Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a lifetime risk exceeding 20% by 80 years of age.\textsuperscript{1} It is associated with significant morbidity related to symptoms, heart failure, and thromboembolism.\textsuperscript{2} Although AF is generally considered a non–life-threatening arrhythmia, it was associated with a 1.5- to 1.9-fold excess mortality after adjustment for pre-existing cardiovascular conditions in the Framingham Heart Study.\textsuperscript{3} Despite these associations, antiarrhythmic drug (AAD) therapy with the goal of maintaining sinus rhythm has not improved outcomes in randomized trials.\textsuperscript{4,5} In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, a strategy of heart rate control was equivalent to heart rhythm control in terms of all-cause mortality but superior in reducing hospitalizations.\textsuperscript{6} No studies have shown a reduction in stroke or heart failure when rhythm control is attempted in patients with AF. If the patient has risk factors for thromboembolism, anticoagulation is maintained in either strategy. Therefore, the major reason to pursue sinus rhythm in patients with AF is to improve their symptoms and quality of life.

During the past decade, attention has shifted from AADs toward catheter ablation. Catheter ablation was found to be superior to AAD therapy for maintaining sinus rhythm in many small, randomized trials of selected patients in whom treatment with an AAD had failed.\textsuperscript{7} Although these findings are intriguing, they require confirmation in a prospective randomized controlled trial. In addition, a benefit with respect to survival and morbidity has yet to be confirmed. Nonetheless, ablation is now regarded as an acceptable therapy for symptomatic patients who desire to remain in sinus rhythm and who have not had a response to ≥1 antiarrhythmic medication.\textsuperscript{4,5} But has ablation achieved sufficient safety and efficacy to be considered first-line therapy for all patients with paroxysmal AF (PAF)?

A recent consensus statement concluded that catheter ablation is a reasonable option for patients with symptomatic PAF before therapy with an AAD.\textsuperscript{8} However, the issue under discussion here is not whether a catheter ablation is either possible or useful in many patients but whether it should be used as first-line therapy in all patients with PAF. As we will show for most patients, the evidence does not yet exist to support catheter ablation as first-line therapy.
AAD Therapy

A 2006 meta-analysis reviewed the clinical efficacy and safety of AAD and radiofrequency ablation in the treatment of AF. Electronic searches were conducted in EMBASE and MEDLINE from 1990 to 2007. The AAD review focused on the 5 AADs that are currently recommended for use in the treatment of AF: amiodarone, propafenone, dofetilide, flecainide, and sotalol. Among the 34 AAD studies, there were 11 amiodarone treatment groups, 16 propafenone treatment groups, 9 sotalol treatment groups, 2 dofetilide treatment groups, and 7 flecainide treatment groups.

An important variable in the assessment of efficacy for arrhythmia treatment is the choice of monitoring. The majority of studies for both the AAD and the radiofrequency ablation treatments evaluated patients with ECGs performed at specified intervals during follow-up visits. A minority of studies used Holter or event monitors to assess arrhythmia recurrence between visits. The overall success rate (generally defined by authors as disappearance of arrhythmia during the follow-up period) for all drug treatment groups was 52% (95% confidence interval, 47%–57%) in 32 treatment arms with 3180 patients (Figures I and II in the Data Supplement).

In comparison, the single-procedure success rate of ablation off AAD therapy was 57% (95% confidence interval, 50%–64%), the multiple procedure success rate off AAD was 71% (95% confidence interval, 65%–77%), and the multiple procedure success rate on AAD or with unknown AAD usage was 77% (95% confidence interval, 73%–81%). This is an important point as it demonstrates the fact that catheter ablation does not necessarily obviate the long-term use of AADs. Many patients require continued AAD therapy after catheter ablation.

From a safety standpoint, major complications of catheter ablation occurred in 4.9% of patients. Adverse events for AAD studies, although more common (30%), were less severe. A comparison of the number and types of complications resulting from radiofrequency ablation versus AAD therapy reveals one of the challenges in weighing the risks and benefits of the 2 therapies. Although at first consideration, the 30% complication rate for AAD therapy significantly overwhelms the 5% complication rate associated with radiofrequency ablation, there are significant differences in the seriousness of the complications reported. It is difficult to compare cardiac tamponade or pulmonary vein (PV) stenosis with gastrointestinal complications. In the case of AAD complications, the drug can be withdrawn with resolution of the effects in most cases. However, the complications of catheter ablation can be catastrophic with long-term effects or require further invasive interventions. Furthermore, the authors of this study note that the majority of the ablation studies were single center case series and therefore it is likely that adverse events were reported with less rigor than in typical multicenter randomized controlled drug trials.

This review included a broad range of study designs, treatment settings, ablation techniques, and study inclusion criteria. In addition, the majority of the patients had failed ≥1 AAD before enrollment. To better compare the 2 treatment strategies as first-line therapy, Cosedis Nielsen et al. conducted the Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial, which compared catheter ablation with AAD therapy in patients with PAF in whom treatment with an AAD had not previously failed. Two hundred ninety-four patients with PAF and no history of AAD use were randomized to an initial treatment strategy of either radiofrequency catheter ablation or therapy with class IC or class III antiarrhythmic agents. Follow-up included 7-day Holter-monitor recording at 3, 6, 12, 18, and 24 months. Primary end points were the cumulative and per-visit burden of AF. In an intention-to-treat analysis, they found no significant difference between treatment groups in the cumulative burden of AF (Figure III in the Data Supplement).

In addition, quality of life based on the SF-36 physical component and mental-component summary scores improved significantly from baseline in both treatment groups. Given the results of this multicenter, randomized trial and the risk of complications with ablation, it would be difficult to advocate for catheter ablation as first-line treatment in all patients with PAF especially considering the primary reason for treatment is improvement in quality of life.

Catheter Ablation

Efficacy

When considering the published literature on catheter ablation of AF, it is important to recognize that until the writing of the initial consensus report in 2007, there had been no standardization in the design of clinical trials for AF ablation. As such, there are many important variables of an AF ablation trial that can affect the results, not least of which is the frequency and intensity of arrhythmia monitoring. Some studies have defined success as freedom from symptomatic AF during follow-up, whereas other studies have defined success as freedom from symptomatic and asymptomatic episodes of AF. A third definition of success used by other studies is the proportion of patients free from AF in a given period of time or on an ECG or Holter monitor administered a certain period of time after the ablation procedure. A fourth definition of success is AF control defined as a >90% reduction of AF burden.

Other important considerations in defining procedural success are the duration of the blanking period, whether patients with atrial flutter or atrial tachycardia during follow-up are classified as successes or failures, the use of AADs, and the frequency and timing of repeat ablation procedures. During the past several years, a large number of meta-analyses have been performed in the hope of better defining the efficacy of AF ablation. One of the most recent meta-analyses examined the results of 8 randomized clinical trials. Overall, the success rate was 77.8% in the ablation arm. However, this included studies in which ≥1 procedure was performed and again, these were patients who had failed ≥1 antiarrhythmic medication before enrollment.

A worldwide survey on the methods, efficacy, and safety of catheter ablation of AF was published in 2005. This survey
was completed by >180 centers located throughout the world. The outcomes of ~9000 AF ablation procedures were reported by these centers. More than 1 ablation procedure was performed in 27% of patients. The success rate, defined as freedom from symptomatic AF in the absence of antiarrhythmic therapy, was 52%, which is significantly lower than the results of the published clinical trial data. It is important to note that freedom from symptomatic AF is not the same as freedom from AF. In the Discerning Symptomatic and Asymptomatic Episodes Pre and Post Radiofrequency Ablation of Atrial Fibrillation (DISCERN AF) trial, the authors found that ratio of asymptomatic to symptomatic AF episodes increased from 1.1 before to 3.7 after ablation. Symptoms alone underestimate postablation AF burden, with 12% of patients having asymptomatic recurrences only. Therefore, there may be some degree of placebo effect after ablation.\textsuperscript{32}

Most of these published studies have reported data from short-term follow-up, usually 12 months, but what about long-term efficacy? During the past 2 to 3 years, several groups have reported their 5-year data.\textsuperscript{23–29} The reported recurrence rates of atrial arrhythmias ranged from 25% to 71%. Numerous patients required ≥1 repeat ablations and many remained on AADs to maintain sinus rhythm. These findings highlight the difficulty with which permanent pulmonary vein isolation can be achieved with current ablation technologies. It is important to recognize that in these studies follow-up was often incomplete and that standardized monitoring protocols and end points were generally not used.

Complications
Few therapies can be administered without safety concerns. Catheter ablation of AF is one of the most complex interventional electrophysiologic procedures. It is therefore to be expected that the risk associated with AF ablation is higher than for ablation of most other cardiac arrhythmias. The first world-wide survey of AF ablation reported that ≥1 major complication was seen in 6% of patients.\textsuperscript{21} A follow-up survey published in 2011 reported major complications in 741 of 16,309 patients (4.5%; Table I in the Data Supplement).\textsuperscript{30} Although these data might be regarded as providing representative complication rates, it must be recognized that the data were from voluntary surveys and likely underestimated the true complication rates. Using data from the Healthcare Utilization Project California State Inpatient Database, Shah et al\textsuperscript{31} reported on AF ablation procedural complications and repeat hospitalizations. Among 4156 patients who underwent an initial AF ablation between 2005 and 2008, 5% had periprocedural complications and 9% were readmitted within 30 days. However, in a controlled, prospective trial such as MANTRA-PAF, adverse events occurred in 20 of 146 (13.7%) patients in the ablation arm, thus indicating that adverse events may occur more frequently than reported in a survey or retrospective single center report.\textsuperscript{10}

Cardiac Tamponade
Cardiac tamponade is the most common potentially life-threatening complication associated with AF ablation.\textsuperscript{32} It has been reported with an incidence of ≤6%. The markedly higher incidence of cardiac tamponade during AF ablation compared with other electrophysiologic procedures can be attributed to several important differences, including extensive intracardiac catheter manipulation and ablation, the common need for ≥2 transpulmonary punctures and the need for systemic anticoagulation. Most but not all patients presented with warning symptoms, but 13% of patients presented with hypotension and shock.\textsuperscript{8}

PV Stenosis
PV stenosis is a well-recognized complication of AF ablation that results from thermal injury to the PVs, including the media, intima, adventitia, and PV musculature. Since first reported in 1998, numerous studies have sought to determine the incidence, cause, diagnostic strategy, and treatment approach for PV stenosis. The published incidence of PV stenosis varies widely from 0% to 38%.\textsuperscript{33–35} This variation results from differences in the ablation technique, definition of PV stenosis, and intensity of screening. The worldwide survey of AF ablation reported a 0.32% incidence of acute PV stenosis and a 1.3% incidence of persistent PV stenosis.\textsuperscript{21} Percutaneous or surgical intervention for treatment of PV stenosis was required in 53 cases (0.6%). In the 2012 Consensus Statement, it is recommended that a significant PV stenosis be defined as a >70% reduction in luminal diameter.\textsuperscript{8} Symptoms of PV stenosis include chest pain, dyspnea, cough, hemoptysis, recurrent lung infections, and symptoms of pulmonary hypertension.\textsuperscript{34,35} It is unknown whether early diagnosis and treatment of asymptomatic PV stenosis provide any long-term advantage to the patient.

Esophageal Injury
Because the esophagus is invariably in close apposition to the posterior wall of the left atrium and ≥1 PVs, the esophagus and periesophageal nerves are at risk of injury when ablation is performed in these areas. Esophageal ulceration, perforation, or development of a left atrial-esophageal fistula have been reported after catheter ablation of AF. Although left atrial-esophageal fistulae are rare, occurring after <0.1% to 0.25% of AF ablation procedures, they are associated with a high morbidity that includes air embolism, sepsis, and a mortality rate that is >80%.\textsuperscript{21,30,32,36,37} Survivors of left atrial-esophageal fistulae are often left with disability from cerebrovascular events. Other injuries to the esophagus are more common after AF ablation. In several clinical studies, endoscopy performed 1 to 3 days after AF ablation identified an asymptomatic esophageal ulcer in 4% to 60% of patients.\textsuperscript{38–41} Risk factors for this potentially fatal complication have not been established.

Phrenic Nerve Injury
Phrenic nerve injury is an important complication of AF ablation.\textsuperscript{42–44} It results from direct thermal injury, usually to the right phrenic nerve, which is located near the right superior PV and the superior vena cava. The most common scenario in which phrenic nerve injury has been reported is cryoballoon ablation of the right-sided PVs but it is also seen in electric
isolation of the SVC with radiofrequency energy. Rarely, ablation within the left atrium appendage can result in left phrenic nerve damage. Phrenic nerve damage can be asymptomatic or can cause dyspnea, hiccups, atelectasis, pleural effusion, cough, and thoracic pain. There is no active treatment known to aid phrenic nerve healing.

**Thromboembolism**

The incidence of thromboembolism associated with AF ablation is reported to be between 0% and 7%. Thromboembolic events typically occur within 24 hours of the ablation procedure with the high-risk period extending for the first 2 weeks after ablation. Several potential explanations for the development of thromboembolic complications have been proposed. These include the development of thrombi on or within stationary sheaths or ablation catheters positioned within the left atrium, char formation at the tip of the ablation catheter and at the site of ablation, disruption of a thrombus located in the atrium before the ablation procedure, and, possibly, electric cardioversion during procedures.

Silent cerebral embolism is defined as an occlusion of a blood vessel in the brain because of an embolus that does not result in any acute clinical symptoms and is therefore silent. Recently, several centers have reported that diffusion-weighted MRI can detect new acute lesions created by emboli after 7% to 38% of AF ablation procedure. In 674 AF ablation patients reported in the literature in whom a diffusion-weighted MRI was obtained before and 24 to 48 hours after ablation, the overall incidence of acute lesions was 17%. Although the long-term consequences of this finding are not well understood, there is concern for postoperative neurocognitive dysfunction. A recent study sought to determine whether the postoperative neurocognitive dysfunction occurred after AF ablation. The study showed that AF ablation is associated with a 13% to 20% prevalence of postoperative neurocognitive dysfunction at long-term follow-up compared with 0% in a nonprocedural control population of age-matched patients with AF.

The thromboembolic risk can be minimized by adequate peri-procedural anticoagulation, which could potentially increase the risk of bleeding complications. Optimal peri-procedural anticoagulation protocols to minimize these complications are still largely debated and have become more complicated with the introduction of the novel oral anticoagulants. Several recently published studies have reported that peri-procedural dabigatran use significantly increases the risk of bleeding and thromboembolic complications compared with uninterrupted warfarin therapy. Given the rising number patients taking novel oral anticoagulants, further studies are necessary to identify the optimal peri-procedural anticoagulation strategies in patients on novel oral anticoagulants undergoing AF ablation.

**Vascular Complications**

Vascular complications are the most common complications of AF ablation and include groin hematoma, retroperitoneal bleed, femoral arterial pseudoaneurysm, or femoral arteriovenous fistula. More significant vascular complications can lead to substantial morbidity and prolonged hospital stay and can necessitate blood transfusion and percutaneous or open surgical repair. Rarely, vascular complications with large tense hematomas can lead to femoral neurological sequelae and a requirement for rehabilitation. The published incidence of vascular complications varies from 0% to 13%. A worldwide survey of 8745 AF ablation procedures found an incidence of femoral pseudoaneurysm and arteriovenous fistulae of 0.53% and 0.43%, respectively.

**Radiation Exposure**

Catheter ablation of AF is often a complex and long procedure requiring long fluoroscopy exposure time and often preceded by computed tomographic scans. An important, less easily recognized, potential complication of AF ablation is the delayed effect of the radiation received by the patients, including acute and subacute skin injury, malignancy, and genetic abnormalities. One study reported mean fluoroscopy durations for AF procedures of >60 minutes in both left anterior oblique and right anterior oblique projections. The mean peak skin doses were 1.0±0.5 Gy in right anterior oblique and 1.5±0.4 Gy in left anterior oblique projection. This translates into a lifetime risk of excess fatal malignancies of 0.07% for female and 0.1% for male patients. This study demonstrated that catheter ablation of AF required significantly greater fluoroscopy duration and radiation exposure than simpler catheter ablation procedures. This is especially important because of the fact that AF ablation procedures often need to be repeated.

**Mortality**

Of the previously discussed complications, some may ultimately lead to death. In a recent survey, death was reported in 32 of 32,569 (0.1%) patients undergoing 45,115 AF ablation procedures worldwide. The most frequent cause of death was cardiac tamponade, accounting for 25% of the deaths. Stroke was responsible in 16%. Atrioesophageal fistula also accounted for 16% of the deaths, with massive pneumonia responsible for 6%. Less common causes of death observed in the peri-procedural phase included myocardial infarction, irreversible torsades de pointes, septicemia, sudden respiratory arrest, extrapericardial PV perforation, occlusion of both lateral PVs, hemotorax, and anaphylaxis, which were each responsible for 3% of early deaths. Twenty-two percent of all deaths occurred >30 days after the procedure. Awareness about the risk of death needs to be considered in the patient decision-making process.

**Operator Dependence**

The technical skills needed for ablation of AF are substantial. These include transeptal needle puncture and cannulation of the left atrium, precise manipulation of the catheter for mapping and ablation, identification of the pulmonary ostia, adjustment of the energy used for ablation, and the appropriate use of fluoroscopy, radiographic contrast for imaging, 3-dimensional mapping systems, or intracardiac echocardiography.
American College of Cardiology/American Heart Association 2008 update of the clinical competence statement on invasive electrophysiology studies, catheter ablation, and cardioversion proposed a minimum of 30 to 50 AF ablation procedures for those who undergo fellowships in clinical cardiac electrophysiology. These numbers underestimate the experience required for a high degree of proficiency. Comparisons of high- and low-volume centers suggest that outcomes are better at centers that have performed >100 procedures. Deshmukh et al published supporting data in 2013, which showed low annual operator (<25 procedures) and hospital volume (<50 procedures) were significantly associated with adverse outcomes.

Cost Effectiveness

One study formally analyzed the cost-effectiveness of catheter ablation compared with amiodarone therapy and a rate-control strategy. Among 65-year-old patients at moderate risk of stroke, the incremental cost-effectiveness ratio of catheter ablation was $51,800 (2004 dollars) per quality-adjusted life-year. In 55-year-old patients at moderate risk of stroke, catheter ablation had an incremental cost-effectiveness ratio of $28,700 per quality-adjusted life-year compared with rate control. However, in patients with no risk factors for stroke, catheter ablation had an incremental cost-effectiveness ratio of $98,900 per quality-adjusted life-year. Further analysis indicated that in 65-year-old patients at moderate risk of stroke and with an 80% 1-year success rate of catheter ablation, the relative risk of stroke after catheter ablation would need to decrease by ≥42% compared with anticoagulated patients in AF for the incremental cost-effectiveness ratio of catheter ablation to be ≤$50,000. Of note is that $50,000 generally is considered to be the threshold value for cost effectiveness of a therapy. However, the model assumed that successful ablation of AF eliminates the excess risk of stroke, which is yet to be proven in a prospective study.

Continued Need for Anticoagulation

The Task Force Writing Group that published the 2012 consensus statement on catheter ablation of AF recommended that systemic anticoagulation be continued indefinitely in patients with a high risk for stroke as estimated by currently recommended schemes (CHADS2 or CHA2DS2-VASc) and especially in those who are ≥75 years of age or have had a prior stroke or transient ischemic attack. This recommendation is based on several observations: (1) recurrences of AF are common both early and late after AF ablation, (2) asymptomatic AF is common after AF ablation, (3) AF ablation destroys a portion of the atria and the impact of this on stroke risk is uncertain, (4) there have been no large randomized prospective trials that have assessed the safety of stopping anticoagulation in this patient population, and (5) the use of direct thrombin inhibitors or factor Xa inhibitors, such as dabigatran, rivaroxaban, and apixaban, is more convenient than warfarin. The Task Force also noted that in a subgroup analysis of The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk (TRENDS) study, 73% of patients who experienced a stroke or systemic emboli had a zero AF burden within 30 days before the stroke or embolic event. These data have important implications for the post–AF ablation population as they remind us that the mechanisms of stroke are not limited to cardioembolism caused by AF.

Patient Selection

The patients enrolled in the majority of the published data to date are young, with symptomatic PAF and without other major heart disease. This profile represents fewer than a quarter of the patients with AF who are encountered in practice. These results should not be extrapolated to the broader population of patients with AF, the majority of whom are elderly with coexisting conditions. It is hoped that the large-scale Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial will begin to shed some light on the role of AF ablation in patients not well represented in previously published clinical trials. This study will randomize 3000 patients to a strategy of catheter ablation versus pharmacological therapy with rate or rhythm control drugs. Patients will be older, ≥65 years old, or <65 years old with >1 risk factor for stroke. They will be followed up for >2 years, and the primary outcome is to determine whether catheter ablation is superior to drug therapy for reducing total mortality.

Conclusions

Despite the tremendous progress that has been made in the development of catheter ablation of AF, it should not be recommended as first-line therapy in all patients with PAF. For most patients, the evidence does not yet exist to support such a broad sweeping statement. Catheter ablation of AF is associated with variable efficacy and significant procedure-related complications. Careful patient selection and discussion on the procedure-related risks are of utmost importance in the patient decision-making process. It is also important to realize that the decision to forego catheter ablation as first-line therapy does not obviate its use later in the appropriate patient. We look forward to further investigation into the long-term impact of catheter AF ablation on major morbidity and mortality, particularly in the setting of underlying disease because the data are not currently available.

Disclosures

Peter R. Kowey has served as a consultant for Medtronic, Boston Scientific and St. Jude as well as Sanofi, Pfizer, and Gilead. The other authors report no conflicts.

References


Response to Colleen M. Hanley, MD, Douglas Esberg, MD, FACC, FHRs, Peter R. Kowey, MD, FAHA, FHRs

Pasquale Santangeli, MD, Luigi Di Biase, MD, PhD, Andrea Natale, MD

To support the position that catheter ablation (CA) should not be considered the first-line therapy for paroxysmal atrial fibrillation (PAF), Hanley et al mostly focus on studies that have not been designed to test CA as a first-line therapy. The only first-line ablation study discussed in details was the Medical AntiArrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTA-PAF); as stated in our position article, we think that the results of the MANTA-PAF should be interpreted with extreme caution, given the discretionary adoption of obsolete CA techniques such as circumferential pulmonary vein ablation without confirmation of pulmonary vein isolation and, most importantly, of the exceptionally high rate of crossover to CA, which accounted for one third of patients initially assigned to antiarrhythmic drug therapy. The efficacy data quoted by Healey et al mostly derive from confirmation of pulmonary vein isolation and, most importantly, of the exceptionally high rate of cross-over to CA, which accounted for one third of patients initially assigned to antiarrhythmic drug therapy. The efficacy data quoted by Healey et al mostly derive from confirmation of pulmonary vein isolation and, most importantly, of the exceptionally high rate of cross-over to CA, which accounted for one third of patients initially assigned to antiarrhythmic drug therapy. The efficacy data quoted by Healey et al mostly derive from confirmation of pulmonary vein isolation and, most importantly, of the exceptionally high rate of cross-over to CA, which accounted for one third of patients initially assigned to antiarrhythmic drug therapy.
Ablation Versus Drugs: What Is the Best First-Line Therapy for Paroxysmal Atrial Fibrillation?: Antiarrhythmic Drugs Are Outmoded and Catheter Ablation Should Be the First-Line Option for All Patients With Paroxysmal Atrial Fibrillation: Con
Colleen M. Hanley, Douglas Esberg and Peter R. Kowey

Circ Arrhythm Electrophysiol. 2014;7:747-754
doi: 10.1161/CIRCEP.113.001281

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/7/4/747

Data Supplement (unedited) at:
http://circep.ahajournals.org/content/suppl/2014/08/14/CIRCEP.113.001281.DC1
<table>
<thead>
<tr>
<th>Type of Complication</th>
<th>No. of Patients</th>
<th>Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>25</td>
<td>0.15</td>
</tr>
<tr>
<td>Tamponade</td>
<td>213</td>
<td>1.31</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>15</td>
<td>0.09</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>4</td>
<td>0.02</td>
</tr>
<tr>
<td>Sepsis, abscesses, or endocarditis</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>Permanent diaphragmatic paralysis</td>
<td>28</td>
<td>0.17</td>
</tr>
<tr>
<td>Total femoral pseudoaneurysm</td>
<td>152</td>
<td>0.93</td>
</tr>
<tr>
<td>Total artero-venous fistula</td>
<td>88</td>
<td>0.54</td>
</tr>
<tr>
<td>Valve damage/requiring surgery</td>
<td>11/7</td>
<td>0.07</td>
</tr>
<tr>
<td>Atrium-esophageal fistula</td>
<td>6</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>37</td>
<td>0.23</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>115</td>
<td>0.71</td>
</tr>
<tr>
<td>PV stenosis requiring intervention</td>
<td>48</td>
<td>0.29</td>
</tr>
<tr>
<td>Total</td>
<td>741</td>
<td>4.54</td>
</tr>
</tbody>
</table>

Supplemental Table 1: Major Complications in the Overall Population. (Reproduced with permission from Reference 28)
Supplemental Figure 1: Efficacy of AADs in patients with AF outcome presented as meta-analyzed proportion with 95% CIs, indicated with number of treatment arms and number of patients. (Reproduced with permission from Reference 7)
Supplemental Figure 2: Efficacy of AADs in patients with AF outcome presented as meta-analyzed proportion with 95% CIs, indicated with number of treatment arms and number of patients. (Reproduced with permission from Reference 7)
Supplemental Figure 3: Burden of Atrial Fibrillation and Proportion of Patients Who Were Free of Atrial Fibrillation during the 2-Year Study Period, According to Treatment Group. Shown are the burden of atrial fibrillation (upper graph) and the number of patients without atrial fibrillation (lower graph) in 7-day Holter-monitor recordings at baseline, at each follow-up visit, and cumulatively during follow-up. The mean rank (Mann–Whitney test) and P values for group comparisons of the burden of atrial fibrillation are shown at the bottom of the figure. (Reproduced with permission from Reference 10)