# CAtheter-Based Ablation of atrial fibrillation compared to conventional treatment in patients with Heart Failure with Preserved Ejection Fraction - Investigator-initiated, prospective, parallel-group, randomized, open, blinded endpoint assessment (PROBE), interventional multicenter strategy trial

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The objective of CABA-HFPEF is to assess whether catheter ablation (CA) for atrial fibrillation (AF) can prevent adverse cardiovascular (CV) outcomes in patients with heart failure (HF) with preserved or mildly reduced ejection fraction (HFpEF or…

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Cardiac arrhythmias |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON56877

**Source**
ToetsingOnline

**Brief title**
CABA-HFpEF-DZHK27

### Condition

- Cardiac arrhythmias

**Synonym**
Atrial fibrillation and HFpEF, heart failure with a preserved ejection fraction

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Charité Universitätsmedizin Berlin
**Source(s) of monetary or material Support:** Boston Scientific Cooperation International,Het onderzoek wordt gefinancierd door het Duitse centrum voor Cardiovasculair Onderzoek (DZHK) en Boston Scientific International S.A.

## Intervention

**Keyword:** Ablation, Atrial Fibrillation, HFpEF

## Outcome measures

### Primary outcome

The primary outcome is defined as a composite of cardiovascular death, stroke

(first and recurrent), and total (first and recurrent) unplanned cardiovascular

hospitalization for heart failure or acute coronary syndrome.

### Secondary outcome

Secondary endpoints:

1. All-cause mortality,

2. CV death,

3. Stroke (first and recurrent),

4. Total (first and recurrent) unplanned CV hospitalization for heart failure

or acute coronary syndrome,

5. Unplanned hospitalization for atrial arrhythmia,

6. Total (first and recurrent) planned and unplanned CV

hospitalizations,

7. Nights spent in hospital,

8. Days alive and out of hospital,

9. AF burden (percentage of AF at 12 months FU Holter ECG),

10. Change in LVEF,

11. Change in NYHA class and EHRA score,

12. Change in quality of life

Exploratory outcome parameters:

1. Type of ablation strategy

2. Structural and functional changes at 12 months FU (echocardiography),

3. Biomarker effects and changes at 12 months FU (e.g. NT-proBNP, CRP),

4. Renal function (eGFR),

5. Other measures of quality of life,

6. Cost-effectiveness

Secondary safety endpoints:

The safety outcome parameter is a composite of total mortality, stroke within 90 days after AF ablation, and serious adverse events of special interest related to CA or other rhythm control therapies. All outcome parameters will be centrally adjudicated by the Endpoint Review Committee (ERC). All safety outcome parameters will be analysed descriptively only but are not part of the biometrical model of the trial.

# Study description

**Background summary**

Heart failure (HF) is associated with high morbidity and mortality and is among the most common reasons for hospitalization in developed countries (1). HF with preserved ejection fraction (HFpEF) accounts for approximately half of HF diagnoses (2). Although the prevalence of atrial fibrillation (AF) in HF with mildly reduced ejection fraction (HFmrEF; 40-60%) is lower than that of HFpEF, it is higher than that of HFrEF (3).

The incidence rates of all-cause mortality, HF hospitalizations and stroke seem to be a little lower in HFmrEF patients than in HFpEF or HFrEF patients (3). There are fewer treatment options for patients with HFpEF than for those with HFrEF. Some medications are under development, such as Empagliflozin which is yet not recommended for HFpEF/HFmrEF by the current ESC HF guidelines (refer to Appendix I), but advisable after EMA approval based on EMPEROR-Preserved trial (4).

Patients with HFpEF are predisposed to developing AF, with a prevalence of AF up to 65% (3, 5-8). Among those in sinus rhythm, one-third of patients with HFpEF will develop AF within the 3 to 5 years after HFpEF diagnosis. Conversely, the presence of AF increases the likelihood of subsequent HFpEF by up to 4-fold across diverse populations (9). LV diastolic dysfunction associated with HFpEF renders patients in a hemodynamically vulnerable state, which can further be aggravated by the loss of atrial contraction and reduction in cardiac output associated with AF. Thus, presence of AF in HFpEF patients leads to a significant increase in hospitalization, mortality and stroke (3, 7, 10-12).

Restoring and maintaining sinus rhythm in patients with HFpEF and AF could reduce cardiovascular (CV) outcomes. In the EAST-AFNET 4 trial, early rhythm control therapy led to a 21% reduction in CV events in patients with recently diagnosed AF who received contemporary, guideline-directed therapy (13). Conversely, a recent analysis of the AFFIRM trial (*rate vs rhythm*), which relied entirely on antiarrhythmic drugs (AAD) suggested no difference in outcome (14). Also in patients with AF and HF, AAD therapy compared to rate control did not show significant differences in all-cause mortality, CV mortality, or HF hospitalizations (15-16). Catheter-based ablation (CA), particularly when performed as initial rhythm control, results in less recurrences of AF than with AAD therapy (13, 17). In the CASTLE-AF trial, a randomized multicenter study in patients with HF with reduced ejection fraction (HFrEF) and AF, CA showed a significant reduction in all-cause mortality and worsening HF admissions compared to medical therapy (either rhythm control and rate control) (18). Thus, CA is now recommended (class IIa) in selected patients with symptomatic AF and HFrEF.

In patients with HFpEF and AF, small observational studies showed that restoration of sinus rhythm (mostly by means of CA) resulted in improved quality of life and improved HF symptoms (19, 20). A retrospective observational study including 283 patients with HFpEF and AF reported a lower rate of a composite of CV death or hospitalization for HF with rhythm (mostly CA) versus rate control (21).

A HF subanalysis of the CABANA trial found a significant clinical benefit of CA (i.e., 36% relative reduction) in patients with HF (i.e., NYHA class >=II) (22). Similar clinical benefit was found in a subgroup of patients with HF of the EAST-AFNET 4 trial (23). Of the 802 patients with HF enrolled in the EAST-AFNET 4 trial, 94/396 randomized to early rhythm control experienced a first primary outcome, 26% less than the 130/402 patients randomized to usual care. In this subanalysis, the reduction in CV death (46%, HR 0.54) and stroke (54%, HR 0.46) was particularly pronounced. All considered, these hypothesis-generating data suggest that rhythm control based on CA could be especially useful in patients with AF and HF.

As for HFpEF, no prior adequately sized randomized study has examined the role of CA in patients with AF and HFmrEF. A subgroup analysis in the EAST-AFNET4 trial showed a reduction of cardiovascular events with early rhythm control including CA in patients with AF and HF (defined as NYHA II-III and LVEF <50%) but included only 16.8% HFmrEF patients (23). A subgroup analysis in the CABANA trial showed a reduction in mortality and improved quality of life relative to AAD therapy in patients with AF and HF (defined as NYHA >II) and included 11.7% patients with an EF between 40% and 50% (22).

Until now, no clinical trial has tested or is currently testing the effects of CA on CV outcomes in patients with HFmrEF or HFpEF and AF. To address this, CABA-HFPEF tests whether CA can improve CV outcomes compared to usual care in these patients. The results of CABA-HFPEF will significantly contribute to the current evidence on ablation-based rhythm control to this large population in dire need for treatments that improve clinical outcomes.

## Study objective

The objective of CABA-HFPEF is to assess whether catheter ablation (CA) for atrial fibrillation (AF) can prevent adverse cardiovascular (CV) outcomes in patients with heart failure (HF) with preserved or mildly reduced ejection fraction (HFpEF or HFmrEF, respectively).

## Study design

Investigator-initiated, prospective, parallel-group, randomized, open, blinded endpoint assessment (PROBE), interventional multicenter strategy trial.

**Intervention**

Patients will be randomized 1:1 into two study arms:

- Interventional arm (group 1): Rhythm control treatment with catheter ablation for atrial fibrillation in addition to therapy for heart failure according to the current guidelines of the European Society of Cardiology.

- Control arm (group 2): Usual medical care according to the current ESC Guidelines for diagnosis and management of atrial fibrillation in addition to guideline-based therapy for heart failure. Catheter ablation is discouraged for patients in the control arm, but an option if medically required during the course of the trial.

CABA-HFPEF compares a strategy of systematic, early CA in addition to usual care in patients with HFmrEF/HFpEF and AF. The trial has the potential to improve prognosis in this cohort of patients who are difficult to treat. None of the therapies employed in CABA-HFPEF is investigational. Patients receive approved, CE-marked and recommended therapies for AF within indications according to the current guidelines.

**Study burden and risks**

The patients participating in this clinical study are not subjected to any special risks that would not also exist in the course of a regular treatment.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Age >=18 years
2. Signed written informed consent
3. Clinical evidence of symptomatic heart failure (NYHA class II-III)
4. Paroxysmal or persistent atrial fibrillation documented (12-lead, multiple, or single leads) at least once within the last 12 months.
5. Left ventricular ejection fraction (LVEF) 40-49% OR LVEF >=50% with at least one of the following
HFpEF echocardiography findings (any local measurement made during the screening epoch):
a. Left atrial (LA) enlargement defined by at least 1 of the following: LA width (diameter) >=3.8
cm or LA length >=5.0 cm or LA area >=20 cm2 or LA volume >=55 ml or LA volume index >=29
ml/m2
b. Left ventricular hypertrophy (septal thickness or posterior wall thickness >=1.1cm or relative
wall thickness >0.42)
6. Patients with at least 1 of the following:
a. HF hospitalization (defined as HF listed as the major reason for hospitalization) within 6
months prior to the screening visit and NT-proBNP >200 pg/ml for patients in sinus rhythm
(SR) or >600 pg/ml for patients in AF at the time of blood sampling
b. NT-proBNP >300 pg/ml for patients in SR or >900 pg/ml for patients in AF on screening ECG

## Exclusion criteria

1. Patient is unable or unwilling to provide informed consent
2. Patient is not suitable for rhythm control of AF (e.g. permanent AF, long-standing persistend AF)
3. Previous left atrial CA or surgical therapy of AF
4. Acutely decompensated HF, NYHA IV (patients can be enrolled after stabilization)
5. Valvular heart disease needing interventional or surgical treatment within 3 months
6. Heart surgery planned within 3 months
7. Prior heart transplant or listed for heart transplant or cardiac assist device implantation
8. Untreated hypothyroidism or hyperthyroidism (after successful treatment of thyroid dysfunction,
patients may be enrolled)
9. Patient has contra-indication to oral anticoagulation
10. Any disease that limits life expectancy to less than 1 year
11. Active systemic infection (after successful treatment of infection, patients may be enrolled)
12. Women currently pregnant or breastfeeding or women of childbearing potential without highly
effective contraception (PEARL-Index < 1%),
13. Patient is included in another clinical trial
14. Inability to comply with the study procedures

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Health services research

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 24-09-2024 |

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| Enrollment: | 111 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 27-06-2024 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 11-10-2024 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| ClinicalTrials.gov | NCT05508256 |
| CCMO | NL86442.100.24 |