E-TEAM - HFpEF

Electroporation Treatment for Early AF Management in Heart Failure with preserved Ejection Fraction (HFpEF) Pilot Study

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1. Abbreviations

AAD	Antiarrhythmic drug
AE	Adverse event
AF	atrial fibrillation
FpC	FARAPULSE Catheter
CRF	case report form
EC	Ethics Committee
ECG	Electrocardiography
ECV	electrical cardioversion
ESC	European Society of Cardiology
ER	Emergency Room
ICF	Informed Consent Form
LA	Left atrial/atrium
PV	pulmonary vein
PVI	Pulmonary vein isolation
RFC	radiofrequency current
SAE	Serious adverse event
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
UADE	unanticipated adverse device effect

2. Responsibilities

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Electroporation **T**reatment for **E**arly **A**F **M**anagement in **H**eart **F**ailure with **p**reserved **E**jection **F**raction (HFpEF) Pilot Study – **E-TEAM**

Investigator Statement

I have read this protocol and agree to conduct this study in accordance with all stipulations of the Clinical Investigation Plan, any applicable standards for the conduct of clinical investigations with human patients, any requirements imposed by the responsible competent authority/ethics committee, any other applicable local, institutional or legal requirements and in accordance with the principles outlined in the Declaration of Helsinki.

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3. Background

Atrial fibrillation (AF) represents the most common sustained arrhythmia in western societies. Currently, in Germany, approximately two million patients are affected by AF and are exposed to an increased risk of stroke, heart failure and mortality [1]. AF often coexists with heart failure with preserved ejection fraction (HFpEF)[2] [3]. Due to the co-occurrence of AF and HFpEF in this population many patients require emergency hospitalization. However, diagnosis and optimal therapy of this combined entity remains often uncertain despite of recent developments. Due to the progressive ageing of our society and demographic development, the number of AF patients is expected to double over the next several years [4]. Moreover, AF has emerged as one of the most common reasons for patients seeking treatment in emergency rooms (ER) who are subsequently admitted for in-hospital treatment [5]. For many years, it has been well established that second line catheter ablation is more effective than escalation of antiarrhythmic drug treatment (AAD) with regards to rhythm control [6]. However, technical complexity of AF ablation, safety concerns and lack of reproducibility has limited widespread utilization of the former gold standard of radiofrequency current (RF) energy ablation. Importantly, the globally-performed CABANA trial failed to demonstrate reduction of mortality, but confirmed a lower AF burden following ablation therapy [7]. Recently, the randomized EAST strategy trial comparing rhythm control (achievement of sinus rhythm via intervention) vs. best medical care (rate control medication) demonstrated a 20% reduction of clinical endpoints such as cardiovascular mortality, stroke, embolism in the group randomized to rhythm control [8]. However, RF catheter ablation was utilized in only 20% of patients. Interestingly, very recently three independent randomized trials compared first line single shot PVI (Cryoballoon) vs. AAD treatment in more than 700 patients [9, 10, 11]. Importantly, the findings were uniformly showing increased efficacy for first line ablation using single shot device. The Farapulse electroporation device has demonstrated its ease in use, very short procedure times and a high procedural safety even in complex anatomy [12] [13]. Catheter ablation using electroporation (non-thermal energy source) differs substantially from thermal energy sources such as Cryo or RF energy and demonstrated a favorable safety profile. (Ekanem et al. Europace 2022).Thus, the concept of an early rhythm control strategy using a safe and reproducible single-shot ablation technology, such as electroporation, appears to be suitable to investigate the role of a stringent rhythm control in AF patients with HFpEF vs. usual care after emergency hospitalization.

4. Methods

Symptomatic AF patients diagnosed with HFpEF seeking emergency treatment that meet all inclusion and none of the exclusion criteria will be randomized according to E-TEAM in two groups (1:1 randomization) as follows:

Group 1: early catheter ablation within 7 days post AF-related emergency treatment using the FARAPULSE electroporation technology (n = 100)

OR

Group 2: best medical AF treatment including rhythm and rate control (n=100)

All patients will receive (direct) oral anticoagulation and heart failure treatment according to their CHA_2DS_2-VASC Score and current ESC guidelines [1] [2].

5. Ablation

The FARAPULSE AF ablation system represents a unique single shot ablation technology associated with a high rate of acute and durable PV isolation [14]. In principle, electroporation delivers a cardiac selective ablation, thus sparing non-cardiac tissue. The endpoint of the catheter ablation procedure is defined to PVI. Therefore, this technology offers a unique beneficial profile combining a high procedural efficacy and safety.

6. Endpoints

The **primary endpoint** is a composite of cardiovascular hospitalization (worsening heart failure, acute coronary syndrome, AF/AT recurrence, cardioversions, re-ablations), death, systemic embolism, stroke (ischemic, hemorrhagic) and emergency (E) treatment for cardiovascular reasons.

Secondary endpoints are defined to safety parameters such peri-procedural complications (major bleeding requiring intervention, phrenic nerve palsy, pericardial tamponade, thromboembolic events, atrio-esophageal fistula, death) or discontinuation of AAD due to side effects and documented recurrence of AF or any atrial tachyarrhythmia lasting longer than 30 seconds between day 90 and 365 after the index procedure as well as number of nights spent in the hospital per year.

Study Design

The proposed pilot study is a prospective, randomized, multi-center feasibility study, enrolling 200 patients with symptomatic AF. Per protocol, 100 patients will undergo a FARAPULSE electroporation PVI and 100 patients will receive standard AF medical treatment.

Prior enrollment, all patients will be informed on the risk and benefits of the PVI procedure as well as the medical treatment. In addition, particular information on the rationale of the study, including a detailed risk/benefit analysis, will be provided to all patients.

After obtaining written informed consent and randomization, patients will be treated according to the assigned groups (FARAPULSE electroporation PVI vs. optimized medical care). Follow-Up duration is 12 months. Importantly, cross-over between both groups is strongly discouraged. If deterioration occurs in group 2, PVI is advised.

Risk-Benefit-Analysis

Catheter ablation of AF represents an invasive procedure but is linked to a lower AF recurrence rate if compared to medical treatment. Participants in Group 2 (control group) will receive best medical treatment including the option for electrical cardioversions and AAD treatment.

The novel energy source using electroporation appears to be appealing due to its potential of short procedure times and cardiomyocyte selectivity resulting in a benign safety profile. The participants in Group 1 will be scheduled to receive the ablation therapy early after the AF diagnosis (within 7 days).

In general, catheter ablation for AF is an invasive treatment associated with potential complications. Of note, as stated above electroporation appears to be associated with a very benign risk profile. General AF related complications and corresponding incidences are summarized in the following:

- Vascular access complications such as vascular damage, neural damage, hematoma, bleeding (approx. 2-3%)
- Pericardial tamponade (<1%)
- Systemic Infection (<1%)
- Thrombo-embolic complications including air embolism, transient ischemic attack and stroke (<1%)
- Pulmonary vein stenosis or occlusion (<0,5%)
- Atrio-esophageal fistula (< 1‰)
- Death (< 0.1‰)

All devices utilized for the ablation procedure are fully licensed, CE mark approved and are used in the clinical routine. Patients randomized to Group 2 will receive standard medication including all non-interventional options for a rhythm control strategy in the treatment of AF. Therefore, no patient will be exposed to a higher risk due to the participation in the E-TEAM-Trial.

6.1 Inclusion and Exclusion Criteria

6.1.1 Inclusion Criteria

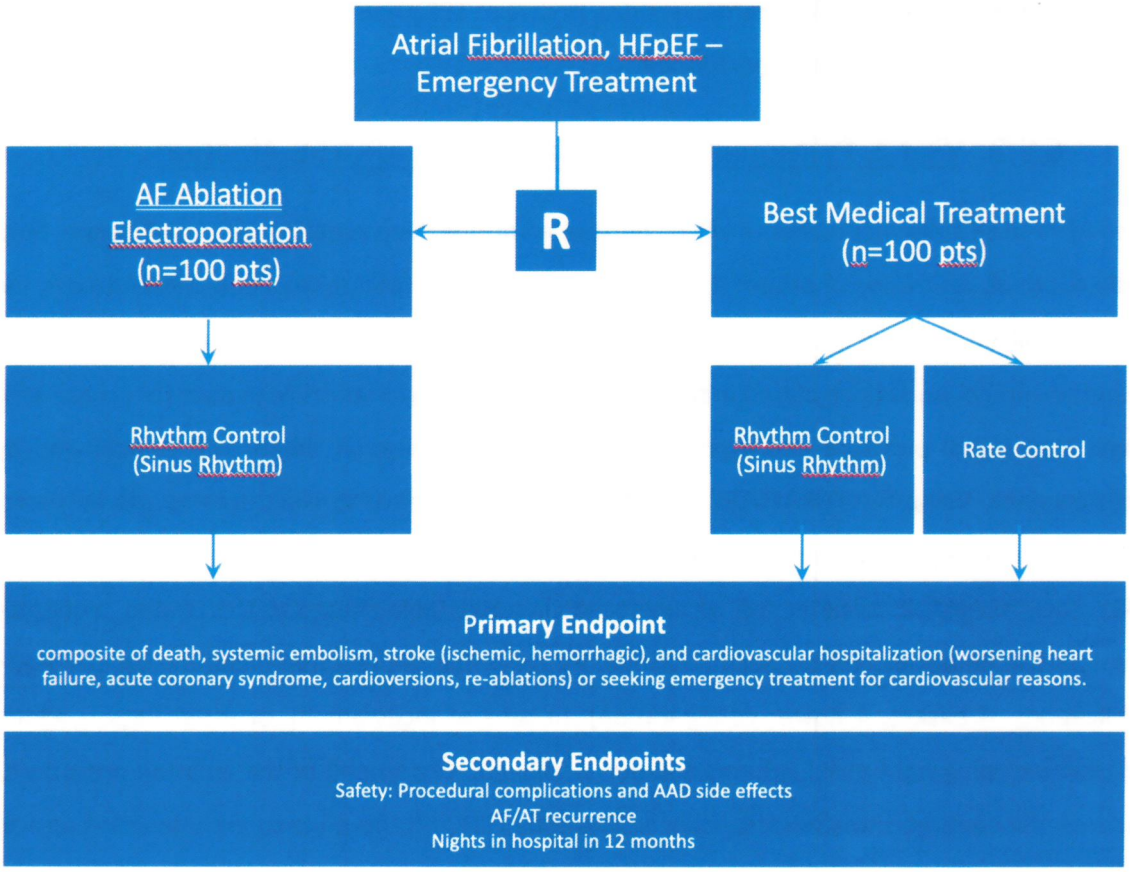
1. Seeking emergency (E) treatment including emergency room (ER) presentation
2. Paroxysmal and persistent AF diagnosed according to current ESC guidelines
3. Diagnosis of HFpEF according to ESC guidelines 2021 (clinical symptoms, EF>50%, objective evidence of functional abnormality: LV diastolic dysfunction, NT-proBNP (non acute setting): sinus rhythm: 125pg/ml or AF: 365pg/ml, vs. acute HF: >450 pg/ml if aged <55 years, >900 pg/ml if aged between 55 and 75 years and >1800 pg/ml if >75ys.
4. Age between 18 and 80 years
5. Left atrial size, LA < 55mm
6. Left ventricular ejection fraction, EF >50%
7. Patients able to provide informed consent and willing to comply with all pre-, post- and follow-up requirements as per study protocol

6.1.2 Exclusion Criteria

1. Currently participating in an interventional (drug, device, biologic, etc.) clinical trial
2. Any disease that limits life expectancy to less than one year
3. Contraindications for PVI
4. Contraindication for AAD therapy
5. Active systemic infection
6. Thrombocytosis, thrombocytopenia
7. Known pre-existing hemi-diaphragmatic paralysis
8. Any untreated or uncontrolled hyperthyroidism or hypothyroidism
9. Reduced immune function or otherwise at high risk for infection per physician discretion
10. Active malignancy or history of chemotherapy or radiation treatment
11. Prior left atrial ablation or surgical procedure (including left atrial appendage closures)
12. Any cardiac surgery, myocardial infarction, PCI/PTCA or coronary artery stenting which occurred within the 3 months before the eligibility assessment

13. Instable angina pectoris
14. Primary pulmonary hypertension
15. Any condition contraindicating chronic anticoagulation
16. Any cerebral ischemic event (strokes or TIAs) which occurred within the 3 months before the consent date
17. Presence of any cardiac prosthetic valves
18. Left atrial diameter > 55 mm (anteroposterior) by TTE
19. Presence of any pulmonary vein stents
20. Presence of any pre-existing pulmonary vein stenosis (identified by CT or MRI and defined as at least 70% reduction of the PV diameter)
21. Endocarditis, pericarditis or pericardial effusion
22. Pregnant or breastfeeding women or women of childbearing potential not on adequate birth control.
23. Substance abuse
24. Unwilling to follow the study protocol and to attend follow-up visits

6.2 Study course



6.2.1 Visit 1, Pre-procedural, Day -2 to 0

Following emergency hospital admission diagnostic work up including physical examination, 12 lead ECG, emergency blood examination (NT-proBNP) and chest X-ray initial cardiac ultrasound. Initiation and optimization of emergency therapy including iv diuretics if required. Routine diagnostic work up during hospital stay including daily clinical evaluation, weight loss determination, complete cardiac ultrasound, 12 lead ECG, telemetry, routine blood examination (30 ml) for blood cell count, INR, creatinine, ALAT, ASAT, electrolytes, TSH, NT-proBNP according to clinical needs.

Randomization (1:1) will be performed by the E-TEAM after all the patients' questions were clarified and the ICF was signed. All patients randomized to Group 1 will proceed to preparation of Visit 2, pulmonary vein isolation. The patients randomized in Group 2 will receive best medical treatment and if rhythm control was attempted TEE guided cardioversion and AAD according to the patients clinical needs as well as all information regarding the medical treatment.

In order to exclude intracardiac thrombi, a transesophageal echocardiogram (TEE) will be performed in patients randomized to Group 1 and considered at risk for thrombus formation and stratified to rhythm control (Group 2, before cardioversion). In case of TEE proven LAA thrombus the scheduled AF ablation or cardioversion can be postponed.

6.2.2 Visit 2, Pulmonary Vein Isolation, FARAPULSE-Ablation

The FARAPULSE ablation procedure will be performed during deep sedation using midazolam, fentanyl and a continuous infusion of propofol. Vital parameters will be monitored. For catheter access, two 8F sheaths will be inserted into the femoral veins guided by ultrasound. One multipolar diagnostic catheter will sequentially be placed in the coronary sinus and right ventricle to pace for in case of need. Single transseptal puncture and insertion of one 8.5 F transseptal sheath will be followed by PV angiographies. Using the FARAPULSE catheter, pulmonary vein (PV) electrograms will be recorded. Unfractionated heparin will be administered to maintain an activated clotting time between 300 and 400s. The FARAPULSE catheter will be advanced via a steerable sheath to the LA and sequential PV isolation will be performed for each individual PV following the recommended dosing strategy (1+7 applications: 4 basket, 4 flower configuration). In case of incessant AF or atrial flutter, additional ablation including right atrial isthmus ablation is allowed. At the end of the ablation procedure, the patients will undergo transthoracic echocardiography (TTE) on the table to exclude acute pericardial effusion.

6.2.3 Visit 3, Hospital Discharge

Until discharge, all patients will be monitored using telemetry and all patients in Group 1 will undergo a repeat TTE to exclude pericardial effusion and a daily 12 lead electrocardiography (ECG) to document the heart rhythm. A blood sample (20 ml) will be routinely collected to exclude bleeding (blood cell count) or renal function deterioration (creatinine and electrolytes). Therapeutic anticoagulation preferentially using a novel oral anticoagulant (NOAC) over Vitamin K antagonist will be initiated or resumed the evening after the procedure and maintained for at least 8 weeks after ablation. Continued anticoagulation will be performed if necessary, according to the individual CHA2DS2-Vasc-Score. In both groups early cardioversions in case of very early recurrence during the index hospital stay are allowed. AAD treatment in Group 1 should be avoided and should be stopped after 3 months, in Group 2 AAD treatment is allowed if rhythm control was selected according to the patients clinical profile. Total nights spent in hospital will be counted.

6.2.4 Visit 4, 3 Months Follow-Up after PVI/Randomization (± 7 Days)

An outpatient visit including the collection of a brief history (complications, medication), physical examination, 12 lead ECG, TTE and 72h-Holter-ECG will be performed at 3 Months ± 7 Days post procedure (Group 1) or post randomization (Group 2). All antiarrhythmic drugs (AAD) except beta-blockers prescribed for other medical conditions (i.e. arterial hypertension) have to be stopped for all patients in Group 1. If necessary, all medication including AAD for the patients in Group 2 should be adjusted.

6.2.5 Visit 5, 6 Months Follow-Up after PVI/Randomization (± 14 Days)

An outpatient visit including the collection of a brief history (complications, medication), physical examination, 12 lead ECG, TTE and 72h-Holter-ECG will be performed at 6 Months ± 14 Days post procedure (Group 1) or post randomization (Group 2).

6.2.6 Visit 6, 12 Months Follow-Up after PVI/Randomization (± 14 Days)

An outpatient visit including the collection of a brief history (complications, medication), physical examination, 12 lead ECG, TTE and 72h-Holter-ECG will be performed at 12 Months ± 7 Days post procedure (Group 1) or post randomization (Group 2).

6.3 Repeat ablation

No blanking period will be utilized in this study. During the first 90 days after the index procedure any arrhythmia recurrence shall be treated conservatively, e.g. by antiarrhythmic medication and/or ECV. Of note, re-ablation is strongly discouraged within the first 3 months. At day 90 however, all AAD drugs should be stopped in the ablation group and all re-ablation afterwards will meet the primary endpoint. In case of re-ablation the patient has reached the primary endpoint. The Follow-Up visits should be continued as per protocol.

7. Participant withdrawal or termination of participation

Prior to study entry, all participants will be informed that they are free to withdraw from the study at any time and for any reason without prejudice to their future medical care by a physician or the institution. Participants are free to withdraw from participation in the study at any time upon request. The withdrawal will cause no penalty or loss of benefits, to which the patients may otherwise be entitled. The investigator may ask and document the patients' motivation.

An investigator may also terminate a patients' participation in the study if:

- Withdrawal is in the subjects' best interest.
- Subject withdraws consent.
- Subject is lost to follow up.

8. Statistical Analysis

No interim-analysis will be performed.

The following events will trigger a premature study termination:

- Occurrence of serious adverse events in more than 10% of the study population associated with the ablation procedure. Of note, re-hospitalization for cardiovascular reasons meets the primary study endpoint.
- Occurrence of any unexpected, currently unknown complication or risk (Change of Risk-Benefit Ratio).

Occurrence of >10% major procedural complications defined as cardiac tamponade, stroke/TIA, air embolism, major bleeding the study has to be stopped. Of note re-hospitalization for cardiovascular reasons meets the primary endpoint."

9. Adverse Events

All adverse events (AEs) experienced by participants during the study, beginning with the first study related procedure and continuing through the end of study, will be recorded on case report forms (CRFs). Occurrences of atrial fibrillation and atrial flutter will be recorded and reported on as part of the efficacy assessment, and are not considered adverse events.

Serious adverse events (SAEs) are events that place the participants health in jeopardy and that occur despite following all labeling precautions and instructions for use and where all attempts at correction by medical intervention do not resolve the event. All SAEs must be reported to the Ethics Committee (EC) within 48 hours of the investigator becoming aware of the SAE. Re-hospitalization for cardiovascular reasons is part of the primary endpoint and therefore does not qualify as an SAE.

An unanticipated adverse device effect (UADE) is defined as any SAE on health or safety, or any life-threatening problem or death caused by, or associated with, the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application. An UADE is also defined as any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Should an UADE occur, the investigator is required to notify the EC as soon as possible, but in no event later than 10 working days after the investigator first learns of the event. An immediate evaluation of any UADE will be conducted. If there is significant new information that could affect the risk/benefit analysis as given in Section 7.1 of this protocol, the ECs will be informed and if appropriate, actions such as study hold, patient re-consent or study termination will be taken.

All participant deaths must be immediately reported to the EC (24 h upon investigators knowledge). When possible and permitted by family members, an autopsy shall be performed. The death certificate, coroner's report, and laboratory and autopsy reports, if available, should be provided to the EC.

10. Documentation

All patient data will be documented in CRFs. Personal data such as name, address, contact data etc. are excluded from the documentation in the eCRF. Names of all patients will be pseudomized and underlie national data protection laws. The principal investigator will conserve the patient identification list, the signed informed consent forms and the original data including the patient chart for 15 years.

11. Study organization

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