Results From a Single-Blind, Randomized Study Comparing the Impact of Different Ablation Approaches on Long-Term Procedure Outcome in Coexistent Atrial Fibrillation and Flutter (APPROVAL)

Sanghamitra Mohanty, MD, MS; Prasant Mohanty, MBBS, MPH; Luigi Di Biase, MD, PhD, FHRS; Rong Bai, MD, FHRSG; Pasquale Santangeli, MD; Michela Casella, MD, PhD; Antonio Dello Russo, MD, PhD; Claudio Tondo, MD, PhD; Sakis Themistocakis, MD; Antonio Raviele, MD; Antonio Rossillo, MD; Andrea Corrado, MD; Gemma Pelargonio, MD; Giovanni Forleo, MD; Andrea Natale, MD, FHRSG, FECC, FACC

Background—This study examined the impact of different ablation strategies on atrial fibrillation (AF) recurrence and quality of life in coexistent AF and atrial flutter (AFL).

Methods and Results—Three-hundred sixty enrolled patients with documented AF and AFL were blinded and randomized to group 1, AF±AFL ablation (n=182), or group 2, AFL ablation only (n=178). AF recurrence was evaluated with event recording and 7-day Holter at 3, 6, 9, and 12-month follow-ups. Quality of life was assessed at baseline and at the 12-month follow-up with 4 questionnaires: the Medical Outcome Study Short Form, the Hospital Anxiety and Depression Score, the Beck Depression Inventory, and the State-Trait Anxiety Inventory. Of the 182 patients in group 1, 58 (age, 63±8 years; 78% male; left ventricular ejection fraction, 59±8%) had AF+AFL ablation and 124 (age, 61±11 years; 72% male; left ventricular ejection fraction, 59±7%) had AF ablation only. In group 2 (age, 62±9 years; 76% male; left ventricular ejection fraction, 58±10%), only AFL was ablated by achieving bidirectional isthmus conduction block. Baseline characteristics were not different across groups. At 21±9 months of follow-up, 117 in group 1 (64%) and 34 in group 2 (19%) were arrhythmia free (P<0.001). In group 1, scores on most quality-of-life subscales showed significant improvement at follow-up, whereas group 2 patients derived relatively minor benefit.

Conclusions—In coexistent AF and AFL, lower recurrence rate and better quality of life are associated with AF ablation only or AF+AFL ablation than with lone AFL ablation. Furthermore, quality of life directly correlates with freedom from arrhythmia, as shown in this study for the first time in patients blinded to the procedure.


Key Words: ablation techniques ■ atrial fibrillation ■ atrial flutter ■ pulmonary veins ■ quality of life ■ recurrence

© 2013 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.113.001855

Received September 7, 2012; accepted March 29, 2013
From the Texas Cardiac Arrhythmia Institute, St. David’s Medical Center, Austin (S.M., P.M., L.D.B., R.B., P.S., A.N.); School of Biological Sciences (S.M.) and Department of Biomedical Engineering (L.D.B., A.N.), University of Texas at Austin, Austin; University of Foggia, Foggia, Italy (L.D.B., P.S.); Department of Internal Medicine, Tong-Ji Medical College, Huazhong University of Science and Technology, Wuhan, China (R.B.); RCCS Monzino Hospital, Milan, Italy (M.C., A.D.R., C.T.); Ospedale dell’Angelo, Mestre/Venice, Italy (S.T., A.R., A.C.); Catholic University, Rome, Italy (G.F.); University Tor Vergata, Rome, Italy (G.F.); and Albert Einstein College of Medicine at Montefiore Hospital, New York, NY (L.D.B.).

Correspondence to Andrea Natale, MD, FHRSG, FECC, FACC, Texas Cardiac Arrhythmia Institute, St. David’s Medical Center, 3000 N I-35, Ste 720, Austin, TX 78705. E-mail dr.natale@gmail.com

Arrhythmia/Electrophysiology

The available options for coexistent AF and AFL are pulmonary vein antrum isolation (PVAI) with or without AFL.
ablation and AFL ablation alone. We aimed to compare the impact of the 2 ablation strategies on long-term procedural success and overall QoL in patients presenting with both AF and AFL simultaneously.

Because QoL could be affected by a placebo effect of the procedure, the patients were kept blinded to the type of ablation procedure performed.

Methods

Patient Population

Between January 2009 and September 2011, 360 consecutive patients undergoing AF ablation at our centers with history of paroxysmal AF and right AFL were enrolled in this prospective, randomized, single-blind, multicenter study. Patients were enrolled at Monzino Hospital, Milan, Italy; Ospedale dell’Angelo, Mestre, Venice, Italy; Catholic University, Rome, Italy; University of Rome Tor Vergata, Rome, Italy; and Texas Cardiac Arrhythmia Institute, Austin, TX.

Inclusion criteria were history of paroxysmal AF with failed treatment at least 1 antiarrhythmic drug (AAD) and preablation evidence of typical AFL documented by 12-lead surface ECG. Paroxysmal AF was defined according to the consensus documents by the Heart Rhythm Society/European Heart Rhythm Association/American Heart Association/American College of Cardiology.11 Patients were excluded from the study if they were <18 or >85 years old, if they had had previous ablation, if they had left atrium size ≥5 cm, or if they had a contraindication to oral anticoagulation.

The study was approved by the institutional review boards of each of the above-mentioned institutions.

After the pathophysiology of the underlying disease and details of the ablation procedures were carefully explained, all participants provided signed informed consent. Enrolled patients were randomly assigned (1:1 ratio) to 2 groups (Figure 1). A central stratified randomization scheme was used to facilitate effective randomization. The scheme involved block randomization technique with block size of 4, and enrolled participants were randomly assigned within blocks on the basis of a 1:1 allocation ratio. The randomization sequence was generated with SAS 9.2 (SAS Institute Inc, Cary, NC).

Group 1

A total of 182 patients were randomized to group 1 (PV AI+ AFL). Of the 182, 124 received AF ablation (PV AI) and 58 had ablation of both AF and AFL (PV AI+AFL). The decision to perform PV AI+AFL ablation was made if the patient presented with right-sided isthmus-dependent flutter at ablation or during catheter manipulation or the above flutter was provoked by isoproterenol challenge.

Group 2

All patients randomized to group 2 received AFL ablation (n=178). Randomization was performed at a central coordinating center. Patients, the referring physician, and the follow-up monitoring team (AF nurses) were blinded to the procedure assignment. Only the physicians performing the procedures were aware of the ablation strategy.

Assessment of QoL

Several self-administering survey tools are available to assess QoL. We used 4 of these tools in this prospective study to measure baseline and 1-year follow-up QoL. The questionnaires used were the Beck Depression Inventory (BDI), the Medical Outcome Study Short Form-36 (SF-36), the Hospital Anxiety and Depression Score (HAD), and the State-Trait Anxiety Inventory (STAI). The survey was done for all patients before and 12 months after ablation.

The Medical Outcome Study Short Form-36

The most widely used self-reporting questionnaire, the SF-36 consists of 36 questions that measure 8 health concepts (individual scales), namely physical functioning, role limitations resulting from physical health, mental health, role limitations resulting from emotional problem, social functioning, bodily pain, general health, and vitality. Higher score indicates better QoL. The scales are scored from 0 (worst health status) to 100 (best possible state). We also used a summated scoring algorithm in which the 8 individual scales were grouped into 2 summary measures: the Physical Component Summary and Mental Component Summary scores. The Physical Component Summary included physical functioning, role limitations resulting from physical health, general health, and bodily pain; the Mental Component Summary consisted of the mental health, role limitations resulting from emotional problem, vitality, and social functioning subscales.

The Beck Depression Inventory

The BDI is considered the gold standard for measuring the severity of depression. The survey consists of 21 questions, with higher scores indicating a greater level of depressive symptoms, which translates to a lower QoL.

The Hospital Anxiety and Depression Score

The HAD is a commonly used 14-term self-rating instrument for anxiety and depression in patients not in a psychiatric hospital. It includes subscales for the measurement of anxiety and depression separately. A higher score indicates a higher level of anxiety and depression and thus a poorer QoL.

The State-Trait Anxiety Inventory

The STAI is used extensively to measure anxiety in adults. It assesses short-term anxiety in a specific situation (state anxiety) and anxiety as a general trait (trait anxiety). A higher score predicts a higher level of anxiety and an inferior QoL.

Ablation Procedure

PV AI for AF11 and ablation of cavotricuspid isthmus (CTI) for AFL212 were done following previously described protocols. All procedures were performed under general anesthesia. AADs were withdrawn 5 half-lives before the ablation. Patients on amiodarone discontinued the medication 5 to 6 months before the procedure.

Brief Summary of the Ablation Procedures

Periprocedural Anticoagulation Management. Standard periprocedural anticoagulation protocol was followed for all patients using continuous warfarin. The international normalized ratio was

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Study design flow chart. AF indicates atrial fibrillation; AFL, atrial flutter; and PAF, paroxysmal atrial fibrillation.
monitored every week for 4 weeks preceding the procedure to ascertain therapeutic level (>2.0). A transeosophageal echocardiography was performed if the international normalized ratio was therapeutic in the preceding 4 weeks and on the day of ablation. A heparin bolus of 10000 U was given during the transseptal puncture to all patients. Activated clotting time was measured periodically throughout the procedure, and the infusion rate of heparin was adjusted to maintain an activated clotting time at >300 seconds. Heparin was partially reversed by 30-40 mg of protamine at the end of the procedure. There was no change in their warfarin dose before, during, or after the procedure.

**AF Ablation.** PVAI was performed with radiofrequency energy of power up to 45 W, maximum temperature of 42°C, and flow rate of 30 cm³/min that was delivered via 3.5-mm Thermocool catheter (Biosense-Webster). The ablation procedure was guided by a circular mapping catheter and intracardiac echocardiography. In patients with paroxysmal AF, pulmonary vein antra and the portion of the posterior wall within the pulmonary vein area were targeted for isolation. In all patients, challenge with isoproterenol infusion up to 30 µg/min was performed to identify non–pulmonary vein triggers, and they were ablated with the use of further radiofrequency energy.

The procedural end point of PVAI was the local elimination of all the pulmonary vein potentials along the antra with demonstration of entry block.

**AFL Ablation.** Radiofrequency catheter ablation was performed by creating a linear lesion from the tricuspid annulus to the inferior vena cava with a 3.5-mm Thermocool catheter. Radiofrequency catheter ablation was continued until bidirectional conduction block was documented across the isthmus.

**End Point**
The primary end point was freedom from arrhythmia during the follow-up period beginning after the 12-week blanking period postablation.

Any episode of AF/atrial tachycardia/AFL >30 seconds in the absence of AADs at follow-up was considered a recurrence. Episodes that occurred during the first 12 weeks (blanking period) after the procedure were not considered recurrences.11

The secondary end points were improvements in QoL, hospitalizations, and complications.

**Follow-Up**
After overnight observation following ablation, patients were discharged on their previously ineffective AADs, which were continued during the blanking period (12 weeks). After the blanking period, AADs were discontinued. In case of recurrence after the blanking period, patients were given either previously ineffective AADs or new antiarrhythmic agents or were scheduled for repeat ablation.

Follow-up was performed at 3, 6, 9, and 12 months after the procedure with cardiology evaluation, 12-lead ECG, and 7-day Holter monitoring. Patients were given an event recorder for the first 5 months after ablation and were asked to transmit their rhythm every time they had symptoms compatible with arrhythmias and at least twice a week even if asymptomatic.

QoL surveys were conducted before ablation (baseline) and at the 12-month follow-up.

**Statistical Analysis**
This prospective study was designed to detect a 15% improvement in recurrence-free survival (improving the success rate from 45% [AF ablation only] to 60% [with PVAI±AFL ablation]). With a 2-sided type I error of 5% and a power of 80%, a sample size of 350 (175 per group) was required to detect an effect size of 15%.

Continuous data are described as means±SD; categorical data, as counts and percent. The Student *t* test, 1-way ANOVA, χ² test, and Fisher exact test were used to compare groups. Paired *t* tests were used to compare QoL scores at baseline and the 12-month follow-up. Pearson linear correlation coefficient (r) and Spearman rank correlation coefficient (ρ) were calculated to assess correlation between individual scales. Multivariable general linear models were used to identify significant predictors of QoL improvement. Multivariable Cox regression was used to assess predictors of AF recurrence. Potential confounders were entered into the model on the basis of known or expected clinical relevance, regardless of their statistical significance. Controlling variables used in the model were age, sex, hypertension, diabetes mellitus, body mass index, obstructive sleep apnea, left ventricular ejection fraction, and left atrial size. The discrimination ability of the models in predicting AF recurrence was assessed by c statistics and receiver-operating characteristic curve. The proportional hazard assumption was tested by Schoenfeld residual analysis, and it was concluded that the data have satisfied the proportional hazard assumption for this model. The hazard ratio and 95% confidence interval of AF recurrence were computed and are presented in the Results.

All tests were 2 sided, and a value of *p*<0.05 was considered statistically significant. Analyses were performed with SAS (SAS Institute Inc).

**Results**
Table 1 summarizes the clinical characteristics of the study groups. A total of 360 patients had documented episodes of AF and AFL at baseline and were included in the study. At the time of ablation, 273 (76%) presented in sinus rhythm (group 1, 135 [74%] versus group 2, 138 [78%]; *P*=0.46), 46 (13%) in AF (group 1, 25 [14%] versus group 2, 21 [12%]; *P*=0.58), and 41 (11%) in AFL (group 1, 22 [12%] versus group 2, 19 [11%]; *P*=0.67). Among the 182 patients in group 1, 124 (68%) underwent radiofrequency catheter ablation targeting AF only (61±11 years, 74% male, 59±7% left ventricular ejection fraction) and 58 patients had the combined procedure AF+ AFL (63±8 years, 78% male, 59±8% left ventricular ejection fraction). In 178 patients in group 2 (age, 62±9 years; 76% male; left ventricular ejection fraction, 58±10%), only AFL was ablated by achieving bidirectional isthmus conduction block. The use of various AADs at baseline was identically distributed across the 2 groups (Table 2). The groups were comparable, showing no differences in their sociodemographic and clinical health backgrounds.

**Long-Term Follow-Up**

**Recurrence of Arrhythmia**
At 21±9 months of follow-up, 117 patients in group 1 (64%) and 47 in group 2 (26%) were arrhythmia free on or off previously ineffective AADs. The off-AAD success rate was substantially lower in group 2 (117 in group 1 [64%] versus 34 in group 2 [19%]; log-rank *P*<0.001).

Among the subpopulations of group 1, the success rate in patients undergoing AF ablation only was not different from those having ablation of AF+AFL. With or without previously ineffective AADs, 84 (68%) and 41 (71%) patients remained arrhythmia free in the AF and AF+AFL cohorts, respectively (log-rank *P*=0.657). The off-AAD success rate was 79 (64%) in AF alone and 38 (66%) in the AF+AFL population (log-rank *P*=0.812).

Figure 2 presents the Kaplan–Meier curves for the 2 subpopulations of group 1 (AF and AF+AFL) and group 2 together and compares the off-AAD recurrence-free survival using the log-rank test (log-rank *P*<0.001).
Use of AADs in the Postblanking Period

The 65 patients in group 1 and 144 in group 2 who were not arrhythmia free off AADs were continued on their previously ineffective AAD regimen.

Change in QoL

Assessment of QoL before and 1 year after the procedure was available for 332 patients (92%). The baseline QoL scores were not different between the 2 groups. However, the magnitude of QoL change at 1 year, as assessed by paired pre/post comparison, was different across the groups. Patients undergoing AF±AFL ablation (group I) derived significant improvement in QoL. In this group, except for physical functioning, bodily pain, and STAI scores, the change at 1 year was statistically significant for all other QoL components (Figure 3). In particular, the mental health subscales of SF-36 (role limitations resulting from physical health, role limitations resulting from emotional problem, vitality, and social functioning), HAD anxiety/depression, and BDI depression recorded substantial change. It was interesting to note that both subpopulations of group 1 (AF and AF+AFL) experienced equally robust improvement in most QoL scales (Table 3).

In terms of QoL improvement at 1 year, group 2 patients demonstrated relatively minor benefit in some SF-36 subscales, but except for general health, none of these reached statistical significance. Although significant improvement in HAD anxiety was observed, change in HAD depression and BDI scores did not reach statistical significance (Figure 3). Baseline scores, along with improvement/deterioration at the 1-year follow-up, are presented in Table 3.

Change in QoL: According to Arrhythmia Recurrence

Group 1 (AF, AF+AFL Ablation) QoL assessment at the 1-year follow-up was available for 95% of patients (118 of 124) undergoing AF ablation alone and 93% (54 of 58) undergoing AF+AFL ablation. In both subgroups, successful ablation was associated with significant improvement in the Physical Component Summary (change, 14.1±15.2 [P=0.002] and 13.2±11.8 [P<0.001], respectively) and Mental Component Summary (change, 5.2±8.3 [P=0.044] and 4.2±7.5 [P=0.037], respectively) subscales. On the other hand, among patients who failed, no significant difference in QoL scores was found between the baseline and 1-year assessments. Similarly, the reductions in HAD and BDI scores were larger with ablation success. After AF ablation alone and the AF+AFL procedure, the change in HAD anxiety was −2.4±0.3 (P=0.032) and −0.3±0.19 (P=0.014), in HAD depression was −2.0±0.1 (P=0.006) and −1.0±0.4 (P=0.023), and in BDI was −2.0±0.3 (P=0.041) and −1.6±0.5 (P=0.042), respectively. STAI scores did not show any association with ablation success.

### Table 1. Baseline Characteristics of Patients Undergoing PVAI±AFL and AFL Ablation Only

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=182)</th>
<th>Group 1A: AF Ablation (n=124)</th>
<th>Group 1B: AF+AFL Ablation (n=58)</th>
<th>P Value, Group 1A vs 1B</th>
<th>Group 2 (n=178)</th>
<th>P Value, Group 1 vs 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>61±10</td>
<td>61±11</td>
<td>63±8</td>
<td>0.216</td>
<td>62±9</td>
<td>0.274</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>138 (76)</td>
<td>93 (74)</td>
<td>45 (78)</td>
<td>0.704</td>
<td>135 (76)</td>
<td>0.991</td>
</tr>
<tr>
<td>AF duration, mean±SD, mo</td>
<td>89±62</td>
<td>94±62</td>
<td>80±69</td>
<td>0.329</td>
<td>78±60</td>
<td>0.112</td>
</tr>
<tr>
<td>BMI, mean±SD, kg/m²</td>
<td>29±5</td>
<td>29±6</td>
<td>30±5</td>
<td>0.271</td>
<td>28±6</td>
<td>0.115</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>76 (42)</td>
<td>53 (43)</td>
<td>23 (39)</td>
<td>0.694</td>
<td>84 (47)</td>
<td>0.299</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>34 (19)</td>
<td>14 (19)</td>
<td>10 (17)</td>
<td>0.269</td>
<td>25 (14)</td>
<td>0.235</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>22 (12)</td>
<td>15 (12)</td>
<td>7 (12)</td>
<td>0.996</td>
<td>22 (12)</td>
<td>0.937</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>80 (44)</td>
<td>56 (45)</td>
<td>24 (42)</td>
<td>0.632</td>
<td>64 (36)</td>
<td>0.121</td>
</tr>
<tr>
<td>Previous CVA, n (%)</td>
<td>7 (4)</td>
<td>5 (4)</td>
<td>2 (3)</td>
<td>0.216</td>
<td>11 (6)</td>
<td>0.131</td>
</tr>
<tr>
<td>Renal insufficiency, n (%)</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>1 (2)</td>
<td>0.164</td>
<td>5 (3)</td>
<td>0.279</td>
</tr>
<tr>
<td>LA diameter, mean±SD, mm</td>
<td>42.6±7</td>
<td>42.6±7</td>
<td>42.5±6</td>
<td>0.925</td>
<td>42.1±8</td>
<td>0.525</td>
</tr>
<tr>
<td>LVEF, mean±SD, %</td>
<td>59±8</td>
<td>59±7</td>
<td>59±8</td>
<td>1.000</td>
<td>58±10</td>
<td>0.273</td>
</tr>
<tr>
<td>Follow-up, mean±SD, mo</td>
<td>21±5</td>
<td>17±4</td>
<td>16±3</td>
<td>0.112</td>
<td>14±6</td>
<td>0.151</td>
</tr>
<tr>
<td>Failed AADs, mean±SD, n</td>
<td>2.5±1.0</td>
<td>2.6±1.2</td>
<td>2.2±0.8</td>
<td>0.086</td>
<td>2.7±1.7</td>
<td>0.175</td>
</tr>
<tr>
<td>ACE inhibitor, mean±SD, n (%)</td>
<td>66 (36)</td>
<td>47 (38)</td>
<td>19 (33)</td>
<td>0.501</td>
<td>58 (33)</td>
<td>0.463</td>
</tr>
<tr>
<td>β-Blockers, mean±SD, n (%)</td>
<td>78 (43)</td>
<td>55 (44)</td>
<td>23 (40)</td>
<td>0.551</td>
<td>67 (38)</td>
<td>0.313</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drugs; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; CAD, coronary artery disease, CVA, cerebrovascular accident; LA, left atrium; LVEF, left ventricular ejection fraction; and PVAI, pulmonary vein antrum isolation.

### Table 2. Preablation Use of AADs

<table>
<thead>
<tr>
<th>AAD</th>
<th>Group 1 (n=182), n (%)</th>
<th>Group 2 (n=178), n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>25 (14)</td>
<td>35 (20)</td>
<td>0.13</td>
</tr>
<tr>
<td>Propafenone</td>
<td>23 (13)</td>
<td>19 (11)</td>
<td>0.56</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>25 (14)</td>
<td>27 (15)</td>
<td>0.69</td>
</tr>
<tr>
<td>Sotalol</td>
<td>21 (12)</td>
<td>20 (11)</td>
<td>0.93</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>28 (15)</td>
<td>32 (18)</td>
<td>0.51</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>78 (43)</td>
<td>67 (38)</td>
<td>0.313</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>13 (7)</td>
<td>21 (12)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drugs.
Group 2 (AFL Ablation)

Among the 178 patients in this group who had CTI isolation for AFL elimination but did not undergo pulmonary vein isolation, QoL data were available for 160 patients (90%). In those patients, freedom from arrhythmia resulted in significant association with improvement in the Physical Component Summary score (change, 11.7±9.3; P=0.004) and reduction in HAD anxiety level (−04.1±01.8; P=0.001). However, no significant change was reported in the Mental Component Summary, HAD depression, BDI, and STAI scores.

Multivariate Analysis

Multivariate analysis of QoL improvement was performed with a general linear model. After adjustment for important confounders, freedom from arrhythmia after the blanking period was an independent predictor of improvement in the Mental Component Summary of SF-36, HAD anxiety and depression, and BDI score: coefficient, 3.1 (95% confidence interval, 2.3–4.5) for the Mental Component Summary, 0.81 (95% confidence interval, 0.17–0.95) for HAD, and 0.79 (95% confidence interval, 0.23–0.85) for BDI.
Predictors of recurrence-free survival were assessed with the multivariate Cox proportional hazards model. The covariates in the model are described in the Statistical Analysis section. After adjustment for important confounders, ablation of AFL alone was associated with an ≈6-times-higher recurrence than AF±AFL ablation (hazard ratio, 5.8; 95% confidence interval, 2.9–11.4; P<0.001).

Hospitalization
The hospitalization rate was substantially higher in group 2. A total of 12 patients in group 1 (6.6%) and 55 in group 2 (30.9%) required rehospitalization after the index procedure (P<0.001). Arrhythmia-related conditions were the most frequent reason for rehospitalization during follow-up: 7 reported in group 1 (4%) and 41 in group 2 (23%; P<0.001). Other causes of rehospitalization in group 1 were hematoma 4 (2.2%) and heart failure 1 (0.5%). In group 2, 5 patients (2.8%) were hospitalized for hematoma, 7 (3.9%) for heart failure, 1 (0.6%) for pseudoaneurysm, and 1 (0.6%) for gastrointestinal hemorrhage.

Major Complications
Two patients in group 1 (1.1%) had pericardial effusion that was conservatively managed with fresh-frozen plasma and protamine. No major periprocedural complications were reported in group 2 (P=0.49).

Discussion
This study aimed to compare the recurrence of atrial arrhythmia and improvement in QoL scores measured with multiple scales between the 2 different ablation strategies in patients presenting with AF and AFL. Our findings clearly suggested that AF±AFL ablation is more effective than AFL ablation alone in providing higher recurrence-free survival and improving the QoL of patients presenting with both AF and AFL. Furthermore, between the 2 ablation strategies in group 1, AF ablation alone demonstrated to be equally effective as AF+AFL ablation.

QoL is defined as the subjective perception of a disease or deformity. The SF-36 scale examined the impact of AF and AFL on routine physical, mental, and social activity before and after ablation; BDI, HAD, and STAI measured the affective status of the patients, which includes anxiety and depression. It is understandable that elimination or reduction of the severity and frequency of arrhythmic episodes would result in a better perspective toward life, create a more positive attitude and optimism, lessen the load of anxiety and depression, and enable the patient to become more productive physically and socially. Therefore, ideally speaking, a successful ablation should cause an improvement in all of the subscales of QoL measurement tools. However, the association between ablation outcome and QoL is not as direct as it appears. Certain other important confounding factors such as age, sex, comorbidities, and the relative efficacy of the ablation strategies play a critical role in the interpretation of this relationship.

Between the 3 ablation approaches for coexistent AF and AFL, several studies have demonstrated that the combined ablation strategy (PVAI+CTI) results in very low AF recurrence,14,15 that PVAI alone without CTI ablation has an early recurrence of AFL in 24%,16 and that the rate of AF recurrence after CTI isolation alone has been reported to be as high as 80% and up to 30% in those on AADs after isthmus isolation.16 Roithinger et al17 hypothesized that AF organizes to AFL in patients presenting with both arrhythmias. Wazni et al16 suggested that pulmonary vein triggers initiate AFL; therefore, curing AF eliminates AFL as well. From our study, it is obvious that ablation of pulmonary vein triggers alone or in combination with CTI ablation is superior to lone CTI ablation in providing long-term freedom from arrhythmia. We observed a comparable success rate in terms of arrhythmia recurrence in PVAI+AFL ablation and PVAI alone, which indicates that AFL ablation does not provide any added advantage and that PVAI alone is sufficient for long-term

Table 3. Baseline QoL Score and Change at the 12-Month Follow-Up According to Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (PVAI±AFL Ablation)</th>
<th>Group 2 (AFL Ablation Only)</th>
<th>P Value, Change in Group 1 vs 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Score</td>
<td>Change at 12 mo</td>
<td>P</td>
</tr>
<tr>
<td>PF</td>
<td>75.9</td>
<td>3.3</td>
<td>0.32</td>
</tr>
<tr>
<td>RP</td>
<td>64.55</td>
<td>15.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RE</td>
<td>71.05</td>
<td>13.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VT</td>
<td>54.1</td>
<td>10.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MH</td>
<td>76.75</td>
<td>3.5</td>
<td>0.03</td>
</tr>
<tr>
<td>SF</td>
<td>77.9</td>
<td>8.3</td>
<td>0.01</td>
</tr>
<tr>
<td>BP</td>
<td>78.35</td>
<td>−0.6</td>
<td>0.85</td>
</tr>
<tr>
<td>GH</td>
<td>64.2</td>
<td>4.3</td>
<td>0.03</td>
</tr>
<tr>
<td>HAD anxiety</td>
<td>4.25</td>
<td>−0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HAD depression</td>
<td>3.6</td>
<td>−1.2</td>
<td>0.01</td>
</tr>
<tr>
<td>BDI score</td>
<td>7.45</td>
<td>−1.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Trait–anxiety score</td>
<td>49.1</td>
<td>−0.6</td>
<td>0.58</td>
</tr>
<tr>
<td>State–anxiety score</td>
<td>39.3</td>
<td>2.3</td>
<td>0.61</td>
</tr>
</tbody>
</table>

AFL indicates atrial flutter; BDI, Beck Depression Inventory; BP, bodily pain; GH, general health; HAD, Hospital Anxiety and Depression; MH, mental health; PF, physical functioning; PVAI, pulmonary vein antrum isolation; QoL, quality of life; RE, role limitations resulting from emotional problem; RP, role limitations resulting from physical health; SF, social functioning; and VT, vitality.
ablation success. This observation reinforces the theory that disorganized AF gets organized eventually because of anatomic and electric barriers and activates the right atrium by a single wavelet initiating AFL. Thus, elimination of the initiating arrhythmia cures AFL in most cases when they share common triggers.16 The limited numbers of recurrent atrial arrhythmic events after PVAI±AFL ablation can reflect either non–pulmonary vein triggers or reconnection around the ablated PVs.

A significantly higher rate of arrhythmia recurrence was observed after AFL ablation alone. The mechanistic relationship between AF and AFL is poorly understood, although their association is commonly observed. Evidence from previous studies suggests that pulmonary vein triggers are responsible for the development of both arrhythmias in coexistent AF and AFL.16,18 Therefore, eradication of flutter circuit alone does not prevent eventual manifestation of AF.19 Bertaglia et al13 reported a cumulative probability of recurrence of to of 62% in patients undergoing AFL ablation, whereas we observed a recurrence rate of 74% after AFL ablation alone. The difference in results can be attributed to disparities in the study population; 62% of the patients in the Bertaglia et al study had preablation AF, whereas 100% of our participating patients had AF to begin with. Preablation AFL identifies patients in whom there is a structural and electrophysiological substrate that allows multi-reentrant circuits favoring AF that is known to be significantly associated with the occurrence of AF after transisthmic ablation.11 Thus, it can be safely postulated that for those patients who had recurrence, AFL was not the primary or predominant arrhythmia and AF was not a consequence of it.20 Rather, AF was probably caused by marked structural and electric remodeling of atrial muscles, which required a different ablation strategy than simple AFL ablation.

AF seems to be the major culprit here, and if AF is taken care of, the symptom burden and subsequent limitations associated with those symptoms are dramatically reduced in most patients. Our study reported a significant improvement in almost all subscales of QoL in group 1 patients. At the long-term follow-up, 64% with AF ablation and 66% with AF+AFL ablation in group 1 remained arrhythmia free off AADs. The rarity of symptoms, withdrawal of medication, and absence of side effects of AADs, as well as the elimination of the need for frequent use of healthcare resources, plausibly contributed to the profound improvement in QoL in these patients in the postablation period. Substantial change in physical functioning and bodily pain in the SF-36 scales was not noticed in this group, which can be attributed to age-related comorbidities like arthritis and joint replacement.

We observed significant improvement in only the general health subscale of the SF-36 in group 2; there was some positive improvement in other subscales, but the changes were not statistically significant. General health perception in the SF-36 scale includes 5 items that delineate personal assessment of health, including current health, future health perspectives, and resistance to illness.21 Because the patients underwent the ablation procedure by the able hands of their preferred physicians, they were optimistic of their future health perspectives, which would explain the improvement in the general health subscale. However, because most of these patients comorbid with AF and AFL had arrhythmia recurrence and were on AADs after AFL ablation, the arrhythmic symptom burden, the side effects of pharmacological agents, and the relatively higher use of healthcare resources possibly precluded improvement in most of the subscales of SF-36 in group 2.4

In our study, for the first time, affective symptoms were measured with 3 different scales: the BDI, HAD, and STAI. An improvement in anxiety score was noticed in both groups on the HAD scale. However, the magnitude of improvement was much larger in group 1 than in group 2. Significant improvement in depression score on HAD and BDI scale was exhibited by group 1 patients only. Thrall et al22 demonstrated an association between improvement in QoL and positive change in depression score in AF patients. Although we did not specifically check any correlation between depression and QoL, we observed a strong improvement in depression status and QoL in 1 group of patients and not the other.

Furthermore, in this study, patients were blinded to the type of ablation procedure as they were randomized to different study groups. The knowledge and awareness of the extensiveness of their procedure could have resulted in underreporting of undesirable and overreporting of socially favorable responses, which could have resulted in biased QoL data. By blinding the patients to procedure type, we demonstrated that improvement in QoL after ablation is a real event, not a preconceived perception.

Limitations
All questionnaires used in this study were generic, and we could not exclude the impact of comorbidities such as back problems and arthritis on QoL score in this elderly population. A disease-specific survey would have more appropriately measured AF-related QoL. Additionally, our study had limited power to compare the outcomes between the 2 subgroups of group 1; a larger randomized trial would have validated the observation and established an inference. However, this issue has been previously addressed in a randomized study by Wazni et al.16

Conclusions
This study demonstrated that at the 1-year follow-up, patients with symptomatic AF and AFL who are treated with AF±AFL ablation attain higher success rates and better postablation QoL scores than their counterparts undergoing AFL ablation alone. Furthermore, our results suggested that in coexistent AF and AFL, PVAI alone may have an efficiency comparable to that of PVAI+AFL ablation in controlling both arrhythmias and providing improvement in QoL. Also worth mentioning is the fact that this is the first study showing that in patients blinded to the procedure type, improvement in QoL correlates with clinical freedom from arrhythmia recurrence.

Acknowledgments
We acknowledge the contributions of the following physicians to this study: Agnes Pump, MD, David Burkhardt, MD, Joseph G. Gallighouse, MD, Rodney Horton, MD, Javier E. Sanchez, MD, Shane Bailey, MD, and Jason Zagrodzky, MD.

Disclosures
Dr Di Biase is a consultant for Hansen Medical and Biosense Webster. Dr Natale received speaker’s honoraria from Boston Scientific, Biosense Webster, St. Jude Medical, Medtronic, and Life Watch and a research grant from St. Jude Medical. The other authors report no conflicts.
References


CLINICAL PERSPECTIVE

This randomized, single-blinded study compared the impact of different ablation strategies on the long-term procedure outcomes such as arrhythmia recurrence and change in quality of life in patients with coexistent atrial fibrillation and atrial flutter (AFL). In the presence of concurrent atrial fibrillation and AFL, although the literature is limited, the reported results support a variety of procedural approaches. They include either pulmonary vein antrum isolation for atrial fibrillation or cavotricuspid isthmus ablation for AFL or a combined approach of pulmonary vein antrum isolation plus cavotricuspid isthmus ablation. The optimal strategy remains unclear, prompting the present study. Our findings clearly suggested that atrial fibrillation ablation with or without AFL ablation is more effective than AFL ablation alone in achieving recurrence-free survival and improving quality of life. Furthermore, our results indicated that pulmonary vein antrum isolation alone may have an efficacy comparable to that pulmonary vein antrum isolation plus AFL ablation in controlling both arrhythmias and improving quality of life. Also worth mentioning is that this was the first study with patients blinded to the procedure to show that improvement in quality of life correlated with clinical freedom from arrhythmia recurrence. Although this study had certain limitations, it was an attempt to explore the best ablation option for the elimination of arrhythmias in patients with coexistent atrial fibrillation and AFL. There is a pressing need for optimization of a safe and effective ablation approach that would successfully cure both arrhythmias and save the patients from the cost and the stress of recurrences and repeat ablations. Our study is a step forward in that direction.
Results From a Single-Blind, Randomized Study Comparing the Impact of Different Ablation Approaches on Long-Term Procedure Outcome in Coexistent Atrial Fibrillation and Flutter (APPROVAL)

Sanghamitra Mohanty, Prasant Mohanty, Luigi Di Biase, Rong Bai, Pasquale Santangeli, Michela Casella, Antonio Dello Russo, Claudio Tondo, Sakis Themistoclakis, Antonio Raviele, Antonio Rossillo, Andrea Corrado, Gemma Pelargonio, Giovanni Forleo and Andrea Natale

*Circulation*. 2013;127:1853-1860; originally published online April 9, 2013;
doi: 10.1161/CIRCULATIONAHA.113.001855

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/18/1853

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/