

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION, A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25 TRIAL)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056522
Article Type:	Protocol
Date Submitted by the Author:	18-Aug-2021
Complete List of Authors:	<p>Osmancik, Pavel; 3rd Faculty of Medicine, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter  Havránek, Štěpán  Bulková, Veronika; Neuron Medical sro, Dept. of Cardiology  Chovančík, Jan; Hospital AGEL Trinec – Podlesi, Dept. of Cardiology  Roubíček, Tomáš; Liberec, Dept. of Cardiology  Heřman, Dalibor; 3rd Faculty of Medicine, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter  Čarná, Zuzana; 3rd Faculty of Medicine, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter  Tuka, Vladimír  Fiala, Martin; Neuron Medical sro, Dept. of Cardiology  Jiravský, Otakar; Hospital AGEL Trinec – Podlesi, Dept. of Cardiology  Štrégl, Sylvie  Latiňák, Adam; Liberec, Dept. of Cardiology  Kotryová, Jiřina; Masaryk University  Matoulek, Martin; Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic  Jarkovský, Jiří; Faculty of Medicine and the Faculty of Science of the Masaryk University, Institute of Biostatistics and Analyses</p>
Keywords:	Pacing & electrophysiology < CARDIOLOGY, Adult cardiology < CARDIOLOGY, NUTRITION & DIETETICS

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7 **CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK**  
8  
9 **FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION,**  
10  
11 **A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25 TRIAL)**  
12  
13

14  
15 Pavel Osmančík<sup>1</sup>, Štěpán Havránek<sup>2</sup>, Veronika Bulková<sup>3</sup>, Jan Chovančík<sup>4</sup>, Tomáš Roubíček<sup>5</sup>,  
16  
17 Dalibor Heřman<sup>1</sup>, Zuzana Čarná<sup>1</sup>, Vladimír Tuka<sup>2</sup>, Martin Matoulek<sup>2</sup>, Martin Fiala<sup>3</sup>, Otakar  
18  
19 Jiravský<sup>4</sup>, Sylvie Štrégl – Hrušková<sup>5</sup>, Adam Latiňák<sup>5</sup>, Jiřina Kotryová<sup>6</sup>, Jiri Jarkovsky<sup>6</sup>  
20  
21

- 22  
23 1. Dept. of Cardiology, Cardiocenter, 3<sup>rd</sup> Faculty of Medicine and University Hospital  
24 Kralovske Vinohrady, Prague, Czech Republic  
25 2. 2<sup>nd</sup> Department of Internal Medicine - Dept. of Cardiovascular Medicine, 1<sup>st</sup> Faculty of  
26 Medicine, Charles University and General University Hospital, Prague, Czech republic  
27 3. Dept. of Cardiology, Neuron Medical, s.r.o., Brno, Czech republic  
28 4. Dept. of Cardiology, Hospital AGEL Trinec – Podlesi, a.s., Trinec, Czech republic  
29 5. Dept. of Cardiology, Regional Hospital Liberec, Liberec, Czech republic  
30 6. Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech republic  
31  
32

33  
34  
35 **Corresponding author:**

36 Pavel Osmancik, MD, PhD  
37 Dept of cardiology, Cardiocenter  
38 3<sup>rd</sup> Faculty of Medicine and University Hospital  
39 Kralovske Vinohrady  
40 Srobarova 50  
41 10034, Prague  
42 Czech Republic  
43 Phone: 00420-721544447  
44 Email: [pavel.osmancik@gmail.com](mailto:pavel.osmancik@gmail.com)  
45

46 **Keywords:** atrial fibrillation, catheter ablation, antiarrhythmic drugs, risk factor modification  
47  
48

49 **Section:** Trial Design (Protocol of a Study)

50 **Word count:** 4000

51 **Declaration of interest:** none

52 **Running headline:** Protocol of Prague-25 trial

53 **RCT No:** NCT04011800

54 **Financial support:** Research grant of the Ministry of Health Czech Republic, No NU21-02-  
55 00388  
56  
57

## ABSTRACT

**Introduction:** Atrial fibrillation (AF), with a prevalence of 2%, is the most common cardiac arrhythmia. Catheter ablation (CA) has been documented to be superior over treatment by antiarrhythmic drugs (AADs) in terms of sinus rhythm (SR) maintenance. However, in obese patients, substantial weight loss was also associated with AF reduction. So far, no study has compared the modern noninvasive (AADs combined with risk factor modification) approach with modern invasive (CA) treatment. The aim of the trial is to compare the efficacy of modern invasive (catheter ablation) and noninvasive (AADs with risk factor management) treatment of AF.

**Methods and Analysis:** The trial will be a prospective, multicenter, randomized non-inferiority trial. Patients with symptomatic AF and a body-mass index  $> 30$  will be enrolled and randomized to the CA or risk factor modification arm (RFM) in a 1:1 ratio. In the CA arm, pulmonary vein isolation (in combination with additional lesion sets in non-paroxysmal patients) will be performed. For patients in the RFM arm, the aim will be a 10% weight loss over 6–12 months, increased physical fitness, and a reduction in alcohol consumption. The primary endpoint will be any episode of AF or regular AT lasting  $> 30$  sec. The secondary endpoints include AF burden, clinical endpoints associated with AF recurrence, changes in the quality of life assessed using dedicated questionnaires, changes in cardiorespiratory fitness, and metabolic endpoints. An AF freedom of 65% in the RFM and of 60% in the CA is expected; therefore, 202 patients will be enrolled to achieve the non-inferiority with 80% power, 5% one-sided alpha, and a non-inferiority margin of 12%.

1  
2  
3  
4  
5  
6  
7 **Ethics and Dissemination:** The PRAGUE-25 trial will determine if modern noninvasive AF  
8  
9 treatment strategies are non-inferior to catheter ablation.  
10

11 **Registration details:** The study was registered on clinicaltrials.gov as NCT04011800  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21

## 22 **ARTICLE SUMMARY**

### 23 **Strengths of this study**

- 24 • The population of the study (obese patients with AF) is growing
- 25 • For the first time, AADs treatment combined with risk factor modification will be  
26 compared with catheter ablation  
27  
28  
29  
30  
31  
32

### 33 **Limitations of this study**

- 34 • The study is not large enough to compare clinical endpoints
- 35 • The monitoring using implantable loop recorders would be more sensitive  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, having a prevalence of about  $\approx 2\%$  in the general population. Among healthy men and women aged  $> 40$  years, the risk of lifelong AF occurrence is approximately 25% (1). The current estimated prevalence of AF is approximately 50 million patients worldwide, and its incidence has been increasing due to improved diagnostics, better treatment of chronic diseases, and increasing age (2). Therefore, its prevalence is expected to increase by nearly 3-fold during the next three decades. AF is associated with a three-fold increase in the risk of stroke and a two-fold increase in mortality risk (2).

### **Catheter ablation and its limitation**

Catheter ablation (CA) with pulmonary vein isolation (PVI) has been found to be superior to antiarrhythmic drugs (AADs) in terms of AF freedom in several randomized, controlled trials. The one-year efficacy of CA ranges from 40–90% (depending on the type of AF, patient cohort, and follow-up methods) (3). In patients with heart failure, AF, and decreased ejection fraction (EF), CA was associated with decreased mortality (4). However, mortality or clear clinical benefit of CA over AADs was not documented in the broad population of AF patients in the CABANA trial, the largest study on CA in AF (5). Except for the CABANA trial with 2,204 patients enrolled, all other studies have been substantially smaller (median of enrolled patients = 119 patients). In two well-conceived recent trials comparing CA (albeit using cryo-balloon ablation) with AADs, the one-year AF freedom was 74.6% when assessed using 24-hour Holter monitoring, or 57.1% when assessed using implantable loop recorders (6) (7).

### **The efficacy and limitations of the antiarrhythmic drugs**

1  
2  
3  
4  
5  
6  
7 Several AADs (propafenone, flecainide, sotalol, amiodarone) have been documented as being  
8 superior compared to placebo for reducing the recurrence of AF (OR 0.19–0.70 for AADs) (8).  
9  
10 Moreover, in patients with an early AF diagnosis, early treatment of AF (in 86.8% of pts. using  
11 AADs) was associated with a reduction in cardiovascular mortality, stroke, hospitalization for  
12 heart failure, and acute coronary syndromes (9). However, the effect of AADs for SR  
13 maintenance is only modest. In the two most recent randomized control trials (RCT) comparing  
14 AADs (92% of which were flecainide and sotalol), with CA, the complete one-year AF freedom  
15 on AADs was 45%, or 32.2%, depending on the type of monitoring. (6) (7). The long-term use  
16 of AADs is often limited by serious side effects and toxicity. It is especially true for amiodarone,  
17 otherwise the most effective AAD (10), which often causes extracardiac side-effects. especially  
18 during long-term therapy. Therefore it is mainly used as a second or third drug after failure of  
19 other AADs or CA (11).  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33

### 34 **Risk factor modification**

35  
36 According to several observational studies, obesity has been found to be independently  
37 associated with a higher risk of occurrence, and as well as progression of AF (12) (13).  
38  
39 According to a meta-analysis of 51 studies, which included more than 60,000 patients, an  
40 increase in the body-mass index (BMI) by 5 points is associated with a 19%–29% increase in  
41 the incidence of AF(14). Besides obesity, other modifiable risk factors include hypertension,  
42 sleep apnea, and alcohol consumption (15) (16) (17). Importantly, several recent interventional  
43 studies have shown that all the aforementioned factors are not only known epidemiological  
44 variables associated with a higher risk of AF, but their intensive treatment are associated with  
45 a decrease in AF reoccurrences. In the non-randomized ARREST-AF study, 149 patients with  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 a BMI  $\geq 27$  after catheter ablation of AF were offered an opportunity to participate in a  
8  
9 physician-driven intensive risk factor modification (RFM) program, consisting of dietary  
10  
11 changes and regular physical exercise. Risk factor management was associated with a  
12  
13 significant reduction in AF recurrence by 23.9% (18). In the prospective, non-randomized  
14  
15 LEGACY study, risk factor management, which also focused on weight loss, was offered to a  
16  
17 cohort of 355 AF patients with a BMI  $\geq 27$  who had been referred to a tertiary center for AF  
18  
19 treatment (contrary to ARREST-AF study, patients in the LEGACY study had no history of  
20  
21 AF ablation) (19). AF freedom was achieved in 45% of patients with weight loss  $\geq 10\%$ , and  
22  
23 in 22% of patients with weight loss between 3 and 9% (19). Similarly, in a study by Malmo et  
24  
25 al., patients undergoing regular physical activity had AF paroxysms decline from 8.1% to 4.8%  
26  
27 (20). Moreover, last year Voskoboynik et al. documented that a reduction in alcohol  
28  
29 consumption was also associated with a significant reduction of AF paroxysms (21). It seems  
30  
31 that AF treatment could lie, at least in some patients, outside the electrophysiological cath-labs.  
32  
33 However, and it is also important to note, all studies that focused on weight loss were either  
34  
35 observational or had a non-randomized control arm (ARREST-AF, LEGACY). Since  
36  
37 participation, especially in metabolic interventions, requires a high level of patient motivation,  
38  
39 the absence of a control arm potentially introduces a large bias into all the aforementioned  
40  
41 studies.  
42  
43  
44  
45  
46  
47

#### 48 **Structural changes of ventricles and pericardial fat in patients with AF and obesity**

49  
50 As was shown, the amount of epicardial adipose tissue (EAT) is higher in patients with AF.  
51  
52 EAT is independently associated with future occurrences of AF in healthy persons and is also  
53  
54 a predictive factor for AF recurrence after catheter ablation (22) (23). Similarly, the degree of  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7 diffuse myocardial ventricular fibrosis is higher in AF patients compared to healthy subjects  
8  
9 (24). Both the amount of EAT, as well as diffuse myocardial fibrosis, can be assessed using  
10  
11 cardiac magnetic resonance (CMR); the latter recently very sensitively using postcontrast-  
12  
13 enhanced T1 mapping (24). Recently, diffuse myocardial fibrosis assessed using post-contrast  
14  
15 T1 mapping predicted the effect of AF catheter ablation in paroxysmal patients (25). Early  
16  
17 changes on a CMR, such as higher left ventricular mass, or cardiac remodeling index, were also  
18  
19 described in patients with obesity (26).  
20  
21

### 22 23 **Pro-inflammatory markers changes in AF and in obesity**

24  
25 The concentrations of pro-inflammatory markers, such as high-sensitivity CRP, interleukin-6,  
26  
27 TNF- $\alpha$ , and others, have been reported to be elevated in AF patients, as well as in obese  
28  
29 individuals with SR. In obese patients, the adipose tissue is an important source of the pro-  
30  
31 inflammatory cytokines, and the concentrations of several pro-inflammatory cytokines  
32  
33 significantly decrease after weight loss (27). In AF patients, increased pre-ablation levels of  
34  
35 BNP, ANP, IL-6, and hsCRP are associated with a greater risk of AF recurrence after ablation  
36  
37 (28). However, studies focusing on the effect of CA on pro-inflammatory cytokines have shown  
38  
39 mixed results, and in the majority of them, the concentrations remained unchanged in AF  
40  
41 patients after successful AF ablation with SR maintenance after 12 months (29) (30).  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## METHODS AND ANALYSIS

### Study design and objective

The PRAGUE-25 trial is a prospective, multicenter, investigator-initiated, randomized, non-inferiority study registered on [clinicaltrials.gov](http://clinicaltrials.gov) (NCT04011800). The primary objective is to compare the efficacy of modern invasive (catheter ablation) and noninvasive (AADs and RFM) treatment on AF. Secondary endpoints include clinical endpoints, changes in the QoL, cardiorespiratory fitness, pro-inflammatory cytokines concentrations, echocardiography and MRI measures. The CONSORT diagram of the study is shown in **Figure 1**.

### Patient and Public Involvement

A significant portion of patients with AF are obese (e.g. the median BMI was 30 in the CABANA Trial). Important reason of the study was that a significant portion of AF patients are afraid of invasive procedures, ask about and would prefer a noninvasive approach if the efficacy of this approach is known. So, the idea of the study was initiated by the interest of AF patients. The design and protocol of the study was written by investigator without patient's involvement. Regarding the dissemination of the results, apart of scientific conferences, presentation on patient's days organized by the participating hospitals is planned.

### Patient population

The study will enroll symptomatic AF patients with high BMIs. The qualifying criteria are symptomatic documented AF, higher BMI, and patient motivation, since the allocation to the risk factor modification (RFM) arm includes activities that directly require patient activity.

#### *Inclusion criteria:*

- symptomatic AF (paroxysmal, persistent, or long-standing persistent)

- BMI  $\geq$  30
- signed informed consent

*Exclusion criteria:*

- permanent AF
- BMI  $\geq$  40
- severe valve disease (significant aortic stenosis, mitral regurgitation  $\geq$  3)
- left ventricular ejection fraction  $<$  40%
- moderate or severe pulmonary hypertension (sPAP  $\geq$  40 mm Hg)
- history of tachycardia-induced cardiomyopathy
- manifest coronary artery disease
- pregnancy
- left atrial size  $\geq$  60 mm
- indication for surgical treatment of obesity
- age  $\geq$  75 yrs.
- diabetes mellitus needing insulin
- significant physical limitations that could affect physical activity (musculoskeletal disorders, moderate or severe COPD)
- life expectancy  $<$  2 years

**Baseline examinations**

After informed content is given, all patients will undergo baseline anthropometric measurements (weight, waist to hip ratio, body fat measurement) and a baseline functional evaluation. It will include (1) baseline evaluation of physical fitness - cardiopulmonary exercise

1  
2  
3  
4  
5  
6  
7 test, (2) echocardiography, (3) quality of life analysis (using AFEQT questionnaire), (4) blood  
8  
9 biochemistry and cytokine analysis, and (5) a baseline one-week ECG Holter recording. All  
10  
11 these examinations will be done within four weeks after randomization.  
12

### 13 **Randomization**

14  
15  
16 Patients will be randomized to the catheter ablation group (CA) or risk factor modification  
17  
18 group plus AADs (RFM) in a 1:1 ratio; randomization will be done using randomization  
19  
20 software that will account for age, initial BMI, and AF type, with the goal of having comparable  
21  
22 groups relative to those characteristics. The randomization process will be done outside all  
23  
24 participating centers.  
25  
26

### 27 **Functional diagnostic (anthropometric measurement and cardiopulmonary exercise test)**

28  
29  
30 Functional diagnostics will be performed in all patients. Based on the results, an individualized  
31  
32 physical training program will be prepared in patients randomized to the RFM arm.  
33

34  
35 An initial maximum symptom limited cardiopulmonary exercise test (CEPT) will be carried out  
36  
37 within one month of enrollment. The CPET will be carried out on the medication which was  
38  
39 present at enrollment visit. The cycle ergometer will be used in all sites. The protocol will  
40  
41 consist of a 3-min warm-up period with 0 Watt (unloaded pedaling), followed by a ramp test  
42  
43 increase of exercise intensity increased by 0.1 W/kg/min in women and by 0.15 W/kg/min in  
44  
45 men up to the maximum subjective tolerance. A 12-lead ECG tracing will be obtained  
46  
47 throughout the test for heart rate measurement, arrhythmia (especially AF) detection and safety  
48  
49 reasons. Blood pressure will be measured manually with adequately selected cuff size. From  
50  
51 exhaled gas analysis oxygen uptake  $VO_2$ , carbon dioxide production  $VCO_2$  and minute  
52  
53 ventilation (VE) will be determined. Peak  $VO_2$  will be defined as the maximum value of  $VO_2$   
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 averaged over 15 seconds, both absolute values and values indexed to body weight will be used.

8  
9 The VCO<sub>2</sub>/VE slope will be calculated from the beginning of the incremental exercise till the  
10  
11 respiratory compensation point. Both ventilatory thresholds will be calculated.  
12  
13

## 14 15 16 **TREATMENTS**

### 17 18 **Catheter ablation arm**

19  
20 CA will be done within two months of randomization. In paroxysmal patients, a PVI will be  
21  
22 performed. In patients with non-paroxysmal AF forms, additional lesion sets will be allowed  
23  
24 according to the practice of each participating center. The CA will be done using a 3D mapping  
25  
26 system, intracardiac echocardiography, contact-force sensing ablation catheters, and ablation  
27  
28 index to achieve the maximum available safety and efficacy.  
29  
30

31  
32 The first three months following catheter ablation will be considered as a “blinking period,”  
33  
34 i.e., AF reoccurrences won't be assessed as an endpoint. During this period, treatment using  
35  
36 AADs or cardioversion will be allowed. Three months after ablation, AADs will be  
37  
38 discontinued.  
39  
40

### 41 42 **Risk factor modification and AADs arm**

43  
44 The aim will be (1) a 10% weight loss over 6–12 months,(2) an increase in physical fitness, and  
45  
46 (3) a reduction in alcohol consumption. RFM will be performed not by treating cardiologist,  
47  
48 but by teams of dietary specialists and physiotherapists. Nutritional intervention: the initial  
49  
50 patient consultations with nutritional specialists will be done during the first month after  
51  
52 enrollment. A low-calorie, high protein, and low glycemic index dietary menu will be suggested  
53  
54 and optimized by a nutritional specialist for each patient. Except of regular in-person  
55  
56  
57

1  
2  
3  
4  
5  
6  
7 consultations with dietary specialists, phone visits any time during the follow-up; patients will  
8  
9 be encouraged to record the calory intake in the OBEFIS application (either on the web  
10  
11 [www.obefis.cz](http://www.obefis.cz), or using the mobile application), and the recordings will be discussed during  
12  
13 the visits with dietary specialists.  
14

15  
16 All patients will have an initial consultation with a physiotherapist (after the CPET) to set the  
17  
18 type and intensity of the physical intervention. The recommended physical intervention will  
19  
20 consist of three types of activities: (1) regular gym-based training (in small groups or individual  
21  
22 training with trainer),(2i) individual aerobic training (fast walking or similar aerobic activity),  
23  
24 and (3) home-based training: 20 min physical exercise sets. The type and ratio of the  
25  
26 aforementioned physical exercises will be changed over the study period. However, based on  
27  
28 the patient's experiences with physical activity in the past, and their options regarding  
29  
30 participation in the organized training, activities will be individualized. The ESC guidelines  
31  
32 for obese individuals recommend that a minimum of 150 min/week of moderate-intensity  
33  
34 endurance exercise training should be combined with three weekly sessions of resistance  
35  
36 exercise with the heart rate during the activity being 55–74% of the maximum HR (31). As  
37  
38 such, the physical intervention will be based on regular (mainly moderate, ~ 55-74% of the  
39  
40 maximum HR) intensity aerobic exercise that will be gradually increased from 60 min/week up  
41  
42 to 200 min/week. Since the adherence of patients to regular activity is affected by activity  
43  
44 monitoring, all patients will have an opportunity to be monitored during each exercise using  
45  
46 remote heart rate monitoring (fitness bands) and the OBEFIS smartphone application.  
47  
48  
49  
50  
51

52 For patients in the RFM arm, contrary to patients in the CA arm, non-amiodarone AADs will  
53  
54 be allowed during the whole study period. The choice of AAD will occur during the blanking  
55  
56  
57

1  
2  
3  
4  
5  
6  
7 period. Since weight loss goals will take months, the effect of metabolic interventions cannot  
8  
9 be expected as fast as in the CA arm. Therefore, the blanking period for the RFM arm will last  
10  
11 6, instead of 3 months. The reoccurrence as AF/AT as an endpoint will be considered starting  
12  
13 at the 6-month visit, including a 7-day Holter, which is scheduled to be done at the 6-month  
14  
15  
16 visit.

17  
18 In both arms, in case of a reoccurrence of symptomatic AF or atrial tachycardia (AT), re-do  
19  
20 ablations, cardioversion, or AADs treatment during the follow-up period will be allowed in  
21  
22 accordance with the current guidelines and practices of participating centers. However, because  
23  
24 the indication for the aforementioned procedures or AAD initiation will be a reoccurrence of  
25  
26 AF or AT, it will be assessed as the primary endpoint (i.e., AF reoccurrence).  
27  
28  
29  
30  
31

## 32 **OUTPATIENT FOLLOW-UP AND ENDPOINT MONITORING**

33  
34 The follow-up protocol and ECG monitoring will be similar for both arms. Starting on the day  
35  
36 of the catheter ablation (D0 in the ablation arm), or at the start of the metabolic activity (D0 in  
37  
38 the RFM arm, approx. 3–4 weeks after randomization), follow-up visits will be scheduled at 3,  
39  
40 6, 9, and 12 months during the first year, and then every six months. At the 3-month follow-up  
41  
42 visit, patients in AF (from both groups) will undergo electrical cardioversion.  
43  
44

45  
46 A routine 12-lead ECG will be recorded at each follow-up visit, along with a physical  
47  
48 examination of the patient and a medical history update. Long-term ECG recording will be done  
49  
50 using a 7-day Holter recording at baseline, and then at the 6, 9, and 12 months visits during the  
51  
52 first year, and then every six months in the second and third years. At the 12-month follow-up  
53  
54 visit, echocardiography, MRI examination, anthropometric measurements, and CPET will be  
55  
56

1  
2  
3  
4  
5  
6  
7 done. Blood will be drawn for cytokine analysis, and patients will also be asked to complete  
8  
9 follow-up QoL questionnaires.  
10

## 11 **STUDY OUTCOMES**

### 13 **Primary endpoints:**

- 14 1) AF reoccurrence (any AF or atrial tachycardia lasting more than 30 sec)

### 15 **Secondary endpoints**

- 16 1) AF burden: calculated using all Holter recordings as a percentage of time spent in AF  
17 or AT
- 18 2) AF reoccurrence and AF burden at the 12-month visit
- 19 3) Hospitalization for AF reoccurrence and/or emergency room visit due to AF
- 20 4) A composite of stroke, cardiovascular death, or hospitalization for heart failure
- 21 5) Changes in QoL questionnaires between baseline and 12 months
- 22 6) Change in cardiorespiratory fitness as assessed using CPET between baseline and 12  
23 months
- 24 7) Metabolic endpoint: changes in weight, lipid levels, glycated hemoglobin, and pro-  
25 inflammatory cytokines
- 26 8) Imaging endpoints: change in diffuse ventricular fibrosis and EAT between baseline  
27 and the 12-month examination (MRI)

28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48 The AF reoccurrence will be detected either using planned 7-day Holter recordings (at the 6, 9,  
49 and 12 m visits), during all planned outpatient visits using a standard 12-lead ECG, and any  
50  
51 time during the follow-up after the blanking period at an emergency non-planned visit also  
52  
53 using a standard 12-lead ECG. During the planned or emergency visits, AF reoccurrence has to  
54  
55  
56



1  
2  
3  
4  
5  
6  
7 be documented using an ECG (i.e., a patient's description of "palpitations" without ECG  
8 evidence will not be assessed as AF recurrence).

## 11 **STATISTICAL ANALYSIS PLAN AND POWER CALCULATION**

13 The power calculation was based on the results of randomized trials and observational studies  
14 comparing and assessing the effect of AADs vs. placebo, CA vs. AADs, and assessing the effect  
15 of risk factor modification in observational cohort studies. The primary efficacy analysis (non-  
16 inferiority) will be undertaken using the intention-to-treat and per-protocol population. If the  
17 non-inferiority criterion is satisfied, then superiority for the primary endpoint will be tested.

### 25 ***The expected efficacy of AADs and RFM***

27 In a meta-analysis of 24 randomized control trials comparing AADs with placebo, the overall  
28 success rate of AADs, defined as the disappearance of arrhythmia during follow-up, was present  
29 in 52% (95%CI 47%–57%) of patients on AADs (32). In the CABANA trial, by 12 months, the  
30 one-year AF freedom on AADs was present in 47.1% of patients (33). Finally, in the recently  
31 published STOP-AF trial, one-year AF freedom (assessed using repeated 24-Hour Holter  
32 recordings) was present in 45.0% (95%CI 34.6–54.7) of patients. Therefore, a one-year AF  
33 freedom of 45% could be expected for non-amiodarone AADs (6). In the LEGACY study,  
34 45.5% patients with weight loss >10%, 22.2% with weight loss 3–9%, and 13.4% in the weight  
35 loss < 3% remained AF-free without AADs or ablation (19). No study has compared the  
36 additive effect of weight loss on top of AADs; however, an additional effect of 20% could be  
37 expected in these patients. Therefore, we expected a  $\approx$  65% one-year AF freedom in the  
38 noninvasive treated patients.

### 55 ***The expected efficacy of the Catheter ablation***

1  
2  
3  
4  
5  
6  
7 In a meta-analysis of RCT comparing CA with AADs, the single procedure success rate of CA  
8 OFF AADs was 57% (95%CI 50–64%) (32). In the CABANA trial, AF freedom was present  
9 in 63.6% of the ablation patients by 12 months (33). The expected one-year AF freedom in the  
10 CA arm is  $\approx 60\%$ .

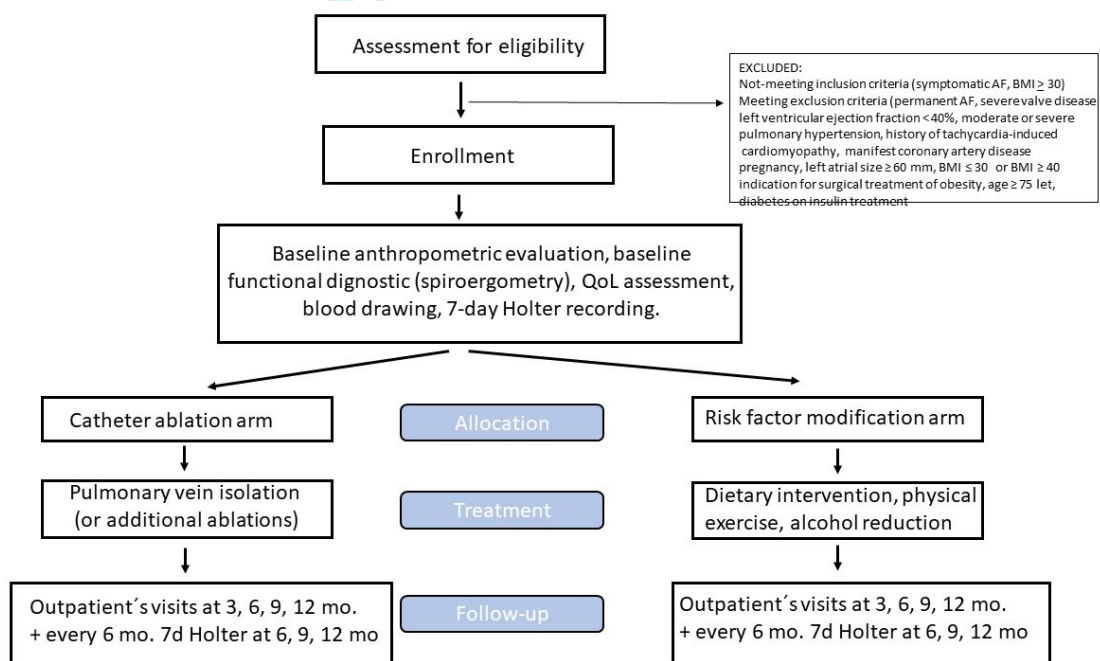
11  
12  
13  
14  
15  
16 According to the aforementioned data, we expect one-year AF freedom in 65% of patients in  
17 the RFM arm and 60% in the CA arm. The primary analysis will be done using the intention-  
18 to-treat principle; however, based on the non-inferiority nature of the study, a per-protocol  
19 analysis will be done. The sample size calculation assumed: 80% power, 5% one-sided alpha,  
20 a non-inferiority margin of 12% (or 1.65, if expressed as an odds ratio). Using this assumption,  
21 202 patients (101 in each arm) will need to be enrolled to prove non-inferiority of the  
22 noninvasive arm relative to the invasive arm. With an expected drop-out rate of 5%, therefore,  
23 212 patients will be enrolled.

### 24 25 26 27 28 29 30 31 32 33 34 ***Non-inferiority margin (NIM) considerations***

35  
36  
37 Regulatory guidelines require that the NIM rules out the minimum effect of treatment in the  
38 control arm (i.e., the CA arm in our study). Statistical guidelines recommend the most liberal  
39 NIM 1.92 (if expressed relatively as OR). From the clinical point of view, several rules exist  
40 for NIM adjustment. Obviously, the margin corresponds to the preservation of 50% benefit of  
41 the known treatment arm over placebo that was recognized in a previous studies comparing  
42 recognized treatment with placebo. The other recommendation for NIM is to use the lower band  
43 of 95% confidence interval of the placebo effect from previous studies comparing actual known  
44 treatment with placebo. Thus, for the study, the first step in selecting NIM was to estimate the  
45 minimum acceptable retention of benefit of CA over placebo. In studies comparing CA with  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

AADs, the single procedure success rate of CA OFF AADs was 57% (95% CI 50–64%). Unfortunately, none of the studies had a placebo arm, and all compared CA with AADs. In the studies comparing AADs vs. placebo, the success of treatment in the placebo arms was 24.9% (95% CI, 15%–34%). So, the selected margin of 12% fulfills the criteria for NIM setting. If it is expressed as an OR, it corresponds to 1.65, which is consistent with regulatory guidelines recommendations (and, e.g., it is similar as it was in large non-inferiority trials comparing NOAC with Warfarin).

**Figure 1 - CONSORT diagram of the study**



### Study organization and data management

The institution responsible for the organization and implementation of the study is the 3<sup>rd</sup> Faculty of Medicine, Charles University in Prague, Czech Republic. Data obtained during each patient visit will be collected using a safe electronic CRF form. A tailor-made website was

1  
2  
3  
4  
5  
6  
7 developed for the study. Each participating medical center will have access to a dedicated part  
8  
9 of the website. The local investigator at each site will be responsible for data completeness and  
10  
11 validity. At the end of the study, all data will be entered and stored on a password-protected  
12  
13 computer. Only the principal investigator will have access to the final data set. All regulations  
14  
15 regarding medical confidentiality and data protection will be fulfilled.  
16  
17

18 The database and randomization software has been prepared by an outside party (i.e., the  
19  
20 Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic), and no  
21  
22 investigator will have access to the database or the randomization software. The Institute of  
23  
24 Biostatistics and Analyses will also independently collect all data, manage the database, and be  
25  
26 responsible for data analysis. No other groups (i.e., device manufacturers or pharmaceutical  
27  
28 companies) were involved in the creation of the protocol or any other part of the study.  
29  
30

### 31 32 **Safety and endpoint monitoring**

33  
34 The local investigator at each site will continuously review safety data during the trial. A Data  
35  
36 Safety Monitoring Board (DSMB) will be constituted before the commencement of the trial.  
37  
38 Reporting of adverse events will be reported to the DSMB immediately by the principal  
39  
40 investigator. Serious adverse events (SAE) will be defined as life-threatening events or events  
41  
42 resulting in death or hospitalization. All SAEs linked with the study will be reported to the  
43  
44 DSMB, to the FNKV Ethics Committee (a multicenter ethics committee, EC), and to the local  
45  
46 ECs within 24 hours of study staff becoming aware of the event. Clinical endpoints will be  
47  
48 analyzed by a dedicated clinical endpoint committee. The recording and analyses of all Holter  
49  
50 recordings in all participating centers will be done centrally using an MDT (medical data  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 transfer) company. A standard, commercially available, 7-day Holter monitors (e.g. Faros 160,  
8  
9 Bittium, Finland, or similar tools ) with daily transtelephonic transfer will be used.  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19

## 20 **DISCUSSION**

21  
22  
23 In the last five years, lifestyle modification with risk factor management has been shown to be  
24  
25 a very promising treatment modality for AF. AF is the most common sustained cardiac  
26  
27 arrhythmia, with an estimated worldwide prevalence of about 33.5 million people (2).  
28  
29 According to recent epidemiological studies, its prevalence may triple by 2050 (19). Even if  
30  
31 catheter ablations were associated with a 100% success rate, it would be impossible to treat the  
32  
33 current or projected numbers using catheter ablations. Furthermore, a substantial number of  
34  
35 patients would prefer a non-invasive treatment if both strategies were comparable. So while  
36  
37 risk factor modification studies may seem to offer a panacea, those studies suffer from  
38  
39 significant limitations and possible biases. For example, the most important and most extensive  
40  
41 studies were both non-randomized, and all patients had either a history of catheter ablation  
42  
43 (ARREST-AF) or were without a history of catheter ablation, but catheter ablation was allowed  
44  
45 without limitations, based on the judgment of the attending physician during the follow-up  
46  
47 period (LEGACY). A randomized study that directly compares catheter ablation with a modern  
48  
49 noninvasive strategy has yet to be done. If the effect of both strategies were comparable, the  
50  
51 noninvasive strategy could be offered to patients with a preference for a noninvasive treatment.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 Only a randomized study can really answer the question of how effective lifestyle modification  
8  
9 is supported by safe non-amiodarone AADs compared to a modern invasive strategy.  
10  
11  
12

### 13 14 **ETHICS AND DISSEMINATION**

15  
16 The enrollment of the population is planned for 2 years. The first results will be published in  
17  
18 the end of the 2023, of in the beginning of 2024. Standard presentation on scientific conferences  
19  
20 and in extenso publication in impact journals is planned. No new drugs or devices are planned  
21  
22 for the study, so there are no specific ethical consideration. However, as it corresponds to the  
23  
24 standard of all RCT, all the serious adverse events will be immediately reported to the  
25  
26 appropriate Ethics Committee, as noted in the protocol.  
27  
28  
29  
30  
31

32 **AUTHORS' CONTRIBUTION:** PO wrote the manuscript and has initiated the study. The  
33  
34 authors SH, VB, JC, TR, DH, ZC, OJ and MF are responsible for the general for the analysis  
35  
36 of the EP literature and the EP part of the protocol. The authors VT, MM, SSH, AL are  
37  
38 responsible for the analysis of the literature on the non-invasive studies and are responsible for  
39  
40 the metabolic part of the protocol. JK and JJ are statisticians, responsible for power calculation,  
41  
42 electronic web-based database.  
43  
44  
45  
46  
47

48 **COMPETING INTEREST:** none  
49

50 **FUNDING STATEMENT** This work was supported by Research grant of the Ministry of  
51  
52 Health Czech Republic, No NU21-02-00388  
53  
54  
55  
56  
57

## REFERENCES

1. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042-6.
2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837-47.
3. Piccini JP, Lopes RD, Kong MH, et al. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009;2:626-33.
4. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018;378:417-27.
5. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA* 2019;321:1261-74.
6. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. *N Engl J Med* 2021;384:316-24.
7. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *N Engl J Med* 2021;384:305-15.
8. Lafuente-Lafuente C, Valembois L, Bergmann JF, et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2015;CD005049.
9. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med* 2020;383:1305-16.
10. Freemantle N, Lafuente-Lafuente C, Mitchell S, et al. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;13:329-45.
11. Goldschlager N, Epstein AE, Naccarelli GV, et al. A practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007;4:1250-9.
12. Lavie CJ, Pandey A, Lau DH, et al. Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise. *J Am Coll Cardiol* 2017;70:2022-35.
13. Middeldorp ME, Pathak RK, Meredith M, et al. PREVENTion and regReSSive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace* 2018;20:1929-35.

14. Wong CX, Sullivan T, Sun MT, et al. Obesity and the Risk of Incident, Post-Operative, and Post-Ablation Atrial Fibrillation: A Meta-Analysis of 626,603 Individuals in 51 Studies. *JACC Clin Electrophysiol* 2015;1:139-52.
15. Conen D, Tedrow UB, Koplan BA, et al. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;119:2146-52.
16. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;49:565-71.
17. Kodama S, Saito K, Tanaka S, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *J Am Coll Cardiol* 2011;57:427-36.
18. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;64:2222-31.
19. Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol* 2015;65:2159-69.
20. Malmo V, Nes BM, Amundsen BH, et al. Aerobic Interval Training Reduces the Burden of Atrial Fibrillation in the Short Term: A Randomized Trial. *Circulation* 2016;133:466-73.
21. Voskoboinik A, Kalman JM, De Silva A, et al. Alcohol Abstinence in Drinkers with Atrial Fibrillation. *N Engl J Med* 2020;382:20-8.
22. Al Chekatie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol* 2010;56:784-8.
23. Mirolo A, Viart G, Savoure A, et al. Epicardial fat thickness predicts atrial fibrillation recurrence after a first pulmonary vein isolation procedure using a second-generation cryoballoon. *Arch Cardiovasc Dis* 2019;112:314-22.
24. Ling LH, Kistler PM, Ellims AH, et al. Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and systolic dysfunction. *J Am Coll Cardiol* 2012;60:2402-8.
25. McLellan AJ, Ling LH, Azzopardi S, et al. Diffuse ventricular fibrosis measured by T(1) mapping on cardiac MRI predicts success of catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;7:834-40.



- 1  
2  
3  
4  
5  
6  
7 26. Eschalier R, Rossignol P, Kearney-Schwartz A, et al. Features of cardiac remodeling,  
8 associated with blood pressure and fibrosis biomarkers, are frequent in subjects with abdominal  
9 obesity. *Hypertension* 2014;63:740-6.  
10  
11 27. Bianchi VE. Weight loss is a critical factor to reduce inflammation. *Clin Nutr ESPEN*  
12 2018;28:21-35.  
13  
14 28. Jiang H, Wang W, Wang C, et al. Association of pre-ablation level of potential blood markers  
15 with atrial fibrillation recurrence after catheter ablation: a meta-analysis. *Europace* 2017;19:392-  
16 400.  
17  
18 29. Sasaki N, Okumura Y, Watanabe I, et al. Increased levels of inflammatory and extracellular  
19 matrix turnover biomarkers persist despite reverse atrial structural remodeling during the first year  
20 after atrial fibrillation ablation. *J Interv Card Electrophysiol* 2014;39:241-9.  
21  
22 30. Bin Waleed K, Yin X, Yang X, et al. Short and long-term changes in platelet and inflammatory  
23 biomarkers after cryoballoon and radiofrequency ablation. *Int J Cardiol* 2019;285:128-32.  
24  
25 31. Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in  
26 patients with cardiovascular disease. *Eur Heart J* 2021;42:17-96.  
27  
28 32. Calkins H, Reynolds MR, Spector P, et al. Treatment of atrial fibrillation with antiarrhythmic  
29 drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ*  
30 *Arrhythm Electrophysiol* 2009;2:349-61.  
31  
32 33. Poole JE, Bahnson TD, Monahan KH, et al. Recurrence of Atrial Fibrillation After Catheter  
33 Ablation or Antiarrhythmic Drug Therapy in the CABANA Trial. *J Am Coll Cardiol* 2020;75:3105-18.  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 **FIGURE LEGENDS**  
8

9 **Figure 1** CONSORT diagram of the trial  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

# BMJ Open

## CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION, A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25 TRIAL)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056522.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Mar-2022
Complete List of Authors:	<p>Osmancik, Pavel; 3rd Faculty of Medicine, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter</p> <p>Havránek, Štěpán; 2. 2nd Department of Internal Medicine - Dept. of Cardiovascular Medicine, 1st Faculty of Medicine, Charles University and General University Hospital</p> <p>Bulková, Veronika; Neuron Medical sro, Dept. of Cardiology</p> <p>Chovančík, Jan; Hospital AGEL Trinec – Podlesi, Dept. of Cardiology</p> <p>Roubíček, Tomáš; Liberec, Dept. of Cardiology</p> <p>Heřman, Dalibor; 3rd Faculty of Medicine, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter</p> <p>Čarná, Zuzana; 3rd Faculty of Medicine, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter</p> <p>Tuka, Vladimír; 2. 2nd Department of Internal Medicine - Dept. of Cardiovascular Medicine, 1st Faculty of Medicine, Charles University and General University Hospital</p> <p>Fiala, Martin; Neuron Medical sro, Dept. of Cardiology</p> <p>Jiravský, Otakar; Hospital AGEL Trinec – Podlesi, Dept. of Cardiology</p> <p>Štrégl, Sylvie; Dept. of Cardiology, Regional Hospital Liberec, Liberec</p> <p>Latiňák, Adam; Liberec, Dept. of Cardiology</p> <p>Kotryová, Jiřina; Masaryk University</p> <p>Matoulek, Martin; Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic</p> <p>Jarkovský, Jiří; Faculty of Medicine and the Faculty of Science of the Masaryk University, Institute of Biostatistics and Analyses</p>
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Pacing & electrophysiology < CARDIOLOGY, Adult cardiology < CARDIOLOGY, NUTRITION & DIETETICS

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7 **CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK**  
8  
9 **FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION,**  
10  
11 **A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25 TRIAL)**  
12  
13  
14

15 Pavel Osmančík<sup>1</sup>, Štěpán Havránek<sup>2</sup>, Veronika Bulková<sup>3</sup>, Jan Chovančík<sup>4</sup>, Tomáš Roubíček<sup>5</sup>,  
16 Dalibor Heřman<sup>1</sup>, Zuzana Čarná<sup>1</sup>, Vladimír Tuka<sup>2</sup>, Martin Matoulek<sup>2</sup>, Martin Fiala<sup>3</sup>, Otakar  
17 Jiravský<sup>4</sup>, Sylvie Štrégl – Hrušková<sup>5</sup>, Adam Latiňák<sup>5</sup>, Jiřina Kotryová<sup>6</sup>, Jiri Jarkovsky<sup>6</sup>  
18  
19

- 20 1. Dept. of Cardiology, Cardiocenter, 3<sup>rd</sup> Faculty of Medicine and University Hospital  
21 Kralovske Vinohrady, Prague, Czech Republic
- 22 2. 2<sup>nd</sup> Department of Internal Medicine - Dept. of Cardiovascular Medicine, 1<sup>st</sup> Faculty of  
23 Medicine, Charles University and General University Hospital, Prague, Czech republic
- 24 3. Dept. of Cardiology, Neuron Medical, s.r.o., Brno, Czech republic
- 25 4. Dept. of Cardiology, Hospital AGEL Trinec – Podlesi, a.s., Trinec, Czech republic
- 26 5. Dept. of Cardiology, Regional Hospital Liberec, Liberec, Czech republic
- 27 6. Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech republic  
28  
29

30 **Corresponding author:**

31 Pavel Osmancik, MD, PhD  
32 Dept of cardiology, Cardiocenter  
33 3<sup>rd</sup> Faculty of Medicine and University Hospital  
34 Kralovske Vinohrady  
35 Srobarova 50  
36 10034, Prague  
37 Czech Republic  
38 Phone: 00420-721544447  
39 Email: [pavel.osmancik@gmail.com](mailto:pavel.osmancik@gmail.com)  
40  
41

42 **Keywords:** atrial fibrillation, catheter ablation, antiarrhythmic drugs, risk factor modification  
43  
44  
45

46 **Section:** Trial Design (Protocol of a Study)

47 **Word count:** 4000

48 **Declaration of interest:** none

49 **Running headline:** Protocol of Prague-25 trial

50 **RCT No:** NCT04011800

51 **Financial support:** Research grant of the Ministry of Health Czech Republic, No NU21-02-  
52 00388  
53  
54  
55  
56  
57  
58  
59  
60

## ABSTRACT

**Introduction:** Atrial fibrillation (AF), with a prevalence of 2%, is the most common cardiac arrhythmia. Catheter ablation (CA) has been documented to be superior over treatment by antiarrhythmic drugs (AADs) in terms of sinus rhythm (SR) maintenance. However, in obese patients, substantial weight loss was also associated with AF reduction. So far, no study has compared the modern non-invasive (AADs combined with risk factor modification) approach with modern invasive (CA) treatment. The aim of the trial is to compare the efficacy of modern invasive (catheter ablation) and non-invasive (AADs with risk factor management) treatment of AF.

**Methods and Analysis:** The trial will be a prospective, multicenter, randomized non-inferiority trial. Patients with symptomatic AF and a body-mass index  $> 30$  will be enrolled and randomized to the CA or risk factor modification arm (RFM+AAD) in a 1:1 ratio. In the CA arm, pulmonary vein isolation (in combination with additional lesion sets in non-paroxysmal patients) will be performed. For patients in the RFM+AAD arm, the aim will be a 10% weight loss over 6–12 months, increased physical fitness, and a reduction in alcohol consumption. The primary endpoint will be an episode of AF or regular AT lasting  $> 30$  sec. The secondary endpoints include AF burden, clinical endpoints associated with AF recurrence, changes in the quality of life assessed using dedicated questionnaires, changes in cardiorespiratory fitness, and metabolic endpoints. An AF freedom of 65% in the RFM+AAD and of 60% in the CA is expected; therefore, 202 patients will be enrolled to achieve the non-inferiority with 80% power, 5% one-sided alpha, and a non-inferiority margin of 12%.

1  
2  
3  
4  
5  
6  
7 **Ethics and Dissemination:** The PRAGUE-25 trial will determine if modern non-invasive AF  
8  
9 treatment strategies are non-inferior to catheter ablation.  
10

11  
12 **Registration details:** The study was registered on clinicaltrials.gov as NCT04011800  
13  
14

## 15 16 17 18 19 **ARTICLE SUMMARY** 20

### 21 22 **Strengths of this study** 23

- 24 • The population of the study (obese patients with AF) is growing
- 25 • For the first time, AADs treatment combined with risk factor modification will be  
26 compared with catheter ablation  
27  
28  
29  
30  
31  
32

### 33 34 **Limitations of this study** 35

- 36 • The study is not large enough to compare clinical endpoints
- 37 • The monitoring using implantable loop recorders would be more sensitive  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, having a prevalence of about  $\approx 2\%$  in the general population. Among healthy men and women aged  $> 40$  years, the risk of lifelong AF occurrence is approximately 25% (1). The current estimated prevalence of AF is approximately 50 million patients worldwide, and its incidence has been increasing due to improved diagnostics, better treatment of chronic diseases, and increasing age (2). Therefore, its prevalence is expected to increase by nearly 3-fold during the next three decades. AF is associated with a three-fold increase in the risk of stroke and a two-fold increase in mortality risk (2).

### **The efficacy of catheter ablations in previous clinical studies**

Catheter ablation (CA) with pulmonary vein isolation (PVI) has been found to be superior to antiarrhythmic drugs (AADs) in terms of AF freedom in several randomized, controlled trials. The one-year efficacy of CA ranges from 40–90% (depending on the type of AF, patient cohort, and follow-up methods) (3). In patients with heart failure, AF, and decreased ejection fraction (EF), CA was associated with decreased mortality (4). However, mortality or clear clinical benefit of CA over AADs was not documented in the broad population of AF patients in the CABANA trial, the largest study on CA in AF (5). Except for the CABANA trial with 2,204 patients enrolled, all other studies have been substantially smaller (median of enrolled patients = 119 patients). In two well-conceived recent trials comparing CA (albeit using cryo-balloon ablation) with AADs, the one-year AF freedom was 74.6% when assessed using 24-hour Holter monitoring, or 57.1% when assessed using implantable loop recorders in the CA arms, or 45.0% and 32.2%, respectively, in the AAD arms (6) (7).



### **The efficacy and limitations of the antiarrhythmic drugs**

Several AADs (propafenone, flecainide, sotalol, amiodarone) have been documented as being superior compared to placebo for reducing the recurrence of AF (OR 0.19–0.70 for AADs) (8). Moreover, in patients with an early AF diagnosis, early treatment of AF (in 86.8% of pts. using AADs) was associated with a reduction in cardiovascular mortality, stroke, hospitalization for heart failure, and acute coronary syndromes (9). However, the effect of AADs for SR maintenance is only modest. In the two most recent randomized control trials (RCT) comparing AADs (92% of which were flecainide and sotalol) with CA, the complete one-year AF freedom on AADs was 45%, or 32.2%, depending on the type of monitoring (6) (7). The long-term use of AADs is often limited by serious side effects and toxicity. It is especially true for amiodarone, otherwise, the most effective AAD (10), which often causes extracardiac side-effects, especially during long-term therapy. Therefore, it is mainly used as a second or third drug after the failure of other AADs or CA (11).

### **Risk factor modification**

According to several observational studies, obesity has been found to be independently associated with a higher risk of occurrence, as well as the progression of AF (12) (13). According to a meta-analysis of 51 studies, which included more than 60,000 patients, an increase in the body-mass index (BMI) by 5 points is associated with a 19%–29% increase in the incidence of AF (14). Besides obesity, other modifiable risk factors include hypertension, sleep apnea, and alcohol consumption (15) (16) (17). Importantly, several recent interventional studies have shown that all the aforementioned factors are not only known epidemiological variables associated with a higher risk of AF, but their intensive treatment is associated with a

1  
2  
3  
4  
5  
6  
7 decrease in AF reoccurrences. In the non-randomized ARREST-AF study, 149 patients with a  
8  
9 BMI  $\geq 27$  after catheter ablation of AF were offered an opportunity to participate in a physician-  
10  
11 driven intensive risk factor modification (RFM) program, consisting of dietary changes and  
12  
13 regular physical exercise. Risk factor management was associated with a significant reduction  
14  
15 in AF reoccurrence by 23.9% (18). In the prospective, non-randomized LEGACY study, risk  
16  
17 factor management, which also focused on weight loss, was offered to a cohort of 355 AF  
18  
19 patients with a BMI  $\geq 27$  who had been referred to a tertiary center for AF treatment (contrary  
20  
21 to ARREST-AF study, patients in the LEGACY study had no history of AF ablation) (19). AF  
22  
23 freedom was achieved in 45% of patients with weight loss  $\geq 10\%$ , and in 22% of patients with  
24  
25 weight loss between 3 and 9% (19). Similarly, in a study by Malmo et al., patients undergoing  
26  
27 regular physical activity had AF paroxysms decline from 8.1% to 4.8% (20). Moreover, last  
28  
29 year Voskoboinik et al. documented that a reduction in alcohol consumption was also associated  
30  
31 with a significant reduction of AF paroxysms (21). It seems that AF treatment could lie, at least  
32  
33 in some patients, outside the electrophysiological catheter-labs. However, it is also important  
34  
35 to note that all studies focused on weight loss were either observational or had a non-  
36  
37 randomized control arm (ARREST-AF, LEGACY). Since participation, especially in metabolic  
38  
39 interventions, requires a high level of patient motivation, the absence of a control arm  
40  
41 potentially introduces a large bias into all the aforementioned studies.  
42  
43  
44  
45  
46  
47

#### 48 **Structural changes of ventricles and pericardial fat in patients with AF and obesity**

49  
50 As was shown, the amount of epicardial adipose tissue (EAT) is higher in patients with AF.  
51  
52 EAT is independently associated with future occurrences of AF in healthy persons and is also  
53  
54 a predictive factor for AF recurrence after catheter ablation (22) (23). Similarly, the degree of  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 diffuse myocardial ventricular fibrosis is higher in AF patients compared to healthy subjects  
8  
9 (24). Both the amount of EAT, as well as diffuse myocardial fibrosis, can be assessed using  
10  
11 cardiac magnetic resonance (CMR); the latter recently very sensitively using postcontrast-  
12  
13 enhanced T1 mapping (24). Recently, diffuse myocardial fibrosis assessed using post-contrast  
14  
15 T1 mapping predicted the effect of AF catheter ablation in paroxysmal patients (25). Early  
16  
17 changes on a CMR, such as higher left ventricular mass, or cardiac remodeling index, were also  
18  
19 described in patients with obesity (26).  
20  
21

### 22 23 **Pro-inflammatory markers changes in AF and in obesity**

24  
25 The concentrations of pro-inflammatory markers, such as high-sensitivity CRP, interleukin-6,  
26  
27 TNF- $\alpha$ , and others, have been reported to be elevated in AF patients, as well as in obese  
28  
29 individuals with SR. In obese patients, the adipose tissue is an important source of the pro-  
30  
31 inflammatory cytokines, and the concentrations of several pro-inflammatory cytokines  
32  
33 significantly decrease after weight loss (27). In AF patients, increased pre-ablation levels of  
34  
35 BNP, ANP, IL-6, and hsCRP are associated with a greater risk of AF recurrence after ablation  
36  
37 (28). However, studies focusing on the effect of CA on pro-inflammatory cytokines have shown  
38  
39 mixed results, and in most of them, the concentrations remained unchanged in AF patients after  
40  
41 successful AF ablation with SR maintenance after 12 months (29) (30).  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## METHODS AND ANALYSIS

### Study design and objective

The PRAGUE-25 trial is a prospective, multicenter, investigator-initiated, open-label, randomized, non-inferiority study registered on [clinicaltrials.gov](https://clinicaltrials.gov) (NCT04011800, v. 1 of the protocol). The primary objective is to compare the maintenance of sinus rhythm using modern invasive (catheter ablation) and non-invasive (RFM+AAD) AF treatment. Secondary endpoints include clinical endpoints, changes in the QoL, cardiorespiratory fitness, pro-inflammatory cytokines concentrations, echocardiography, and MRI measures. The study was approved by multicenter ethics committee and local ethics committees of all participating centers, and an informed consent will be obtained from all participants. The enrollment of patients began in May 2021. The CONSORT diagram of the study is shown in **Figure 1**.

### Patient and Public Involvement

A significant portion of patients with AF are obese (e.g., the median BMI was 30 in the CABANA Trial). Likewise, according to the database of patients who underwent CA at our institutions in the last five years, the median BMI was also 30. It is expected that RFM will have a significant effect on blood pressure, glucose metabolism, etc.; however, whether this approach supported by AADs is comparable with CA has never been tested in a randomized study. If both treatment strategies were comparable in terms of SR maintenance, risk factor modification and AADs could be offered to obese patients as comparable treatment to an invasive procedure. The design and protocol of the study were written by the investigator without the patient's involvement. Regarding the dissemination of the results, apart from

1  
2  
3  
4  
5  
6  
7 scientific conferences, presentations on the patient's days, organized by the participating  
8 hospitals, are planned.

### 11 **Patient population**

12 PRAGUE-25 is a multicenter study; currently, five centers from the Czech Republic are  
13 participating, but other centers may be added based on interest. The study will enroll  
14 symptomatic AF patients with high BMIs from the outpatient departments of the participating  
15 hospitals (AF clinics) and their cooperating outpatient departments (general practice patients).

16 All outpatients from the participating centers and cooperating outpatient departments will be  
17 screened, and patients satisfying the inclusion criteria will be offered an opportunity to enroll.

18 The qualifying criteria are symptomatic documented AF, high BMI, and patient motivation  
19 since the allocation to the risk factor modification (RFM+AAD) arm includes activities that  
20 require direct patient involvement. AF must be documented using a standard 12-lead ECG or  
21 Holter recording. There will be no special cut-off for the length of AF. Patients with long-  
22 standing AF can also enroll; enrollment for patients with a very long history of AF will depend  
23 on the patient's symptoms. An explanation of the efficacy of treatment for longer AF is  
24 routinely done during conversations with outpatients referred to CA. AAD-naive and patients  
25 with a history of AAD treatment can be enrolled; the use of AAD in the past is not an exclusion  
26 criterion. During the enrollment process, all patients will be thoroughly informed about the  
27 dangers of obesity and other metabolic factors as it concerns AF. Participation in the special  
28 dietary intervention will not be an exclusion criterion. Our experienced nutritional specialists  
29 are able to establish AF-friendly diets for almost all patients.

30 *Inclusion criteria:*

- symptomatic AF (paroxysmal, persistent, or long-standing persistent)
- BMI  $\geq$  30
- signed informed consent

*Exclusion criteria:*

- permanent AF
- BMI  $\geq$  40
- severe valve disease (significant aortic stenosis, mitral regurgitation  $\geq$  3)
- left ventricular ejection fraction  $<$  40%
- moderate or severe pulmonary hypertension (sPAP  $\geq$  40 mm Hg)
- history of tachycardia-induced cardiomyopathy
- manifest coronary artery disease
- pregnancy
- left atrial size  $\geq$  60 mm
- indication for surgical treatment of obesity
- age  $\geq$  75 yrs.
- diabetes mellitus needing insulin
- significant physical limitations that could affect physical activity (musculoskeletal disorders, moderate or severe COPD)
- life expectancy  $<$  2 years

**Baseline examinations**

After informed content is given, all patients will undergo baseline anthropometric measurements (weight, waist to hip ratio, body fat measurement) and a baseline functional

1  
2  
3  
4  
5  
6  
7 evaluation. It will include (1) baseline evaluation of physical fitness - cardiopulmonary exercise  
8  
9 test, (2) echocardiography, (3) quality of life analysis (using AFEQT questionnaire), (4) blood  
10  
11 biochemistry, and cytokine analysis, and (5) a baseline one-week ECG Holter recording. All  
12  
13 these examinations will be done within four weeks after randomization.  
14  
15

### 16 **Randomization and blinding**

17  
18 Patients will be randomized to the catheter ablation group (CA) or risk factor modification  
19  
20 group plus AADs (RFM+AAD) in a 1:1 ratio; randomization will be done using randomization  
21  
22 software that will account for age, initial BMI, and AF type, with the goal of having comparable  
23  
24 groups relative to those characteristics. Randomization will be done in blocks but will not be  
25  
26 site-specific (i.e., the proportion of patients randomized to CA vs. RFM-AAD will not be the  
27  
28 same in all centers). The randomization process will be done outside all participating centers  
29  
30 by a project-specific clinical trial management software system. The software will divide BMI  
31  
32 into four categories (30.0–31.9, 32.0–33.9, 34.0–36.9, and 37.0–40.0); in each category, an  
33  
34 additional two variables (i.e., age and AF type) will be taken into account in order to achieve  
35  
36 similar values in both groups. The study will be open-label for study patients and study  
37  
38 physicians. However, the evaluation of the ECG endpoint will be blinded; all Holter recordings  
39  
40 will be evaluated by an organization outside the study that will not have access to patient  
41  
42 information. Similarly, clinical endpoint assessments will also be blinded, and clinical endpoint  
43  
44 committee will not be aware of patient randomizations. Institute of Biostatistics and Analyses  
45  
46 will be responsible for the randomization software, data acquisition, storage, and data analysis.  
47  
48  
49  
50  
51

### 52 **Functional diagnostic (anthropometric measurement and cardiopulmonary exercise test)**

1  
2  
3  
4  
5  
6  
7 Functional diagnostics will be performed in all patients. Based on the results, an individualized  
8  
9 physical training program will be prepared in patients randomized to the RFM+AAD arm.

10  
11 An initial maximum symptom-limited cardiopulmonary exercise test (CEPT) will be carried  
12  
13 out within one month of enrollment. The CPET will be carried out on the medication which  
14  
15 was present at the enrollment visit. The cycle ergometer will be used in all sites. The protocol  
16  
17 will consist of a 3-min warm-up period with 0 Watt (unloaded pedaling), followed by a ramp  
18  
19 test increase of exercise intensity increased by 0.1 W/kg/min in women and by 0.15 W/kg/min  
20  
21 in men up to the maximum subjective tolerance. A 12-lead ECG tracing will be obtained  
22  
23 throughout the test for heart rate measurement, arrhythmia (especially AF) detection, and safety  
24  
25 reasons. Blood pressure will be measured manually with adequately selected cuff size. From  
26  
27 exhaled gas analysis, oxygen uptake  $VO_2$ , carbon dioxide production  $VCO_2$ , and minute  
28  
29 ventilation (VE) will be determined. Peak  $VO_2$  will be defined as the maximum value of  $VO_2$   
30  
31 averaged over 15 seconds; both absolute values and values indexed to body weight will be used.  
32  
33 The  $VCO_2/VE$  slope will be calculated from the beginning of the incremental exercise till the  
34  
35 respiratory compensation point; both ventilatory thresholds will be calculated.  
36  
37  
38  
39  
40

## 41 **TREATMENTS**

### 42 **Catheter ablation arm**

43  
44 CA will be done within two months of randomization. In paroxysmal patients, a PVI will be  
45  
46 performed. In patients with non-paroxysmal AF forms, additional lesion sets will be allowed  
47  
48 according to the practice of each participating center. The CA will be done using a 3D mapping  
49  
50 system, intracardiac echocardiography, contact-force sensing ablation catheters, and ablation  
51  
52 index to achieve the maximum available safety and efficacy. All patients in the CA arm will be  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7 informed about the danger of obesity and other risk factors as they concern AF and will be  
8  
9 instructed to lose weight, reduce alcohol consumption, and increase physical activity at  
10  
11 discharge and again during each follow-up visit.

12  
13 The first three months following catheter ablation will be considered as a “blinking period,”  
14  
15 i.e., AF reoccurrences won't be assessed as an endpoint. During this period, treatment using  
16  
17 AADs or cardioversion will be allowed. Three months after ablation, AADs will be  
18  
19 discontinued.  
20  
21

### 22 23 **Risk factor modification and AADs (RFA+AAD) arm**

24  
25 The aim will be (1) a 10% weight loss over 6–12 months,(2) an increase in physical fitness, and  
26  
27 (3) a reduction in alcohol consumption. RFM will be performed not by the treating cardiologist  
28  
29 but by teams of dietary specialists and physiotherapists. Nutritional intervention: the initial  
30  
31 patient consultations with nutritional specialists will be done during the first month after  
32  
33 enrollment. A low-calorie, high protein, and low glycemic index dietary menu will be suggested  
34  
35 and optimized by a nutritional specialist for each patient. Except for regular in-person  
36  
37 consultations with dietary specialists, phone visits any time during the follow-up; patients will  
38  
39 be encouraged to record the calory intake in the OBEFIS application (either on the web  
40  
41 [www.obefis.cz](http://www.obefis.cz), or using the mobile application), and the recordings will be discussed during  
42  
43 the visits with dietary specialists.  
44  
45  
46  
47

48 All patients will have an initial consultation with a physiotherapist (after the CPET) to set the  
49  
50 type and intensity of the physical intervention. The recommended physical intervention will  
51  
52 consist of three types of activities: (1) regular gym-based training (in small groups or individual  
53  
54 training with a trainer),(2i) individual aerobic training (fast walking or similar aerobic activity),  
55  
56  
57

1  
2  
3  
4  
5  
6  
7 and (3) home-based training: 20 min physical exercise sets. The type and ratio of the  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

and (3) home-based training: 20 min physical exercise sets. The type and ratio of the  
aforementioned physical exercises will be changed over the study period. However, based on  
the patient's experiences with physical activity in the past, and their options regarding  
participation in the organized training, activities will be individualized. The ESC guidelines for  
obese individuals recommend that a minimum of 150 min/week of moderate-intensity  
endurance exercise training should be combined with three weekly sessions of resistance  
exercise with the heart rate during the activity being 55–74% of the maximum HR (31). As  
such, the physical intervention will be based on regular (mainly moderate,  $\approx$  55–74% of the  
maximum HR) intensity aerobic exercise that will be gradually increased from 60 min/week up  
to 200 min/week. Since the adherence of patients to regular activity is affected by activity  
monitoring, all patients will have an opportunity to be monitored during each exercise using  
remote heart rate monitoring (fitness bands) and the OBEFIS smartphone application.

For patients in the RFM+AAD arm, contrary to patients in the CA arm, non-amiodarone AADs  
will be allowed during the whole study period. The AADs that are allowed are AADs that are  
approved by the regulatory authorities for use on the Czech market; currently, this includes  
propafenone, flecainide, dronedarone, and sotalol. The choice of AAD will occur during the  
blinking period. For patients in SR, an AAD will be started immediately after randomization.  
In patients with AF during the baseline visit and in whom electrical cardioversion is planned,  
an AAD will be initiated the day before the electrical cardioversion. The dose and titration of  
AADs will be done during the blinking period and will be left to the discretion of the patient's  
treating physician and in accordance with the prescription rules for each AAD. The titration of  
a particular AAD to the maximum safe dose must be done during the blinking period;

1  
2  
3  
4  
5  
6  
7 subsequent up-titration can only be done if AF recurs. Since weight loss goals will take months,  
8 the effect of metabolic interventions cannot be expected as fast as in the CA arm. Therefore,  
9 the blanking period for the RFM+AAD arm will last six instead of three months. The  
10 reoccurrence as AF/AT as an endpoint will be considered starting at the 6-month visit, including  
11 a 7-day Holter, which is scheduled to be done at the 6-month visit.  
12  
13

14  
15  
16  
17  
18 In both arms, in case of a reoccurrence of symptomatic AF or atrial tachycardia (AT), re-do  
19 ablations, cardioversion, or AADs treatment during the follow-up period will be allowed in  
20 accordance with the current guidelines and practices of participating centers. However, because  
21 the indication for the aforementioned procedures or AAD initiation will be a reoccurrence of  
22 AF or AT, it will be assessed as the primary endpoint (i.e., AF reoccurrence).  
23  
24  
25  
26  
27  
28

### 29 **OUTPATIENT FOLLOW-UP AND ENDPOINT MONITORING**

30  
31  
32 The follow-up protocol and ECG monitoring will be similar for both arms. Starting on the day  
33 of the catheter ablation (D0 in the ablation arm) or at the start of the metabolic activity (D0 in  
34 the RFM+AAD arm, approx. 3–4 weeks after randomization), follow-up visits will be  
35 scheduled at 3, 6, 9, and 12 months during the first year, and then every six months. At the 3-  
36 month follow-up visit, patients in AF (from both groups) will undergo electrical cardioversion.  
37 A routine 12-lead ECG will be recorded at each follow-up visit, along with a physical  
38 examination of the patient and a medical history update. Long-term ECG recording will be done  
39 using a 7-day Holter recording at baseline, and then at the 6, 9, and 12 month visits during the  
40 first year, and then every six months in the second and third years. Holter recordings will be  
41 blinded, and analyzed by physicians outside the study. At the 12-month follow-up visit,  
42 echocardiography, MRI examination, anthropometric measurements, and CPET will be done.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56

1  
2  
3  
4  
5  
6  
7 Blood will be drawn for cytokine analysis, and patients will also be asked to complete follow-  
8 up QoL questionnaires.  
9

## 10 **STUDY OUTCOMES**

### 11 **Primary endpoints:**

- 12 1) AF reoccurrence (any AF or atrial tachycardia lasting more than 30 sec)

### 13 **Secondary endpoints**

- 14 1) AF burden: calculated using all Holter recordings as a percentage of time spent in AF  
15 or AT
- 16 2) AF reoccurrence and AF burden at the 12-month visit
- 17 3) Hospitalization for AF reoccurrence and/or emergency room visit due to AF
- 18 4) A composite of stroke, cardiovascular death, or hospitalization for heart failure
- 19 5) Changes in QoL questionnaires between baseline and 12 months
- 20 6) Change in cardiorespiratory fitness as assessed using CPET between baseline and 12  
21 months
- 22 7) Metabolic endpoint: changes in weight, lipid levels, glycated hemoglobin, and pro-  
23 inflammatory cytokines
- 24 8) Imaging endpoints: change in diffuse ventricular fibrosis and EAT between baseline  
25 and the 12-month examination (MRI)

26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48 The AF reoccurrence will be detected either using planned 7-day Holter recordings (at the 6, 9,  
49 and 12 month visits), during all planned outpatient visits using a standard 12-lead ECG, and  
50 any time during the follow-up after the blanking period at an emergency non-planned visit also  
51 using a standard 12-lead ECG. During the planned or emergency visits, AF reoccurrence has to  
52  
53  
54  
55  
56

1  
2  
3  
4  
5  
6  
7 be documented using an ECG (i.e., a patient's description of "palpitations" without ECG  
8 evidence will not be assessed as AF recurrence).

## 11 **STATISTICAL ANALYSIS PLAN AND POWER CALCULATION**

13 The power calculation was based on the results of randomized trials and observational studies  
14 comparing and assessing the effect of AADs vs. placebo, CA vs. AADs, and assessing the effect  
15 of risk factor modification in observational cohort studies. The primary efficacy analysis (non-  
16 inferiority) will be undertaken using the per-protocol population. If the non-inferiority criterion  
17 is satisfied, then superiority for the primary endpoint will be tested. Secondary analysis will be  
18 done using the intention-to-treat principle. Cross-over is only allowed for cases of treatment  
19 failure, i.e., only patients with AF/AT recurrences could be crossed-over, and the outcomes of  
20 crossed-over patients will be censored.

### 23 ***The expected efficacy of AADs and RFM***

24 In a meta-analysis of 24 randomized control trials comparing AADs with placebo, the overall  
25 success rate of AADs, defined as the disappearance of arrhythmia during follow-up, was present  
26 in 52% (95%CI 47%–57%) of patients on AADs (32). In the CABANA trial, by 12 months, the  
27 one-year AF freedom on AADs was present in 47.1% of patients (33). Finally, in the recently  
28 published STOP-AF trial, one-year AF freedom (assessed using repeated 24-Hour Holter  
29 recordings) was present in 45.0% (95%CI 34.6–54.7) of patients. Therefore, a one-year AF  
30 freedom of 45% could be expected for non-amiodarone AADs (6). In the LEGACY study,  
31 45.5% patients with weight loss >10%, 22.2% with weight loss 3–9%, and 13.4% in the weight  
32 loss < 3% remained AF-free without AADs or ablation (19). No study has compared the  
33 additive effect of weight loss on top of AADs; however, an additional effect of 20% could be

1  
2  
3  
4  
5  
6  
7 expected in these patients. Therefore, we expected a  $\approx 65\%$  one-year AF freedom in the  
8  
9 RFM+AAD arm.

### 11 ***The expected efficacy of the Catheter ablation***

12  
13 In a meta-analysis of RCT comparing CA with AADs, the single procedure success rate of CA  
14  
15 OFF AADs was 57% (95%CI 50–64%) (32). In the CABANA trial, AF freedom was present  
16  
17 in 63.6% of the ablation patients by 12 months (33). The expected one-year AF freedom in the  
18  
19 CA arm is  $\approx 60\%$ .

20  
21  
22  
23 According to the aforementioned data, we expect one-year AF freedom in 65% of patients in  
24  
25 the RFM+AAD arm and 60% in the CA arm. The primary analysis will be done using the  
26  
27 intention-to-treat principle; however, based on the non-inferiority nature of the study, a per-  
28  
29 protocol analysis will be done. The sample size calculation assumed: 80% power, 5% 2-sided  
30  
31 alpha, a non-inferiority margin of 12% (or 1.65, if expressed as an odds ratio). Using this  
32  
33 assumption, 202 patients (101 in each arm) will need to be enrolled to prove non-inferiority of  
34  
35 the non-invasive arm relative to the invasive arm. With an expected drop-out rate of 5%,  
36  
37 therefore, 212 patients will be enrolled.

### 39 ***Non-inferiority margin (NIM) considerations***

40  
41  
42  
43 Regulatory guidelines require that the NIM rules out the minimum effect of treatment in the  
44  
45 control arm (i.e., the CA arm in our study). Statistical guidelines recommend the most liberal  
46  
47 NIM 1.92 (if expressed relatively as OR). From the clinical point of view, several rules exist  
48  
49 for NIM adjustment. Obviously, the margin corresponds to the preservation of 50% benefit of  
50  
51 the known treatment arm over placebo that was recognized in previous studies comparing  
52  
53 recognized treatment with placebo. The other recommendation for NIM is to use the lower band  
54  
55  
56  
57

1  
2  
3  
4  
5  
6  
7 of 95% confidence interval of the placebo effect from previous studies comparing actual known  
8  
9 treatment with placebo. Thus, for the study, the first step in selecting NIM was to estimate the  
10  
11 minimum acceptable retention of the benefit of CA over placebo. In studies comparing CA with  
12  
13 AADs, the single procedure success rate of CA OFF AADs was 57% (95% CI 50–64%).  
14  
15 Unfortunately, none of the studies had a placebo arm, and all compared CA with AADs. In the  
16  
17 studies comparing AADs vs. placebo, the success of treatment in the placebo arms was 24.9%  
18  
19 (95% CI, 15%–34%. So, the selected margin of 12% fulfills the criteria for the NIM setting. If  
20  
21 it is expressed as an OR, it corresponds to 1.65, which is consistent with regulatory guidelines  
22  
23 recommendations (and, e.g., it is similar as it was in large non-inferiority trials comparing  
24  
25 NOAC with Warfarin).  
26  
27  
28  
29  
30  
31

### 32 **Study organization and data management**

34 The institution responsible for the organization and implementation of the study is the 3<sup>rd</sup>  
35  
36 Faculty of Medicine, Charles University in Prague, Czech Republic. Data obtained during each  
37  
38 patient visit will be collected using a safe electronic CRF form. A tailor-made website was  
39  
40 developed for the study. Each participating medical center will have access to a dedicated part  
41  
42 of the website. The local investigator at each site will be responsible for data completeness and  
43  
44 validity. At the end of the study, all data will be entered and stored on a password-protected  
45  
46 computer. Only the principal investigator will have access to the final data set. All regulations  
47  
48 regarding medical confidentiality and data protection will be fulfilled.  
49  
50  
51

52 The database and randomization software has been prepared by an outside party (i.e., the  
53  
54 Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic), and no  
55  
56  
57

investigator will have access to the database or the randomization software. The Institute of Biostatistics and Analyses will also independently collect all data, manage the database, and be responsible for data analysis. No other groups (i.e., device manufacturers or pharmaceutical companies) were involved in the creation of the protocol or any other part of the study. The investigator team will be responsible for final data analysis and interpretation.

### **Safety and endpoint monitoring**

The local investigator at each site will continuously review safety data during the trial. A Data Safety Monitoring Board (DSMB) will be constituted before the commencement of the trial. Reporting of adverse events will be reported to the DSMB immediately by the principal investigator. Serious adverse events (SAE) will be defined as life-threatening events or events resulting in death or hospitalization. All SAEs linked with the study will be reported to the DSMB, to the FNKV Ethics Committee (a multicenter ethics committee, EC), and to the local ECs within 24 hours of study staff becoming aware of the event. Clinical endpoints will be analyzed by a dedicated clinical endpoint committee. The recording and analyses of all Holter recordings in all participating centers will be done centrally using an MDT (medical data transfer) company. A standard, commercially available, 7-day Holter monitor (e.g., Faros 160, Bittium, Finland, or similar tools ), with daily telephone transfers, will be used.

### **DISCUSSION**

In the last five years, lifestyle modification with risk factor management has been shown to be a very promising treatment modality for AF. AF is the most common sustained cardiac arrhythmia, with an estimated worldwide prevalence of about 33.5 million people (2). According to recent epidemiological studies, its prevalence may triple by 2050 (19). Even if



1  
2  
3  
4  
5  
6  
7 catheter ablations were associated with a 100% success rate, it would be impossible to treat the  
8  
9 current or projected numbers using catheter ablations. Furthermore, a substantial number of  
10  
11 patients would prefer a non-invasive treatment if both strategies were comparable. So while  
12  
13 risk factor modification studies may seem to offer a panacea, those studies suffer from  
14  
15 significant limitations and possible biases. For example, the most important and most extensive  
16  
17 studies were both non-randomized, and all patients had either a history of catheter ablation  
18  
19 (ARREST-AF) or were without a history of catheter ablation, but catheter ablation was allowed  
20  
21 without limitations, based on the judgment of the attending physician during the follow-up  
22  
23 period (LEGACY). A randomized study that directly compares catheter ablation with a modern  
24  
25 non-invasive strategy has yet to be done. If the effect of both strategies were comparable, the  
26  
27 non-invasive strategy could be offered to patients with a preference for a non-invasive  
28  
29 treatment. Only a randomized study can really answer the question of how effective lifestyle  
30  
31 modification is supported by safe non-amiodarone AADs compared to a modern invasive  
32  
33 strategy.  
34  
35  
36  
37  
38

### 39 **ETHICS AND DISSEMINATION**

40  
41 The enrollment of the population is planned for two years. The first results will be published at  
42  
43 the end of 2023 and at the beginning of 2024. Standard presentation on scientific conferences  
44  
45 and in extenso publication in impact journals is planned. No new drugs or devices are planned  
46  
47 for the study, so there are no specific ethical considerations. However, as it corresponds to the  
48  
49 standard of all RCT, all the serious adverse events will be immediately reported to the  
50  
51 appropriate Ethics Committee, as noted in the protocol.  
52  
53  
54  
55  
56  
57

1  
2  
3  
4  
5  
6  
7 **AUTHORS' CONTRIBUTION:** PO wrote the manuscript and has initiated the study. Authors  
8  
9 SH, VB, JC, TR, DH, ZC, OJ, and MF are responsible for the general analysis of the EP  
10  
11 literature and the EP part of the protocol. Authors VT, MM, SSH, and AL are responsible for  
12  
13 the analysis of the literature on non-invasive studies and are responsible for the metabolic part  
14  
15 of the protocol. JK and JJ are the statisticians responsible for power calculation and the web-  
16  
17 based electronic database.  
18  
19

20 **COMPETING INTEREST:** none  
21  
22

23 **FUNDING STATEMENT:** This work was supported by a Research Grant from the Ministry  
24  
25 of Health, Czech Republic, No NU21-02-00388  
26  
27

## 28 **FIGURE LEGENDS**

29  
30 **Figure 1 CONSORT diagram of the study**  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042-6.
2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837-47.
3. Piccini JP, Lopes RD, Kong MH, et al. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009;2:626-33.
4. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018;378:417-27.
5. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA* 2019;321:1261-74.
6. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. *N Engl J Med* 2021;384:316-24.
7. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *N Engl J Med* 2021;384:305-15.
8. Lafuente-Lafuente C, Valembois L, Bergmann JF, et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2015;CD005049.
9. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med* 2020;383:1305-16.
10. Freemantle N, Lafuente-Lafuente C, Mitchell S, et al. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;13:329-45.
11. Goldschlager N, Epstein AE, Naccarelli GV, et al. A practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007;4:1250-9.

12. Lavie CJ, Pandey A, Lau DH, et al. Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise. *J Am Coll Cardiol* 2017;70:2022-35.
13. Middeldorp ME, Pathak RK, Meredith M, et al. PREVENTion and regReSSive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace* 2018;20:1929-35.
14. Wong CX, Sullivan T, Sun MT, et al. Obesity and the Risk of Incident, Post-Operative, and Post-Ablation Atrial Fibrillation: A Meta-Analysis of 626,603 Individuals in 51 Studies. *JACC Clin Electrophysiol* 2015;1:139-52.
15. Conen D, Tedrow UB, Koplan BA, et al. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;119:2146-52.
16. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;49:565-71.
17. Kodama S, Saito K, Tanaka S, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *J Am Coll Cardiol* 2011;57:427-36.
18. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;64:2222-31.
19. Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol* 2015;65:2159-69.
20. Malmo V, Nes BM, Amundsen BH, et al. Aerobic Interval Training Reduces the Burden of Atrial Fibrillation in the Short Term: A Randomized Trial. *Circulation* 2016;133:466-73.
21. Voskoboinik A, Kalman JM, De Silva A, et al. Alcohol Abstinence in Drinkers with Atrial Fibrillation. *N Engl J Med* 2020;382:20-8.
22. Al Chekatie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol* 2010;56:784-8.

- 1  
2  
3  
4  
5  
6  
7 23. Mirolo A, Viart G, Savoure A, et al. Epicardial fat thickness predicts atrial fibrillation  
8 recurrence after a first pulmonary vein isolation procedure using a second-generation  
9 cryoballoon. *Arch Cardiovasc Dis* 2019;112:314-22.
- 10  
11  
12 24. Ling LH, Kistler PM, Ellims AH, et al. Diffuse ventricular fibrosis in atrial  
13 fibrillation: non-invasive evaluation and relationships with aging and systolic dysfunction. *J*  
14 *Am Coll Cardiol* 2012;60:2402-8.
- 15  
16  
17 25. McLellan AJ, Ling LH, Azzopardi S, et al. Diffuse ventricular fibrosis measured by  
18 T(1) mapping on cardiac MRI predicts success of catheter ablation for atrial fibrillation. *Circ*  
19 *Arrhythm Electrophysiol* 2014;7:834-40.
- 20  
21  
22 26. Eschalier R, Rossignol P, Kearney-Schwartz A, et al. Features of cardiac remodeling,  
23 associated with blood pressure and fibrosis biomarkers, are frequent in subjects with  
24 abdominal obesity. *Hypertension* 2014;63:740-6.
- 25  
26  
27 27. Bianchi VE. Weight loss is a critical factor to reduce inflammation. *Clin Nutr ESPEN*  
28 2018;28:21-35.
- 29  
30  
31 28. Jiang H, Wang W, Wang C, et al. Association of pre-ablation level of potential blood  
32 markers with atrial fibrillation recurrence after catheter ablation: a meta-analysis. *Europace*  
33 2017;19:392-400.
- 34  
35  
36 29. Sasaki N, Okumura Y, Watanabe I, et al. Increased levels of inflammatory and  
37 extracellular matrix turnover biomarkers persist despite reverse atrial structural remodeling  
38 during the first year after atrial fibrillation ablation. *J Interv Card Electrophysiol*  
39 2014;39:241-9.
- 40  
41  
42 30. Bin Waleed K, Yin X, Yang X, et al. Short and long-term changes in platelet and  
43 inflammatory biomarkers after cryoballoon and radiofrequency ablation. *Int J Cardiol*  
44 2019;285:128-32.
- 45  
46  
47 31. Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and  
48 exercise in patients with cardiovascular disease. *Eur Heart J* 2021;42:17-96.
- 49  
50  
51 32. Calkins H, Reynolds MR, Spector P, et al. Treatment of atrial fibrillation with  
52 antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-  
53 analyses. *Circ Arrhythm Electrophysiol* 2009;2:349-61.
- 54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 33. Poole JE, Bahnson TD, Monahan KH, et al. Recurrence of Atrial Fibrillation After  
8 Catheter Ablation or Antiarrhythmic Drug Therapy in the CABANA Trial. *J Am Coll Cardiol*  
9 2020;75:3105-18.  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

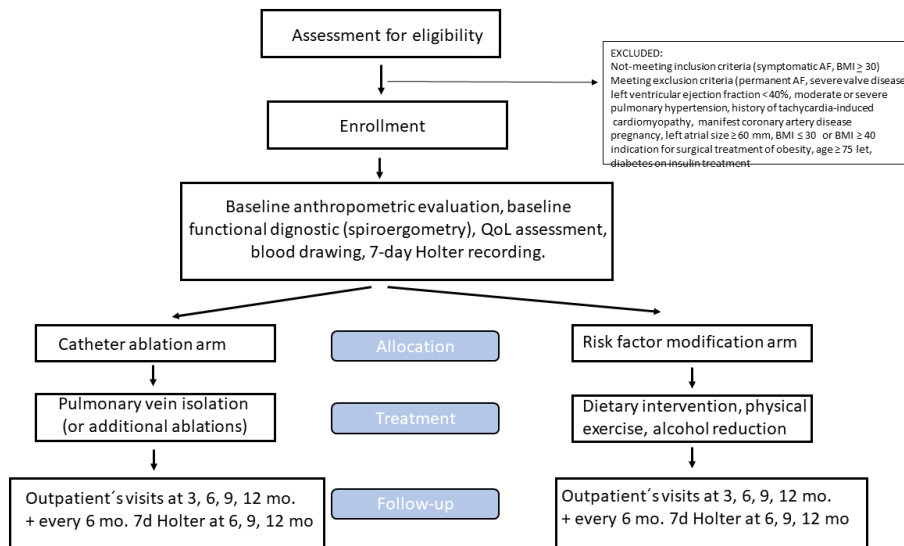


Figure 1

338x190mm (96 x 96 DPI)

1  
2  
3 **SPIRIT checklist for the article „CATHETER ABLATION VS.**  
4 **ANTIARRHYTHMIC DRUGS WITH RISK FACTOR MODIFICATION FOR**  
5 **TREATMENT OF ATRIAL FIBRILLATION, A RANDOMIZED**  
6 **CONTROLLED TRIAL (PRAGUE-25 TRIAL)“**  
7  
8  
9

10 **Administrative information**

- 11  
12 1. Title p.1  
13  
14 2. Trial registration p. 1  
15  
16 3. Protocol version p.8  
17  
18 4. Funding p, 1  
19  
20 5. Roles and responsibilities p. 19, 20  
21

22 **Introduction**

- 23  
24 6. Background and rationale p.4,5,6,7  
25  
26 7. Objectives p.8  
27  
28 8. Trial design p.8  
29

30 **Methods, participants, interventions, outcomes**

- 31 9. Study setting p.8  
32  
33 10. Eligibility criteria p.9, 10  
34  
35 11. Interventions p.12, 13  
36  
37 12. Outcomes p.16  
38  
39 13. Participant timeline p.15  
40  
41 14. Sample size p.17, 18  
42  
43 15. Recruitment p.8, 9  
44

45 **Methods, assignment of interventions**

- 46 16. Allocation p.11  
47  
48 17. Blinding (masking) p.11  
49

50 **Methods, data collection, management, analysis**

- 51  
52 18. Data collection methods p.19, 20  
53  
54 19. Data management p.20  
55  
56 20. Statistical methods p. 17  
57

58 **Methods, monitoring**

- 59 21. Data monitoring p. 20  
60



1  
2  
3 22. Harms p.20  
4

5 23. Auditing p.20  
6

7 **Ethics and dissemination**

8  
9 24. Research ethics approval p.8

10  
11 25. Protocol amendments p. 8

12  
13 26. Consent or assent p.8

14  
15 27. Confidentiality p.19, 20

16  
17 28. Declaration of interest p.8

18  
19 29. Access to data p. 19, 20

20  
21 30. Ancillary and post-trial care p. 21

22  
23 31. Dissemination policy p.21

24 **Appendices**

25  
26 32. Informed consent materials

27  
28 33. Biological specimens  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Along with your revised manuscript, please include a copy of the SPIRIT checklist indicating the page/line numbers of your manuscript where the relevant information can be found

(<http://www.spirit-statement.org/>)

# BMJ Open

## CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION: A PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25 TRIAL)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056522.R2
Article Type:	Protocol
Date Submitted by the Author:	05-May-2022
Complete List of Authors:	<p>Osmancik, Pavel; Charles University, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter</p> <p>Havránek, Štěpán; Charles University</p> <p>Bulková, Veronika; University Hospital Brno, Dept. of Cardiology</p> <p>Chovančík, Jan; Charles University, Dept. of Cardiology</p> <p>Roubíček, Tomáš; Regional Hospital Liberec, Dept. of Cardiology</p> <p>Heřman, Dalibor; Charles University, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter</p> <p>Čarná, Zuzana; Charles University, Dept. of Cardiology, Cardiocenter; University Hospital Kralovske Vinohrady, Dept. of Cardiology, Cardiocenter</p> <p>Tuka, Vladimír; Charles University</p> <p>Matoulek, Martin; Charles University</p> <p>Fiala, Martin; University Hospital Brno, Dept. of Cardiology</p> <p>Jiravský, Otakar; Charles University, Dept. of Cardiology</p> <p>Stregl-Hruskova, Sylvie; Regional Hospital Liberec</p> <p>Latiňák, Adam; Regional Hospital Liberec, Dept. of Cardiology</p> <p>Kotryová, Jiřina; Masaryk University</p> <p>Jarkovský, Jiří; Brno University of Technology, Institute of Biostatistics and Analyses</p>
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Pacing & electrophysiology < CARDIOLOGY, Adult cardiology < CARDIOLOGY, NUTRITION & DIETETICS

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 **CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK**  
8  
9 **FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION:**  
10  
11 **A PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25**  
12  
13 **TRIAL)**  
14  
15  
16

17 Pavel Osmančík<sup>1</sup>, Štěpán Havránek<sup>2</sup>, Veronika Bulková<sup>3</sup>, Jan Chovančík<sup>4</sup>, Tomáš Roubíček<sup>5</sup>,  
18 Dalibor Heřman<sup>1</sup>, Zuzana Čarná<sup>1</sup>, Vladimír Tuka<sup>2</sup>, Martin Matoulek<sup>2</sup>, Martin Fiala<sup>3</sup>, Otakar  
19 Jiravský<sup>4</sup>, Sylvie Štrégl – Hrušková<sup>5</sup>, Adam Latiňák<sup>5</sup>, Jiřina Kotryová<sup>6</sup>, Jiri Jarkovsky<sup>6</sup>  
20  
21

- 22 1. Dept. of Cardiology, Cardiocenter, 3<sup>rd</sup> Faculty of Medicine and University Hospital  
23 Kralovske Vinohrady, Prague, Czech Republic
- 24 2. 2<sup>nd</sup> Department of Internal Medicine - Dept. of Cardiovascular Medicine, 1<sup>st</sup> Faculty of  
25 Medicine, Charles University and General University Hospital, Prague, Czech republic
- 26 3. Dept. of Cardiology, Neuron Medical, s.r.o., Brno, Czech republic
- 27 4. Dept. of Cardiology, Hospital AGEL Trinec – Podlesi, a.s., Trinec, Czech republic
- 28 5. Dept. of Cardiology, Regional Hospital Liberec, Liberec, Czech republic
- 29 6. Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech republic  
30  
31

32 **Corresponding author:**

33 Pavel Osmancik, MD, PhD  
34 Dept of cardiology, Cardiocenter  
35 3<sup>rd</sup> Faculty of Medicine and University Hospital  
36 Kralovske Vinohrady  
37 Srobarova 50  
38 10034, Prague  
39 Czech Republic  
40 Phone: 00420-721544447  
41 Email: [pavel.osmancik@gmail.com](mailto:pavel.osmancik@gmail.com)  
42  
43  
44

45 **Keywords:** atrial fibrillation, catheter ablation, antiarrhythmic drugs, risk factor modification  
46  
47

48 **Section:** Trial Design (Protocol of a Study)

49 **Word count:** 4000

50 **Declaration of interest:** none

51 **Running headline:** Protocol of Prague-25 trial

52 **RCT No:** NCT04011800

53 **Financial support:** Research grant of the Ministry of Health Czech Republic, No NU21-02-  
54 00388  
55  
56

## ABSTRACT

**Introduction:** Atrial fibrillation (AF), with a prevalence of 2%, is the most common cardiac arrhythmia. Catheter ablation (CA) has been documented to be superior over treatment by antiarrhythmic drugs (AADs) in terms of sinus rhythm (SR) maintenance. However, in obese patients, substantial weight loss was also associated with AF reduction. So far, no study has compared the modern non-invasive (AADs combined with risk factor modification) approach with modern invasive (CA) treatment. The aim of the trial is to compare the efficacy of modern invasive (catheter ablation) and non-invasive (AADs with risk factor management) treatment of AF.

**Methods and Analysis:** The trial will be a prospective, multicenter, randomized non-inferiority trial. Patients with symptomatic AF and a body-mass index  $> 30$  will be enrolled and randomized to the CA or risk factor modification arm (RFM+AAD) in a 1:1 ratio. In the CA arm, pulmonary vein isolation (in combination with additional lesion sets in non-paroxysmal patients) will be performed. For patients in the RFM+AAD arm, the aim will be a 10% weight loss over 6–12 months, increased physical fitness, and a reduction in alcohol consumption. The primary endpoint will be an episode of AF or regular AT lasting  $> 30$  sec. The secondary endpoints include AF burden, clinical endpoints associated with AF reoccurrence, changes in the quality of life assessed using dedicated questionnaires, changes in cardiorespiratory fitness, and metabolic endpoints. An AF freedom of 65% in the RFM+AAD and of 60% in the CA is expected; therefore, 202 patients will be enrolled to achieve the non-inferiority with 80% power, 5% one-sided alpha, and a non-inferiority margin of 12%.

1  
2  
3  
4  
5  
6  
7 **Ethics and Dissemination:** The PRAGUE-25 trial will determine if modern non-invasive AF  
8 treatment strategies are non-inferior to catheter ablation. The study was approved by the Ethics  
9 Committee of the University Hospital Kralovske Vinohrady. Results of the study will be  
10 disseminated on scientific conferences and in peer-reviewed scientific journals. After the end  
11 of follow-up, data will be available upon request to principal investigator.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

23 **Registration details:** The study was registered on clinicaltrials.gov as NCT04011800  
24  
25  
26  
27  
28  
29

## 30 **ARTICLE SUMMARY**

### 31 **Strengths of this study**

- 32 • The population of the study (obese patients with AF) is growing
- 33 • For the first time, AADs treatment combined with risk factor modification will be  
34 compared with catheter ablation  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

### 45 **Limitations of this study**

- 46 • The study is not large enough to compare clinical endpoints
- 47 • The monitoring using implantable loop recorders would be more sensitive  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, having a prevalence of about  $\approx 2\%$  in the general population. Among healthy men and women aged  $> 40$  years, the risk of lifelong AF occurrence is approximately 25% (1). The current estimated prevalence of AF is approximately 50 million patients worldwide, and its incidence has been increasing due to improved diagnostics, better treatment of chronic diseases, and increasing age (2). Therefore, its prevalence is expected to increase by nearly 3-fold during the next three decades. AF is associated with a three-fold increase in the risk of stroke and a two-fold increase in mortality risk (2).

### **The efficacy of catheter ablations in previous clinical studies**

Catheter ablation (CA) with pulmonary vein isolation (PVI) has been found to be superior to antiarrhythmic drugs (AADs) in terms of AF freedom in several randomized, controlled trials. The one-year efficacy of CA ranges from 40–90% (depending on the type of AF, patient cohort, and follow-up methods) (3). In patients with heart failure, AF, and decreased ejection fraction (EF), CA was associated with decreased mortality (4). However, mortality or clear clinical benefit of CA over AADs was not documented in the broad population of AF patients in the CABANA trial, the largest study on CA in AF (5). Except for the CABANA trial with 2,204

1  
2  
3  
4  
5  
6  
7 patients enrolled, all other studies have been substantially smaller (median of enrolled patients  
8 = 119 patients). In two well-conceived recent trials comparing CA (albeit using cryo-balloon  
9 ablation) with AADs, the one-year AF freedom was 74.6% when assessed using 24-hour Holter  
10 monitoring, or 57.1% when assessed using implantable loop recorders in the CA arms, or 45.0%  
11 and 32.2%, respectively, in the AAD arms (6) (7).  
12  
13  
14  
15  
16  
17

### 18 **The efficacy and limitations of the antiarrhythmic drugs**

19  
20 Several AADs (propafenone, flecainide, sotalol, amiodarone) have been documented as being  
21 superior compared to placebo for reducing the recurrence of AF (OR 0.19–0.70 for AADs) (8).  
22  
23 Moreover, in patients with an early AF diagnosis, early treatment of AF (in 86.8% of pts. using  
24 AADs) was associated with a reduction in cardiovascular mortality, stroke, hospitalization for  
25 heart failure, and acute coronary syndromes (9). However, the effect of AADs for SR  
26 maintenance is only modest. In the two most recent randomized control trials (RCT) comparing  
27 AADs (92% of which were flecainide and sotalol) with CA, the complete one-year AF freedom  
28 on AADs was 45%, or 32.2%, depending on the type of monitoring (6) (7). The long-term use  
29 of AADs is often limited by serious side effects and toxicity. It is especially true for amiodarone,  
30 otherwise, the most effective AAD (10), which often causes extracardiac side-effects, especially  
31 during long-term therapy. Therefore, it is mainly used as a second or third drug after the failure  
32 of other AADs or CA (11).  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

### 48 **Risk factor modification**

49  
50 According to several observational studies, obesity has been found to be independently  
51 associated with a higher risk of occurrence, as well as the progression of AF (12) (13).  
52  
53 According to a meta-analysis of 51 studies, which included more than 60,000 patients, an  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7 increase in the body-mass index (BMI) by 5 points is associated with a 19%–29% increase in  
8  
9 the incidence of AF (14). Besides obesity, other modifiable risk factors include hypertension,  
10  
11 sleep apnea, and alcohol consumption (15) (16) (17). Importantly, several recent interventional  
12  
13 studies have shown that all the aforementioned factors are not only known epidemiological  
14  
15 variables associated with a higher risk of AF, but their intensive treatment is associated with a  
16  
17 decrease in AF reoccurrences. In the non-randomized ARREST-AF study, 149 patients with a  
18  
19 BMI  $\geq 27$  after catheter ablation of AF were offered an opportunity to participate in a physician-  
20  
21 driven intensive risk factor modification (RFM) program, consisting of dietary changes and  
22  
23 regular physical exercise. Risk factor management was associated with a significant reduction  
24  
25 in AF reoccurrence by 23.9% (18). In the prospective, non-randomized LEGACY study, risk  
26  
27 factor management, which also focused on weight loss, was offered to a cohort of 355 AF  
28  
29 patients with a BMI  $\geq 27$  who had been referred to a tertiary center for AF treatment (contrary  
30  
31 to ARREST-AF study, patients in the LEGACY study had no history of AF ablation) (19). AF  
32  
33 freedom was achieved in 45% of patients with weight loss  $\geq 10\%$ , and in 22% of patients with  
34  
35 weight loss between 3 and 9% (19). Similarly, in a study by Malmo et al., patients undergoing  
36  
37 regular physical activity had AF paroxysms decline from 8.1% to 4.8% (20). Moreover, last  
38  
39 year Voskoboinik et al. documented that a reduction in alcohol consumption was also associated  
40  
41 with a significant reduction of AF paroxysms (21). It seems that AF treatment could lie, at least  
42  
43 in some patients, outside the electrophysiological catheter-labs. However, it is also important  
44  
45 to note that all studies focused on weight loss were either observational or had a non-  
46  
47 randomized control arm (ARREST-AF, LEGACY). Since participation, especially in metabolic  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 interventions, requires a high level of patient motivation, the absence of a control arm  
8  
9 potentially introduces a large bias into all the aforementioned studies.  
10

### 11 **Structural changes of ventricles and pericardial fat in patients with AF and obesity**

12  
13 As was shown, the amount of epicardial adipose tissue (EAT) is higher in patients with AF.  
14  
15 EAT is independently associated with future occurrences of AF in healthy persons and is also  
16  
17 a predictive factor for AF recurrence after catheter ablation (22) (23). Similarly, the degree of  
18  
19 diffuse myocardial ventricular fibrosis is higher in AF patients compared to healthy subjects  
20  
21 (24). Both the amount of EAT, as well as diffuse myocardial fibrosis, can be assessed using  
22  
23 cardiac magnetic resonance (CMR); the latter recently very sensitively using postcontrast-  
24  
25 enhanced T1 mapping (24). Recently, diffuse myocardial fibrosis assessed using post-contrast  
26  
27 T1 mapping predicted the effect of AF catheter ablation in paroxysmal patients (25). Early  
28  
29 changes on a CMR, such as higher left ventricular mass, or cardiac remodeling index, were also  
30  
31 described in patients with obesity (26).  
32  
33  
34  
35

### 36 **Pro-inflammatory markers changes in AF and in obesity**

37  
38 The concentrations of pro-inflammatory markers, such as high-sensitivity CRP, interleukin-6,  
39  
40 TNF- $\alpha$ , and others, have been reported to be elevated in AF patients, as well as in obese  
41  
42 individuals with SR. In obese patients, the adipose tissue is an important source of the pro-  
43  
44 inflammatory cytokines, and the concentrations of several pro-inflammatory cytokines  
45  
46 significantly decrease after weight loss (27). In AF patients, increased pre-ablation levels of  
47  
48 BNP, ANP, IL-6, and hsCRP are associated with a greater risk of AF recurrence after ablation  
49  
50 (28). However, studies focusing on the effect of CA on pro-inflammatory cytokines have shown  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 mixed results, and in most of them, the concentrations remained unchanged in AF patients after  
8 successful AF ablation with SR maintenance after 12 months (29) (30).  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

## 23 **METHODS AND ANALYSIS**

### 24 **Study design and objective**

25  
26  
27 The PRAGUE-25 trial is a prospective, multicenter, investigator-initiated, open-label,  
28 randomized, non-inferiority study registered on [clinicaltrials.gov](https://clinicaltrials.gov) (NCT04011800, v. 1 of the  
29 protocol). The primary objective is to compare the maintenance of sinus rhythm using modern  
30 invasive (catheter ablation) and non-invasive (RFM+AAD) AF treatment. Secondary endpoints  
31 include clinical endpoints, changes in the QoL, cardiorespiratory fitness, pro-inflammatory  
32 cytokines concentrations, echocardiography, and MRI measures. The study was approved by  
33 multicenter ethics committee and local ethics committees of all participating centers, and an  
34 informed consent will be obtained from all participants. The enrollment of patients begun in  
35 May 2021. The CONSORT diagram of the study is shown in **Figure 1**.  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

### 48 **Patient and Public Involvement**

49  
50 The design and protocol of the study were written by the investigator without the patient's  
51 involvement. Regarding the dissemination of the results, apart from scientific conferences,  
52 presentations on the patient's days, organized by the participating hospitals, are planned.  
53  
54  
55  
56  
57  
58  
59  
60

## Patient population

PRAGUE-25 is a multicenter study; currently, five centers from the Czech Republic are participating, but other centers may be added based on interest. The study will enroll symptomatic AF patients with high BMIs from the outpatient departments of the participating hospitals (AF clinics) and their cooperating outpatient departments (general practice patients). All outpatients from the participating centers and cooperating outpatient departments will be screened, and patients satisfying the inclusion criteria will be offered an opportunity to enroll. The qualifying criteria are symptomatic documented AF, high BMI, and patient motivation since the allocation to the risk factor modification (RFM+AAD) arm includes activities that require direct patient involvement. AF must be documented using a standard 12-lead ECG or Holter recording. There will be no special cut-off for the length of AF. Patients with long-standing AF can also enroll; enrollment for patients with a very long history of AF will depend on the patient's symptoms. An explanation of the efficacy of treatment for longer AF is routinely done during conversations with outpatients referred to CA. AAD-naïve and patients with a history of AAD treatment can be enrolled; the use of AAD in the past is not an exclusion criterion. During the enrollment process, all patients will be thoroughly informed about the dangers of obesity and other metabolic factors as it concerns AF. Participation in the special dietary intervention will not be an exclusion criterion. Our experienced nutritional specialists are able to establish AF-friendly diets for almost all patients.

### *Inclusion criteria:*

- symptomatic AF (paroxysmal, persistent, or long-standing persistent)
- BMI  $\geq$  30

- signed informed consent

*Exclusion criteria:*

- permanent AF
- BMI  $\geq$  40
- severe valve disease (significant aortic stenosis, mitral regurgitation  $\geq$  3)
- left ventricular ejection fraction  $<$  40%
- moderate or severe pulmonary hypertension (sPAP  $\geq$  40 mm Hg)
- history of tachycardia-induced cardiomyopathy
- manifest coronary artery disease
- pregnancy
- left atrial size  $\geq$  60 mm
- indication for surgical treatment of obesity
- age  $\geq$  75 yrs.
- diabetes mellitus needing insulin
- significant physical limitations that could affect physical activity (musculoskeletal disorders, moderate or severe COPD)
- life expectancy  $<$  2 years

**Baseline examinations**

After informed content is given, all patients will undergo baseline anthropometric measurements (weight, waist to hip ratio, body fat measurement) and a baseline functional evaluation. It will include (1) baseline evaluation of physical fitness - cardiopulmonary exercise test, (2) echocardiography, (3) quality of life analysis (using AFEQT questionnaire), (4) blood

1  
2  
3  
4  
5  
6  
7 biochemistry, and cytokine analysis, and (5) a baseline one-week ECG Holter recording. All  
8 these examinations will be done within four weeks after randomization.  
9

### 10 11 **Randomization and blinding**

12  
13 Patients will be randomized to the catheter ablation group (CA) or risk factor modification  
14 group plus AADs (RFM+AAD) in a 1:1 ratio; randomization will be done using randomization  
15 software that will account for age, initial BMI, and AF type, with the goal of having comparable  
16 groups relative to those characteristics. Randomization will be done in blocks but will not be  
17 site-specific (i.e., the proportion of patients randomized to CA vs. RFM-AAD will not be the  
18 same in all centers). The randomization process will be done outside all participating centers  
19 by a project-specific clinical trial management software system. The software will divide BMI  
20 into four categories (30.0–31.9, 32.0–33.9, 34.0–36.9, and 37.0–40.0); in each category, an  
21 additional two variables (i.e., age and AF type) will be taken into account in order to achieve  
22 similar values in both groups. The study will be open-label for study patients and study  
23 physicians. However, the evaluation of the ECG endpoint will be blinded; all Holter recordings  
24 will be evaluated by an organization outside the study that will not have access to patient  
25 information. Similarly, clinical endpoint assessments will also be blinded, and clinical endpoint  
26 committee will not be aware of patient randomizations. Institute of Biostatistics and Analyses  
27 will be responsible for the randomization software, data acquisition, storage, and data analysis.  
28  
29

### 30 31 **Functional diagnostic (anthropometric measurement and cardiopulmonary exercise test)**

32  
33 Functional diagnostics will be performed in all patients. Based on the results, an individualized  
34 physical training program will be prepared in patients randomized to the RFM+AAD arm.  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 An initial maximum symptom-limited cardiopulmonary exercise test (CEPT) will be carried  
8  
9 out within one month of enrollment. The CPET will be carried out on the medication which  
10  
11 was present at the enrollment visit. The cycle ergometer will be used in all sites. The protocol  
12  
13 will consist of a 3-min warm-up period with 0 Watt (unloaded pedaling), followed by a ramp  
14  
15 test increase of exercise intensity increased by 0.1 W/kg/min in women and by 0.15 W/kg/min  
16  
17 in men up to the maximum subjective tolerance. A 12-lead ECG tracing will be obtained  
18  
19 throughout the test for heart rate measurement, arrhythmia (especially AF) detection, and safety  
20  
21 reasons. Blood pressure will be measured manually with adequately selected cuff size. From  
22  
23 exhaled gas analysis, oxygen uptake  $VO_2$ , carbon dioxide production  $VCO_2$ , and minute  
24  
25 ventilation (VE) will be determined. Peak  $VO_2$  will be defined as the maximum value of  $VO_2$   
26  
27 averaged over 15 seconds; both absolute values and values indexed to body weight will be used.  
28  
29 The  $VCO_2/VE$  slope will be calculated from the beginning of the incremental exercise till the  
30  
31 respiratory compensation point; both ventilatory thresholds will be calculated.  
32  
33  
34  
35

## 36 **TREATMENTS**

### 37 **Catheter ablation arm**

38  
39 CA will be done within two months of randomization. In paroxysmal patients, a PVI will be  
40  
41 performed. In patients with non-paroxysmal AF forms, additional lesion sets will be allowed  
42  
43 according to the practice of each participating center. The CA will be done using a 3D mapping  
44  
45 system, intracardiac echocardiography, contact-force sensing ablation catheters, and ablation  
46  
47 index to achieve the maximum available safety and efficacy. All patients in the CA arm will be  
48  
49 informed about the danger of obesity and other risk factors as they concern AF and will be  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 instructed to lose weight, reduce alcohol consumption, and increase physical activity at  
8 discharge and again during each follow-up visit.

9  
10  
11 The first three months following catheter ablation will be considered as a “blinking period,”  
12 i.e., AF reoccurrences won't be assessed as an endpoint. During this period, treatment using  
13 AADs or cardioversion will be allowed. Three months after ablation, AADs will be  
14 discontinued.

### 20 **Risk factor modification and AADs (RFA+AAD) arm**

21  
22  
23 The aim will be (1) a 10% weight loss over 6–12 months,(2) an increase in physical fitness, and  
24 (3) a reduction in alcohol consumption. RFM will be performed not by the treating cardiologist  
25 but by teams of dietary specialists and physiotherapists. Nutritional intervention: the initial  
26 patient consultations with nutritional specialists will be done during the first month after  
27 enrollment. A low-calorie, high protein, and low glycemic index dietary menu will be suggested  
28 and optimized by a nutritional specialist for each patient. Except for regular in-person  
29 consultations with dietary specialists, phone visits any time during the follow-up; patients will  
30 be encouraged to record the calory intake in the OBEFIS application (either on the web  
31 [www.obefis.cz](http://www.obefis.cz), or using the mobile application), and the recordings will be discussed during  
32 the visits with dietary specialists.

33  
34  
35 All patients will have an initial consultation with a physiotherapist (after the CPET) to set the  
36 type and intensity of the physical intervention. The recommended physical intervention will  
37 consist of three types of activities: (1) regular gym-based training (in small groups or individual  
38 training with a trainer),(2i) individual aerobic training (fast walking or similar aerobic activity),  
39 and (3) home-based training: 20 min physical exercise sets. The type and ratio of the



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

aforementioned physical exercises will be changed over the study period. However, based on the patient's experiences with physical activity in the past, and their options regarding participation in the organized training, activities will be individualized. The ESC guidelines for obese individuals recommend that a minimum of 150 min/week of moderate-intensity endurance exercise training should be combined with three weekly sessions of resistance exercise with the heart rate during the activity being 55–74% of the maximum HR (31). As such, the physical intervention will be based on regular (mainly moderate,  $\approx$  55–74% of the maximum HR) intensity aerobic exercise that will be gradually increased from 60 min/week up to 200 min/week. Since the adherence of patients to regular activity is affected by activity monitoring, all patients will have an opportunity to be monitored during each exercise using remote heart rate monitoring (fitness bands) and the OBEFIS smartphone application.

For patients in the RFM+AAD arm, contrary to patients in the CA arm, non-amiodarone AADs will be allowed during the whole study period. The AADs that are allowed are AADs that are approved by the regulatory authorities for use on the Czech market; currently, this includes propafenone, flecainide, dronedarone, and sotalol. The choice of AAD will occur during the blanking period. For patients in SR, an AAD will be started immediately after randomization. In patients with AF during the baseline visit and in whom electrical cardioversion is planned, an AAD will be initiated the day before the electrical cardioversion. The dose and titration of AADs will be done during the blanking period and will be left to the discretion of the patient's treating physician and in accordance with the prescription rules for each AAD. The titration of a particular AAD to the maximum safe dose must be done during the blanking period; subsequent up-titration can only be done if AF recurs. Since weight loss goals will take months,

1  
2  
3  
4  
5  
6  
7 the effect of metabolic interventions cannot be expected as fast as in the CA arm. Therefore,  
8  
9 the blanking period for the RFM+AAD arm will last six instead of three months. The  
10  
11 reoccurrence as AF/AT as an endpoint will be considered starting at the 6-month visit, including  
12  
13 a 7-day Holter, which is scheduled to be done at the 6-month visit.  
14  
15

16 In both arms, in case of a reoccurrence of symptomatic AF or atrial tachycardia (AT), re-do  
17  
18 ablations, cardioversion, or AADs treatment during the follow-up period will be allowed in  
19  
20 accordance with the current guidelines and practices of participating centers. However, because  
21  
22 the indication for the aforementioned procedures or AAD initiation will be a reoccurrence of  
23  
24 AF or AT, it will be assessed as the primary endpoint (i.e., AF reoccurrence).  
25  
26

### 27 **OUTPATIENT FOLLOW-UP AND ENDPOINT MONITORING**

28  
29  
30 The follow-up protocol and ECG monitoring will be similar for both arms. Starting on the day  
31  
32 of the catheter ablation (D0 in the ablation arm) or at the start of the metabolic activity (D0 in  
33  
34 the RFM+AAD arm, approx. 3–4 weeks after randomization), follow-up visits will be  
35  
36 scheduled at 3, 6, 9, and 12 months during the first year, and then every six months. At the 3-  
37  
38 month follow-up visit, patients in AF (from both groups) will undergo electrical cardioversion.  
39  
40 A routine 12-lead ECG will be recorded at each follow-up visit, along with a physical  
41  
42 examination of the patient and a medical history update. Long-term ECG recording will be done  
43  
44 using a 7-day Holter recording at baseline, and then at the 6, 9, and 12 month visits during the  
45  
46 first year, and then every six months in the second and third years. Holter recordings will be  
47  
48 blinded, and analyzed by physicians outside the study. At the 12-month follow-up visit,  
49  
50 echocardiography, MRI examination, anthropometric measurements, and CPET will be done.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 Blood will be drawn for cytokine analysis, and patients will also be asked to complete follow-  
8 up QoL questionnaires.

## 11 **STUDY OUTCOMES**

### 14 **Primary endpoints:**

- 16 1) AF reoccurrence (any AF or atrial tachycardia lasting more than 30 sec)

### 18 **Secondary endpoints**

- 21 1) AF burden: calculated using all Holter recordings as a percentage of time spent in AF  
22 or AT
- 25 2) AF reoccurrence and AF burden at the 12-month visit
- 28 3) Hospitalization for AF reoccurrence and/or emergency room visit due to AF
- 31 4) A composite of stroke, cardiovascular death, or hospitalization for heart failure
- 34 5) Changes in QoL questionnaires between baseline and 12 months
- 37 6) Change in cardiorespiratory fitness as assessed using CPET between baseline and 12  
38 months
- 41 7) Metabolic endpoint: changes in weight, lipid levels, glycated hemoglobin, and pro-  
42 inflammatory cytokines
- 45 8) Imaging endpoints: change in diffuse ventricular fibrosis and EAT between baseline  
46 and the 12-month examination (MRI)

48 The AF reoccurrence will be detected either using planned 7-day Holter recordings (at the 6, 9,  
49 and 12 month visits), during all planned outpatient visits using a standard 12-lead ECG, and  
51 any time during the follow-up after the blanking period at an emergency non-planned visit also  
52 using a standard 12-lead ECG. During the planned or emergency visits, AF reoccurrence has to

1  
2  
3  
4  
5  
6  
7 be documented using an ECG (i.e., a patient's description of "palpitations" without ECG  
8 evidence will not be assessed as AF recurrence).

## 11 **STATISTICAL ANALYSIS PLAN AND POWER CALCULATION**

13 The power calculation was based on the results of randomized trials and observational studies  
14 comparing and assessing the effect of AADs vs. placebo, CA vs. AADs, and assessing the effect  
15 of risk factor modification in observational cohort studies. The primary efficacy analysis (non-  
16 inferiority) will be undertaken using the per-protocol population. If the non-inferiority criterion  
17 is satisfied, then superiority for the primary endpoint will be tested. Secondary analysis will be  
18 done using the intention-to-treat principle. Cross-over is only allowed for cases of treatment  
19 failure, i.e., only patients with AF/AT recurrences could be crossed-over, and the outcomes of  
20 crossed-over patients will be censored.

### 23 ***The expected efficacy of AADs and RFM***

24 In a meta-analysis of 24 randomized control trials comparing AADs with placebo, the overall  
25 success rate of AADs, defined as the disappearance of arrhythmia during follow-up, was present  
26 in 52% (95%CI 47%–57%) of patients on AADs (32). In the CABANA trial, by 12 months, the  
27 one-year AF freedom on AADs was present in 47.1% of patients (33). Finally, in the recently  
28 published STOP-AF trial, one-year AF freedom (assessed using repeated 24-Hour Holter  
29 recordings) was present in 45.0% (95%CI 34.6–54.7) of patients. Therefore, a one-year AF  
30 freedom of 45% could be expected for non-amiodarone AADs (6). In the LEGACY study,  
31 45.5% patients with weight loss >10%, 22.2% with weight loss 3–9%, and 13.4% in the weight  
32 loss < 3% remained AF-free without AADs or ablation (19). No study has compared the  
33 additive effect of weight loss on top of AADs; however, an additional effect of 20% could be

1  
2  
3  
4  
5  
6  
7 expected in these patients. Therefore, we expected a  $\approx 65\%$  one-year AF freedom in the  
8  
9 RFM+AAD arm.

### 11 ***The expected efficacy of the Catheter ablation***

12  
13  
14 In a meta-analysis of RCT comparing CA with AADs, the single procedure success rate of CA  
15  
16 OFF AADs was 57% (95%CI 50–64%) (32). In the CABANA trial, AF freedom was present  
17  
18 in 63.6% of the ablation patients by 12 months (33). The expected one-year AF freedom in the  
19  
20 CA arm is  $\approx 60\%$ .

21  
22  
23 According to the aforementioned data, we expect one-year AF freedom in 65% of patients in  
24  
25 the RFM+AAD arm and 60% in the CA arm. The primary analysis will be done using the  
26  
27 intention-to-treat principle; however, based on the non-inferiority nature of the study, a per-  
28  
29 protocol analysis will be done. The sample size calculation assumed: 80% power, 5% 2-sided  
30  
31 alpha, a non-inferiority margin of 12% (or 1.65, if expressed as an odds ratio). Using this  
32  
33 assumption, 202 patients (101 in each arm) will need to be enrolled to prove non-inferiority of  
34  
35 the non-invasive arm relative to the invasive arm. With an expected drop-out rate of 5%,  
36  
37 therefore, 212 patients will be enrolled.

### 39 ***Non-inferiority margin (NIM) considerations***

40  
41  
42 Regulatory guidelines require that the NIM rules out the minimum effect of treatment in the  
43  
44 control arm (i.e., the CA arm in our study). Statistical guidelines recommend the most liberal  
45  
46 NIM 1.92 (if expressed relatively as OR). From the clinical point of view, several rules exist  
47  
48 for NIM adjustment. Obviously, the margin corresponds to the preservation of 50% benefit of  
49  
50 the known treatment arm over placebo that was recognized in previous studies comparing  
51  
52 recognized treatment with placebo. The other recommendation for NIM is to use the lower band  
53  
54  
55  
56  
57

1  
2  
3  
4  
5  
6  
7 of 95% confidence interval of the placebo effect from previous studies comparing actual known  
8 treatment with placebo. Thus, for the study, the first step in selecting NIM was to estimate the  
9 minimum acceptable retention of the benefit of CA over placebo. In studies comparing CA with  
10 AADs, the single procedure success rate of CA OFF AADs was 57% (95% CI 50–64%).  
11 Unfortunately, none of the studies had a placebo arm, and all compared CA with AADs. In the  
12 studies comparing AADs vs. placebo, the success of treatment in the placebo arms was 24.9%  
13 (95% CI, 15%–34%). So, the selected margin of 12% fulfills the criteria for the NIM setting. If  
14 it is expressed as an OR, it corresponds to 1.65, which is consistent with regulatory guidelines  
15 recommendations (and, e.g., it is similar as it was in large non-inferiority trials comparing  
16 NOAC with Warfarin).

### 17 **Study organization and data management**

18  
19 The institution responsible for the organization and implementation of the study is the 3<sup>rd</sup>  
20 Faculty of Medicine, Charles University in Prague, Czech Republic. Data obtained during each  
21 patient visit will be collected using a safe electronic CRF form. A tailor-made website was  
22 developed for the study. Each participating medical center will have access to a dedicated part  
23 of the website. The local investigator at each site will be responsible for data completeness and  
24 validity. At the end of the study, all data will be entered and stored on a password-protected  
25 computer. Only the principal investigator will have access to the final data set. All regulations  
26 regarding medical confidentiality and data protection will be fulfilled.

27  
28 The database and randomization software has been prepared by an outside party (i.e., the  
29 Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic), and no  
30 investigator will have access to the database or the randomization software. The Institute of

1  
2  
3  
4  
5  
6  
7 Biostatistics and Analyses will also independently collect all data, manage the database, and be  
8 responsible for data analysis. No other groups (i.e., device manufacturers or pharmaceutical  
9 companies) were involved in the creation of the protocol or any other part of the study. The  
10 investigator team will be responsible for final data analysis and interpretation.  
11  
12  
13  
14  
15  
16

#### 17 Data availability statement

18  
19  
20 The primary analysis is planned after 6 months of follow-up of the last enrolled patients. After  
21 that, an extension of follow-up for three additional years is planned according to the protocol.  
22  
23 Study data will be shared when the follow-up extension is finished and analyzed. Data will be  
24 available upon reasonable request. Deidentified data will be stored at the Institute of  
25 Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, and will be available  
26 after request to principal investigator for further analyses and meta-analyses.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

#### 38 **Safety and endpoint monitoring**

39  
40 The local investigator at each site will continuously review safety data during the trial. A Data  
41 Safety Monitoring Board (DSMB) will be constituted before the commencement of the trial.  
42  
43 Reporting of adverse events will be reported to the DSMB immediately by the principal  
44 investigator. Serious adverse events (SAE) will be defined as life-threatening events or events  
45 resulting in death or hospitalization. All SAEs linked with the study will be reported to the  
46 DSMB, to the FNKV Ethics Committee (a multicenter ethics committee, EC), and to the local  
47 ECs within 24 hours of study staff becoming aware of the event. Clinical endpoints will be  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7 analyzed by a dedicated clinical endpoint committee. The recording and analyses of all Holter  
8  
9 recordings in all participating centers will be done centrally using an MDT (medical data  
10  
11 transfer) company. A standard, commercially available, 7-day Holter monitor (e.g., Faros 160,  
12  
13 Bittium, Finland, or similar tools ), with daily telephone transfers, will be used.

## 16 **DISCUSSION**

17  
18 In the last five years, lifestyle modification with risk factor management has been shown to be  
19  
20 a very promising treatment modality for AF. AF is the most common sustained cardiac  
21  
22 arrhythmia, with an estimated worldwide prevalence of about 33.5 million people (2).  
23  
24 According to recent epidemiological studies, its prevalence may triple by 2050 (19). Even if  
25  
26 catheter ablations were associated with a 100% success rate, it would be impossible to treat the  
27  
28 current or projected numbers using catheter ablations. Furthermore, a substantial number of  
29  
30 patients would prefer a non-invasive treatment if both strategies were comparable. So while  
31  
32 risk factor modification studies may seem to offer a panacea, those studies suffer from  
33  
34 significant limitations and possible biases. For example, the most important and most extensive  
35  
36 studies were both non-randomized, and all patients had either a history of catheter ablation  
37  
38 (ARREST-AF) or were without a history of catheter ablation, but catheter ablation was allowed  
39  
40 without limitations, based on the judgment of the attending physician during the follow-up  
41  
42 period (LEGACY). A randomized study that directly compares catheter ablation with a modern  
43  
44 non-invasive strategy has yet to be done. If the effect of both strategies were comparable, the  
45  
46 non-invasive strategy could be offered to patients with a preference for a non-invasive  
47  
48 treatment. Only a randomized study can really answer the question of how effective lifestyle  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7 modification is supported by safe non-amiodarone AADs compared to a modern invasive  
8 strategy.  
9

10  
11 A significant portion of patients with AF are obese (e.g., the median BMI was 30 in the  
12 CABANA Trial). Likewise, according to the database of patients who underwent CA at our  
13 institutions in the last five years, the median BMI was also 30. It is expected that RFM will  
14 have a significant effect on blood pressure, glucose metabolism, etc.; however, whether this  
15 approach supported by AADs is comparable with CA has never been tested in a randomized  
16 study. If both treatment strategies were comparable in terms of SR maintenance, risk factor  
17 modification and AADs could be offered to obese patients as comparable treatment to an  
18 invasive procedure.  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28

### 29 **ETHICS AND DISSEMINATION**

30  
31  
32 The study was approved by the Multicenter Ethics Committee of the University Hospital  
33 Kralovske Vinohrady (approval no. EK-VP/34/0/2020). The enrollment of the population is  
34 planned for two years. The first results will be published at the end of 2023 and at the beginning  
35 of 2024. Results of the study will be disseminated on scientific conferences and in peer-  
36 reviewed scientific journals. No new drugs or devices are planned for the study, so there are no  
37 significant specific ethical considerations, and treatments in both arms are in accordance with  
38 current recommendations. However, as it corresponds to the standard of all RCT, all the serious  
39 adverse events will be immediately reported to the appropriate Ethics Committee, as noted in  
40 the protocol.  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51

52  
53 **AUTHORS' CONTRIBUTION:** PO wrote the manuscript and has initiated the study. Authors  
54 SH, VB, JC, TR, DH, ZC, OJ, and MF are responsible for the general analysis of the EP  
55  
56  
57

1  
2  
3  
4  
5  
6  
7 literature and the EP part of the protocol. Authors VT, MM, SS-H, and AL are responsible for  
8  
9 the analysis of the literature on non-invasive studies and are responsible for the metabolic part  
10  
11 of the protocol. JK and JJ are the statisticians responsible for power calculation and the web-  
12  
13 based electronic database.  
14

15  
16 **COMPETING INTEREST:** none  
17

18 **FUNDING STATEMENT:** This work was supported by a Research Grant from the Ministry  
19  
20 of Health, Czech Republic, No NU21-02-00388  
21  
22

### 23 **FIGURE LEGENDS**

24  
25 **Figure 1 CONSORT diagram of the study**  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## REFERENCES

1. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042-6.
2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837-47.
3. Piccini JP, Lopes RD, Kong MH, et al. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. *Circ Arrhythm Electrophysiol* 2009;2:626-33.
4. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018;378:417-27.
5. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA* 2019;321:1261-74.
6. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. *N Engl J Med* 2021;384:316-24.
7. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *N Engl J Med* 2021;384:305-15.
8. Lafuente-Lafuente C, Valembois L, Bergmann JF, et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2015;CD005049.
9. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med* 2020;383:1305-16.
10. Freemantle N, Lafuente-Lafuente C, Mitchell S, et al. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;13:329-45.
11. Goldschlager N, Epstein AE, Naccarelli GV, et al. A practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007;4:1250-9.

12. Lavie CJ, Pandey A, Lau DH, et al. Obesity and Atrial Fibrillation Prevalence, Pathogenesis, and Prognosis: Effects of Weight Loss and Exercise. *J Am Coll Cardiol* 2017;70:2022-35.
13. Middeldorp ME, Pathak RK, Meredith M, et al. PREVENTion and regReSSive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace* 2018;20:1929-35.
14. Wong CX, Sullivan T, Sun MT, et al. Obesity and the Risk of Incident, Post-Operative, and Post-Ablation Atrial Fibrillation: A Meta-Analysis of 626,603 Individuals in 51 Studies. *JACC Clin Electrophysiol* 2015;1:139-52.
15. Conen D, Tedrow UB, Koplan BA, et al. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;119:2146-52.
16. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;49:565-71.
17. Kodama S, Saito K, Tanaka S, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *J Am Coll Cardiol* 2011;57:427-36.
18. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;64:2222-31.
19. Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol* 2015;65:2159-69.
20. Malmo V, Nes BM, Amundsen BH, et al. Aerobic Interval Training Reduces the Burden of Atrial Fibrillation in the Short Term: A Randomized Trial. *Circulation* 2016;133:466-73.
21. Voskoboinik A, Kalman JM, De Silva A, et al. Alcohol Abstinence in Drinkers with Atrial Fibrillation. *N Engl J Med* 2020;382:20-8.
22. Al Chekakie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol* 2010;56:784-8.

23. Mirolo A, Viart G, Savoure A, et al. Epicardial fat thickness predicts atrial fibrillation recurrence after a first pulmonary vein isolation procedure using a second-generation cryoballoon. *Arch Cardiovasc Dis* 2019;112:314-22.
24. Ling LH, Kistler PM, Ellims AH, et al. Diffuse ventricular fibrosis in atrial fibrillation: non-invasive evaluation and relationships with aging and systolic dysfunction. *J Am Coll Cardiol* 2012;60:2402-8.
25. McLellan AJ, Ling LH, Azzopardi S, et al. Diffuse ventricular fibrosis measured by T(1) mapping on cardiac MRI predicts success of catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;7:834-40.
26. Eschalier R, Rossignol P, Kearney-Schwartz A, et al. Features of cardiac remodeling, associated with blood pressure and fibrosis biomarkers, are frequent in subjects with abdominal obesity. *Hypertension* 2014;63:740-6.
27. Bianchi VE. Weight loss is a critical factor to reduce inflammation. *Clin Nutr ESPEN* 2018;28:21-35.
28. Jiang H, Wang W, Wang C, et al. Association of pre-ablation level of potential blood markers with atrial fibrillation recurrence after catheter ablation: a meta-analysis. *Europace* 2017;19:392-400.
29. Sasaki N, Okumura Y, Watanabe I, et al. Increased levels of inflammatory and extracellular matrix turnover biomarkers persist despite reverse atrial structural remodeling during the first year after atrial fibrillation ablation. *J Interv Card Electrophysiol* 2014;39:241-9.
30. Bin Waleed K, Yin X, Yang X, et al. Short and long-term changes in platelet and inflammatory biomarkers after cryoballoon and radiofrequency ablation. *Int J Cardiol* 2019;285:128-32.
31. Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;42:17-96.
32. Calkins H, Reynolds MR, Spector P, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009;2:349-61.

- 1  
2  
3  
4  
5  
6  
7 33. Poole JE, Bahnson TD, Monahan KH, et al. Recurrence of Atrial Fibrillation After  
8 Catheter Ablation or Antiarrhythmic Drug Therapy in the CABANA Trial. *J Am Coll Cardiol*  
9 2020;75:3105-18.  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

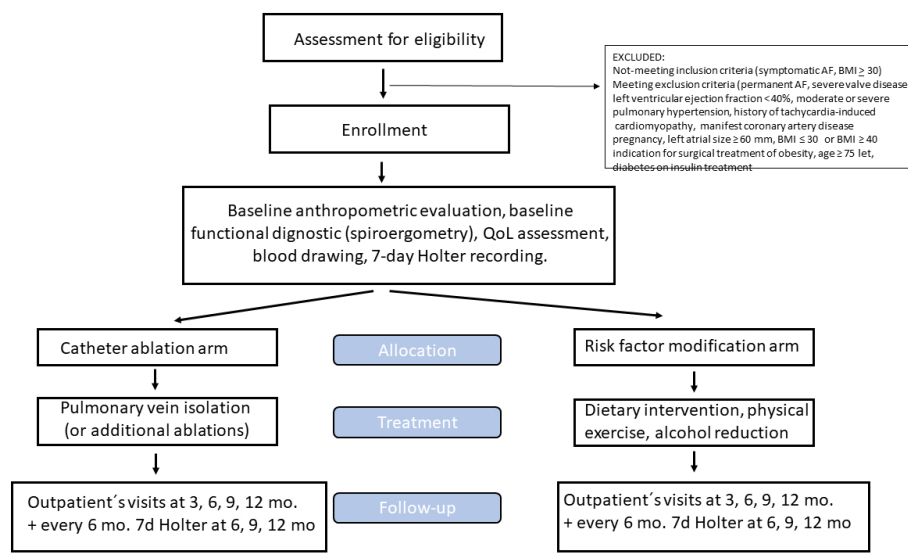


Figure 1

338x190mm (96 x 96 DPI)

1  
2  
3 **SPIRIT checklist for the article „CATHETER ABLATION VS.**  
4 **ANTIARRHYTHMIC DRUGS WITH RISK FACTOR MODIFICATION FOR**  
5 **TREATMENT OF ATRIAL FIBRILLATION, A RANDOMIZED**  
6 **CONTROLLED TRIAL (PRAGUE-25 TRIAL)“**  
7  
8  
9

10  
11 **Administrative information**

- 12 1. Title p.1  
13  
14 2. Trial registration p. 1  
15  
16 3. Protocol version p.8  
17  
18 4. Funding p, 1  
19  
20 5. Roles and responsibilities p. 19, 20  
21

22 **Introduction**

- 23  
24 6. Background and rationale p.4,5,6,7  
25  
26 7. Objectives p.8  
27  
28 8. Trial design p.8  
29

30 **Methods, participants, interventions, outcomes**

- 31 9. Study setting p.8  
32  
33 10. Eligibility criteria p.9, 10  
34  
35 11. Interventions p.12, 13  
36  
37 12. Outcomes p.16  
38  
39 13. Participant timeline p.15  
40  
41 14. Sample size p.17, 18  
42  
43 15. Recruitment p.8, 9  
44

45 **Methods, assignment of interventions**

- 46 16. Allocation p.11  
47  
48 17. Blinding (masking) p.11  
49

50 **Methods, data collection, management, analysis**

- 51 18. Data collection methods p.19, 20  
52  
53 19. Data management p.20  
54  
55 20. Statistical methods p. 17  
56  
57

58 **Methods, monitoring**

- 59 21. Data monitoring p. 20  
60



1  
2  
3 22. Harms p.20  
4

5 23. Auditing p.20  
6

7 **Ethics and dissemination**

8  
9 24. Research ethics approval p.8

10  
11 25. Protocol amendments p. 8

12  
13 26. Consent or assent p.8

14  
15 27. Confidentiality p.19, 20

16  
17 28. Declaration of interest p.8

18  
19 29. Access to data p. 19, 20

20  
21 30. Ancillary and post-trial care p. 21

22  
23 31. Dissemination policy p.21

24 **Appendices**

25  
26 32. Informed consent materials

27  
28 33. Biological specimens  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Along with your revised manuscript, please include a copy of the SPIRIT checklist indicating the page/line numbers of your manuscript where the relevant information can be found (<http://www.spirit-statement.org/>)