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Catheter ablation versus antiarrhythmic drugs with risk factor modification for treatment of atrial fibrillation: a protocol of a randomised 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 to treatment by antiarrhythmic drugs (AADs) in terms of sinus rhythm 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 (RFM)) approach with modern invasive (CA) treatment. The aim of the trial is to compare the efficacy of modern invasive (CA) and non-invasive (AADs with risk factor management) treatment of AF.

Methods and analysis The trial will be a prospective, multicentre, randomised non-inferiority trial. Patients with symptomatic AF and a body mass index >30 will be enrolled and randomised to the CA or RFM 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 atrial tachycardia lasting >30 s. 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 CA. 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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The population of the study (obese patients with atrial fibrillation) is growing.
⇒ For the first time, antiarrhythmic drug treatment combined with risk factor modification will be compared with catheter ablation.
⇒ The study is not large enough to compare clinical endpoints.
⇒ The monitoring using implantable loop recorders would be more sensitive.

Trial registration number ClinicalTrials.gov Registry (NCT04011800).

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 threefold during the next three decades. AF is associated with a threefold increase in the risk of stroke and a twofold 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 randomised controlled trials (RCTs). The 1-year efficacy of CA ranges from 40% to 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 patients with AF in the CABANA trial, the largest study on CA in AF.[5] Except for the CABANA trial with 2204 patients enrolled, all other studies have been substantially smaller (median of enrolled patients=119 patients). In two well-conceived recent trials comparing CA (although using cryoballoon ablation) with AADs, the 1-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 AADs

Several AADs (propafenone, flecainide, sotalol, amiodarone) have been documented as being superior compared with 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 patients using AADs) was associated with a reduction in cardiovascular mortality, stroke, hospitalisation for heart failure and acute coronary syndromes.[9] However, the effect of AADs for sinus rhythm (SR) maintenance is only modest. In the two most recent RCTs comparing AADs (92% of which were flecainide and sotalol) with CA, the complete 1-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 60000 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 apnoea 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-randomised ARREST-AF Study, 149 patients with a BMI ≥27 after CA of AF were offered an opportunity to participate in a physician-driven intensive risk factor modification (RFM) programme, 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-randomised LEGACY Study, risk factor management, which also focused on weight loss, was offered to a cohort of 355 patients with AF with a BMI ≥27 who had been referred to a tertiary centre 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 laboratories. However, it is also important to note that all studies focused on weight loss were either observational or had a non-randomised 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 CA.[22 23] Similarly, the degree of diffuse myocardial ventricular fibrosis is higher in patients with AF compared with 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 post-contrast-enhanced T1 mapping.[24] Recently, diffuse myocardial fibrosis assessed using post-contrast T1 mapping predicted the effect of AF CA in paroxysmal patients.[25] Early changes on a CMR, such as higher left ventricular mass, or cardiac remodelling index, were also described in patients with obesity.[26]

Proinflammatory marker changes in AF and in obesity

The concentrations of proinflammatory markers, such as high-sensitivity C reactive protein (hsCRP), interleukin (IL)-6, TNF-α and others, have been reported to be elevated in patients with AF, as well as in obese individuals with SR. In obese patients, the adipose tissue is an important source of the proinflammatory cytokines, and the concentrations of several proinflammatory cytokines significantly decrease after weight loss.[27] In patients with AF, 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 proinflammatory cytokines have shown mixed results, and in most of them, the concentrations
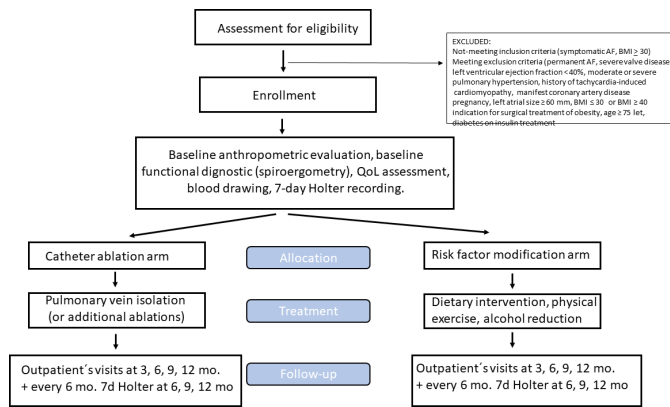
Figure 1 CONSORT diagram of the study. AF, atrial fibrillation; BMI, body mass index; CONSORT, Consolidated Standards of Reporting Trials; QoL, quality of life.

remained unchanged in patients with AF 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, multicentre, investigator-initiated, open-label, randomised, non-inferiority study registered on ClinicalTrials.gov (NCT04011800, V.1 of the protocol). The primary objective is to compare the maintenance of SR using modern invasive (CA) and non-invasive (RFM+AAD) AF treatment. Secondary endpoints include clinical endpoints, changes in the quality of life (QoL), cardiorespiratory fitness, proinflammatory cytokine concentrations, echocardiography and MRI measures. The study was approved by multicentre ethics committee (EC) and local ECs of all participating centres, and informed consent will be obtained from all participants. The enrolment of patients began in May 2021. The Consolidated Standards of Reporting Trials 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 patients' involvement. Regarding the dissemination of the results, apart from scientific conferences, presentations on the patients' days, organised by the participating hospitals, are planned.

Patient population
PRAGUE-25 is a multicentre study; currently, five centres from the Czech Republic are participating, but other centres may be added based on interest. The study will enrol patients with symptomatic AF 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 centres and cooperating outpatient departments will be screened, and patients satisfying the inclusion criteria will be offered an opportunity to enrol. The qualifying criteria are symptomatic documented AF, high BMI and patient motivation since the allocation to

the RFM (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 enrol; enrolment 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 enrolment 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 EF <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 years.
► 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 (CPET), (2) echocardiography, (3) QoL analysis (using AFEQT questionnaire), (4) blood biochemistry and cytokine analysis, and (5) a baseline 1-week ECG Holter recording. All these examinations will be done within 4 weeks after randomisation.

Randomisation and blinding
Patients will be randomised to the CA group or RFM group plus AADs (RFM+AAD) in a 1:1 ratio; randomisation will

be done using randomisation software that will account for age, initial BMI and AF type, with the goal of having comparable groups relative to those characteristics. Randomisation will be done in blocks but will not be site specific (ie, the proportion of patients randomised to CA vs RFM-AAD will not be the same in all centres). The randomisation process will be done outside all participating centres 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, additional two variables (ie, 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 organisation outside the study that will not have access to patient information. Similarly, clinical endpoint assessments will also be blinded, and the clinical endpoint committee will not be aware of patient randomisations. The Institute of Biostatistics and Analyses will be responsible for the randomisation software, data acquisition, storage and data analysis.

Functional diagnostic (anthropometric measurement and CPET)

Functional diagnostics will be performed in all patients. Based on the results, an individualised physical training programme will be prepared in patients randomised to the RFM+AAD arm.

An initial maximum symptom-limited CPET will be carried out within 1 month of enrolment. The CPET will be carried out on the medication which was present at the enrolment visit. The cycle ergometer will be used in all sites. The protocol will consist of a 3-minute warm-up period with 0 W (unloaded pedalling), 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 s; 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 until the respiratory compensation point; both ventilatory thresholds will be calculated.

TREATMENTS
CA arm

CA will be done within 2 months of randomisation. 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 centre. 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 3 months following CA will be considered as a 'blanking period', that is, AF reoccurrences would not be assessed as an endpoint. During this period, treatment using AADs or cardioversion will be allowed. Three months after ablation, AADs will be discontinued.

RFM 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 enrolment. A low-calorie, high-protein, and low glycaemic index dietary menu will be suggested and optimised by a nutritional specialist for each patient. Except for regular in-person consultations with dietary specialists and phone visits anytime during the follow-up, patients will be encouraged to record the calorie 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), (2) 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 organised training, activities will be individualised. The ESC guidelines for obese individuals recommend that a minimum of 150 min/week of moderate-intensity endurance exercise training should be combined with 3 weekly sessions of resistance exercise with the heart rate during the activity being 55%–74% of the maximum hear rate.[31] As such, the physical intervention will be based on regular (mainly moderate, ≈55%–74% of the maximum heart rate) 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 randomisation. 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 6 instead of 3 months. The reoccurrence as AF/atrial tachycardia (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 AT, redo ablations, cardioversion or AAD treatment during the follow-up period will be allowed in accordance with the current guidelines and practices of participating centres. 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 (ie, 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 CA (D0 in the ablation arm) or at the start of the metabolic activity (D0 in the RFM+AAD arm, approximately 3–4 weeks after randomisation), follow-up visits will be scheduled at 3, 6, 9, and 12 months during the first year, and then every 6 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-month, 9-month and 12-month visits during the first year, and then every 6 months in the second and third years. Holter recordings will be blinded and analysed 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 AT lasting more than 30 s).

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. Hospitalisation for AF reoccurrence and/or emergency room visit due to AF.
4. A composite of stroke, cardiovascular death or hospitalisation 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 haemoglobin and proinflammatory 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-month, 9-month and 12-month visits), during all planned outpatient visits using a standard 12-lead ECG, and anytime 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 (ie, 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 randomised trials and observational studies comparing and assessing the effect of AADs versus placebo, CA versus AADs and assessing the effect of RFM 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, that is, 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 RCTs 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% to 57%) of patients on AADs.[32] In the CABANA trial, by 12 months, the 1-year AF freedom on AADs was present in 47.1% of patients.[33] Finally, in the recently published STOP-AF trial, 1-year AF freedom (assessed using repeated 24-hour Holter recordings) was present in 45.0% (95% CI 34.6% to 54.7%) of

patients. Therefore, a 1-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% 1-year AF freedom in the RFM+AAD arm.

The expected efficacy of the CA

In a meta-analysis of RCT comparing CA with AADs, the single-procedure success rate of CA off AADs was 57% (95% CI 50% to 64%).[32] In the CABANA trial, AF freedom was present in 63.6% of the ablation patients by 12 months.[33] The expected 1-year AF freedom in the CA arm is ≈60%.

According to the aforementioned data, we expect 1-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% two-sided alpha, a non-inferiority margin of 12% (or 1.65, if expressed as an OR). 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 considerations

Regulatory guidelines require that the non-inferiority margin (NIM) rules out the minimum effect of treatment in the control arm (ie, 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 recognised in previous studies comparing recognised treatment with placebo. The other recommendation for NIM is to use the lower band of 95% CI 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% to 64%). Unfortunately, none of the studies had a placebo arm, and all compared CA with AADs. In the studies comparing AADs versus placebo, the success of treatment in the placebo arms was 24.9% (95% CI 15% to 34%). So, the selected margin of 12% fulfils the criteria for the NIM setting. If it is expressed as an OR, it corresponds to 1.65, which is consistent with regulatory guideline recommendations (and, for example, it is similar as it was in large non-inferiority trials comparing NOAC with warfarin).

Study organisation and data management

The institution responsible for the organisation and implementation of the study is the Third Faculty of Medicine, Charles University in Prague, Czech Republic. Data obtained during each patient visit will be collected using a safe electronic CRF. A tailor-made website was developed for the study. Each participating medical centre 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 randomisation software has been prepared by an outside party (ie, the Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic), and no investigator will have access to the database or the randomisation 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 (ie, 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 months of follow-up of the last enrolled patients. After that, an extension of follow-up for 3 additional years is planned according to the protocol. Study data will be shared when the follow-up extension is finished and analysed. 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 the 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 (SAEs) will be defined as life-threatening events or events resulting in death or hospitalisation. All SAEs linked with the study will be reported to the DSMB, to the Kralovske Vinohrady University Hospital Ethics Committee (EC) (a multicentre EC), and to the local ECs within 24 hours of study staff becoming aware of the event. Clinical endpoints will be analysed by a dedicated clinical endpoint committee. The recording and analyses of all Holter recordings in all participating centres will be done centrally using a medical data transfer company. A standard, commercially available 7-day Holter monitor (eg, Faros 160, Bittium,

Finland, or similar tools), with daily telephone transfers, will be used.

DISCUSSION

In the last 5 years, lifestyle modification with RFM 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 CAs were associated with a 100% success rate, it would be impossible to treat the current or projected numbers using CAs. Furthermore, a substantial number of patients would prefer a non-invasive treatment if both strategies were comparable. So while RFM 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-randomised, and all patients had either a history of CA (ARREST-AF) or were without a history of CA, but CA was allowed without limitations, based on the judgement of the attending physician during the follow-up period (LEGACY). A randomised study that directly compares CA with a modern non-invasive strategy has yet to be done. If the effects of both strategies were comparable, the non-invasive strategy could be offered to patients with a preference for a non-invasive treatment. Only a randomised study can really answer the question of how effective lifestyle modification is supported by safe non-amiodarone AADs compared with a modern invasive strategy.

A significant portion of patients with AF are obese (eg, 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 5 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 randomised study. If both treatment strategies were comparable in terms of SR maintenance, RFM and AADs could be offered to obese patients as comparable treatment with an invasive procedure.

ETHICS AND DISSEMINATION

The study was approved by the multicentre EC of the University Hospital Kralovske Vinohrady (approval no. EK-VP/34/0/2020). The enrolment of the population is planned for 2 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 RCTs, all the SAEs will be immediately reported to the appropriate EC, as noted in the protocol.

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