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

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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.

Clinical Perspective on p 333

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 (lasted ≥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 anulus calcification), and atrial flutter 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 during the follow-up period.

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 supraaortic trunks, and chest radiography. All patients were treated for 4 weeks with antiplatelet agents (target international normalized ratio, 2–3) before undergoing electric cardioversion. Transeosophageal echocardiography was performed 24 hours before the procedure to exclude the presence of intracavitary thrombus.

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 digitalis 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; Bellville 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.

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 used for recovery by adding a radioactive tracer (tetrated 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 kit (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 acidic 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 (Temaricerca). 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/ml) 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 (λmax, 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/ml) between serum α-tocoph-
The 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.

Cox 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 values 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 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;
Table 2. Patients With or Without AF Recurrence During the 3-Month Follow-Up

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Without AF Recurrence</th>
<th>With AF Recurrence</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>94</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>71.6±5.6</td>
<td>70.3±4.9</td>
<td>0.139</td>
</tr>
<tr>
<td>Male sex</td>
<td>61</td>
<td>52</td>
<td>0.377</td>
</tr>
<tr>
<td>Hypertension</td>
<td>85</td>
<td>90</td>
<td>0.453</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12</td>
<td>16</td>
<td>0.606</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6</td>
<td>4</td>
<td>0.726</td>
</tr>
<tr>
<td>History of stroke</td>
<td>4</td>
<td>6</td>
<td>0.368</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>6</td>
<td>14</td>
<td>0.140</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>60.0±7.3</td>
<td>60.7±6.0</td>
<td>0.537</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>40.6±3.0</td>
<td>42.2±3.3</td>
<td>0.005</td>
</tr>
<tr>
<td>AF duration, d</td>
<td>19 (15–24)</td>
<td>18 (14–22)</td>
<td>0.618</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>43</td>
<td>50</td>
<td>0.482</td>
</tr>
<tr>
<td>Statins</td>
<td>23</td>
<td>22</td>
<td>0.849</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>51</td>
<td>56</td>
<td>0.603</td>
</tr>
<tr>
<td>Vitamin E, μmol/mmol cholesterol</td>
<td>5.0±2.4</td>
<td>3.1±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>α-Tocopherolquinone, μmol/mmol cholesterol</td>
<td>2.1±2.3</td>
<td>3.5±2.3</td>
<td>0.010</td>
</tr>
<tr>
<td>Urinary isoprostanes, pg/mg creatinine</td>
<td>298±164</td>
<td>502±197</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sNOX2-dp, pg/mL</td>
<td>23.1±11.2</td>
<td>31.9±10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP, mg/mL</td>
<td>0.9 (0.5–1.6)</td>
<td>1.3 (0.7–2.0)</td>
<td>0.040</td>
</tr>
<tr>
<td>SUA, mg/mL</td>
<td>5.52±1.20</td>
<td>5.62±1.05</td>
<td>0.617</td>
</tr>
<tr>
<td>WBC count, ×1000/mm³</td>
<td>7.47±1.71</td>
<td>7.44±1.45</td>
<td>0.889</td>
</tr>
</tbody>
</table>

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

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 AF³ and a reduced risk of AF in animals with low formation of reactive oxygen species.⁷ Administration of ascorbic acid, a known antioxidant, has also been used as a tool to investigate whether oxidative stress plays a causative role.⁶,¹⁸,¹⁹ 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.²⁰,²¹

The relationship between oxidative stress and AF has also been explored in patients with AF. Kim et al⁸ 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-

AF with vitamin E <4.1 μmol/mmol cholesterol had higher levels of urinary isoprostanes and serum sNOX2-dp. Event-free analysis by Kaplan-Meier curve analysis demonstrated that patients with vitamin E <4.1 μmol/mmol cholesterol had a higher probability of experiencing AF recurrence compared with patients with values ≥4.1 μmol/mmol cholesterol (Figure 2). In particular, using the Cox proportional hazards model, 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).

Figure 1. Receiver operating characteristic curves demonstrating the relationship between vitamin E and atrial fibrillation recurrence at 3-month follow-up.
plays a key role in the formation of isoprostanes; thus, the recurrence rate 3 months after cardioversion. We measured urinary isoprostanes, which derive from the arachidonic acid interaction with reactive oxygen species, and are considered a reliable marker of oxidative stress.10,28,29 We have recently developed an assay that measures NOX2 activation from the blood levels of NOX2 (sNOX2-dp); the assay maximally detects in the present cohort, which experienced a 34% 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 further explore the interplay between oxidative stress and AF, we analyzed 3 markers of oxidative stress in patients who developed AF after cardiac surgery.22 Consistent with the role of oxidative stress in eliciting AF, Ozaydin et al9 demonstrated that the infusion of N-acetylcysteine, another known antioxidant, significantly reduced the incidence of AF recurrence compared with patients with values of 26% at 3 months and 50% to 75% at 1 year after cardioversion.12 A similar rate of recurrence was demonstrated that the infusion of N-acetylcysteine, another known antioxidant, significantly reduced the incidence of 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

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### 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>
</tr>
<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). ACEI 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.

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Figure 2. Kaplan-Meier estimates of time to atrial fibrillation recurrence by levels of vitamin E (below and above the median).
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 AF31 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.32 The use of markers of antioxidant status and oxidative stress may also help in identifying patients at high risk of AF recurrence. Finally, vitamin E supplementation could represent an interesting therapeutic option that should be considered in future trials in patients with persistent AF undergoing cardioversion.

A limitation of the present study is that the results might be applied only to relatively healthy patients with relatively normal ejection fractions and left atrial sizes. Furthermore, vitamin E and urinary isoprostanes were measured at baseline, therefore we do not know whether they changed during or at the end of follow-up. However, diet was not changed, and patients did not consume antioxidants during the follow-up period.

In conclusion, this study provides further evidence of the interplay between oxidative stress and AF by showing that low values of the antioxidant vitamin E are associated with recurrence in patients undergoing cardioversion. The study warrants future interventional trials to see whether vitamin E supplementation could be of benefit in this clinical setting.

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Disclosures
None.

References


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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