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Association Between C-Reactive Protein and Recurrence of Atrial Fibrillation After Successful Electrical Cardioversion

A Meta-Analysis

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Objectives We conducted a systematic review and meta-analysis of observational studies to examine the association between baseline C-reactive protein (CRP) levels and the recurrence of atrial fibrillation (AF) after successful electrical cardioversion (EC).

Background Current evidence links AF to the inflammatory state. Inflammatory indexes such as CRP have been related to the development and persistence of AF. However, inconsistent results have been published with regard to the role of CRP in predicting sinus rhythm maintenance after successful EC.

Methods Using PubMed, the Cochrane clinical trials database, and EMBASE, we searched for literature published June 2006 or earlier. In addition, a manual search was performed using all review articles on this topic, reference lists of papers, and abstracts from conference reports. Of the 225 initially identified studies, 7 prospective observational studies with 420 patients (229 with and 191 without AF relapse) were finally analyzed.

Results Overall, baseline CRP levels were greater in patients with AF recurrence. The standardized mean difference in the CRP levels between the patients with, and those without AF was 0.35 units (95% confidence interval 0.01 to 0.69); test for overall effect *z*-score = 2.00 ($p = 0.05$). The heterogeneity test showed that there were significant differences between individual studies ($p = 0.02$; $I^2 = 60.2\%$). Further analysis revealed that differences between the CRP assays possibly account for this heterogeneity.

Conclusions Our meta-analysis suggests that increased CRP levels are associated with greater risk of AF recurrence, although there was significant heterogeneity across the studies. The use of CRP levels in predicting sinus rhythm maintenance appears promising but requires further study. (J Am Coll Cardiol 2007;49:1642–8) © 2007 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and its prevalence has increased during the past few decades (1,2). Because AF is independently associated with increased cardiovascular mor-

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bidity and mortality, it unequivocally represents a major public health problem (1,2). Although control of the ventricular response is an acceptable treatment in certain subgroups of patients, restoration and maintenance of sinus rhythm remains the preferred strategy in many patients (2,3). This strategy offers several potential benefits, such as the prevention of electrical and structural remodeling of the atria, improved hemodynamic function, amelioration of symptoms, and improvement in the quality of life (3,4). Although some recent studies indicate increased efficacy of pharmacological cardioversion using combination therapy (5,6), electrical cardioversion (EC) is the most commonly used method for sinus rhythm restoration in patients with persistent AF.

Despite the use of antiarrhythmic agents for sinus rhythm maintenance, a considerable proportion of patients relapse to AF (1,2). It is generally believed that these relapses are associated with older age, atrial dilation, and long duration of the arrhythmia. This tendency to become sustained over time cannot be easily managed, representing a challenging therapeutic problem. An increasing body of evidence suggests the role of inflammation in the genesis and perpetuation of AF (7–10). The possibility that the association of inflammation with AF could be examined with the use of C-reactive protein

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(CRP) has captured the attention of many researchers (11). In the past few years, several studies have investigated the association between baseline CRP levels and AF recurrence rates after successful EC. Although some of these studies indicated a positive association between CRP levels and AF recurrence (12–15), others failed to demonstrate such a relationship (16–18). Therefore, we conducted a systematic review of the evidence obtained from observational studies to evaluate the association between CRP levels before cardioversion and AF recurrence rates after successful EC.

Abbreviations and Acronyms

AF = atrial fibrillation
CRP = C-reactive protein
EC = electrical cardioversion
ELISA = enzyme-linked immunosorbent assay

Methods

Meta-analyses of observational studies present particular challenges because of inherent biases and differences in study designs. Consequently, we performed this analysis according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group (MOOSE) (19).

Inclusion criteria. Studies were considered eligible for this review if they met the following criteria: 1) they were of a prospective observational study design; 2) they evaluated the potential association between CRP levels before cardioversion and AF recurrence after successful EC; 3) they used AF recurrence rates as an outcome; and 4) the period of follow-up was no shorter than 1 week. We included published and unpublished studies without language restriction.

Search strategies. We carefully searched MEDLINE (January 1966 to June 2006), EMBASE (January 1980 to June 2006), and the Cochrane Controlled Trials Register (Cochrane Library Issue 2, 2006) databases to identify relevant studies. We used the following keywords: "C-reactive protein," "inflammation," and "atrial fibrillation." Titles and abstracts as well as the reference lists of all of the identified reports were examined independently by 2 reviewers (T.L. and L.L.) to include potentially relevant studies. The 2 reviewers agreed on the inclusion/exclusion status in 92% of the reviewed studies. Disagreements were resolved by discussion or consensus of a third reviewer (G.L.). Additionally, a manual search was conducted using all review articles on this topic, bibliographies of original papers, and abstracts of the scientific sessions of the American College of Cardiology, the American Heart Association, the European Society of Cardiology, and the North American Society of Pacing and Electrophysiology (Heart Rhythm Society) during the past 5 years.

Quality assessment and data extraction. Because quality scoring is controversial in meta-analyses of observational studies, we systematically assessed several key points of study quality. Two reviewers (T.L. and L.L.) independently appraised each article included in our analysis according to a critical review checklist of the Dutch Cochrane Centre which was proposed by MOOSE (19). The key points of this checklist are as follows: 1) clear definition of study population; 2) clear definition of outcomes and outcome assessment; 3) independent assessment of outcome parameters; 4) sufficient duration of follow-up; 5) no selective loss during follow-up; and 6) important confounders and prognostic factors identified. If a study did not clearly mention one of these key points, we considered that it had not been performed and, consequently, that there was a possibility for underestimation of the reported characteristics.

Two blinded reviewers (T.L. and L.L.) independently performed data extraction using a standard data extraction form to determine eligibility for inclusion and extract data. The extracted data elements of this review included: 1) publication details: first author's last name, publication year, and origin of the studied population; 2) study design; 3) characteristics of the studied population: sample size, age, gender, diagnoses, methods of CRP measurement, duration of follow-up, number of withdrawals, and dropouts; 4) end point evaluation (methods of AF detection); 5) rates of AF recurrence and sinus rhythm maintenance during the follow-up period, and means and SDs of CRP in each group. Disagreements were resolved by consensus with a third reviewer (G.L.).

If the study provided medians and interquartile ranges instead of means and SDs, we imputed the means and SDs as described by Hozo et al. (20). We calculated the lower and upper ends of the range by multiplying the difference between the median and upper and lower ends of the interquartile range by 2 and adding or subtracting the product from the median, respectively.

Statistical analysis. To accommodate differences in the way in which CRP measured and reported across various laboratories, the absolute CRP levels were converted into a common unit by calculating standardized effect sizes. Standardized effect sizes were derived by dividing the mean difference of CRP levels in AF recurrence and no AF recurrence groups of each study by its SD. We used the I^2 statistic to measure the extent of inconsistency among the results and tested the heterogeneity using Cochran's Q test. Because this test has poor power in the case of few studies, we considered both the presence of significant heterogeneity at the 10% level of significance and values of I^2 exceeding 56% as an indicator of significant heterogeneity (21), so a pooled effect was calculated with a random-effects model which was used to take into account within-study and between-study variance, otherwise, with a fixed-effects model. To explore sources of heterogeneity, we performed several sensitivity and subgroup analyses. Publication bias was evaluated using the funnel plot. All analyses were conducted using Review Manager version 4.2 (Revman, The Cochrane Collaboration, Oxford, United Kingdom).

Results

Two hundred twenty-five records were identified by the primary literature search. However, after screening the titles

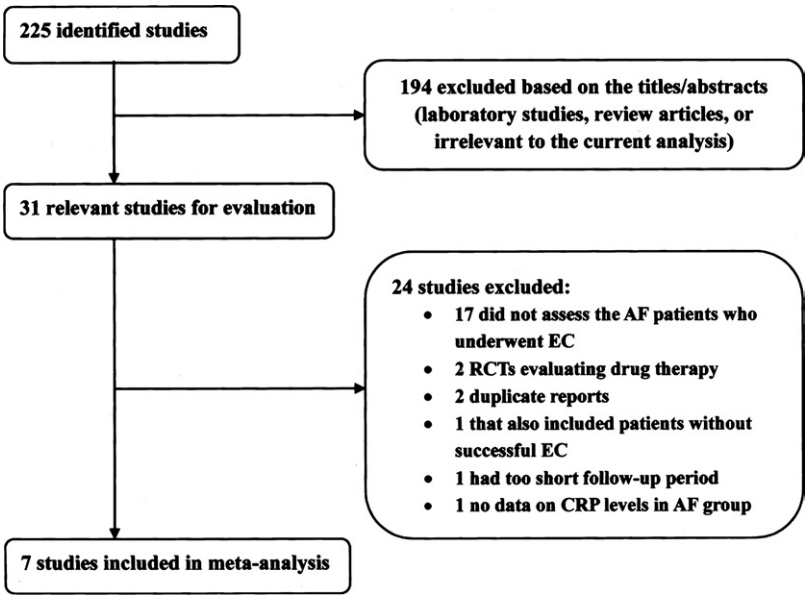

Figure 1 Flow Diagram of the Trial Selection Process

AF = atrial fibrillation; CRP = C-reactive protein; EC = electrical cardioversion; RCTs = randomized control trials.

and abstracts, 194 studies were excluded because they were either laboratory studies, review articles, or irrelevant to the current analysis. Of the 31 reports selected for detailed evaluation, 17 studies did not assess the AF patients who underwent EC, 2 studies were randomized control trials that evaluated drug interventions on AF prevention after successful EC (22,23), and 2 further studies were excluded because they were preliminary abstracts followed by subsequent full manuscripts. One study was excluded because a portion of the studied patients followed after unsuccessful EC (24), whereas in another one the follow-up period was too short (25). Finally, in one additional study, CRP levels were not reported in the AF recurrence group (26). Consequently, 7 prospective observational cohort studies (12–18) finally were included in our meta-analysis (Fig. 1). Overall, there were 420 patients involved in our review: 229 in the AF recurrence group, and 191 in the no AF recurrence group. The follow-up period varied between 7 and 140 days. The quality assessment of the 7 studies is presented in Table 1, whereas the characteristics of each study are depicted in Table 2.

Four studies showed that patients with AF recurrence had greater CRP levels than those without (12–15), whereas CRP levels did not show significant difference between the 2 groups in 3 other studies (16–18). Overall, CRP concentration was greater in patients with AF recurrence. The standardized mean difference in the CRP levels between the patients with, and those without AF recurrence was 0.35 units (95% confidence interval 0.01 to 0.69) (Fig. 2), and the z-score for overall effect was 2.00 ($p = 0.05$). The heterogeneity test showed that there were significant differences between individual studies ($p = 0.02$; $I^2 = 60.2\%$). We subsequently performed sensitivity and subgroup analyses to find the origin of this heterogeneity. After removing 1 study that enrolled patients with atrial flutter or 1 study that had the shortest follow-up period, the analysis did not find a significant influence on the results. Of note, after excluding the study by Zarauza et al. (15), which used a high-sensitivity C-reactive protein enzyme-linked immunosorbent assay (ELISA) to measure CRP levels, heterogeneity test showed that there were no significant differences be-

Table 1 Assessment of the Quality of the 7 Included Studies

	Korantzopoulos et al. (16)	Wanzi et al. (12)	Malouf et al. (13)	Zarauza et al. (15)	Watanabe et al. (14)	Cosgrave et al. (17)	Buob et al. (18)
Clear definition of study population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clear definition of outcomes and outcome assessment?	Yes	Yes	Yes	No	Yes	Yes	Yes
Independent assessment of outcome parameters?	Yes	N/A	N/A	N/A	N/A	N/A	N/A
Sufficient duration of follow-up?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No selective loss during follow-up?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Important confounders and prognostic factors identified?	No	Yes	Yes	Yes	Yes	Yes	No

N/A = not available.

Table 2 Characteristics of the 7 Studies Included in the Meta-Analysis

Author (Ref. #)	Year	Study Population	Patients, n	Men, n	Mean Age, yrs	Measurement of CRP	Recurrence Rate	Follow-Up	Methods of AF Detection
Korantzopoulos et al. (16)	2005	Persistent AF	30	15	68	Immunonephelometric assay	30%	1 week	First 24-h monitoring, ECG at 3- and 7-day follow-up visits or when patients experienced symptoms suggestive of AF
Wanzi et al. (12)	2005	Persistent symptomatic AF	111	81	67	Immunonephelometric assay	68%	76 days	ECG at standard follow-up visits or when patients experienced symptoms suggestive of AF
Malouf et al. (13)	2005	AF (75%) or atrial flutter	67	44	72	Latex particle-enhanced immunoturbidimetric assay	33%	1 month	Physician examination and ECG monitoring or fax ECG
Zarauza et al. (15)	2006	Persistent AF >2 days	37	18	63	hsCRP enzyme-linked immunosorbent assay	43%	1 month	Patients were evaluated as outpatients 30 days after cardioversion
Watanabe et al. (14)	2006	AF ≥1 day	84	56	63	Latex nephelometry	76%	140 days	First 24-h monitoring, ECG at 1 and 14 days, then every month and 24-h Holter every month
Cosgrave et al. (17)	2006	Persistent AF	66	51	62	Rate nephelometry	48.5%	2 months	ECG at follow-up visit
Buob et al. (18)	2006	Persistent symptomatic AF	25	21	66	Immunonephelometric assay	44%	1 month	Physician examination and ECG at 1-month follow-up visit

AF = atrial fibrillation; CRP = C-reactive protein; hsCRP = high-sensitivity C-reactive protein; ECG = electrocardiogram.

tween the remaining 6 studies ($p = 0.32$; $I^2 = 14.1\%$), whereas the standardised mean difference in the CRP levels between the patients with and without AF recurrence was 0.23 units (95% CI 0.02 to 0.45); the z-score for overall effect was 2.11 ($p = 0.03$). Therefore, differences in the CRP assay may be a possible source of heterogeneity.

In addition, we performed a prespecified subgroup analysis of studies with a follow-up period of at least 2 months and those of <2 months. The proportion of total variation across studies that was due to heterogeneity rather than chance was $I^2 = 58.4\%$ ($p = 0.09$) in the 3 studies with a follow-up period of at least 2 months, and $I^2 = 69.5\%$ ($p = 0.02$) in the 4 studies with a follow-up period of <2 months. Thus, it did not explain the cause of heterogeneity in our results. The funnel plot (Fig. 3) suggested that there was little publication bias, although the small number of studies made it difficult to interpret.

Discussion

In this meta-analysis of 7 prospective observational studies, we demonstrated that increased baseline CRP levels are associated with greater risk for AF recurrence after successful external EC, although there was significant heterogeneity across the studies. After excluding a study that caused heterogeneity (15), the overall effect of CRP elevation on AF relapse was more prominent (z-score = 2.11, $p = 0.03$). Keeping in mind the clinical importance of sinus rhythm maintenance after successful EC, as well as the inconsistent published results regarding the effect of inflammation in this setting, this meta-analysis is of special importance.

The pathophysiological mechanism that underlies the development of electrophysiological and structural substrate that promotes AF maintenance and recurrence has been named "atrial remodelling" (27). Currently, there is an increasing research interest on the role of inflammation and oxidative stress in the pathophysiology of AF (7–11,28). It has also been speculated that these processes are interrelated and contribute to the atrial remodeling (7,9,10,28). Remarkably, an increasing body of evidence links AF to the inflammatory state (9,10). Inflammatory indexes, mainly CRP, have been related to future AF development, AF recurrences after cardioversion, and to the associated prothrombotic state (9,10). Moreover, the persistence of AF has been associated with the degree of inflammation (29). Also, several pharmacological approaches with nonchannel blocking drugs that, among other pleiotropic, have anti-inflammatory properties, show favorable effects on AF (10,22,28,30,31). These include inhibitors of the renin-angiotensin system, statins, dietary antioxidants, corticosteroids, n-3 fatty acids, and others (10,22,28,30,31). Dernellis and Panaretou (32) indicated the efficacy of corticosteroid treatment in preventing recurrent AF but, more interestingly, they demonstrated that corticosteroid treatment significantly reduced the CRP levels from the first month,

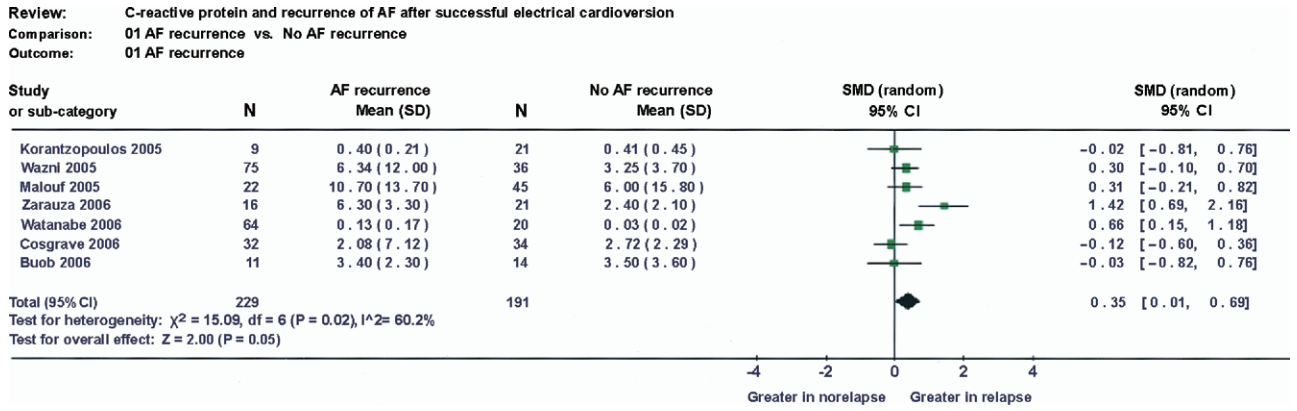

Figure 2 **Comparison of CRP Levels Between AF Recurrence and No AF Recurrence Groups in the 7 Included Studies**

AF = atrial fibrillation; CI = confidence interval; CRP = C-reactive protein; SMD = standardized mean difference.

whereas a strong relationship between CRP increase and the risk of AF recurrence was observed (32).

Despite the aforementioned evidence, it is not yet clear whether inflammation is a primary pathogenetic event or a consequence of AF. However, there is a possibility that both processes feeding each other leading to a vicious cycle. It could be hypothesized that ongoing inflammation can enhance atrial remodeling, thus promoting AF recurrence (13). This hypothesis is supported by the temporal relation of increases in inflammatory indexes (CRP, complement, white blood cell count) after cardiac surgery and the onset of postoperative AF (33,34). Moreover, elevated CRP levels have been reported very early (even in the first 24 h) after AF initiation, suggesting that inflammation may promote AF persistence (29). Very recently, it was demonstrated that in patients with acute myocardial infarction there seems to be an independent positive association between elevated CRP and new-onset AF suggesting a pathogenetic role for inflammation (35,36).

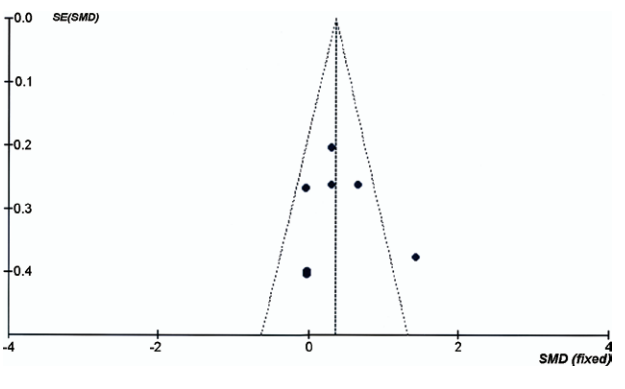

Figure 3 **Funnel Plot of the Meta-Analysis**

Review: C-reactive protein and recurrence of AF after successful electrical cardioversion. Comparison: 01 AF recurrence versus no AF recurrence. Outcome: 01 AF recurrence. SE = standard error; other abbreviations as in Figure 2.

However, if inflammation simply accompanies atrial remodeling, then the restoration of sinus rhythm might lead to the gradual decrease of the inflammatory markers, whereas failure of the reverse atrial remodeling and the impeding recurrence of the arrhythmia might be indicated by the abolishment of this decrease. Of note, some investigators claim that the abnormal inflammatory state may be related, at least in part, to other comorbidities. Regardless of the presence or not of a causal relationship, the study of baseline CRP levels and/or their variation after cardioversion may provide significant prognostic information regarding sinus rhythm maintenance (16,37). C-reactive protein is an acute-phase protein that has been emerged as a reliable biomarker of systemic inflammation in several cardiovascular diseases (11,38). Importantly, CRP is an easily determined marker in everyday clinical practice worldwide and thus, successive measurements can be easily performed.

Undoubtedly, a unique basal measurement of CRP before AF cardioversion cannot reflect the inflammatory process throughout time. To date, only 1 small study examined the time-course of the inflammatory indexes after cardioversion (16). In this study, serial measurements of CRP, fibrinogen, and white blood cell count were performed on the first, third, and seventh day after cardioversion. It was demonstrated that fibrinogen levels increased significantly in patients who relapsed to AF but remained stable in patients who remained in sinus rhythm. In the latter patients, CRP values tended to decrease after cardioversion, but white blood cell count was significantly lower on the seventh day compared with baseline values (16). It could be therefore speculated that the variation of inflammatory indexes after EC of persistent AF might have prognostic implications (16). Moreover, successive measurement of simple inflammatory indexes might be clinically useful in monitoring the

effectiveness of various anti-inflammatory treatments in patients with AF (16). In 2 further studies, CRP levels were determined only once after cardioversion. Cosgrave et al. (17) measured CRP at baseline and 8 weeks after cardioversion and found no differences in patients who recurred to AF as well as in those who remained in sinus rhythm. Similar results also were obtained by Buob et al. (18) by measuring CRP at baseline and 1 month after EC.

In our analysis, we included 1 study that had a short follow-up period of just 1 week (16). We consider that this time interval is sufficient and critical because the greatest incidence of AF recurrence occurs during the first days after cardioversion. Tieleman et al. (39) have demonstrated that the recurrence rate can reach the level of 35% in the first 5 days after cardioversion. It also has been suggested that atrial electrical remodeling resolves during the first days after cardioversion of persistent AF and may be related to early recurrence rates (39). In addition, as already mentioned, the removal of this study from the analysis did not have a significant impact on the results.

When between-study variation cannot be explained by chance, exploration of the reasons for heterogeneity rather than derivation of a single summary estimate have been emerged as the main goal of a meta-analysis (40). The heterogeneity test of our analysis showed that there were significant differences between individual studies. Subsequently, sensitivity and subgroup analyses were performed to investigate the underlying causes; differences between the measurements of CRP in the studies may be a possible source of heterogeneity. In the aforementioned 7 studies, in 6 of them (12–14,16–18) researchers used immunonephelometric assay to measure CRP concentrations, and only in 1 study (15) did researchers assess CRP by using ELISA. The ELISA methodology is used primarily for research purposes and is not ideal for routine use in highly automated clinical laboratories (41). Recently, latex-enhanced immunonephelometric method and the immunoturbidimetric assay have been evaluated and validated clinically (42). These assays possess improved sensitivity and precision at low concentrations of CRP. Finally, we demonstrated that enrolment of patients with atrial flutter and short follow-up duration did not explain the aforementioned heterogeneity.

Study limitations. We feel that our study adds to the current understanding of the association between inflammation and AF recurrence. However, some potential limitations may be apparent. Firstly, our analysis is based on observational studies and may be subjected to the potential biases of such studies. Therefore, our results should be interpreted cautiously. Second, converting non-normally distributed statistics (median and range) to normally distributed statistics (mean and SD) may be a cause of bias in our analysis. Third, because the number of studies in our meta-analysis was small, we cannot exclude the possibility of publication bias, although our funnel plot showed that publication bias is unlikely, (43). Fourth, although most of the studies attempted to control the potential confounders, the degree to which this was accomplished varied among them. Fifth, no study of those included in the meta-analysis provided information regarding the inflammatory state before the beginning of AF. Finally, methods of AF detection were different between the trials and therefore some asymptomatic episodes of AF may be overlooked.

Conclusions

In conclusion, our meta-analysis suggests that increased baseline CRP levels are associated with higher risk of AF recurrence after successful EC, although there was a significant heterogeneity across the studies. Our results need to be confirmed by larger well-designed randomized studies with longer follow-up periods. The merit of successive measurement of CRP after cardioversion, as well as the examination of the role of other inflammatory markers such as white blood cell count, and interleukin-6, constitutes a subject for future research.

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