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The burden of proof: The current state of atrial fibrillation prevention and treatment trials

Running title: AF prevention and treatment trials

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Abstract

Atrial fibrillation (AF) is an age-related arrhythmia of enormous socio-economic significance. In recent years, our understanding of the basic mechanisms that initiate and perpetuate AF has evolved rapidly, catheter ablation of AF has progressed from concept to reality, and recent studies suggest lifestyle modification may help prevent AF recurrence. Emerging developments in genetics, imaging, and informatics also present new opportunities for personalised care. However considerable challenges remain. These include a paucity of studies examining AF prevention, modest efficacy of existing antiarrhythmic therapies, diverse ablation technologies and practice, and limited evidence to guide management in high-risk patients with multiple comorbidities. Studies examining the long-term effects of AF catheter ablation on morbidity and mortality outcomes are not yet completed. In many ways, further progress in the field is heavily contingent on the feasibility, capacity and efficiency of clinical trials to incorporate the rapidly evolving knowledge base and to provide substantive evidence for novel AF therapeutic strategies. This review outlines the current state of AF prevention and treatment trials including the foreseeable challenges, as discussed by a unique forum of clinical trialists, scientists, and regulatory representatives in a session endorsed by the Heart Rhythm Society at the 12th Global CardioVascular Clinical Trialists (CVCT) Forum in Washington, December 3-5, 2015.

Key words: Atrial fibrillation; randomised controlled trial; prevention; ablation; personalised medicine.

Introduction

Atrial fibrillation (AF) is a public health concern of global and epidemic proportions, inextricably linked to an aging population, expanding burden of predisposing factors, and enhanced arrhythmia surveillance¹⁻³. Symptoms associated with AF may be severe and disabling, and AF represents an independent risk factor for stroke, heart failure (HF), dementia, and death^{4, 5}. Patients with AF are hospitalised twice as often as those without AF and the incremental costs attributable to AF-related care present important challenges for existing healthcare systems⁴⁻⁶. Accordingly, the treatment and prevention of AF has become a key priority for clinical and translational research efforts⁷⁻⁹.

In recent years there have been significant advances in our understanding of the basic mechanisms underlying AF initiation and maintenance^{10, 11}. It has become clear that aging, genetics, environmental factors, cardiac and non-cardiac conditions further contribute to a favourable atrial substrate¹². Moreover, surgical and catheter ablation techniques for AF have been at the forefront of rapid technological innovation^{4, 5, 13}. Central to these endeavours, integration of basic science and observational findings into a defined therapeutic strategy and its uniform application and validation within a randomised controlled trial (RCT) has remained the benchmark for safety and efficacy required for any change in clinical practice¹⁴.

Currently, however, there are insufficient high quality and generalisable RCT data to support the needs of 'real-world' clinical practice¹⁵. Broadly speaking, prevailing challenges with respect to AF management include: i) limited RCT evidence relating to lifestyle and risk factor modification, prediction and prevention of AF, ii) diverse ablation practices, underrepresentation of long-term and patient reported outcomes within existing AF intervention trials, and iii) evolving demands for design and validation of personalised and mechanism-orientated AF therapies in order to improve patient

adherence and outcomes. A comprehensive discussion of these issues and the current state of AF prevention and treatment RCTs took place within a unique forum composed of clinical trialists, scientists, and regulatory representatives, at the 12th Global CardioVascular Clinical Trialists (CVCT) Forum in Washington, DC, December 3-5, 2015, the details of which are outlined in this review. Note that AF-related stroke prevention and anticoagulation, whilst essential to AF management, are beyond the scope of this manuscript.

AF prevention trials

Primary and secondary AF prevention

Epidemiological studies have described an array of potentially modifiable risk factors for AF including: hypertension, obesity, metabolic syndrome, diabetes mellitus, obstructive sleep apnoea, cigarette smoking, and excessive alcohol intake. Many of these are also risk factors for atherosclerotic cardiovascular disease, myocardial infarction and HF, which themselves predispose to AF. Recent consensus documents advocate targeting prevention efforts to individuals with the highest risk, typically those with multiple predisposing conditions^{8, 16}. Putative risk scores have been developed with this in mind, though are not yet widely in use¹⁷.

Unfortunately, the current framework for scientific investigation limits feasibility of dedicated AF primary prevention RCTs by the large population size and prolonged duration required to achieve an adequate number of recognised endpoints. A first presentation of symptomatic AF may occur years after recruitment and the expediency of prolonged ECG monitoring in asymptomatic individuals is low. Looking forwards, smartphone-based ECG applications, implantable and convenient wearable recorders with single-lead ECG recording capabilities are likely to become more pervasive in RCTs; emerging literature supports their utility and diagnostic performance in population-

based settings¹⁸⁻²⁰. Furthermore, detection of frequent atrial ectopy, may prove to be a precursor or surrogate marker of AF, allowing enrichment of study populations with individuals at sufficiently high risk²¹. Presently, however, further delineation of its natural history is required.

Secondary prevention of AF (delaying recurrence of AF after an initial episode or delaying progression from paroxysmal to persistent AF) has received greater attention, albeit a clinical rather than pathological classification. Basic research in animal models and humans has demonstrated progressive atrial electrical and structural remodelling occurring in the setting of cardiometabolic risk factors, which are thought to be responsible for AF initiation and perpetuation of AF maintenance¹¹. Since this process develops insidiously, AF risk is realistically a continuum, and in most individuals will result from a combined effect of several interacting factors, often without definite threshold values. This may explain why isolated treatment of hypertension, although arguably one of the strongest contributors to AF burden²², has not been shown to reduce AF risk consistently and no target blood pressure has been identified. Hence, contemporary RCTs, as in clinical practice, have recognised the need to incorporate a strategy of comprehensive risk factor modification with individual AF prevention and treatment interventions. The fact that AF induces further electrical remodelling in animal models²³ (*'AF begets AF'*), further highlights the importance of early intervention.

Non-pharmacological approaches to AF prevention

Among candidate non-pharmacological interventions, inaugural studies of weight loss and exercise have shown efficacy for secondary, though not yet primary, AF prevention within a comprehensive risk factor modification programme (**Table 1**).

Weight loss

Primary prevention RCT data regarding lifestyle intervention and weight loss in overweight and obese individuals with type II diabetes and no prior AF were available in the Look AHEAD trial²⁴. Secondary analyses did not demonstrate a reduction in AF incidence over 9 years of follow up, though AF was not a pre-specified end-point and the overall weight loss achieved was modest²⁴. Conversely, in overweight and obese patients with documented paroxysmal AF, randomised to a physician-instructed low-calorie diet and exercise routine, Abed et al. reported a more significant reduction in BMI and improved blood pressure control at 15 months follow-up, associated with less frequent and shorter duration AF episodes (Holter monitoring) and lower self-reported symptom severity, compared with patients receiving standard lifestyle and weight loss advice²⁵. Both groups received aggressive management of concomitant cardiometabolic risk factors. In ARREST-AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation) overweight and obese patients undergoing first-time catheter ablation for either paroxysmal or persistent AF, who opted to undergo a focussed cardiometabolic risk factor management programme, showed consistently greater reductions in weight, systolic blood pressure, markers of AF burden, and freedom from AF recurrence (32.9% vs 9.7% in control subjects) at 42 months follow-up, compared with patients choosing standard post-ablation care²⁶. Finally, a longitudinal cohort study of overweight and obese patients with paroxysmal or persistent AF participating in a physician-led weight management clinic (Long Term Effect of Goal Directed Weight Management on Atrial Fibrillation Cohort: A 5 year Follow-Up Study; LEGACY-AF), reported a dose-response relationship between weight loss and reduction in AF symptoms and arrhythmia burden (7-day Holter) at 5-year follow-up²⁷.

Taken together, the CVCT believes that these seminal findings from a dedicated single-centre team strongly support a strategy of purposeful weight loss to accompany risk factor modification for obese and overweight patients with existing AF. Replication of

these findings across multiple centres is now a priority for the clinical community and will require appropriate support from funding agencies. Notably, only one of the aforementioned studies was randomised²⁵ and patients with significant valvular or ventricular dysfunction have so far been excluded.

Exercise and cardiovascular fitness

Regular physical activity and aerobic exercise training delay development of atherosclerotic cardiovascular disease²⁸. Exercise has been cautiously advocated in AF prevention and management, due to an increased risk of AF among individuals engaging in high-intensity and endurance training. However, it is worth highlighting that pro-arrhythmic levels of exercise exceed those practised by the majority of patients with AF and recent data demonstrate an inverse relationship between physical activity and AF incidence in non-athlete cohorts^{29, 30}, akin to a J-shaped phenomenon.

Indeed, short-term exercise training has been shown to benefit secondary prevention of AF^{31, 32}. The CardioFIT study (Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation), of overweight and obese patients with symptomatic paroxysmal or persistent AF, exhibited a dose-response relationship between baseline cardiorespiratory fitness and long-term freedom from AF without antiarrhythmic drugs or ablation³¹. Cardiorespiratory fitness gain from a tailored programme of aerobic and resistance training further prolonged AF freedom, over and above the effect of weight loss³¹. Malmö et al. corroborated these findings in a referral cohort with paroxysmal or persistent AF undergoing first-time ablation, in a different centre, randomised to 12 weeks adjuvant high intensity aerobic interval training versus no exercise prescription³². Despite fewer cardiometabolic risk factors in this cohort, compared with prior prevention trials, exercise training yielded improvements in BMI, lipid profile and exercise capacity with attendant reduction in mean AF time

(implantable loop recording), and fewer and less severe self-reported AF symptoms, compared with the control group³².

These data demonstrate that short-term gains in cardiorespiratory fitness are attainable, safe, and confer reductions in arrhythmia burden, with and without rhythm control strategies, in ambulatory patients with symptomatic AF. Whether these benefits can be sustained long-term now needs to be addressed. In the HF-ACTION trial, initial gains from supervised exercise training over 12-weeks were diluted by poor adherence when supervision ended, yielding modest overall improvement at final follow-up³³. Furthermore, in LEGACY-AF, >5% annual fluctuation in weight partially offset the benefits of weight loss and exercise on arrhythmia-free survival at 5-years²⁷. Thus, the CVCT Forum concluded that while public health-level arguments in favour of exercise and weight management programmes are strong, funding and resources for long-term physician-led face-to-face counselling and exercise clinics will be needed to realise their potential for AF prevention in clinical practice.

Risk factor modification in patients with heart failure

Patients with AF and HF present a unique challenge to the weight loss hypothesis. There are currently no published RCT data investigating the effect of weight loss in patients with AF and HF and it remains unclear whether severe atrial remodelling, as may occur in AF and HF, can be interrupted or reversed by weight loss, which is among its reported benefits. Furthermore, it is uncertain how weight loss interventions may impact the reported 'obesity paradox', in which overweight and mildly obese patients with HF appear to have better short-term outcomes compared with lean HF patients³⁴. Interestingly, a similar paradox has been reported in a large trial cohort of patients with AF (without HF) on oral anticoagulant therapy³⁵, despite compelling RCT data supporting weight loss for secondary AF prevention. Acknowledging that the nature

of this paradox remains controversial, future AF trials may benefit from more refined characterization of an obesity phenotype, beyond BMI alone. At present, however, empirical evidence does not support the practice of asking HF patients to lose weight and AF studies to date have not defined a target weight or weight range within which AF burden is minimised. Notably, cardiorespiratory fitness, itself associated with AF burden, reportedly alters the relationship between adiposity and prognosis in HF patients and attenuates the obesity paradox in younger patients with reduced ejection fraction³⁶. Thus, the combined impact of exercise and weight optimisation in patients with AF and HF warrants prospective investigation.

Pharmacological approaches to AF prevention

Upstream therapy refers to the use non-antiarrhythmic drugs to modify the atrial substrate or target specific mechanisms of AF^{37, 38}. The concept is supported by compelling experimental evidence showing protective effects of renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, and polyunsaturated fatty acids, on atrial structural and electrical remodelling^{37, 38}. Unfortunately, however, clinical performance of these agents in RCTs has been generally disappointing.

RAAS inhibitors have been associated with reduced incidence of AF in patients with left ventricular systolic dysfunction or hypertrophy in retrospective analyses of RCTs with ≥ 3 years of follow-up³⁸. The addition of a mineralocorticoid receptor antagonist (MRA), Eplerenone, to RAAS inhibition and beta-blockade was associated with a lower incidence of AF in patients with systolic heart failure (LVEF \leq 35%) and mild symptoms (NYHA class II) in the EMPHASIS trial³⁹. No convincing benefit of RAAS inhibitors or MRAs has been observed in patients without underlying heart disease or for secondary AF prevention. In retrospective studies of patients undergoing cardiac surgery, statins appeared to protect against new-onset AF, though conflicting RCT data exist^{40, 41}. There

are insufficient clinical data to support the use of polyunsaturated fatty acids in primary or secondary prevention of AF^{37, 38}. Only, short-term colchicine use has been associated with lower rates of post-operative AF⁴² and reduced early AF recurrence after catheter ablation⁴³. Concomitant reductions in inflammatory markers, C-reactive protein and Interleukin-6 support an anti-inflammatory mechanism. Colchicine use appears to be safe and generally well tolerated, although the optimal dose and duration need to be confirmed.

As cardiac surgery and catheter ablation initiate inflammation, it is likely that colchicine's anti-inflammatory action represents a good example of matching pathology with treatment. The failure of other agents to prevent AF in RCTs, despite convincing experimental data, may relate to inappropriately heterogeneous patient cohorts or a failure of experimental models to account for potentially neutralising effects of comorbidities accompanying AF. Upstream agents may be unable to reverse advanced atrial remodelling, and trials of generally ≤ 1 year duration may have been too short to demonstrate their effects. Future RCTs may consider combining agents or refining AF ascertainment methods to assess true impact on total AF burden. The Routine versus Aggressive upstream rhythm Control for prevention of Early AF in heart failure (RACE 3) RCT has taken this approach and will test the hypothesis that aggressive combination upstream therapy increases persistence of sinus rhythm in patients with early AF and mild-to-moderate early systolic or diastolic HF undergoing electrical cardioversion, when compared with conventional rhythm control alone (NCT00877643)⁴⁴.

AF treatment trials: Filling in the gaps

Rate versus rhythm control

The major goals of AF therapy are to reduce cardiovascular symptoms and AF-related morbidity and mortality. These aims should be pursued in parallel. Both rate and

rhythm control strategies have demonstrated improvements in quality of life and exercise capacity, however the first wave of large RCTs failed to show a mortality benefit with rhythm control⁴⁵⁻⁴⁹. Reasons cited included a failure of rhythm control strategies to achieve and sustain sinus rhythm, a high rate of cross over between treatment arms, and harmful effects of antiarrhythmic drugs which may have offset the benefits of restoring sinus rhythm. Consequently, it remains uncertain as to whether one strategy is superior to the other with respect to major cardiovascular endpoints. A prevailing view is that AF at least contributes to its associated adverse outcomes, as well as representing a marker of cardiovascular disease, and thus a more efficacious and less toxic strategy of restoring and maintaining sinus rhythm is expected to improve prognosis. On-treatment analysis of the AFFIRM trial suggested that sinus rhythm, where achieved, was associated with a reduction in mortality⁴⁷; thus providing qualification for on-going efforts to optimise rhythm control.

Non-pharmacological (invasive) approaches to AF treatment

State-of-the-art non-pharmacological rhythm control therapy is based on radiofrequency endocardial catheter ablation, with pulmonary vein isolation (PVI) as the mainstay (**Figure 1A**). Prompted from a clinical observation⁵⁰, translational research has corroborated the importance of pulmonary vein triggers for AF initiation, and several RCTs have demonstrated superiority of catheter ablation over antiarrhythmic drug therapy, with respect to freedom from arrhythmia recurrence, particularly in young patients with paroxysmal AF, and without major comorbidity⁵¹⁻⁵⁵ (**Table 2**). Contemporary guidelines have endorsed catheter ablation for patients with symptomatic paroxysmal (class I) or persistent (class IIa) AF who are intolerant or resistant to one or more antiarrhythmic drugs^{5, 13}. Importantly, however, this endorsement is not without caveats.

The Forum emphasized that available RCT and registry data show that PVI in its current form does not represent a *cure* for AF and several evidence gaps remain.

Pulmonary vein isolation

Only 50-66% of patients with paroxysmal AF achieve sustained sinus rhythm after a single PVI procedure and 70-80% after a second attempt⁵⁶. Success rates are compromised further when follow-up is extended beyond 1 year⁵⁶. These real world outcomes are inferior to the initial results reported by expert centres, prompting efforts to improve completeness of acute PVI (**Table 3**) and the discovery of PV reconnection as an important mechanism for AF recurrence⁵⁷.

Recent efficacy studies of novel irrigated-tip catheters have suggested an optimal contact force (CF) between the catheter tip and atrial tissue (20g with a force-time integral of 400g per ablation lesion⁵⁸), which may improve transmural lesion formation and eliminate conduction gaps by improving lesion continuity. The first prospective multicentre RCT comparing CF-guided PVI against conventional PVI (TaciCath Contact Force Ablation Catheter Study For Atrial Fibrillation; TOCCASTAR⁵⁹) met its primary non-inferiority safety and efficacy endpoints, and in secondary analyses reported that 76% of CF-PVI patients were free from arrhythmia at 12 months off antiarrhythmic drugs compared with 58% undergoing non-CF ablation. Non-radiofrequency approaches are also being considered. Cryoablation utilises a balloon, positioned at the pulmonary vein ostia, which is cooled with liquid nitrous oxide. Iterative modifications have led to changes in freeze duration, homogeneity, balloon pressure and positioning, yielding greater efficacy and fewer serious complications (phrenic nerve paralysis, atrio-oesophageal ulceration or fistula formation). The first prospective multicentre randomised trial of cryoablation versus conventional PVI recently met its non-inferiority safety and efficacy endpoints (Fire and Ice, Clinicaltrials.gov NCT01490814; **Table 3**)⁶⁰.

Additionally, peri-procedural adenosine administration has been used to unmask ‘dormant’ pulmonary veins ostensibly at risk of reconnecting, prompting further prophylactic lesion sets to be delivered during the index procedure. The multicentre ADVICE trial (Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial⁶¹) demonstrated improvement in 12-month arrhythmia-free survival with this approach compared with standard ablation practice, without an increase in periprocedural complications⁶¹. Still, the overall clinical impact of adenosine testing is likely to depend on the ablation technologies utilised, patient cohort, and resultant prevalence of dormant conduction. In the UNDER-ATP (UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate) trial, where the prevalence of dormant conduction after ablation with combined anatomical and electrophysiological guidance was 20-30% among patients with paroxysmal, persistent or longstanding persistent AF (versus 50% in the ADVICE trial), no significant reduction in the incidence of recurrent atrial arrhythmias was observed compared with conventional PVI⁶² (**Table 3**).

It may be relevant that the positive aforementioned trials exclusively studied patients with paroxysmal AF. Even within this cohort, our understanding of the relevance of PV reconnection is derived from a biased subset of patients who have failed antiarrhythmic therapy and re-presented with symptomatic AF after a failed ablation. Purists may argue that PVI, at its conception, was never compared against a placebo control (i.e. sham-procedure), and thus the true effect size may have been overestimated. Indeed, RCTs in drug naïve patients comparing catheter ablation with antiarrhythmic drug therapy have either shown a lack of benefit or at best modest reduction in AF recurrence^{52, 54} (**Table 2**). Salient data from electrophysiology studies of patients without AF recurrence, have highlighted that pulmonary vein reconnection is also common in this setting^{57, 63, 64}. Hence, while pulmonary vein sources are

undoubtedly associated with AF initiation and maintenance in many patients, the current trend of performing multiple procedures in order to attain complete PVI is largely without corroborating evidence for long-term or universal clinical benefit.

Ablation of extra-pulmonary vein targets

Ablation success rates for patients with persistent AF are lower than for paroxysmal AF, particularly in the setting of comorbidities⁶⁵, ranging between 30-40% after a single or multiple procedures^{56, 66}. Current guidelines recommend consideration of more extensive ablation in this cohort in order to address a higher number of non-pulmonary vein triggers⁶⁷. However RCT data for this approach has been inconsistent (**Table 3**).

Creation of linear lesions to compartmentalize the left atrium has been incorporated into clinical practice, adopted from the surgical Cox-MAZE procedure⁶⁸, and is thought to disrupt the critical mass of tissue needed to sustain AF (**Figure 1B**). Complex fractionated atrial electrograms (CFAEs) are electrograms of long duration, thought to highlight areas of slowed conduction and anchoring points for continuous re-entry^{69, 70}. Targeting CFAEs in patients with persistent AF has been associated with improved sinus rhythm maintenance in non-randomised studies and subgroup analyses^{71, 72} (**Figure 1C**). However, until recently, these empirical methods of substrate modification had little randomised or comparative data to support their use.

In the largest multicentre RCT to date (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II, STAR AF II⁷³), three ablation strategies: PVI alone, PVI plus linear lesions (mitral isthmus and roof line), and PVI plus CFAE ablation, were compared in 589 patients undergoing first-time ablation for drug-refractory persistent AF. Contrary to expectations, no statistically significant difference in outcomes was observed after a first or repeat procedure (same strategy), with or without

antiarrhythmic drugs, at 18 months' follow up. In fact, PVI alone tended to be superior at sinus rhythm maintenance, and was associated with shorter procedure and radiation times, though the trial was not adequately powered for this assessment. These compelling data highlight the importance of scientifically rigorous investigation to guide standard of care. Thus, in patients with persistent AF, there is currently no clear advantage to adjuvant CFAE ablations or empiric linear lesions not targeting arrhythmogenic substrate.

That said, the discrepancy between index AF ablation success rates and long-term pulmonary vein isolation has spurred interest in targeting other mechanisms of AF. Where present, ablation of patient-specific focal triggers may allow less overall tissue ablation, upholding the recommendations of STAR AF II. Proposed targets include: rapid drivers/dominant frequency, ganglion plexi ablation, and focal impulse or rotor modulation (FIRM).

Dominant frequency ablation predicates that AF is driven by areas of high frequency activity not possessing the fractionation of CFAEs⁷⁴. The RADAR-AF trial demonstrated that high frequency source ablation (HFSA) alone was not inferior to PVI for patients with paroxysmal AF at 12 months follow-up and displayed fewer complications, potentially due to less tissue ablation⁷⁵. Conversely, for patients with persistent AF where a superiority endpoint was sought, HFSA failed to demonstrate incremental value when added to PVI⁷⁵. The autonomic nervous system may modulate AF triggers and substrate^{76, 77}. In patients with paroxysmal AF, ablation of peri-pulmonary vein ganglion plexi (**Figure 1D**) was inferior to PVI alone, but when combined with PVI improved 2-year freedom from AF from 56% to 74%, without increasing the rate of iatrogenic atrial flutter⁷⁸. An incremental effect of ganglion plexi ablation in patients with persistent AF has not yet been studied. A further body of research has proposed that spiral re-entry waves, or 'rotors', perpetuate AF. FIRM mapping software may be

used to identify and direct ablation of patient-specific rotors. The CONFIRM trial demonstrated that rotors were present in 97% of subjects with paroxysmal or persistent AF, and FIRM-guided cases of PVI exhibited higher rates of freedom from AF when compared with PVI alone⁷⁹. The same investigators presented data corroborating FIRM-guided ablation as a stand-alone procedure for patients with paroxysmal AF⁸⁰, although this was not published and, controversially, others have been unable to replicate these findings^{81, 82}.

Summarising these studies, the Forum stresses that there is currently insufficient randomised evidence to change the ablative approach for persistent AF beyond isolated PVI, at least for an index procedure. Moving forward, the field would benefit from standardisation of the definitions used for extra-pulmonary vein targets and the approach to ablation; it may be argued that discrepancies in the prevalence, electrophysiological characteristics, and clinical outcomes between early studies largely result from methodological differences. Furthermore, it is not known whether successful ablation of AF, regardless of technique, will result in reduced mortality. This is under investigation in the Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA; ClinicalTrials.gov NCT00911508) and Catheter Ablation versus Standard Conventional Treatment in Patients With LV Dysfunction and AF (CASTLE-AF; ClinicalTrials.gov NCT00643188⁸³) trials.

Additional considerations

The rapid evolution of catheter designs and ablation techniques presents a challenge for evidence-based medicine and the premium placed on RCTs. Stringent protocols, high costs and cumbersome operational requirements have given rise to a number of short-duration trials, often with non-inferiority end points, where clinical decision making and patient choice may be better guided by demonstrating superiority of

one strategy over another and long-term outcomes. Equally disadvantageous is the prospect of a lengthy trial examining ablation strategies that vary markedly over time, where the primary outcome may be biased by earlier utilised and less efficacious techniques. There are some concerns this may apply to the CABANA trial (ClinicalTrials.gov NCT00911508).

Operator proficiency and centre-related factors must also be considered. A worldwide survey in 2005 reported higher ablation success rates in high-volume compared with low-volume centres⁸⁴. Single-⁸⁵ and multicentre⁸⁶ studies have also demonstrated an independent association between individual operator volume and procedure efficacy, complication rates and procedure times. Most importantly, the available evidence for AF catheter ablation has been derived from recognised regional, national and international centres of expertise. As a result, a consensus statement from the Heart Rhythm Society and European Heart Rhythm Association has been published specifying minimum institutional and operator criteria⁸⁷.

Patient reported outcome measures

Symptoms are a major reason that patients with AF seek medical attention and are the primary justification for ablation. In recognition of this, contemporary AF RCTs are increasingly utilising quality of life and AF-specific symptom questionnaires when comparing treatment strategies. However, these data continue to serve secondary endpoints or ancillary analyses. Probable impediments to the adoption of patient reported outcome measures (PROMs) as major endpoints in AF trials include the lack of an accepted gold standard assessment tool unique to AF, uncertainty regarding the fundamental mechanisms for symptoms or meaningful levels of change, and enormous heterogeneity in symptom profiles between and even within the same patients over time.

While there is no simple solution to these challenges, it is no longer acceptable to omit qualitative endpoints in an era of patient-centred medicine. This is particularly important where trade-offs may exist, for example between modestly efficacious antiarrhythmic drugs and potential associated adverse effects. Furthermore, although restoration of sinus rhythm remains the desired clinical goal, for some patients with symptomatic AF, a reduction in frequency or duration of AF episodes (AF burden) may be an acceptable outcome. Alternatively, improvement in functional capacity was demonstrated to be a feasible and clinically relevant AF intervention endpoint in the ARC-HF trial⁸⁸. For other patients, a holistic approach to include detection and treatment of comorbidities may offer greater benefit. The impact of spironolactone on exercise capacity, health-related quality of life and left ventricular diastolic function in patients with AF and HF with preserved ejection fraction (HFpEF) is under investigation in the IMPRESS-AF trial (ClinicalTrials.gov NCT02673463). Wokhlu et al. observed that long-term improvements in quality of life were unrelated to rhythm status in patients undergoing index AF ablation, though the exact reasons for this finding were unclear⁸⁹.

Since the majority of tools used to assess quality of life, symptoms and functional status were not specifically developed for patients with AF, future systematic research is warranted to define the pathophysiological mechanisms underlying AF-related symptoms, their relationship to functional status, and their distinction, if any, from symptoms caused by other cardiac diseases such as heart failure and valvular disease.

AF ablation in patients with heart failure

The vacillation between rate and rhythm control strategies for the management of AF extends to patients with HF and reduced ejection fraction (HFrEF). Persistent AF is more common in this group and adverse haemodynamic and neurohumoral factors present additional complexity. Nevertheless, among the few RCTs examining ablation as

second-line therapy in dedicated HFrEF cohorts, overall efficacy rates are similar to those for patients without HF, albeit repeat procedures are more often required (**Table 4**). Improvements in quality of life, functional class and exercise tolerance have also been documented following AF ablation, when compared with atrioventricular node ablation⁹⁰ and pharmacological rate control^{88, 91}, though ablation was not superior to rate control in an early trial of digoxin therapy alone⁹². Notably, definitions of adequate ventricular rate control in HF remain arbitrary. Whether AF ablation can reduce the risk of death or major adverse cardiovascular events is currently being investigated in the CABANA, RAFT AF (A Randomised Ablation-based Atrial Fibrillation Rhythm Control Trial in Patients with Heart Failure and High Burden Atrial Fibrillation), and CASTLE AF (Catheter Ablation Versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trials (**Table 4**). Encouraging results were recently obtained in the AATAC trial (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device) where AF ablation in HFrEF patients achieved greater freedom from AF, reduced mortality and fewer unplanned hospital admissions compared with amiodarone therapy⁹³.

Outstanding areas in need of RCT level-evidence include the optimal AF management strategy for patients with HFpEF, and the role of catheter ablation as first-line therapy for AF in patients with HF, although early rhythm control approaches are being considered in the CABANA and EAST AF trials (**Table 4**).

Pharmacological approaches to AF treatment

Ventricular rate control is recommended for all patients with AF, and a lenient strategy (resting heart rate <110bpm) is supported by the RACE II trial⁹⁴. Beyond this, there is little RCT data to inform optimal heart rate targets or the choice of negatively

chronotropic agent with respect to morbidity, mortality and symptoms. Contemporary strategies are under evaluation in the pilot RATE AF study (Rate Control Therapy Evaluation in Permanent Atrial Fibrillation; NCT02391337).

Antiarrhythmic drugs are recommended as first line therapy for patients with AF-related symptoms after adequate rate control^{4, 5}. Unfortunately, however, existing agents are of modest and unpredictable efficacy and confer significant risks of pro-arrhythmia and off-target adverse effects. Flecainide (Vaughan Williams class Ic) is frequently utilised in patients without structural heart disease, although amiodarone has the widest repertoire of antiarrhythmic actions and approximately twice the efficacy of class Ic and class III agents⁹⁵. Even so, in the landmark Canadian Trial of Atrial Fibrillation (CTAF), 35% of patients receiving amiodarone experienced AF recurrence at long-term follow up (mean 16 months) and 18% experienced adverse events requiring discontinuation of the drug⁹⁵. The sheer size of the AF population and current restricted indications for catheter ablation indicate a large unmet need for more effective antiarrhythmic drugs to manage AF.

Dronedarone, the first new anti-AF agent to appear in several years, was engineered to have structural similarities to amiodarone without the iodine moiety, thus eliminating thyroid toxicity. Dronedarone successfully reduced cardiovascular hospitalisation and death in patients with paroxysmal or persistent AF and one additional high-risk factor (ATHENA trial⁹⁶). However, subsequent trials demonstrated increased mortality associated with its use in patients with structural heart disease and left ventricular dysfunction (PALLAS, ANDROMEDA^{97, 98}). Dronedarone is now contraindicated in this setting.

As with amiodarone, dronedarone has a non-specific mode of action that increases the risk of off-target effects. This has prompted the development of atrial-specific agents with potentially superior efficacy and safety profiles. Although the

majority are still in pre-clinical studies, vernakalant, a novel Na⁺- and K⁺-channel blocker, has demonstrated efficacy and an acceptable safety profile for acute termination of new-onset AF (<48h) in medium-sized placebo-controlled RCTs⁹⁹⁻¹⁰¹ when compared with amiodarone (Active-controlled, superiority study of Vernakalant versus amiodarone in Recent Onset atrial fibrillation; AVRO trial¹⁰²). Vernakalant has been approved by the European Medicines Agency for patients without structural heart disease, although there has been limited uptake; post-approval studies are currently underway. In the USA and Canada it remains an investigational drug.

Overall, the sparse and slow progress in drug therapy for AF reflects existing barriers to pharmacological innovation. Even when limitations in AF experimental models and techniques have been navigated and initial validation in human studies attained, regulatory requirements for new drug development are strict. Understandable caution is exercised with regard to patient safety, however, it is widely appreciated that escalating operational complexity of drug RCTs and prohibitive costs have somewhat diminished interest from industry. Demands for large RCTs with mortality endpoints and the desire for profitable broad indications may also impede clinical translation of promising compounds. In view of these challenges, across the spectrum of cardiovascular disease, efforts are underway to improve clinical trial and regulatory enterprises¹⁰³.

Surgical and hybrid therapy for AF

The suboptimal efficacy of either pharmacological therapy or catheter ablation for AF has given rise to the concept of hybrid therapy. Antiarrhythmic drugs are frequently used in patients undergoing catheter ablation, though there is wide variation in clinical practice and no consensus or prospective randomised data confirming the optimal duration of adjuvant drug therapy. Open-chest surgical AF ablation is reserved for selected symptomatic patients who have failed catheter ablation and are typically

undergoing cardiac surgery for another indication^{4, 5}. In this setting, epicardial ablation adds little additional operative risk. A novel minimally invasive approach, performed through video-assisted thoracoscopic surgery has also demonstrated superiority to catheter ablation in achieving one-year freedom from AF among patients with paroxysmal or persistent AF, with a dilated left atrium and hypertension, or previous failed catheter ablation¹⁰⁴. However, periprocedural adverse event rates were notably higher in the surgical group, including pneumothorax, major bleeding and conversion to sternotomy¹⁰⁴. The on-going multicentre CASA-AF trial will provide a contemporary appraisal of its safety and efficacy exclusively among patients with longstanding persistent AF (ClinicalTrials.gov NCT02755688).

A hybrid approach, combining epicardial and endocardial ablation, has also been developed; providing freedom from AF rates approaching 90% at 1 year. Two small prospective studies reported superior 1- and 2-year outcomes compared with conventional percutaneous ablation in patients with persistent AF^{105, 106}. Importantly, however, this strategy is still in its infancy and restricted to specialist centres with surgical expertise. Nevertheless, for patients without prohibitive surgical risk and symptomatic AF resistant to other therapies, it broadens future therapeutic options. Further data will be available from the on-going Hybrid versus Catheter Ablation in Persistent AF trial (HARTCAP-AF; ClinicalTrials.gov NCT02441738).

Future directions: Towards personalised AF therapy

To some extent the clinical management of AF is already personalised^{4, 5}. The decision to undergo cardioversion, ablation or to receive antiarrhythmic drug therapy is based on patient symptoms and preference. Additional consideration is given to comorbidities, duration of AF, left atrial size, drug efficacy, pharmacological interactions and adverse effects. Likewise, thromboembolism prophylaxis is prescribed according to

validated risk prediction scores based on clinical characteristics. However, despite nuanced clinical judgements, the complexity of AF remains a challenge and AF recurrence, progression to persistent AF, and response to treatment are largely unpredictable. This has prompted calls to improve our taxonomy of AF in order to facilitate a personalised or 'precision medicine' approach where therapy is tailored to an individual's unique clinical, genetic and molecular determinants of disease.

Substrate-guided therapy

The concept of electrical AF substrate characterisation is widely acknowledged and continues to inform the development of ablation techniques. However, recent trials, including STAR AF II, have demonstrated, that non-selective electrical substrate modification is not clearly associated with clinical benefit. To better tailor the interventional treatment of AF, more refined substrate characterisation alongside prospective delineation of AF triggers and drivers will be important.

The 4th AFNET/EHRA consensus conference proposed a new clinical classification of AF incorporating distinct (monogenic, focally induced and post-operative AF) and complex subtypes (polygenic, valvular, and AF in the elderly)¹⁰⁷. Patients would be assigned to the most relevant group, ostensibly reflecting the dominant pathology of AF, while AF not fulfilling these definitions would be 'unclassified'. Albeit, many patients will have overlapping mechanisms and 'unclassified AF' may be a common outcome. An alternative substrate-based approach has been proposed by an EHRA/HRS/APHRS/SOLAEAC consensus group, describing the atrial cardiomyopathy associated with AF. EHRAS classes I to IV identify primarily cardiomyocyte-dependent, fibroblast-dependent (fibrotic), mixed-dependency, and primarily non-collagen atrial infiltration, respectively¹⁰⁸. Although this classification is not intended to describe disease progression or severity, and may vary over time and atrial sites, the framework proposed

may enable the design of therapeutic strategies tailored to an individual's histopathophysiology where atrial tissue is available for examination. In the majority of patients with AF, for whom atrial tissue is unlikely to be available or the risks of biopsy are not justified, advanced imaging techniques may provide an alternative means of substrate characterisation.

Left atrial enlargement, identified on echocardiography or cardiac magnetic resonance imaging (MRI), has traditionally been associated with failure of rhythm control in AF. More recently, left atrial fibrosis quantified by MRI has emerged as a potentially superseding structural marker of disease severity. Three-dimensional assessment of left atrial myocardial delayed enhancement (DE-MRI) as a marker of interstitial fibrosis has been correlated with areas of low voltage by electro-anatomical mapping¹⁰⁹ and more frequent AF recurrence after index catheter ablation. In the *DECAAF* multicentre prospective observational study of patients with paroxysmal and persistent AF (n=272), the risk of recurrent AF increased from 15% for stage I fibrosis (<10% of the left atrial wall) to 69% for stage IV fibrosis (>30% left atrial wall fibrosis)¹¹⁰. This association persisted after covariate adjustment, including left atrial volume. Additional proof-of-concept studies from specialist centres have demonstrated DE-MRI visualisation of catheter ablation lines¹¹¹ and lesion gaps¹¹². These data may assist patient selection for ablation, enabling priority to be given to patients with lower left atrial fibrotic burden, or in providing anatomical guidance for patients requiring a repeat procedure. This is currently being investigated in the *DECAAFII* trial (ClinicalTrials.gov NCT02529319). Importantly however, left atrial imaging is technically difficult and 17% of the initial *DECAAF* study cohort (n=57 subjects) were excluded due to poor quality DE-MRI images¹¹⁰. Furthermore, whether cardiac MRI has sufficient resolution to identify focal regions with incomplete scar remains uncertain. Additional development of cardiac MRI techniques, expertise, and correlation with electro-anatomical mapping will be an essential

prerequisite to its widespread application. Similarly, the use of circulating biomarkers of extracellular matrix remodelling and novel molecular imaging using radiotracers specific for cardiac fibrosis-related targets, while promising, are still early in development.

Genotype-directed therapy

In the last decade, positional cloning and candidate-gene approaches have identified rare forms of AF with Mendelian inheritance. Probands with AF, largely in the absence of structural heart disease, exhibit mutations within genes encoding cardiac ion channels¹¹³⁻¹¹⁵, gap junction proteins¹¹⁶, atrial natriuretic peptide (ANP)¹¹⁷ and nucleoporins (NUP155)¹¹⁸. For affected individuals, these mutations confer large effect sizes and might therefore permit gene-directed pharmacotherapy, although this approach has not yet been tested.

From a population perspective, the goal is to elucidate common genetic variants identifying AF-susceptible individuals or AF subtypes who may benefit from preventive interventions or differentially respond to therapy. Thus far, genome wide association studies have identified 14 independent genetic loci with genome-wide significance¹¹⁹. While recognizing the small effect size of individual single nucleotide polymorphisms (SNPs), genetic risk may well be clinically meaningful in the presence of additional risk factors ('two hit hypothesis')^{120, 121}. For example, an AF susceptibility allele at chromosome 4q25 (near the *PITX2* gene) is present in approximately one-third of the general population and associated polymorphisms have been independently linked to AF recurrence following antiarrhythmic drug therapy¹²², cardioversion¹²³, and catheter ablation¹²⁴ in European cohorts, though not replicated in an Asian population¹²⁵. Patients with a common β_1 adrenergic receptor polymorphism (G389R) appear more likely to respond to a rate-control strategy and require lower doses of rate-lowering medication (beta-blockers or calcium channel antagonists) compared with non-G389R carriers¹²⁶.

Other common SNPs have also been directly or inversely associated with greater prevalence of non-pulmonary vein triggers and enhanced left atrial scarring following catheter ablation¹²⁷.

Notably, a recent report from the AF-Gen consortium highlighted minimal incremental discriminatory value of polygenic AF risk scores when compared with recognised clinical risk factors for incident AF¹²⁸. Thus, there are currently insufficient data to recommend routine genetic testing in patients with AF¹²⁹, and caution must be attributed to case control studies and data mining of large registries where genotype-phenotype associations may be skewed. RCT data are currently being sought after including a randomised genotype-directed sequential crossover study of flecainide and sotalol (ClinicalTrials.gov NCT02347111) and a pre-specified genotype association sub-study of patients enrolled in the large CABANA trial (ClinicalTrials.gov NCT00911508).

Pragmatic trial design for precision AF therapy

Our current classification of AF, based on duration of episodes, belies the diverse mechanisms underlying AF initiation and maintenance. Furthermore, classical RCTs informing AF management guidelines quantify an average treatment response for a uniformly applied therapeutic strategy, when compared with placebo or standard of care, typically within unselected populations. These approaches conceal individual phenotypic characteristics and treatment effects, including potentially informative data from outlying super- or non-responders, which could inform a precision medicine approach. Pre-specified subgroup analyses are limited to high incidence subtypes that are frequently underpowered to demonstrate statistical benefit. Hence, while advances in genetics, informatics and imaging technologies will enable more refined classification and selection of patients with AF, concomitant changes in clinical trial design and accepted metrics of efficacy will likely also be needed to advance a precision medicine approach.

Envisioned future management algorithms for AF may involve comprehensive genetic, biochemical and cardiac structural (imaging) profiling alongside routine clinical and electrocardiographic assessments (**Figure 2**). These data could be integrated into electronic health records and informatics platforms, with links to clinical registries and registry-networks, preferably equipped with intelligent real-time decision support tools, to assist classification of patients into relevant, small incidence, subtypes based on their dominant or relative contributions of different AF mechanisms. Extrapolating from principles of patient-centric trials in oncology¹³⁰, all patients eligible for treatment may be presented with one of several rate or rhythm control treatment options within a single trial or network of trials (**Figure 2**). Where a reversible cause or suitable biomarker is available, therapies may be cause-specific and biomarker-guided. Unselected new therapeutic strategies may still be investigated for incremental benefit in single-arm, staged designs. Where no reversible cause is recognised, novel therapies may be compared with standard of care, in which patients are still monitored to provide opportunities for biomarker discovery and validation. A majority of AF patients screened would be assigned to a treatment option within a trial, thereby maximising therapeutic development while minimising the psychosocial, financial and time costs of screening failures. Large registries may also be used as a cost-effective and convenient platform for large-scale, simple clinical trials^{8, 131}.

With respect to data analyses, traditional interim analyses may be substituted by adaptive trial design features to allow modification of trial elements (e.g. sample size, randomisation ratio, number of treatment arms) based on accumulated results, with full control of type I error¹³². Greater use of repeated measures (e.g. serial imaging, assessment of PROMs) would allow detection of temporal changes in disease characteristics and treatment responses for individual patients. Consideration should be given to selecting endpoints most appropriate to the patients under study. Restoration

and maintenance of sinus rhythm may remain the desired outcome for symptomatic patients with isolated paroxysmal AF, whereas in patients with AF and heart failure, delineating global determinants of impaired functional capacity may be of greater clinical value. Increasingly, remote or implantable monitoring technologies can be utilised to quantify AF burden as well as symptomatically 'silent' AF recurrences following intervention. The association between device-detected AF and adverse outcomes, including stroke risk, is an active area of investigation and the field awaits the definition of an acceptable threshold of AF burden, if any¹³³. Finally, recent literature has highlighted the shifting epidemiology of AF, with heart failure now representing the most common incident non-fatal event after AF diagnosis¹³⁴. Moving forward, it is incumbent on AF registries and long-term intervention trials to include incident HF as a legitimate endpoint alongside mortality and stroke rates.

Ultimately, successful and integrated development of AF precision medicine strategies will require wide collaboration between investigators, industry and regulatory groups to ensure standardisation of practice, broad access to therapeutics in development, and adequate scientific rigour to support clinical translation.

Conclusion

Several decades of concerted research has increased our understanding of the mechanisms underlying AF and given rise to novel therapeutic strategies. Systematic validation of these in RCTs has reliably informed evidence-based practice and produced broad improvements in health outcomes. However, significant evidence gaps remain in our understanding of the AF substrate and traditional RCTs designed for the 'average' patient incompletely address the complexity of the AF population. In realising the value of individual patient characteristics and treatment responses, the concept of precision

medicine offers exciting opportunities to accelerate clinical translation of targeted interventions designed to treat and prevent AF.

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Figure legends

Figure 1. Atrial fibrillation ablation strategies. Schematic posterior view of the left and right atria with example ablation lesion sets. **A.** Pulmonary vein isolation with circumferential ablation lesions and **B.** Linear lesion sets including: a) roof line, b) mitral isthmus line, c) anterior linear lesion, d) cavotricuspid isthmus line, e) additional linear lesions between the superior and inferior pulmonary veins, f) electrical isolation of the superior vena cava. **C.** Common sites of ablation when complex fractionated electrograms are targeted. **D.** Sites of the major left atrial autonomic ganglionated plexi (GP) and axons (superior left GP, inferior left GP, anterior right GP, inferior right GP, and ligament of Marshall). *IVC*, inferior vena cava; *LIPV*, left inferior pulmonary vein; *LSPV*, left superior pulmonary vein; *RIPV*, right inferior pulmonary vein; *RSPV*, right superior pulmonary vein. *Figure adapted from Calkins et al.*⁸⁷

Figure 2. Proposed algorithm for personalised atrial fibrillation care. *Management/clinical trial allocation' *adapted from Biankin et al.*¹³⁰

Table 1. Clinical studies of lifestyle modification for atrial fibrillation prevention

Study	Design	Patient population	N	Intervention	Comparator	Endpoints	Follow-up (mean±SD)	Outcomes
Abed et al. ²⁵	RCT Single-blind Single-centre	Obese (BMI>27kg/m ²). PAF (58%) or persistent AF Mean age 60±10y 67% male	150	Physician-led weight loss and RFM programme	Self-directed general lifestyle measures	<u>Primary:</u> Symptom burden and severity <u>Secondary:</u> AF burden and echocardiographic parameters	Control 12.0±4.0 months Intervention 12.9±2.6 months	RFM resulted in greater weight loss (from mean BMI 32.8kg/m ² to 27.2kg/m ²) and improved cardiometabolic profile, reduced symptom burden and severity, decreased AF burden, LA area and LV wall thickness
ARREST-AF Pathak et al. ²⁶	Prospective cohort Single-centre	Obese (BMI≥27kg/m ²). ≥1 cardiometabolic risk factor Initial catheter ablation Symptomatic PAF (60%) or persistent AF despite anti-arrhythmic therapy Pooled mean age 58±10y 64% male	149	Physician-led weight loss and RFM programme	Self-directed general lifestyle measures	<u>Primary:</u> Recurrent AF <u>Secondary:</u> AF frequency, duration, and symptom burden	Control 42.1±14.2 months Intervention 1.6±12.5 months	RFM resulted in greater weight loss and improved cardiometabolic profile, greater freedom from AF after a single or multiple ablation procedures, and greater reduction in AF frequency, duration, symptoms and symptom severity.
LEGACY Pathak et al. ²⁷	Prospective cohort Single-centre	Obese (BMI≥27kg/m ²). PAF (53%) and persistent AF Weight loss categorized as: ≥10% (group 1), 3-9% (group 2), <3% (group 3) Pooled mean age 63±11y 66% male	825	Physician-led weight loss and RFM programme	n/a	<u>Primary:</u> AF burden <u>Secondary:</u> Echocardiographic parameters	34±15 months	Greatest improvement in AF burden and symptom severity in group 1. Greatest benefit in patients with stable (vs. fluctuating) weight after initial weight loss. Groups 1 and 2 had reductions in LA area and LV wall thickness.

CARDIO-FIT Pathak et al. ³¹	Prospective cohort	<p>Obese (BMI≥27kg/m²) and able to undergo exercise training.</p> <p>Symptomatic PAF (53%) or persistent AF</p> <p>Baseline CRF categorized as low (<85% predicted METs), adequate (86-100% predicted METs), high (>100% predicted METs)</p> <p>Improvement in CRF categorized as ≥2METs vs. <2METs</p> <p>Pooled mean age 60±11y</p> <p>48%male</p>	308	Physician-led weight loss, RFM, and tailored exercise programme	n/a	<p><u>Primary:</u></p> <p>Freedom from AF and symptom burden</p> <p><u>Secondary:</u></p> <p>echocardiographic parameters</p>	49±19 months	<p>Greatest ablation and drug-free AF-free survival and reduction in symptoms in patients with high CRF (vs. low or adequate CRF).</p> <p>Greater reduction in AF burden and symptom severity in patients with ≥2METs gain in CRF (vs. <2METs).</p> <p>More favourable reductions in LA area and LV wall thickness in patients with ≥2METs gain in CRF (vs. <2METs).</p>
Malmo et al. ³²	RCT Single-blind Single-centre	<p>Paroxysmal (57%) or persistent AF, able to undergo exercise training.</p> <p>Pooled mean age 59±8y</p> <p>82% male</p>	51	Aerobic interval training	Self-directed usual exercise regimen	<p><u>Primary:</u></p> <p>AF burden</p> <p><u>Secondary:</u></p> <p>VO₂, echocardiographic parameters, lipid status, quality of life, AF-related hospital admissions.</p>	4 weeks	Aerobic interval training was associated with reduced AF burden, improvement in AF symptoms, peak VO ₂ , quality of life, and LA and LV function.

CRF, cardiorespiratory fitness; LA, left atrium; LV, left ventricular; METs, metabolic equivalents; PAF, paroxysmal AF; RCT, randomised controlled trial; RFM, risk factor management; VO₂; oxygen uptake.

Table 2. Randomised clinical trials of catheter ablation for atrial fibrillation

Study	Design	Patient population	N	Intervention	Comparator	Endpoints	Follow-up (mean±SD)	Outcomes
1st line therapy								
RAAFT-1 Wazni et al. ¹³⁵	RCT Multicentre	Symptomatic PAF (96%) and persistent AF Pooled mean age 53±8y % male not reported	70	PVI	AAD	<u>Primary:</u> Recurrent AF <u>Secondary:</u> Hospitalisation, quality of life	12 months	87% PVI vs. 37% AAD group freedom from AF recurrence 9% PVI vs 54% AAD hospitalisation Greater improvement in quality of life with PVI
MANTRA-PAF Cosedis Nielson et al. ⁵⁴	RCT Multicentre	Symptomatic PAF Pooled mean age 55±10y 70% male	294	PVI+ additional ablation at operator's discretion	AAD	<u>Primary:</u> Burden of AF <u>Secondary:</u> Freedom from AF, symptoms, time to first recurrence, quality of life	24 months	No significant difference in cumulative burden of AF 9% PVI vs 18% AAD AF burden at 24 months 85% PVI vs. 71% AAD freedom from any AF recurrence Quality of life improved equally in both groups.
RAAFT-2 Morillo et al. ⁵²	RCT Multicentre	Symptomatic PAF Pooled mean age 55±10y 76% male	127	PVI + additional ablation at operator's discretion	AAD	<u>Primary:</u> Recurrent AF <u>Secondary:</u> Symptomatic AF, quality of life	24 months	45% PVI vs. 28% AAD freedom from AF recurrence 53% PVI vs 41% AAD freedom from recurrent symptomatic AF Quality of life improved equally in both groups
2nd line therapy								
A4 Study Jais et al. ⁵¹	RCT Multicentre Superiority	Symptomatic drug- refractory PAF Pooled mean age 51±11y 84% male	108	PVI+ additional ablation at operator's discretion	AAD	<u>Primary:</u> Recurrent AF at 3-12 months, freedom from AF after ≤3procedures,	12 months	Greater freedom from AF in the ablation (89%) vs AAD (23%) group. More favourable symptom scores, exercise capacity, and quality of life in the ablation group.

						changes in AAD within 3 months <u>Secondary:</u> Time to recurrent AF, quality of life, exercise capacity, AF burden		
APAF study Pappone et al. ¹³⁶	RCT Single-centre	Symptomatic drug-refractory PAF Pooled mean age 56±10y 67% male	198	PVI+ additional ablation at operator's discretion	AAD	<u>Primary:</u> Freedom from AF at 12 months	12 months	Greater freedom from AF in the ablation vs. AAD group (93% vs. 35% at 1 year). Fewer cardiovascular hospitalisations in ablation group.
Wilber et al. ⁵⁵	RCT Multicentre	Symptomatic drug-refractory PAF Pooled mean age 56y (95%CI 54.1-57.4) 67% male	167	PVI+ additional ablation at operator's discretion	AAD	<u>Primary:</u> Freedom from symptomatic AF; safety <u>Secondary:</u> Freedom from any atrial arrhythmia, quality of life	PVI group: median 12.5 (95%CI 11.9-13.1) months AAD group: median 14.3(95%CI 9.4-15.5) months	Greater freedom from AF in the ablation vs. AAD group (66% vs. 16% at 9 months). Greater freedom from any atrial arrhythmia in the ablation vs. AAD group (70% vs. 19% at 9 months). More favourable quality of life scores in the ablation vs. AAD group.

AAD, antiarrhythmic drug therapy; PVI, pulmonary vein isolation.

Table 3. Seminal clinical trials of novel techniques for atrial fibrillation ablation

Study	Design	Patient population	N	Intervention	Comparator	Endpoints	Follow-up (mean±SD)	Outcomes
Contact force								
TOCCASTAR Reddy et al. ⁵⁹	RCT Multicentre Non-inferiority	Symptomatic drug-refractory PAF Pooled mean age 60±10y 65% male	295	Ablation with CF-sensing catheter	Ablation with non-CF catheter	Primary: Efficacy (acute PVI; freedom from symptomatic AF off AAD); safety Secondary: Optimal vs. non-optimal CF; quality of life	12 months	Efficacy: 67.8% CF vs. 69.4% control (non-inferiority endpoint met) Efficacy within stratified CF arm: 75.9% optimal CF, vs. 58.1% non-optimal CF Serious adverse events in 2.0% CF vs. 1.4% control (safety non-inferior end point met)
Cryoablation								
FIRE and ICE Kuck et al. ¹³⁷	RCT Multicentre Non-inferiority	Symptomatic drug-refractory PAF Pooled mean age 60±10y 61% male	750	Cryoablation	Standard ablation	Primary: Efficacy (time to first recurrence of arrhythmia, AAD use or repeat ablation); safety Secondary: Quality of life	18 months	Non-inferiority efficacy and safety endpoints met No significant difference among the four types of ablation catheters.
CFAE								
STAR AF Verma et al. ¹³⁸	RCT Multicentre Superiority	Symptomatic drug-refractory PAF (65%) or persistent AF Pooled mean age 57±10y 74% male	100	1. CFE alone 2. CFE+PVI	PVI alone	Primary: Freedom from AF Secondary: Freedom from any arrhythmia, complications, procedural characteristics	12 months	PVI+CFE had the highest freedom from AF vs PVI alone or CFE alone. CFE alone had the lowest success rate after one- or two-procedures, and a higher incidence of repeat procedures required.
STAR AF II	RCT	Symptomatic	589	1. PVI +	PVI alone	Primary: Freedom	18 months	No significant difference in outcomes

Verma et al. ⁷³	Multicentre	drug-refractory persistent AF Pooled mean age 60±9y 78% male		CFAE 2. PVI + linear ablation		from atrial arrhythmia after index ablation off AAD or repeat ablation <u>Secondary:</u> Freedom from any AF after 2 procedures, freedom from any atrial arrhythmia, AAD use, complications, procedural characteristics		between groups after a first or repeat procedure. PVI alone tended to be associated with shorter procedure and radiation times.
Rotor modulation								
CONFIRM Narayan et al. ⁷⁹	RCT Single-centre	Symptomatic PAF (28%) or persistent AF Pooled mean age 62±8y 95% male	92	FIRM-guided ablation +conventional ablation	Conventional ablation: WACA (+LA roof line for persistent AF cases)	<u>Primary:</u> Acute procedural termination of AF, long-term freedom from AF, safety <u>Secondary:</u> Freedom from AF following first ablation, freedom from all atrial arrhythmias	Median 22 months	Acute procedural endpoint achieved in 86% FIRM-guided vs. 20% conventional ablation cases Total ablation time the same for both groups Greater freedom from AF for FIRM-guided (82%) vs. conventional (45%) after a single procedure Safety: no significant difference in complication rates between groups.
Dominant frequency ablation								
RADAR AF Atienza et al. ⁷⁵	RCT Multicentre Single-blind Non-inferiority	Symptomatic PAF (50%) and persistent AF Pooled mean age 54±10y 80% male	232	PAF: HFSA Persistent AF: PVI	PAF: PVI Persistent AF: PVI+HFSA	<u>Primary:</u> Freedom from AF at 6 months post index ablation <u>Secondary:</u> Freedom from AF/AT at 6 and 12 months; periprocedural complications; adverse events; quality of life.	12 months	<u>PAF:</u> HFSA was non-inferior to PVI at 12 months (failed to achieve non-inferiority at 6 months). Fewer serious adverse events in the HFSA group. <u>Persistent AF:</u> No significant difference between HFSA and PVI for primary or secondary endpoints, but a trend towards more serious adverse events with PVI+HFSA.

Adenosine								
ADVANCE Macle et al. ⁶¹	RCT Multicentre Superiority	Symptomatic AF undergoing ablation Pooled mean age 60±10y 71% male	534	PVI + adenosine guided dormant conduction ablation	PVI alone	<u>Primary:</u> Time to first recurrence of atrial tachyarrhythmia after index ablation or repeat ablation <1 year <u>Secondary:</u> Time to first recurrence of atrial tachyarrhythmia; AAD use; periprocedural complications	12.2±1.4 months	Adenosine unmasked dormant PV conduction in 53% of patients. Adenosine guided ablation associated with greater freedom from AF (69% vs. 42%). Similar occurrence of serious adverse events in each group.
UNDER-ATP Kobori et al. ⁶²	RCT Multicentre Superiority	Symptomatic PAF or persistent AF undergoing first-time ablation Pooled mean age 63.3±10y 74% male	2113	PVI + adenosine guided dormant conduction ablation	PVI alone	<u>Primary:</u> Recurrent atrial tachyarrhythmia <1 year <u>Secondary:</u> Repeat ablation for any atrial tachyarrhythmia; periprocedural complications	Median 384 days (interquartile range 366-450 days)	No significant difference in the incidence of recurrent atrial tachyarrhythmias at 1 year between the 2 groups.
Ganglion plexi ablation								
Katritsis et al. ⁷⁸	RCT 2 centre	Symptomatic PAF Pooled mean age 56±8y 66% male	242	1. PVI + ganglion plexi ablation 2. Ganglion plexi ablation alone	PVI alone	<u>Primary:</u> Freedom from AF/AT after index ablation <u>Secondary:</u> RF delivery time, fluoroscopy time, adverse events	2 years	Addition of GP ablation to PVI conferred a significantly higher success rate compared with either PVI or GP alone in patients with PAF.

AAD, antiarrhythmic drug; AT, atrial tachycardia; CF, contact force; CFAE, contact force atrial electrograms; FIRM, focal impulse and rotor modulation; HFSA, high frequency source ablation; PVI, pulmonary vein isolation; WACA, wide area circumferential ablation.

Table 4. Randomised controlled trials of atrial fibrillation ablation in patients with heart failure

Study	Design	Patient population	N	Intervention	Comparator	Endpoints	Follow-up	Outcomes
PABA-CHF Khan et al. ⁹⁰	RCT Multicentre	Symptomatic HF (EF≤40%) and PAF (49%) or persistent AF. LVEF 27-35% NYHA class 2-3 Pooled mean age 60±8y 91% male	81	PVI + additional ablation at operator's discretion	AV node ablation with biventricular pacing	Primary: Composite of improvement in EF, 6MWD, QOL score vs. baseline Secondary: Freedom from AF, LA dimensions	6 months	Significance criteria for the primary composite endpoint met. Improved QOL and 6MWD in the ablation group.
MacDonald et al. ⁹²	RCT Multicentre	Symptomatic HFrEF (EF<35%), persistent AF LVEF 36-41% NYHA class 2-4, mean 2.9 Pooled mean age 63±7y 78% male	41	PVI + linear ablation + CFAE ablation + medical therapy	Medical therapy: HF therapy (+digoxin if HR>80bpm)	Primary: EF by CMR Secondary: EF by radionuclide imaging, 6MWD, NT-proBNP, quality of life, other CMR indices	6 months	No significant difference in EF improvement between the groups No difference in QOL and 6MWD between groups.
ARC-HF Jones et al. ⁸⁸	RCT Single centre	Symptomatic HFrEF (EF≤35%) and persistent AF LVEF 21-32% NYHA class 2-4, mean 2.4 Pooled mean age 63±9y 87% male	52	PVI+ linear ablation +CFAE ablation	Rate control	Primary: Change in peak VO ₂ at 12 months Secondary: Quality of life, BNP, 6MWD, EF	12 months	Improved QOL and peak VO ₂ (+3ml/kg/min difference) and reduced BNP in the ablation group. Non-significant improvements in 6MWD and EF
CAMTAF Hunter et al. ⁹¹	RCT Single centre	Symptomatic HFrEF (EF<50%) and persistent AF LVEF 32-40% NYHA class 2-4, mean 2.7 Pooled mean age 57±11y 87% male	50	PVI+ additional ablation at operator's discretion	Rate control	Primary: EF at 6 months, Secondary: % reduction in LVESV at 6 months, peak VO ₂ , BNP, NYHA class, quality of life	6 months	Improved QOL, NYHA class, peak VO ₂ and reduced BNP in the ablation group.

AATAC Di Biase et al. ⁹³	RCT Multicentre	HFrEF (EF≤40%), persistent AF, and an implanted device (CRTD/ICD) LVEF 29±5% NYHA class 2-3 Pooled mean age 61±10y 74% male	203	PVI+ additional ablation at operator's discretion	Amiodarone	<u>Primary:</u> Freedom from AF, <u>Secondary:</u> All-cause mortality, unplanned AF- and HF-related hospital admissions, change in LVEF, 6MWD, quality of life	2 years	Greater freedom from AF in the ablation group (70%) vs amiodarone group (34%) after 2 years. Improved QOL, exercise capacity, reduced unplanned hospital admissions and reduced mortality in the ablation group.
<i>Trials in progress</i>								
CASTLE AF Marrouche et al. ⁸³	RCT Multicentre	Symptomatic HFrEF and AF https://clinicaltrials.gov/ct2/show/NCT00643188	420	PVI+ additional ablation at operator's discretion	Conventional therapy	<u>Primary:</u> All-cause mortality or worsening HF requiring unplanned hospitalisation	Minimum 3 years	
RAFT AF Tang, Wells et al.	RCT Multicentre	Symptomatic HFrEF or HFpEF (NYHA class 2-3) PAF or persistent or long-term persistent AF https://clinicaltrials.gov/ct2/show/NCT01420393		PVI+ additional ablation at operator's discretion	Rate control	<u>Primary:</u> Composite of all-cause mortality and hospitalization for heart failure	5 years	
EAST Kirchhof et al.	RCT Multicentre	Symptomatic PAF or persistent AF. Includes patients with HFrEF (EF<50%) https://clinicaltrials.gov/ct2/show/NCT01288352		Early rhythm control: 1. AAD 2. PVI 3. Combined AAD + PVI	Usual care: rate control as 1 st line; rhythm control for patients with refractory symptoms	<u>Primary:</u> A composite of cardiovascular death, stroke, or hospitalization due to worsening of heart failure or acute coronary syndrome	8 years	

CABANA Packer et al.	RCT Multicentre	Symptomatic PAF, persistent or longstanding persistent AF. Includes patients with HFrEF and HFpEF https://clinicaltrials.gov/ct2/show/NCT00911508		PVI + additional ablation at operator's discretion	AAD or rate control	<u>Primary:</u> A composite of total mortality, disabling stroke, serious bleeding or cardiac arrest		
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BNP, brain natriuretic peptide; EF, ejection fraction; LVESV, left ventricular end systolic volume; NYHA, New York Heart Association class; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; VO₂, peak exercise oxygen consumption.