

# Progress toward the prevention and treatment of atrial fibrillation: A summary of the Heart Rhythm Society Research Forum on the Treatment and Prevention of Atrial Fibrillation, Washington, DC, December 9–10, 2013



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**ABBREVIATIONS** ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; A-II = angiotensin-II; ANP = atrial natriuretic peptide; ARB = angiotensin receptor blocker; BP = blood pressure; BMI = body mass index; BNP = brain natriuretic peptide; CaMKII = calmodulin-dependent kinase II; DAD = delayed afterdepolarization; EAD = early afterdepolarization; ECM = electrocardiographic mapping; EHR = electronic health record; ET-1 = endothelin-1; GGA = geranyl-geranylacetone; GP = ganglionated plexi; HDAC6 = histone deacetylase-6; HF = heart failure; HSP = heat shock protein; LA = left atrium; LAA = left atrial appendage; LGE-CMR = late gadolinium enhanced cardiac magnetic resonance imaging; LV = left ventricle; MRI = magnetic resonance imaging; NIH = National Institutes of Health; NOAC = non-vitamin K-dependent oral anticoagulant; NP = natriuretic peptide; OAC =

oral anticoagulant; PAC = premature atrial contraction; pAF = paroxysmal atrial fibrillation; PV = pulmonary vein; PVI = pulmonary vein isolation; RAAS = renin-angiotensin-aldosterone system; RCT = randomized controlled trial; RSD = renal sympathetic denervation; SDB = sleep disordered breathing; SR = sarcoplasmic reticulum; TGF = transforming growth factor; TTR = time in therapeutic range (Heart Rhythm 2015;12:e5–e29)

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## Introduction

The Heart Rhythm Society convened a research symposium on December 9–10, 2013, in Washington, DC, that focused on the prevention of atrial fibrillation (AF) as well as AF-related stroke and morbidity. Attendees sought to summarize advances in understanding AF since a 2008 National Institutes of Health (NIH) conference on this topic<sup>1</sup> and to identify continued knowledge gaps and current research priorities. The research symposium also sought to identify key deficiencies and opportunities in research infrastructure, operations, and methodologies. The committee sought to identify both basic research targets and how clinical AF research could be improved in the current health care environment. This whitepaper summarizes our deliberations in an effort to accelerate progress toward preventing AF and its consequences. Although largely focused on primary prevention of AF, the paper also addresses some aspects of secondary prevention of recurrent AF due to the continuum of risk factors that contribute to arrhythmogenesis, permissive left atrial (LA) substrates, and the emergence of AF.

## Scope of the problem

More than 33 million individuals worldwide have AF, and there are approximately 5 million new cases each year.<sup>2</sup> AF incidence and prevalence increase with age; the prevalence of AF increases 3-fold between the 6th and 8th decade of life. The increasing frequency of AF is particularly notable in industrialized nations where the increment in AF is more than 2-fold greater than in developing nations.<sup>2</sup> Based on estimates from the Framingham Study, the lifetime risk of developing AF has been estimated at 1 in 4.<sup>3</sup> Accordingly, treatment of AF has been targeted as a top priority for

comparative effectiveness research by the Institute of Medicine.<sup>4</sup>

AF leads to a 5-fold increased risk of stroke, a 2-fold risk of dementia, as well as increased risk of myocardial infarction, heart failure (HF), and death.<sup>5</sup> Over the past 2 decades, hospital admissions for AF have increased by two-thirds. Direct expenditures related to AF cost Medicare at least \$6 billion annually.<sup>5</sup> In addition to higher morbidity and mortality, AF-related strokes are associated with 20% greater health care costs relative to non-AF strokes.<sup>6</sup> Currently approved AF therapies are only partially effective and are associated with substantial morbidity and mortality. Whereas many studies have focused on the treatment of AF, relatively few have been directed at prevention of AF. In contrast to coronary heart disease and stroke, preventive strategies and therapies for AF remain unproven.<sup>1</sup>

Analysis of clinical practice guidelines reveals a gap between the need for evidence and its availability.<sup>7</sup> Patients seek evidence-based guidance related to diet, exercise, and lifestyle for risk factor modification and AF prevention, but systematic studies in these areas are currently quite limited. More research is required to support evidence-based recommendations as part of a comprehensive approach to prevention and treatment of AF. Developing an evidence base from which we can adequately predict and prevent AF is an important public health goal.

Most trials are underpowered to answer clinically meaningful questions, and many critical trials funded by industry and the NIH are not published.<sup>8,9</sup> These findings suggest that the clinical research enterprise lacks effective prioritization. There is currently no (1) consensus-derived list of top priorities for research in AF nor (2) a systematic portfolio analysis focused on benefit to patients or providers. This manuscript seeks to begin to address these gaps.

## Recent progress with respect to fundamental AF mechanisms, key knowledge gaps, and therapeutic opportunities

### Relation of atrial ectopy to development of AF

Frequent atrial ectopy (premature atrial contractions [PACs]) during 24-hour Holter recordings has been identified as a strong predictor of AF development, with discriminatory power similar to the Framingham risk score over 5 to 10 years of follow-up and even better at 15 years.<sup>10</sup> Atrial ectopy has significant prognostic potential that may help to identify patients at greatest risk for AF and for whom early treatment may enable primary prevention of AF. PAC frequency has been positively associated with age, height, and brain natriuretic peptide (BNP) levels; PAC frequency has been inversely related to HDL levels and physical activity.<sup>11</sup> Studies testing the causal link(s) between PAC burden and incident AF are needed. Studies testing the hypothesis that early treatment in these patients is beneficial are also warranted, but the current lack of therapies that are both highly effective and safe remains an obstacle. Safety is a critical consideration in preventive medicine.<sup>12</sup>

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