The burden of atrial fibrillation (AF) on Western countries healthcare systems is steadily increasing, with >2 million Americans and 4 million Europeans affected by this condition.1 It is by far the most common sustained arrhythmia encountered in clinical practice,2 with a striking impact on morbidity and mortality.3,4 With these premises, achieving a definite cure is highly desirable, as this would have profound social and economic implication. In patients with drug-refractory paroxysmal AF (PAF), multiple clinical trials have established the superiority of catheter ablation (CA) over further antiarrhythmic drug (AAD) therapy for the long-term maintenance of sinus rhythm, to improve quality of life, and reduce hospitalizations.5,6 Whether CA should be adopted as a first-line therapy is still a matter of controversy. Approximately 8 years ago, Verma and Natale7 released an article in Circulation defending the thesis that CA should be adopted as a first-line therapy for AF; in their support, they referenced the results of a pivotal randomized trial by the same authors (ie, Radiofrequency Ablation versus Antiarrhythmic drugs for the Treatment of symptomatic atrial fibrillation [RAFT]),8 together with additional considerations such as the mortality benefit of sinus rhythm maintenance,9–11 the ineffectiveness of AAD for the rhythm control of AF,12–14 and the significant risks associated with AAD therapy.15–17 In an antagonist article, Padanilam and Prystowsky18 defended the role of AAD, given the insufficient evidence supporting CA as a first-line therapy, together with the lack of knowledge on the long-term efficacy and risks of CA, the cost-effectiveness of this strategy, and the reproducibility of the results across different institutions and operators. Today, we think that sufficient evidence has been acquired.8,19–22 In the present article, we adopted a systematic review method to summarize the available evidence and give an opinion on the role of CA as a first-line therapy for PAF. Such an approach has been preferred to the more classical narrative review,7,18 to minimize the risk of subjective statements23 and base the conclusions on quantitative numbers rather than personal opinions.

Response by Hanley et al on p 746

Methods

We adapted a systematic review protocol developed by the Cochrane collaboration21 and previously published by our group.20 In brief, 2 trained investigators (P.S., L.D.B.) independently searched Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), BioMed

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Central, Cardiosource, clinicaltrials.gov, and ISI Web of Science (January 1970 to October 2013). Search keywords included atrial fibrillation AND, first line, catheter ablation, ablation, randomized, observational. No language restriction was used. Proceedings from the annual American Heart Association, American College of Cardiology, European Society of Cardiology, Heart Rhythm, and European meetings for the past 5 years were also manually searched. Web sites of American College of Cardiology, American Heart Association, and European Society of Cardiology were also screened for oral presentations and expert slide presentations. Two reviewers performed study selection. Citations initially selected by systematic search were first retrieved as a title and abstract and preliminarily screened. Potentially relevant reports were then retrieved as complete articles and assessed for compliance to inclusion criteria. Studies were included if they tested CA as a first-line therapy in patients with AF. First-line therapy was defined as treatment before any attempt with AAD. The end points of interest were freedom from recurrent AF/atrial tachycardia and total complications. Other important end points such as AF burden, quality of life measurements, and hospitalizations were not included because they were not consistently reported in the included studies. Outcomes were analyzed according to the Mantel–Haenszel model to compute individual odds ratios with pertinent 95% confidence intervals, and pooled summary effect estimate was calculated by means of a fixed-effect model as previously described.21 In case of statistical significance, a calculation of the pooled estimate of the number needed to treat (NNT) was obtained. Statistical level of significance was defined at a $P<0.05$ (2-tailed). Analyses were performed using the STATA 12.0 software package (Stata Corporation, College Station, TX).

### Search Results

The search permitted the retrieval of 5 studies fulfilling the systematic review inclusion criteria.1,8,19,20 Three studies had a prospective multicenter randomized design.8,15,20 Two studies had an observational design.19,22 The baseline characteristics and main outcomes of these studies are summarized in Tables 1 and 2.8,19–22

## Randomized Trials on CA as a First-Line Therapy for AF

The RAAFT trial was the first study to suggest the benefit of CA as a first-line therapy for AF.19 In this trial, 70 patients with symptomatic episodes of AF for ≥3 months (96% PAF; mean age, 54 years) were randomized to either CA or AAD therapy. The ablation protocol adopted in the RAAFT was consistent across the 4 participating institutions (1 in the United States, 1 in Germany, and 2 in Italy) and included pulmonary vein (PV) antrum isolation confirmed by recordings from a circular mapping catheter.19 In this early trial only nonirrigated tip ablation catheters (8 mm) were used. At the end of a 1-year follow-up, 63% of patients assigned to AAD therapy experienced ≥1 recurrence of symptomatic AF, as compared with 13% of those assigned to the PV antrum isolation arm. These figures accounted for 80% relative risk reduction with CA ($P<0.001$; Figure 1), with a corresponding NNT with CA to prevent 1 episode of recurrent AF at 1 year of 2. In addition, PV antrum isolation was associated with a significantly lower rate of hospitalization (9% versus 54%; $P<0.001$) and improved quality of life. It is important to emphasize that the benefit of CA shown in the RAAFT might even have been underestimated, given the high rate of crossover to CA in patients initially assigned to AAD (51%). Complications were also comparable between the 2 treatment groups (12.5% in the CA arm [2 patients with mild/moderate PV stenosis and 2 patients with bleeding complications] versus 11.5% in the AAD group [1 bleeding complication and 3 drug-induced bradycardia]; Figure 2). After the encouraging results of the RAAFT, 2 larger multicenter randomized trials on CA as a first-line therapy for AF have been reported.19,20 The Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial compared CA versus AAD therapy for the first-line therapy of symptomatic PAF.19 A total of 10 European institutions participated in the trial. At variance with the RAAFT, the ablation techniques adopted in the MANTRA-PAF were highly heterogeneous and varied from PV isolation guided by circular mapping catheter to circumferential PV ablation guided by 3-dimensional electroanatomic mapping system (CARTO, Biosense-Webster, Diamond Bar, CA); choice between different ablation methods was left to the discretion of the enrolling physician. The primary study end point was cumulative AF burden (symptomatic and asymptomatic) during 7-day Holter recordings after 3, 6, 12, 18, and 24 months of follow-up. Freedom from any AF after 24 months, quality of life and burden of symptomatic AF were included among the secondary end points. A total of 294 patients (mean age, 55 years) were included in the study and were randomized in a 1:1 fashion to either CA (N=146) or AAD (N=148).19 The trial failed to meet its primary end point, namely reduction of the cumulative burden of AF ≥2 years19; however, CA was still associated with lower rate of AF recurrence compared with AAD (15% versus 29%, respectively; $P=0.004$; Figure 1). The corresponding NNT with

### Table 1. Characteristics of Studies Evaluating Catheter Ablation as a First-Line Therapy for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>RAAFT8</th>
<th>MANTRA-PAF19</th>
<th>RAAFT-220</th>
<th>Tanner et al22</th>
<th>Namdar et al21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>2005</td>
<td>2011</td>
<td>2012</td>
<td>2011</td>
<td>2011</td>
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<tr>
<td>No. of patients</td>
<td>70</td>
<td>294</td>
<td>127</td>
<td>72</td>
<td>18</td>
</tr>
<tr>
<td>Randomized</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Design</td>
<td>CA vs AAD</td>
<td>CA vs AAD</td>
<td>CA vs AAD</td>
<td>First-line CA</td>
<td>First-line CA</td>
</tr>
<tr>
<td>Percentage of PAF</td>
<td>94%</td>
<td>100%</td>
<td>98%</td>
<td>74%</td>
<td>100%</td>
</tr>
<tr>
<td>CA approach</td>
<td>PVAI with 8-mm NIC</td>
<td>CPVA or PVI, OIC or 8-mm NIC</td>
<td>PVAI with OIC</td>
<td>PVI with OIC</td>
<td>PW with cryoballoon</td>
</tr>
<tr>
<td>Primary end point</td>
<td>AF recurrences</td>
<td>AF burden</td>
<td>AF recurrences</td>
<td>AF recurrences</td>
<td>AF recurrences</td>
</tr>
<tr>
<td>No. of institutions</td>
<td>4</td>
<td>10</td>
<td>16</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>12</td>
<td>24</td>
<td>24</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; CA, catheter ablation; CPVA, circumferential pulmonary vein ablation; MANTRA-PAF, Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation; NIC, nonirrigated ablation catheter; OIC, open-irrigated ablation catheter; PAF, paroxysmal atrial fibrillation; PV, pulmonary vein isolation; PVAI, pulmonary vein antrum isolation; and RAAFT, Radiofrequency Ablation versus Antiarrhythmic drugs as First-line Treatment of symptomatic atrial fibrillation.
The worse treatment effect in the MANTRA-PAF as compared with what reported in the RAAFT might be well explained by the adoption of obsolete ablation techniques in the MANTRA-PAF, with discretionary use of circumferential ablation without confirmation of PV isolation with a circular mapping catheter. The latter has been demonstrated inferior to PV isolation confirmed by a circular mapping catheter. Khaykin et al randomized 60 patients with drug-refractory AF to PV isolation or circumferential PV ablation; the study end point was long-term procedural success defined as the absence of atrial arrhythmias off AAD. The mean procedural time was comparable between the 2 approaches, although PV isolation was associated with longer fluoroscopy time. At a mean follow-up of 24±12 months, PV isolation was more likely to achieve control of atrial tachyarrhythmias off AADs (57% versus 27%; P=0.02). Karch et al conducted a randomized study on 100 patients comparing circumferential PV ablation and segmental PV isolation guided by a circular mapping catheter. In this study, PV isolation guided by circular mapping catheter was associated with shorter procedural time as compared with circumferential PV ablation (256±72 versus 284±86 minutes; P=0.02), although the fluoroscopy time with
a circular mapping–guided approach was confirmed longer (72±26 versus 45±21 minutes; P<0.01, respectively). At 6-month follow-up, 42% of patients allocated to circumferential PV ablation and 66% of those receiving PV isolation were free of atrial tachyarrhythmia episodes (P=0.02 for comparison). In conclusion, electroanatomic mapping–guided circumferential PV ablation seems unreliable in completely isolating the PVs and has been associated with worse long-term arrhythmia-free survival compared with PV isolation in direct comparison studies. An indirect analysis of treatment effects from randomized trials comparing CA with AAD therapy further confirms this notion (Figure 3).6,8,28–30 Accordingly, confirmation of PV isolation with a circular mapping catheter is endorsed by the most recent Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement on CA of AF.31 Also in the MANTRA-PAF, the CA arm had similar rate of complications compared with the AAD group (ie, 17% versus 15%; Figure 2). Among the most relevant complications occurring in the CA group, 2 stroke/transient ischemic attacks, 3 cardiac tamponades, and 1 perforation during the transseptal puncture were reported. In this regard, it is conceivable that such complications would have been minimized if state-of-the-art ablation strategies were consistently adopted in the trial, including performing procedures without therapeutic warfarin discontinuation32–34 and using intracardiac echocardiography to assist the transseptal puncture, catheter manipulation, and radiofrequency power titration (Figure 4).35,36 The relatively high rate of crossover to CA in patients initially assigned to AAD therapy (36% of patients allocated to AAD) might have further diluted the results as outcomes were analyzed according to the intention-to-treat principle. The recently completed first-line RAAFT-2 trial shares with the RAAFT similar inclusion criteria, end points, and ablation techniques, with the notable exception of the adoption of irrigated-tip ablation catheters.8,20 The results of the RAAFT-2 have been presented at the 2012 Scientific Sessions of the Heart Rhythm Society meeting.20 A total of 127 patients with symptomatic PAF were enrolled in 16 different institutions across the United States, Canada, and Europe. Patients were randomized in a 1:1 fashion to either CA or AAD. After 2-year follow-up, AF/atrial tachycardia recurred in 54.5% of the CA group compared with 72.1% of the AAD group (P=0.016 for comparison); the corresponding NNT with CA to prevent 1 episode of recurrent AF/atrial tachycardia was 6. Also in the RAAFT-2, the rate of crossover from AAD to CA was substantial (26%).

Observational Studies on CA as First-Line Therapy for AF

Two observational studies, both conducted in Europe, evaluated the role of CA as a first-line therapy for AF.21,22 Tanner et al22 reported the outcomes of first-line therapy with CA in a consecutive series of patients...
patients with symptomatic PAF or persistent AF. During an 8-year time frame the authors performed CA as first-line approach in 72 of 434 (17%) patients, predominantly driven by patient preference. PV isolation guided by recordings from a circular mapping catheter was the ablation approach adopted in this study. The baseline characteristics and outcomes of included patients were compared with those of the remaining 362 patients undergoing CA as a second-line therapy (after failure of ≥2 AADs). Baseline clinical characteristics were comparable between the 2 patient populations. After 1-year follow-up, 78% of patients in the first-line CA group achieved freedom from recurrent AF (Figure 1) compared with 64% of patients undergoing CA of drug-refractory AF (P=0.03). The overall complication rate in the first-line CA group was 8% (P=0.58 for comparison with CA of drug-refractory AF; Figure 2). In an observational study including data from 3 institutions, Namdar et al43 performed cryoballoon PV isolation as a first-line therapy in 18 consecutive patients (mean age, 44 years) with PAF. After a mean follow-up of 14±9 months, 89% of patients were free from recurrent AF (Figure 1). Procedural-related complications occurred in 2 (11%) patients (Figure 2) and consisted of 1 case of transient phrenic nerve palsy and 1 vascular pseudoaneurysm requiring surgical correction.

Quantitative Data Synthesis

Thus far, a total of 578 patients (96% with PAF; mean age: range, 44–58 years) have been included in studies evaluating CA as a first-line therapy for AF. The large majority of patients enrolled in these studies had no or only minimal structural heart disease. The ablation techniques adopted were heterogeneous and included PV isolation confirmed by a circular mapping catheter, circumferential PV ablation, and cryoballoon ablation. A total of 34 different institutions across the United States, Canada, and Europe have participated in these studies. After a mean follow-up of 17 months (range, 12–24 months), the pooled success rate of CA was 67% compared with 48% in the AAD group (odds ratio, 0.36; 95% confidence interval, 0.24–0.54; P <0.001), accounting for a NNT with CA to prevent 1 episode of recurrent AF of 5 (Figure 1). The pooled complication rate in the CA group was also similar to that reported in the AADs group (12.9% versus 15.6%, respectively; odds ratio, 0.89; 95% confidence interval, 0.53–1.45; P=0.612; Figure 2). As mentioned, the number of complications in the CA arm could have been even lower if state-of-the-art ablation techniques were consistently adopted across the studies. In conclusion, a pooled analysis of the available evidence shows that, in relatively young patients with PAF and minimal structural heart disease, first-line CA is more effective than AAD in achieving long-term freedom from recurrent arrhythmia, with comparable rates of complications. Such benefits were reproducible across different institutions, operators, and types of ablation approaches.

Cost-Effectiveness of CA as a First-Line Therapy for AF

Based on the results of the first RAAFT trial, Khaykin et al45 evaluated the cost-effectiveness of CA as a first-line therapy for AF. The analysis was conducted from the perspective of a publicly funded healthcare payer, using Canadian healthcare cost estimates. The authors showed that, despite the initial higher costs associated with CA, the significantly higher rate of AF recurrences in the AAD arm and higher hospitalization rates counterbalanced the initial costs of CA. After 2 years of follow-up, CA was cost neutral (Figure 5). The analysis by Khaykin et al45 might even underestimate the cost-effectiveness of CA as a first-line therapy in current cohorts of AF patients. For instance, in the RAAFT study, warfarin was discontinued before the ablation procedure, and bridging with low-molecular-weight anti-
heparin plus preprocedural transesophageal echocardiogram was consistently adopted. This resulted in an additional $106,510 costs. Current populations of AF patients typically undergo ablation without discontinuation of therapeutic warfarin, which allows to avoid bridging with heparin and preprocedural transesophageal echocardiogram. With these premises, an updated analysis taking into account the results of the MANTRA-PAF and RAAFT-2 would be warranted to evaluate the cost-effectiveness of first-line CA in current cohorts of patients.

Limitations
Patients enrolled in studies evaluating the role of CA as a first-line therapy for PAF were relatively young with minimal structural heart disease, which represent the minority of patients with AF (Figure 6). Hence, it would be inappropriate to generalize the results of our pooled analysis also to elderly patients with AF or to subjects with significant structural heart disease. The follow-up duration was also relatively short (mean, 17 months) and whether the benefit of first-line CA is maintained at long-term follow-up warrants further investigation. In this regard, scant long-term data exist also on the safety and efficacy of AADs; in a recent analysis from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial, a significantly lower risk of mortality and cardiovascular hospitalizations during a 5-year follow-up was reported in the rate-control arm compared with AADs (ie, amiodarone, sotalol, or class Ic agents). Whether CA is associated with better long-term safety profile compared with AADs warrants further investigation. Finally, detailed data on complications and the impact on individual patients were not retrievable, and there was some heterogeneity in the efficacy of CA although the differences in outcomes were not significantly different between the included studies. However, high-volume institutions and experienced operators participated in the studies, evaluating CA as a first-line treatment for AF. Whether the results can be generalized to less experienced operators or lower volume centers warrants further investigation.

Conclusions
In relatively young patients with PAF and minimal structural heart disease, a first-line therapy with CA is more effective than AAD for the long-term maintenance of sinus rhythm and is associated with comparable rates of adverse events. These results were consistently reproducible among different institutions, multiple operators, and different ablation approaches. A preliminary analysis based on the results of the first RAAFT trial suggests that first-line CA has also a better cost-effectiveness profile. These results support the notion that AADs are outmoded and CA should be the first-line option for PAF patients with similar characteristics to those enrolled in the studies above, namely relatively young patients with minimal structural heart disease. Whether such benefits extend also to elderly patients with PAF, to patients with associated structural heart disease, or non-PAF warrant further investigations.

Disclosures
Dr Natale has received consultant fees or honoraria from Biosense-Webster, Boston Scientific, Medtronic, Biotronik, and LifeWatch. Dr Di Biase is a consultant for Hansen Medical, Biosense Webster, and St Jude Medical and has received speaker honoraria/travel from Biotronik, EpiEP, and Atricure. The other author reports no conflicts.

References


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

Colleen M. Hanley, MD, Douglas Esberg, MD, FACC, FHRS, Peter R. Kowey, MD, FAHA, FHRS

Santangeli, Di Biase, and Natale assert that sufficient evidence has been acquired to adopt catheter ablation (CA) of atrial fibrillation (AF) as first-line therapy. We do not think that the data they quoted are adequate to justify a wholesale adoption of this technique in treatment of AF. Data Santangeli et al performed a systematic review to support their argument. Because there has never been a properly sized single trial, they identified 5 small studies (1 with 18 patients) with a mean follow-up of 17 months. How this qualifies for long-term, robust experience is not comprehensible when studying a disease that lasts decades. They reported a pooled success rate of CA of 67%, compared with 48% in the antiarrhythmic drug, and state that the outcomes are reproducible across different institutions and operators. This is hardly the case. First of all, there has been a remarkable homogeneity on treatment results across studies (including those they quoted) for every category of AF ablation with a strong publication bias. Most importantly, we have no data from low-volume centers, particularly disturbing because recent registry data suggest that >70% of AF ablations in the United States are performed at hospitals that do less than a procedure a week. One of us (P.R.K.) has advocated for a national registry to understand the outcomes and safety of CA across all centers without success. Although Santangeli et al decry the toxicity of antiarrhythmic drugs, the pooled complication rate in their series was similar between the groups. We would also point out that although the numbers were similar, the severity of the complications was different, which is why many patients and clinicians prefer a trial of antiarrhythmic drug before proceeding to CA. The authors contend that after 2 years, the cost of CA versus antiarrhythmic drug is neutral. They do not, however, take into account the need for multiple procedures in a sizable percentage of patients nor do they know what will happen as time passes. The emerging data from 5-year follow-up have not been entirely favorable. Assuming that patients are cured of a disease that we know to be progressive and inexorable is simply not warranted. Finally, as Santangeli et al admit, the patients included in their studies were young and had normal hearts. This represents a minority of the patients encountered in clinical practice. The tools to select low-risk patients who might benefit from an early invasive approach are crude. All of us who do clinical trials should pay heed to the renal denervation experience. It was not until the AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) an assessment of individual antiarrhythmic drug therapies compared with rate control with propensity score-matched analyses. J Am Coll Cardiol. 2011;58:1975–1985.

Key Words: atrial fibrillation • catheter ablation

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: Pro
Pasquale Santangeli, Luigi Di Biase and Andrea Natale

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