DESIGN PAPER

Electrographic flow–guided ablation in redo patients with persistent atrial fibrillation (FLOW-AF): design and rationale

Tamas Szili-Torok, MD, PhD,* Petr Neuzil, MD, PhD,† Anke Langbein, MD,‡ Jan Petru, MD,† Moritoshi Funasako, MD, PhD,† Leon Dinshaw, MD,§ Sip Wijchers, MD,* Rohit Bhagwandien, MD,* Andreas Rillig, MD,§ Stefan G. Spitzer, MD,‡ Andreas Metzner, MD,§ Melissa H. Kong, MD,‖ Vivek Y. Reddy, MD†¶

*From the *Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands, †Department of Cardiology, Homolka Hospital, Prague, Czech Republic, ‡Department of Cardiology, Praxisklinik Herz und Gefaesse, Dresden, Germany, §Department of Cardiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, ‖Ablacon, Inc, Wheat Ridge, Colorado, and ¶Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai, New York, New York.*

BACKGROUND Electrographic flow (EGF) mapping enables the dynamic detection of functional or active atrial fibrillation (AF) sources outside the pulmonary veins (PVs), and the presence or absence of these sources offers a novel framework for classifying and treating persistent AF patients based on the underlying pathophysiology of their AF disease.

OBJECTIVE The primary objective of the FLOW-AF trial is to evaluate the reliability of the EGF algorithm technology (Ablamap software) to identify AF sources and guide ablation therapy in patients with persistent AF.

METHODS The FLOW-AF trial (NCT04473963) is a prospective, multicenter, randomized clinical study in which patients with persistent or long-standing persistent AF who have failed prior PV isolation (PVI) undergo EGF mapping after confirmation of intact PVI. In total, 85 patients will be enrolled and stratified based on the presence or absence of EGF-identified sources. Patients with an EGF-identified source above the predetermined activity threshold of $\geq$26.5% will be randomized in a 1:1 fashion to PVI only vs PVI + ablation of EGF-identified extra-PV sources of AF.

RESULTS The primary safety endpoint is freedom from serious adverse events related to the procedure through 7 days following the randomization procedure; and the primary effectiveness endpoint is the successful elimination of significant sources of excitation with the target parameter the activity of the leading source.

CONCLUSIONS The FLOW-AF trial is a randomized study designed to evaluate the ability of the EGF mapping algorithm to identify patients with active extra-PV AF sources.

KEYWORDS Atrial fibrillation; Electrographic flow mapping; Ablation outcomes; Sources; Ablation

(Heart Rhythm O^2 2023;4:391–400)

Introduction

The classification system for clinical atrial fibrillation (AF) established in the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline for the management of patients with AF is the most widely used framework for defining temporal persistence, selecting therapies, and outlining inclusion and exclusion criteria for clinical trials.[1,2] However, this current clinical classification schema adequately reflects neither the actual temporal persistence of AF nor any inherent pathophysiological characteristics of the individual patient's AF.[1,3] As a result of this discordance, patients classified in the same clinical AF category may be fundamentally heterogeneous in terms of the composition and interplay of electrical and structural substrate that influence their AF disease process in terms of recurrence, persistence, AF burden, and disease progression.[3,4] Treatment of this heterogeneous patient population with any uniform ablation strategy may contribute to the ceiling of efficacy encountered with catheter ablation of persistent AF despite the use of different ablation energies, catheter technologies, ablation techniques, and lesion sets.[5–7]

That the development and persistence of AF depends on a localized source, trigger, or driver as well as a susceptible

Address reprint requests and correspondence: Dr Vivek Y. Reddy, Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, PO Box 1030, New York, NY 10029. E-mail address: vivek.reddy@mountsinai.org.

2666-5018/

https://doi.org/10.1016/j.hroo.2023.04.001

KEY FINDINGS

- Electrographic flow mapping is an innovative method for visualizing in vivo, near real-time atrial electrical wavefront propagation and can identify active extrapulmonary vein (extra-PV) sources of excitation for targeted ablation.
- Beyond the PVs, the development and persistence of atrial fibrillation (AF) depends on localized sources (triggers/drivers) as well as on susceptible substrate.
- While many different methods have been put forth to detect and ablate these extra-PV sources of AF, at this time, no mapping system exists to reliably identify such sources or to guide their ablation and elimination.
- The FLOW-AF trial is a multicenter, prospective, randomized controlled trial to evaluate the novel electrographic flow mapping software as a diagnostic and prognostic tool for identifying AF sources in redo patients with persistent AF.

substrate such as re-entrant circuits or regions of high-frequency electrical activity has become increasingly recognized and accepted.[1,8–10] Efforts to hone in on AF mechanisms underlying persistent AF have multiplied, and several different methods for identifying these localized sources have been put forth using global or panoramic mapping techniques.[11–14] However, due to the chaotic nature of the intracardiac electrograms (EGMs) characteristic of AF, identifying active focal sources relevant to the initiation and maintenance of AF has remained challenging.

Electrographic flow (EGF) mapping is an innovative technology that uses well-established principles of optical flow and fluid dynamics on a machine learning platform to visualize in vivo, near real-time atrial electrical activation and can identify active sources of excitation and distinguish them from passive rotational activity that do not generate action potentials.[15,16] EGF mapping can detect extrapulmonary vein (extra-PV) sources of AF throughout the right atrium (RA) and left atrium (LA), with most EGF-identified sources representing anatomically feasible targets for ablation.[17] Furthermore, a first-in-human case report recently demonstrated interprocedural EGF map reproducibility showing spatiotemporal stability of EGF-identified sources in the same patient during 2 separate procedures performed 18 months apart.[18] Previously published retrospective analyses have shown that only active sources that generate excitation and are active more than a quarter of the time are significant predictors for AF recurrence after PV isolation (PV).[19] The goal of this randomized clinical study is to evaluate this novel mapping software as a diagnostic and prognostic tool for identifying AF sources in humans with persistent AF such that the heterogeneous persistent AF population may be classified and treated based on their underlying pathophysiology, rather than based on the temporal persistence of their documented AF episodes. Active AF sources outside the PVs can be identified by EGF mapping throughout the RA and LA and represent a dynamic target that may be eliminated or altered by ablation.

Materials and Methods

Primary objective

The primary objective of the FLOW-AF trial (NCT04473963) is to evaluate the reliability of the EGF algorithm technology (Ablamap software; Ablacon, Wheat Ridge, CO) to identify AF sources and guide ablation therapy in patients with persistent AF.

Study design

The FLOW-AF trial is a prospective, multicenter, randomized clinical study in which patients with persistent or long-standing persistent AF for which they have undergone prior PVI undergo EGF mapping after confirmation of intact PVI. These redo patients then undergo evaluation of their prior PVI, and touch-up ablation with a radiofrequency (RF) ablation catheter is performed as indicated to eliminate any PV reconnections.

EGF mapping

EGF mapping is performed by recording unipolar EGMs from a 64-electrode basket catheter connected to a proprietary, CE-marked recording system (EPMap-System, Herdecke, Germany) and processed using the EGF software. Further information regarding the signal processing and the proprietary algorithm are detailed in a previously published white paper.[16] EGF mapping essentially displays the dominant patterns of the AF excitation wave propagation and measures their consistency over time.[20] Starting with a 64-electrode basket catheter, unipolar EGMs are recorded and processed. Using a combination of Green's formula-based spline interpolation with Horn-Schunck's iterative flow estimation, the EGF algorithm transforms the intensity values into a derived energy-optimized intensity surface and then into a visualization of time-dependent activations during AF. The EGF algorithm utilizes a multiple-frame variant of the Horn-Schunck method to analyze consecutive frame pairs for consecutive iterations until convergence occurs when the resulting flow vector field reaches a stable vector length with no further systematic growth per iteration.

EGF maps are generated from a 1-minute recording of the unipolar EGMs from the 64-basket electrodes. The EGF Summary Map visually summarizes all active sources and their prevalence, any passive rotational phenomena, and the overall flow consistency detected over the full 1-minute recording (Figure 1A). Each EGF Summary Map consists of 30 EGF Segment Maps that dynamically display the flow patterns over a 2-second interval (Figure 1B). Each Segment Map is calculated based on the analysis of 105

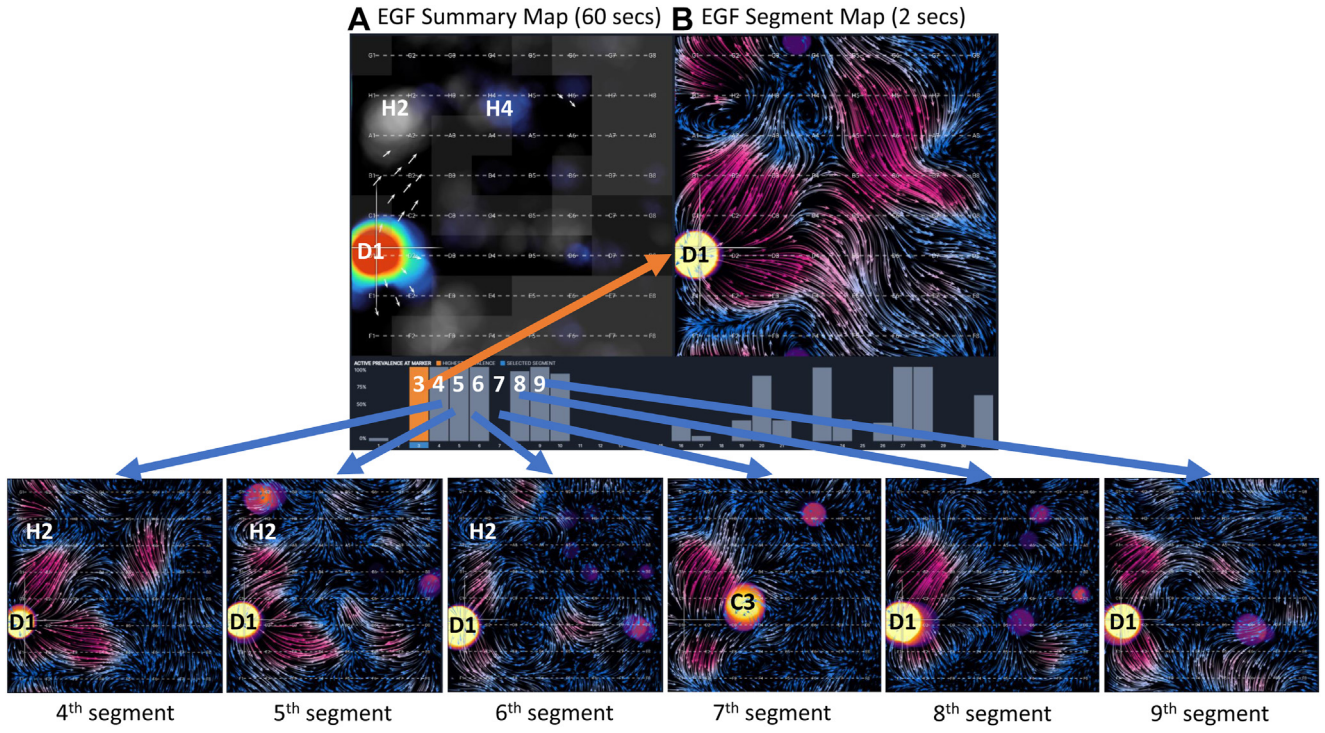

Figure 1 Electrographic flow (EGF) summary map and EGF segment maps. **A:** The EGF Summary Map displays a statistical summary of the relevant features that were detected during the 60-second recording of the unipolar electrograms. The dark red spot at D1 indicates an active source, and the crosshairs are placed on the active source with the highest prevalence over the 1-minute recording. There is a second, far less prevalent source seen at H4. In addition, a passive rotational phenomenon is seen around H2 (white cloud). There are also regions of more stable, higher flow consistency emanating focally from the active source at D1 (white arrows). **B:** The EGF Segment Map is a dynamic video showing 2 seconds of flow behavior. By default, the software highlights the segment with the most prevalent source (segment 3 in this example as highlighted in orange in the histogram bar plot that is always displayed below the EGF maps). The user can scroll through each of the segments recorded and examine the flow patterns every 2 seconds In this example, the highlighted third segment is shown to the right of the EGF Summary Map and in the row below the fourth, fifth, sixth, seventh, eighth, and ninth segments are each shown. In the software, each of these maps would be animated as a 2-second video. By looking at the individual segments, it can be appreciated that the active source at D1 is active in the fourth, fifth, sixth, eighth, and ninth segments but is inactive in the seventh segment. This can be noted by glancing at the histogram bar plot as well, which shows no activity in the seventh segment. However, a different, albeit much less prevalent source at C3 is active during the seventh segment. The passive rotational phenomenon can also be seen in the fourth, fifth, and sixth segments around H2. Overall, this patient has low flow consistency (predominantly blue flow vectors seen in the segments shown), but there are small patches of more consistent (more magenta) flow.

consecutive 19 ms frames of data for each 2-second segment.[16]

The identification of statistical singularities are called sources and active sources are defined by divergent wavefront propagation emanating from a singularity of flow vectors. Passive rotations do not generate flow and exhibit convergent flow fields.[15] Source activity (SAC) is the percentage of time during which the source with the highest prevalence was detected as active or originating EGF. A statistically derived threshold of SAC $\geq$26.5% was selected using retrospective data to define clinically relevant sources as the presence of active sources with SAC above threshold correlated with recurrent AF.[19]

Flow consistency analyzes a sequence of vector field estimates in which the vector length represents a measure of the consistency of the observed wavefront patterns. If the same wavefront propagation is repeatedly observed at a given location, the respective vector length will be greater, indicating higher flow consistency (magenta) than at locations with more chaotic activation wavefronts and low flow consistency (blue).

EGF-identified SAC and EGF consistency measured post-PVI will be used to stratify patients into 4 phenotypes based on their inherent flow consistency and the presence or absence of sources (Table 1).

Type I

With high flow consistency and no active sources, these patients have stable, more homogeneous wavefront propagation through the endocardium during AF and no other mechanism of AF beyond the PV triggers that were eliminated with PVI. A representative biatrial EGF map of this AF subtype is shown in Figure 2.

Type II

With high flow consistency, active sources, these patients also have stable, more homogeneous wavefront propagation through the endocardium during AF, but after PVI to eliminate their PV triggers, EGF mapping identifies extra-PV sources driving their AF.

Type III

With low flow consistency, active sources, these patients have chaotic activation wavefronts through the endocardium

Table 1 Four EGF phenotypes of AF

Type	Flow consistency	Presence of extra-PV sources	Mechanistic description of EGF findings
Type I	High	No	Wavefront propagation flows consistently through the endocardium during AF, and no other mechanism of AF beyond the PV triggers that were eliminated with PVI is identified with EGF mapping.
Type II	High	Yes	Wavefront propagation flows consistently through the endocardium during AF, but after PVI to eliminate PV triggers, EGF mapping identifies extra-PV sources driving AF.
Type III	Low	Yes	Chaotic activation wavefronts collide through the endocardium during AF, and after PVI to eliminate PV triggers, EGF mapping identifies extra-PV sources driving AF.
Type IV	Low	No	Chaotic activation wavefronts collide through the endocardium during AF, but no other mechanism of AF beyond the PV triggers that were eliminated with PVI is identified with EGF mapping.

AF = atrial fibrillation; EGF = electrographic flow; PV = pulmonary vein; PVI = pulmonary vein isolation.

during AF, and after PVI to eliminate their PV triggers, EGF mapping still identifies extra-PV sources driving their AF.

Type IV

With low flow consistency, no active sources, these patients also have chaotic activation wavefronts through the endocardium during AF but no other mechanism of AF beyond the PV triggers that were eliminated with PVI.

In the FLOW-AF trial, patients will be stratified based on the presence or absence of clinically relevant sources. Patients will not be randomized based on degree of flow consistency; thus, patients with both high and low flow consistency should be found in all arms of the study. As this study specifically examines the challenging redo population with persistent AF, all patients undergoing randomization will have already had a prior PVI and at the time of the redo procedure will undergo evaluation of the prior PVI and PVI touch-up as indicated for any PV reconnections. For the purpose of data collection, all patients in sustained AF will undergo EGF mapping both pre- and post-PVI, and all EGF mapping will be performed in triplicate (ie, 3 serial 1-minute recordings will be made at each of 3 standardized basket positions required in the RA and at each of a minimum of 2 standardized basket positions required in the LA). For significantly enlarged LA, the operator may decide to collect a third basket position. These pre-specified standardized basket positions were selected to optimize endocardial coverage of the atria.

If any PVI touch-up is performed, a minimum 20-minute wait is required after the final RF application, and then all PVs must be rechecked to confirm electrical isolation. Once isolation is confirmed post-PVI, the EGF software will be used to record post-PVI biatrial EGF maps. If post-PVI, no active EGF-identified AF sources are identified with a prevalence above the clinically relevant threshold, then the EGF map indicates a no sources patient who may be either type I (no sources with high flow consistency) or type IV (no sources with low flow consistency). If an active EGF-identified AF source is identified in either the RA or the LA, then the patient is designated an active sources patient or a patient with extra-PV triggers or drivers of AF who may be either type II (sources present with high flow consistency) or type III (sources present with low flow consistency).

Among redo patients with active AF sources, patients will be randomized in a 1:1 fashion to either the control or treatment condition of their EGF-identified AF sources (Figure 3B): (1) in the control condition, the patient is cardioverted (if indicated) after PVI only and the procedure ends, and no ablation of EGF-identified active sources is performed; (2) in the treatment condition, using standard RF ablation techniques, ablation is performed of EGF-identified active sources in both atria followed by immediate remapping to confirm successful source elimination. Patients are cardioverted (if indicated) after all relevant sources above threshold have been ablated.

Due to the nature of the mapping and ablation procedures, operators cannot be blinded to the randomization. A 1:1 blocked randomization scheme stratified by site will be used for randomization. Enrollment will occur at 4 centers in the European Union. The research reported in this paper adheres to Helsinki Declaration guidelines. The study protocol received approval by the Ethics Committees at each institution prior to study enrollment. Written informed consent will be obtained from each patient prior to study inclusion. Internal data generated as part of the risk analysis of the EGF software indicate there were no patient or user safety issues or hazards identified. There are no specific tests outside the standard practice required by this clinical study protocol. Therefore, there is no foreseen direct increased risk to participating subjects (other than, of course, the downsides of additional ablation as directed by the software).

At a single center, a smaller cohort of persistent AF patients will be enrolled via the run-in pathway as de novo subjects, who have never previously undergone LA ablation for AF. Once enrolled, these subjects will undergo an initial PVI procedure using an approved, commercially available single-shot ablation strategy including cryoablation (Artic Front Advance; Medtronic, Minneapolis, MN), laser balloon ablation (HeartLight X3; CardioFocus, Marlborough, MA), or pulse-field ablation (Farawave; Farapulse, Menlo Park, CA) during their index procedure (Figure 3A). The EGF software will be used prior to and following the PVI procedure—again, after a minimum 20-minute wait and

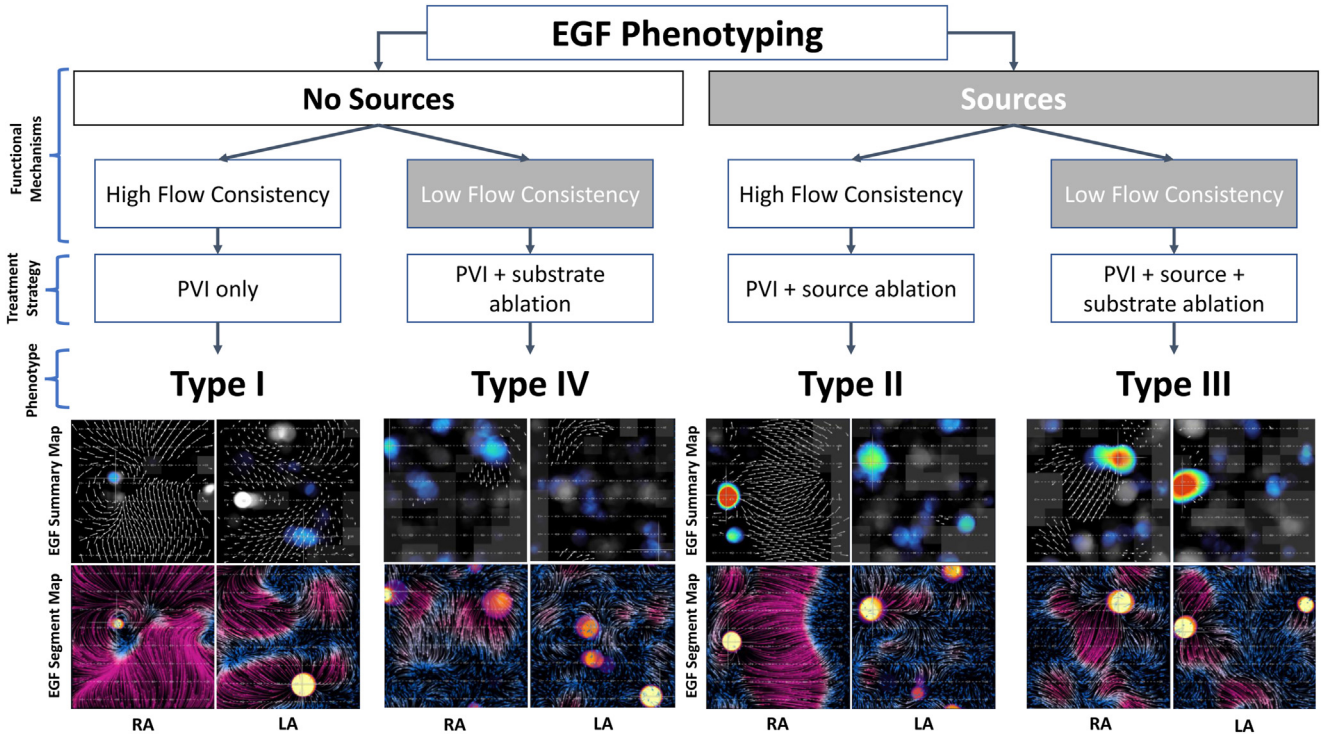

Figure 2 Electrographic flow (EGF) phenotypes of atrial fibrillation (AF). LA = left atrium; PVI = pulmonary vein isolation; RA = right atrium.

confirmation of electrical isolation of the PVs—to map and analyze the intracardiac EGM data. During this PVI-only index procedure, no EGF-guided ablations are allowed even if active sources above threshold are identified.

Patients enrolled via the run-in pathway will return for a remapping procedure and possible randomization 3 months following their index procedure. During the remap procedure, if the patient is in AF or if AF can be induced using standard

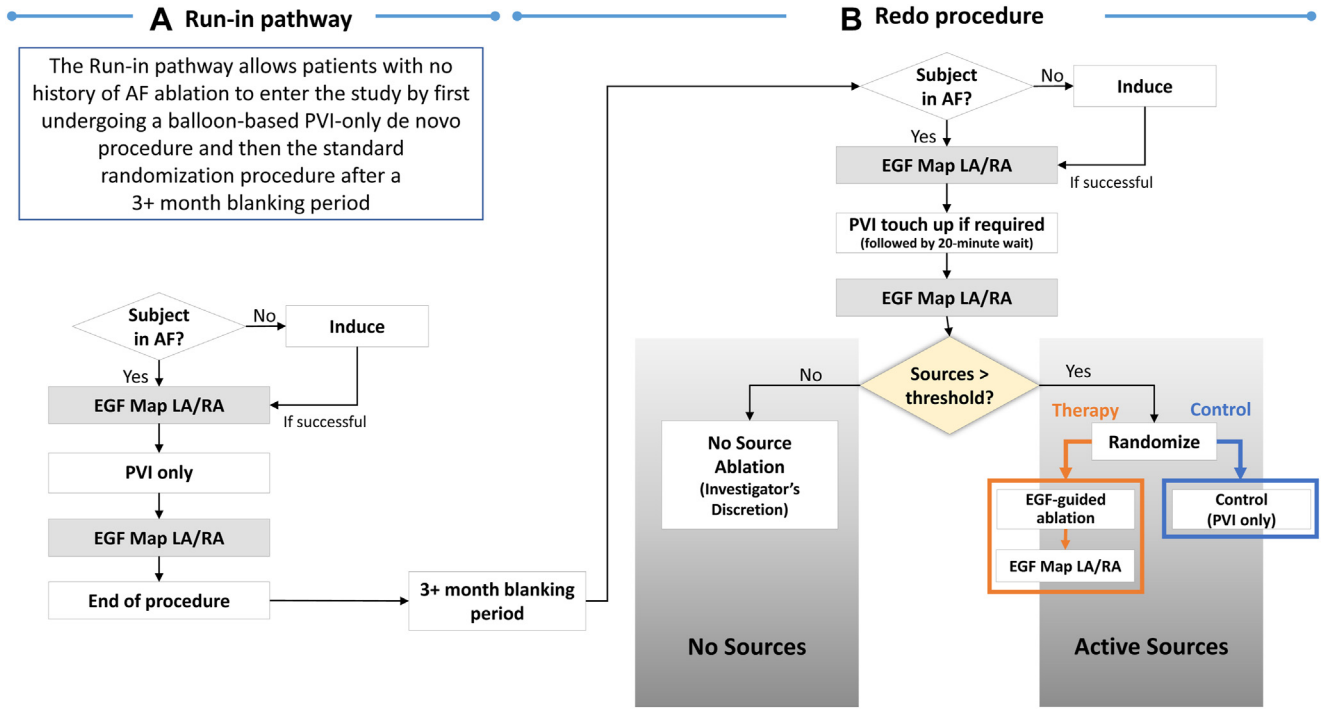

Figure 3 FLOW-AF trial enrollment. **A:** The run-in pathway will enroll de novo persistent atrial fibrillation (AF) patients who have not previously undergone pulmonary vein isolation (PVI). **B:** After a 90-day blanking period post–pulmonary vein isolation (PVI), patients enrolled via the run-in pathway will return for their redo procedure. The majority of patients enrolled will be redo persistent AF patients who had symptomatic recurrence after a prior PVI and randomization occurred if electrographic flow (EGF) mapping post-PVI revealed an EGF-identified active source above threshold. LA = left atrium; RA = right atrium.

Table 2 Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Suitable candidate for intracardiac mapping and ablation of arrhythmias 2. Above 18 years of age or of legal age to give informed consent specific to state and national law 3. Subjects with a history of documented symptomatic, persistent, or long-standing persistent AF $\leq$36 mo 4. Subject agrees to comply with study procedures and be available (geographically stable) for follow-up visits for at least 12 mo 5. Treatment of AF with ablation therapy presenting with recurrent symptoms of AF (not applicable to de novo subjects)	1. LA diameter >5.5 cm 2. LVEF <35% 3. Presence of intramural thrombus, tumor, or abnormality that precludes vascular access, catheter introduction, or manipulation 4. Coagulopathy, bleeding diathesis, or suspected procoagulant state 5. Known allergies or intolerance to anticoagulant and antiplatelet therapies to be used in conjunction with the study or contrast sensitivity that cannot be adequately pretreated prior to the ablation procedure 6. Positive pregnancy test results for female patients of childbearing potential or breastfeeding 7. Acute or chronic medical condition that in the judgment of the investigator would increase risk to the patient or deem the patient inappropriate to participate in the study 8. Mitral valve stenosis and/or severe mitral regurgitation 9. Valvular AF 10. Prosthetic valves 11. NYHA functional class IV 12. History of MI within 3 mo prior to procedure 13. ASD or LAA closure device 14. AF from a reversible cause (eg, surgery, hyperthyroidism, sarcoidosis, or pericarditis) 15. Life expectancy <12 mo based on medical history or the medical judgment of the investigator 16. Presence of any transvenous pacing, ICD, or CRT leads

AF = atrial fibrillation; ASD = atrial septal defect; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; LA = left atrial; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association.

induction pacing protocols, then EGF mapping with the EGF software will be performed in both atria followed by evaluation of the prior PVI and touch-up ablation with an RF ablation catheter as indicated to eliminate any PV reconnections. Again, if any PVI touch-up is required, a minimum 20-minute wait will be mandatory prior to confirming electrical isolation and once isolation is confirmed, post-PVI EGF maps in both atria will be obtained. If active AF sources are identified with SAC $\geq$26.5%, the patient will be randomized. For this subset of patients, 2 separate written informed consents will be obtained—one for the initial de novo procedure and the second for the remapping procedure after the 90-day blanking period. This separate remapping procedure was approved by the Ethics Committee in Homolka Hospital, Prague, Czech Republic, and this subset of patients was only enrolled at this single center.

Eligibility criteria

Written informed consent will be obtained from every patient before study inclusion. Separate consent forms will be provided to patients depending on whether they are being enrolled via the run-in pathway or as a redo patient, as the former group will require consent for a remapping procedure 90 days after the initial procedure. All enrolled patients will then proceed to complete the screening and baseline testing. If they do not meet the eligibility criteria, they will exit from the study and will not count toward the treated study population. Detailed study inclusion and exclusion criteria are outlined in Table 2.

Procedures

For all de novo ablation patients entering the study via the run-in phase, during the index procedure they will undergo a single-shot PVI procedure (cryoballoon or laser balloon or pulse-field ablation) to optimize the homogeneity of the PVI procedure. For the redo procedure, all patients will undergo catheter ablation of AF according to their randomized strategy as detailed above. For all patients, antiarrhythmic drugs (AADs) will be discontinued at least 5 half-lives prior to their procedures, except for amiodarone, which will be recommended to be stopped ideally 3 months (or a minimum of 1 month) prior the procedure and not restarted after the ablation procedure. During the redo procedure, all patients will undergo catheter ablation using RF energy, regardless of strategy. Prior to ablation, a transthoracic or transesophageal echocardiography must be performed if one has not been performed within 6 months of the enrollment procedure.

All procedures will be performed via transseptal access to the LA. A multipolar diagnostic catheter will be positioned in the coronary sinus and a circular mapping catheter will be used for mapping and confirmation of PVI. A 64-electrode basket catheter (FIRMap; Abbott, Abbott Park, IL) will be introduced into both the LA and RA, and unipolar EGMs from the basket catheter will be recorded at least 3 times for 1 minute each time. Per the instructions for use of the 64-electrode basket catheter, intravenous heparin will be administered to achieve and maintain an activated clotting time >300 seconds before insertion of the basket catheter. All RF ablations will be performed using

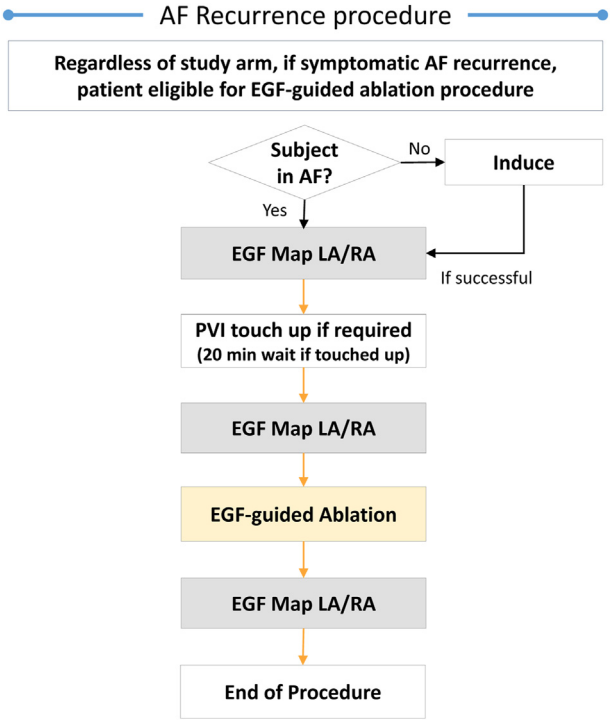

Figure 4 Recurrence procedure is electrographic flow (EGF)–guided ablation. AF = atrial fibrillation; LA = left atrium; PVI = pulmonary vein isolation; RA = right atrium.

approved, commercially available, open irrigated-tip, ablation catheters. No other guidelines or restrictions will be placed on ablation technique or ablation generator settings, which will be determined by the operating physician. All procedures will be guided using a 3-dimensional cardiac electroanatomic navigation system (EnSite NavX [Abbott] or CARTO [Biosense Webster, Irvine, CA]) to enable 3-dimensional reconstruction of the RA, LA, PVs, and LA appendage. No parenteral AADs will be used during ablation to organize or terminate AF.

Repeat ablation procedures

Per the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement on catheter and surgical ablation of AF, a 3-month blanking period will be observed after both the index ablation procedure for the de novo patients in the run-in group and after the redo procedure for all patients.[1] During the blanking period, recurrences of AF, atrial tachycardia, and atrial flutter will not be counted toward the secondary efficacy endpoint. At the operating physicians' discretion, AADs other than amiodarone may be continued for the first 3 months postablation to minimize early recurrences; however, at 3 months postablation, all AADs must be discontinued to assess for clinical recurrence, unless the attending physician deems this to be clinically not feasible. Amiodarone may not be used during the blanking period given its long half-life that may interfere with endpoint assessment at longer-term follow-up intervals. Patients who present with recurrent symptoms of AF at any time after the 3-month blanking period following the redo procedure may return for a repeat ablation procedure (Figure 4). Regardless of the study arm in which the patient is enrolled, when patients return for a recurrence procedure, the EGF software will be used to record biatrial EGF maps. The PVs will be checked to evaluate for PV reconnections and if PV touch-up is required, RF ablation will be performed. After a minimum 20-minute wait post-PVI, if PVI is intact, EGF mapping will be repeated and any EGF-identified active AF sources above threshold will be ablated. Remapping will continue until active EGF-identified AF sources have been eliminated. If the patient remains in AF at the end of the procedure, cardioversion will be performed. If any recurrences occur between any study procedures, cardioversion is allowed as often as clinically indicated. The number of cardioversions for each patient will be recorded.

Additional ablation

During any ablation procedure performed for symptomatic recurrence after completion of the randomization procedure, the operating physician will have the option of mapping and ablating any additional atrial tachycardia or atrial flutter or other supraventricular tachycardias that may arise. If any patient presents with symptomatic AF recurrence, they will be eligible for an EGF-guided ablation procedure.

Follow-up schedule

The FLOW-AF trial follow-up schedule is detailed in Table 3. All patients will be followed per protocol in relation to the date of their redo procedure. Follow-up will be required prior to hospital discharge, and at 7 days, 3 months, 6 months, and 12 months post–redo procedure. The follow-up schedule will remain the same and will not be reset if the patient requires a recurrence procedure.

Study endpoints

The primary endpoints for this study to assess the safety and effectiveness of the EGF software to identify persistent AF patients with active AF sources are as follows: (1) the primary safety endpoint of the study is freedom from serious adverse events (SAEs) related to the procedure through 7 days following the redo procedure and (2) the primary effectiveness endpoint of the study is the successful elimination of significant sources of excitation with the target parameter the SAC of the leading source.

According to previously analyzed and published retrospective data, the threshold for clinical significance of a source is SAC >26%.[19] In this study, the effect of targeted ablation will be statistically analyzed by determining the rate of reduction of SAC below threshold. If an ablation does not successfully reduce SAC or if the location of the targeted source changes after ablation, ablation will be repeated. Sources above threshold that are deemed by the operating physician not to be amenable to catheter ablation (eg, in anatomical locations such as the midseptum that pose an

Table 3 Follow-up schedule

Subject visit description	Time frame/visit window	Medication assessment	Adverse events monitoring	Protocol deviations	Required monitoring
Randomization procedure	Day 0	X		X	
Predischarge	Prior to discharge following ablation procedure	X	X	X	12-lead ECG
7-d follow-up (phone)	7 ± 3 d	X	X	X	
3-mo follow-up	90 ± 15 d	X	X	X	12-lead ECG
6-mo follow-up	180 ± 30 d	X	X	X	Follow-up visit 12-lead ECG 7-d Holter monitor
12-mo follow-up	365 ± 45 d	X	X	X	Follow-up visit 12-lead ECG 7-d Holter monitor
Unscheduled visits for symptoms suggestive of atrial arrhythmias	As needed/necessary	X	X	X	As needed/necessary

Values are mean ± SD.
ECG = electrocardiogram.

independent risk such as damage to the AV node) will be separately counted.

As a secondary parameter, we will monitor the change in SAC at the location of a source upon ablation. In addition, another secondary parameter is the individual patient's source history between their first and second procedure and pre- and post-PVI. The following safety and efficacy secondary endpoints will be evaluated to support the results of the primary endpoints: (1) the secondary safety endpoint of the study is freedom from SAEs related to the procedure through 12 months following the redo procedure; and (2) the secondary efficacy endpoints include the consistency of sources identified by the EGF algorithm between the run-in procedure and the redo procedure or any applicable subsequent EGF-guided procedures, freedom from documented episodes of AF recurrence following the blanking period through 12 months, total number of EGF-identified AF source ablations, total time of EGF-identified AF source ablations, total fluoroscopy time and dose, and overall procedure time.

Study organization

The FLOW-AF trial is funded by Ablacon (Wheat Ridge, CO). However, all data will be independently collected, managed, and analyzed with a restricted-access, Code of Federal Regulations–compliant database. The FLOW-AF Steering Committee includes the principal investigators (V.Y.R. and P.N) and the independent investigators listed as coauthors of the paper. The steering committee is responsible for the design and conduct of this study and will have full access to the final study data and statistical programming. Statistical assistance will be provided by third-party research statisticians. An independent Clinical Events Committee consisting of 2 cardiac electrophysiologists and 1 interventional cardiologist will be responsible for performing unbiased reviews and classification of serious adverse events reports by the clinical study investigators. None of the members of the Clinical Events Committee are participating in the FLOW-AF trial, and none have any significant investment in the Sponsor or any of their entities. Data monitoring and site management was performed by 2 independent contract research organizations in the Czech Republic (High Tech Med Consult, Prague, Czech Republic) and the Netherlands (Brommet Clinical Research, North Brabant, the Netherlands).

Statistical considerations

The study protocol specifies that a maximum of 150 subjects will be enrolled in this study. The primary and secondary endpoints of the study will be analyzed for both the intention-to-treat and per-protocol populations; hypothesis testing will be performed using the intention-to-treat population, and analyses using the per-protocol population will be supportive.

The primary safety endpoint will be analyzed using a chi-square or Fisher's exact test to compare 7-day SAE rates between EGF-guided and control groups, and a P value of $<.05$ will be considered to indicate statistical significance. The primary effectiveness endpoint of the study is the successful elimination of significant sources of excitation. The target parameter is the activity of the leading source. According to previously analyzed retrospective data, the threshold for significance of a source is an activity of 27%. Significance of the leading source will be tested in each patient at multiple times in every procedure performed, in both atria, before and after PVI or PV touch-up and before and after any source ablation. The effect of targeted source ablation will be statistically analyzed by determining the rate of reduction of leading SAC below threshold upon ablation. If an ablation does not successfully reduce the SAC or if the location of the leading source changes upon ablation, ablation will be repeated. Sources above threshold that are located in anatomical locations that do not allow reasonably safe ablation because of an

independent risk (eg, a septal source near the AV node) will be separately counted. As a secondary parameter, we will monitor the change of activity at the location of a source upon ablation. Another secondary parameter is the individual patient source history between first and second procedure and before and after PVI. The expectation is that more than half of the suprathreshold active sources will be successfully ablated in the EGF-guided group.

For the secondary safety endpoint, the log-rank test will be used to compare the probability of having no SAEs through 12 months in those randomized to EGF-guided ablation with those randomized to the control condition. To account for subjects who are event-free but have incomplete follow-up, the Kaplan-Meier method will be used; subjects free from SAEs related to the procedure will be censored at the last time that they were known to be event-free.

Secondary endpoint of the study is the significantly higher recurrence rate in patients in which the leading source of any of the atria is above threshold. We will analyze the level of significance of this difference based on the patients with significant sources in the control group in which these sources were not ablated within the first 3 months and the therapy group in which ablation was unsuccessful vs all other patients (successful ablations, no sources). For the secondary effectiveness endpoint of freedom from AF from 90 days through 12 months, the length of time to the recurrence of AF in each group will be analyzed using Kaplan-Meier curves; subjects with no report of AF will be censored at their latest 12-lead electrocardiogram or Holter, whichever is later. This study is not powered to detect a statistically significant difference between the treatment and control groups.

Discussion

For patients with persistent and long-standing persistent AF, extra-PV drivers or triggers play an increasingly critical role in the pathophysiology of the difficult-to-treat patients who have already failed at least 1 prior catheter ablation procedure for the treatment of their AF. Mechanistic information that identifies which patients have these extra-PV sources and where they are located has the potential to improve our ability to treat and effectively manage these patients. At this time, no mapping systems exist to reliably identify such sources or to guide their ablation and elimination. The FLOW-AF randomized clinical study will evaluate the novel EGF mapping software as both a diagnostic and prognostic tool for identifying these extra-PV sources of AF such that the heterogeneous persistent AF population may be classified and the treated accordingly based on the mapping and visualization of each individual's underlying pathophysiology, rather than based on the temporal persistence of their documented AF episodes. Because the EGF algorithm is proprietary, and there is skepticism in the electrophysiology field for seemingly "black box" algorithms, data collected from this study will also be used to further characterize the spatial and temporal resolution of EGF-based source detection; for example, one of the planned mechanistic secondary analyses is to evaluate the consistency of sources identified for patients undergoing both the run-in and redo procedures. The results of this trial will demonstrate whether EGF mapping has the ability to identify non-PV sources of AF and guide therapy to improve ablation outcomes.

Conclusion

The FLOW-AF trial is a multicenter, multinational, randomized controlled clinical study designed to evaluate the ability of the EGF software to reliably identify active AF sources in humans with persistent AF to optimize ablation success in this challenging and clinically heterogenous patient population. To date, there has not been a multicenter randomized study to assess the EGF-guided identification and ablation of AF sources, and as such, this study represents an important advance in the patient segmentation and treatment of persistent AF.

Funding Sources: The FLOW-AF trial was funded by Ablacon, Inc.

Disclosures: Tamas Szili-Torok has a received a research grant and served as a consultant for Ablacon. Petr Neuzil has received grant funding from Ablacon and support from a Scientific Grant from the Ministry of Health Czech Republic, DRO (NNH, IG 180504). Jan Petru has received support from a Scientific Grant from the Ministry of Health Czech Republic, DRO (NNH, IG 180504). Moritoshi Funasako has received support from a Scientific Grant from the Ministry of Health Czech Republic, DRO (NNH, IG 180504). Leon Dinshaw has received speaker fees from Abbott. Andreas Rillig has received research and travel grants from Ablacon and travel grants from Abbott. Stefan G. Spitzer has received lecture grants from Abbott, Biotronik, Edwards, and Medtronic; advisory board and travel grants from Medtronic; and research grants from Ablacon, Medtronic, and Lifetech Scientific. Andreas Metzner has no relevant disclosures. Melissa H. Kong is an employee of and owns equity in Ablacon. Vivek Y. Reddy has served as a consultant for and owns equity in Ablacon; in addition, unrelated to this article, he has served as a consultant for and hownsas equity in Acutus Medical, Affera-Medtronic, Anumana, Apama Medical-Boston Scientific, APN Health, Aquaheart, Atacor, Autonomix, Axon Therapies, Backbeat, BioSig, CardiaCare, CardioNXT/AFTx, Circa Scientific, CoRISMA, Corvia Medical, Dinova-Hangzhou DiNovA EP Technology, East End Medical, EPD-Philips, EP Frontiers, Epix Therapeutics-Medtronic, EpiEP, Eximo, Farapulse-Boston Scientific, Field Medical, Focused Therapeutics, HRT, Intershunt, Javelin, Kardium, Keystone Heart, LuxMed, Medlumics, Middlepeak, Nuvera-Biosense Webster, Oracle Health, Restore Medical, Sirona Medical, SoundCath, and Valcare; unrelated to this work, he has served as a consultant for Abbott, AtriAN, Biosense-Webster, BioTel Heart, Biotronik, Boston Scientific, Cairdac, Cardiofocus, Cardionomic, CoreMap, Fire1, Gore & Associates, Impulse Dynamics, Medtronic, Novartis, Novo Nordisk, Philips, and Pulse Biosciences; and owns equity in Manual Surgical Sciences, Newpace, Nyra Medical, Surecor, and Vizaramed. The other authors have no conflicts of interest to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Written informed consent will be obtained from each patient prior to study inclusion.

Ethics Statement: The research reported in this paper adheres to Helsinki Declaration guidelines. The study protocol received approval by the Ethics Committees at each institution prior to study enrollment.

References

1. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275–e444.

2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014; 130:e199–e267.
3. Charitos EI, Purerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. J Am Coll Cardiol 2014;63:2840–2848.
4. Zaman JAB, Baykaner T, Clopton P, et al. Recurrent post-ablation paroxysmal atrial fibrillation shares substrates with persistent atrial fibrillation : an 11-center study. J Am Coll Cardiol EP 2017;3:393–402.
5. Clarnette JA, Brooks AG, Mahajan R, et al. Outcomes of persistent and long-standing persistent atrial fibrillation ablation: a systematic review and meta-analysis. Europace 2018;20:f366–f376.
6. Berger WR, Meulendijks ER, Limpens J, et al. Persistent atrial fibrillation: a systematic review and meta-analysis of invasive strategies. Int J Cardiol 2019; 278:137–143.
7. Saglietto A, Ballatore A, Gaita F, et al. Comparative efficacy and safety of different catheter ablation strategies for persistent atrial fibrillation: a network meta-analysis of randomized clinical trials. Eur Heart J Qual Care Clin Outcomes 2022;8:619–629.
8. Lim HS, Hocini M, Dubois R, et al. Complexity and distribution of drivers in relation to duration of persistent atrial fibrillation. J Am Coll Cardiol 2017; 69:1257–1269.
9. Haissaguerre M, Hocini M, Sanders P, et al. Localized sources maintaining atrial fibrillation organized by prior ablation. Circulation 2006;113:616–625.
10. Sanders P, Berenfeld O, Hocini M, et al. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. Circulation 2005; 112:789–797.
11. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012;60:628–636.
12. Honarbakhsh S, Schilling RJ, Dhillon G, et al. A novel mapping system for panoramic mapping of the left atrium: application to detect and characterize localized sources maintaining atrial fibrillation. J Am Coll Cardiol EP 2018;4:124–134.
13. Verma A, Sarkozy A, Skanes A, et al. Characterization and significance of localized sources identified by a novel automated algorithm during mapping of human persistent atrial fibrillation. J Cardiovasc Electrophysiol 2018;29:1480–1488.
14. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation 2014;130:530–538.
15. Bellmann B, Lin T, Ruppersberg P, et al. Identification of active atrial fibrillation sources and their discrimination from passive rotors using electrographical flow mapping. Clin Res Cardiol 2018;107:1021–1032.
16. Haines DE, Kong MH, Ruppersberg P, et al. Electrographic flow mapping for atrial fibrillation: theoretical basis and preliminary observations. 2022. [E-pub ahead of print Aug 15]. J Interv Card Electrophysiol 2022.
17. Haines DE, Kong MH, Ruppersberg P, et al. Anatomic distribution of active sources identified using electrographic flow mapping. Heart Rhythm 2022; 19:S201–S202.
18. Gagyi RB, Ruppersberg P, Kong MH, Hoogendijk M, Wijchers S, Szili-Torok T. First-in-human demonstration of 18-month spatiotemporal stability of active atrial fibrillation source detected by electrographic flow mapping in persistent atrial fibrillation. HeartRhythm Case Rep 2021;7:599–604.
19. Szili-Torok T, Kis Z, Bhagwandien R, et al. Functional electrographic flow patterns in patients with persistent atrial fibrillation predict outcome of catheter ablation. J Cardiovasc Electrophysiol 2021;32:2148–2158.
20. Haines DE, Kong MH, Ruppersberg P, et al. Analysis of behavior of AF sources with electrographic flow mapping. Heart Rhythm 2021;18:1626–1627.