Ectopy Triggering Ganglionated Plexus Ablation to Prevent Atrial Fibrillation (GANGLIA-AF)

ClinicalTrials.gov ID: NCT02487654

Document date: 13th December 2021

STUDY PROTOCOL

GANGLIA-AF (ClinicalTrials.gov identifier NCT02487654) was a prospective, multicenter, randomized, single-blinded clinical study recruiting patients with paroxysmal AF indicated clinically for AF ablation. The recruitment period was between May 2017 and May 2019. Three UK centers participated in the study: Hammersmith Hospital, Imperial College Healthcare NHS Trust, UK; Derriford Hospital, University Hospitals Plymouth NHS Trust, UK; St Bartholomew's Hospital, Barts Health NHS Trust, UK. All patients gave written informed consent, and the study was approved by the local research ethics committee. Patients with symptomatic drug-refractory paroxysmal AF indicated for ablation were recruited to the study. The inclusion and exclusion criteria are included on the ClinicalTrials.gov PRS.

Patients were randomized to PVI or to GPA without PVI. Randomization was performed using a permuted block "sealed envelope" approach. The first block of randomization was performed on 21 consecutive patients, randomized 2:1 to GPA (GPA, n = 14; PVI, n = 7). This was in anticipation for a high rate of crossover from the GPA group as experienced in our previous pilot study.

Afterward, randomization was switched to 1:1 in blocks of 10 for the remainder of the recruitment. Patients and their cardiologists providing their usual care were blinded to their randomization. Operators on the day of ablation, the data collector, and the analyst were unblinded to randomization.

Protocol for all patients

Preoperative work-up

All patients discontinued AADs and β-blockers 5 half-lives before the procedure. Amiodarone was discontinued at least 2 months before the procedure. All patients provided written informed consent for participation in the study, which was approved by the health research authority and the local research ethics committee. Complete blood count, urea and electrolytes, C-reactive protein were measured on the morning before the procedure to ensure suitability for ablation.

Clinical procedures

All patients had general anesthesia. Local policies were followed for anticoagulation and assessment of cardiac thrombus using transesophageal echocardiography. A decapolar catheter was positioned in the coronary sinus. After transseptal puncture, a 20-pole circumferential catheter (LassoNav, Biosense Webster, Diamond Bar, CA) was used to create a respiratory-gated 3-dimensional electroanatomic map of the left atrium (CARTO, Biosense Webster). Blood pressure was continuously monitored using a radial arterial line. Heparin was administered throughout the cases to maintain the activated clotting time of >300 seconds. All data were recorded at 1000 Hz by the electrophysiology recording system (Bard EP, Lowell, MA). At the end of the procedure, heparin was reversed with protamine, and patients were discharged the next morning if well.

GP mapping and ablation

High frequency stimulation (HFS) was performed to locate the left atrial GPs in patients randomized to GPA. A Grass S88 stimulator (Astro-Med, West Warwick, RI) was used to deliver HFS from the distal electrode of a bipolar 3.5-mm irrigated-tip contact force sensing ablation catheter (SmartTouc, Biosense Webster), with a minimum contact force of 3g. A PV catheter was always placed in the nearest PV to the site of HFS testing to capture the earliest PV ectopy signals. Approximately 6 mm spacing was used between each HFS test site to achieve an evenly spaced global left atrial GP map. We did not test for GPs inside the PVs or in the left atrial appendage. We aimed to test up to 80 HFS sites, as this was usually sufficient

to cover all the left atrial surface available for testing as in our previous pilot study. The exact number of HFS sites tested varied between patients, depending on the size of their left atrium and the procedure time.

Two types of HFS techniques were used: “synchronized HFS” to detect ET-GPs and “continuous HFS” to detect AVD-GPs. The synchronized HFS technique was first described by Schauerte et al in canines, who demonstrated that atrial ectopy–triggering response with HFS are abolished with atropine and attenuated with β-blockade, confirming its autonomic mechanism. This was also reproduced in clinical studies.

In this study, for our synchronized HFS protocol, the left atrium was paced at high output (10 V) from the ablation catheter during sinus rhythm (SR) to check for atrial capture and to exclude ventricular capture. Then, we delivered short bursts of HFS trains (10 V, 80 ms duration, 40 Hz) coupled to each paced stimulus to ensure that HFS was delivered within the local atrial refractory period. This stimulated only the nerves and avoided direct myocardial capture. We delivered up to 15 trains of synchronized HFS per test site. If atrial ectopy or AF was triggered, we discontinued pacing and HFS immediately to avoid direct myocardial capture and sustained AF.

Continuous HFS was performed during AF by delivering HFS (10 V, 20 Hz) continuously for up to 10 seconds or until asystole occurred.

The definition for a *positive ET-GP* was reproducible induction of PV or atrial ectopy, AF, or atrial tachycardia (AT). Reproducibility was assessed up to 3 times with HFS. The definition for a *positive AVD-GP* was ≥50% increase in the R-R interval during HFS compared with the average 10 R-R intervals before HFS.

The main goal of our study was to map ET-GPs with synchronized HFS during SR. However, if patients developed sustained AF during GP mapping, GPs were ablated until successful restoration of SR. A positive response to GPA during sustained AF was termed “acute AF modulation,” and this was defined as follows: (1) termination to SR, (2) organization to AT, and (3) slowing of AF cycle length by ≥30 ms. A subgroup analysis was performed in patients who underwent GPA to correlate long-term freedom from ≥30 seconds of AF/AT recurrence. Patients who underwent GPA were divided into those who had (1) <100% success in acute AF modulation, (2) 100% success in acute AF modulation, and (3) no sustained AF with GP stimulation.

If all GPs were ablated and the patient was still in AF, up to 3 direct current cardioversions were performed to restore SR and to complete GP mapping. If patients remained in incessant AF, AVD-GPs were mapped with continuous HFS and ablated. We targeted AVD-GPs as well in this instance because significant overlap exists with ET-GPs and we wanted to target as many ET-GPs as possible.
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After completing GP mapping, all GPs were ablated by delivering a cluster of 3 point-by-point lesions around each GP site, with the contact force of >3g. Each ablation lesion was for 30 seconds at 30 W except in the posterior wall, where it was limited to 25 W. Catheter irrigation was set to 17 mL/min. This was usually adequate to render any GP negative for any response with repeat HFS testing. All ablated GPs were retested with HFS after ablation. If there was still a positive response, further ablation was performed until no further positive responses could be evoked.

PVI

For patients randomized to the PVI arm, wide antral circumferential ablation was performed around the PVs by using contiguous point-by-point radiofrequency (RF) ablation lesions. The

entry and exit blocks of PVs were confirmed using a PV catheter. Operators used the ablation index to guide PVI on >60% of patients who completed PVI.

Clinical follow-up

Patients were followed up and monitored for 12 months, with continuous remote contact with a clinician. Patients were fitted with 48-hour Holter monitors at 3-, 6-, 9-, 12-month intervals. If patients experienced symptoms between these 3-monthly time points, they were offered further Holter monitors in an attempt to record their symptomatic arrhythmia. Patients with pacemakers, loop recorder devices, and personal AliveCor Kardia electrocardiogram (ECG) (AliveCor Inc, Mountain View, CA) monitoring devices were interrogated throughout their follow-up. Any significant arrhythmia identified on their interrogation counted toward the primary end point regardless of the Holter results. We encouraged patients to discontinue all antiarrhythmic drugs (AADs) following the 3-month blanking period after their ablation procedures, but this was not mandated in the protocol.

Repeat AF ablation

Patients who were randomized to GPA returning for redo AF ablation procedures had repeat HFS testing. This identified any recurrence of GPs or new GPs not previously identified. All GPs identified in the redo procedure were ablated in addition to PVI. Patients who were randomized to PVI returning for redo AF ablation procedures had repeat PVI only.

End point definition

The primary end point was any documented atrial arrhythmia (AF, AT, or atrial flutter) lasting for ≥30 seconds consecutively recorded on the Holter monitor, 12-lead ECG, pacemaker, loop recorder, and AliveCor Kardia recorded ECG after a 90-day blanking period.

The secondary end points included repeat ablation for AF/AT/atrial flutter after a 90-day blanking period, mortality, and any significant complications related to the procedure (bleeding, thrombosis, phrenic nerve palsy, and cardiac tamponade) requiring intervention.

Statistics

Data analyses were conducted using the per-protocol (PP) study population. The PP study population excluded patients who were withdrawn after randomization. For sample size calculation, it was estimated that at a statistical power of 80% at a 5% significance level, 108 patients were required to detect 25% difference in primary end point, where 45% in PVI and 20% in GPA are predicted to have recurrent AF/AT. We enrolled 116 patients to allow for ∼5% not completing follow-up.

Statistical analysis was performed using SPSS Version 28 (IBM Corporation, Armonk, NY) and Prism 5 (GraphPad, San Diego, CA). Continuous variables were expressed as mean ± SD. Categorical variables were expressed as number and percentage. D'Agostino and Pearson omnibus and Shapiro-Wilk tests were performed to assess the normality of continuous variables before the comparison of means tests. Mann-Whitney *U* test, Fisher exact test, and unpaired *t* test were used for comparison of means. An event-free survival was estimated using a Kaplan-Meier curve for the primary end point. Clinical parameters associated with AF recurrence and other procedural parameters were studied using univariate and stepwise multivariate analysis in a Cox regression model. All variables with *P* values ≤.05 from the univariate analysis and well-established risk factors for AF recurrence, such as age and hypertension, were entered into the multivariate regression analysis. A *P* value of <.05 indicated statistical significance.