Serum Levels of Vitamin E Are Associated With Early Recurrence of Atrial Fibrillation After Electric Cardioversion

Domenico Ferro, MD; Pasquale Franciosa, MD; Roberto Cangemi, MD, PhD; Roberto Carnevale, PhD; Pasquale Pignatelli, MD, PhD; Lorenzo Loffredo, MD; Ludovica Perri, MD; Elisa Catasca, MD; Francesco Violi, MD

Background—Oxidative stress is suggested to play a role in favoring the occurrence of atrial fibrillation (AF). We analyzed whether vitamin E, a known antioxidant, or markers of oxidative stress are associated with AF recurrence in patients undergoing electric cardioversion.

Methods and Results—A total of 144 patients (83 men; mean age, 71.1 ± 5.4 years) underwent successful biphasic electric cardioversion of nonvalvular persistent AF. At baseline, urinary 8-isoprostaglandin F2α and serum soluble NOX2-derived peptide (sNOX2-dp), high-sensitivity C-reactive protein (hs-CRP), and vitamin E levels were measured in each patient. All patients underwent 3 months of clinical follow-up, including an office visit with ECG every week or in cases of symptom recurrence. During the follow-up, 94 patients maintained sinus rhythm, whereas 50 experienced AF recurrence. In unadjusted analysis, left atrial diameter and levels of urinary isoprostanes and serum sNOX2-dp and hs-CRP were significantly higher and serum vitamin E lower in patients with AF recurrence. In multivariable Cox analysis, serum vitamin E (hazard ratio, 0.734; 95% CI, 0.605–0.891; \( P = 0.001 \)) and, to a lesser extent, hs-CRP (\( P = 0.047 \)) remained significantly associated with AF recurrence. Urinary isoprostanes and serum sNOX2-dp levels were inversely correlated with serum vitamin E level (\( r = -0.626, P < 0.001 \), and \( r = -0.460, P < 0.001 \), respectively).

Conclusions—The study shows that low serum vitamin E levels are associated with AF recurrence in patients who underwent cardioversion. Because vitamin E inversely correlated with oxidative stress, the findings reinforce the hypothesis of an interplay between oxidative stress and AF.

Key Words: atrial fibrillation ■ cardioversion ■ oxidative stress ■ vitamin E

Atrial fibrillation (AF) is the most common cardiac arrhythmia that is associated with a high risk of cardiovascular events, such as ischemic stroke. There is a growing body of clinical and experimental evidence indicating a link between AF and inflammation, suggesting a role for oxidative stress in eliciting inflammation. Thus, experimental models of atrial electrophysiological stimulation are associated with enhanced oxidative stress, and antioxidant treatment is able to prevent vulnerability to AF. Interestingly, animals deficient of myeloperoxidase, an enzyme that elicits oxidative stress by producing hypochlorous acid, were protected from AF induced by atrial electrophysiological stimulation. Studies in humans corroborated this hypothesis, showing that atrial myocytes from the right atrial appendage produce an abundant amount of reactive oxygen species through NADPH oxidase activation and that antioxidant treatment reduces the occurrence of AF in patients undergoing cardiac surgery. These findings suggest that oxidative stress might be implicated in the occurrence of AF and that markers of oxidative stress could be a useful tool in identifying patients who are more prone to AF.

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Vitamin E is a natural molecule that exerts an antiinflammatory effect with a mechanism that is partly related to its antioxidant property. To our knowledge, no data have been reported so far on the relationship between vitamin E and AF. Because of its antioxidant and antiinflammatory properties, we hypothesized that serum vitamin E is predictive of AF. To explore this hypothesis, we analyzed the relationship between serum levels of vitamin E and AF recurrence in patients with persistent AF who underwent electric cardioversion to restore sinus rhythm.
Methods

Study Design
We studied 146 consecutive patients (83 men; mean age, 71.1±5.4 years) who underwent elective electric cardioversion because of nonvalvular persistent AF (lasting >7 days). Patients were enrolled between October 2009 and March 2011. Written informed consent was obtained from all patients. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee.

Patient Selection
Patients were excluded if they had rheumatic AF and other cardiac reasons for exclusion, including echocardiographic evidence of intracardiac thrombosis or tumor, left ventricular aneurysm, severe congestive heart failure (New York Heart Association functional class III or IV), the presence of prosthetic valves, acute myocardial infarction or unstable angina during the previous month, carotid endarterectomy or coronary or peripheral revascularization procedures performed during the previous 6 months, acquired or congenital valvular disease (except mitral valve prolapse or mitral annulus calcification), and atrial endocardial or other atrial tachyarrhythmias. We also excluded patients with inflammatory or neoplastic diseases and thyroid dysfunction and patients treated long term with corticosteroids. Further, we excluded patients with liver or pancreatic insufficiency and serious renal disorders (serum creatinine >2.8 mg/dL) and patients who were current smokers or who were taking antioxidant vitamins. Neurological exclusion criteria included CT brain scan evidence of cerebral hemorrhage, documented arteriovenous malformation or tumor, severe involutive cerebral disease, and the presence of a carotid lesion requiring surgical intervention.

Baseline
At entry, each patient’s medical history was taken, and he or she underwent a physical examination. The following diagnostic procedures were performed: routine blood laboratory tests, baseline 12-lead ECG, M-mode and 2D echocardiography with color Doppler echocardiography, color Doppler echocardiography of the supravalvular trunks, and chest radiography.

All patients were treated for 4 weeks with anticoagulants (target international normalized ratio, 2–3) before undergoing electric cardioversion. Transesophageal echocardiography was performed 24 hours before the procedure to exclude the presence of intracavitary thrombus.

Given that dietary changes could potentially influence anticoagulation rate by warfarin, patients were advised not to modify their diet composition. Nutritional parameters were monitored during 3 months of follow-up by a validated food frequency questionnaire to quantitatively estimate the level of adherence to the Mediterranean diet. Moreover, patients were asked not to consume antioxidant vitamins during the follow-up period.

Electric Cardioversion Protocol
After obtaining written informed consent, electric cardioversion was performed under sedation with intravenous midazolam (0.05 mg/Kg) and thiopental sodium (60 mg/Kg). R-wave-synchronized electric cardioversion was performed using an external biphasic defibrillator (Zoll M Series Biphasic; Zoll Medical Corp) in all patients with increasing energy, starting at 100 J to ≤200 J. If cardioversion terminated AF successfully, the patient’s cardiac rhythm was monitored for 15 minutes to detect an atrial premature beat or recurrence of AF. If AF returned within 15 minutes of termination of cardioversion, amiodarone 150 mg was administered intravenously, and the energy shock was repeated. Patients in whom AF remained even after being given a 200-J cardioversion shock or who exhibited repeated immediate recurrence of AF in spite of amiodarone and a second shock were defined as failed cardioversions and excluded from the study.

Follow-Up
All patients underwent clinical follow-up, including an office visit with ECG every week or in cases of symptom recurrence. A Holter ECG (24 or 48 hours) was recorded at the end of cardioversion and every month in patients who did not have a recurrence. Follow-up was performed up to 3 months in all cases. Patients were treated with amiodarone, class IC antiarrhythmic drugs, or sotalol. Antiarrhythmic therapy began before cardioversion and continued during follow-up or until AF recurrence. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium antagonists (non-dihydropyridines), diuretics, statins, and digitals were continued on the basis of patient clinical status.

Blood Collection and Laboratory Analysis
Blood samples were drawn without stasis to minimize platelet activation from patients who had fasted for 12 hours, directly mixed in a Vacutainer (Vacutainer Systems; Belliver Industrial Estate) with 1 part 3.8% Na citrate (ratio, 9:1), and immediately centrifuged for 20 minutes at 2000g at −4°C. Plasma samples were stored at −80°C until use.

Isoprostanes: Urinary 8-Isoprostaglandin F2α Assays
Urinary 8-isoprostaglandin F2α (8-iso-PGF2α) was measured by a previously described and validated enzyme immunoassay method. Ten milliliters urine was extracted on a C-18 solid phase extraction column; the purification was tested for recovery by adding a radioactive tracer (titrated 8-iso-PGF2α (Cayman Chemical). The eluates were dried under nitrogen, recovered with 1 mL of buffer, and assayed with an 8-iso-PGF2α-specific enzyme immunoassay (Cayman Chemical). Urinary 8-iso-PGF2α concentration was corrected for recovery and creatinine excretion. Values are expressed as pg/mg of creatinine.

Soluble NOX2
Serum levels of soluble NOX2-derived peptide (sNOX2-dp) were detected by ELISA method as previously described. The peptide was recognized by a specific monoclonal antibody against the amino acid sequence (224–268) of the extramembrane portion of NOX2. Values are expressed as pg/mL; intraassay and interassay coefficients of variation were 5.2% and 6%, respectively.

C-Reactive Protein
High-sensitivity C-reactive protein (hs-CRP) was measured by commercially available immunoassay (Temaricera). Intraassay and interassay coefficients of variation were 9.5% and 9.0%, respectively.

Serum α-Tocopherol (Vitamin E) and α-Tocopherolquinone (Products of α-Tocopherol Oxidation)

Vitamin E
Serum samples (100 μL) were supplemented with tocopheryl acetate (internal standard), deproteinized by the addition of ethanol, and extracted with hexane. Phase separation was achieved by centrifugation. The collected upper phase was evaporated and analyzed using an Agilent 1200 Infinity series high-performance liquid chromatography system equipped with an Eclipse Plus C18 column (4.6×100 mm). Levels were given as the ratio (μmol/mmol) between serum α-tocopherol concentration (μmol/L) and serum total cholesterol concentration (mmol/L), which better express the circulating levels of vitamin E.

α-Tocopherolquinone
A standard solution of α-tocopherolquinone was prepared by oxidation of α-tocopherol with FeCl3 and was analyzed by high-performance liquid chromatography using UV detection (Amax, 262 nm). Serum samples (100 μL) were supplemented with vitamin E (internal standard), extracted, and analyzed following the procedure just described. Levels were given as the ratio (μmol/mmol) between serum α-tocoph-
erolquinone concentration (μmol/L) and serum total cholesterol concentration (mmol/L).

**Statistical Analysis**
Categorical variables were reported as counts (percentages) and continuous variables as means±SD, unless otherwise indicated. Independence of categorical variables was assessed by χ² test. Normal distribution of parameters was assessed by Kolmogorov-Smirnov test. Student unpaired t test and Pearson product moment correlation analysis were used for normally distributed continuous variables. Appropriate nonparametric tests (Mann-Whitney U test and Spearman rank correlation test) were used for all the other variables.

Proportional hazards analysis was used to calculate the adjusted relative hazards of AF recurrence by each clinical variable. In addition to vitamin E serum values, the following variables (assessed at the baseline evaluation) were considered as potential predictors of AF recurrence: age, sex, heart failure, diabetes, history of stroke, history of myocardial infarction, ejection fraction, left atrial diameter, treatment with amiodarone, class IC antiarrhythmic drugs, sotalol, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, urinary isoprostanes, and sNOX2-dp. Nonnormally distributed continuous variables were transformed by a base 2 logarithm (Ln). Only variables with P<0.10 in the univariate analysis were candidates for the multivariable model, which was finally determined in a forward stepwise variable selection procedure.

A receiver operating characteristic curve analysis was used to determine the ability of vitamin E to distinguish between patients with or without AF recurrence within 3 months after electric cardioversion. After dividing the AF population into 2 groups (patients with vitamin E values equal to or above the median and patients with vitamin E levels below the median), the cumulative risk of AF recurrence within each group was estimated through the Kaplan-Meier method. The survival curves of the 2 groups were then formally compared using the log-rank test.

Only P<0.05 was regarded as statistically significant. All tests were 2 tailed, and analyses were performed using STATA version 8.0 (StataCorp) or SPSS version 13.0 (SPSS Inc) statistical software.

**Sample Size Determination**
We calculated that 142 patients were required to have a 90% chance of detecting at the 5% level a decrease of AF recurrence within 3 months, from 38% in the group with low vitamin E levels (below the median value) to 15% in the group with high vitamin E levels (equal to or above the median value).

**Results**
Biphasic electric cardioversion was successful in all but 2 patients, who were excluded from the study. An early recurrence (≤1 minute) was detected in 6 patients. Patients were treated with amiodarone (55%), class IC antiarrhythmic drugs (32%), or sotalol (11%); they were on antiarrhythmic therapy at least 2 weeks before cardioversion and continued during follow-up or until AF recurrence. Angiotensin converting enzyme inhibitor and angiotensin receptor blockers were used in 47% of the population, whereas statins were used in 22.5%. The 3-month follow-up was completed in all patients.

Clinical characteristics of the 144 patients included in the study are reported in Table 1. As expected, hypertension was the most frequent cause of underlying disease associated with AF (87%); 13% of the patients had diabetes mellitus, 5% had heart failure and a history of stroke, and 9% had a myocardial infarction.

<table>
<thead>
<tr>
<th>Table 1. Patient Baseline Characteristics</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>No. patients</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Age &gt;75 y</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>History of stroke</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
</tr>
<tr>
<td>Ejection fraction, (%)</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
</tr>
<tr>
<td>AF duration, d</td>
</tr>
<tr>
<td>ACEI/ARB</td>
</tr>
<tr>
<td>Statins</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Class IC antiarrhythmic drugs</td>
</tr>
<tr>
<td>Sotalol</td>
</tr>
<tr>
<td>Vitamin E, μmol/mmol cholesterol</td>
</tr>
<tr>
<td>α-Tocopherolquinone, μmol/mmol cholesterol</td>
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<tr>
<td>Urinary isoprostanes, pg/mg creatinine</td>
</tr>
<tr>
<td>hSCRP, mg/mL</td>
</tr>
<tr>
<td>SUA, mg/mL</td>
</tr>
<tr>
<td>WBC count, ×1000/mm³</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, percentage, or median (interquartile range), unless otherwise indicated.

At baseline, correlation analyses among markers of oxidative stress and inflammation (hs-CRP) demonstrated that serum vitamin E was inversely correlated with urinary isoprostanes (r = −0.626; P < 0.001), serum α-tocopherolquinone (r = −0.658; P < 0.001), and serum sNOX2-dp (r = −0.460; P < 0.001) and that sNOX2-dp significantly correlated with urinary isoprostanes (r = 0.731; P < 0.001).

During the 3-month follow-up, 50 (34%) patients experienced an AF recurrence. Compared with patients without AF recurrence, those with AF recurrence had similar clinical characteristics with the exception of higher left atrial diameter and levels of urinary isoprostanes and serum sNOX2-dp and hs-CRP and lower serum vitamin E levels. No difference in antiarrhythmic therapy was observed between patients who had or did not have a recurrence (Table 2).

Unadjusted proportional hazards models confirmed left atrial diameter (P = 0.003) and baseline values of urinary isoprostanes (P < 0.001) and serum sNOX2-dp (P = 0.001), hs-CRP (Ln) (P = 0.049), and vitamin E (P < 0.001) were associated with AF recurrence within 3 months. Age; sex;
heart failure; diabetes; history of stroke; history of myocardial infarction; ejection fraction; and treatment with amiodarone, class IC antiarrhythmic drugs, sotalol, statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were not significantly associated with AF recurrence.

A multivariable Cox proportional hazards model adjusted for left atrial diameter, baseline values of urinary isoprostanes and serum sNOX2-dp, hs-CRP (Ln), and vitamin E demonstrated that vitamin E (hazard ratio [HR], 0.734; 95% CI, 0.605–0.891; P<0.001) and, to a lesser extent, hs-CRP (hazard ratio, 1.542; 95% CI, 1.005–2.366; P=0.047) were associated with AF recurrence within 3 months. Receiver operating characteristic curve analysis demonstrated that patients with serum levels of vitamin E below the median were more likely to experience AF recurrence than patients with vitamin E above the median, after adjusting for all the other predictors in the model (hazard ratio, 2.4; 95% CI, 1.3–4.3; P=0.003).

Discussion

To our knowledge, this study provides the first evidence that circulating vitamin E is associated with recurrence of AF in patients who underwent cardioversion. Oxidative stress has been implicated in AF, with experimental models of atrial pacing showing an association of markers of oxidative stress, such as peroxynitrite, with AF and a reduced risk of AF in animals with low formation of reactive oxygen species. Administration of ascorbic acid, a known antioxidant, has also been used as a tool to investigate whether oxidative stress plays a causative role. However, data are conflicting and difficult to interpret because ascorbic acid was administered either intravenously or orally, though it is well established that ascorbic acid behaves as an antioxidant in vivo only when given intravenously.

The relationship between oxidative stress and AF has also been explored in patients with AF. Kim et al demonstrated that NOX2, the catalytic subunit of NADPH oxidase, is the main source of oxidative stress in human atrial myocytes and is increased in the right atrial appendage of patients with AF. The enhanced activity of NOX2 seemed to be independent from its expression but could be attributable to posttransla-
Table 3. Baseline Characteristics of Patients According to Level of Vitamin E

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low Level of Vitamin E (&lt;4.1 µmol/mmol Cholesterol)</th>
<th>High Level of Vitamin E (≥4.1 µmol/mmol Cholesterol)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>72</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>71.2±5.1</td>
<td>71.1±5.7</td>
<td>0.878</td>
</tr>
<tr>
<td>Male sex</td>
<td>64</td>
<td>51</td>
<td>0.129</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90</td>
<td>83</td>
<td>0.325</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15</td>
<td>11</td>
<td>0.460</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6</td>
<td>4</td>
<td>0.698</td>
</tr>
<tr>
<td>History of stroke</td>
<td>6</td>
<td>3</td>
<td>0.404</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>10</td>
<td>8</td>
<td>0.771</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>59.8±6.8</td>
<td>60.7±6.9</td>
<td>0.431</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>41.6±3.5</td>
<td>40.7±2.9</td>
<td>0.121</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>44</td>
<td>46</td>
<td>0.867</td>
</tr>
<tr>
<td>Statins</td>
<td>24</td>
<td>22</td>
<td>0.843</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>56</td>
<td>50</td>
<td>0.504</td>
</tr>
<tr>
<td>Urinary isoprostanes, pg/mg creatinine</td>
<td>468±177</td>
<td>269±164</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sNOX2-dp, pg/mL</td>
<td>30.5±11.4</td>
<td>21.8±10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP, mg/mL</td>
<td>1.2 (0.5–1.8)</td>
<td>1.1 (0.6–1.6)</td>
<td>0.520</td>
</tr>
<tr>
<td>SUA, mg/mL</td>
<td>5.54±1.22</td>
<td>5.56±1.07</td>
<td>0.934</td>
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<tr>
<td>WBC count, ×1000/mm³</td>
<td>7.56±1.68</td>
<td>7.37±1.60</td>
<td>0.501</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, percentage, or median (interquartile range). ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; sNOX2-dp, soluble NOX2-derived peptide; hs-CRP, highsensitivity C-reactive protein; SUA, serum uric acid; WBC, white blood cell.

Figure 2. Kaplan-Meier estimates of time to atrial fibrillation recurrence by levels of vitamin E (below and above the median).

urinary formation of isoprostanes is downregulated in patients with hereditary deficiency of NOX2 and is increased in patients with NOX2 upregulation.24 In accordance with these findings, the AF population disclosed a significant association between urinary isoprostanes and sNOX2-dp.

To explore the antioxidant status, we measured the circulating levels of vitamin E, a known antioxidant that is consumed coincidentally with the generation of lipid peroxides.23,24 Accordingly, we found an inverse correlation between vitamin E and urinary isoprostanes.

The novelty of the present study was the association between 2 markers of oxidative stress, namely urinary isoprostanes and serum sNOX2-dp, as well as between circulating vitamin E and AF recurrence. However, multivariable Cox regression analysis showed that only low vitamin E values were associated with AF recurrence, even when including statin therapy, which is known to enhance the circulating levels of vitamin E.26,27 Regression analysis was corroborated by survival analysis because patients with vitamin E <4.1 µmol/mmol cholesterol were at higher risk of recurrence compared with patients with values >4.1 µmol/mmol cholesterol. Taking into account that serum levels of vitamin E were inversely related not only to urinary isoprostanes, but also to its oxidized product, these data imply that vitamin E is consumed by oxidative stress and could be implicated in the pathogenesis of AF. However, we cannot exclude that such association reflects other antiinflammatory properties, because vitamin E has been shown to inhibit muscle cell proliferation, monocyte-endothelial adhesion, and inflammatory cytokine release.10,28,29

A previous meta-analysis found that increased CRP values are associated with a higher risk of AF recurrence, but the heterogeneity across the studies limited conclusion.30 In the present study, increased CRP values at baseline showed borderline association with AF recurrence, suggesting further...
investigation of this inflammation marker in this setting. Of note, however, CRP did not correlate with any marker of oxidative stress, indicating that CRP and oxidative stress are related to different pathways of the inflammatory disease.

The results of the present study have potential pathophysiological and clinical implications and limitations. The study supports and extends previous data that indicate a potential role of oxidative stress in the pathogenesis of AF. In particular, the findings agree with a previous study showing that NOX2 activation is an early phenomenon in the natural history of AF and suggest that its downregulation could prevent AF recurrence. This suggestion could explain why statins, which inhibit NOX2 activation, are effective in AF primary prevention and less effective in secondary prevention, where other sources of reactive oxygen species are associated with AF.


39. Sangiorgi P, Violi F. Early decrease of oxidative stress by atorvastatin in...

**CLINICAL PERSPECTIVE**

Experimental studies suggest that oxidative stress may be implicated in the occurrence of atrial fibrillation (AF). Despite pharmacological or electric cardioversion, patients with persistent AF show a high rate of recurrence. In the present study, we investigated whether vitamin E, a known antioxidant, or markers of oxidative stress are associated with AF recurrence in 144 patients undergoing electric cardioversion. As markers of oxidative stress, we measured the urinary excretion of isoprostanes, an established marker of oxidative stress, and serum levels of soluble NOX2-derived peptide, the catalytic subunit of NADPH oxidase. All patients were followed for 3 months, including an office visit with an ECG every week or in case of symptom recurrence. During the follow-up, 94 patients maintained sinus rhythm, whereas 50 experienced AF recurrence. In multivariable Cox analysis, serum vitamin E and, to a lesser extent, high-sensitivity C-reactive protein levels were significantly associated with AF recurrence. The study provides the first evidence that low serum levels of vitamin E are associated with AF recurrence in patients who underwent cardioversion. Because vitamin E is inversely correlated with oxidative stress, the findings reinforce the hypothesis of an interplay between oxidative stress and AF. These findings suggest that measuring serum vitamin E could be a potentially useful approach to identifying patients with persistent AF who are at high risk of recurrence. Additionally, they provide a rationale to explore whether vitamin E supplementation may reduce the risk of recurrence.
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