



Ablation versus Anti-Arrhythmic Therapy for Reducing All Hospital Episodes from Recurrent Atrial Fibrillation (AVATAR-AF): Design and rationale

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Background Atrial Fibrillation (AF) ablation using the cryoballoon is effective at reducing symptomatic AF episodes. The prevalence of AF is increasing with the aging population and access to such treatment would be enhanced by reducing the resource requirements. Relinquishing electrical mapping of the pulmonary veins (PV) removes the need for PV catheters, electrical recording equipment and staff trained in using this equipment. Moreover, the majority of complications are peri-procedural so overnight hospitalization maybe unnecessary. We tested this streamlined approach to AF ablation against medical therapy using the endpoint of time to all hospital episodes.

Methods The AVATAR-AF study is a prospective, multicenter, randomized controlled trial testing the primary hypothesis that AF ablation done without PV mapping or overnight hospitalization is more effective than anti-arrhythmic drugs at reducing all hospital episodes related to recurrent atrial arrhythmias. We included a third arm to test a secondary hypothesis that confirming PV entrance block as per consensus guidelines can improve outcomes. Three hundred twenty-one patients with documented paroxysmal AF will be randomized in a 1:1:1 manner to one of three investigation arms: (1) AVATAR protocol cryoballoon ablation without assessment of acute PV isolation or overnight hospitalization; (2) medical therapy with anti-arrhythmic drugs; or (3) conventional cryoballoon ablation with assessment of acute PV isolation. The primary endpoint is defined as the time to all hospital episodes (including outpatient consultation) related to treatment for atrial arrhythmia.

Conclusion The AVATAR-AF study will determine whether the resource utilization for AF ablation can be reduced whilst maintaining superiority over medical therapy. (Am Heart J 2019;214:36-45.)

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia requiring specialist hospital management. It is now well established that AF episodes can be reduced in frequency and duration by antral isolation of the pulmonary veins (PVs). Randomized studies have shown that catheter

ablation techniques that encircle the PVs are more effective than anti-arrhythmic agents at preventing the endpoint of 'any detectable AF'.¹⁻³ This has led to dramatic growth in both the number of pulmonary vein isolation (PVI) cases performed worldwide and the available technology for supporting these procedures. However, the success rates from PVI have remained largely unchanged over the last decade suggesting that these are the best results that can be achieved when electrical isolation of the PVs is the goal of the procedure.

On this background, we re-evaluated the approaches for PVI to determine whether the current resource utilization was indeed necessary to achieve the clinical outcomes from the procedure. We identified the Advance™ Cryoballoon (Medtronic, Minneapolis) as being widely used and producing acute PVI in more than 90% of veins with a single freeze application.⁴ However, chronic reconnection is common with 94% of patients with AF recurrence having at least one pulmonary vein reconnected, but even 90% of asymptomatic patients will have recovery of pulmonary vein conduction.⁵

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The rapid PV reconnection rates following confirmed intraprocedural electrical isolation may therefore undermine the validity of this procedural endpoint. Use of a surrogate procedural endpoint, such as PV occlusion, might obviate the requirement for mapping PV signals when using the cryoballoon. If the procedure is done without PV mapping, there are multiple cost savings which include the PV mapping catheter, EP recording equipment and specialist staff. Avoiding PV mapping would also shorten the procedure time and may enable most patients to be completed as a day case, providing further cost saving implications through reduced bed occupancy, although this is not a trial objective. One series has suggested that nearly 90% of patients can already be discharged safely as a day case.⁶ We also noted that most complications occurred during the procedure or during the immediate post-operative period so the option of discharging patients from hospital on the same day should be possible. We have considered the peri-procedural period to be from 6 hours before the beginning of the procedure, to 6 hours after the end of ablation in AVATAR-AF. We honed these concepts into a streamlined 'AVATAR protocol'.

Consensus guidelines indicate that symptoms are the only recommended indication for AF ablation but symptoms are too subjective to use as an endpoint for trials and therefore 'any detectable AF' has been used to assess procedural outcome.^{3,7-10} For similar reasons, pharmacological studies have used hospitalization as a clinically relevant and objective endpoint. However, a significant proportion of specialist hospital management for AF is conducted in the outpatient setting. We would propose that 'symptom control not needing hospital review' could be used as a meaningful 'real-world' endpoint to objectively judge AF outcomes. 'If successful, you will not need to attend hospital' is a pragmatic statement that can be understood by patients, clinicians and healthcare commissioners. However, this would be a novel endpoint and it raises the question of whether AF ablation remains superior to medical therapy with this endpoint. Changing the definition of a successful ablation to not needing hospital review may enable further cost reduction by avoiding monitoring for AF except when symptoms occur.

The AVATAR-AF study is designed to test the primary hypothesis that PV antral ablation without verification of electrical isolation or overnight hospitalization is more effective than anti-arrhythmic drugs using the endpoint of freedom from any hospital based treatment for atrial arrhythmias. We will also test whether the consensus view that verification of electrical isolation improves outcomes as a secondary hypothesis.

Methods

The primary objective of the AVATAR-AF study is to determine if antral AF ablation without electrophysiological confirmation of PVI or overnight hospitalization is

more effective than anti-arrhythmic agents at achieving freedom from hospital-based treatment. The secondary objective is to determine whether such an approach is less effective than the conventional ablation approach, in which acute PVI is confirmed.

Study design

AVATAR-AF ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier number NCT02459574) is a multicenter (13 UK centers), randomized, open trial comparing a "streamlined" AVATAR-protocol daycase ablation procedure which excludes the assessment for acute PVI, to anti-arrhythmic therapy. A secondary control arm will also compare the AVATAR-protocol ablation to conventional cryoballoon ablation with formal assessment for acute PVI and overnight hospitalization. The protocol was approved by the research ethics committee (14/LO/0117).

Patients considered to be failing their current treatment strategy for documented paroxysmal AF will be recruited. These may include 'pill-in-pocket' regimen, regular anti-arrhythmics or conservative approach without anti-arrhythmics. The target recruitment number is 321 with 1:1:1 randomization to a treatment strategy of either AVATAR-protocol ablation, additional anti-arrhythmic therapy or conventional AF ablation, with a 1-year follow-up period (Figure 1).

Randomization

Randomization is performed electronically using an electronic data capture system (InForm version 4.6, Oracle Health Sciences, USA) and stratified by site. The first ablation procedure or change in drug treatment will be performed 28 (± 7) days from the date of randomization.

This study will be conducted in accordance with the protocol, Good Clinical Practice (GCP) and all applicable regulatory requirements.

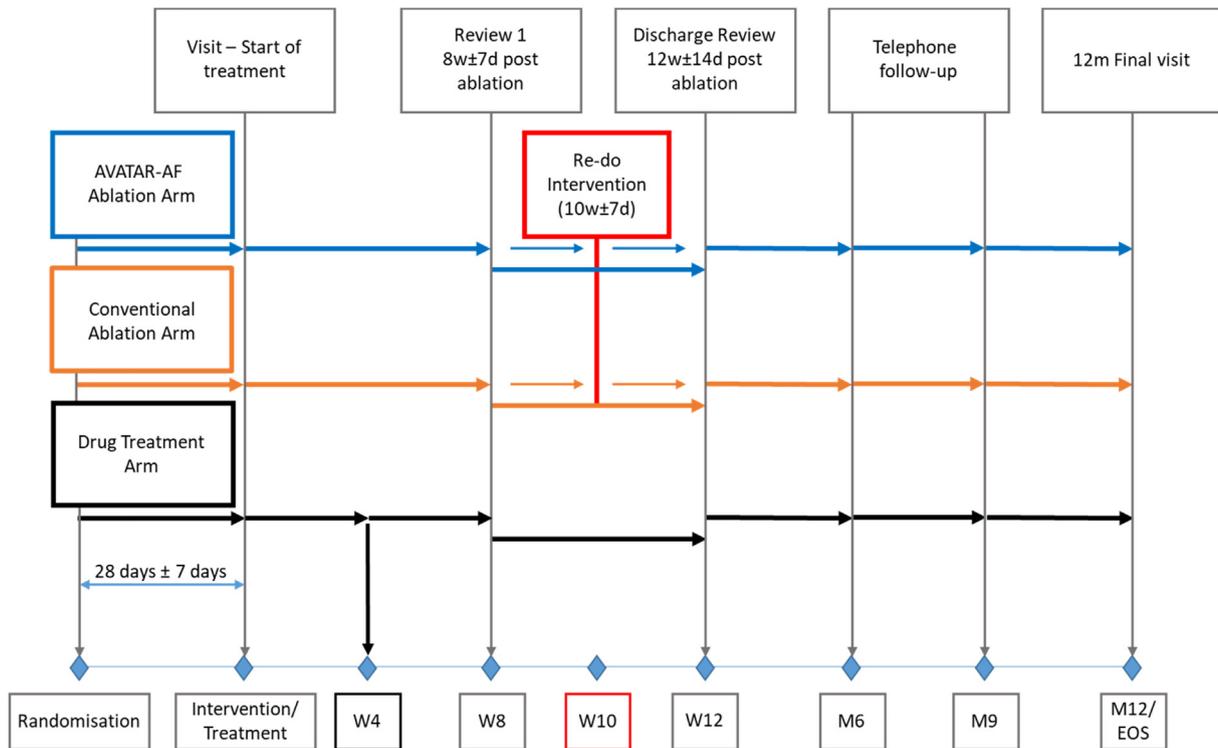
Eligibility criteria

Prior to study inclusion, all eligible patients will be required to provide written informed consent to participate. Patients should be suitable candidates for catheter ablation, with documented evidence of paroxysmal AF. Paroxysmal AF is defined as an episode of AF that spontaneously terminates within 7 days. Detailed inclusion and exclusion criteria are shown in Table 1. It is common to see atrial flutter in patients with atrial fibrillation and specific guidance was given for these patients as detailed in Appendix 1.

Treatment arms

The peri-procedural anticoagulation regime is according to physician discretion but in line with established HRS/ESC guidelines and the CHA₂DS₂-VASc scoring system. Anticoagulated patients in an ablation arm were free to follow a continuous, bridging or without anticoagulation as per local preference.

Figure 1



Schedule for patients recruited to each of the three investigation arms from the point of randomization to study completion at the 12 month visit.

Ablation procedures can be performed under sedation or general anesthetic according to local preference. Trans-esophageal echocardiography (TEE) and ultrasound guidance for femoral access is also by physician discretion.

In the 28 (± 7) days between randomization and 1st intervention, there is no change to the patient's arrhythmia treatment. All three treatment arms follow the same scheduling protocol regardless of intervention.

An independent Data Safety Monitoring Board (DSMB) was appointed to review safety data after 75 and 150 patients have received treatment and at regular intervals thereafter. The DSMB Charter included the monitoring the efficacy of treatment.

AVATAR-AF ablation protocol. A single trans-septal puncture is performed under TEE, intra-cardiac echocardiography (ICE), coronary sinus (CS) catheter or aortic pigtail guidance. If a CS catheter is used, it should be performed without electrograms to avoid the need for specialist equipment.

The sheath is exchanged for a Cryosheath or other suitable large sheath, and pulmonary venography undertaken. An Arctic Front Advance balloon is used to occlude PVs so that there is minimal/no dye leak on injection (Grade 3/4). Two cryoablation applications will be delivered to each vein lasting 180 seconds each. During

right sided PV treatment, the phrenic nerve is monitored with a temporary trans-venous pacing wire and box. No specialist EP catheters are deployed and no formal assessment of pulmonary vein isolation is done. The activated clotting time should be maintained above 300 seconds, and protamine reversal can be used at the end of the procedure according to operator preference.

A bedside transthoracic echocardiogram, hemoglobin check and femoral puncture site assessment is carried out 6 hours post-procedure. If all parameters are stable, the patient is discharged as a day case procedure.

All medication is continued for 4 weeks post-ablation and then all agents being used for anti-arrhythmic effect are stopped. This enables early assessment of symptoms following ablation and whether redo-ablation will be necessary. Anti-arrhythmic management during this phase is to be considered at the discretion of the investigator.

Patients are reviewed in clinic at 8 weeks (± 7 days) post-1st intervention date. If symptoms are continuing to improve or patients are asymptomatic, they are reviewed again in clinic at 12 weeks (± 14 days) to decide if they can enter the discharge protocol. If symptoms are ongoing or worse, patients are offered a repeat ablation at 10 weeks (± 7 days) post first intervention.

Table 1. Main inclusion and exclusion criteria.

MAIN INCLUSION CRITERIA

1. Documented paroxysmal atrial fibrillation
2. Modification or initiation of anti-arrhythmic agent required for symptom control
3. Males or females eighteen (18) to eighty (80) years of age
4. Suitable candidate for catheter ablation
5. Signed informed consent

MAIN EXCLUSION CRITERIA

1. Contraindication to catheter ablation
2. Previous left atrial ablation
3. No carer to enable day case discharge
4. Arrhythmias other than AF documented unless they have had curative ablation (eg, for atrial flutter)
5. No documentation of sinus rhythm within 3 months
6. Valvular or other heart disease needing regular follow up
7. EF <45% or moderate/severe LV dysfunction (determined by Echocardiogram in the last 6mths)
8. Active gastrointestinal disease precluding anticoagulation or trans-esophageal echocardiogram
9. Renal failure with creatinine >200 μ mol/L or on dialysis
10. Active fever or infection at the time of AF documentation
11. Life expectancy shorter than the trial
12. Allergy to contrast
13. Severe cerebrovascular disease precluding day case discharge
14. Bleeding or clotting disorders or inability to receive heparin
15. Uncontrolled diabetes (HbA1c \geq 73 mmol/mol or HbA1c \leq 64 mmol/mol and Fasting Blood Glucose \geq 9.2 mmol/L) (shown in the last 6 months without evidence of being brought under control)
16. Serum Potassium [K+] <3.5 mmol/L or > 5.0 mmol/L (shown in the last 6 months without evidence of being brought under control)
17. Malignancy needing surgery, chemotherapy or radiotherapy
18. Pregnancy or women of child-bearing potential not using a highly effective method of contraception
19. Must not have previous (4 weeks prior to screening) or current participation in another clinical trial with an investigational drug or investigational device
20. Unable to give informed consent
21. Uncontrolled thyroid disease defined as abnormal thyroid function tests causing cardiac manifestations within the last 6mths
22. Unable to attend follow-up visits

Anti-arrhythmic therapy protocol. The anti-arrhythmic agent, or change in dose that was previously discussed with the patient during the initial screening visit is initiated at the 1st intervention date. The anti-arrhythmic treatment chosen should be done in accordance with local practice and guidelines.

The patient will undergo two reviews prior to entering the discharge protocol; Review 1 at 4 weeks (+/-7 days), and Review 2 at 8 weeks (+/-7 days) post-1st intervention. At each review, the medication can be left unchanged, increased/decreased in dose, or change to a different agent as required. Drug dosing must be maximized to achieve symptom control but avoid intolerable side effects. Following the 4 and 8 week review, patients are reviewed to decide if they can enter the discharge protocol at 12 weeks \pm 14 days.

Conventional ablation protocol. A single or double trans-septal puncture may be performed under TEE, aortic pigtail, ICE or CS catheter guidance. The sheath is exchanged for a Cryosheath or other suitable large sheath, and pulmonary venography undertaken. An Arctic Front Advance balloon is used to occlude the PV with minimal/no dye leak (Grade 3/4). Two cryoablation applications will be delivered to each vein for 180 seconds. Phrenic nerve monitoring is carried out during

treatment delivery to the right sided PVs in according with local protocol.

The PVs are mapped using a circular mapping catheter of the operator's choice, and the number of veins isolated with this approach documented. PV isolation is completed with either repeat cryoballoon application, deflectable cryotherapy catheter or radiofrequency catheter as per operator preference.

The patient is monitored as an inpatient overnight, and will have a bedside transthoracic echocardiogram, hemoglobin check and femoral puncture site assessment prior to discharge. If all parameters are stable, the patient is discharged.

All medication is continued for 4 weeks post-ablation and then all agents being used for anti-arrhythmic effect are stopped. Anti-arrhythmic management during this phase is to be considered at the discretion of the investigator.

Patients are reviewed in clinic at 8 weeks (+/-7 days) post-1st intervention date. If symptoms are continuing to improve or patients are asymptomatic, they are reviewed again in clinic at 12 weeks (+/-14 days) post intervention to decide if they can enter the discharge protocol. If symptoms are ongoing or worse, patients are offered a repeat ablation at 10 weeks (+/-7 days) post-1st intervention.

Repeat ablation protocol (10 weeks \pm 7 days). A single or double trans-septal puncture is performed under TEE, ICE, aortic pigtail or CS catheter guidance. Pulmonary venography is undertaken and PV mapping performed. Further ablation can be performed according to operator preference by radiofrequency ablation, Cryoballoon or cryocatheter.

A bedside transthoracic echocardiogram, hemoglobin check and femoral puncture site assessment is carried out 6 hours post-procedure.

Patients in the AVATAR-AF protocol arm are discharged as a day case procedure and given appropriate instructions and advice on potential concerns and process for seeking advice.

Patients in conventional ablation arm remain as an inpatient overnight, and are discharged home the following day.

All medication being used for anti-arrhythmic effect is stopped in both ablation arms.

Study endpoints

All study endpoints will be reported from the date of 1st intervention. The primary endpoint starts at 12 weeks. A re-do procedure at 10 weeks is not considered part of the primary endpoint, however any treatment after 12 weeks would be considered an endpoint. Treatment performed within the 12 week period (eg, cardioversion) is not considered an endpoint. However, if it were done after 12 weeks it would be an endpoint. This 12 week period is effectively a blanking period for all arms.

Primary endpoint

Time to any hospital episode (Emergency Room or patient request for OPD) related to treatment for atrial arrhythmia and includes 'failure to discharge at 12 weeks' due to ongoing problems.

Secondary endpoints

Time to death or stroke from any cause.

Any complications caused by the procedure (pericardial effusion, bleeding >2 units, phrenic nerve palsy and other) or the anti-arrhythmic drug (GI disturbance, skin irritation and other).

All hospital episodes which result in a change in therapy for atrial arrhythmia

Discharge protocol and telephone follow-up

Patients from all therapy arms will enter the discharge protocol 12 weeks \pm 14 days post-1st intervention. If the patient has evidence of symptoms that need further treatment or complications needing follow-up, the patient is unable to enter the discharge protocol and considered to have reached the primary endpoint. Secondary endpoints related to treatment will be documented and as long as further review is not needed, the patient can enter the discharge protocol.

All subsequent contact with the patient is with a Research Nurse or designee blinded to the patient's treatment arm. Patients are given the Research Nurse's contact details, and are able to request an unscheduled visit if they experience recurrent symptoms and need hospital review at any stage. The blinded Research Nurse or designee will contact the patient by telephone every 3 months (months 6, 9 and 12 post 1st intervention date) to ensure that no endpoints have occurred. The patient will be advised that the Research Nurse or designee making the phone call is not aware of the treatment arm that they have received. Standardized questions asked during this follow-up will cover hospital attendance (reason/outcome/medication changes/investigations), any symptoms experienced and whether the patient needs to see the research team for an unscheduled visit. The Month 12 questions can be done by either telephone or face to face as a part of the End of Study Visit. Please see the Appendix 2 for the details of the telephone questions. The Atrial Fibrillation Effect on Quality-of-Life (AFEQT) and EQ5D-5 L quality of life questionnaires are completed at the baseline visit, and at the 12 month visit as part of the ongoing symptomatic assessment.

Patients not able to enter the discharge protocol at 12 weeks will have necessary advice (further OPD, procedure) which will be a primary endpoint. The date of the endpoint will be the date of the subsequent event.

Crossover between therapies

If the primary endpoint is reached by a patient from any group, the Investigator may initiate further drug therapy or schedule a standard ablation procedure for the patient. However, the following are required;

i) Ablation Arms (Conventional and AVATAR-AF): can start anti-arrhythmic drugs or further redo-ablation if there is ECG/Holter documentation of recurrent AF/AT.

ii) Drug Therapy Arm: may receive ablation therapy if failed one anti-arrhythmic at maximum standard dose or two anti-arrhythmic agents at sub-maximal dose or due to side effects.

iii) New tachycardia documented that needs treatment (VT/AVNRT/AVRT). The patient is withdrawn from the study.

Endpoint adjudication

Endpoint adjudication will be done by an independent Endpoint Adjudication Committee (EAC). The EAC will centrally review and classify suspected outcome events, verifying whether they meet protocol definitions (Appendix 3). Any hospital episodes (Emergency Room or outpatient) related to treatment for atrial arrhythmia, stroke or death from any cause, any complications caused by the procedure (pericardial effusion, bleeding >2 units, phrenic nerve palsy and other) or the anti-arrhythmic drug (GI disturbance, skin irritation and other), all hospital episodes which result in a change in therapy for atrial arrhythmia.

Any attendance to hospital or specialist cardiac clinic will require the documentation of a discharge letter or clinic letter for primary endpoint adjudication.

Statistical consideration

In this time-to-event study of hospital episodes, required sample numbers have been estimated using the log-rank test under the Freedman method based on the occurrence of first event during the 12-month follow-up period. The null hypothesis is that there is no difference in the distributions. Adopting a conservative approach, an initial two-sided alpha of 0.05 is chosen, given the need to allow for the inherent multiple testing between the three arms of the study, the conservative Bonferroni correction is applied and the alpha value used in the power calculations is reduced to 0.025.

Estimating the proportion experiencing a hospital episode in the follow-up period in the anti-arrhythmic arm as 0.63 and the corresponding proportion in the AVATAR ablation arm as 0.40, assuming the occurrence of 103 events, with 100 evaluable patients in each of the two treatment arms yields a power of 0.80. A similar power is obtained for the comparison of the AVATAR ablation arm (0.40) and the conventional AF ablation arm (0.20).

A sensitivity analysis indicates that these sample size estimates are reasonable. It is anticipated that the loss to follow-up will be small, approximately 7%. Consequently, 321 patients will be randomized in a 1:1:1 manner to a treatment strategy of either AVATAR-protocol ablation, anti-arrhythmic therapy or conventional AF ablation and followed-up for 1 year.

Failure is counted when a patient experiences any hospital episode related to treatment for atrial arrhythmia. Time to failure will be taken as the time from 1st intervention to the time of event.

Data will be analyzed using the intention-to-treat principle and a p-value of 0.025 or less will be considered significant. Primary outcome will be analyzed using Kaplan-Meier statistics and differences between treatment arms will be assessed using log-rank testing and proportional hazards models. A sensitivity per-protocol analysis will also be performed. Secondary endpoint analysis of time to death or stroke; time to procedural/drug-based complication and time to hospital episode resulting in change in therapy will be analyzed using Kaplan-Meier statistics. Differences between treatment arms will be assessed using log-rank testing and proportional hazards models. In addition to the primary analysis above, the model will be adjusted to account for the following co-variables: site, weight, hypertension, number of anti-arrhythmics taken by patient prior to 1st intervention.

Discussion

Demographics of atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, resulting in

significant associated morbidity and mortality. In 2010, an estimated 20.9 million men and 12.6 million women were suffering with AF.¹¹ With an aging population, significant growth in this number is predicted. By 2030 within Europe alone, 14–17 million AF patients have been projected, with 120,000–215,000 newly diagnosed patients per year.^{12,13} At present, the direct cost of AF approximates to 1% of the total healthcare spending in the UK, primarily driven by the complications of AF. Patients suffering with AF have between a 10–40% chance of hospitalization each year. Furthermore, around 20–30% of all strokes are due to AF, while other complications such as left ventricular dysfunction, decreased quality of life, depression, cognitive decline and vascular dementia remain strongly associated. AF is also independently associated with a 1.5-fold increased risk of all-cause mortality in men, and 2-fold increased risk in women.¹⁴⁻¹⁶ The changing demographics present significant challenges to healthcare resources.

Methods for reducing costs of treatments

Trials are often conducted to demonstrate treatment benefit but there is an increasing need to deliver the same outcomes for less expenditure. The costs of healthcare can vary widely between countries and the pricing of consumables and equipment is also susceptible to local procurement practices. However, physicians do use the same clinical endpoints and approaches to deliver therapy. Therefore, removing steps from the procedure and thereby reducing the resources required should lead to an advantageous reduction in healthcare costs, irrespective of the country in which treatment is delivered. Of course, there would be little support for such a move unless outcomes can be shown to be minimally affected.

In the case of AF treatment, acute PV isolation is the target of AF ablation and has been shown to be the most effective method for preventing episodes of AF by prolonged ECG monitoring. We reviewed the steps in an AF ablation procedure and determined that a technology that was capable of producing PV isolation reliably and reproducibly may not need catheters to confirm PV isolation. The cryoballoon appears to meet this criterion as it seems to be highly effective at achieving this in 94% of veins after a single freeze.⁴ Significant time and financial investment is then made to push this figure up to near 100%. Despite this effort, chronic isolation of all veins is only found in 10% of asymptomatic patients.⁵ This raises the question as to why durable pulmonary vein isolation with catheter ablation is so difficult, and indeed whether it is essential to achieve 100% acute isolation. Therefore, it may be reasonable to perform cryoballoon procedure without the use of PV mapping catheter, provided outcomes are acceptable.

The cryoballoon is of further interest as it can be used without any other EP equipment in a standard cardiac catheter laboratory. This enables multiple further cost savings which include not needing EP recording equipment

or specialist staff as a temporary pacing wire and box can be used for phrenic nerve monitoring. This would also shorten the procedure and may enable most patients to be completed as a day case providing a cost saving through reduced bed occupancy. The cost savings are not related to the price of the Achieve wire, which is often included in the negotiated package price. One series has suggested that nearly 90% of patients can already be discharged safely as a day case.⁶ It is not suggested that forgoing PV mapping enables daycase discharge, but that its cumulative benefit is feasible to reduce resource utilization. Since the inception of the AVATAR-AF study, the recent FIRE & ICE trials has suggested that the cryoballoon has similar efficacy profile to radiofrequency ablation and may have some long term reductions in hospitalization.^{17,18}

Atrial fibrillation trial endpoints

In the case of AF ablation procedures the goal is symptom control, but using the endpoint of 'any detectable AF' appears to justify spiraling costs by trying to eradicate all episodes of AF. Single procedure success rates for paroxysmal AF remains stable at around 70%. This owes largely to the way that procedural success is defined. The current 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus continue to recommend assessing outcome by 'any detectable AF' which is defined as episodes of at least 30 seconds duration.¹⁹ In the previous 2007 and 2012 guidelines, it was recommended that Holter monitoring should be performed every 6 months for a period of 2 years.^{20,21} In the present guidance, the consensus statement for AF monitoring post-ablation is for a minimum of 3 visits (eg, at 3, 6, and 12 months), with a 12-lead ECG at each visit, a 24 hour Holter at the end of the follow-up period (12 months), and a more limited event recording from the end of the 3-month blanking period to the end of follow-up, both at regular periods and with patient activated recordings obtained at the time of symptoms. Follow-up beyond 1 year is encouraged, and suggested to occur every 6 months with Holter and ECG.¹⁹ These outcome measures are effective for determining the efficacy of a technology but have limited use for decision making in patients. With the current stringent definition, a 1-minute episode of asymptomatic paroxysmal AF detected on a 24 hour Holter monitor at 12 months post-ablation would therefore be deemed a procedural failure on scientific grounds. Despite the 'procedural failure' it would not result in a change in medication or consideration of further ablation in clinical practice. Furthermore, patients would be expected to attend for frequent hospital review and investigation, regardless of symptom control. This comes at substantial inconvenience to the patient, and is associated with significant healthcare resource consumption without a requirement for a change in management strategy.

We propose that the definition of success in AF ablation and its implications requires re-evaluation. Other potential clinical endpoints might include reduction in total AF burden, improvement in quality of life (QOL), or elimination

of stroke risk. Elimination of stroke risk needs frequent monitoring and prevention of all episodes of AF both symptomatic and asymptomatic. Such an approach may need aggressive ablation endpoints with increased procedural and long term follow-up costs.²² This may be justified by the number of strokes prevented. Studies addressing such endpoints would require several thousand patients, similar to RELY²³, ROCKET-AF²⁴ and ARISTOTLE²⁵, which is probably beyond the scope of interventional studies at present.²⁶ Quality of life questionnaires have been used, but patients can find these restrictive and challenging to understand, and the data less objective and challenging to interpret for the physician.²⁷ As an alternative we would propose that attending hospital appointments and investigations both electively or as an emergency are objective and measurable events. Hospitalization for inpatient treatment is a well-established endpoint. Adding routine outpatient appointments is a minimal change but is more relevant to this type of symptom monitoring. Symptom control that is good enough to prevent the need for regular review after an AF ablation could be used as a 'success' measure. 'If successful, you will not need to attend hospital' is an easily understandable outcome measure for the patient, unlike the current outcome target of 'any detectable AF' regardless of symptoms. There are also limitations to the current definition with regard to the method of detection of AF. Furthermore, using hospital episodes aligns the results of the procedure with those used by healthcare commissioners.

Requirement for a three-arm trial

By proposing an alternative measure of clinical success, we raise the concern that AF ablation has not been shown to be more effective than medical therapy using the endpoint of not needing hospital based specialist treatment. Therefore, it is first necessary to confirm that the streamlined AVATAR-protocol ablation is still superior to medical therapy using this new endpoint. This was the primary objective of this study. However, the majority of electrophysiologists (and consensus guidelines) would consider checking the pulmonary veins to be an essential part of the procedure and doing so would improve outcomes. Therefore, our secondary objective was to test whether conventional AF ablation with confirmation of PV isolation is superior to the AVATAR-protocol ablation using this new endpoint. A non-inferiority design was not chosen because that would require larger patient cohort and we do not believe there is sufficient evidence to justify the approach. On this basis a three-arm study was designed to address these issues and answer the question of whether the absolute costs of AF ablations can be reduced whilst maintaining clinical benefits.

Limitations

In trials comparing medical therapy against a procedural intervention, there could be bias due to the patients not being blinded to treatment. We attempted to reduce this by

counseling the patients during the informed consent process that the goal of treatment was symptom control irrespective of initial randomization, and if assigned treatment was ineffective they would be able to cross-over. The Data Safety Monitoring Board charter included review of assigned treatment to ensure that the optimal therapy was being delivered according to the protocol. The un-blinded design with a symptom based outcome could introduce bias to the trial in favor of the more invasive strategies, however only a blinded sham arm would avoid this limitation. Anti-arrhythmic drug use has been allowed in both ablation arms, but not used as a stratification variable in randomization, which might result in residual confounding. We did not track every piece of equipment used in each case, but are looking at generic cost reductions such as overnight stay, PV mapping related costs, and follow-up monitoring costs. It is possible that there will be unexpected increases in other costs.

Summary

The increasing population burden of AF will need more cost effective approaches to treatment of symptoms. It is not known whether current benefits of antral pulmonary vein ablation can be retained whilst reducing the resources used to deliver therapy.

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Appendix A. Appendix 1: Managing atrial flutter.

(I) 12 lead ECG documentation of typical atrial flutter during screening

- *Patient should not be recruited to the AVATAR study and should undergo Cavo-Tricuspid Isthmus line (CTI)ablation.*
- *If symptomatic atrial fibrillation is still present then the patient can be considered for AVATAR recruitment.*

(II) 12-Lead ECG documentation of typical atrial flutter after randomization.

- *Patient should be suspended from the AVATAR study intervention and should undergo CTI ablation.*
- *If symptomatic atrial fibrillation still present then the patient can be considered for AVATAR intervention.*

(III) Holter monitor - Atrial fibrillation + organized atrial activity suggestive of paroxysmal atrial flutter.

- *Can be recruited to AVATAR study, but cannot have CTI at first ablation.*

(IV) CTI dependent flutter (or any other arrhythmia) occurs during AF ablation procedure.

- *These patients should not be ablated during the first ablation procedure*

Appendix B. Appendix 2: Telephone questions

i) Have you attended hospital for any reason other than for routine blood tests (yes/no)

If yes -.

a) Was the problem related to your atrial fibrillation? (yes/no).

b) What were you suffering from? (palpitations/ breathlessness/fainting/ bleeding/weakness/ confusion).

c) What was the outcome? (Reassured (no further appointments or tests needed)/Asked to see your Cardiologist/Asked to see another hospital specialist/ Asked to see GP).

d) Did you had any of the following investigations done in hospital? (ECG, Non-invasive ambulatory cardiac monitoring (including Holter/memo etc.) /Echo/Exercise test/Coronary angiogram/MRI/CT/Ultrasound/endoscopy/CXR).

e) Were you given any drugs for you heart?

If yes - which ones.

f) Were you advised to change any of your medications?

If yes - which one.

g) Did you have any procedures whilst you were in hospital

If yes - what was it

ii) Have you had any of the following symptoms;

a) racing heart beat lasting more than half an hour.

if yes - <1/week or> 1/week.

b) racing heart beat more than 5mins but less than half an hour.

if yes - <1/week or> 1/week.

c) Have you had any unexplained breathlessness, dizzy spells, chest pain, fainting attacks/weakness/confusion.

if yes which-.

iii) Do you think you the situation is bad enough that you need to change medication or have another procedure to help make you better? (yes/no).

iv) Do you think you are having side effects or complications from your treatment? (yes/no).

v) If you have answered yes to any of the questions we recommend that you see your GP and discuss whether you need another appointment with you heart specialist. We will pass on the information from the phone call to you heart specialist and they may contact you directly if they are concerned about any of the answers you have given.

Appendix 3: AVATAR-AF Endpoint definitions

Symptoms of atrial fibrillation/tachycardia: Palpitations lasting >5 min, transient dizziness or fainting, lethargy, shortness of breath on exertion, chest discomfort. ECG documentation of AF: Irregularly narrow QRS without p-waves lasting >30 s narrow QRS with A > V evident or 1:1 at >100 bpm with sudden onset lasting >30 s or incessant at constant rate.	
Pericardial effusion:	global echo-lucent space around myocardium >0.5 cm maximally in diastole <ul style="list-style-type: none"> • SEVERE: pericardial drain inserted, sternotomy, • MODERATE: delayed discharge
Vascular bleeding:	Bleeding visualized by hematoma or imaging associated with Hb drop of >2 g/dl <ul style="list-style-type: none"> • SEVERE: Surgical intervention, transfusion required
Phrenic nerve palsy:	Reduced excursion of hemi-diaphragm on chest x-ray in inspiration and expiration more than 1 day after procedure <ul style="list-style-type: none"> • SEVERE: exertional symptoms with CXR changes at >3mth • MODERATE: asymptomatic with CXR changes at >3mth
PV stenosis:	Evidence of >50 reduction in ostial PV diameter by any form of imaging. <ul style="list-style-type: none"> • SEVERE: exertional symptoms at >3mth • MODERATE: asymptomatic at >3mth
Drug side effect:	Symptoms that are well recognized with drug or stop after ceasing drug
Stroke:	logical symptoms/signs associated with MRI or CT evidence of neurological bleeding/ischemia

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