Background Little direct information is available on the effect of C-Reactive Protein (CRP) lowering on the reduction of recurrent atrial fibrillation (AF).

Methods and Results We compared low-dose glucocorticoid therapy (16 mg methylprednisolone for 4 weeks tapered to 4 mg for 4 months) and placebo in 104 patients who had experienced persistent AF with a median concentration of CRP 1.14 mg/dL (min = 0.01, max = 2.58). Methylprednisolone reduced recurrent AF (primary end-point) from 50% in the placebo group to 9.6% in the glucocorticoid group and permanent AF (expanded end-point) from 29% in the placebo group to 2% in the glucocorticoid group. Survival distributions for methylprednisolone were significantly different (for both primary and expanded end-point, \( P < 0.001 \)). In multivariate Cox analysis, average CRP concentrations during follow-up were significant predictors of the primary end-point, with a relative risk 6.72 (\( P = 0.006 \)) and the expanded end-point, with a relative risk of 11.67 (\( P = 0.0006 \)).

Conclusions CRP concentration is a risk factor for recurrent and permanent AF. Methylprednisolone successfully prevents recurrent and permanent AF.

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Introduction

Inflammation plays a pivotal role in the pathogenesis of coronary atherosclerosis and acute coronary events.\(^1\) C-reactive protein (CRP) has been shown to predict major adverse cardiac events among the healthy population, patients with stable coronary artery disease or acute coronary syndrome.\(^2,3\) The role of inflammation in the pathogenesis of atrial fibrillation (AF) has not yet been evaluated but histological changes, consistent with myocarditis, were reported in 66% of biopsy specimens from patients with lone AF.\(^5\) Recently, the relationship between CRP and AF has been studied. CRP is elevated in AF patients compared to controls and CRP may be a potent determinant of successful cardioversion of paroxysmal AF in sinus rhythm.\(^6\) Inflammatory mechanisms may form a basis for new agents more likely to prevent recurrent episodes of AF.

In other recent studies, CRP was also found to be elevated in AF patients. Persistent AF patients had a higher CRP than paroxysmal AF patients and both groups had higher CRP levels than controls.\(^7\) CRP is not only associated with the presence of AF but may also predict patients at increased risk for future development of AF.\(^8\)

Whether persistent or permanent, AF is a chronic disorder, and recurrence is likely at some point in most patients. In patients with AF, the first aim is to stop an attack, and the second is to prevent recurrences.\(^9\) Glucocorticoid therapy may be effective in preventing recurrent AF, thus raising the possibility that methylprednisolone may prevent arrhythmia by reducing inflammation. This present study was designed to assess the interaction between methylprednisolone and CRP in AF.
Methods

Patient population

The study group consisted of 104 patients (52 men and 52 women, mean age 66 years, range 52–84 years) referred to our Department for treatment of the first symptomatic and persistent episode of AF. CRP concentration in these patients was elevated (median = 1.14 mg/dL) compared to CRP in patients with paroxysmal and/or asymptomatic AF (median = 0.80 mg/dL) measured in a previous study. Similar findings of elevated CRP in symptomatic and persistent AF have been recently published. Patients with AF secondary to a precipitating condition such as acute myocardial infarction or unstable angina, cardiac surgery, acute pericarditis or myocarditis, thyrotoxicosis, or acute pulmonary disease and patients with inflammatory or neoplastic conditions were excluded. The vast majority of these disorders can be diagnosed easily by a complete history and physical examination. Specific tests were carried out only when there was substantive clinical evidence suggesting a relevant diagnosis, as these tests have poor predictive value when used in a screening fashion.

The rate of recurrent AF is about 50% and to detect at least one-third reduction in the glucocorticoid group (15%) at a level of $\alpha = 0.05$ with a power (with continuity correction) greater than 0.80, the sample size should be 32 patients in each group.

Cardiac studies and laboratory tests

Cardiac studies included non-invasive tests (i.e., ECG with Holter monitoring and two-dimensional echocardiology with Doppler analysis). The bi-plane method of discs was used to measure left ventricular ejection fraction. Left atrial size was measured by a simple antero-posterior dimension of the chamber from the M-Mode parasternal long-axis view. All patients underwent routine laboratory tests, including those for glycaemia, creatinaemia, blood urea nitrogen, serum electrolytes (Na⁺ and K⁺), transaminase (sGOT and sGPT), erythrocyte sedimentation rate, blood cell count, thyroid function tests (T₃, T₄ and thyroid-stimulating hormone) and CRP. Measurements were carried out with an Olympus System autoanalyzer (model AU 640, Medicon Hellas, Gerakas, Greece); CRP was measured quantitatively by means of an immuno-turbidimetric assay (Reagent 800, Lismeehan, Co. Clare, Ireland.). CRP reacts specifically with anti-human CRP antibodies to yield insoluble aggregates. The absorbance of these aggregates is proportional to the CRP concentration in the sample. The normal range of serum CRP levels in adults had a detection limit of 0.01 mg/dL and an upper limit of $\leq 0.5$ mg/dL. The repeatability co-efficient concerning CRP values was 0.013 mg/dL. CRP levels were measured on two occasions during the first hospitalisation (first, on admission and second, 24 h later) and after 4 weeks, 4 months, 6 months and every 6 months afterward for the duration of the trial.

Study protocol

The study was approved by the hospital’s Ethics Committee. After informed consent was obtained, patients received 2.7 g amiodarone intravenously over 24 h (112.5 mg/h). To prevent thrombo-embolic episodes, all patients who were still in AF after 24 h were started on heparin treatment. After 24 h of treatment patients were re-evaluated. Eleven patients who had not converted to normal sinus rhythm after 24 h of high dose amiodarone treatment were treated by electrical cardioversion. Prophylactic drug therapy with propafenone (450 mg daily dose) to prevent early recurrence of AF was administered to all 104 patients (both placebo and treatment groups) who were cardioverted into normal sinus rhythm and the prophylactic administration of propafenone was maintained during the entire follow-up time. All patients were kept under observation in the cardiology department for at least three days before being discharged.

Data of patients admitted because of AF were collected according to a protocol. Information on age, sex, cardiovascular risk profile, and complications was recorded for every patient. Patients were then assigned at random to either glucocorticoid (methylprednisolone 16 mg for 4 weeks tapered to 4 mg for 4 months) or placebo therapy (52 patients in each group). With respect to the therapy the study was blinded.

The planned duration of the study was 30 months; the last patient entered at least 3 months before study termination (27th month of the study). All patients were followed-up for a median period of 23.65 months (with 25, 50 and 75 percentiles 11, 23.65 and 26 months, respectively) and no patients were lost from follow-up. Patients were examined in the outpatient department 4 weeks, 4 months, and 6 months after the first admission and every 6 months afterward for the duration of the trial. Patients who were admitted for recurrent AF (primary end-point) were treated again with amiodarone 2.7 g intravenously over 24 h and if they were not cardioverted, electrical cardioversion was applied. Patients with recurrent AF, who were not cardioverted either with amiodarone or electrical cardioversion, were designated as having permanent AF (expanded end-point).

Definition of terms

We avoided the term paroxysmal AF because it specifically relates to an event occurring in paroxysms, which are the sudden onset of symptoms that have no specific time frame or termination. Instead we use the term persistent AF to denote a symptomatic and persistent episode of AF which can be cardioverted to sinus rhythm. Permanent AF indicates the inability of pharmacological or electrical cardioversion to restore sinus rhythm.

Statistical analysis

Variables were tested for normal distribution with the Kolmogorov–Smirnov one-sample test. To detect significant differences between the groups regarding the remaining variables $t$ test was used. Dichotomous variables were compared by $\chi^2$ test. The Friedman Test was used to compare CRP measurements during follow-up in placebo and glucocorticoid group.

The probability of survival in glucocorticoid and placebo groups was estimated by the Kaplan–Meier method. Log rank statistics were used to test the equality of the survival distributions for the placebo and glucocorticoid groups.

The most recent CRP concentration refers to either the CRP measurement on admission of a patient to the hospital with a recurrent AF event, or the final CRP measurement in the trial for patients who did not experience an event during follow-up. Most recent CRP concentrations were divided into three tertiles, chosen to have approximately the same number of events in each tertile. This method of recoding is useful for identifying non-linear effects of the CRP and provides more stable relative risk estimates. Since the linearity assumption had been violated, logarithmic transformation of the CRP measurement was applied and then the transformed CRP value was entered into the Cox
The characteristics of the enrolled patients (placebo and glucocorticoid groups) are summarised in Table 1. We found that about 75% of patients experienced at least one episode of palpitations before the onset of the first symptomatic and persistent episode of AF. The mean duration of persistent AF was approximately 6 h. Forty-one of the 52 (79%) patients receiving amiodarone were successfully converted to sinus rhythm within the first 24 h. Eleven patients who failed to convert while on amiodarone underwent electrical cardioversion, which was successful in all cases (100%). There was no difference between amiodarone responders and electrically cardioverted patients in response to propafenone during follow-up. At baseline there were no differences between the two groups according to age, sex, body mass index, diabetes, current smoking, history of palpitations, history of hypertension, mean left ventricular ejection fraction and left atrial diameter.

In the glucocorticoid group, 5 patients (9.6%) had recurrent AF and four of these had been successfully converted to sinus rhythm with an intravenous administration of amiodarone. The remaining 1 patient of the glucocorticoid group (1.9%) developed permanent AF. In the placebo group 26 patients (50%) had recurrent AF; eleven of them had been successfully converted in sinus rhythm with intravenous administration of amiodarone (n = 8) or electrical cardioversion (n = 3). The remaining 15 patients of the placebo group (28.9%) developed permanent AF.

In the glucocorticoid group, 4 patients (8%) from the 5 patients who were hospitalised for recurrent AF mentioned at least one episode of palpitations and 15 patients (32%) from the 47 patients who did not have recurrent AF had palpitations, P < 0.001. In the control group, 22 (85%) of the 26 patients with recurrent AF had palpitations and 9 (35%) of the patients without recurrent AF had palpitations, P < 0.001. In the total cohort, 19 patients (37%) who received methylprednisolone refer palpitations while 31 patients (60%) of control group had palpitations, P < 0.001.

There were no differences, at presentation, in CRP values between the 5 patients that did experience a recurrence of AF in the glucocorticoid group and the remainder that did not, P-value non-significant (NS). However, the most recent CRP concentration, taken during follow-up, was higher in the 5 patients that did experience a recurrence of AF, when compared with the remainder that did not (median = 0.58, min = 0.22, max = 0.60 versus median = 0.16, min = 0.00, max = 0.46 mg/dL, P < 0.01).

In the placebo group, patients who did not have recurrent AF had a significantly decreased CRP (median = 0.49, min = 0.04, max = 0.97 mg/dL) compared with patients who did (median = 2.03, min = 1.31, max = 2.57 mg/dL), P < 0.001. Furthermore, the CRP

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Table 1 The principal baseline characteristics of the enrolled patients divided into the placebo and glucocorticoid groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo group (n = 52)</th>
<th>Glucocorticoid group (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.5 ± 4.9</td>
<td>66.5 ± 5.9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>26/26</td>
<td>26/26</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 2.4</td>
<td>23.7 ± 2.2</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Palpitations (%)</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Duration (h)</td>
<td>6.1 ± 0.7</td>
<td>6.2 ± 0.6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53.1 ± 0.6</td>
<td>52.9 ± 0.6</td>
</tr>
<tr>
<td>LAD (cm)</td>
<td>3.74 ± 0.42</td>
<td>3.84 ± 0.45</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.14 (0.04–2.57)</td>
<td>1.13 (0.01–2.58)</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.13 (0.03–2.59)</td>
<td>0.24 (0.00–0.60)</td>
</tr>
<tr>
<td>Recurrent AF (%)</td>
<td>50</td>
<td>9.6</td>
</tr>
<tr>
<td>Permanent AF (%)</td>
<td>28.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

BMI, body mass index; Palpitations, history of at least one episode of palpitations before the onset of the first symptomatic and persistent episode of AF; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; CRP, the most recent of C-reactive protein concentration during follow-up (see text). Values of CRP and CRP refer to median (min–max).
concentrations at the time of AF recurrence was increased (median = 1.83, min-max = 1.31–2.59 mg/dL) compared to the most recent CRP concentration during follow-up in patients who did not experience a recurrence of AF (median = 0.36, min-max = 0.03–0.94 mg/dL), \( P < 0.001 \). Finally, CRP was increased in patients who developed permanent AF (median = 2.12, min-max = 0.60–2.59 mg/dL) compared with those who did not (median = 0.34, min-max = 0.00–1.76), \( P < 0.001 \).

Methylprednisolone significantly lowered CRP by an average of 80% in the first month, and this reduction was maintained for the duration of the study (\( P < 0.001 \), Fig. 1). No patient developed a recurrence of CRP increase during follow-up after termination of methylprednisolone treatment, and the placebo group did not show any difference in CRP during the study. This was an expected finding, as CRP remains relatively constant for a long period of time.

Median survival time for the glucocorticoid group according to primary end-point was 24.00 (with 95% confidence interval (CI): 21.01–26.57) months and for the placebo group 11.10 (95% CI: 10.37–13.61) months, \( P < 0.001 \) (Log rank, Fig. 2). Median survival time for the glucocorticoid group according to expanded end-point was 34.00 (95% CI: 31.12–36.88) months and for the placebo group 31.9 (95% CI: 28.32–34.68) months, \( P < 0.001 \) (Log rank, Fig. 2). Survival distributions were significantly different between glucocorticoid and placebo group (\( P < 0.001 \)).

The relationship between follow-up average CRP and AF events in the total cohort was determined to be non-linear by the use of tertile analysis. The estimated hazard ratios in the total cohort for the primary end-point declined sharply from the 1st tertile (RR = 9.51, 95% CI = 3.05–15.97) to the 2nd tertile (RR = 3.37, 95% CI = 1.32–5.41), and 3rd tertile (RR = 2.57, 95% CI = 1.16–3.92), Fig. 3(a). Similarly, the estimated hazard ratios in the total cohort for the expanded end-point declined sharply from the 1st tertile (RR = 10.31, 95% CI = 2.50–18.00) to the 2nd tertile (RR = 3.80, 95% CI = 0.75–6.99), and 3rd tertile (RR = 2.29, 95% CI = 0.69–3.78), Fig. 3(b).

In the total cohort, the average CRP concentrations during follow-up, when modelled as a linear variable and adjusted for baseline risk factors, correlated significantly (\( P < 0.001 \)) with the risk of a primary or expanded AF end-point (Table 2). The results were very similar when the CRP value used in the analysis was the average or the most recent value with adjustment for the baseline risk factors having little effect on the results. However, there was no significant correlation between initial CRP values at presentation and the recurrence of AF, \( P = \text{NS} \).

The relationship between average CRP during treatment and the AF events in the placebo and the glucocorticoid group, considered separately was also significant for both primary and expanded end-points (Table 2).

The best CRP cut-off point for detection of the primary end-point is about 0.62 mg/dL (Fig. 4). Only four patients (13%) who reached the primary end-point had decreased CRP (<0.62 mg/dL) and only eight patients (11%) who did not reach the primary end-point had increased CRP (>0.62 mg/dL). The best CRP cut-off point for detection of the expanded end-point was approximately 1.56 mg/dL (Fig. 4). Only two patients (12.5%) who reached the expanded end-point had decreased CRP (<1.56 mg/dL) and only five patients (5.7%) who did not reach the primary end-point had increased CRP (>1.56 mg/dL).

No severe adverse effects necessitating drug discontinuation during cardioversion or follow-up occurred. There were no bronchial asthma, bundle branch block
formation or pro-arrhythmic effects, defined as the new onset of sustained ventricular tachycardia, ventricular fibrillation or *torsades de point*, either during amiodarone or during propafenone administration. Adherence to the therapy was excellent for the entire duration of the trial. Furthermore, no patients developed significant sinus bradycardia (<50 bpm), although eleven patients developed mild phlebitis at the intravenous access of amiodarone and five patients receiving glucocorticoid therapy needed to re-adjust drug therapy for diabetes mellitus and four patients for essential hypertension.

**Discussion**

Recent studies implicate a mechanistic link between inflammation and AF and it is possible that CRP is related to the mechanisms of AF. The use of low-dose glucocorticoid

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**Table 2** Relationship between transformed CRP levels during treatment and AF events

<table>
<thead>
<tr>
<th></th>
<th>Primary end-point</th>
<th></th>
<th>Expended end-point</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>CI</td>
<td>P</td>
<td>RR</td>
</tr>
<tr>
<td>Total cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln (CRP)</td>
<td>6.72</td>
<td>1.73–11.02</td>
<td>0.006</td>
<td>11.67</td>
</tr>
<tr>
<td>Placebo group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln (CRP)</td>
<td>5.17</td>
<td>1.32–10.19</td>
<td>0.02</td>
<td>11.22</td>
</tr>
<tr>
<td>Glucocorticoid group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln (CRP)</td>
<td>66.67</td>
<td>33.39–90.57</td>
<td>0.03</td>
<td>23.80</td>
</tr>
</tbody>
</table>

Relative risks (RR) with 95% confidence interval (CI). Primary end-point was recurrent AF; expanded end-point was persistent AF. Age, sex, body mass index (BMI), current smoking, diabetes, hypertension, left ventricular ejection fraction, and left atrial diameter were entered as co-variates in Cox proportional models.
as a primary treatment for prevention of recurrent AF has been validated. Glucocorticoid and propafenone therapy resulted in recurrent AF in only 9.6% of patients, while placebo and propafenone therapy resulted in recurrent AF in 50% of patients. Permanent AF was developed in 1.9% of patients in the glucocorticoid group and in 28.9% of patients in the placebo group.

CRP predicts recurrent and permanent AF

The risk of recurrent AF is increased by approximately 7 times for an increase of 1 mg/dL in plasma levels of CRP. And the risk of permanent AF is increased about 12 times for an increase of 1 mg/dL in plasma levels of CRP. Plasma CRP, an acute phase reaction protein, is directly correlated with the inflammatory process, which is also a cardiovascular risk factor. Inflammatory processes in the atrial myocytes and interstitium can directly lead to fluctuations in the membrane potential.19 Inflammation and infections are involved in the pathogenesis of coronary artery disease. The infection theory of AF development is one possible piece in the complex puzzle of AF development. The effect of chronic infections, like herpes simplex type I and Chlamydia pneumoniae, is emphasised in subjects with ongoing inflammation, denoted by increased CRP levels.20

Our findings are in accordance with recent studies,7,8 which found that CRP was increased in patients with paroxysmal AF compared to control patients; in addition CRP was much more elevated in patients with persistent AF compared to patients with paroxysmal AF.7 Furthermore, baseline CRP predicted higher risk for developing future AF.

The precise mechanism for the increased circulating CRP is uncertain but might reflect active participation of CRP in the local inflammatory response in the atrial myocardium because of ligand binding and the ability of CRP to activate the classic complement pathway.22 In patients with AF, CRP may localise in atrial tissue, possibly binding to the membranes of myocardial cells in inflamed tissues, which suggests that this acute-phase protein promotes local complement activation, and hence tissue damage. Complement activation functions as an amplification system in atrial inflammation. In the presence of Ca²⁺ ions, CRP specifically binds to phosphatidylcholine, particularly when lysophosphatidylcholine is present. Long-chain acylcarnitines and lysophosphatidylchoelines are generated from phosphatidylcholine and can both contribute to membrane dysfunction by inhibiting the exchange of sodium and calcium ions in sarcosomal vesicles and thus lead to the development of arrhythmia. This may explain the association between raised levels of CRP and the occurrence of AF.25

Low dose glucocorticoid therapy reduces the risk of recurrent and permanent AF

Glucocorticoid therapy decreased plasma CRP levels and significantly prevented recurrent and permanent AF in patients with increased CRP levels who had experienced an episode of persistent AF. Furthermore, glucocorticoid therapy significantly reduced the episodes of palpitations from 60%, in the control group, to 37% in the active group. The rate of AF events was associated strongly with the plasma CRP concentrations during treatment in the total cohort consisting of the patients treated with glucocorticoid or placebo. This is an expected finding, considering that glucocorticoids reduce CRP concentrations via the anti-inflammatory effect and that CRP is closely related with AF events. Similar results were found in patients with ventricular arrhythmias,21 immunosuppressive therapy in addition to conventional antiarrhythmic treatment can lead to the reduction or complete suppression of spontaneous and inducible arrhythmia.

Propafenone at a dose of 450 mg daily may be antiarrhythmic, neutral or pro-arrhythmic in patients with AF. We considered the possibility that this analysis did not detect the possible relationship between glucocorticoid, propafenone and AF recurrences. We found that the relative risk of a primary or expanded end-point in patients in the glucocorticoid group was similar to the relative risk of patients in the placebo group with the same level of CRP concentration. This suggests that the clinically important reduction in recurrent and permanent AF was probably a consequence of the reduction of CRP caused by glucocorticoid therapy.

The decrease in AF events, regardless of the mechanism, was obtained after a low-dose glucocorticoid treatment period, and may present a useful additional effective therapy for the prevention of AF. A central finding of this study is that the relationship between CRP during treatment and AF events is not linear but rather appears that glucocorticoid therapy has the maximal effect in patients with the highest plasma levels of CRP with a median value of 1.59 mg/dL and a minimal value of 0.60 mg/dL.

Another important finding of this study is the determination of the cut-off point for predicting recurrent and permanent AF. Recurrent AF happened when the CRP plasma level was greater than 0.62 mg/dL, while permanent AF occurred when CRP was greater than 1.56 mg/dL. The increased concentration of CRP resulted in an increased possibility of recurrent AF; a further increase in CRP > 1.56 mg/dL led to the development of permanent AF. Because CRP reflects inflammation these results show a gradation of the effects of inflammation on the severity of the form of AF. It has also been suggested that the inflammatory process is a likely cause of AF. Frustaci et al.,5 have also found that in patients with active atrial myocarditis, steroid treatment was associated with the absence of AF recurrence, which occurred in the patients on electrophysiologic study (EPS)-guided antiarrhythmic therapy; these results are in accordance with the findings of our study.

Methodological considerations

Although there are recent studies6–8 showing the link between CRP and AF, the AF inflammatory hypothesis needs more study to be widely acceptable. This study
found that the glucocorticoid therapy reduced CRP levels, which were correlated with the AF events. This may be an indirect proof of the inflammatory hypothesis because only AF patients with elevated CRP were included.

The identification of a non-linear relationship between follow-up CRP concentrations and AF events with cut-off points of 0.62 and 1.56 mg/dL are derived from an explanatory analysis and should be examined in future trials. This type of analysis is based on randomised groups and the possibility of unidentified variables confounding the results is limited, although the association of AF with risk factors for atherosclerosis limits this study, we did not find evidence for important confounding events by the known non-inflammatory variables that affect outcomes in patients with AF. Thus, it is difficult to imagine other different factors that could have a significant effect on AF events and to be responsible for the non-linearity.

Amiodarone was administered intravenously in all patients with an increased dosage (2.7 g) prior to electrical cardioversion in order to succeed an efficient blood concentration of amiodarone and thus eliminate possible immediate recurrences of AF. An increased dose of amiodarone administered for a short time (<24 h) seems to be faster and more effective in AF conversion without serious complications than lower doses of amiodarone administered for longer periods. We gave propafenone, for the prevention of AF, to all patients in order to have homogeneity in our sample. A possible interaction between methylprednisolone and low dose propafenone could, therefore, have influenced the study results of the active group, although it was necessary to give propafenone in both groups for the purposes of matching the study groups.

Although the number of patients in this study is limited, the large reduction in AF events eliminates the possibility of a type II error. The acute phase response is biochemically characterised by changes in levels of various acute-phase proteins. CRP is the prototypical acute-phase protein in humans and the most widely used as an index of inflammation. Another limitation is that we did not use an ultra-sensitive CRP assay. We measured CRP by means of an immuno-turbidimetric test, whereas other investigators have used immuno-nephelometry to measure CRP; thus, the values of CRP levels in our study were approximately 10-fold the CRP values found by those authors. However, this increment in CRP values was stable at approximately 10-fold in all groups of patients as well as in controls and was similar to that found in a previous study. In conclusion, because the increase in CRP is non-specific, it cannot be interpreted without a complete clinical history, and even then only by comparison with previous values obtained with the same analytic technique.

Clinical study implications

The use of glucocorticoid therapy may reduce the risk of recurrent and permanent AF. If AF is associated with increased plasma levels of CRP, there may be patients in whom conventional anti-arrhythmic drug therapy is insufficient to provide prophylaxis against recurrences; there may also be patients with decreased CRP levels, in whom the anti-arrhythmic drug concentration exceeds that needed for a therapeutic effect, with a corresponding increase in adverse events. These problems are highly clinically relevant when considering the prevention of recurrence for patients with AF. Our finding of a risk factor in recurrent and permanent AF, therefore, provides hope that anti-inflammatory glucocorticoid therapy, aiming for a consistent CRP target of less than 0.62 mg/dL, is likely to provide adequate anti-arrhythmic “cover” for recurrent AF.

In conclusion, this study has established that patients suffering from AF, with increased CRP levels, could benefit from receiving anti-inflammatory treatment to reduce the risk of recurrent and permanent AF. Our findings suggest that the lowering of CRP levels to <0.62 and <1.56 mg/dL, by glucocorticoid treatment, was largely responsible for the reductions in recurrent and permanent AF, respectively.

References