

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



Rosita Zakeri, MBChB, PhD,* David R. Van Wagoner, PhD, FHRS,[†] Hugh Calkins, MD, FHRS,[‡] Tom Wong, MD, FRCP,* Heather M. Ross, DNP, ANP-BC, FHRS,[§] E. Kevin Heist, MD, PhD, FHRS,[¶] Timothy E. Meyer, PhD,^{||} Peter R. Kowey, MD, FHRS,** Robert J. Mentz, MD,^{††} John G. Cleland, MD,* Bertram Pitt, MD,^{‡‡} Faiez Zannad, MD, PhD,^{§§} Cecilia Linde, MD, PhD, MS^{¶¶}

From the *Royal Brompton & Harefield NHS Trust, London, United Kingdom, [†]Cleveland Clinic, Cleveland, Ohio, [‡]Johns Hopkins Hospital, Baltimore, Maryland, [§]Arizona State University, Phoenix, Arizona, [¶]Massachusetts General Hospital, Boston, Massachusetts, ^{||}Boston Scientific, St Paul, Minnesota, ^{**}Lankenau Heart Institute and Jefferson Medical College, Wynnewood, Pennsylvania, ^{††}Duke Clinical Research Institute, Durham, North Carolina, ^{‡‡}University of Michigan, Ann Arbor, Michigan, ^{§§}INSERM, Centre d'Investigations Cliniques Plurithématique 1433, INSERM U1116, Université de Lorraine, CHRU de Nancy, F-CRIN INI-CRCT, France, and ^{¶¶}Karolinska Institute, Stockholm, Sweden.

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 personalized 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 of 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 Forum in Washington, DC, December 3–5, 2015.

KEYWORDS Atrial fibrillation; Randomized controlled trial; Prevention; Ablation; Personalized medicine

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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 surveillance.^{1–3} 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 hospitalized twice as often as those without AF, and the incremental costs attributable to AF-related care present important challenges for existing health care systems.^{4–6} Accordingly, the treatment and prevention of AF have become key priorities for clinical and translational research efforts.^{7–9}

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, and cardiac and noncardiac

conditions further contribute to a favorable atrial substrate.¹² Moreover, surgical and catheter ablation techniques for AF have been at the forefront of rapid technological innovation.^{4,5,13} Central to these endeavors, integration of basic science and observational findings into a defined therapeutic strategy and its uniform application and validation within a randomized controlled trial (RCT) has remained the benchmark for safety and efficacy required for any change in clinical practice.¹⁴

Currently, however, there are insufficient high-quality and generalizable RCT data to support the needs of “real-world” clinical practice.¹⁵ Broadly speaking, prevailing challenges with respect to AF management include (1) limited RCT evidence relating to lifestyle and risk factor modification, prediction, and prevention of AF; (2) diverse ablation practices, and underrepresentation of long-term and patient-reported outcomes within existing AF intervention trials; and (3) evolving demands for design and validation of personalized 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 along with recently reported RCTs. Note that AF-related stroke prevention and anticoagulation, although essential to AF management, are beyond the scope of this article.

AF prevention trials

Primary and secondary AF prevention

Epidemiologic studies have described an array of potentially modifiable risk factors for AF, including hypertension, obesity, metabolic syndrome, diabetes mellitus, obstructive sleep apnea, 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, although they are not yet widely in use.¹⁷

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 recognized 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 forward, smartphone-based ECG applications and 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 settings.^{18–20} 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 risk.²¹ 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 pathologic classification. Basic research in animal models and humans has demonstrated progressive atrial electrical and structural remodeling occurring in the setting of cardiometabolic risk factors, which are thought to be responsible for AF initiation and perpetuation of AF maintenance.¹¹ Because 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 burden,²² has not been shown to reduce AF risk consistently, and no target blood pressure has been identified. Contemporary RCTs, as in clinical practice, have recognized 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 remodeling in animal models²³ (“*AF begets AF*”) also highlights the importance of early intervention.

Nonpharmacologic approaches to AF prevention

Among candidate nonpharmacologic 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 program (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 trial.²⁹ Secondary analyses did not demonstrate a reduction in AF incidence over 9 years of follow-up, although AF was not a prespecified endpoint, and the overall weight loss achieved was modest.²⁹ Conversely, in overweight and obese patients with documented paroxysmal AF, randomized to a physician-instructed low-calorie diet and exercise routine, Abed et al²⁴ reported a more significant reduction in body mass index (BMI) and improved blood pressure control at 15-month 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 advice. 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 focused cardiometabolic risk factor management program, showed consistently

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