA	3 mg/l	45.9 (1.3-1600)	8
Mazza A 2009	Cardioverted patients of Persistent AF	158	Post cardioversion AF/ EKG	Immunonephelometry	3 mg/l	1.47 (1.05-2.06)	9
Korantzopoulos 2008 ¶	Cardioverted patients of Persistent AF	60	Post cardioversion AF/ EKG	Immunonephelometry	4.3mg/l	6.3 (3.1-12.7)	8

¶ Not included in the final meta-analysis. § Studies reporting no association between CRP and AF. RR=relative risk; CI= onfidence interval; CRP=C-reactive protein; EKG= electrocardiogram; CABG=coronary artery bypass grafting; ACS=acute coronary syndrome; CAD= coronary artery disease.

remaining 45 were reviewed separately by two of the authors (V.A, S.T). 34 more were subsequently excluded as they did not meet the inclusion criteria and the remaining 11 were selected for systematic review.[10-20] The concise detail of these studies is shown in [Table 1]. Of these, only 8 studies in which absolute numbers (of subjects at risk for AF and subjects with AF) for a CRP cut off of around 3 mg/l could be obtained were included in the final meta-analysis.[10-13, 15, 17-19] The 8 studies included 7507 subjects of which 719 had AF. Of these, one study (n=5806) pertained to prevalent AF in patients enrolled in a Cardiovascular study registry [10], 2 studies (n=282) dealt with post cardiac surgery AF,[11, 13] one (n=1011) pertained to incident AF in normal healthy adults and the remaining 4 studies (n=408) pertained to AF recurrence after successful cardioversion.[15,17-19] The mean age of the study populations varied between 45-70 and males constituted 50-75%.

Meta-analysis of the 8 studies yielded a relative risk of 1.63 (1.43, 1.86) for occurrence of AF when CRP was elevated above 3-3.5 mg/l [figure 2]. In an influence analysis, none of the individual studies had an overwhelming effect on the summary effect estimate and it remained relatively stable and significant on excluding one study at a time. There was no publication bias observed on the funnel plot [figure 3] and Egger's weighted regression method p-value was 0.20. Three of the studies selected for review were not included in the final meta-analyses as the cut off CRP used was quite dissimilar.[14, 16, 20] The studies by Korantzopoulos et al[20] and Kotsakaou et al[14] used CRP cutoffs of 4.3 and 4.9 mg/l respectively. Secondary analysis using the data from these studies and that from Dernellis et al,[12] where numbers for a similar CRP cut off (4.85 mg/l) were available, yielded a relative risk of 4.03 (3.1, 5.25) for AF [Figure 4].

Review of studies

Two of the 11 studies selected for systematic review accounting for 1141 subjects reported lack of independent association between CRP and AF.[12,13]

Figure 2: Forest plot of AF risk associated with CRP elevation (>3-3.5mg/l)

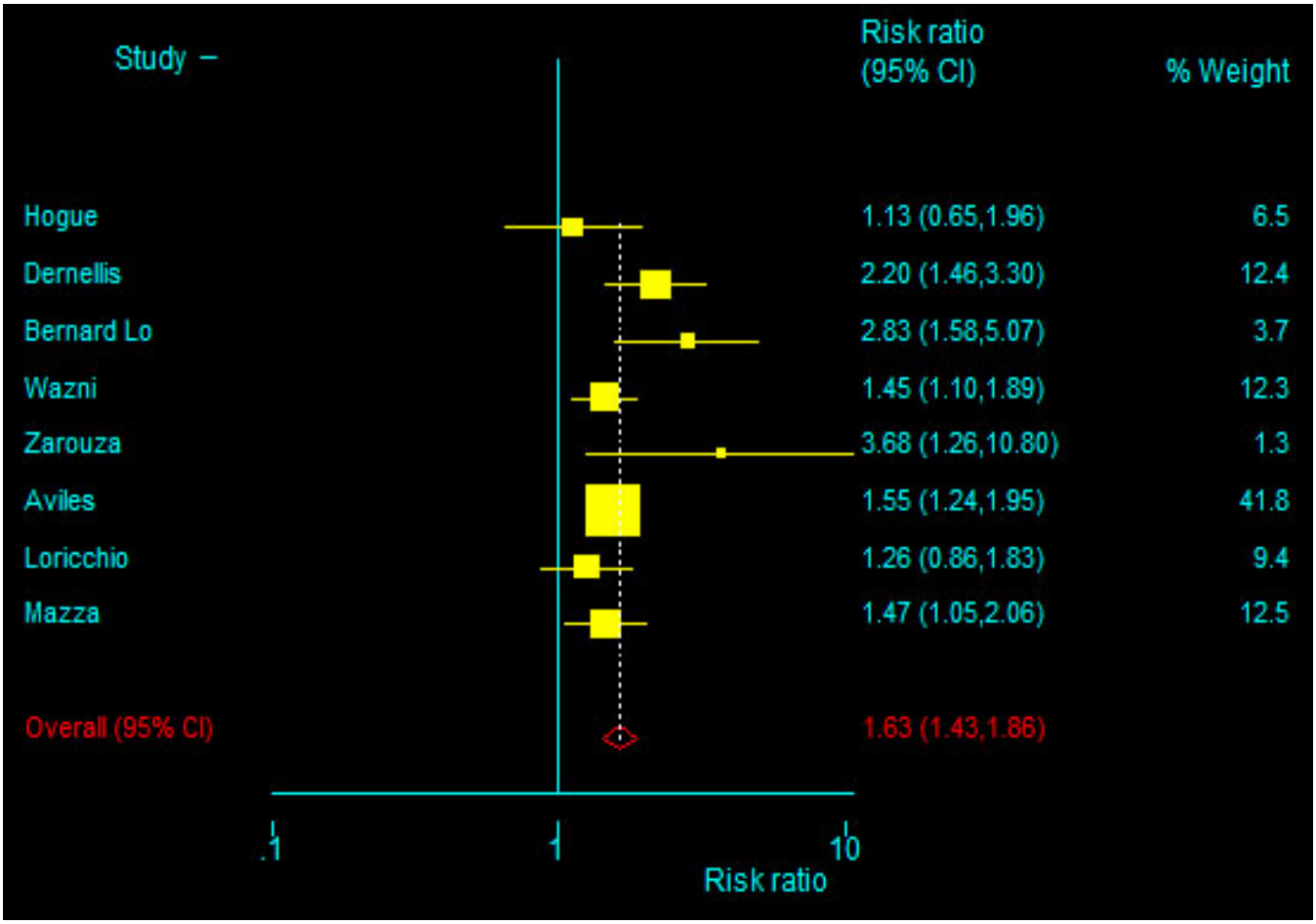
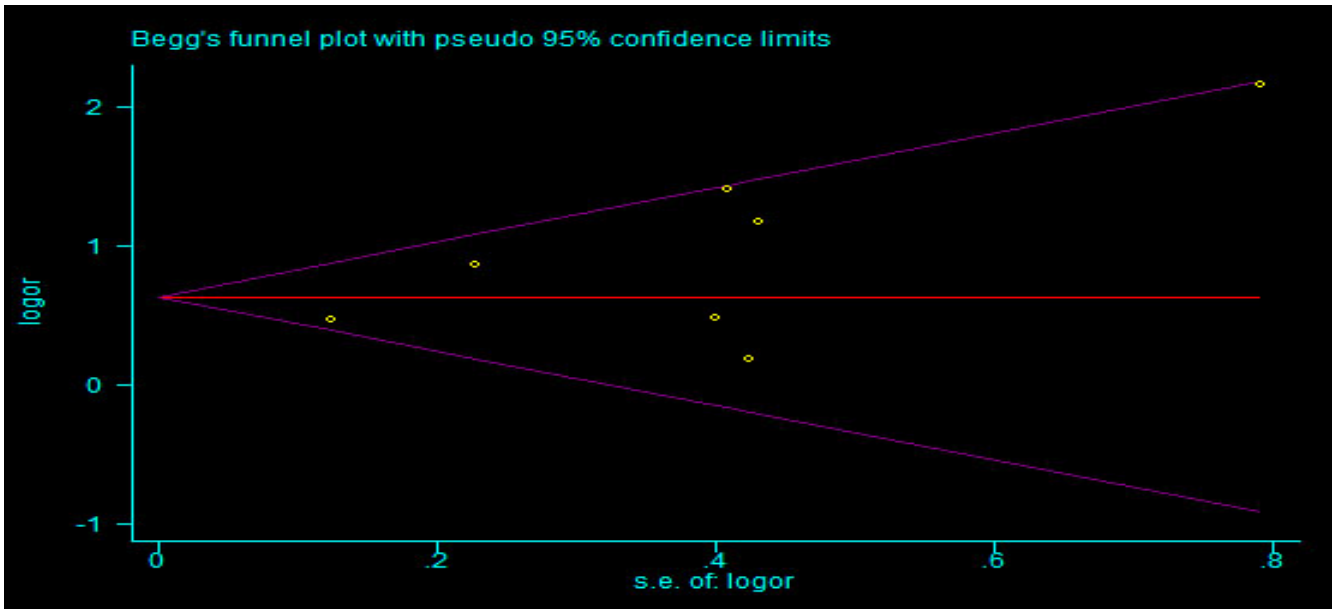


Figure 3: Funnel plot of the selected studies to assess for publication bias



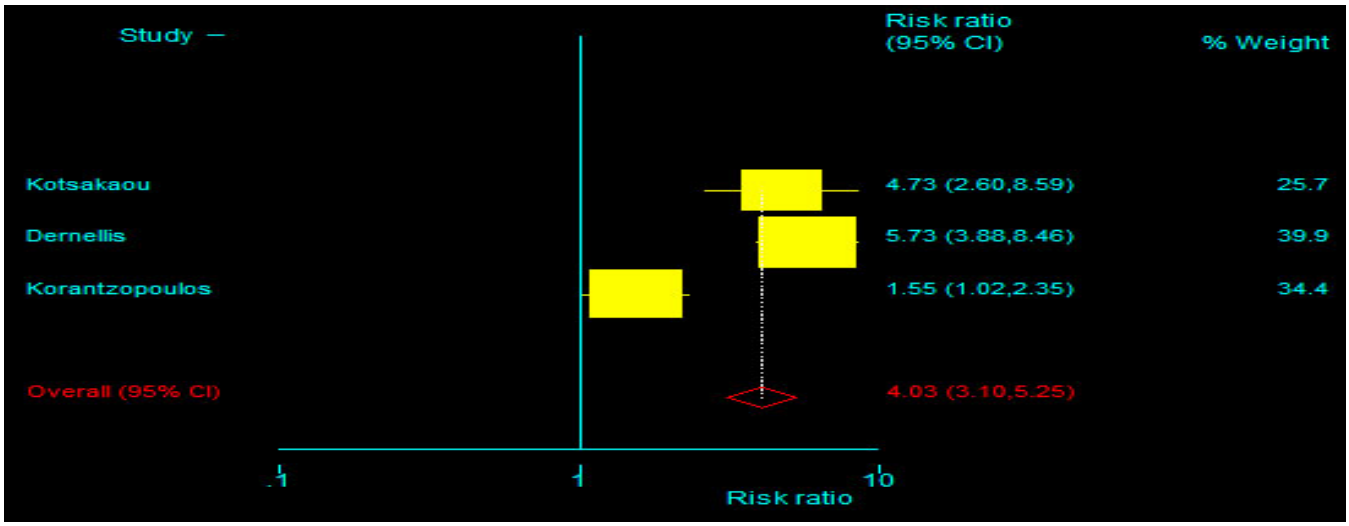
In the study by Dernellis et al,[12] elevated CRP was predictive of AF only in the presence of concomitant elevation of complement. The poor ability of CRP in predicting incident AF in this study was probably due to the low risk population studied (relatively young, exclusion of those with CAD, CHF or other heart diseases). Additionally, measuring downstream products of inflammation (complement components) could have led to underestimation of the association between CRP and AF in this study. It is known that women have more elevations in inflammatory markers at baseline.[21] This might have been a potential reason for the poor predictive value of CRP in the study by Hogue et al,[13] which was done in a small and select group of women (post menopausal women > 55 years of age undergoing cardiac surgery). Further studies evaluating the sex specific limitations in the utility and applications of CRP are therefore warranted.

The 5 studies that addressed recurrent AF following electrical cardioversion[15,17-20] were limited by their observational design, lack of uniformity in the study population, follow up, and their small size. In the study by Aviles et al,[10] elevated CRP was predictive of both prevalent and incident AF. Watanabe et al[16] used a CRP cutoff of 0.6 mg/l (falls into low risk category by AHA definition) and demonstrated a relative risk of 5.3 for post cardio version AF recurrence. This was included neither in the primary nor the secondary analysis because of the extremely low cut off used (which was very dissimilar to most other studies). It is well known that the median CRP level in healthy Japanese and Chinese subjects is much lower compared to their western counterparts.[22-23] The high risk of AF despite relatively low CRP levels in Asian populations could be related to differences in body mass index and genetic constitution which alter inflammatory response and CRP levels.[23-25]

Discussion

The pathophysiology of AF is complex and to date is not completely understood. It is now known that pulmonary veins serve a crucial role in the initiation of this arrhythmia.[26] Once initiated, AF sets in motion a process of self propagation through electrical, biophysical and structural remodeling of the atria.[27-30] There is a strong association between AF and inflammation. Numerous serum markers of inflammation like TNF α, IL-6, leukocyte count and CRP have been shown to be elevated in AF [5, 30].It is known that AF and inflammation alter myocardial energy kinetics and increase oxidative stress which can further perpetuate the arrhythmia.[29, 31] In addition, CRP leads to complement activation and tissue damage locally in the atrial myocardium further increasing the substrate for AF.[32] Moreover, CRP levels progressively increase with increasing AF burden[33] but it is unclear whether inflammation is a cause or consequence of AF. Some investigators have shown that anti inflammatory therapy reduces recurrences of AF with parallel reductions in CRP suggesting a pos-

Figure 4: Forest plot of AF risk associated with CRP elevation (>4.5-5mg/l)



sible cause effect relationship.[34, 35] However, this remains unproven.

The present systematic review and meta-analysis supports the strong association between elevated CRP and occurrence of AF across a variety of clinical settings. Moreover, our study suggests possible incremental relationship with higher CRP levels conferring a relatively higher risk of AF. It is important to bear in mind a number of limitations while interpreting and applying results of metaanalyses. The potential for publication bias against negative studies and small studies is the foremost concern. This might have caused our study to overestimate the risk attributable to elevated CRP. Thirteen out of the 45 studies initially selected for review, showed no independent association between AF and CRP. Only 2 of these 13 studies met the criteria for inclusion.[12-13] On the other hand, 32 out of the 45 studies reported a significant independent association between CRP and AF and 11 of these met the inclusion criteria.[10, 11, 14-20] It is apparent that publication bias against negative studies would not have a major impact on our study as more than a third of the reviewed studies reported no association between CRP and AF. In addition, both Begg's Funnel plot and Eggers test did not reveal any effect of publication bias on our results. However, a potential shortcoming of our study could be the inclusion of more studies reporting a positive result in the final analysis. Of note, a majority of the negative studies that were excluded were small and poorly designed. On the other hand, the studies that reported a positive association had to be excluded because of lack of absolute numbers in the high and low CRP groups or absolute values for CRP cut off despite better design and higher numbers. Thus, with the relatively small number of subjects in the excluded negative studies, it is unlikely that we would have erroneously detected an association between CRP and AF in the true absence of one.

Another major concern would be the issue of bias. As with any study on AF, all the studies in our analysis had a propensity for ascertainment bias because the follow up for AF was periodic and not continuous. Additionally, despite adjustment for confounding factors like coronary artery disease, hypertension, diabetes, heart failure, age and smoking status by the individual investigators, residual confounding cannot be excluded. The lack of original data from the included trials precluded our ability to perform a logistic regression analysis to independently assess the effects of these confounders. Moreover, it is both impractical and impossible to adjust for the confounding effects of the innumerable inflammatory markers and cytokines; leaving enormous scope for'residual confounding'. Other potential limitations of our analysis are exclusion of studies not published in English, wide variation in the study populations and the heterogeneity of CRP assay among the individual studies. All of these inherent problems adversely influence the applicability of the results and make it difficult to make general conclusions regarding the relation between CRP and AF. Finally, all the included studies utilized single measurements of CRP for stratification; whereas, it is

generally recommended that for improved specificity, CRP be measured at least 2 different times (2 weeks apart) when being used for risk assessment of cardiovascular diseases.[7] Only a small number of patients with elevated CRP have AF and not all patients with AF have elevated CRP. Thus, the lack of specificity limits the general applicability of CRP in predicting the presence or the occurrence of AF. As in the case of coronary artery disease where CRP measurement is best used for further risk stratification of patients at intermediate risk, it is imperative to identify appropriate populations for CRP testing in the context of AF. Review of literature supports a potential role for CRP testing in the following scenarios. In patients with a prior history of AF, CRP can help discriminate between those who will and will not have a recurrence and identify patients at a higher risk for complications like embolism.[36] CRP testing can potentially identify patients at risk for developing postoperative AF and AF following acute myocardial infarction.[37] In addition, recent data suggests that CRP can predict recurrence of AF following the first episode of paroxysmal AF, success of cardioversion for persistent AF and recurrent AF following successful cardioversion.[38, 39] In our study, secondary analysis using studies that addressed post cardioversion AF recurrence [15, 17-19] yielded a relative risk of 1.49 (1.23, 1.79) for AF recurrence when CRP was >3-3.5 mg/l. This is consistent with the findings of previously published studies assessing the association between CRP and AF recurrence following cardioversion.[38] Thus, CRP has the potential to be an invaluable tool in identifying patients who would require increased surveillance and serve as a guide to determine the intensity of treatment and follow up.

Conclusions

Overall the evidence linking elevated CRP and AF is robust and the strength of association is strong. There is fair consistency in the data supporting this association and there seems to be an incremental relationship with higher CRP levels conferring proportionately increased risk. Elevated CRP (usually above 3.0-3.5 mg/l) is associated with about 1.6 times increased risk of AF compared to CRP < 3 mg/l. The major limitation in the clinical utility of CRP is its poor specificity (as it could be elevated in multiple other disease states). The potential benefit of CRP lies in our ability to use it in selected groups of patients at risk for AF (heart failure, acute myocardial infarction) and in specific settings like post operative state, post cardioversion etc. The importance of using the mean value of CRP measurements made over time as opposed to single measurements should be emphasized and encouraged. There is therefore, a pressing need for further large and well designed prospective studies to test the association of CRP with AF and its utility in clinical practice.

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