Special Report

Prevention of Atrial Fibrillation
Report From a National Heart, Lung, and Blood Institute Workshop

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Abstract—The National Heart, Lung, and Blood Institute convened an expert panel April 28 to 29, 2008, to identify gaps and recommend research strategies to prevent atrial fibrillation (AF). The panel reviewed the existing basic scientific, epidemiological, and clinical literature about AF and identified opportunities to advance AF prevention research. After discussion, the panel proposed the following recommendations: (1) enhance understanding of the epidemiology of AF in the population by systematically and longitudinally investigating symptomatic and asymptomatic AF in cohort studies; (2) improve detection of AF by evaluating the ability of existing and emerging methods and technologies to detect AF; (3) improve noninvasive modalities for identifying key components of cardiovascular remodeling that promote AF, including genetic, fibrotic, autonomic, structural, and electrical remodeling markers; (4) develop additional animal models reflective of the pathophysiology of human AF; (5) conduct secondary analyses of already-completed clinical trials to enhance knowledge of potentially effective methods to prevent AF and routinely include AF as an outcome in ongoing and future cardiovascular studies; and (6) conduct clinical studies focused on secondary prevention of AF recurrence, which would inform future primary prevention investigations. (***Circulation*. 2009;119:606-618.**)

Key Words: atrial fibrillation ■ atrium ■ epidemiology ■ prevention ■ risk factors ■ National Heart, Lung, and Blood Institute

Atrial fibrillation (AF) is the most common arrhythmia in the United States and other developed countries. AF is associated with significant morbidity and mortality, including a 4- to 5-fold increased risk for stroke,[1,2] a doubling of risk for dementia,[3,4] a tripling of risk for heart failure,[2] and a 40% to 90% increased risk for overall mortality.[2,5] Growth in the size of the AF population and increased recognition of the morbidity, mortality, diminished quality of life, and high healthcare costs associated with AF have spurred numerous investigations to develop more effective treatments for AF and its complications. Many risk factors for AF have been described, and some promising preventive strategies have been identified. However, although AF treatment has been studied extensively, AF prevention has received relatively little attention. Over the last 10 years, PubMed has contained almost 4 times as many citations for *atrial fibrillation treatment* as for *atrial fibrillation prevention*. When *stroke* was excluded from the search, citations related to treatment outnumbered those for prevention by ≈7-fold.

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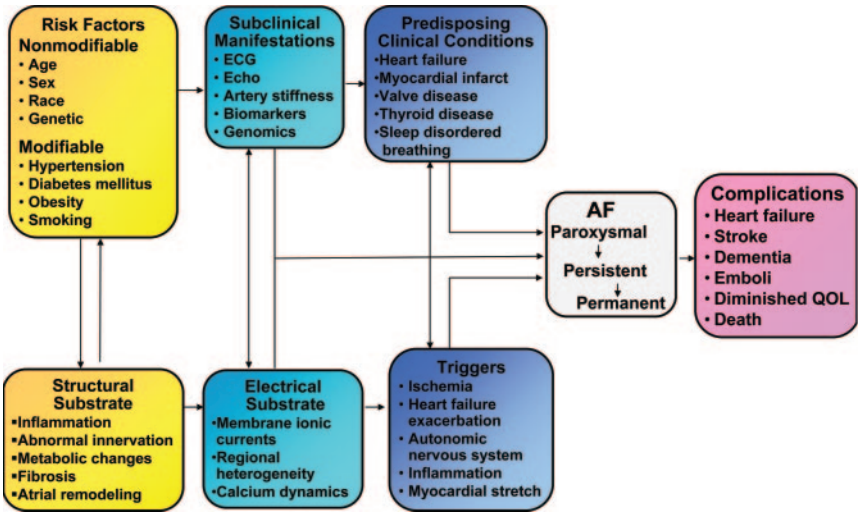

Figure. Opportunities for AF prevention. The figure depicts the conceptual model of the pathogenesis and progression to AF over the lifetime of individuals at risk. Understanding the pathophysiological contributors to AF onset will enhance opportunities for discovering effective AF prevention strategies. Risk factors and cardiovascular subclinical disease contribute to structural and electrical remodeling. Risk factors (upper yellow box) have bidirectional relations with alterations in cardiovascular structural substrates such as inflammation, fibrosis, and remodeling. Risk factors also contribute to the development of subclinical cardiovascular diseases, which can be detected by noninvasive modalities such as imaging, biomarkers, and genomics. Subclinical diseases (upper turquoise box) contribute to the development of clinical disease such as heart failure and myocardial infarction, which can precipitate AF. Similarly, structural alterations (lower yellow box) lead to electrical remodeling (lower turquoise box). Both clinical cardiovascular disease and electrical remodeling contribute to the triggers (lower blue box) that initiate AF. AF may progress to complications (pink box). The prevention of AF may occur at multiple points along the causal pathways, such as lifestyle and therapeutic interventions to prevent and treat risk factors, structural substrate alterations, subclinical perturbations, electrical remodeling, and clinical cardiovascular disease. Once AF is initiated, secondary prevention efforts will focus on preventing the development of persistent forms of AF. QOL indicated quality of life.

On April 28 and 29, 2008, the National Heart, Lung, and Blood Institute (NHLBI) convened an expert panel to recommend research directions and strategies in AF prevention for consideration by the NHLBI and the greater research community. The panel was asked to consider 3 general areas: (1) discovery of AF risk factors through the use of existing data sets; (2) identification of measures to be added to future data collection efforts in large observational studies and clinical trials; and (3) directions for basic science and clinical research on AF prevention. After deliberation regarding available data and outstanding issues, the group came to a consensus, identifying investigational gaps and developing research recommendations in the 6 high-priority areas discussed below.

The Figure illustrates the conceptual model of relevant pathways that emerged, underscoring opportunities for AF prevention, including therapeutic and lifestyle interventions that modify the risk factors; structural, electrical, and pathophysiological substrates; and clinical diseases and triggers that contribute to the initiation, progression, and complications of AF. The 6 recommendations are outlined in the Table; background information pertinent to each of the 6 recommendations follows below. The Workshop's Executive Summary is posted at http://www.nhlbi.nih.gov/meetings/workshops/prevent-af.htm.

Recommendation 1: Enhance Understanding of the Epidemiology of AF

Background

Epidemiological Considerations

Current understanding of the epidemiology of AF is based on studies of predominantly white cohorts from North America and Western Europe. The adjusted incidence and prevalence of AF roughly double for each advancing decade of life,[6–8] and, at any given age, men have an ≈50% higher incidence of AF than women.[6] At 40 years of age, the remaining lifetime risk for developing AF is ≈1 in 4 for both white men and women, and it remains as high at older ages because of the steeply increasing risk for AF with advancing age (the comparable lifetime risk in men and women is due to the greater longevity of women).[9,10] The pathophysiology underpinning the greater age-adjusted likelihood of AF in men and the increased risk with advancing age is incompletely understood.

Established risk factors for AF include cardiac conditions, such as systolic and diastolic heart failure, valvular heart disease, and myocardial infarction, and cardiovascular risk factors, such as hypertension, diabetes mellitus, obesity, and cigarette smoking.[6,8,11–13] Subclinical markers indicating increased AF risk include increased arterial stiffness[14] and echocardiographic evidence of structural heart disease, such as left atrial enlargement, left ventricular hypertrophy, and left ventricular systolic and diastolic dysfunction.[15,16] Recently identified novel markers associated with increased risk for AF include inflammatory and neurohumoral biomarkers,[17,18] obstructive sleep apnea,[19] and metabolic syndrome.[20]

Despite hundreds of publications regarding predictors of AF, it is still difficult to determine an individual's risk of developing AF in a given time frame. The roles of lifestyle factors, subclinical disease indicators, biomarkers, genomic variation, and proteomic and metabolomic measures in risk stratification for the development of AF and its complications remain uncertain. Accurate risk prediction will help to define

Table. Summary of Specific Research Recommendations for the Prevention of AF

Recommendation 1: Enhance understanding of the epidemiology of AF
Identify symptomatic and asymptomatic AF in NIH-sponsored and other appropriately designed cohort studies to better define the clinical course of AF.
Routinely collect hospital and outpatient records for AF events, particularly in studies of ethnic/racial minorities.
Develop and validate incident AF risk prediction models across cohorts.
Conduct meta-analyses of AF clinical, subclinical, and genetic markers across studies.
Recommendation 2: Improve detection of AF
Examine the feasibility, cost, and utility of existing and emerging methods and technologies to detect asymptomatic and symptomatic paroxysmal and persistent AF.
Conduct intensive surveillance methods in subsets of participants to determine the most effective and efficient methods for ascertaining and defining the clinical course of AF.
Recommendation 3: Improve noninvasive modalities for identifying key components of cardiovascular remodeling factors that promote AF
Develop methods in animals and humans to quantify noninvasively components of electrical and atrial structural remodeling in vivo.
Develop biological, genetic, fibrosis, autonomic, inflammatory, structural, and electrical remodeling markers of AF risk in human hearts in vivo.
Recommendation 4: Develop additional animal models of AF
Develop and validate new animal models, including paroxysmal and persistent AF occurring in the setting of advanced age, hypertension, and atrial remodeling, and animal models with AF originating from the thoracic veins.
Recommendation 5: Conduct secondary analyses of already-completed clinical trials and add AF end points to studies to enhance knowledge of potentially effective methods to prevent AF.
Examine AF as a secondary point in existing data sets and trials of therapeutic and lifestyle interventions.
Include AF as a prespecified secondary outcome and systematically ascertain both symptomatic and asymptomatic AF in appropriately designed future clinical trials.
Recommendation 6: Conduct studies of secondary prevention of recurrent AF
Conduct secondary intervention studies in patients with presumed early AF (eg, after the initial onset of AF) to prevent recurrent symptomatic and asymptomatic AF and include morbidity and mortality end points.
Use results of secondary prevention studies to inform future primary AF prevention studies.

the incremental value of potential new tests and markers and will aid identification of individuals most likely to benefit from primary prevention interventions.

Data from Europe and North America suggest that the age-adjusted incidence and prevalence of AF are increasing.[21–26] Based solely on the aging of the population, the prevalence of AF in the United States has been projected to increase from ≈2 to 5 million in 2000 to ≈6 to 12 million in 2050, with estimates reaching almost 16 million if the increase in age-adjusted AF incidence continues.[7,27] Aging of the population, increased surveillance, and improved survival in patients with comorbid conditions all likely contribute to the increase in AF prevalence.

Surprisingly little is known about the epidemiology, risk factors, prognosis, and temporal trends for AF in developing countries and nonwhite ethnic/racial groups in developed countries. For instance, despite the greater burden of cardiovascular disease risk factors, blacks and Hispanic Americans have been reported to have a lower prevalence and incidence of AF compared with their white, European-descent counterparts.[7,28–30] The factors that underlie racial, ethnic, regional, and international variability in the prevalence and incidence of AF have not been well characterized.

Advances in understanding the epidemiology of AF will emerge through more systematic collection of AF cases in longitudinal observational studies, through both routine questioning and more careful investigation of study participants regarding AF occurrence. Misclassification of AF can be minimized through systematic collection of hospital and outpatient medical records and ECG data for AF events, with the use of rigorous validation and adjudication methods. Existing and emerging techniques for AF detection need to be evaluated and validated to capture the burden of clinically asymptomatic AF more fully and precisely (see Recommendation 2).

Genetic Epidemiology

AF is strongly associated with heart disease and aging, yet it is clear that genetic factors also contribute to the development of AF. Data from community-based studies in Framingham and Iceland show that an individual's risk for AF is significantly increased if a first-degree relative has AF.[31,32] Heritability of AF appears even stronger in individuals with lone AF (ie, AF without structural heart disease or other known risk factors).[31–33] Since the discovery that a *KCNQ1* mutation is associated with familial AF,[34] multiple ion channel variants and a connexin 40 (*GJA5*) variant have been reported in individuals and kindreds with AF.[35–43] However, resequencing of AF patient cohorts suggests that recognized ion channel mutations account for only a small fraction of all AF cases.[44]

A genomewide association study in Icelanders with replication in 3 additional cohorts demonstrated a clear association between AF and 2 single nucleotide polymorphisms on chromosome 4q25.[45] Approximately 35% of individuals of European descent have at least 1 of the variants; the risk of AF increases by ≈1.4- to 1.7-fold per variant copy. However, neither variant is located in a gene. The closest gene is *PITX2*, a transcription factor that has critical functions in determining

cardiac left-right asymmetry and development of the myocardial sleeve extending into the pulmonary vein.[46,47] The mechanism(s) by which these noncoding variants adjacent to *PITX2* increase AF risk remain unknown.

A key challenge in translational medicine is accurate definition of intermediate phenotypes, ie, quantitative traits that precede and predispose to the emergence of disease. Identifying quantitative intermediate phenotypes will help to identify patient subsets for genomic analysis (see Recommendation 3). For complex traits like AF, dilution of genetic effects by etiologic heterogeneity and environmental influences makes validation of genotype-phenotype associations challenging.[48] Phenotyping issues are further complicated by the paroxysmal and often asymptomatic nature of AF. Further research involving meta-analyses of existing or ongoing genomewide association data, as well as of gene-gene and gene-environment interactions, is needed to better define the genetic determinants of AF. It is also important to understand the functional mechanisms by which genetic variation may lead to AF to facilitate the design of mechanism-based prevention strategies. Research is needed to evaluate the utility of genotype and sequence data in guiding AF risk prediction, prevention, and management.

Knowledge Gaps

- The role and basis of age, sex, racial/ethnic, and regional variations in AF onset and progression need to be better understood.
- The prevalence, incidence, lifetime risk, risk factors, and prognosis of AF in most ethnic/racial minority groups are not well characterized.
- There is limited understanding of secular trends in AF, such as why the prevalence and incidence of AF appear to be increasing in North America and Western Europe.
- The ability to predict AF onset in the individual is limited.
- The roles of genes (including gene-gene and gene-environment interactions) and novel biomarkers for prediction of AF are undefined.
- The mechanisms and genetic determinants of AF subphenotypes, such as AF occurring in the setting of advanced age, hypertension, heart failure, obesity, or structural heart disease, are incompletely understood.

Specific Research Recommendations 1

- Systematically and longitudinally identify both symptomatic and asymptomatic AF in National Institutes of Health (NIH)–sponsored and other appropriately designed cohort studies to better define AF risk factors and secular trends.
- Better define the clinical course of AF in longitudinal natural history studies, including intensive monitoring of high-risk subsets.
- Routinely collect hospital and outpatient AF events (eg, diagnosis, procedure codes, and ECGs), conduct routine surveillance ECGs, and query NHLBI cohort study participants about whether a healthcare provider has diagnosed AF, particularly in cohorts involving ethnic/racial minorities.
- Develop and validate incident AF risk prediction models in multiple independent cohorts.
- Conduct genetic epidemiology analyses and meta-analyses of AF genetic and biomarker data across studies to examine risk for AF, including examination of environmental interactions (eg, gene or biomarker interactions with age, sex, and obesity) and gene-gene interactions.

Recommendation 2: Improve Detection of AF

Background

Observational population-based and clinical studies suggest that AF is frequently asymptomatic and often detected only incidentally by pulse assessment[49] and/or ECG screening.[8] Even in studies of patients monitored closely after cardioversion, ≈70% of AF recurrences are asymptomatic.[50] Consequently, the true prevalence of AF in the community is unknown and almost certainly is systematically underestimated. Failure to detect AF presents a challenge to the treating clinician because the potential adverse consequences of AF, such as stroke and heart failure, may occur before AF is diagnosed. The clinical researcher also is faced with challenges because identifying effective preventive measures or therapy for AF depends on the ability to diagnose AF as a study end point. To be resource effective, one might target subsets of individuals at particularly high risk of AF onset. Inexpensive and easily used noninvasive methods for identifying and characterizing incident and recurrent AF will advance our ability to prevent AF. A better understanding of the natural history of AF, particularly how often persistent and permanent forms of AF are preceded by recurrent paroxysmal forms, may help to focus secondary prevention efforts.

Knowledge Gaps

- The frequency of and predisposing factors for symptomatic and asymptomatic AF onset and the transition from paroxysmal AF to persistent and permanent AF are incompletely understood.
- The optimal methods to detect and study the prevalence, burden, and natural history of asymptomatic AF need to be determined.

Specific Research Recommendations 2

- Carefully examine the feasibility, cost, and utility of existing and emerging methods and technologies to detect asymptomatic and symptomatic paroxysmal, persistent, and permanent AF and use promising technologies to improve detection in clinical and research settings.
- Conduct more intensive surveillance in subsets of participants to determine the most effective and efficient methods for ascertaining AF.

Recommendation 3: Improve Noninvasive Modalities for Identifying Key Components of Cardiovascular Remodeling That Promote AF

3a. Atrial Fibrosis and Remodeling

Background

Pathological structural and electrophysiological remodeling are important contributors to the development of AF.[51,52] In

the case of structural remodeling, previous studies have shown a strong association between atrial fibrosis and AF. Fibrosis is one of the sequelae of atrial injury and inflammation. Increased fibrosis, along with other contributors to AF such as aging, hypertension, and heart failure, contributes to the development and persistence of AF both in various animal models[53–56] and in human patients.[57,58] Thus, it seems reasonable to hypothesize that prevention of atrial inflammation and fibrosis may be key targets for prevention of AF.

The pathophysiological and genetic factors that promote atrial fibrosis remain incompletely understood. A variety of signaling pathways and cytokines have been implicated in the development of fibrosis,[57] including transforming growth factor-β, platelet-derived growth factor, and the renin-angiotensin-aldosterone system (RAAS). Recent studies also have demonstrated that cardiac fibroblasts undergo remodeling during rapid atrial activation.[59] Increasing atrial and pulmonary vein fibrosis promotes conduction block, reentrant excitation, and triggered activity.[55,60–63]

In addition to atrial fibrosis, electrical remodeling involving alterations in ion channel expression or function, abnormalities of metabolism, and/or structural alterations associated with increased left atrial pressure and dilation also are associated with the development of AF.[60,61,64–68] These pathological changes can facilitate the initiation and maintenance of AF by promoting ectopic triggers of arrhythmia and by facilitating reentry as a result of shortened wavelength.

Interventions such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers,[52] and dietary omega-3 fatty acids[69] show potential promise in preventing AF on the basis of analyses of clinical trials and epidemiological data. Development of more effective noninvasive imaging techniques capable of detecting and tracking atrial inflammation and fibrosis will provide new insights into the pathogenesis of AF. The ability to conduct prospective randomized trials of agents and interventions that modify atrial remodeling will be greatly advanced when it is feasible to quantitatively and serially assess atrial structural and electrical remodeling with noninvasive or minimally invasive methods. Whereas ion channel remodeling is associated with AF, the extent to which electrical remodeling causes AF versus results from AF is unclear. Specifically, some data in human myocytes suggest that ionic changes attributed to electrical remodeling may be insufficient to cause AF.[70,71] Efforts that focus on determining whether atrial remodeling can be prevented or reversed and whether interventions that suppress remodeling can reduce the burden of AF will provide critical mechanistic insights into the pathogenesis and prevention of AF.

Knowledge Gaps

- The genetics and signaling processes involved in electrical and structural remodeling in animal models and human AF remain unclear.
- There are presently no valid methods available to quantify in vivo atrial fibrosis and other components of the tissue remodeling process.

Specific Research Recommendations 3a

- Develop methods to noninvasively quantify components of atrial remodeling such as fibrosis, electrical remodeling, and inflammation within animal and human hearts in vivo. Potential methods could include the following:
  - Imaging of atrial collagen or other fibrous tissue markers, atrial inflammatory changes or mediators, key atrial metabolic substrates, and products to define the contribution of fibrosis, inflammatory changes, and metabolic abnormalities to the initiation and perpetuation of human AF.
  - Discovery of novel biological or genetic markers that detect or predict risk of synthesis or breakdown of atrial collagen.

3b. Autonomic Innervation

Background

Clinical observations suggest that often the onset of an AF episode is related to variations in autonomic tone.[72] Altered autonomic tone may be an important intermediate mechanism underlying the association of nocturnal oxygen desaturation occurring in patients with sleep apnea and incident AF.[19] In an ambulatory canine model, simultaneous discharges from the stellate ganglia and vagal nerves often precede the onset of paroxysmal atrial arrhythmias, whereas stellate ganglion and vagal ablation may help to prevent AF.[73,74] In addition to extrinsic cardiac innervation, there are intrinsic ganglionated plexi in both atria.[75] Ablation of neural elements in the autonomic ganglia at the base of the pulmonary veins may contribute to the effectiveness of pulmonary vein–directed ablation procedures.[76]

Therapies that modulate the autonomic nervous system may present novel targets for AF prevention. Preliminary studies suggest that the modulation of autonomic tone is one of the possible beneficial effects of omega-3 fatty acids in the prevention of AF.[69]

Knowledge Gaps

- The precise role of autonomic factors in clinical AF occurrence and persistence is poorly understood. Translating promising findings in the field of autonomic regulation to human AF prevention is difficult because there are no effective noninvasive methods capable of defining or monitoring autonomic innervation and function in the atria. The absence of such methods limits the ability to evaluate therapeutic strategies for AF prevention that target atrial innervation.

Specific Research Recommendations 3b

- Develop methods to locate and quantify extrinsic and intrinsic autonomic nerve structures that innervate the atria and thoracic veins and to determine their function. Useful modalities likely would involve imaging technologies that detect specific autonomic neurotransmitters or their precursors and localize them to structures of interest.

Recommendation 4: Develop Additional Animal Models of AF

Background

Work in animal models has significantly advanced our understanding of AF mechanisms and therapy,[51] but currently available affordable animal models do not capture a number of aspects important in human AF. For instance, AF incidence increases dramatically with aging in humans,[6,8] yet most investigators have used juvenile or adult rather than older animals to study AF mechanisms. Similarly, hypertension is commonly associated with human AF.[6,8,14] However, there are only limited studies of hypertension-related AF in clinically relevant animal models, and there is a lack of clarity on the mechanisms by which hypertension and other predisposing pathology (such as stretch, fibrosis, and humoral factors) may interact with thoracic veins to cause AF.

There are also species differences in the atrial substrate predisposing to AF. Whereas thoracic veins such as pulmonary veins, vein of Marshall, and superior vena cava play important roles in the initiation and maintenance of human AF, there are relatively few animal models of AF originating from thoracic veins. There is also varying atrioventricular conduction and ventricular rate response to AF among different animal species.[77] Additional examples of species-related differences include AF-induced remodeling of atrial mitochondria and gap junctions.[78] Species variability could produce differences in electrophysiological parameters accompanying AF among different animal models.[79] It is important to develop animal models that better simulate human pathobiology of AF to determine the basic mechanisms by which risk factors lead to manifest disease. Appropriate animal models also will assist in conducting valid preclinical testing of strategies that might lead to effective AF prevention.

Knowledge Gaps

- There is a lack of animal models of age-related AF.
- There are no animal models that mimic AF associated with hypertension.
- There are no animal models that adequately reproduce the pathophysiology of clinically occurring paroxysmal AF originating from the thoracic veins.

Specific Research Recommendations 4

- Develop and validate new animal models to closely reflect or "recreate" the pathobiology of important human AF subtypes, permitting study of underlying mechanisms and facilitating critical evaluation of novel prevention strategies. Important components of this goal include the following:
  - For age-related models: the identification of affordable animal models in which physiological aging is quantifiable and AF predilection increases with advancing age similar to humans; dissemination of the models to interested investigators; development of tools to assess underlying mechanisms; assessment of therapeutic interventions that affect these mechanisms; and validation of the relevance of the mechanisms to human aging and human AF prevention.
  - For hypertension-related models: the evaluation of AF occurrence and vulnerability in existing animal models of hypertension; the clarification of mechanisms associating hypertension with AF in these models; the comparison of pathophysiology in these models with AF features in hypertensive patients; and an evaluation of the efficacy of antihypertensive therapy in preventing hypertension-associated AF.
  - For paroxysmal thoracic vein activation and atrial remodeling–related AF: development of animal models that exhibit frequent self-limited paroxysms of AF originating in thoracic vein sources; assessment of the underlying mechanisms; defining the relation between the features of these animal models and clinical AF; and identifying mechanism-based therapeutic approaches capable of suppressing AF paroxysms.
  - Other relevant models that warrant development include AF related to atrial ischemia, left atrial enlargement/dysfunction, and ventricular diastolic dysfunction.

Recommendation 5: Conduct Secondary Analyses and Add AF End Points to Studies to Enhance Knowledge of Potentially Effective Methods to Prevent AF

Background

Observational data suggest that some lifestyle habits, dietary variables, and medications may be associated with lower AF rates (see Background sections of Recommendation 1: Epidemiology and Recommendation 3: Atrial Fibrosis). Further clues to AF prevention may be gleaned from ongoing and completed trials that collected AF data, even if AF was not the trial focus. For instance, in a meta-analysis of clinical trial data from >56 000 patients in studies of heart failure, hypertension, and myocardial infarction, RAAS inhibitors were associated with a 28% reduction in new-onset AF.[52] Similarly, a meta-analysis that included 3557 patients enrolled in randomized statin therapy trials showed a 61% reduction in risk of clinically detected incident AF.[80] In addition, the Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery (ARMYDA-3) trial found that initiation of a statin reduced in-hospital AF after elective cardiac surgery from 57% (placebo-treated patients) to 35%.[81] The mechanisms by which statins reduce AF onset are uncertain, and diverse mechanisms have been proposed, including anti-inflammatory or antioxidant properties, enhanced endothelial function, and reduced neurohormonal activation.[82,83] Finally, a meta-analysis of β-blockers in heart failure showed a 27% risk reduction for incident AF.[84] However, no effect of β-blockers on AF as an adverse event was found in the SENIORS study, which included patients aged ≥70 years.[85] It is uncertain if the lack of efficacy in the SENIORS study suggests that there is a finite window in terms of age or comorbidity for a therapeutic impact on the prevention of AF.

There are multiple challenges to examining existing clinical trial data. Frequently, AF has not been prespecified as a primary or secondary end point. Hence, AF occurrence is not systematically collected. Post hoc AF analyses likely ascertain only the most severe or symptomatic cases of AF. Furthermore, without primary access to and review of ECGs and hospital records, there may be nonrandom misclassification of AF and its treatments, introducing biases that are difficult to overcome in post hoc analyses.

In evaluating data from trials of conditions other than AF, the mechanisms of benefit leading to AF reduction may be difficult to determine. For instance, because AF was not a primary end point, data that might shed light on mechanisms outlined in Recommendation 3, such as measures of atrial remodeling for RAAS inhibitors, anti-inflammation, antineurohormonal activation for statins, or autonomic regulation for β-blockers, were not systematically ascertained. In addition, it is challenging to determine whether medication efficacy occurs via direct or indirect mechanisms. For example, the potential efficacy of RAAS inhibitors may be due directly to diminished atrial fibrosis; alternatively, patient benefit may accrue from optimizing treatment of the underlying heart failure.

To gain insights into potential primary prevention therapies, AF should be specified as a secondary end point in ongoing clinical cardiovascular trials. Systematic efforts to collect AF events might include surveillance questions regarding the occurrence of AF, examining pulse rate and regularity, obtaining ECGs more frequently, and systematic review of medical encounters and hospital records. Substudies intensively monitoring participants considered at high risk of AF (Recommendation 1), with methods outlined in Recommendations 2 and 3, will maximize opportunities for gaining pathophysiological insights into AF initiation.

Because most of the studies investigating the prevention of new-onset AF have been secondary analyses, definitive evidence is lacking about which classes of cardiovascular drugs are truly effective for prevention and in which patient subgroups. Still, given the wealth of information available in completed large clinical trials—including those funded by the NHLBI—in heart failure, coronary disease, hypertension, obesity, and other conditions with a high AF risk, similar analyses of existing published and unpublished data may provide better guidance for the implementation of large-scale prevention trials.

Knowledge Gaps

- The available AF prevention information is based largely on post hoc analyses of existing data. Neither atrial remodeling nor AF incidence end points are available as primary goals of most existing clinical trials.
- It is unknown whether observational data on the associations between lifestyle habits (eg, weight loss or increased physical activity) and AF can be translated into effective preventive methods.
- Data from existing randomized clinical trials that may have ascertained AF events have not been fully exploited to understand the potential of a variety of therapeutic maneuvers for AF prevention.
- There is a lack of adequate AF monitoring in relevant clinical trials of populations at risk for AF.

Specific Research Recommendations 5

- Build on existing data from clinical trials and cohorts by examining existing and future data that systematically include AF as a prespecified outcome.
- Prespecify systematic ascertainment of both symptomatic and asymptomatic AF in NIH and other appropriately designed clinical trials not specifically focused on AF, including inpatient and outpatient diagnostic codes and hospital and outpatient surveillance ECGs.

Recommendation 6: Conduct Studies of Prevention of Recurrent AF

Background

Randomized clinical trials with mortality end points are widely considered the gold standard for evidence-based recommendations for clinical care, and such trials have been conducted to address the treatment and management of established AF. The prevention of a first episode of AF in patients at high risk for the rhythm is considered primary prevention. Impediments to the successful conduct of a primary prevention trial for AF include difficulties identifying groups at sufficiently high risk, the time necessary to achieve an adequate number of relevant end points, incomplete understanding of the fundamental mechanisms underlying AF initiation and perpetuation, the lack of clearly defined interventions for testing, and difficulty distinguishing the impact of an intervention on AF development directly versus via effects on other forms of heart disease or comorbidities. For example, preventive interventions aimed at avoiding or reversing obesity might favorably affect both atrial size and inflammation and delay AF onset. However, an obesity treatment trial aimed at AF prevention would influence many end points, such as myocardial infarction and heart failure, which themselves predispose to AF. In addition, the prime candidates for inclusion in an AF primary prevention study would be individuals at highest risk for AF onset. However, such individuals often have hypertension and heart failure and thus have other indications for the currently available medications likely to be most effective at preventing AF onset, RAAS and statin drugs. Hence, randomized controlled trials to test strategies (pharmaceutical or lifestyle-modifying interventions) for primary prevention of AF have not been performed thus far and would likely be extremely large and expensive.

Risk factors for the transition from paroxysmal to persistent or permanent forms of AF may be similar to those predisposing to incident AF,[86] but effective approaches for secondary prevention (delaying recurrence after an initial AF episode or delaying progression from paroxysmal to persistent or permanent AF) have not yet been identified. Implementing secondary prevention shortly after the first episode of AF might be expected to be particularly effective in abolishing further episodes because progressive fibrosis and other structural changes that occur with longstanding AF may make the arrhythmia

difficult or impossible to suppress.[57,58] However, the aforementioned challenges in detecting asymptomatic AF add to the complexity of secondary prevention trials, particularly by making it difficult to identify study candidates with a first presentation of AF.

Inclusion of "hard" end points, including mortality and stroke, is important for studies of AF prevention because of the known dissociation between rhythm control and mortality risk in trials involving antiarrhythmics for ventricular tachycardia.[87] Most AF trials have shown a lack of correlation between rhythm control and mortality. The NHLBI-sponsored Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM, NCT00000556)[88] trial established rate control as an acceptable alternative to rhythm control (using current antiarrhythmic therapies and cardioversion) as a primary therapeutic option. The lack of superiority of rhythm control compared with rate control was recently supported in patients with heart failure (NCT00597077),[89] an AF subgroup who might have been expected to particularly benefit from maintenance of sinus rhythm. Meta-analyses of rate versus rhythm control studies serve as reminders that secondary AF prevention studies must examine end points aside from the occurrence of symptomatic AF.[90,91] Furthermore, reducing the risk of future episodes of arrhythmia is not known to obviate the need for chronic anticoagulation in patients at risk for stroke.[88]

The panel submits that a secondary prevention trial aimed at patients having experienced a first detected AF event represents the most feasible strategy for addressing prevention of AF at present. Successful secondary prevention trials would serve as important steps toward the design and implementation of larger-scale primary prevention trials. Given the disappointing performance of traditional antiarrhythmic drugs for secondary prevention, other pathways and mechanisms may prove to be useful. Potential interventions might include RAAS inhibition, statins, β-blockers, omega-3 fatty acids, aggressive risk factor modification, anti-inflammatory strategies (discussed above in Recommendations 3 and 4), continuous positive airway pressure therapy for sleep-disordered breathing, catheter ablation, or some combination of these interventions. An example of an AF secondary prevention study is the recently completed randomized clinical trial Gruppo di Ricerca (GISSI-AF, NCT00376272), which tested whether valsartan was superior to placebo in reducing AF recurrence.[92] The GISSI-AF randomized controlled trial may help to elucidate whether an observed effect is specific to the prevention of AF because usual medical therapy of any underlying cardiac condition was included in both groups.

Knowledge Gaps

- There is a paucity of data on the utility of therapeutic interventions or lifestyle modifications for AF primary and secondary prevention.
- It is unproven that preventing or postponing the transition from an initial episode to recurring and persistent AF improves subsequent morbidity and mortality.

Specific Research Recommendations 6

- Conduct secondary intervention studies in patients with an initial episode of AF to prevent recurrent symptomatic and asymptomatic AF and to examine morbidity (heart failure, stroke) and mortality end points.
- Use results of secondary prevention studies to inform future primary AF prevention studies.

Conclusion

Several lines of evidence suggest that AF is preventable, but relatively little research has been directed at AF prevention. Epidemiology and clinical studies point to many common contributing conditions, such as hypertension and left atrial enlargement, which could serve as therapeutic targets to prevent AF. Recent discoveries of genes that increase AF risk provide further opportunities to identify high-risk groups and understand the pathophysiology of its development, such as genes involved in pulmonary vein development and physiology. Barriers to further progress include a lack of clinically adaptable noninvasive measures of cardiac structure and electrophysiological alterations preceding AF and a lack of animal models that mimic some important components of human disease. Further understanding of several key aspects of AF, including the patterns of occurrence in different populations, risk factors, and underlying pathophysiology, can lead to the identification and testing of candidate therapies for AF prevention in selected populations to prevent AF. A concerted research effort is thus needed on several fronts, as outlined by the panel in the Table. Appropriately focused research efforts will bring closer the ultimate goal of preventing AF and its complications.

Sources of Funding and Disclosures

No.	Name	CTA	Conflict	No.	Brief Description	> or <$10K
1	Emelia J. Benjamin	Y	1. Research grant	3	HL076784 and AG028321	>$10K
					Identification of Common Genetic Variants for AF and PR Interval, 1RO1HL092577-01A1 Benjamin & Ellinor (pending)	
2	Peng-Sheng Chen	Y	1. Research grants		R01 HL71140, R01 HL78932, P50 HL78931	>$10K
		Y	2. Other research support	1	Medtronic and CryoCath donated equipment to my laboratory	>$10K
			7. Consultant/Advisory Board	1	I am a consultant to Medtronic Inc	<$10K
3	Diane E. Bild	Y	None	0	NIH, NHLBI employee	
4	Alice Mascette	Y	Consultant/Advisory Board		PRECISION Trial, NCT00346216	$0
5	Christine M. Albert	Y	None	0		
6	Alvaro Alonso	Y	1. Research grant	1	Coinvestigator to contract funded by NIH (ARIC and MESA)	>$10K
7	Hugh Calkins	Y	1. Research grants	3	BioSense Webster—study	>$10K
					CryoCath—clinical trial	>$10K
					ProRhythm—clinical trial	>$10K
			4. Honoraria	3	BioSense Webster	<$10K
					Medtronic	<$10K
					Sanofi-Aventis	<$10K
			7. Consultant/Advisory Board	5	CryoCath	<$10K
					Ablation Frontiers	<$10K
					ProRhythm	<$10K
					Sanofi-Aventis	<$10K
					BioSense Webster	<$10K
					Medtronic	<$10K
8	Stuart J. Connolly	?	1. Research grants	2	Sanofi-Aventis	>$10K
					BMS	>$10K
9	Anne B. Curtis	Y	1. Research grant	1	CV Therapeutics	<$10K
			7. Consultant/Advisory Board	2	Sanofi-Aventis	<$10K
10	Dawood Darbar	Y	1. Research grant	2	Genetic Basis of AF, 5K23HL075266	>$10K
					QT Remodeling in AF, 1 RO1 HL085690	>$10K
11	Patrick T. Ellinor	Y	1. Research grant	2	The Genetic Basis of AF, 5 RO1HL075431 MacRae	>$10K
					Identification of Common Genetic Variants for AF and PR Interval, 1RO1HL092577-01A1 Benjamin & Ellinor (pending)	>$10K
			3. Speaker's Bureau	1	Sanofi-Aventis	<$10K
12	Alan Go	Y	1. Research grant	1	Research grant from Johnson & Johnson	>$10K
13	Nora Goldschlager	Y	4. Honoraria	1	St Jude Medical	<$10K
			5. Expert witness	1		<$10K
14	Susan R. Heckbert	Y	1. Research grant	1	NHLBI grant 068986, Atrial Fibrillation Incidence, Risk Factors, and Genetics	>$10K
15	Jose Jalife	Y	1. Research grant	3	RO1HL039707	>$10K
					RO1HL087226	>$10K
					RO1HL070074	>$10K
			4. Honoraria	2	Boston AF Symposium	<$10K
					Johnson & Johnson	<$10K
16	Charles R. Kerr	Y	1. Research grant	2	St. Jude Medical, Canada	>$10K
					Sanofi-Aventis, Canada, Canadian Registry of Atrial Fibrillation	>$10K
			Consultant/Advisory Board	1	Sanofi-Aventis, Canada	<$10K
17	Daniel Levy	Y	None	0		
18	Don Lloyd-Jones	Y	None	0		

(*Continued*)

Sources of Funding and Disclosures (Continued)

No.	Name	CTA	Conflict	No.	Brief Description	> or <$10K
19	Barry M. Massie		1. Research grants	3	VA HSR&D: Optimal Use and Cost-effectiveness of ICDs in the VA Health Care System	~$1,200,000 over 5 years
					Bristol-Myers Squibb	~$100,000 over 6 years
					Sanofi Aventis	~$120,000 over 4 years
		Y	4. Speaking honoraria	1	Heart Failure Society of America (CME Program)	<$10K
					Merck	<$10K
			7. Consulting	6	Sanofi-Aventis	<$10K
					Merck	<$10K
					GlaxoSmithKline	<$10K
					Novartis	<$10K
					Duke Clinical Research Institute	>$10K
					Bristol-Myers Squibb	>$10K
			DSMB payments	4	Takeda	<$10K
					Scios J&J	<$10K
					Corthera	<$10K
					Medtronic (just beginning, no payments but expect to be <$10,000)	<$10K
20	Stanley Nattel	Y	Institution/employer	3	I am listed as investigator on Montreal Heart Institute Intellectual Property for Statin Drugs to Treat AF	<$10K
					Pierre Fabre Company (France), study of fish oil derivative, AF model	>$10K
					Canadian Institutes of Health Research MOP 44365 and MGP 6957	
21	Jeffrey E. Olgin	Y	1. Research grant	1	InterMune Inc, grant to study effects of an antifibrotic on AF	>$10K
22	Douglas Packer	Y	1. Research grant	6	Boston Scientific/EPT	>$10K
					St Jude Medical/St Jude Foundation	>$10K
					CryoCath Technologies	>$10K
					ProRhythm	>$10K
					Cardio Focus	>$10K
					BioSense Webster Inc	>$10K
			4. Honoraria	3	BioSense Webster Inc	<$10K
					St Jude Medical	<$10K
					CryoCath Technologies	<$10K
			6. Ownership interests	1	I receive royalties from St Jude Medical/EST for licensed intellectual property	
			7. Consultant/Advisory Board	6	Boston Scientific/EPT	<$10K
					St Jude Medical/St Jude Foundation	<$10K
					CryoCath Technologies	<$10K
					ProRhythm	<$10K
					Cardio Focus	<$10K
					BioSense Webster Inc	<$10K
23	Sunny Po	Y	1. Research grant	1	Nanoparticles as a Lone Delivery System (PI)	>$10K
			4. Honoraria	1	AtriCure	<$10K
24	Teresa S.M. Tsang	Y	1. Research grant	3	NIH NIA, Pathophysiology of AF	>$10K
					American Society of Echocardiography—LA remodeling	>$10K
					CR20 Mayo Foundation	>$10K
25	David R. Van Wagoner	Y	1. Research grant	3	Atrial Fibrillation Innovation Center, Ohio Wright Center Initiative	>$10K
					Fondation Leducq Atrial Fibrillation Research Consortium	>$10K
					NIH RO1, Genetics of Atrial Fibrillation	>$10K

(*Continued*)

Sources of Funding and Disclosures (Continued)

No.	Name	CTA	Conflict	No.	Brief Description	> or <$10K
			4. Honoraria	3	Consulting, Procter & Gamble Pharmaceuticals	<$10K
					Consulting, Wyeth Pharmaceuticals	<$10K
					Scientific Advisory Board, Boehringer-Ingelheim Pharmaceuticals	<$10K
26	Albert L. Waldo	Y	1. Research grant	3	Boehringer Ingelheim RELY trial	>$10K
					Bristol-Myers Squibb— (Aristotle trial), anticipated has not yet started	>$10K
					CARDAX Pharmaceuticals	>$10K
			2. Other research support	1	Wright Third Frontier grant from the State of Ohio	>$10K
			4. Honorarium	4	Grand Rounds, Vanderbilt	<$10K
					NIH/NHLBI-CCRN DSMB	<$10K
					NEOSPE Symposium	<$10K
					Boston AF Symposium	<$10K
			7. Consultant/Advisory Board	2	Astellas	<$10K
					Biotronik	
					St Jude Medical	
					AstraZeneca	
					Deugen; SCIOS; Bristol-Myers Squibb	<$10K
					BioSense Webster; Solvay; CryoCor; Sanofi-Aventis	>$10K
27	D. George Wyse	Y	4. Honorarium	1	Talk on advisory board at Astellas	<$10K
			7. Consultant/Advisory Board	9	(a) Boehringer Ingelheim—DSMB Member	<$10K
					(b) Novartis Advisory Board to plan RCT	<$10K
					(c) Cardiome/Astellas—Advisory Board concerning new product	<$10K
					(d) Medtronic—Advisory Board to plan RCT; DSMB; Advisory Board for Registry Study	<$10K
					(e) Sanofi-Aventis—Chair DSMB	<$10K
					(f) CV Therapeutics—Advisory Board to plan RCT	<$10K
					(g) Transoma—Advisory Board to plan RCT	<$10K
					(h) Bristol-Myers Squib— DSMB Member	<$10K
					(i) Biotronik—Chair DSMB	<$10K

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