Improvements in Symptoms and Quality of Life in Patients With Paroxysmal Atrial Fibrillation Treated With Radiofrequency Catheter Ablation Versus Antiarrhythmic Drugs

Matthew R. Reynolds, MD, MSc; Joshua Walczak, MS; Sarah A. White, MPH; David J. Cohen, MD, MSc; David J. Wilber, MD

Background—In patients with paroxysmal atrial fibrillation (AF), catheter ablation maintains sinus rhythm more effectively than antiarrhythmic drugs (AADs), but its effect on symptoms and quality of life (QOL) has not been fully characterized.

Methods and Results—We evaluated symptoms and QOL in a multicenter, randomized trial comparing catheter ablation with AADs as second-line treatment for patients with paroxysmal AF. The Short Form (SF)-36 health survey and the AF Symptom Checklist were administered at baseline and 3, 6, and 9 months after a blanking or dose-titration period. The primary between-group comparisons were conducted at 3 months because of permitted crossover from AAD to ablation beyond this time. Additional analyses based on subsequent follow-up were performed, including the construction of mixed linear regression models to assess the impact of multiple factors on follow-up QOL scores.

At baseline in both the ablation (n=103) and the AAD (n=56) groups, 7 of 8 SF-36 scales were well below population norms, as were the physical (PCS) and mental (MCS) summary scores. At 3 months, the same 7 SF-36 scales were significantly (P<0.01) higher in the ablation than in the AAD group, as were the PCS (52.0±7.8 versus 47.1±10.6; P<0.01) and MCS (52.4±8.1 versus 46.6±9.8; P<0.01) scores, whereas symptom frequency (9.3±9.2 versus 19.0±12.6; P<0.001) and symptom severity (7.7±7.2 versus 16.2±10.0; P<0.001) were significantly reduced. In multivariable analysis, ablation and recurrent arrhythmias most strongly correlated with QOL changes over time.

Conclusions—For second-line therapy of paroxysmal AF, ablation is superior to AAD treatment at improving symptoms and QOL.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00116428.

Key Words: antiarrhythmia agents ■ atrial fibrillation ■ catheter ablation ■ quality of life ■ clinical trials randomized

A n estimated 3 to 5 million Americans have atrial fibrillation (AF) today, and AF prevalence will increase as the population ages and more individuals survive with chronic cardiovascular disease.1,2 Although some patients with AF experience no symptoms, most seek treatments to reduce symptoms and improve or preserve quality of life (QOL), which is lower than population norms in the majority of these patients.3,4

A variety of treatment strategies, including rate control alone, have been shown to improve symptoms and QOL in patients with AF.5 Despite the completion of a number of previous comparative trials, substantial uncertainty persists about whether 1 treatment strategy is clearly better than another on QOL end points.6–10

Radiofrequency catheter ablation (RFA) has emerged as an important option for patients with AF whose rhythm and symptoms are not well controlled with initial guideline-recommended treatments.11 In several previous small randomized trials, RFA has proved superior to antiarrhythmic drug therapy at maintaining sinus rhythm, primarily in a second-line treatment setting.12–16 Two of these studies also reported superior improvements in QOL for patients treated with ablation.12,15

A recently completed multicenter trial compared catheter ablation with antiarrhythmic drug therapy for patients with
symptomatic, paroxysmal AF refractory to 1 or more drugs and showed clear superiority favoring ablation on rhythm-related end points.\textsuperscript{17} QOL results presented in the initial publication were limited to the first 3 months of follow-up, and subscale scores were not reported. The goals of this prospectively designed substudy were to characterize more fully the magnitude and nature of QOL improvements following AF ablation (eg, by reporting full results for all measured subscales and results following crossover from drug therapy to ablation), to compare improvements in QOL following ablation with those of the control group, and to explore the relative contributions of ablation and sinus rhythm maintenance to QOL improvements over time.

**WHAT IS KNOWN**

- For patients with paroxysmal atrial fibrillation (AF) who have failed on 1 or more antiarrhythmic drugs, randomized trials have shown that radiofrequency catheter ablation more successfully maintains sinus rhythm than treatment with a different antiarrhythmic drug.
- Analysis of symptoms and quality of life (QOL) in prior randomized trials comparing AF ablation and drugs have been limited but tended to suggest better outcomes with ablation.

**WHAT THIS STUDY ADDS**

- All domains of the Short Form-36, except bodily pain, as well as symptom frequency and severity returned to normal ranges in patients treated with ablation and were significantly better than for patients treated with antiarrhythmic drugs by 3 months after a blanking or dose-titration period.
- All QOL and symptom measures remained improved in ablation patients until the end of follow-up, whereas no measures convincingly improved in patients who remained on the drugs.
- In multivariable analysis, the factors most strongly associated with improvement from baseline in all QOL scores were ablation and freedom from recurrent arrhythmia.

**Methods**

The ThermoCool AF trial was a prospective, randomized, multicenter study that compared the safety and effectiveness of ablation using a saline-irrigated RFA catheter with antiarrhythmic drug therapy for patients with paroxysmal AF not controlled by 1 or more courses of drug therapy. The methods and main clinical findings from the study have been published.\textsuperscript{17} In brief, the trial randomized patients with ≥3 symptomatic episodes of AF in 6 months, despite prior drug treatment, in a 2:1 fashion to either RFA, with a procedural end point of electric pulmonary vein isolation, or treatment with a previously untreated, Food and Drug Administration-approved antiarrhythmic drug ( dofetilide, flecainide, propafenone, sotalol, or quinidine). Effectiveness was assessed over a 9-month interval following a 90-day blanking period in the catheter ablation arm, during which repeat ablation was permitted, or a 14-day dose-titration period in the drug arm. The primary end point of the study was documented symptomatic AF recurrence or changes in therapy potentially related to treatment failure or intolerance.\textsuperscript{17} The study followed an adaptive Bayesian design, using prespecified stopping rules based on the probability of observing superiority on the primary efficacy end point. The primary study results\textsuperscript{17} and the current analysis were performed following the completion of planned follow-up for all available subjects. All study subjects provided written, informed consent in accordance with human protection policies at the enrolling centers.

**QOL Assessment**

Symptoms and QOL were assessed in the study using version 2 of the Short Form-36 (SF-36) (standard 4-week recall) and the AF Symptom Checklist.\textsuperscript{18} The SF-36 is an extensively validated generic QOL measure and has been used in the study of numerous health conditions, including AF.\textsuperscript{6,10,12,15,19} The SF-36 assesses 8 specific QOL domains,\textsuperscript{20} 4 each related to physical and mental health and functioning. The 8 subscale scores can range from 0 to 100; population means are shown in Figure 1A and 1B. These 8 scales also have been reduced into physical component summary (PCS) and mental component summary (MCS) scores, each of which is normalized to an overall population mean±SD of 50±10. For all SF-36 scales, higher scores represent better functioning and QOL than lower scores.

The AF Symptom Checklist asks respondents to rate the frequency (from 0 to 4 or never to always) and severity (from 1 to 3, mild, moderate, or extreme) of 16 symptoms potentially associated with AF, thereby generating frequency and severity scores ranging from 0 to 64 and 0 to 48, respectively, with higher scores indicating greater symptomatology. In a previous study, healthy subjects without AF reported mean frequency and severity scores of 10 and 8 points, respectively, whereas patients with AF reported scores more than twice as high as the controls.\textsuperscript{3}

The SF-36 and AF Symptom Checklist were self-administered at the patients’ enrolling centers at baseline and again 3, 6, and 9 months after the blanking or dose-titration period. Per protocol, antiarrhythmic drug subjects who underwent ablation were subsequently followed as if they had been initially assigned to ablation, completing a new set of baseline questionnaires and repeating them at 3, 6, and 9 months after a 90-day postablation blanking period. All completed QOL forms were forwarded to a QOL core laboratory for data entry and analysis.

**Statistical Analysis**

Baseline characteristics of the study population were compared using Fisher exact test for categorical variables and 2-sample t tests or Wilcoxon tests for continuous variables, as noted. We calculated individual domain, PCS, and MCS scores for the SF-36 according to the developer’s scoring specifications.\textsuperscript{21} The 8 specific domain scores are reported with their original 0-to-100 scaling in order to facilitate comparison with prior studies.

The prespecified primary QOL analysis involved between-group comparisons for each QOL measure 3 months into the chronic efficacy evaluation period (ie, roughly 6 months after the initial ablation procedure or 3.5 months after the initiation of new antiarrhythmic drug treatment). This time point was chosen because the effects of antiarrhythmic drug therapy generally are observed more quickly than those of ablation, because QOL changes with AF therapies tend to plateau after 3 to 6 months,\textsuperscript{22} and because the number of drug group patients proceeding with ablation was expected to increase significantly thereafter. For drug group patients who underwent catheter ablation before completing the 3-month questionnaires (n=9), the QOL scores measured just before the ablation procedure were used instead. In this manner, the primary analysis compared QOL end points with little or no bias from crossover or censoring. All between-group comparisons were made using 2-sample t tests. In addition, follow-up scores were compared with baseline scores within each group using paired t tests.
Several additional supportive analyses were conducted in order to assess more fully the trajectory of QOL in both randomization groups, accounting for crossovers, and to estimate the effect of ablation on the full study population. First, descriptive results for the 4 main summary measures (PCS, MCS, symptom frequency, and severity) were plotted, dividing the patients into 3 groups: randomized to ablation, and randomized to antiarrhythmic drugs with or without subsequent ablation. Paired *t* tests were used to make within-group comparisons of each time point with baseline for all patients in the ablation group. Drug group patients were censored from subsequent within-group comparisons following crossover to ablation therapy.

Additionally, we used multivariable analysis in order to estimate the effects of both ablation and maintenance of sinus rhythm on changes in QOL from baseline. Using data from all study subjects at all follow-up time points, mixed linear regression models were constructed for each of the 4 main summary measures, using change from baseline as the dependent variable. The mixed linear regression approach was chosen in order to account for intrapatient correlations of scores across multiple time points. Candidate variables entered in these models as random effects included baseline QOL scores, randomization group, patient demographics and baseline comorbid conditions previously shown to correlate with QOL results in patients with AF; and the time (in days) from randomization to the respective QOL measurement.

The models also included a variable signifying whether the patient had undergone any ablation procedure before that time point (the covariate of principal interest), and another variable indicating whether any atrial tachyarrhythmia had been observed in the 30 days before the QOL measurement. The rhythm status was defined in this manner because of the 4-week and 1-month recall periods of the QOL measures. Electrocardiographic follow-up in the trial included transtelephonic monitoring whenever patients had cardiac symptoms as well as weekly transmissions during the first 8 weeks of the efficacy evaluation period and then monthly transmissions until the final study visit. All electrocardiographic tracings were reviewed by a blinded, independent core laboratory.

We added interaction terms between the ablation variable and the rhythm status variable (recurrent atrial arrhythmia within 30 days of a QOL time point) to each model given our interest in the potential relationship between these 2 important factors and the QOL outcomes. However, we decided that negative interaction terms would not be retained in the final models.

All analysis was performed using SAS version 9.1.3. All reported *P* values are 2 sided, and we considered any *P* < 0.05 to denote statistical significance. All analyses for this article were performed...
independently of the study sponsor. The authors had full access to the study data and results and vouch for all presented results.

Results

Patient Population and Baseline Findings

As previously reported,17 the trial ceased recruitment after randomizing 167 participants across 19 global centers when interim statistical analysis indicated a 99.9% probability of superiority on the primary efficacy end point favoring the catheter ablation group. Of these patients, 8 did not complete their assigned treatment regimen mainly because of withdrawal of consent. The remaining 159 patients form the basis for this report. Freedom from occurrence of the primary efficacy end point was 66% for the catheter ablation group compared with 16% in the antiarrhythmic drug group. Freedom from recurrent symptomatic atrial arrhythmia during the chronic efficacy period was similarly 70% versus 19%.

Selected baseline characteristics of the study population as well as baseline QOL results are shown in Table 1. The majority of the patients were men with a mean age of 56 years. Although roughly half of the patients had a history of hypertension, few had significant structural heart disease.

As shown in Table 1 and Figure 1, all baseline SF-36 subscale scores, except bodily pain, were well below population means, in most cases, by 10 to 20 points (on 0-to-100 scales), and the PCS and MCS scores were below US population means of 50 points. The baseline symptom frequency and severity scores were high, as expected. None of the baseline QOL scores significantly differed between the randomized groups.

QOL Changes From Baseline to 3 Months

Figure 1A and 1B show the changes from baseline to 3 months for the SF-36 scales pertaining to physical and mental health. For all 8 scales, statistically significant and clinically meaningful (0.6 to 1.0 SD) increases were observed in the catheter ablation group but not in the antiarrhythmic drug group. The 3-month scores for the ablation group approximated or exceeded US population means for all 8 scales. Additionally, for 7 of the 8 scales (all except for bodily pain), the mean 3-month scores were significantly higher for the ablation group than the drug group at 3 months, 0.64 and 0.98). Within-group comparisons for the ablation group and between-group comparisons at 3 months were all highly statistically significant (P<0.001 for all comparisons).

Complete QOL Results According to Follow-Up Treatment

During follow-up, 36 (64%) of the 56 patients assigned to antiarrhythmic drug therapy underwent an ablation procedure because of recurrent AF, treatment-related adverse events, or both. The median interval from the baseline QOL assessment to the ablation procedure was 123 days (25th to 75th percentiles, 73 to 151 days) in this group. Thus, based on the 2:1 randomization scheme, 139 (87%) of the 159 subjects analyzed in this report underwent an ablation procedure at some point during the study.

Mean QOL scores for each time point for the ablation group as well as drug group patients who did and did not undergo subsequent ablation are shown in Figure 3. Table 2 shows mean within-group changes and P values for all QOL scales at each time point, both for the ablation group and for the drug group patients who did not undergo subsequent ablation (ie, drug group patients were censored from subsequent comparisons at the time of crossover). The changes observed from baseline to 3 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Catheter Ablation Group (n=103)</th>
<th>Antiarrhythmic Drug Group (n=56)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.5 ± 9.4</td>
<td>55.8 ± 13.1</td>
<td>0.86</td>
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<tr>
<td>AF history</td>
<td>3 (2, 8)</td>
<td>4 (2, 9)</td>
<td>0.65*</td>
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<td>Male sex</td>
<td>71 (69)</td>
<td>35 (63)</td>
<td>0.48</td>
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<td>Hypertension</td>
<td>50 (49)</td>
<td>28 (50)</td>
<td>0.87</td>
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<tr>
<td>Diabetes</td>
<td>10 (10)</td>
<td>7 (13)</td>
<td>0.60</td>
</tr>
<tr>
<td>Structural heart disease†</td>
<td>10 (10)</td>
<td>9 (16)</td>
<td>0.31</td>
</tr>
<tr>
<td>NYHA heart failure class, n/</td>
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<td></td>
<td>&gt;0.99</td>
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<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>80/92 (87)</td>
<td>46/54 (85)</td>
<td></td>
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<tr>
<td>II</td>
<td>12/92 (13)</td>
<td>8/54 (15)</td>
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<td>Baseline QOL data</td>
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<tr>
<td>SF-36 subscales‡</td>
<td></td>
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<tr>
<td>PF</td>
<td>72 ± 22 (103)</td>
<td>74 ± 25 (55)</td>
<td>0.59</td>
</tr>
<tr>
<td>RP</td>
<td>59 ± 24 (98)</td>
<td>66 ± 23 (54)</td>
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<td>BP</td>
<td>67 ± 27 (102)</td>
<td>73 ± 26 (54)</td>
<td>0.16</td>
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<tr>
<td>GH</td>
<td>64 ± 20 (103)</td>
<td>64 ± 19 (55)</td>
<td>0.99</td>
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<tr>
<td>VR</td>
<td>52 ± 22 (97)</td>
<td>52 ± 20 (53)</td>
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<tr>
<td>SF</td>
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<tr>
<td>RE</td>
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<td>71 ± 28 (54)</td>
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</tr>
<tr>
<td>MH</td>
<td>67 ± 19 (97)</td>
<td>67 ± 19 (53)</td>
<td>0.87</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>46.1 ± 9 (97)</td>
<td>47.6 ± 9 (53)</td>
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<tr>
<td>SF-36 MCS</td>
<td>44.5 ± 11 (97)</td>
<td>44.0 ± 12 (53)</td>
<td>0.79</td>
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<tr>
<td>Symptom frequency score</td>
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<td>18.6 ± 9 (51)</td>
<td>0.18</td>
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<tr>
<td>Symptom severity score</td>
<td>17.1 ± 7 (76)</td>
<td>16.0 ± 8 (44)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, median (25th, 75th percentile), No. (%), or mean ± SD (n), unless otherwise indicated. BP indicates bodily pain; GH, general health; MH, mental health; NYHA, New York Heart Association; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VR, vitality.

*By Wilcoxon test.
†Defined as any of ischemic cardiomyopathy, left ventricular hypertrophy, hypertrophic cardiomyopathy, nonischemic dilated cardiomyopathy, significant valve disease or replacement, or congenital heart disease.
‡The (n) refers to the number of patients for whom scale scores could be calculated. These numbers vary due to patients skipping individual survey items.
in the ablation group remained well preserved to the end of follow-up (within-group comparisons for all measures at all time points were <0.0001). Among drug group patients who did not undergo ablation, both SF-36 and AF Symptom Checklist scores appeared to improve modestly over time (Figure 3). However, paired comparisons within this group only reached statistical significance for symptom severity at 9 months (mean decrease, 5.6 points; \( P=0.02 \)). For crossover patients, all scores following ablation appeared similar to those observed during follow-up in the group originally randomized to ablation.

**Mixed Linear Regression Model Results**

The parameter estimates, SEs, and \( P \) values for the mixed linear regression models are shown in Table 3. The dependent

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**Figure 2.** AF symptom frequency and severity scores at baseline and 3 months are shown for both study groups.

**Figure 3.** PCS (A), MCS (B), symptom frequency (C), and symptom severity (D) scores are plotted over time for the ablation group and for the antiarrhythmic drug group, subgrouped according to whether patients crossed over to ablation during follow-up. The shaded areas in A and B represent the range of median scores for PCS and MCS for members of the US population aged 45 to 54 years or 55 to 64 years.
variables in these models were the change from baseline in the respective QOL measure at each follow-up time point. Each model adjusted for baseline scores, age, sex, and time from randomization to ablation. The estimated coefficients from these models represent the average change from baseline (across multiple time points) in the respective QOL measure associated with each covariate. Of the baseline characteristics evaluated, only diabetes consistently exhibited an adverse association with symptoms and QOL in the study population.

In all models, both catheter ablation at any time before the QOL measurement and the documentation of atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) on transtelephonic monitoring within 30 days of the QOL measurement exhibited strong relationships with the change from baseline in QOL scores. As expected, catheter ablation was associated with improved QOL and reduced symptoms, whereas recurrent atrial arrhythmias were associated with the opposite. Interaction terms between ablation and arrhythmia recurrence were nonsignificant when added to each model and, therefore, were not retained in the final models.

Discussion
Our analysis provides several important insights regarding QOL outcomes in patients with paroxysmal AF for whom previous drug therapy has not controlled symptoms. First, both within-group and between-group comparisons showed that QOL and symptoms improved substantially after catheter ablation but not with antiarrhythmic drug therapy, such that outcomes were clearly superior for the ablation group. Second, improvement was observed following ablation for 7 of the 8 QOL domains evaluated by the SF-36, including physical functioning, social functioning, and mental health, in all cases, returning to or exceeding US population norms. Likewise, symptom scores following RFA fell $>50\%$, into a range previously reported by healthy controls. Finally, multivariate analysis found nearly equal and opposite effects on QOL changes from baseline for catheter ablation and recurrent arrhythmia, suggesting that the improvements in QOL associated with ablation at any given time would be significantly reduced by arrhythmia recurrence.

The results from the current study add to a growing body of literature that catheter ablation improves QOL in patients with AF to a greater extent than antiarrhythmic drug therapy, at least in selected populations. As previously reviewed,$^{6}$ or more observational series ranging from 30 to $\approx 100$ patients have shown substantial improvements in SF-36 scores following different ablative approaches to AF but do not permit direct comparison to other AF therapies.$^{23-28}$
In restoring QOL to normal levels for reference populations, catheter ablation for AF compares favorably with other invasive cardiovascular therapies, such as surgical aortic valve replacement or percutaneous coronary intervention. These findings may also have important implications for the potential cost-effectiveness of RFA for AF, relative to medical therapy, because 2 modeling studies have suggested that such cost-effectiveness results are highly contingent on the magnitude of improvement in QOL.

The current results do need to be interpreted with several important limitations in mind. First, this trial involved only patients with paroxysmal AF, and the majority of the patients were relatively healthy, with minimal structural heart disease. The results of this study, therefore, cannot be extrapolated to patients with more severe heart disease or other patterns of AF. This study had a limited follow-up duration such that potential QOL outcomes over a longer time horizon remain unknown. The blanking (ablation arm) and dose-titration (drug arm) periods at the beginning of the study were not of equal duration, and this uneven timing could have affected our results if some of the observed changes are thought to be time dependent. The randomization scheme also resulted in a relatively small number of patients in the antiarrhythmic drug group, particularly when split into subgroups.

Perhaps most importantly, this study was unblinded; thus, the QOL results could have been affected by expectation or placebo effects. We believe that the improvements in QOL following ablation observed in this study were unlikely to be wholly attributable to a placebo effect because our multivariate analysis suggests that recurrent arrhythmia had a similar or greater impact on follow-up QOL scores than RFA itself. This view is consistent with 1 prior study in which improvements in SF-36 scores 12 months after ablation were much larger in patients without documented AF recurrences than in patients with recurrences. The existence of a potential placebo effect could only be proven or disproven by a trial with a sham procedure arm.

In conclusion, this carefully conducted, multicenter, randomized trial of symptomatic patients with paroxysmal AF with at least 1 prior antiarrhythmic drug failure showed large and clinically significant improvements across multiple QOL domains following RFA but no improvements with alternative antiarrhythmic drug treatment. For patients like those enrolled in this trial, RFA appears to be superior at improving symptoms and QOL in the first year after ablation.

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References


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