Multielectrode Pulmonary Vein Isolation Versus Single Tip Wide Area Catheter Ablation for Paroxysmal Atrial Fibrillation
A Multinational Multicenter Randomized Clinical Trial

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Background—Single-shot ablation techniques may facilitate safe and simple pulmonary vein isolation to treat paroxysmal atrial fibrillation. Multielectrode pulmonary vein isolation versus single tip wide area catheter ablation-paroxysmal atrial fibrillation is the first multinational, multicenter, prospective, noninferiority randomized clinical trial comparing multielectrode-phased radiofrequency ablation (MEA) to standard focal irrigated radiofrequency ablation (STA) using 3-dimensional navigation.

Methods and Results—Patients with paroxysmal atrial fibrillation were randomized to MEA (61 patients) or STA (59 patients). Preprocedure transesophageal echocardiogram and computed tomography/magnetic resonance imaging (also 6-month postprocedure) were performed. Mean age was 57 years, 25% female sex, BMI was 28, CHA2DS2–VASc score was 0 to 1 in 82%, 8% had previous right atrial ablation, whereas all had at least 1 antiarrhythmic drug failure. The MEA group had significantly shorter mean procedure time (96±36 versus 166±46 minutes, \(P<0.001\)) and fluoroscopy time (23±9 versus 27±9 minutes, \(P=0.023\)). The total radiofrequency energy duration was 22±8 minutes for MEA versus 36±13 minutes for STA (\(P<0.001\)) with confirmed pulmonary vein isolation in all patients. Hospital admission was 1 day in both groups, without major adverse events either during the procedure or during 30-day follow-up. Two patients in the STA group had 1 PV with asymptomatic narrowing >50%. Freedom of atrial fibrillation for MEA and STA was 86.4% and 89.7% at 6 months, dropping to 76.3% and 81.0% at 12 months.

Conclusions—In this multicenter, randomized clinical trial, MEA and STA had similar rates of single-procedure acute pulmonary vein isolation without serious adverse events in the first 30 days. MEA had slightly lower long-term arrhythmia freedom, but showed marked and significantly shorter procedure, fluoroscopy, and radiofrequency energy times.

Clinical Trial Registration—URL: www.clinicaltrials.gov; Unique identifier: NCT01696136.

Key Words: atrial fibrillation • catheter ablation • fluoroscopy • freedom • pulmonary vein

Catheter ablation (CA) is an accepted treatment option for symptomatic atrial fibrillation (AF). Historically, CA has been performed with a point-by-point technique, using standard focal radiofrequency catheters and 3-dimensional (3D) navigation systems, with a procedural end point of electric pulmonary vein isolation (PVI). However, this CA approach requires advanced training and operator skill, has a relatively long procedure time, and is associated with a risk of complications. Single-shot devices for PVI have been developed to address these limitations, including the cryoballoon, laser balloon, and multielectrode radiofrequency systems. Multiple single-center and nonrandomized studies indicate that the multielectrode, duty-cycled, phased radiofrequency ablation system (Pulmonary Vein Ablation Catheter [PVAC]; Medtronic, Minneapolis, MN) may have a similar safety and efficacy profile as the standard approach, but with reduced procedure and fluoroscopy. Herein, we report the results of the first multinational, multicenter, prospective, randomized, study to compare procedural parameters, acute safety, and AF monitoring of multielectrode ablation (MEA) versus the standard CA technique (MYSTIC-PAF; NCT01696136).

See Editorial by Ernst
WHAT IS KNOWN

- Pulmonary vein isolation with irrigated radiofrequency energy through a single-tip ablation catheter guided by 3-dimensional navigation is the standard treatment for patients with drug-refractory paroxysmal atrial fibrillation.
- This procedure requires a high operator skill and remains time consuming and is not without complications.
- New techniques, such as a multielectrode array using phased radiofrequency energy, specifically and anatomically designed for pulmonary vein isolation may offer benefits both for efficacy and safety.

WHAT THE STUDY ADDS

- In this randomized multicenter clinical trial, comparing multielectrode-phased radiofrequency to standard single-tip irrigated radiofrequency ablation, both techniques showed a high efficacy to treat paroxysmal atrial fibrillation, although single-tip ablation was marginally better.
- There were no procedural complications with either technique, but a few cases of pulmonary vein stenosis were observed after single-tip ablation.
- Multielectrode-phased radiofrequency ablation significantly reduced the procedure time by more than an hour, making it an attractive technique to facilitate easier pulmonary vein isolation for more patients.

Methods

Multielectrode pulmonary vein isolation versus single tip wide area catheter ablation-paroxysmal atrial fibrillation (MYSTIC-PAF) was a prospective, randomized, multicenter, multinational, noninferiority study to evaluate the safety and effectiveness of MEA versus standard focal CA (STA) for treatment of symptomatic PAF. The study was conducted according to good clinical practice and the Declaration of Helsinki, and listed on www.clinicaltrials.gov. All patients gave written consent, with approval by each center’s Ethics Committee. Serious adverse events were reported to Ethics Committee’s and Regulatory Agencies according to local regulation/policy.

A total of 120 patients eligible for CA according to the ESC guidelines were entered from study start in January 2011 to end of follow-up in July 2013. Patients aged 18 to 70 years, with a history of symptomatic PAF documented in the past 12 months, and refractory to ≥1 antiarrhythmic drug (AAD) could participate in the trial. Patients were excluded if any of the following were present: significant structural heart disease (including previous cardiac surgery other than coronary artery bypass grafting), heart failure of New York Heart Association class ≥2, left ventricular ejection fraction <40%, left atrial diameter >50 mm, ongoing myocardial ischemia, myocardial infarction within the previous 3 months, valvular disease ≥grade II, congenital heart disease (not including atrial septal defect or patent foramen ovale without a right to left shunt), previous atrial septal defect or patent foramen ovale closure, hypertrophic cardiomyopathy >15 mm, pulmonary hypertension (PA pressure >50 mmHg), previous LA ablation for AF, any ablation within the previous 3 months, cardioversion <7 days before CA, enrollment in any other ongoing arrhythmia study protocol, any ventricular tachycardia with treatment that might interfere with the study, active infection or sepsis, history of cerebrovascular disease (including stroke or transient ischemic attack), pregnancy or lactation, untreated contrast media allergy, any diagnosis of AF secondary to reversible or noncardiovascular causes, history of blood clotting (bleeding or thrombotic) abnormalities, known sensitivities to heparin or warfarin, severe chronic obstructive pulmonary disease (forced expiratory volume 1 <1), severe comorbidity, or poor general physical/mental health.

Randomization was performed via a web-based process at the coordinating center, with additional randomization to balance inclusion across participating centers. To minimize bias, all centers were asked to enroll a similar number of patients, and only operators experienced (>50 cases) with both techniques could perform study CA procedures.

Preablation procedures for all patients followed standard hospital practice, including medical history and physical examination, 12-lead ECG, CHADS, and CHA2DS2-VASc scoring, transthoracic and transesophageal echocardiogram within 1 week before procedure (to exclude left atrial thrombus), and magnetic resonance imaging (MRI) or computed tomography for measurement of PV diameters.

Procedures

Patients were randomized into 1 of 2 treatment arms, MEA with the phased radiofrequency system or standard focal irrigated radiofrequency ablation with PVI as a procedural end point. For STA, any model of irrigated focal catheters was allowed, with power and temperature settings according to operator’s preference and manufacturer’s instructions. PVI could be verified with the PVC or a standard decapolar circular mapping catheter. All procedures were performed under intravenous heparin, with target activated clotting time of >250 s during the procedure. Patients maintained continuous vitamin K antagonist with therapeutic international normalized ratio (INR) levels or were bridged with low-molecular weight heparin if INR was subtherapeutic. LA access was obtained either through a patent foramen ovale or standard transseptal puncture per the Brockenhour technique. Biplane or monoplane fluoroscopy was used to visualize catheter introduction and manipulation. A standard coronary sinus catheter was used for pacing maneuvers to verify PVI and pacing in case of bradycardia. Postprocedural patient management was per hospital standard. All patients (re)started vitamin K antagonist with bridging low-molecular weight heparin until INR >2.0 and for at least the first 3 months after the procedure.

MEA Procedure

A 25-mm diameter, decapolar catheter with platinum 3-mm electrodes with 3-mm spacing (PVC; Ablation Frontiers/Medtronic Inc, Carlsbad CA) was used with the GENius Generator version 14 (Ablation Frontiers/Medtronic Inc). This procedure has been explained in detail elsewhere. Briefly, the decapolar multielectrode catheter is positioned around each PV, with a guidewire placed within the target PV for positioning. Radiofrequency applications are then delivered during 60 s, with a target temperature of 60°C, and maximum power output of 8 W or 9 W (in 4:1 and 2:1 energy modes, respectively). Electrodes failing to reach target temperature, or with power <3 W were deselected. To avoid overheating, electrode 1 or 10 were disabled if within close proximity.

STA Procedure

Standard open irrigated catheters of any brand with a 3.5- to 4.0-mm tip were used. Power was set a 43°C with a maximum output of 30 W, with a flow of 17 mL/min. Applications lasted 60 s in case of point-by-point ablation or were continuous in case of a dragging technique. Nonfluoroscopic catheter visualization was performed with CARTO (Biosense Webster, Diamond Bar, CA) or NavX (St. Jude, Minneapolis, MN) by constructing a 3D electroanatomic map...
of the LA and PVs. The PVs were mapped by using any brand of a decapolar circular mapping catheter.

Follow-Up
Patients were screened preprocedure, followed during the procedure, post procedure, at hospital discharge, and follow-up at 3, 6, 12 months, as well as any unscheduled visit. The follow-up was performed at each participating centers outpatient clinic, and included a 12-lead ECG and 48-hour Holter, as well as an AF Symptom Severity Quality of Life assessment. In symptomatic patients with a normal ECG and Holter, event recorders were used to record arrhythmias. At the 3-month visit, all AADs were stopped (except amiodarone that was stopped at 1 month post procedure). At the 6-month visit, MRI or computed tomographic scanning was repeated for the purposes of measuring asymptomatic PV narrowing, defined as a >50% reduction in diameter compared with preprocedure imaging. Radiologists at participating centers conducted the PVS image analysis. All follow-ups were entered into a web-based eCRF (electronic case report form) by participating centers, and the R&D Department of the coordinating center conducted periodic monitoring visits. A centralized Core Laboratory analyzed all Holters from the 3, 6, and 12 months visits.

Statistical Analysis
The primary hypothesis was that MEA is not inferior to STA for treatment of patients with symptomatic PAF. The trial was designed as a noninferiority trial, with noninferiority margin set at 0.15, power of ≥0.80 for chronic efficacy (60% to 70%), and sample size required to test the hypothesis of N=114. The acute primary effectiveness end point was isolation of all PVs, defined as entrance or exit block documented with either the PVAC or a decapolar circular mapping catheter. The chronic effectiveness end point was the absence of any LA arrhythmia lasting >60 s, off all class I and III AADs from the blanking period at 3 to 12 months, after a single ablation procedure, using Westlake–Schuirmann test for analysis of proportions in noninferiority testing. For the analysis of the repeated measures of the AF Symptom Severity Score, we used a linear mixed model with baseline AF Symptom Severity Score treated as covariate to compute the F value for the treatment group by time interaction. The primary acute safety end point was a composite of major complications occurring within 30 days of the ablation procedure. Major complications included but were not limited to: cerebrovascular accident, major bleeding requiring surgical intervention, cardiac tamponade, PV stenosis, myocardial infarction, diaphragmatic paresis/paralysis, atrioesophageal fistula, or other major cardiac or neurological event not mentioned that required intervention to prevent death.

Results

Patient Characteristics
A total of 120 patients were included in the trial, 61 patients to MEA and 59 to STA, with no difference in baseline criteria between groups (Table 1). Mean age was 57 years and 25% of patients were female, mean BMI was 28, LA diameter was 41 mm, left ventricular ejection fraction >0.40 in all and >0.55 in 77%. The New York Heart Association class was 0 to 1 in 95% of patients, CHA2DS2–VASc score was 0 to 1 in 83%, whereas all had at least 1 AAD failure and 48% had ≥2, and 8 had a previous ablation for right atrial flutter. One patient randomized to STA was inadvertently treated with PVAC and was analyzed in the PVAC group as on-treatment. Two patients were classified as New York Heart Association 3 but were allowed in the study in the absence of structural heart disease. All patients had PAF documented within 6 months before the procedure. All patients were symptomatic, most commonly with palpitations and dizziness, fatigue, shortness of breath, chest pain, and less frequently syncope.

Procedure and Follow-Up to 1 Year
All patients underwent a complete index procedure, with most (78%) presenting in SR on the procedure day (Table 2). MEA procedures had significantly shorter total procedure (96±36

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Multielectrode Ablation (MEA); N=61 (51%)</th>
<th>Standard Focal Ablation (STA); N=59 (49%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>56.1 (8.7)</td>
<td>56.9 (8.9)</td>
<td>119</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>48 (79%)</td>
<td>42 (72%)</td>
<td>120</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.8 (2.9)</td>
<td>27.1 (4.0)</td>
<td>119</td>
</tr>
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<td>Previous atrial flutter*</td>
<td>4 (7%)</td>
<td>6 (10%)</td>
<td>119</td>
</tr>
<tr>
<td>History of AF (mo), median</td>
<td>33 (7–66)</td>
<td>14 (4–57)</td>
<td>114</td>
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<tr>
<td>Failed AADs, median†</td>
<td>2 (1–2)</td>
<td>1 (1–2)</td>
<td>115</td>
</tr>
<tr>
<td>CHA2DS2–VASc score, mean (SD)</td>
<td>0.63 (0.76)</td>
<td>0.96 (0.87)</td>
<td>117</td>
</tr>
<tr>
<td>LA diameter, mm, mean (SD)</td>
<td>41.2 (5.63)</td>
<td>39.8 (5.62)</td>
<td>103</td>
</tr>
<tr>
<td>LV ejection fraction, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%–55%</td>
<td>14 (25%)</td>
<td>11 (21%)</td>
<td>108</td>
</tr>
<tr>
<td>&gt;55%</td>
<td>42 (75%)</td>
<td>41 (79%)</td>
<td></td>
</tr>
<tr>
<td>AF symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>51 (84%)</td>
<td>52 (88%)</td>
<td>120</td>
</tr>
<tr>
<td>Dizziness</td>
<td>32 (53%)</td>
<td>34 (58%)</td>
<td>120</td>
</tr>
<tr>
<td>Near syncope</td>
<td>12 (20%)</td>
<td>21 (36%)</td>
<td>120</td>
</tr>
<tr>
<td>Syncope</td>
<td>4 (7%)</td>
<td>6 (10%)</td>
<td>120</td>
</tr>
<tr>
<td>Weakness</td>
<td>31 (51%)</td>
<td>33 (56%)</td>
<td>120</td>
</tr>
<tr>
<td>Fatigue</td>
<td>43 (71%)</td>
<td>44 (75%)</td>
<td>120</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>24 (39%)</td>
<td>30 (51%)</td>
<td>120</td>
</tr>
<tr>
<td>Chest pain</td>
<td>15 (25%)</td>
<td>14 (24%)</td>
<td>120</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (10%)</td>
<td>7 (12%)</td>
<td>119</td>
</tr>
<tr>
<td>1</td>
<td>52 (85%)</td>
<td>46 (79%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Rhythm</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sinus rhythm</td>
<td>47 (77%)</td>
<td>47 (80%)</td>
<td>120</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (12%)</td>
<td>8 (14%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (12%)</td>
<td>4 (7%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are displayed as: Categorical variables, N (%); Normally distributed variables, mean (SD); Non-normally distributed variables, median (25th–75th percentile). *P values only indicate precision; AF indicates atrial fibrillation; LA, left artery; LV, left ventricle; and NYHA, New York Heart Association. †Antiarrhythmic drugs (AAD) include β-blockers, digoxin, verapamil, and diltiazem.
versus 166±46 minutes, P<0.001), fluoroscopy (23±9 versus 27±9 minutes, P=0.023), and radiofrequency time (22±8 versus 166±46 minutes, P<0.001), but similar time to transseptal access (18±10 versus 20±11 minutes, P=0.217) with all times given as mean with SD. PVI was achieved for all veins without the need for other catheters or techniques; thus, the primary acute efficacy end point was exactly the same for both groups. In both groups, for the primary safe end point there were no major adverse events reported such as stroke, tamponade, or major bleeding, either during the procedure or during the first 30 days after the procedure. Length of hospital stay was equal for MEA and STA in both groups (1 day, 77% versus 71%; 2 days 22% versus 21%; and >2 days 2%–5.3%; Fisher Exact test, P=0.626).

After the 3-month blanking period and discontinuation of AAD, during the rhythm follow-up from month 3 to month 12, the ablation efficacy outcome was analyzed in 117 of 120 patients; 3 patients were excluded from the analysis because of a second ablation within the blanking period, which was considered an essential protocol violation. Freedom of LA arrhythmia without AADs at 6 months was achieved in 51 of 59 patients (86.4%) of the MEA group versus 52 of 58 patients (91.4%) in the STA group (risk difference, 3.2%; 95% confidence interval, −9.2% to +15.8%; Westlake–Schuirmann test, P=0.626). At 12 months of follow-up, freedom of LA arrhythmia without AADs was 45 of 59 patients (76.3%) in the MEA group versus 47 of 58 patients (80.0%) in the STA group (risk difference, 4.7%; 95% confidence interval, −9.1% to +22.4%; Westlake–Schuirmann test, P=0.006). As the confidence interval exceeded the upper bound of the noninferiority margin, the primary efficacy end point was not satisfied.

Computed tomography/MRI was performed pre- and post ablation in 110 of 120 patients to evaluate the potential for PV narrowing. A PV diameter reduction of >50% was observed in 1 vein each in 2 (3.4%) patients in the STA group; had a left superior PV reduction from 9 to 3 mm (−67%), and right superior PV reduction from 10 to 2 mm (−80%). There was no apparent clue to the reason for the PV stenosis in these patients. The AF Symptom Severity Score (Table 3) showed a significant Quality of Life improvement of around 50% after ablation during follow-up (P<0.0001), which was no different between MEA versus STA (P=0.7566).

### Discussion

In this multicenter, randomized clinical trial, MEA and STA had the same rate of single-procedure acute PVI without serious adverse events in the first 30 days. MEA had only a slightly lower (4.7%) arrhythmia freedom at 1 year, but had a procedure time that was more than an hour shorter, as well as significantly shorter fluoroscopy, and radiofrequency energy times.

### Effectiveness of Ablation Technology

The STA is the most common approach for PVI in patients that undergo AF ablation in Europe. Electrophysiologists are trained and familiar with this technology as the workhorse for ablation of all types of arrhythmias. During the past 5 years, the so-called single-shot devices, including balloon-based or multielectrode designs, have become a viable and widely used alternative. The single-procedure results in MYSTIC-PAF for both technologies are similar to other reports in the literature. Up to 80% 1-year single-procedure efficacy is favorable for both techniques. There is a trend toward longer follow-up of 2 to 5 years using more intense monitoring, such as continuous implantable loop recorders. For this trial, which was designed in 2010, multiple 48-hour Holter recordings were used during a 1-year follow-up period, which is in line with the HRS Expert Consensus recommendations. The study was designed to compare 2 treatment strategies. The finding that MEA and STA have similar efficacy seems to be a valid conclusion in that respect.

Several studies have compared the safety, efficacy, and procedural parameters of MEA versus STA, but primarily consist of parallel registries or historical control groups. Among 3 randomized studies, only 1 was a multicenter study. Bulava et al showed in 102 patients, that MEA had similar freedom of AF at follow-up compared with STA using CARTO (77% versus 71%, P=0.8), but significantly shorter procedure and fluoroscopy times (107±31 minutes versus 118±37 minutes, P=0.003).

### Table 2. Procedural Outcome Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Multielectrode Ablation (MEA); N=61</th>
<th>Standard Focal Ablation (STA); N=59</th>
<th>P Value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, venous access to catheters out</td>
<td>96 (36)*</td>
<td>166 (46)*</td>
<td>&lt;0.001*</td>
<td>119*</td>
</tr>
<tr>
<td>Time, venous access to transseptal (min)</td>
<td>18 (10)</td>
<td>20 (11)</td>
<td>0.192</td>
<td>118</td>
</tr>
<tr>
<td>Fluoroscopy duration (min)</td>
<td>23 (9)*</td>
<td>27 (9)*</td>
<td>0.023*</td>
<td>120*</td>
</tr>
<tr>
<td>RF duration (min)</td>
<td>22 (8)*</td>
<td>36 (13)*</td>
<td>&lt;0.001*</td>
<td>101*</td>
</tr>
<tr>
<td>Maximum RF ablation temperature (°C)</td>
<td>58 (12)*</td>
<td>44 (6)*</td>
<td>&lt;0.001*</td>
<td>108*</td>
</tr>
<tr>
<td>RF applications (N)</td>
<td>26 (21)*</td>
<td>71 (35)*</td>
<td>&lt;0.001*</td>
<td>114*</td>
</tr>
<tr>
<td>Max RF ablation power (W)</td>
<td>10 (5)*</td>
<td>33 (4)*</td>
<td>&lt;0.001*</td>
<td>108*</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>1 (0)</td>
<td>1 (1)</td>
<td>0.271</td>
<td>117</td>
</tr>
</tbody>
</table>

Data are displayed as mean (SD) using Student t test. RF indicates radiofrequency.

### Table 3. AF Symptom Severity Score

<table>
<thead>
<tr>
<th>AF Symptom Severity Score Time Point</th>
<th>Multielectrode Ablation (MEA); N=59</th>
<th>Standard Focal Ablation (STA); N=58</th>
<th>P Value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12.2 (4.2)</td>
<td>13.2 (3.9)</td>
<td>0.181</td>
<td>113</td>
</tr>
<tr>
<td>Mo 3</td>
<td>7.4 (3.4)</td>
<td>7.7 (4.3)</td>
<td>0.717</td>
<td>114</td>
</tr>
<tr>
<td>Mo 6</td>
<td>6.9 (2.7)</td>
<td>7.0 (3.2)</td>
<td>0.872</td>
<td>107</td>
</tr>
<tr>
<td>Mo 12</td>
<td>6.5 (2.6)</td>
<td>6.6 (3.5)</td>
<td>0.819</td>
<td>107</td>
</tr>
</tbody>
</table>

P<0.83 for difference between MEA and STA using linear mixed model. P<0.01 for change from baseline for both the groups.
208±46 minutes, P<0.0001 and 16±5 minutes versus 28±8 minutes, P<0.0001, respectively). Bittner et al12 in 80 patients showed similar shorter PVAC procedure times (171±40 versus 224±27 minutes, P<0.001; 26±8 versus 35±9 minutes, P<0.001, respectively), also with similar efficacy (72% versus 68%, P=ns). In neither of the trials, serious procedural complications were seen. Both trials were single-center efforts with a mean follow-up slightly longer than 6 months, studied a mixed population of paroxysmal to persistent AF, and were underpowered to detect meaningful differences in efficacy. More recently, McCready et al13 published the first multicenter randomized trial of MEA versus STA with 1-year follow-up in 188 patients with PAF, performed in UK based centers. After 6 months, the freedom of AF was 78% versus 77%, declining to 60% versus 56% (P=ns) after 12 months follow-up, whereas procedure and fluoroscopy times were less disparate but still shorter for PVAC (140±43 versus 167±42 minutes P=0.0001, fluoroscopy 35±16 versus 42±20 minutes P=0.05). Our multicenter randomized clinical trial data are in line with the results of registries and other randomized clinical trial showing no meaningful efficacy difference between MEA and STA with iRF. The 12 months efficacy data in this study are higher for both technologies than in the article by McCready et al,13 which may be because of evolution of the PVAC technology or patient selection because the rhythm follow-up strategy with Holter and event recording was similar. The procedure and fluoroscopy times in the MYSTIC trial are impressively shorter for PVAC than STA with iRF, in line with the other trials and regardless of whether CARTO or NavX was used. Of note, in the MYSTIC trial, procedure and fluoroscopy times are in general significantly shorter compared with the other randomized clinical trial studies. This may be because of operator experience and evolution of the technology. It may seem strange that fluoroscopy times should be longer when STA procedures are guided by nonfluoroscopic mapping systems, but this pattern is seen invariably when comparing both techniques. Apparently, the construction of a 3D map of the LA and PVs, and catheter manipulation during the ablation are still time consuming and still require visual confirmation with fluoroscopy by many operators.

Safety

In the current trial, there were no procedural complications observed for either MEA or STA, in line with the randomized clinical trials by Bulava et al11 and Bittner et al12 but in contrast to McCready et al,13 who observed several tamponade cases in the STA group, which is a known risk of AF ablation. Avoiding this complication is one rationale for using novel contact-force sensing during CA, which provides feedback to users to avoid high pressures, especially in vulnerable or previously ablated areas. However, in the MEA group, McCready et al13 observed 2 strokes (2%). The reported incidence of stroke after AF ablation varies from 0.5% to 1.0%.

Mulder et al14 reported a 0.3% stroke rate in 663 patients treated with phased radiofrequency in a single-center registry. In a 2700 patient survey of the MEA system, Scharf et al10 report a stroke/transient ischemic attack rate of 1.1% for phased radiofrequency, when compared with 1.0% in the World Wide Survey for regular radiofrequency by Cappato et al.17 There may be several explanations for stroke in the study by McCready et al.13 In their study, most patients discontinued vitamin K antagonists and were bridged with unfractionated heparin before the procedure. Recently, the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) trial by Di Biase et al18 showed that bridging is associated with a higher stroke risk. Another factor in the study by McCready et al13 was use of the version 11 GENius generator. This version was discovered to carry a potential risk of underestimating actual tissue temperature, resulting in higher power output and overheating, which may cause thrombus or char formation with embolization to the brain. In the MYSTIC trial, version 14.4 of the Genius generator was used, which mitigates overshooting power output and the associated risk of overheating.

Another factor of influence may be the evolution of the use of the MEA system. In 2010, Gaita et al19 showed that asymptomatic cerebral embolism (ACE) in 11% of patients accompanied AF ablation. Subsequent registries20,21 showed that the ACE rate seemed to be higher for PVAC than for focal irrigated radiofrequency and cryoballoon ablation. Further investigation by Haines et al22 demonstrated that the root cause for embolism was electrode overheating, which was predominantly found when electrodes 1 and 10 were in close proximity during ablation. In the Evaluation and Reduction of Asymptomatic Cerebral Embolism (ERACE) study, systematic disconnection of either electrode 1 or 10, in combination with uninterrupted vitamin K antagonist,23,24 target procedural INR>2.0, and activated clotting time >350 s, demonstrated a low ACE rate of 1.7%.25 This best practice strategy was already adopted early on in the MYSTIC trial as 3 of the 4 study centers also participated in ERACE. This may have lowered the potential risk for ACE and stroke in the current trial, although diffusion-weighted MRI testing was not part of this study, which had commenced in January 2011 before ACE data having increased importance. In 2014, the novel PVAC GOLD design was introduced, which eliminates electrode 10 and uses gold electrode material instead of platinum. This increases thermal conductivity by ~4×, resulting in increased electrode cooling. PVAC GOLD was used in the PRECISION GOLD trial, a study similar to ERACE, and similarly had a low ACE rate (2.1%).26

One of the early complications associated with STA ablation was PV stenosis, which was attributed to high-radiofrequency power delivery within the tubular portion of the PV. As a result, wider area ablation strategies were pursued to avoid ablation within the PV. The MEA system has been reported to have PV stenosis rated ranging from 0% to 5%, depending on the definition used.27,28 In the current trial, patients underwent computed tomographic or MRI imaging before and 6 months after procedure to assess the potential for asymptomatic PV narrowing. Significant PV narrowing (>50%) was observed in only in 2 patients in the STA group. This may be explained by the investigators experience with both MEA and STA, and knowledge of maneuvers to avoid ablation inside the PV.

Limitations

The inclusion period for the trial from 2011 to 2013 was prolonged because of the limited number of centers, a dip in
inclusion in 2012 when concerns about ACE arose, and the requirement for documented paroxysmal AF. During this time, the MEA technology and its recommended use have evolved which may have affected the outcomes with PVAC. Similarly, single-tip CA is nowadays more often performed with contact-force catheters, which may change these outcomes as well. Although the new PVAC GOLD and GENius generator (v15) and ST with CF catheters have replaced prior procedures, we think the results are still relevant to determine the viability of the MEA system.

Diffusion-weighted MRI imaging was not used to evaluate ACE, as the trial was already well underway when this risk developed as a key concern for AF ablation. Other research and publications have established the root cause for ACE, and the ERACE and PRECISION GOLD results demonstrate that procedural and technical improvements with the MEA system are in the lowest range compared with other AF ablation technologies.

In the current trial, intermittent ECG and Holter recordings were used to establish freedom of AF. This may underestimate the true incidence of, especially asymptomatic, AF episodes. Although longer duration Holter monitoring, or continuous monitoring with implantable loop recorders, are feasible to determine the absolute burden and freedom of arrhythmias, the AF monitoring approach in this trial was chosen primarily for comparison of treatment strategies.

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Disclosures

Dr Boersma is a consultant for Medtronic, and all honoraria go to the Cardiology Department. Dr Dekker is associated with speaker bureau of Medtronic. Dr Wijffels is associated with speaker bureau, and honoraria go to the Cardiology Department. Dr DeGreef is a consultant for Medtronic. The other authors report no conflicts.

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