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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 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 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%.

Ethics and Dissemination: The PRAGUE-25 trial will determine if modern noninvasive AF treatment strategies are non-inferior to catheter ablation.

Registration details: The study was registered on clinicaltrials.gov as NCT04011800

ARTICLE SUMMARY

Strengths of this study

- The population of the study (obese patients with AF) is growing
- For the first time, AADs treatment combined with risk factor modification will be compared with catheter ablation

Limitations of this study

- The study is not large enough to compare clinical endpoints
- The monitoring using implantable loop recorders would be more sensitive

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, having a prevalence of about ≈ 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, controled 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

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 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, and as well as 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 are associated with a decrease in AF reoccurrences. In the non-randomized ARREST-AF study, 149 patients with

a BMI ≥ 27 after catheter ablation of AF were offered an opportunity to participate in a physician-driven intensive risk factor modification (RFM) program, consisting of dietary changes and regular physical exercise. Risk factor management was associated with a significant reduction in AF reoccurrence by 23.9% (18). In the prospective, non-randomized LEGACY study, risk factor management, which also focused on weight loss, was offered to a cohort of 355 AF patients with a BMI ≥ 27 who had been referred to a tertiary center for AF treatment (contrary to ARREST-AF study, patients in the LEGACY study had no history of AF ablation) (19). AF freedom was achieved in 45% of patients with weight loss ≥ 10%, and in 22% of patients with weight loss between 3 and 9% (19). Similarly, in a study by Malmo et al., patients undergoing regular physical activity had AF paroxysms decline from 8.1% to 4.8% (20). Moreover, last year Voskoboinik et al. documented that a reduction in alcohol consumption was also associated with a significant reduction of AF paroxysms (21). It seems that AF treatment could lie, at least in some patients, outside the electrophysiological cath-labs. However, and it is also important to note, all studies that focused on weight loss were either observational or had a non-randomized control arm (ARREST-AF, LEGACY). Since participation, especially in metabolic interventions, requires a high level of patient motivation, the absence of a control arm potentially introduces a large bias into all the aforementioned studies.

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

As was shown, the amount of epicardial adipose tissue (EAT) is higher in patients with AF. EAT is independently associated with future occurrences of AF in healthy persons and is also a predictive factor for AF recurrence after catheter ablation (22) (23). Similarly, the degree of

diffuse myocardial ventricular fibrosis is higher in AF patients compared to healthy subjects (24). Both the amount of EAT, as well as diffuse myocardial fibrosis, can be assessed using cardiac magnetic resonance (CMR); the latter recently very sensitively using postcontrast-enhanced T1 mapping (24). Recently, diffuse myocardial fibrosis assessed using post-contrast T1 mapping predicted the effect of AF catheter ablation in paroxysmal patients (25). Early changes on a CMR, such as higher left ventricular mass, or cardiac remodeling index, were also described in patients with obesity (26).

Pro-inflammatory markers changes in AF and in obesity

The concentrations of pro-inflammatory markers, such as high-sensitivity CRP, interleukin-6, TNF-α, and others, have been reported to be elevated in AF patients, as well as in obese individuals with SR. In obese patients, the adipose tissue is an important source of the pro-inflammatory cytokines, and the concentrations of several pro-inflammatory cytokines significantly decrease after weight loss (27). In AF patients, increased pre-ablation levels of BNP, ANP, IL-6, and hsCRP are associated with a greater risk of AF recurrence after ablation (28). However, studies focusing on the effect of CA on pro-inflammatory cytokines have shown mixed results, and in the majority of them, the concentrations remained unchanged in AF patients after successful AF ablation with SR maintenance after 12 months (29) (30).

METHODS AND ANALYSIS

Study design and objective

The PRAGUE-25 trial is a prospective, multicenter, investigator-initiated, randomized, non-inferiority study registered on clinicatrial.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 ≥ 30
- signed informed consent

Exclusion criteria:

- permanent AF
- BMI ≥ 40
- severe valve disease (significant aortic stenosis, mitral regurgitation ≥ 3)
- left ventricular ejection fraction < 40%
- moderate or severe pulmonary hypertension (sPAP ≥ 40 mm Hg)
- history of tachycardia-induced cardiomyopathy
- manifest coronary artery disease
- pregnancy
- left atrial size ≥ 60 mm
- indication for surgical treatment of obesity
- age ≥ 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 biochemistry and cytokine analysis, and (5) a baseline one-week ECG Holter recording. All these examinations will be done within four weeks after randomization.

Randomization

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

Functional diagnostic (anthropometric measurement and cardiopulmonary exercise test)

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

An initial maximum symptom limited cardiopulmonary exercise test (CEPT) will be carried out within one month of enrollment. The CPET will be carried out on the medication which was present at enrollment visit. The cycle ergometer will be used in all sites. The protocol will consist of a 3-min warm-up period with 0 Watt (unloaded pedaling), followed by a ramp test increase of exercise intensity increased by 0.1 W/kg/min in women and by 0.15 W/kg/min in men up to the maximum subjective tolerance. A 12-lead ECG tracing will be obtained throughout the test for heart rate measurement, arrhythmia (especially AF) detection and safety reasons. Blood pressure will be measured manually with adequately selected cuff size. From exhaled gas analysis oxygen uptake VO_2, carbon dioxide production VCO_2 and minute ventilation (VE) will be determined. Peak VO2 will be defined as the maximum value of VO2

averaged over 15 seconds, both absolute values and values indexed to body weight will be used. The VCO2/VE slope will be calculated from the beginning of the incremental exercise till the respiratory compensation point. Both ventilatory thresholds will be calculated.

TREATMENTS

Catheter ablation arm

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

The first three months following catheter ablation will be considered as a "blanking period," i.e., AF reoccurrences won´t be assessed as an endpoint. During this period, treatment using AADs or cardioversion will be allowed. Three months after ablation, AADs will be discontinued.

Risk factor modification and AADs arm

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

consultations with dietary specialists, phone visits any time during the follow-up; patients will be encouraged to record the calory intake in the OBEFIS application (either on the web www.obefis.cz, or using the mobile application), and the recordings will be discussed during the visits with dietary specialists.

All patients will have an initial consultation with a physiotherapist (after the CPET) to set the type and intensity of the physical intervention. The recommended physical intervention will consist of three types of activities: (1) regular gym-based training (in small groups or individual training with trainer),(2i) individual aerobic training (fast walking or similar aerobic activity), 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, ~ 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 arm, contrary to patients in the CA arm, non-amiodarone AADs will be allowed during the whole study period. The choice of AAD will occur during the blanking

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

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

OUTPATIENT FOLLOW-UP AND ENDPOINT MONITORING

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

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

done. Blood will be drawn for cytokine analysis, and patients will also be asked to complete follow-up QoL questionnaires.

STUDY OUTCOMES

Primary endpoints:

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

Secondary endpoints

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

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

be documented using an ECG (i.e., a patient´s description of "palpitations" without ECG evidence will not be assessed as AF reoccurrence).

STATISTICAL ANALYSIS PLAN AND POWER CALCULATION

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

The expected efficacy of AADs and RFM

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

The expected efficacy of the Catheter ablation

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

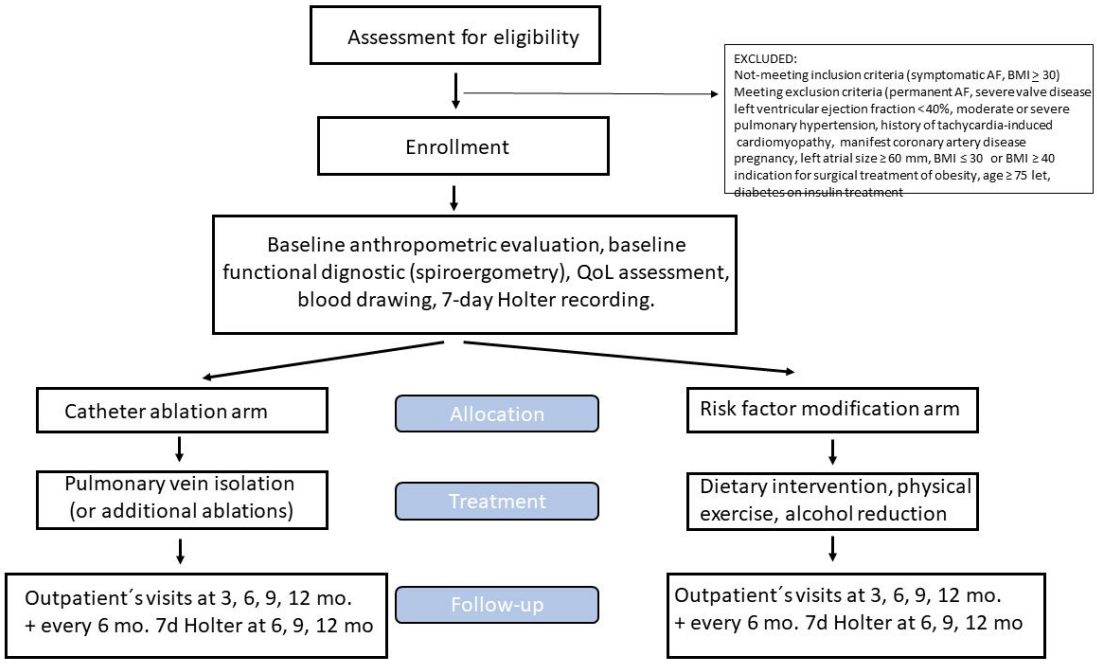
According to the aforementioned data, we expect one-year AF freedom in 65% of patients in the RFM arm and 60% in the CA arm. The primary analysis will be done using the intention-to-treat principle; however, based on the non-inferiority nature of the study, a per-protocol analysis will be done. The sample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

Non-inferiority margin (NIM) considerations

Regulatory guidelines require that the NIM rules out the minimum effect of treatment in the control arm (i.e., the CA arm in our study). Statistical guidelines recommend the most liberal NIM 1.92 (if expressed relatively as OR). From the clinical point of view, several rules exist for NIM adjustment. Obviously, the margin corresponds to the preservation of 50% benefit of the known treatment arm over placebo that was recognized in a previous studies comparing recognized treatment with placebo. The other recommendation for NIM is to use the lower band of 95% confidence interval of the placebo effect from previous studies comparing actual known treatment with placebo. Thus, for the study, the first step in selecting NIM was to estimate the minimum acceptable retention of benefit of CA over placebo. In studies comparing CA with

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 d*ata management*

The institution responsible for the organization and implementation of the study is the 3rd 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

developed for the study. Each participating medical center will have access to a dedicated part of the website. The local investigator at each site will be responsible for data completeness and validity. At the end of the study, all data will be entered and stored on a password-protected computer. Only the principal investigator will have access to the final data set. All regulations regarding medical confidentiality and data protection will be fulfilled.

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

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 monitors (e.g. Faros 160, Bittium, Finland, or similar tools) with daily transtelephonic transfer 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 catheter ablations were associated with a 100% success rate, it would be impossible to treat the current or projected numbers using catheter ablations. Furthermore, a substantial number of patients would prefer a non-invasive treatment if both strategies were comparable. So while risk factor modification studies may seem to offer a panacea, those studies suffer from significant limitations and possible biases. For example, the most important and most extensive studies were both non-randomized, and all patients had either a history of catheter ablation (ARREST-AF) or were without a history of catheter ablation, but catheter ablation was allowed without limitations, based on the judgment of the attending physician during the follow-up period (LEGACY). A randomized study that directly compares catheter ablation with a modern noninvasive strategy has yet to be done. If the effect of both strategies were comparable, the noninvasive strategy could be offered to patients with a preference for a noninvasive treatment.

Only a randomized study can really answer the question of how effective lifestyle modification is supported by safe non-amiodarone AADs compared to a modern invasive strategy.

ETHICS AND DISSEMINATION

The enrollment of the population is planned for 2 years. The first results will be published in the end of the 2023, of in the beginning of 2024. Standard presentation on scientific conferences and in extenso publication in impact journals is planned. No new drugs or devices are planned for the study, so there are no specific ethical consideration. However, as it corresponds to the standard of all RCT, all the serious adverse events will be immediately reported to the appropriate Ethics Committee, as noted in the protocol.

AUTHORS´ CONTRIBUTION: PO wrote the manuscript and has initiated the study. The authors SH, VB, JC, TR, DH, ZC, OJ and MF are responsible for the general for the analysis of the EP literature and the EP part of the protocol. The authors VT, MM, SSH, AL are responsible for the analysis of the literature on the non-invasive studies and are responsible for the metabolic part of the protocol. JK and JJ are statisticians, responsible for power calculation, electronic web-based database.

COMPETING INTEREST: none

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FIGURE LEGENDS

Figure 1 CONSORT diagram of the trial

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

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

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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%.

Ethics and Dissemination: The PRAGUE-25 trial will determine if modern non-invasive AF treatment strategies are non-inferior to catheter ablation.

Registration details: The study was registered on clinicaltrials.gov as NCT04011800

ARTICLE SUMMARY

Strengths of this study

- The population of the study (obese patients with AF) is growing
- For the first time, AADs treatment combined with risk factor modification will be compared with catheter ablation

Limitations of this study

- The study is not large enough to compare clinical endpoints
- The monitoring using implantable loop recorders would be more sensitive

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, having a prevalence of about ≈ 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

decrease in AF reoccurrences. In the non-randomized ARREST-AF study, 149 patients with a BMI ≥ 27 after catheter ablation of AF were offered an opportunity to participate in a physician-driven intensive risk factor modification (RFM) program, consisting of dietary changes and regular physical exercise. Risk factor management was associated with a significant reduction in AF reoccurrence by 23.9% (18). In the prospective, non-randomized LEGACY study, risk factor management, which also focused on weight loss, was offered to a cohort of 355 AF patients with a BMI ≥ 27 who had been referred to a tertiary center for AF treatment (contrary to ARREST-AF study, patients in the LEGACY study had no history of AF ablation) (19). AF freedom was achieved in 45% of patients with weight loss ≥ 10%, and in 22% of patients with weight loss between 3 and 9% (19). Similarly, in a study by Malmo et al., patients undergoing regular physical activity had AF paroxysms decline from 8.1% to 4.8% (20). Moreover, last year Voskoboinik et al. documented that a reduction in alcohol consumption was also associated with a significant reduction of AF paroxysms (21). It seems that AF treatment could lie, at least in some patients, outside the electrophysiological catheter-labs. However, it is also important to note that all studies focused on weight loss were either observational or had a non-randomized control arm (ARREST-AF, LEGACY). Since participation, especially in metabolic interventions, requires a high level of patient motivation, the absence of a control arm potentially introduces a large bias into all the aforementioned studies.

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

As was shown, the amount of epicardial adipose tissue (EAT) is higher in patients with AF. EAT is independently associated with future occurrences of AF in healthy persons and is also a predictive factor for AF recurrence after catheter ablation (22) (23). Similarly, the degree of

diffuse myocardial ventricular fibrosis is higher in AF patients compared to healthy subjects (24). Both the amount of EAT, as well as diffuse myocardial fibrosis, can be assessed using cardiac magnetic resonance (CMR); the latter recently very sensitively using postcontrast-enhanced T1 mapping (24). Recently, diffuse myocardial fibrosis assessed using post-contrast T1 mapping predicted the effect of AF catheter ablation in paroxysmal patients (25). Early changes on a CMR, such as higher left ventricular mass, or cardiac remodeling index, were also described in patients with obesity (26).

Pro-inflammatory markers changes in AF and in obesity

The concentrations of pro-inflammatory markers, such as high-sensitivity CRP, interleukin-6, TNF-α, and others, have been reported to be elevated in AF patients, as well as in obese individuals with SR. In obese patients, the adipose tissue is an important source of the pro-inflammatory cytokines, and the concentrations of several pro-inflammatory cytokines significantly decrease after weight loss (27). In AF patients, increased pre-ablation levels of BNP, ANP, IL-6, and hsCRP are associated with a greater risk of AF recurrence after ablation (28). However, studies focusing on the effect of CA on pro-inflammatory cytokines have shown mixed results, and in most of them, the concentrations remained unchanged in AF patients after successful AF ablation with SR maintenance after 12 months (29) (30).

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 clinicatrial.gov (NCT04011800, v. 1 of the protocol). The primary objective is to compare he 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 begun 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

scientific conferences, presentations on the patient´s days, organized by the participating hospitals, are planned.

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-naive 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 ≥ 30
- signed informed consent

Exclusion criteria:

- permanent AF
- BMI ≥ 40
- severe valve disease (significant aortic stenosis, mitral regurgitation ≥ 3)
- left ventricular ejection fraction < 40%
- moderate or severe pulmonary hypertension (sPAP ≥ 40 mm Hg)
- history of tachycardia-induced cardiomyopathy
- manifest coronary artery disease
- pregnancy
- left atrial size ≥ 60 mm
- indication for surgical treatment of obesity
- age ≥ 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 biochemistry, and cytokine analysis, and (5) a baseline one-week ECG Holter recording. All these examinations will be done within four weeks after randomization.

Randomization and blinding

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

Functional diagnostic (anthropometric measurement and cardiopulmonary exercise test)

Functional diagnostics will be performed in all patients. Based on the results, an individualized physical training program will be prepared in patients randomized to the RFM+AAD arm.

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

TREATMENTS

Catheter ablation arm

CA will be done within two months of randomization. In paroxysmal patients, a PVI will be performed. In patients with non-paroxysmal AF forms, additional lesion sets will be allowed according to the practice of each participating center. The CA will be done using a 3D mapping system, intracardiac echocardiography, contact-force sensing ablation catheters, and ablation index to achieve the maximum available safety and efficacy. All patients in the CA arm will be

informed about the danger of obesity and other risk factors as they concern AF and will be instructed to lose weight, reduce alcohol consumption, and increase physical activity at discharge and again during each follow-up visit.

The first three months following catheter ablation will be considered as a "blanking period," i.e., AF reoccurrences won´t be assessed as an endpoint. During this period, treatment using AADs or cardioversion will be allowed. Three months after ablation, AADs will be discontinued.

Risk factor modification and AADs (RFA+AAD) arm

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

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

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, ≈ 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, the effect of metabolic interventions cannot be expected as fast as in the CA arm. Therefore, the blanking period for the RFM+AAD arm will last six instead of three months. The reoccurrence as AF/AT as an endpoint will be considered starting at the 6-month visit, including a 7-day Holter, which is scheduled to be done at the 6-month visit.

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

OUTPATIENT FOLLOW-UP AND ENDPOINT MONITORING

The follow-up protocol and ECG monitoring will be similar for both arms. Starting on the day of the catheter ablation (D0 in the ablation arm) or at the start of the metabolic activity (D0 in the RFM+AAD arm, approx. 3–4 weeks after randomization), follow-up visits will be scheduled at 3, 6, 9, and 12 months during the first year, and then every six months. At the 3-month follow-up visit, patients in AF (from both groups) will undergo electrical cardioversion. A routine 12-lead ECG will be recorded at each follow-up visit, along with a physical examination of the patient and a medical history update. Long-term ECG recording will be done using a 7-day Holter recording at baseline, and then at the 6, 9, and 12 month visits during the first year, and then every six months in the second and third years. Holter recordings will be blinded, and analyzed by physicians outside the study. At the 12-month follow-up visit, echocardiography, MRI examination, anthropometric measurements, and CPET will be done.

Blood will be drawn for cytokine analysis, and patients will also be asked to complete follow-up QoL questionnaires.

STUDY OUTCOMES

Primary endpoints:

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

Secondary endpoints

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

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

be documented using an ECG (i.e., a patient´s description of "palpitations" without ECG evidence will not be assessed as AF reoccurrence).

STATISTICAL ANALYSIS PLAN AND POWER CALCULATION

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

The expected efficacy of AADs and RFM

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

expected in these patients. Therefore, we expected a ≈ 65% one-year AF freedom in the RFM+AAD arm.

The expected efficacy of the Catheter ablation

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

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

Non-inferiority margin (NIM) considerations

Regulatory guidelines require that the NIM rules out the minimum effect of treatment in the control arm (i.e., the CA arm in our study). Statistical guidelines recommend the most liberal NIM 1.92 (if expressed relatively as OR). From the clinical point of view, several rules exist for NIM adjustment. Obviously, the margin corresponds to the preservation of 50% benefit of the known treatment arm over placebo that was recognized in previous studies comparing recognized treatment with placebo. The other recommendation for NIM is to use the lower band

of 95% confidence interval of the placebo effect from previous studies comparing actual known treatment with placebo. Thus, for the study, the first step in selecting NIM was to estimate the minimum acceptable retention of the benefit of CA over placebo. In studies comparing CA with 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 the 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).

Study organization and d*ata management*

The institution responsible for the organization and implementation of the study is the 3rd 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 developed for the study. Each participating medical center will have access to a dedicated part of the website. The local investigator at each site will be responsible for data completeness and validity. At the end of the study, all data will be entered and stored on a password-protected computer. Only the principal investigator will have access to the final data set. All regulations regarding medical confidentiality and data protection will be fulfilled.

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

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

catheter ablations were associated with a 100% success rate, it would be impossible to treat the current or projected numbers using catheter ablations. Furthermore, a substantial number of patients would prefer a non-invasive treatment if both strategies were comparable. So while risk factor modification studies may seem to offer a panacea, those studies suffer from significant limitations and possible biases. For example, the most important and most extensive studies were both non-randomized, and all patients had either a history of catheter ablation (ARREST-AF) or were without a history of catheter ablation, but catheter ablation was allowed without limitations, based on the judgment of the attending physician during the follow-up period (LEGACY). A randomized study that directly compares catheter ablation with a modern non-invasive strategy has yet to be done. If the effect of both strategies were comparable, the non-invasive strategy could be offered to patients with a preference for a non-invasive treatment. Only a randomized study can really answer the question of how effective lifestyle modification is supported by safe non-amiodarone AADs compared to a modern invasive strategy.

ETHICS AND DISSEMINATION

The enrollment of the population is planned for two years. The first results will be published at the end of 2023 and at the beginning of 2024. Standard presentation on scientific conferences and in extenso publication in impact journals is planned. No new drugs or devices are planned for the study, so there are no specific ethical considerations. However, as it corresponds to the standard of all RCT, all the serious adverse events will be immediately reported to the appropriate Ethics Committee, as noted in the protocol.

AUTHORS´ CONTRIBUTION: PO wrote the manuscript and has initiated the study. Authors SH, VB, JC, TR, DH, ZC, OJ, and MF are responsible for the general analysis of the EP literature and the EP part of the protocol. Authors VT, MM, SSH, and AL are responsible for the analysis of the literature on non-invasive studies and are responsible for the metabolic part of the protocol. JK and JJ are the statisticians responsible for power calculation and the web-based electronic database.

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FIGURE LEGENDS

Figure 1 CONSORT diagram of the study

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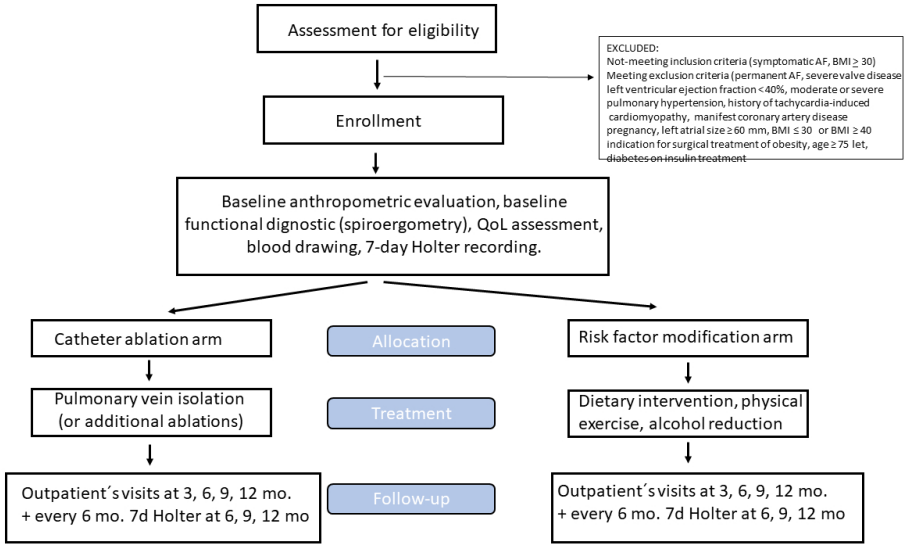

Figure 1

338x190mm (96 x 96 DPI)

SPIRIT checklist for the article „CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION, A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25 TRIAL)“

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

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

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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%.

Ethics and Dissemination: The PRAGUE-25 trial will determine if modern non-invasive AF treatment strategies are non-inferior to catheter ablation. The study was approved by the Ethics Committee of the University Hospital Kralovske Vinohrady. Results of the study will be disseminated on scientific conferences and in peer-reviewed scientific journals. After the end of follow-up, data will be available upon request to principal investigator.

Registration details: The study was registered on clinicaltrials.gov as NCT04011800

ARTICLE SUMMARY

Strengths of this study

- The population of the study (obese patients with AF) is growing
- For the first time, AADs treatment combined with risk factor modification will be compared with catheter ablation

Limitations of this study

- The study is not large enough to compare clinical endpoints
- The monitoring using implantable loop recorders would be more sensitive

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, having a prevalence of about ≈ 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 decrease in AF reoccurrences. In the non-randomized ARREST-AF study, 149 patients with a BMI ≥ 27 after catheter ablation of AF were offered an opportunity to participate in a physician-driven intensive risk factor modification (RFM) program, consisting of dietary changes and regular physical exercise. Risk factor management was associated with a significant reduction in AF reoccurrence by 23.9% (18). In the prospective, non-randomized LEGACY study, risk factor management, which also focused on weight loss, was offered to a cohort of 355 AF patients with a BMI ≥ 27 who had been referred to a tertiary center for AF treatment (contrary to ARREST-AF study, patients in the LEGACY study had no history of AF ablation) (19). AF freedom was achieved in 45% of patients with weight loss ≥ 10%, and in 22% of patients with weight loss between 3 and 9% (19). Similarly, in a study by Malmo et al., patients undergoing regular physical activity had AF paroxysms decline from 8.1% to 4.8% (20). Moreover, last year Voskoboinik et al. documented that a reduction in alcohol consumption was also associated with a significant reduction of AF paroxysms (21). It seems that AF treatment could lie, at least in some patients, outside the electrophysiological catheter-labs. However, it is also important to note that all studies focused on weight loss were either observational or had a non-randomized control arm (ARREST-AF, LEGACY). Since participation, especially in metabolic

interventions, requires a high level of patient motivation, the absence of a control arm potentially introduces a large bias into all the aforementioned studies.

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

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

Pro-inflammatory markers changes in AF and in obesity

The concentrations of pro-inflammatory markers, such as high-sensitivity CRP, interleukin-6, TNF-α, and others, have been reported to be elevated in AF patients, as well as in obese individuals with SR. In obese patients, the adipose tissue is an important source of the pro-inflammatory cytokines, and the concentrations of several pro-inflammatory cytokines significantly decrease after weight loss (27). In AF patients, increased pre-ablation levels of BNP, ANP, IL-6, and hsCRP are associated with a greater risk of AF recurrence after ablation (28). However, studies focusing on the effect of CA on pro-inflammatory cytokines have shown

mixed results, and in most of them, the concentrations remained unchanged in AF patients after successful AF ablation with SR maintenance after 12 months (29) (30).

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 clinicatrial.gov (NCT04011800, v. 1 of the protocol). The primary objective is to compare he 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 begun in May 2021. The CONSORT diagram of the study is shown in **Figure 1**.

Patient and Public Involvement

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 scientific conferences, presentations on the patient´s days, organized by the participating hospitals, are planned.

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-naive 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 ≥ 40
- severe valve disease (significant aortic stenosis, mitral regurgitation ≥ 3)
- left ventricular ejection fraction < 40%
- moderate or severe pulmonary hypertension (sPAP ≥ 40 mm Hg)
- history of tachycardia-induced cardiomyopathy
- manifest coronary artery disease
- pregnancy
- left atrial size ≥ 60 mm
- indication for surgical treatment of obesity
- age ≥ 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

biochemistry, and cytokine analysis, and (5) a baseline one-week ECG Holter recording. All these examinations will be done within four weeks after randomization.

Randomization and blinding

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

Functional diagnostic (anthropometric measurement and cardiopulmonary exercise test)

Functional diagnostics will be performed in all patients. Based on the results, an individualized physical training program will be prepared in patients randomized to the RFM+AAD arm.

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

TREATMENTS

Catheter ablation arm

CA will be done within two months of randomization. In paroxysmal patients, a PVI will be performed. In patients with non-paroxysmal AF forms, additional lesion sets will be allowed according to the practice of each participating center. The CA will be done using a 3D mapping system, intracardiac echocardiography, contact-force sensing ablation catheters, and ablation index to achieve the maximum available safety and efficacy. All patients in the CA arm will be informed about the danger of obesity and other risk factors as they concern AF and will be

instructed to lose weight, reduce alcohol consumption, and increase physical activity at discharge and again during each follow-up visit.

The first three months following catheter ablation will be considered as a "blanking period," i.e., AF reoccurrences won´t be assessed as an endpoint. During this period, treatment using AADs or cardioversion will be allowed. Three months after ablation, AADs will be discontinued.

Risk factor modification and AADs (RFA+AAD) arm

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

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

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

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

OUTPATIENT FOLLOW-UP AND ENDPOINT MONITORING

The follow-up protocol and ECG monitoring will be similar for both arms. Starting on the day of the catheter ablation (D0 in the ablation arm) or at the start of the metabolic activity (D0 in the RFM+AAD arm, approx. 3–4 weeks after randomization), follow-up visits will be scheduled at 3, 6, 9, and 12 months during the first year, and then every six months. At the 3-month follow-up visit, patients in AF (from both groups) will undergo electrical cardioversion. A routine 12-lead ECG will be recorded at each follow-up visit, along with a physical examination of the patient and a medical history update. Long-term ECG recording will be done using a 7-day Holter recording at baseline, and then at the 6, 9, and 12 month visits during the first year, and then every six months in the second and third years. Holter recordings will be blinded, and analyzed by physicians outside the study. At the 12-month follow-up visit, echocardiography, MRI examination, anthropometric measurements, and CPET will be done.

Blood will be drawn for cytokine analysis, and patients will also be asked to complete follow-up QoL questionnaires.

STUDY OUTCOMES

Primary endpoints:

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

Secondary endpoints

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

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

be documented using an ECG (i.e., a patient´s description of "palpitations" without ECG evidence will not be assessed as AF reoccurrence).

STATISTICAL ANALYSIS PLAN AND POWER CALCULATION

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

The expected efficacy of AADs and RFM

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

expected in these patients. Therefore, we expected a ≈ 65% one-year AF freedom in the RFM+AAD arm.

The expected efficacy of the Catheter ablation

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

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

Non-inferiority margin (NIM) considerations

Regulatory guidelines require that the NIM rules out the minimum effect of treatment in the control arm (i.e., the CA arm in our study). Statistical guidelines recommend the most liberal NIM 1.92 (if expressed relatively as OR). From the clinical point of view, several rules exist for NIM adjustment. Obviously, the margin corresponds to the preservation of 50% benefit of the known treatment arm over placebo that was recognized in previous studies comparing recognized treatment with placebo. The other recommendation for NIM is to use the lower band

of 95% confidence interval of the placebo effect from previous studies comparing actual known treatment with placebo. Thus, for the study, the first step in selecting NIM was to estimate the minimum acceptable retention of the benefit of CA over placebo. In studies comparing CA with 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 the 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).

Study organization and d*ata management*

The institution responsible for the organization and implementation of the study is the 3rd 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 developed for the study. Each participating medical center will have access to a dedicated part of the website. The local investigator at each site will be responsible for data completeness and validity. At the end of the study, all data will be entered and stored on a password-protected computer. Only the principal investigator will have access to the final data set. All regulations regarding medical confidentiality and data protection will be fulfilled.

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

Data availability statement

The primary analysis is planned after 6 monts of follow-up of the last enrolled patients. After that, an extension of follow-up for three additional years is planned according to the protocol. Study data will be shared when the follow-up extension is finished and analyzed. Data will be available upon reasonable request. Deidentified data will be stored at the Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, and will be available after request to principal investigator for further analyses and meta-analyses.

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 catheter ablations were associated with a 100% success rate, it would be impossible to treat the current or projected numbers using catheter ablations. Furthermore, a substantial number of patients would prefer a non-invasive treatment if both strategies were comparable. So while risk factor modification studies may seem to offer a panacea, those studies suffer from significant limitations and possible biases. For example, the most important and most extensive studies were both non-randomized, and all patients had either a history of catheter ablation (ARREST-AF) or were without a history of catheter ablation, but catheter ablation was allowed without limitations, based on the judgment of the attending physician during the follow-up period (LEGACY). A randomized study that directly compares catheter ablation with a modern non-invasive strategy has yet to be done. If the effect of both strategies were comparable, the non-invasive strategy could be offered to patients with a preference for a non-invasive treatment. Only a randomized study can really answer the question of how effective lifestyle

modification is supported by safe non-amiodarone AADs compared to a modern invasive strategy.

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.

ETHICS AND DISSEMINATION

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

AUTHORS´ CONTRIBUTION: PO wrote the manuscript and has initiated the study. Authors SH, VB, JC, TR, DH, ZC, OJ, and MF are responsible for the general analysis of the EP

literature and the EP part of the protocol. Authors VT, MM, SS-H, and AL are responsible for the analysis of the literature on non-invasive studies and are responsible for the metabolic part of the protocol. JK and JJ are the statisticians responsible for power calculation and the web-based electronic database.

COMPETING INTEREST: none

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FIGURE LEGENDS

Figure 1 CONSORT diagram of the study

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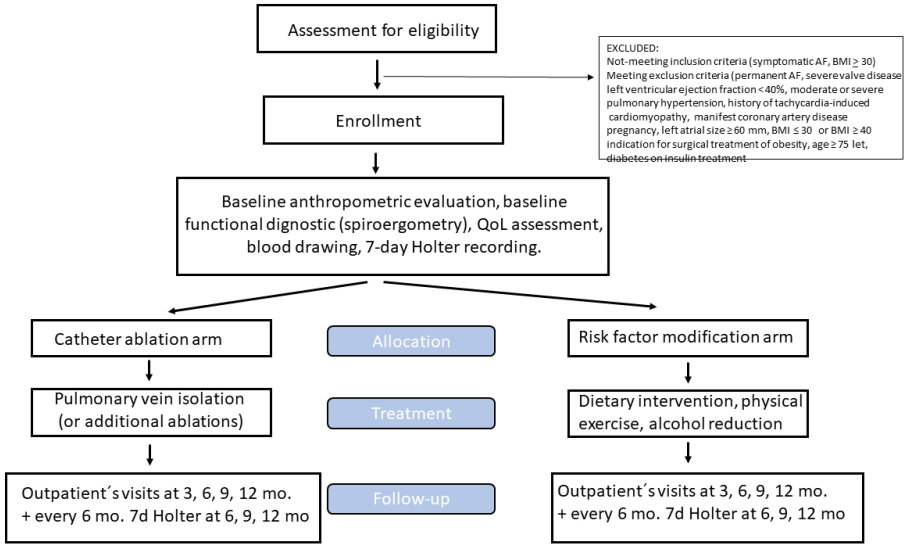

Figure 1

338x190mm (96 x 96 DPI)

SPIRIT checklist for the article „CATHETER ABLATION VS. ANTIARRHYTHMIC DRUGS WITH RISK FACTOR MODIFICATION FOR TREATMENT OF ATRIAL FIBRILLATION, A RANDOMIZED CONTROLLED TRIAL (PRAGUE-25 TRIAL)“

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