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Authors

Benjamin, Emelia J
Al-Khatib, Sana M
Desvigne-Nickens, Patrice
et al.

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SPECIAL REPORT

Research Priorities in the Secondary Prevention of Atrial Fibrillation: A National Heart, Lung, and Blood Institute Virtual Workshop Report

Emelia J. Benjamin, MD, ScM; Sana M. Al-Khatib, MD, MHS; Patrice Desvigne-Nickens, MD; Alvaro Alonso, MD, PhD; Luc Djoussé, MD, ScD, MPH; Daniel E. Forman, MD; Anne M. Gillis, MD; Jeroen M. L. Hendriks, PhD; Mellanie True Hills, BS; Paulus Kirchhof, PhD; Mark S. Link, MD; Gregory M. Marcus, MD, MAS; Reena Mehra, MD, MS; Katherine T. Murray, MD; Ratika Parkash, MD, MSc; Ileana L. Piña, MD, MPH; Susan Redline, MD, MPH; Michiel Rienstra, MD, PhD; Prashanthan Sanders, MBBS, PhD; Virend K. Somers, MD, PhD; David R. Van Wagoner, PhD; Paul J. Wang, MD; Lawton S. Cooper, MD, MPH; Alan S. Go, MD

ABSTRACT: There has been sustained focus on the secondary prevention of coronary heart disease and heart failure; yet, apart from stroke prevention, the evidence base for the secondary prevention of atrial fibrillation (AF) recurrence, AF progression, and AF-related complications is modest. Although there are multiple observational studies, there are few large, robust, randomized trials providing definitive effective approaches for the secondary prevention of AF. Given the increasing incidence and prevalence of AF nationally and internationally, the AF field needs transformative research and a commitment to evidenced-based secondary prevention strategies. We report on a National Heart, Lung, and Blood Institute virtual workshop directed at identifying knowledge gaps and research opportunities in the secondary prevention of AF. Once AF has been detected, lifestyle changes and novel models of care delivery may contribute to the prevention of AF recurrence, AF progression, and AF-related complications. Although benefits seen in small subgroups, cohort studies, and selected randomized trials are impressive, the widespread effectiveness of AF secondary prevention strategies remains unknown, calling for development of scalable interventions suitable for diverse populations and for identification of subpopulations who may particularly benefit from intensive management. We identified critical research questions for 6 topics relevant to the secondary prevention of AF: (1) weight loss; (2) alcohol intake, smoking cessation, and diet; (3) cardiac rehabilitation; (4) approaches to sleep disorders; (5) integrated, team-based care; and (6) nonanticoagulant pharmacotherapy. Our goal is to stimulate innovative research that will accelerate the generation of the evidence to effectively pursue the secondary prevention of AF.

Key Words: atrial fibrillation ■ cardiac rehabilitation ■ prevention ■ research ■ risk factors ■ sleep

The secondary prevention of atrial fibrillation (AF) is of major public health importance because the incidence, prevalence, and lifetime risk of AF are increasing in the United States and globally.[1] AF also predisposes to major morbidities, including ischemic stroke, other systemic embolism, dementia, heart failure, myocardial infarction, chronic kidney disease, diminished quality of life, functional limitations, increased healthcare use, higher costs, and excess death.[1] Research into the secondary prevention of AF is critical

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Correspondence to: Emelia J. Benjamin, MD, ScM, Cardiovascular Medicine, Collamore 8, Boston University School of Medicine, 72 E Concord St, Boston, MA 02118. E-mail: emelia@bu.edu

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Nonstandard Abbreviations and Acronyms

AMPK	AMP-activated protein kinase
CR	cardiac rehabilitation
HFpEF	heart failure with preserved ejection fraction
NHLBI	National Heart, Lung, and Blood Institute
NLRP3	nucleotide-binding domain-like receptor protein 3

because with the exception of stroke prevention, the evidence base for the prevention of AF recurrence, AF progression, and AF-related complications lacks robust data in the general population, in contrast with the strong evidence base underlying guidelines for secondary prevention of coronary heart disease and heart failure with reduced left ventricular ejection fraction.

There also is a need for evidence-based strategies to address the secondary prevention of AF in high-risk subgroups because of the disproportionate burden of worse AF outcomes in women, systemically disadvantaged groups (eg, Black/Hispanic/Indigenous individuals), and older adults. A meta-analysis of 30 studies reported that compared with men, women with AF had significantly higher relative risks for all-cause mortality, stroke, cardiac events, and heart failure.[2] In the community, compared with White individuals, Black individuals with AF had about 1.5-fold to 2-fold higher rate differences (rate in those with versus without AF) for stroke, heart failure, coronary heart disease, and death.[3]

The care of AF has largely been relegated to interventions that can be provided only by healthcare providers, but emerging evidence favors the critical role of lifestyle factors, which are more directly determined by patients themselves. The efficiency of public health initiatives may be enhanced by informing patients and the lay public about modifiable behaviors that influence their AF risk, signifying the need for particular lifestyle-related research initiatives in the secondary prevention of AF.

Over a decade ago, the National Heart, Lung, and Blood Institute (NHLBI) convened a workshop to promote research into the primary prevention of AF.[4] From 2019 through 2021, the NHLBI is convening a series of 7 virtual workshops to again promote acceleration of high-priority research in AF. The innovative virtual format provides an effective way to assemble international experts to identify the most pressing research gaps and to articulate the highest-priority research challenges. The other webinars examined research priorities for AF ablation,[5] bidirectional relations with heart failure,[6] screening,[7] stroke prevention, and molecular mechanisms; the final webinar will address social determinants of AF.

Our special report summarizes the proceedings of the NHLBI virtual workshop on the secondary prevention of AF recurrence, progression, and complications, which occurred on May 15, 2020. The scope of the special report does not include the relationship of ablation to secondary prevention,[5] the specific topic of secondary prevention of heart failure in AF,[6] or an in-depth examination of molecular/genetic mechanisms underlying AF, which were covered by other workshops. Expert participants identified major knowledge gaps and prioritized opportunities in 6 broad areas of AF secondary prevention research: (1) weight loss and body composition; (2) alcohol intake, smoking cessation, and diet; (3) cardiac rehabilitation (CR); (4) approaches to sleep disorders; (5) integrated, team-based care; and (6) nonanticoagulant pharmacotherapy. Our goal is to stimulate innovative research that will accelerate development of effective strategies for the secondary prevention of AF.

WEIGHT LOSS AND BODY COMPOSITION

Background

Obesity is a global epidemic. Population-based studies have reported that obesity is strongly associated with the risk of incident AF, with a 29% increase in AF incidence for every 5-unit increase in body mass index.[8] Genetic Mendelian randomization studies also support a causal association between obesity and AF; per 1-kg/m^2 body mass index, the age- and sex-adjusted hazard ratio (HR) for AF is 1.15.[9] Obesity is associated with higher AF burden and increased progression from paroxysmal to persistent AF.[10] More important, obesity curtails the effectiveness of therapies aimed at maintaining sinus rhythm.[8]

Weight loss achieved through lifestyle modification or bariatric surgery has been associated with improvement in or reduced incidence of risk factors for AF, including elevated blood pressure, hyperglycemia, diabetes mellitus, sleep disorders, myocardial infarction, and heart failure. In a randomized controlled trial (RCT), weight loss achieved through increased physical activity, significant caloric restriction, and healthier eating choices was associated with improved blood pressure, sleep apnea, glycemic control, and lipid profiles.[11] Bariatric surgery was associated with sustained weight loss and remission of diabetes mellitus in meta-analysis of RCTs,[12] and in meta-analysis of observational data with reduced incidence of diabetes mellitus, hypertension, sleep apnea, and coronary heart disease.[13]

Recent largely observational studies have demonstrated that comprehensive approaches to treating risk factors, with a focus on targeting weight loss,

have been associated with reduction of AF symptoms and AF burden, and improvement in the maintenance of sinus rhythm and quality of life.[14,15] There also is evidence for a reversal of AF progression with a transition from persistent to paroxysmal or no AF.[16] Emerging observational data suggest that similar findings may be achieved using bariatric surgery.[17] However, the risks of AF after bariatric surgery are complex and vary over time. Examining US administrative data from 4 states, investigators reported that the risk of AF-related emergency department visits and hospitalizations was increased in the 12 months after bariatric surgery (n=523 adults undergoing bariatric surgery; adjusted odds ratio [OR], 1.53; 95% CI, 1.13–2.07; *P*=0.006).[18] In longer-term follow-up (median, 7.9 years; interquartile range, 7.2–19.0 years), a meta-analysis of 7 cohort studies observed that compared with referents, bariatric surgery (n=7681) was associated with an OR of 0.42 (95% CI, 0.22–0.83) for incident AF.[19]

On the basis of observational and clinical trial evidence, the 2019 focused update of the American Heart Association/American College of Cardiology/Heart Rhythm Society guideline document on AF included a class I, level of evidence B-R recommendation of weight loss combined with risk factor modification in patients with AF who are overweight or obese.[20] However, the 2020 European AF guidelines gave weight loss only a class IIa, level of evidence B recommendation.[21]

Knowledge Gaps

Mechanisms for Development of the Substrate for AF

Experimental studies have demonstrated that obesity directly affects the atrial myocardium with structural and electrophysiological changes, supporting the milieu for AF (Abed, 2013, number 3666). There is activation of both the transforming growth factor and endothelin pathways, and altered distribution of cell-to-cell connections. However, the signaling pathways that lead to these changes have remained elusive.

Studies have demonstrated that epicardial fat and myocardial fat infiltration increase in obesity.[22] The secretome of epicardial fat has been demonstrated to promote the AF substrate, including myocardial fibrosis.[23] However, the constituents and mechanisms associated with this phenomenon remain unknown.

Obesity is associated with numerous comorbidities, including hypertension, diabetes mellitus, sleep apnea, heart failure, and myocardial infarction, that are known to be associated with AF,[24,25] although obesity remains a risk factor for AF after adjustment for coexistent risk factors.[26] However, the signaling pathways and the interaction between obesity and associated comorbidities on the risk of AF remain incompletely understood.

Reversibility of the AF Substrate

Clinical studies have demonstrated that the AF substrate can be reversed with substantial weight loss and risk factor management.[16] In an experimental model of obese sheep, 30% weight loss was associated with atrial electrophysiological and structural reverse remodeling, and improved inflammatory and growth factor markers; the changes were accompanied by a reduced propensity for AF independent of other AF risk factors, including elevated blood pressure. However, the mechanisms by which weight loss and risk factor management alter the AF substrate remain only partially determined.

Generalizability of Studies

In a modest-sized (n=150), single-center, short-term randomized study of patients with AF, investigators in Adelaide, Australia, have reported achieving remarkable weight loss, reductions in AF symptoms and burden, and improved maintenance of sinus rhythm.[11] A meta-analysis of the Adelaide groups' 5 studies (4 observational and 1 RCT, total 548 patients) reported that at least 10% weight loss in overweight and obese individuals was accompanied by at least 71% less AF recurrence and significantly lower episode length and symptom severity.[15]

Studies replicating the marked sustained weight loss and AF burden improvement through lifestyle modification observed in the Australian studies have not been reported from other investigators,[27] other countries, and more racially/ethnically and socioeconomically diverse populations. Implementation of weight loss programs requires the development of reproducible and effective tools and strategies for achieving sustained weight loss and other risk factor modification in diverse populations and health systems.

Clinical Outcomes

Developing effective secondary prevention implementation strategies in diverse populations with AF is critical given sex, racial/ethnic, and socioeconomic inequities in clinical outcomes after recognition of AF.[1–3] It is essential to design adequately powered studies including diverse individuals (age, sex, racial/ethnic, and socioeconomic status) to evaluate the potential influence of weight loss on AF recurrence and burden, and clinical outcomes such as stroke, cognitive decline, myocardial infarction, heart failure, quality of life, healthcare use, cost-effectiveness, and mortality. Historically, RCTs examining hard end

points have been complex and resource intensive. Hence, innovative, pragmatic, clinical trials will be critical to addressing the relations between secondary prevention and outcomes. The mechanisms, consequences, and critical research opportunities relating obesity to the secondary prevention of AF are illustrated in Figure 1.

Research Opportunities

1. Identify populations in whom successful weight loss leads to reversal of the atrial substrate for AF, and determine the mechanisms associated with the reversibility of epicardial fat and atrial fibrosis/substrate, including weight loss per se and regression of the comorbidities associated with obesity.
2. Develop and test effective, reproducible, scalable tools and strategies required to achieve and sustain significant weight loss and risk factor management over the long-term in diverse populations (eg, age, sex, race/ethnicity, and socioeconomic status) with AF and then implement the appropriate public health initiatives in different health systems and diverse populations.
3. Conduct multicenter pragmatic RCTs of the effect of weight loss, including bariatric surgery and risk factor management, in diverse individuals with AF on AF recurrence, burden, progression, and outcomes, including stroke, cognitive decline, heart failure, myocardial infarction, quality of life, healthcare use, costs, and mortality.

ALCOHOL, SMOKING, AND DIET

Background

Extensive observational evidence indicates that excessive alcohol consumption[28] and cigarette smoking[29] are associated with the risk of developing AF, whereas the data linking diet and AF are less consistent.[30,31] Understanding of the effect of alcohol, smoking, and dietary interventions on the secondary prevention of AF is more limited.

Alcohol Intake

A meta-analysis of the association of alcohol consumption with incident AF demonstrated a convincing dose-response relationship (adjusted relative risk by

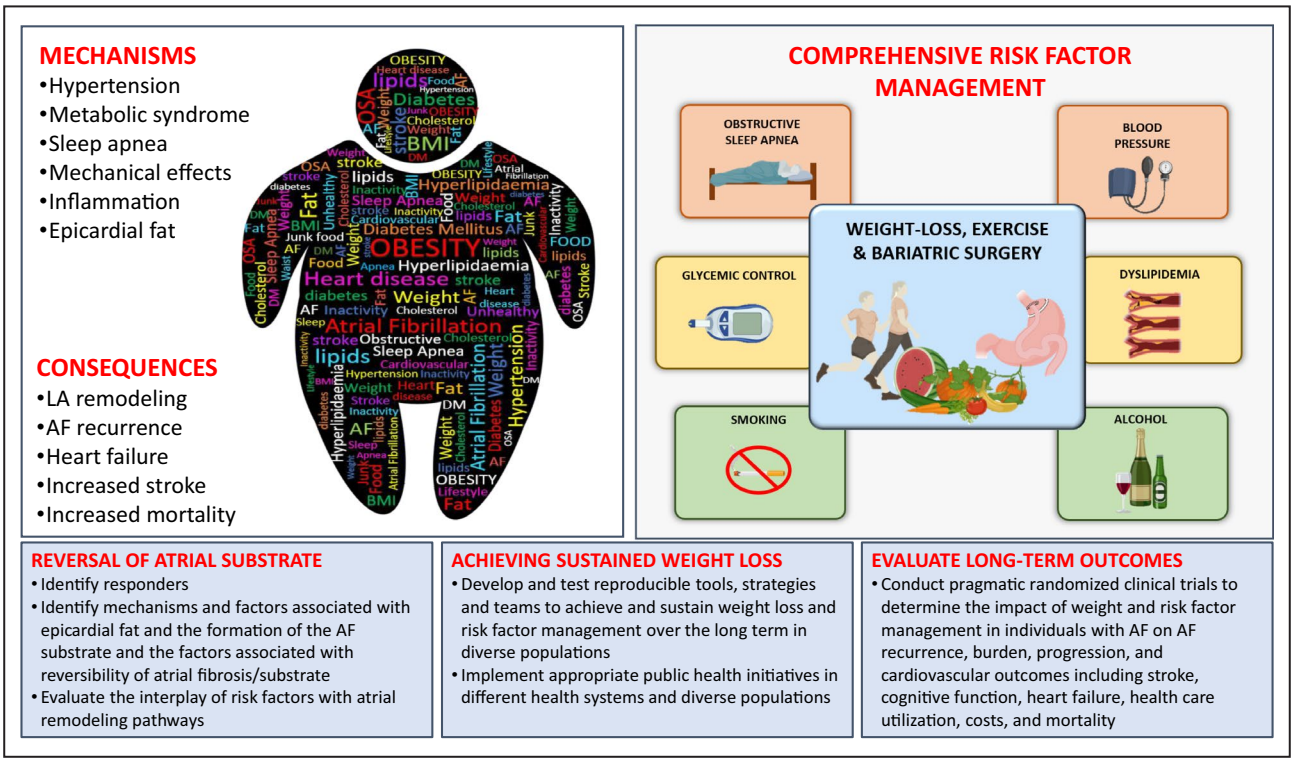

Figure 1. Current knowledge and prioritized research opportunities to advance atrial fibrillation (AF) secondary prevention through weight management.
The figure highlights known associations and the consequences that link obesity with AF. Weight loss has been demonstrated in the short-term to reduce AF burden when performed in the context of a comprehensive risk factor management program. However, there remain several research priorities, highlighted in the blue panels, that are required to (1) improve our understanding of the mechanisms; (2) improve the tools and strategies to achieve sustained weight loss; and (3) evaluate the outcomes of sustained weight loss. Figure is original, created with BioRender.com. BMI indicates body mass index; DM, diabetes mellitus; LA, left atrial; and OSA, obstructive sleep apnea.

drinks per day was 1.08 for 1, 1.17 for 2, 1.26 for 3, 1.36 for 4, and 1.47 for 5).[28] Alcohol intake is a common trigger for AF episodes[32] and has been associated with atrial enlargement,[33] adverse electrical atrial remodeling,[34] and higher risk of AF recurrence after ablation.[35] An Australian open-label RCT of 140 patients (15% women; mean age, 62 years) with paroxysmal or persistent AF who consumed ≥10 drinks per week randomized half to abstain and half to usual alcohol consumption.[36] Patients in the abstinence group reduced their alcohol consumption by 88% and experienced longer periods before AF recurrence and reduced AF burden.[36]

Smoking

A meta-analysis of observational studies reported a dose-response association between cigarette smoking and incident AF.[29] There is limited evidence linking smoking with secondary prevention of AF. In an observational study, smoking was found to be a predictor of AF recurrence after ablation and was therefore included in a risk score for recurrent AF (adjusted HR, 1.88 [95% CI, 1.40–2.51]).[37] Proposed mechanisms include proarrhythmogenic effects of nicotine as well as the overall adverse association of smoking with cardiovascular risk.[38]

Diet

Few studies have evaluated whether specific dietary patterns, foods, or nutrients improve outcomes in AF. Fish oil supplementation has been tested as a potential intervention for AF secondary prevention, but results have shown inconsistent effects.[39] The Vital-Rhythm Study (NCT02178410), a 2×2 factorial RCT, revealed that neither omega-3 fatty acids nor vitamin D reduced or increased incident AF.[40] A post hoc analysis of a large RCT reported a protective effect of the Mediterranean dietary pattern on AF incidence.[41] On the basis of these findings, a new study (NCT03053843) is testing the effectiveness of this dietary pattern to reduce AF recurrence after ablation.[42]

Knowledge Gaps

Most research into the influence of modifiable exposures, such as alcohol, smoking, and diet, on AF risk has focused on long-term patterns of consumption as predictors of new-onset disease among cohorts of individuals, leaving 3 overarching gaps in knowledge: (1) the effects of these exposures and interventions among those already diagnosed with the disease, including AF recurrence and complications; (2) the risk of an immediate exposure, such as a particular drinking event, a cigarette smoked, or short-term ingestion of a dietary component, and the near-term risk of a discrete AF event; and (3) how interactions with common genetic variants may result in heterogeneity of these effects among individuals (Figure 2). Specific knowledge gaps include the following.

Alcohol

It is important to determine whether regular light to moderate alcohol consumption (such as one drink per day) increases the risk of recurrent AF given observational studies reporting cardiovascular benefits compared with no alcohol intake. The mechanisms by which short-term consumption can induce discrete episodes and the mechanisms linking long-term alcohol consumption to AF are important knowledge gaps. There also is a lack of AF secondary prevention data with respect to drinking patterns (eg, frequency of drinking for the same amount of alcohol, such as consumption of multiple drinks on the same day compared with an equal amount split over a week, and with or without meals). It would be useful to definitively determine whether alcohol cessation improves the effectiveness of ablation and pharmacologic therapies and decreases the complications after AF onset.

Smoking

Whether and to what extent smoking cessation can reduce the burden and complications of AF remain an important knowledge gap. It is also uncertain whether electronic cigarettes are associated with an increased risk of AF. In addition, it will be important to determine effective implementation strategies to ensure individuals with AF who smoke receive evidence-based effective smoking cessation interventions.

Diet

Identifying which dietary components (nutrients and foods) or dietary patterns acutely or chronically increase or decrease the risk of discrete AF events or burden and complications is important. How certain diets can chronically influence left atrial remodeling and affect AF burden has yet to be determined.

The most compelling evidence for the effectiveness of alcohol consumption, smoking, and dietary factors will be derived from RCTs. In addition, a major unmet need is to develop resource-effective policies and pragmatic implementation approaches to scale interventions to diverse communities (age, sex, race/ethnicity, and socioeconomic status) and to enhance the sustainability of lifestyle behaviorally based interventions. For instance, can programs be implemented in community-based settings, such as places of worship,

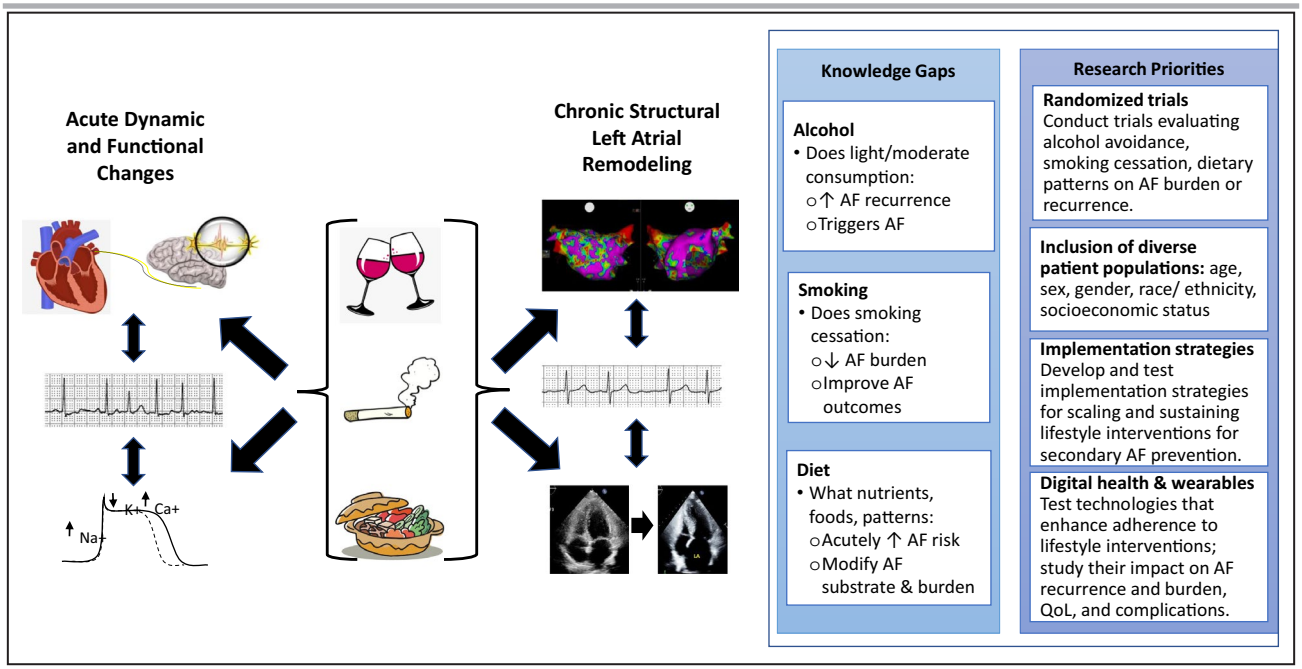

Figure 2. Current knowledge and prioritized research opportunities to advance atrial fibrillation (AF) secondary prevention through modifying alcohol consumption, smoking, and diet.
Alcohol, smoking, and various dietary patterns, foods, and nutrients may lead to discrete episodes of recurrent AF via acute changes, such as proarrhythmic autonomic effects (top left) or acute electrophysiologic effects (bottom left), or may lead to greater propensity for AF via chronic structural changes, such as diffuse left atrial remodeling (manifested as low voltages as shown in the left atrial electroanatomic map in the upper right) and left atrial enlargement (as shown in the echocardiographic images in the bottom left). Knowledge gaps in these areas as well as research priorities moving forward are highlighted (right text boxes). QoL indicates quality of life.

barbershops, and gyms? Can digital health and wearable technologies be harnessed to improve adherence to lifestyle modification and monitor AF recurrence and burden?

Research Opportunities

1. RCTs of specific interventions, including (1) alcohol reduction or abstinence; (2) intensive smoking cessation; and (3) heart healthy diets (eg, Dietary Approaches to Stop Hypertension type, plant based, and Mediterranean), versus usual care should be conducted, evaluating their efficacy in reducing AF burden or recurrence, improving quality of life, and reducing complications among diverse patients (eg, age, sex, gender, race/ethnicity, and socioeconomic status) with AF, including those with new-onset disease, those with paroxysmal AF, postcardioversion, and individuals managed with pharmacological therapies or AF ablation procedures.
2. Develop and test implementation strategies to scale and sustain lifestyle interventions proven to be effective for secondary prevention of AF, potentially including (1) reducing or avoiding alcohol; (2) intensive smoking cessation; and (3) heart healthy diets in diverse communities and community-based settings; and study their effect on AF recurrence, AF burden, quality of life, healthcare use, and complications (eg, stroke, cognitive decline, heart failure, myocardial infarction, frailty, and death).
3. Test the effectiveness of digital health and wearable technologies to enhance adherence to effective lifestyle interventions (alcohol and smoking cessation and dietary modification) in diverse communities and community-based settings, and study their effect on AF burden, AF recurrence, quality of life, healthcare use, and AF complications.

EXERCISE AND CR PROGRAMS

Background

Exercise, lifestyle modification, and CR have the potential to mitigate the intrinsic pathophysiological features of AF, improve other AF risk factors (eg, blood pressure, obesity, and sleep), and improve outcomes (eg, hospitalization, physical function, and quality of life) in those with AF.[43] CR is a multifaceted approach that links exercise training with elements of risk factor reduction (eg, tobacco, unhealthy diet, obesity, and hypertension) for patients with known cardiovascular disease.[44,45]

A meta-analysis of 22 observational studies (n=656 750 participants) reported that sedentary lifestyle was associated with increased risk of incident

AF (OR, 2.47 [95% CI, 1.25–3.7]), whereas women (OR, 0.91 [95% CI, 0.78–0.97]) and men (OR, 0.81 [95% CI, 0.26–1.004]) engaging in moderate physical activity were less likely to develop AF.[46] However, a J-shaped relation to physical activity has been noted, with men engaged in vigorous physical activity having significantly higher risk of AF (OR, 3.30 [95% CI, 1.97–4.63]).[46]

AF is not a primary indication for CR in AF guidelines,[20,21,47] which potentially undercuts an opportunity to improve care for adults who are afflicted with AF or who seek primary ablative therapies. The data for secondary prevention of AF with CR are based on modest numbers of participants and studies. A meta-analysis by Smart et al of 9 studies (1 observational and 8 randomized) reported CR was not associated with reduction in all-cause mortality but was associated with improvements in health-related quality of life, exercise capacity, and AF symptom burden.[48]

Knowledge Gaps

Existing studies of CR on secondary prevention of AF were small and largely short-term (≤6 months), had heterogeneous inclusion criteria, varied CR protocols and interventions, and diverse outcomes, and were unable to determine the effect of CR on types of AF or the optimal training intensity (see Table S1 for published CR trials in AF).[48] For instance, the Smart et al meta-analysis study was modestly powered; the included studies comprised 483 exercise-based CR participants and 476 controls. The generalizability of the findings to most individuals with AF was also uncertain as the mean age of participants was typically ≤70 years and most studies included <30% women (Table S1). Furthermore, none of the studies reported on level of educational attainment; only 1 reported on household income; and only 3 specified race (most were European ancestry), of which 2 specified race as White race or other (other race, 3% and 15%), whereas in 1 study, 20% (n=78) of those with AF studied were Black individuals.[49] Most of the studies of AF and CR registered in ClinicalTrials.gov also are small, are single center, and have many of the limitations of prior studies (Table S2).

Specific subgroups of patients with AF to target for CR trials include the following (Figure 3).

Diverse Individuals

The RCT evidence base for CR is modest, and particularly limited for women, participants with lower educational attainment/income, and individuals of diverse races/ethnicities. Social determinants of health and ethnic/racial disparities in access to care, as well as inherent cultural differences, also may influence how CR is applied or used. Large, high-quality RCTs are needed to evaluate the efficacy of CR for secondary prevention of AF with adequate representation of women, individuals with lower educational attainment/income, and participants who are Black, Asian, Pacific Islander, Indigenous, or Hispanic race/ethnicity.

Older Individuals

The incidence and prevalence of AF increase dramatically with advancing age, yet there is a paucity of data for the effectiveness and safety of CR in older adults with AF. Older age is also accompanied by multiple comorbidities, alterations in muscle composition and strength, inflammation, and poorer attendance to center-based CR.[50]

Heart Failure With Preserved Ejection Fraction

Older age also is associated with increased prevalence of heart failure with preserved ejection fraction (HFpEF) that also is conducive to AF. The benefits of CR for AF with comorbid HFpEF, a growing population, are uncertain.[51] The RACE3 (Routine versus Aggressive upstream rhythm Control for prevention of Early persistent atrial fibrillation in heart failure study 3) RCT of patients with AF and mild-to-moderate heart failure (both reduced and preserved left ventricular ejection fraction) reported that an intervention consisting of mineralocorticoid receptor antagonists, statins, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and CR resulted in a higher likelihood of sinus rhythm at 1 year (75% versus 63% in conventional care; OR, 1.8; P=0.04).[52] However, the study had limited power to detect whether CR had the same benefit in individuals with preserved versus reduced ejection fraction. The degree to which the CR component of the intervention was responsible for the improved outcomes also was uncertain.

Another area of interest is the role of specific CR elements or alternative CR locations.

Specific CR Elements

Optimal exercise training modes and intensities for AF prevention remain undetermined. Although there is evidence for greater cardiorespiratory benefits with higher-intensity interval training, its application to AF prevention remains controversial because of concerns that it could potentially exacerbate the arrhythmia.[46] Similarly, there is evidence for yoga[53] and Tai Chi[54] as training modes that afford integrated cardiovascular, respiratory stretching, and meditative benefits, but it is not clear they achieve sufficient physiological intensity to reduce AF burden and complications.

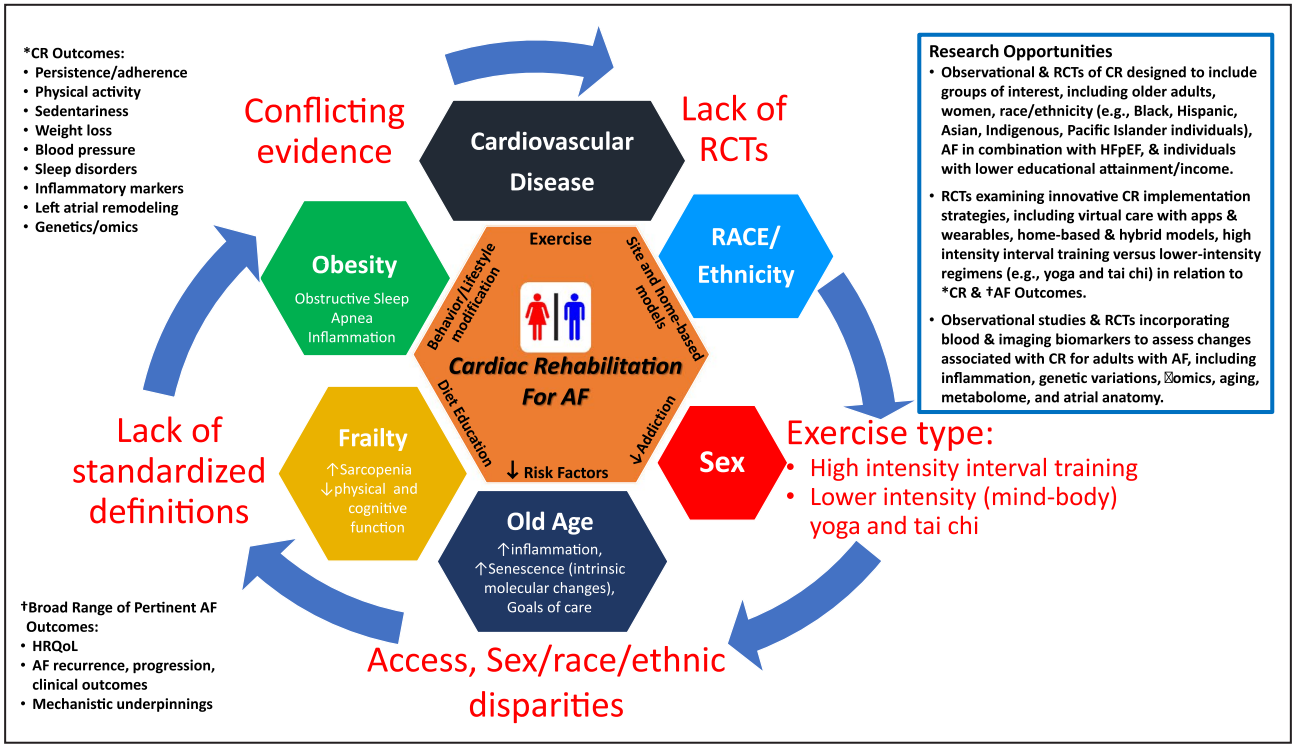

Figure 3. Figure showing the complexities of secondary prevention of atrial fibrillation (AF) with cardiac rehabilitation (CR). Inner hexagon: core components of CR include exercise training, risk factor reduction, education, lifestyle and behavior modification, and addiction curtailment (eg, alcohol and smoking), as well as new models of home-based care that may all provide utility for AF, but specific benefits of multifaceted CR for AF remain poorly studied. Colored hexagons: (top to clockwise) depict some of the many issues that affect CR, and influence AF (eg, cardiovascular disease, race and ethnicity, sex, older age, frailty, and obesity). All remain poorly studied in relation to CR and AF. Red labels: (top to clockwise) depict some of the complex dynamics that factor into the limitations of contemporary CR research and clinical care.

- Lack of randomized controlled trials (RCTs) inclusive of diverse demographics, including sex, race, and ethnicity, as well as broader functional end points that may better reflect utility of CR for AF.
- Lack of precision in regard to exercise modes and intensities, with understanding of both physiological and behavioral implications that factor into CR for AF.
- Lack of inclusion of older adults with focus on related complexities of frailty, sarcopenia, cognitive changes, and intrinsic aging physiological features that may factor into particular benefits of CR for AF.
- Lack of inclusion of obese subgroups with distinctive behavioral, biological, and clinical challenges pertaining to CR for AF.

Black lettering (left top to clockwise) highlights some of the factors needed for improved AF research within CR:

- *Broad CR outcomes.
- †Broad range of pertinent AF outcomes.
- Research opportunities.

HFpEF indicates heart failure with preserved ejection fraction; and HRQoL, health-related quality of life.

Mobile- and Home-Based CR

There is growing awareness that patients often prefer to exercise outside the hospital, but home-based or mobile health-based CR is highly understudied in AF. In one small RCT of 158 patients referred for CR after heart valve surgery or AF ablation, patients could choose center-based (n=87) or self-managed home (n=71) CR.[55] Of note, regardless of setting, patients had similar benefits in physical functioning and self-reported quality-of-life outcomes (with the exception of modestly higher mean depression score in the center-based CR; AF recurrence was not assessed). The COVID-19 pandemic has underscored the desirability of home- and mobile health-based exercise options.

Molecular Markers of CR Efficacy

Another understudied area of CR in AF is how potential mechanistic biomarkers correlate with efficacy of CR in reducing recurrent AF. Biomarkers (eg, genetics, molecular signals, imaging indexes, and inflammation)[56] may identify causal mechanisms and prognostic benchmarks for AF. Once identified, such biomarkers may be applied for participant selection

or as modifiable surrogate end points to evaluate the relative utility of different exercise options and/or other CR treatments.

Research Opportunities

1. Observational studies and RCTs of CR should oversample understudied subgroups of patients with AF, including older adults, women, Black/Hispanic/Asian/Pacific Islander/Indigenous individuals, HFpEF, and individuals with lower educational attainment/income. Outcomes should include success of risk factor modification (eg, if indicated smoking/alcohol cessation, weight loss, and control of blood pressure and diabetes mellitus) and AF-related symptoms, recurrence, progression, and clinical complications.
2. RCTs should examine innovative implementation of CR strategies and their potential efficacy for reduced AF recurrence and complications in diverse representative AF populations:
   - Harnessing technology: virtual care with apps and wearables.
   - Home-based and hybrid models.
   - High-intensity interval training versus lower-intensity regimens (eg, yoga and tai chi).
3. Substudies of CR observational studies and RCTs should examine the association of CR with AF-related biomarkers, including biomarkers of inflammation, genetic variation, omics, aging, metabolome, and atrial imaging.

SLEEP DISORDERS

Background

Sleep disorders and disturbances are common, share risk factors with cardiovascular disease, and are implicated as causal factors in multiple chronic health problems. Of the sleep disorders, obstructive sleep apnea (OSA) has been most studied in relationship to AF. OSA is present in 21% to 74% of patients with AF[57] and is associated with increased hospitalization rates and symptom burden,[58] and recurrent AF after cardioversion.[59] Meta-analyses estimate that untreated OSA is associated with a 40% increased risk of AF recurrence after catheter ablation.[60]

There are well-described physiological mechanisms linking OSA to AF incidence and recurrence through effects on atrial structural and electrical remodeling (eg, negative thoracic pressure swings increasing atrial stretch/dilation and preload; hypoxia increasing afterload and triggering inflammatory and oxidative stress pathways; altered sympathovagal activity).[61] The molecular mechanisms of OSA-related atrial fibrosis and conduction and sinus node abnormalities are less understood, but studies implicate connexin remodeling, dysregulation of myocardial excitation/coupling, and phosphorylation of sodium channels.[62]

Investigators have examined screening for and treating OSA as an approach to mitigating AF disease burden. Observational studies suggest that continuous positive airway pressure (CPAP) is associated with reduced risk of recurrent AF after cardioversion[59] or catheter ablation.[60] A lower recurrence rate following ablation therapy in patients with OSA treated with CPAP was reported to parallel CPAP-related reductions in blood pressure, atrial size, and ventricular mass,[63] supporting a potential physiological benefit of CPAP on risk of recurrent AF. However, there are no RCTs to support benefit. Only one small (n=25) RCT was conducted specifically to study AF recurrence, with negative results, but it was underpowered.[64] SAVE (The Sleep Apnea Cardiovascular Endpoints) trial (2717 participants; 37 AF events) also did not demonstrate a benefit of CPAP on new-onset AF; but AF was an underpowered secondary outcome.[65]

Recent studies suggest that other sleep disturbances that impair quality or quantity of sleep also may be associated with increased risk of AF, including short sleep duration,[66] reduced rapid eye movement sleep,[67] insomnia,[67] and periodic limb movement disorder.[68] However, some associations vary by age/sex, and the effect of these sleep disturbances on AF burden has not been addressed. Although circadian physiological features have profound effects on multiple organ systems and AF displays increased nocturnal occurrences,[69] there is little research addressing circadian influences on AF.

Knowledge Gaps

Mechanisms and Identification of At-Risk Sleep Disorder Phenotypes

OSA is a complex heterogeneous disorder that generates physiological stressors related to variations in inspiratory obstruction, gas exchange abnormalities, arousal, and sleep disruption. Although the apnea-hypopnea index is most frequently used to characterize OSA, it does not comprehensively describe alterations in physiological stresses and underlying disease mechanisms, nor does it consistently predict all types of adverse cardiovascular outcomes. In contrast, compared with the apnea-hypopnea index, measures of hypoxia better predict cardiovascular disease and death, as well as recurrent AF.[70] There is thus a need to better understand the physiologic drivers of AF burden, the underlying phenotypes of individuals with OSA most at risk for AF, and the sleep metrics that best identify individuals likely to benefit from OSA treatment.

Mechanisms underlying the relations between sleep disruption and AF independent of OSA remain

largely unknown and are worthy of additional study. Elucidating distinctions between chronic and acute effects may be revealing. For example, although multiple observational cohort studies have demonstrated *chronic* sleep disruption as a risk factor for incident disease,[67] selected patients with AF describe *acute* lack of sleep as a common trigger of discrete AF episodes.[32]

Subgroup Susceptibility

In addition to identifying which OSA subtypes represent those most at risk for recurrent AF and related morbidity, there is incomplete understanding of how age, sex/gender, race/ethnicity, underlying heart disease, and comorbid sleep disorders (eg, insomnia and periodic limb movements) moderate risk. It is unknown whether the association between central sleep apnea and incident AF in community-based cohorts[71] reflects risk associated with a unique central sleep apnea phenotype (eg, enhanced autonomic phenotype), or reflects primarily unrecognized subclinical heart disease present at baseline in individuals with central sleep apnea.

Screening

There is a need to understand what settings are most effective for screening for OSA/sleep disorders in patients with AF, and to understand which tools (eg, questionnaires, wearables, oximetry, and mobile health) have optimal predictive value. There are patient and health system barriers to sleep laboratory testing for OSA. Hence, the role of home-based screening and wearable technologies merits further research. There is also a need to better apply data analytics, including machine learning, to data from remote monitoring of physiological signals (eg, from implantable devices) to improve screening[72] and management of OSA and other sleep disorders (Figure 4).

Therapeutic Interventions

The literature on treating OSA in individuals with AF is largely limited to observational studies of CPAP, an intervention with variable tolerance and adherence. Adequately powered RCTs are needed that test CPAP coupled with interventions to enhance adherence,[73] as well as test other OSA interventions (mandibular

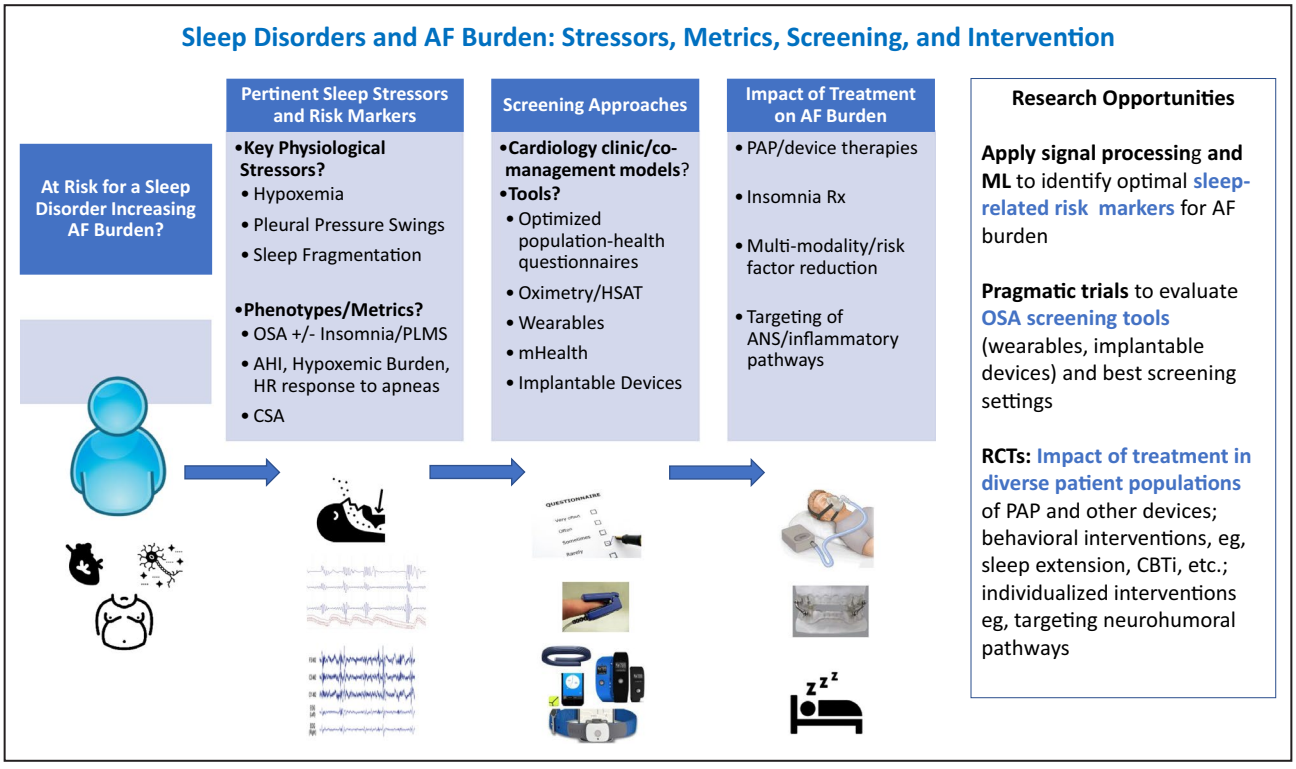

Figure 4. Sleep disorders and atrial fibrillation (AF) burden: stressors, metrics, screening, and intervention.
A high proportion of patients with AF have obstructive sleep apnea (OSA) and other sleep disorders that can increase AF burden through atrial remodeling, autonomic nervous system (ANS) alterations, and metabolic/inflammatory pathways. AF burden may be reduced by improved understanding of the metrics and phenotypes that identify risk for sleep-related AF burden and implementing cost-effective screening. Randomized controlled trials (RCTs) are needed to evaluate the impact of sleep disorders screening/treatment on AF burden. AHI indicates apnea-hypopnea index; CBTi, cognitive-behavioral therapy for insomnia; CSA, central sleep apnea; HR, heart rate; HSAT, home sleep apnea test; ML, machine learning; PAP, positive airway pressure; PLMS, periodic limb movements in sleep; and Rx, treatment.

devices, hypoglossal/phrenic nerve stimulation, positional therapy, and others). Although OSA and obesity aggregate, there are only a few studies that have begun to address multi–risk factor reduction strategies for reducing AF burden in sleep disorders.[11]

A major mechanism linking OSA to AF is the autonomic nervous system; however, it remains uncertain how to apply novel interventions for AF risk reduction that target this mediating pathway (eg, renal sympathetic nerve denervation, ablation of cardiac ganglia, low-level vagal or baroreflex stimulation, β blockers, and anti-inflammatory drugs).[74]

Research Opportunities

1. Conduct secondary analyses of observational and RCT databases to determine which sleep disorder metrics, subphenotypes, and risk clusters reflect the highest risk for recurrent AF and AF burden and complications. Develop new metrics derived by applying advanced signal analysis and machine learning to physiological signals collected during sleep (eg, polysomnography and electrocardiography), used alone or combined with symptoms and other data to identify high-risk clusters, and test their role in predicting AF burden and complications.
2. Conduct pragmatic RCTs that compare alternative OSA screening approaches (eg, questionnaires, oximetry, and wearables) for identifying patients with AF with clinically important levels of OSA (ie, at increased risk for AF burden) and those likely to respond to OSA-related interventions.
3. Conduct adequately powered RCTs that test interventions to improve sleep, examining recurrent AF and AF burden and complications in diverse samples of patients with AF to evaluate for potential differences in responses by age, sex, race/ethnicity, and sleep disorder subtype, including patients undergoing AF ablation. Intervention targets should include OSA as well as insomnia, short sleep duration, and periodic limb movements, and test interventions that include but are not limited to CPAP (eg, mandibular advancement devices and cognitive-behavioral therapy for insomnia). Perform secondary analyses of observational and RCT data to evaluate the potential roles for tailored/individualized interventions for treating patients with AF and OSA/central sleep apnea that target intermediate mechanisms (eg, neurohumoral modulation and anti-inflammatory therapy).

INTEGRATED, TEAM-BASED CARE

Background

AF poses a high burden on the healthcare system; in the United States, AF accounts for $28.4 billion (US$2016) dollars in healthcare spending; about 29.8% of healthcare costs are for AF-related hospitalizations and 29.4% for ambulatory care.[75] Moreover, AF management can be complex and demanding and should include rate control, rhythm management, stroke prevention, risk factor management, and lifestyle modification.[44,76]

Multiple studies have demonstrated the importance of risk factor modification to significantly reduce the burden of AF and maintain sinus rhythm.[14,15,52] Questions have emerged, including whether such comprehensive care can be appropriately provided by a single healthcare professional and what is the optimal role of the patient in managing AF.

Novel models of AF care have been identified to prevent fragmentation of care and potentially improve clinical outcomes. Integrated care in this context is an approach that includes 4 fundamental and indispensable elements[47]: (1) active involvement of the patient, including shared decision-making and self-management; (2) a multidisciplinary team approach; (3) use of technology to support integrated care; and (4) a comprehensive care approach involving rate and rhythm control, anticoagulation, and risk factor management, as appropriate. International guidelines for clinical AF management recommend integrated care as the leading approach to manage AF, to improve guideline adherent therapy, and to improve outcomes. The Australian and New Zealand Guidelines considered integrated care to have a high strength level and high evidence grade,[47] whereas in 2020, the European Guidelines gave integrated management (AF Better Care holistic pathway) a class IIa recommendation, level of evidence B.[21] In contrast, the US guidelines do not address the topic of integrated care.[20]

Initial studies (meta-analysis, 3 studies with 1383 patients,[77] and post hoc analysis of an RCT with 712 patients newly diagnosed with AF[78]) have demonstrated promising results in relation to integrated care in patients with AF with significantly reduced cardiovascular hospitalizations and mortality,[77,78] and better cost-effectiveness compared with usual care.[79,80] A recent multicenter study of 1375 patients (44% women; mean age, 64 years) with AF, however, did not demonstrate significant differences in cardiovascular hospitalization and mortality between 671 randomized to nurse-led care versus 683 in usual care in the primary analysis.[81] However, a prespecified subgroup analysis demonstrated that the benefits of integrated care were heterogeneous ($P_{interaction}<0.001$); nurse-led care appeared beneficial in experienced centers (HR, 0.52 [95% CI, 0.37–0.71]), but not in inexperienced centers (HR, 1.24 [95% CI, 0.94–1.63]).[81] Given the ongoing increasing prevalence of AF, novel models of care, incorporating integrated team-based

care, should be investigated and improved to provide appropriate care to the growing population of individuals with AF.

Knowledge Gaps

Defining Integrated Care

Integrated care has been defined by international guidelines as having the 4 fundamental elements outlined above. Some interventions have been reported as representing integrated care despite not including all 4 fundamental elements, such as studies including patient education[82] and the AF Better Care pathway.[83] It is uncertain whether each of the 4 elements of integrated care are essential, or whether equivalent outcomes could be achieved with specific elements of integrated care in defined subgroups of patients with AF (Figure 5).

Selection of Patients for Integrated Care

Can we define subgroups of individuals with AF who will most benefit from integrated care, and conversely identify subgroups who will not have better outcomes with team-based care and avoid the associated costs?

Team-Based Approach as a Fundamental Element of Integrated Care Is Understudied

The general belief is that team-based approaches are expensive. However, data on the relative benefits versus costs of integrated care in AF are scarce and have not been reported from the United States.

Practical Implications of Establishing a Dedicated AF Team for Individual Patients With AF

Uncertainties exist on how to build a systematic approach to improve outcomes while preventing fragmentation of care. What are the practical implications and considerations to implement a team-based approach in clinical practice, particularly in the midst of the current pandemic?

Optimal Outcomes and Experience Measures of Integrated Care Pathways

What are the most relevant outcomes to assess in relation to integrated care? Is it sufficient to improve patient-reported outcome and experience

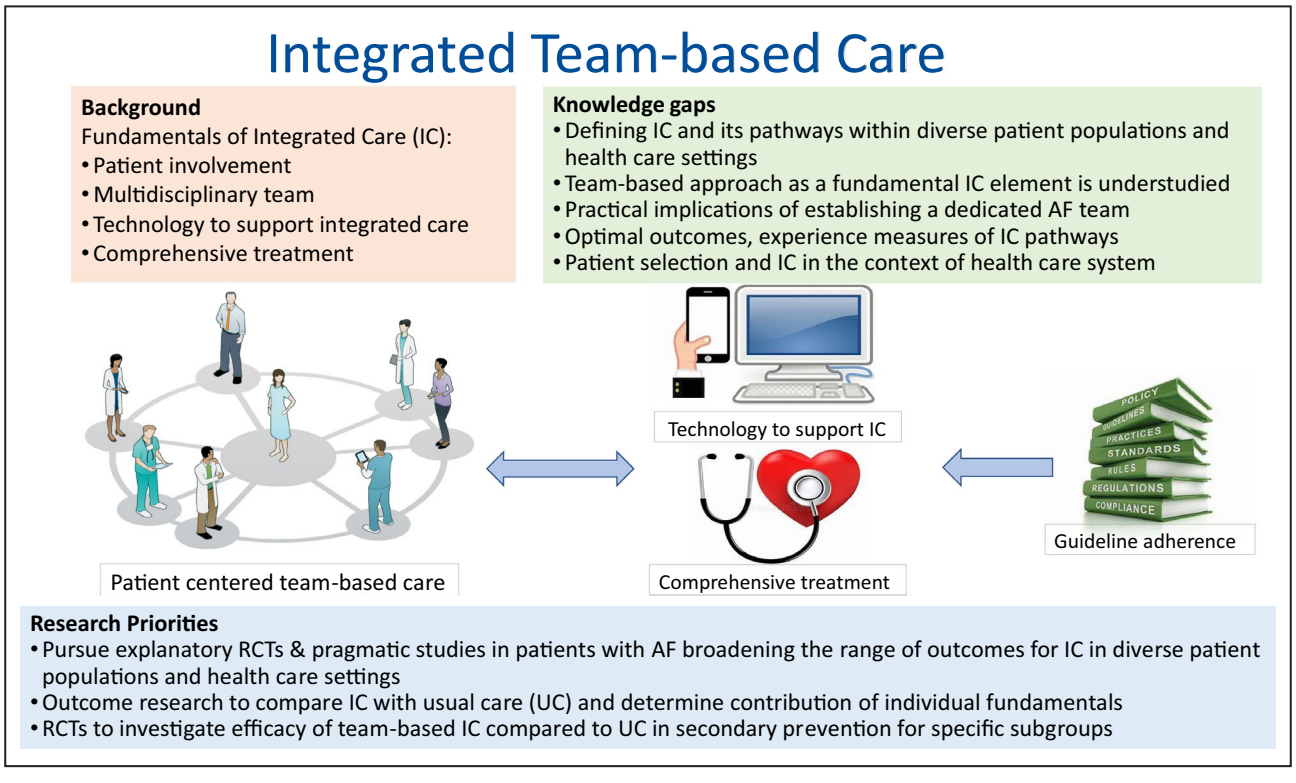

Figure 5. Integrated team-based care in atrial fibrillation (AF).
The integrated team-based care for AF management comprises 4 crucial fundamentals: (1) patient-centered care with active role for patients; (2) multidisciplinary team approach; (3) use of technology to support integrated care; and (4) comprehensive treatment comprising AF management, prevention of thromboembolic complications, cardiovascular risk factor management, and lifestyle modification, which is steered by evidence-based guideline recommendations. IC indicates integrated care; RCT, randomized controlled trial; and UC, usual care.

measures, including patient perceived burden of care, or must integrated care also demonstrate reductions in AF burden and AF-related complications (eg, stroke and heart failure), hospitalizations, costs, and mortality?

Integrated Care in Its Context of Health Systems

The published RCTs of integrated care have largely been from the Netherlands, Canada, and Australia. Will the benefits of integrated care generalize to other countries and healthcare settings? It is unclear how varied health systems, cultural differences, and patient populations diverse in age, sex, race/ethnicity, health literacy, and socioeconomic status will influence implementation and outcomes observed with integrated care.

Research Opportunities

1. Pursue explanatory RCTs and pragmatic studies broadening the range of outcomes for integrated AF care compared with usual care, including patient-reported outcomes (eg, quality of life), AF recurrence and burden (eg, assessed with remote monitoring), team-based outcomes (eg, efficiency and workforce), and intermediate outcomes (eg, physical functional status), as well as clinical end points (eg, stroke, heart failure, hospitalization, or death) and healthcare costs, understanding that interpreting results may be challenging with ongoing temporal trends in management changes (eg, improved oral anticoagulation treatment). Critical to advancing the field will be to test integrated care approaches in a variety of healthcare settings and countries, including the United States and diverse patient populations.
2. Conduct outcomes research to compare integrated care strategies with guideline-based usual care and determine the benefits and risks of the individual elements fundamental to the integrated AF care approach (ie, active patient involvement, multidisciplinary team approach, use of mobile health technology to support integrated care, and comprehensive treatment approach).
3. Conduct RCTs to investigate the efficacy for AF recurrence, progression, and complications of multidisciplinary, team-based integrated care in secondary prevention versus usual care, oversampling specific subgroups of patients diverse in age, sex, race/ethnicity, and low socioeconomic status, ensuring that interventions are appropriately tailored to diverse demographics. Identify subgroups of patients with AF (eg, AF type or comorbidities) most likely to benefit compared with usual care approach provided by a single healthcare professional.

NONANTICOAGULANT PHARMACOTHERAPY

Background

Pharmacologic antiarrhythmic drug therapy continues to have limited efficacy in AF rhythm control and has adverse effects. Numerous risk factors for AF are associated with systemic inflammation, and anti-inflammatory agents have demonstrated some efficacy at suppressing AF, albeit with significant adverse effects.[84,85] The NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome is a critical mediator for activation of the innate immune system, particularly in response to noninfectious molecules (Figure 6). This complex system is upregulated in human AF, and NLRP3 inhibition can prevent AF in animal models.[86]

The most powerful risk factor for AF is aging, which increases oxidative and metabolic stress, with a decline in proteostasis integrity and mitochondrial function.[87,88] Novel mediators of these processes have been identified as potential targets for prevention of AF, with encouraging preclinical preliminary results. Isolevuglandins are highly reactive products of lipid oxidation identified as key drivers of oxidative stress-related injury,[89] and small-molecule isolevuglandin scavengers reduce AF in people with hypertension.[90] Dysfunctional proteostasis results in misfolded and aggregated proteins, and these cytotoxic oligomers can be prevented by isolevuglandin scavengers, such as 2-hydroxybenzylamine (NCT NCT04433091). Proteostasis also can be improved by the heat shock protein modulator geranylgeranylacetone, and both therapeutic strategies suppress AF in animal models.[90,91]

Mitochondrial metabolism is an important source of oxidative stress and a critical determinant of atrial energetics. AMP-activated protein kinase (AMPK) plays a central role in cellular metabolism and energy homeostasis, and reduced AMPK activity causes spontaneous AF in animal models.[92] Drugs, such as metformin, that activate AMPK and promote mitophagy have been associated with lower incidence of AF in certain observational and in vitro studies,[93] making AMPK activity and mitochondrial function potentially attractive therapeutic targets. An RCT is currently testing the effect of metformin on AF burden in a sample of patients both with and without diabetes mellitus (NCT03603912). Similarly, in a post hoc analysis of RCT data, treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors appeared to reduce new-onset and recurrent AF events in patients with type 2 diabetes mellitus.[94] Like metformin, SGLT2 inhibitors also alleviated atrial remodeling and improved mitochondrial

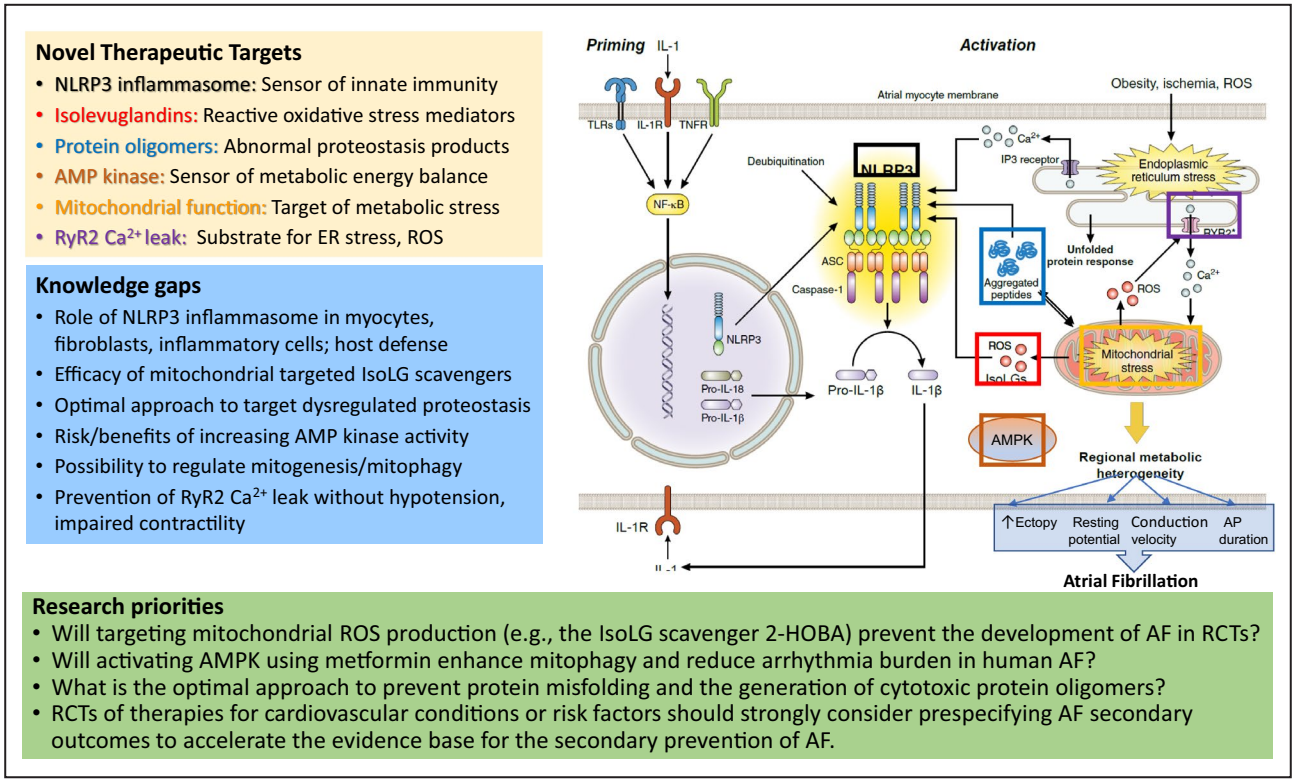

Figure 6. Emerging pharmacologic targets for the prevention of atrial fibrillation (AF).
Molecular components involved in priming and activation of the NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome, which has been linked to AF susceptibility. Obesity and ischemia promote endoplasmic reticulum (ER) stress and mitochondrial stress/dysfunction. These increase production of reactive oxygen species (ROS) and isolevuglandins (IsoLGs). ROS and IsoLGs promote aggregation of intracellular peptides/oligomers that can further impair mitochondrial function and activate NLRP3-induced cytokine production. AMP-activated protein kinase (AMPK) plays a central role in cellular metabolism and energy homeostasis, and reduced AMPK activity causes spontaneous AF in animal models. Increased spontaneous Ca^{2+} release from the sarcoplasmic reticulum contributes to atrial ectopy that can initiate episodes of AF. AP indicates action potential; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; 2-HOBA, 2-hydroxybenzylamine; IL, interleukin; IP3, inositol trisphosphate; NF-κB, nuclear factor κ light chain enhancer of activated B cells; RCT, randomized controlled trial; RyR2 Ca^{2+}, cardiac ryanodine receptor; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor.

dysfunction in a rat model of diabetes mellitus.[95] It will be of interest to determine the effects of both metformin and SGLT2 inhibitors on AF burden in patients without diabetes mellitus.

Calcium overload promotes uncoupling of the electron transport chain, increasing mitochondrial generation of reactive oxygen species, reducing the efficiency of oxidative phosphorylation, and increasing oxidation of critical calcium cycling proteins that include calcium/calmodulin-dependent protein kinase II and the ryanodine receptor.[96] Mitochondrial targeted antioxidants and/or other agents that attenuate calcium leak from oxidized or hyperphosphorylated ryanodine receptors are likely to reduce ectopic atrial activity.[97,98] Ryanodine receptor inhibitors reduce AF in animal models.[99]

Knowledge Gaps

Encouraging preliminary data on these novel mediators have generated additional questions and controversies. Inflammasomes are primarily expressed in inflammatory cells, whereas the NLRP3 inflammasome also has been identified in atrial cardiomyocytes. The relative contribution of NLRP3 activation in different cell populations to AF susceptibility as well as the optimal pharmacologic approach for inhibition remain unclear. The NLRP3 inflammasome is activated preferentially by damage rather than pathogen-associated molecules. The relative risk of infection with NLRP3 inhibitors compared with other anti-inflammatory agents, such as anti-cytokine targeted antibodies, like canakinumab, is unknown. The best studied isolevuglandin scavenger, 2-hydroxybenzylamine, has an elimination half-life in humans of 2 hours. New scavengers that preferentially target the mitochondria and/or have longer half-lives have been developed, but it is unclear whether these properties translate to increased efficacy in preventing AF recurrence.

Dysfunctional proteostasis is improved by both isolevuglandin scavengers and geranylgeranylacetone

(an inducer of heat shock gene expression), but which approach is most important and whether these approaches are redundant or additive have not been determined. Another unresolved issue is whether mitochondrial-targeted drugs will be effective in reducing excessive mitochondrial reactive oxygen species generation and whether it would influence AF recurrence or burden. It is unknown whether therapeutic agents that increase AMPK or anti–diabetes mellitus substances with additional cardiac effects, such as SGLT2 inhibitors, will be effective in patients with AF both with and without diabetes mellitus. Current agents that effectively suppress excessive calcium leak through ryanodine receptors can depress left ventricular systolic function and/or blood pressure, and it remains uncertain whether compounds can be identified that lack these detrimental properties.

There is increasing awareness that pharmacotherapies can have protective, neutral, and deleterious effects on cardiovascular outcomes. Unfortunately, although many trials of cardiovascular conditions and risk factors prespecify myocardial infarction and heart failure as outcomes, AF is often not specified a priori. Prespecifying AF onset, AF recurrence, AF progression, and AF-associated complications as outcomes for RCTs would accelerate the evidence base for the secondary prevention of AF.

Research Opportunities

1. Will targeting mitochondrial reactive oxygen species production (eg, the isolevuglandin scavenger 2-hydroxybenzylamine) prevent the development of AF in RCTs?
2. Will activating AMPK using metformin or other approaches enhance mitophagy and reduce arrhythmia burden in human AF?
3. To reduce AF burden and progression, what is the optimal approach to preventing protein misfolding and the generation of cytotoxic protein oligomers?
4. RCTs of therapies for cardiovascular conditions (eg, heart failure and myocardial infarction) or risk factors should strongly consider prespecifying AF onset, recurrence, progression, and associated complications as secondary outcomes to accelerate the evidence base for the secondary prevention of AF.

DISCUSSION

The NHLBI workshop participants identified multiple themes across our 6 domains of focus for the secondary prevention of AF recurrence, progression, and complications and identified critical research opportunities to advance the field (Table). There is a lack of mechanistic understanding on the pathophysiological features (eg, fibrosis, inflammation, mitochondrial reactive oxygen species, and dysfunctional proteostasis) linking risk factors and atrial electrical and structural remodeling to AF progression, remission, and complications. Furthermore, many risk factors for AF (eg, alcohol consumption, smoking, poor dietary patterns, obesity, diabetes mellitus, hypertension, sedentary lifestyle, and sleep disorders) are interrelated. It is unclear whether modification of a specific risk factor (eg, obesity) per se is sufficient, or must be addressed in the context of multiple risk factors to significantly prevent AF progression and complications.

Although strong observational data link risk factors to AF progression and complications, apart from anticoagulation for ischemic stroke prevention, RCTs for AF secondary prevention, which are vital to guideline development, have notable limitations. Previously conducted studies tend to be small to modest in size, are predominantly conducted in individuals of European ancestry, generally have been performed in the Netherlands, Australia, and Canada, typically are of short to medium duration, and examine intermediate end points (eg, AF burden), thus raising concerns about the studies' generalizability and robustness of their interventions to alter important clinical outcomes (eg, dementia, heart failure, myocardial infarction, chronic kidney disease, and death). There is a need to prespecify AF-related end points (onset, recurrence, progression, and clinical complications) in RCTs of other conditions (eg, heart failure, myocardial infarction, hypertension, and diabetes mellitus).

There is a paucity of AF secondary prevention data in diverse populations (eg, older adults, women, individuals of Black, Hispanic, Indigenous, Pacific Islander, and Asian ancestry, and those with lower educational attainment and lower income) and important clinical subgroups (eg, individuals with HFpEF). Hence, it is not definitive that AF risk factor management (eg, weight loss, alcohol abstinence, smoking cessation, CR, improved sleep, and integrated care) (1) has been designed to improve outcomes in diverse patients with AF; (2) would have similar benefits in patients with different types of AF or varying comorbidities (eg, HFpEF); and (3) whether changes in AF burden will translate into improved clinical outcomes.

Fundamentally, wider implementation of AF secondary prevention requires pragmatic, randomized implementation trials to develop strategies that are scalable, sustainable, practical, resource efficient, and clinically effective in diverse patient populations. One avenue for scalability is digital health. The role of mobile and wearable technology for the monitoring of AF burden and AF risk factors has been understudied for AF secondary prevention. It will be critical to investigate whether home-based implementation and monitoring

Table. Prioritized Research Opportunities for the Secondary Prevention of AF

Weight loss and body composition
Identify populations in whom successful weight loss leads to reversal of the atrial substrate for AF, and determine the mechanisms associated with the reversibility of epicardial fat and atrial fibrosis/substrate, including weight loss per se and regression of the comorbidities associated with obesity
Develop and test effective, reproducible, scalable tools and strategies required to achieve and sustain significant weight loss and risk factor management over the long-term in diverse populations (eg, age, sex, race/ethnicity, and socioeconomic status) with AF and then implement the appropriate public health initiatives in different health systems and diverse populations
Conduct multicenter pragmatic RCTs of the effect of weight loss, including bariatric surgery, and risk factor management in diverse individuals with AF on AF recurrence, burden, progression, and outcomes, including stroke, cognitive decline, heart failure, myocardial infarction, quality of life, healthcare use, costs, and mortality
Alcohol, smoking, and diet
RCTs of specific interventions, including (1) alcohol reduction or abstinence; (2) intensive smoking cessation; (3) heart healthy diets (eg, DASH type, plant based, and Mediterranean) vs usual care should be conducted, evaluating their efficacy in reducing AF burden or recurrence, improving quality of life, and reducing complications among diverse patients (eg, age, sex, gender, race/ethnicity, and socioeconomic status) with AF, including those with new-onset disease, those with paroxysmal AF, postcardioversion, and individuals managed with pharmacological therapies or AF ablation procedures
Develop and test implementation strategies to scale and sustain lifestyle interventions proven to be effective for secondary prevention of AF, potentially including (1) reducing or avoiding alcohol; (2) intensive smoking cessation; (3) heart healthy diets in diverse communities and community-based settings; and study their effect on AF recurrence, AF burden, quality of life, healthcare use, and complications (eg, stroke, cognitive decline, heart failure, myocardial infarction, frailty, and death)
Test the effectiveness of digital health and wearable technologies to enhance adherence to effective lifestyle interventions (alcohol and smoking cessation and dietary modification) in diverse communities and community-based settings, and study their effect on AF burden, AF recurrence, quality of life, healthcare use, and AF complications
Cardiac rehabilitation
Observational studies and RCTs of CR should oversample understudied subgroups of patients with AF, including older adults, women, Black/Hispanic/Asian/Pacific Islander/Indigenous individuals, HFpEF, and individuals with lower educational attainment/income. Outcomes should include success of risk factor modification (eg, if indicated smoking/alcohol cessation, weight loss, and control of blood pressure and diabetes mellitus) and AF-related symptoms, recurrence, progression, and clinical complications
RCTs should examine innovative implementation of CR strategies and their potential efficacy for reduced AF recurrence and complications in diverse representative AF populations: • Harnessing technology: virtual care with apps and wearables. • Home-based and hybrid models. • High-intensity interval training vs lower-intensity regimens (eg, yoga and tai chi).
Substudies of CR observational studies and RCTs should examine the association of CR with AF-related biomarkers, including biomarkers of inflammation, genetic variation, -omics, aging, metabolome, and atrial imaging
Sleep disorders
Pursue explanatory RCTs and pragmatic studies broadening the range of outcomes for integrated AF care, including patient-reported outcomes (eg, quality of life), AF recurrence and burden (eg, assessed with remote monitoring), team-based outcomes (eg, efficiency and workforce), intermediate outcomes (eg, physical functional status), as well as clinical end points (eg, stroke, heart failure, hospitalization, or death) and healthcare costs with the comparator being usual care, understanding that interpreting results may be challenging with ongoing temporal trends in management changes (eg, improved oral anticoagulation treatment). Critical to advancing the field will be to test integrated care approaches in a variety of healthcare settings and countries, including the United States, and diverse patient populations
Conduct outcomes research to compare integrated care strategies with guideline-based usual care and determine the benefits and risks of the individual elements fundamental to the integrated AF care approach (ie, active patient involvement, multidisciplinary team approach, use of mobile health technology to support integrated care, and comprehensive treatment approach)
Conduct RCTs to investigate the efficacy for AF recurrence, progression, and complications of multidisciplinary, team-based integrated care in secondary prevention vs usual care, oversampling specific subgroups of patients diverse in age, sex, race/ethnicity, and low socioeconomic status, ensuring that interventions are appropriately tailored to diverse demographics. Identify subgroups of patients with AF (eg, AF type or comorbidities) most likely to benefit compared with usual care approach provided by one single healthcare professional
Integrated, team-based care
Pursue explanatory RCTs and pragmatic studies broadening the range of outcomes for integrated AF care compared with usual care, including patient-reported outcomes (eg, quality of life), AF recurrence and burden (eg, assessed with remote monitoring), team-based outcomes (eg, efficiency and workforce), and intermediate outcomes (eg, physical functional status), as well as clinical end points (eg, stroke, heart failure, hospitalization, or death) and healthcare costs, with the comparator being usual care, understanding that interpreting results may be challenging with ongoing temporal trends in management changes (eg, improved oral anticoagulation treatment). Critical to advancing the field will be to test integrated care approaches in a variety of healthcare settings and countries, including the United States, and diverse patient populations
Conduct outcomes research to compare integrated care strategies with guideline-based usual care and determine the benefits and risks of the individual elements fundamental to the integrated AF care approach (ie, active patient involvement, multidisciplinary team approach, use of mobile health technology to support integrated care, and comprehensive treatment approach)
Conduct RCTs to investigate the efficacy for AF recurrence, progression, and complications of multidisciplinary, team-based integrated care in secondary prevention vs usual care, oversampling specific subgroups of patients diverse in age, sex, race/ethnicity, and low socioeconomic status, ensuring that interventions are appropriately tailored to diverse demographics. Identify subgroups of patients with AF (eg, AF type or comorbidities) most likely to benefit compared with usual care approach provided by a single healthcare professional

(*Continued*)

Table 1. Continued

Nonanticoagulant pharmacotherapy
Will targeting mitochondrial ROS production (eg, the isolevuglandin scavenger 2-HOBA) prevent the development of AF in RCTs?
Will activating AMPK using metformin or other approaches enhance mitophagy and reduce arrhythmia burden in human AF?
To reduce AF burden and progression, what is the optimal approach to preventing protein misfolding and the generation of cytotoxic protein oligomers?
RCTs of therapies for cardiovascular conditions (eg, heart failure and myocardial infarction) or risk factors should strongly consider prespecifying AF onset, recurrence, progression, and associated complications as secondary outcomes to accelerate the evidence base for the secondary prevention of AF

2-HOBA indicates 2-hydroxybenzylamine; AF, atrial fibrillation; AMPK, AMP-activated protein kinase; CR, cardiac rehabilitation; DASH, Dietary Approaches to Stop Hypertension; HFpEF, heart failure with preserved ejection fraction; RCT, randomized controlled trial; and ROS, reactive oxygen species.

of weight, alcohol/smoking/dietary habits, activity, CR, and sleep enhance the adherence, efficiency, and effectiveness of risk factor monitoring and modification for AF secondary prevention.

The secondary prevention of AF progression and its complications is of vital public health importance because ≈5.2 million individuals in the United States are known to have AF (2010 estimate).[1] Since 1990, the global prevalence of AF has approximately doubled to 59.7 million individuals in 2019.[100] Furthermore, over the same time period, the age-standardized prevalence, disability-adjusted life years, and mortality have not substantially changed.[100] Hence, AF will continue to lead to substantial morbidity as well as excess health care use, costs, and mortality. Although there are robust guidelines for the prevention of stroke after AF onset, there is a lack of class I evidence to strongly support the secondary prevention of dementia, heart failure, myocardial infarction, chronic kidney disease, diminished quality of life, functional limitations, and increased healthcare use after AF is diagnosed. The authors hope this workshop will catalyze research that will advance the evidence base for the secondary prevention of the recurrence, progression, and complications of AF.

ARTICLE INFORMATION

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Affiliations

Cardiovascular Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA (E.J.B.); Department of Epidemiology, Boston University School of Public Health, Boston, MA (E.J.B.); Division of Cardiology and Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (S.M.A.); Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD (P.D., L.S.C.); Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA (A.A.); Division of Aging, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (L.D.); Divisions of Geriatrics and Cardiology, University of Pittsburgh Medical Center, Aging Institute, University of Pittsburgh, VA Pittsburgh Healthcare System, Pittsburgh, PA (D.E.F.); Libin Cardiovascular Institute of Alberta, University of Calgary, Alberta, Canada (A.M.G.); Centre for Heart Rhythm Disorders, University of Adelaide, and Royal Adelaide Hospital, Adelaide, Australia (J.M.L.H., P.S.); Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Adelaide, Australia (J.M.L.H.); StopAfib.org, American Foundation for Women's Health, Decatur, TX (M.T.H.); Department of Cardiology, University Heart and Vascular Center UKE Hamburg, Hamburg, Germany (P.K.); Institute of Cardiovascular Science, University of Birmingham, United Kingdom (P.K.); German Center for Cardiovascular Research, Partner Site Hamburg/Kiel/Lübeck, Berlin, Germany (P.K.); AFNET, Münster, Germany (P.K.); Division of Cardiology, Department of Medicine, UT Southwestern Medical Center, Dallas, TX (M.S.L.); Division of Cardiology, University of California, San Francisco, San Francisco, CA (G.M.M.); Sleep Disorders Center, Neurologic Institute, Respiratory Institute, Heart and Vascular Institute, and Molecular Cardiology Department of the Lerner Research Institute, Cleveland Clinic, Cleveland, OH (R.M.); Vanderbilt University School of Medicine, Nashville, TN (K.T.M.); Division of Cardiology, QEII Health Sciences Center/Dalhousie University, Halifax, Nova Scotia, Canada (R.P.); Wayne State University, Detroit, MI (I.L.P.); Central Michigan University, Mt Pleasant, MI (I.L.P.); FDA, OPEQ, Center for Devices and Radiological Health, Silver Spring, MD (I.L.P.); Department of Medicine, Brigham and Women's Hospital, Boston, MA (S.R.); Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands (M.R.); Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (V.K.S.); Cleveland Clinic Lerner College of Medicine, Cleveland, OH (D.R.V.W.); Stanford University School of Medicine, Palo Alto, CA (P.J.W.); Division of Research, Kaiser Permanente Northern California, Oakland, CA (A.S.G.); Department of Health System Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA (A.S.G.); Departments of Epidemiology, Biostatistics and Medicine, University of California, San Francisco, San Francisco, CA (A.S.G.); and Departments of Medicine, Health Research and Policy, Stanford University, Stanford, CA (A.S.G.).

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Supplementary Material

Tables S1–S2
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Supplemental Material

Table S1. Published Cardiac Rehabilitation Studies.

Study	Study	AF type	CR versus control	N(%) women	N(%); Race	Inc.; educ	Mean age	Results
Studies included in Smart et al. meta-analysis[48]								
Hegbom F, *J Cardiopulm Rehabil* 2006[101] Characteristics gleaned *Int J Cardiol*[102] 2007 Oslo, Norway	RCT 2-month exercise training vs. control, followed by training, crossover, single center	Permanent AF	15/15 randomized 13/15 analyzed	Training: 13/0 ♂/♀ Control 13/2 ♂/♀	Race NR, Norway	NR	age 64 ± 7 years 62 training 65 control; Age<75 yr	Significant improvement in health related QoL 4/8 SF-35 scales improved significantly with training
Malmo[103] *Circulation* 2016 Trondheim, Norway	RCT; single center; aerobic interval training	51 pts nonpermanent AF	26/25 randomized and analyzed aerobic interval training 12 weeks vs. control	3(12%) control; 6 (23%) exercise	Trondheim, Norway Race NR	NR	56±8*	Aerobic interval training improved time in AF, AF symptom frequency & severity, QO_2 peak, LVEF, QoL
Osbak[104] *Am Heart J* 2011 Copenhagen, Denmark	RCT 12-wk aerobic exercise vs. control; single center	Permanent AF	49 25/24 randomized 24/23 analyzed 12 wk aerobic exercise training vs. control	♂:♀ ratio 0.75	Copenhagen, Denmark Race not specified	NR	70.2 ± 7.8 years	Exercise training improved exercise capacity, 6 minute walk test, QoL assessed by MN Living With Heart Failure questionnaire
Pippa[105] traditional Chinese medicine (qi gong) training *Prev Cardiol* 2007 Hospital of Lanciano, Italy	16 week RCT qi Gong Vs. wait list control; single center	Permanent AF	22/21 randomized and analyzed 16-week medically assisted qi gong training program	30 men and 13 women	Italy Race NR	<€18,000/yr Low Income 5 (23%) Rx; 8 (38.1) control; education NR	mean age, 68±8 years	qi gong training program associated with 114 meters more walking at end of treatment & 57 meters more at 16 additional weeks
Wahlstrom[106] yoga *Eur J Cardiovasc Nurs* 2017 Stockholm, Sweden	RCT Yoga vs. control	80 PAF yoga group 33 patients completed 12 weeks	40/40 randomized 33/36 analyzed Standard Rx vs. standard Rx + yoga	Yoga male/female 16 (48)/ 17(52)	Stockholm, Sweden Race NR	NR	64±7 years	Yoga with light movements & deep breathing led to improved QoL, lower blood pressure

Study	Study	AF type	CR versus control	N(%) women	N(%); Race	Inc.; educ	Mean age	Results
Zeren[107] Clin Rehabil 2016;30:1165–74. Istanbul, Turkey	RCT "inspiratory muscle training at 30% of maximal inspiratory pressure for 12 weeks + standard medical Rx; single center	Permanent AF	19/19 randomized 17/16 analyzed; inspiratory muscle training 30% max inspiratory pressure for 15 min 2/day, 7days/week 12weeks	½ women	Istanbul, Turkey Race NR	NR	~67 years	Inspiratory muscle training enhanced pulmonary function, respiratory muscle, strength & functional capacity
Risom[108] Am Heart J 2016 Copenhagen, Denmark Risom[109] 2013 design paper NCT01523145 12 & 24 mo f/u[110]	RCT; two centers; $CopenHeart_{RFA}$	72% PAF 28% persistent AF Treated for AF with catheter ablation	105/105 randomized* 210	26% women; 74% men	Copenhagen[109] Race NR	NR 2013 paper: educational status & occupation collected	59 years	improved physical capacity vs. usual care, but not mental health; -12 mo Mean VO_2peak higher CR; -24 mo CR lower anxiety. - NS: admissions or death
Skielboe[111] *PLoS One* 2017 Copenhagen University Hospital, Amager and Hvidovre	12-week RCT 403 potentially eligible; 126 asked to participate 50 declined	76 patients with paroxysmal/ persistent Exclude permanent AF	RCT low (50%) or high (80%) intensity max perceived exertion 38/38 randomized† 26/29 analyzed†	76 pts, 63 completed f/u; Low: 42% women High: 41% women	Low: 97% High: 97% N=2 "other" race	NR	Low: 64 High: 61	ITT analysis no statistical difference in burden of AF between low vs high intensity exercise Incidence rate ratio 0.74 [95% CI, 0.29-1.91]; *P*=0.54
Luo[49] *J Am Coll Cardiol* 2017 HF-Action site investigators US (n=67), Canada (n=9), France (n=6)[112]	HF-ACTION multicenter RCT 2,292 total ambulatory patients with HF with LVEF ≤35%	382 (17%) AF 1602 (70%) SR 308 (13%) other	RCT exercise training vs. usual care Median f/u 2.6 yrs	30% women overall AF: 16% women SR: 537/1,602 (33.5)	AF: Black individuals 78/378 (20.6%) White 280/378 (74.1%) SR: 591/1,577 (37.5) Black individuals	NR	AF: Median: 63.1 IQR: 55.7-72.8 yr SR: 57 yr	NS AF event rates by RCT in overall population or baseline AF; no interaction AF & exercise training functional status or clinical outcomes

Study	Study	AF type	CR versus control	N(%) women	N(%); Race	Inc.; educ	Mean age	Results
Studies not included in Smart et al. meta-analysis;[48] published 2018 & later								
Reed[113] *Can J Cardiol* 2018 Ottawa, Ontario, Canada	Retrospective Observational study pts with heart disease. Matched AF: no AF attending CR	persistent or permanent AF; Patients free of AF referents	3 months CR AF n=47 vs. no AF n=47 94 patients	23% ♀; 77% ♂	85% White	NR	69.9 AF 69.7 no AF Matched	Observational; In patients with heart disease CR improved QoL to greater extent in pts w/o AF vs. with AF
Alharbi[114] *Can J Cardiol*. 2019; Halifax, Nova Scotia	Single center retrospective cohort study	566 newly dx AF 133 (23.5%) underwent CR; 197 ()34.8% AFC; 236 (41.7%) usual specialist care	AF ED visits & CV hospitalizations 7.5% CR; 16.8% AFC; 29.9% Usual Care	Female: CR: 35% AFC: 45% UC: 45%	NR, Canada	NR	Age ≥75 yrs CR: 22% AFC: 24% UC: 27.5%	Propensity match vs. CR: UC OR 4.91 [95% CI, 2.09-11.53]; AFC OR, 2.75 [95% CI, 1.14-6.6]
Kato[115] *Eur J Prev Cardiol*. 2019 Shizuoka Medical Center, Shizuoka Japan	Single-center RCT Consecutive AF pts 2014-16	61 pts post-ablation persistent AF	30 CR 6-month exercise-based CR; 2 dropped out analyzed 28 vs. 31 control	19 women 20% 48 men 80%	NR Japanese	NR	66±9 years	CR, significant increase 6-min walk test, handgrip & leg strength, LVEF, sign. Decrease CRP; NS in AF recurrence
Rienstra[52] *Eur Heart J*,. 2018 Netherlands, UK[116,117]	RACE3 Multicenter RCT	Persistent AF and HF	CR, mineralocorticoid antagonists, statins, ACEi/ARB, rhythm control vs usual care 119/126	193 men (79%) 52 women (21%)	NR	NR	65±9 years	Improvement in sinus rhythm maintenance, BP, NT-proBNP
Joensen[118] *J Rehabil Med* 2019 Denmark	Single center RCT	Paroxysmal (48%) and persistent AF (52%)	12 week CR; 28/30; 6 dropped out 24 vs 28	18 women (35%) 34 men (65%)	NR	NR	61 years	Improved QOL at 6 months; attenuated at 12 months; increased exercise capacity

Study	Study	AF type	CR versus control	N(%) women	N(%); Race	Inc.; educ	Mean age	Results
Borland[119] *Translational Sports Medicine*. 2020 Sweden NCT02493387	Multicenter RCT	Permanent AF	**PT-X** Physiotherapist-led exercise CR with physical activity (60 min group session & home-based exercise 2/wk) vs. **PAP** physical activity prescription (40 min walking 4x/wk)	96 pts; 28 women	NR Swedish	NR	74±5 years	PT-X Significant improvement exercise tolerance, muscle endurance; PAP significant increase energy expenditure NS: Health-related QOL
Multi-Center, Multi-Country Study designed, currently enrolling								
RASTA AF NCT03682991 Canada/Netherlands PI: R Parkash	Multi-center PROBE RCT;	Symptomatic Paroxysmal, persistent AF undergoing ablation	Home-based CR, alcohol reduction, sleep apnea, BP, smoking **vs** usual care	pending	Pending; Estimated enrollment n=670	Pending	Pending	Start date 7/2019; Estimated completion 12/2022; Estimated release 2023

AF, atrial fibrillation; AFC, specialized atrial fibrillation clinic; BP, blood pressure; CR, cardiac rehabilitation; educ, education; HF, heart failure; inc, income; LVEF, left ventricular ejection fraction; NR, not reported; pts, patients; RCT, randomized controlled trial; Rx, treatment; SR, sinus rhythm; QoL, quality of life; UC, usual care; US, United States

Table S2. Cardiac Rehabilitation (CR) Studies in Clinicaltrial.gov.

NCT Number	Title	Status	Conditions	Interventions	Characteristics	Sponsor/Collaborators	Dates	Locations	Design
NCT04414007 PI: Guozhen Sun, MD & Zhipeng BAO	The Application of Internet+ Home-based Cardiac Rehabilitation in Atrial Fibrillation Patients After RFCA	Recruiting	Atrial Fibrillation Cardiac Rehabilitation	Behavioral: Internet+ home-based cardiac rehabilitation •Behavioral: Conventional rehabilitation	Study Type: Interventional	•Nanjing Medical University	Study Start: January 1, 2019 Study Completion: June 30, 2022	•The First Affiliated hospital of Nanjing Medical University, Najing, Jiangsu, China	Randomized; single center; surrogate outcomes HbA1C at 12 months
NCT04092166 PI: Suneet Mittal, MD	Impact of a Structured Cardiac Rehabilitation Program on Cardiorespiratory Fitness in Patients With Atrial Fibrillation	Recruiting	•Atrial Fibrillation	Other: Stationary Bike Study	Interventional	•Valley Health System	Study Start: May 1, 2019 Study Completion: May 2022	•Valley Health System •The Valley Hospital, Paramus, New Jersey, United States	Randomized, single center; n=120; primary outcome, increase in cardiorespiratory fitness
NCT04600713 PI: Maria Borland, PhD RPT	Physiotherapist-led Exercise Within Cardiac Rehabilitation and Paroxysmal Atrial Fibrillation and COVID-19.	Not yet recruiting	•Atrial Fibrillation Paroxysmal	Other: PT-X and IMT	Interventional	Vastra Gotaland Region	Study Start: 1/2021 Study Completion:10/ 2025	Vastra Gotaland Region	Randomized; n=180; single center; HRQOL with SF36
NCT03389633 PI: Paul Dendale, prof. dr.	Does Cardiac Rehabilitation Reduce the Risk of Recurrence of Atrial Fibrillation Following the First Catheter Ablation?	Completed	Atrial Fibrillation	Other: rehabilitation Study; 3 months	Type: Interventional	•Hasselt University	Study Start: January 1, 2007 Study Completion: July 31, 2016		Non-randomized; n=462; number of recurrences of AT or need for new ablation

NCT Number	Title	Status	Conditions	Interventions	Characteristics	Sponsor/Collaborators	Dates	Locations	Design
NCT04500184 PI: Dong Seop Jeong, PhD	Exercise-based Cardiac Rehabilitation After Thoracoscopic Ablation In Patients With Persistent Atrial Fibrillation	Completed	Atrial Fibrillation Persistent Cardiac Rehabilitation •Cardio-pulmonary Fitness	Other: cardiac rehabilitation	Observational Retrospective	Samsung Medical Center	Study Start: June 1, 2017 Study Completion: May 31, 2020	•Samsung Medical Center, Seoul, Korea, Republic of	Observational case-control, retrospective, n=24; recurrence of AF, exercise capacity and IPAQ
NCT03035539 PI: Albert Marni Joensen, MD, PhD	Rehabilitation of Patients With Atrial Fibrillation	Completed	Atrial Fibrillation	Other: Cardiac rehabilitation •Other: Standard treatment	Interventional	Aalborg University Hospital	May 2012 Study Completion: April 2014	Aalborg Hospital, Aalborg, Denmark	Randomized, n=58; outcome QOL (AFEQT, AF-QOL, GAD7, PHQ-9); single center
NCT00877643 See Table S1 Rienstra[52] PIs: Marco Alings, MD, PhD; Isabelle C Van Gelder, MD, PhD; Harry J Crijns, MD, PhD	Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure	Active, not recruiting	•Atrial Fibrillation	Other: Upstream therapy •Other: Conventional rhythm control	Study Type: Interventional	•I.C. Van Gelder •The Interuniversity Cardiology Institute of the Netherlands •Netherlands Heart Foundation •Dutch Network for Cardiovascular Research •Trial Coordination Center UMC Groningen •Bayer •Boehringer Ingelheim •Medtronic •Biotronik SE & Co.KG •Abbott Medical Devices •and 3 more	Study Start: May 2009 Study Completion: January 2021	**Netherlands** •Ziekenhuisgroep Twente, Almelo/Hengelo •Onze Lieve Vrouwe Gasthuis, Amsterdam •Hospital Rijnstate, Arnhem/Velp, •Ter Gooi Hospital, Blaricum, •Amhia Hospital, Breda •Ommelander Hospital Group, Delfzijl, •Deventer Hospital, Deventer, •Oosterscheldeziekenhuis, Goes, •Martini Hospital, Groningen, •University Medical Center Groningen, Groningen •and 10 more	Long term follow up of RACE 3 which is already published and included in our discussion

NCT Number	Title	Status	Conditions	Interventions	Characteristics	Sponsor/Collaborators	Dates	Locations	Design
NCT02493387 See Borland Table S1; Study Director: Asa Cider, PhD RPT	Supervised Exercise Compared with PAP in Patients With Permanent Atrial Fibrillation	Completed	•Atrial Fibrillation	•Other: Exercise •Other: Physical activity	Study Type: Interventional	•Göteborg University	Study Start: 1/2013 Study Completion: 11/ 2018	•Sahlgrenska University Hospital and Alingsås Hospital	Randomized; n=96; outcome physical fitness; single center
NCT03259893 PI: Robert Helm, MD	Boston Medical Center Secondary Prevention of Atrial Fibrillation	Terminated	Paroxysmal AF	Risk factor targeting: hypertension, obesity, physical inactivity, sleep hygiene, & smoking; referral to CR clinic	hybrid Type 3 implementa-tion-effectiveness study; Primary outcome: Feasibility	Boston Medical Center	Actual Study Start Date: 2/1/2018; Study terminated 5/11/2020	Urban safety-net hospital Boston Medical Center, Boston, MA	3 patients enrolled; terminated
NCT02219841 Mohanty Abstract *Circulation* 2017[120] PIs: Andrea Natale, MD; Mitra Mohanty, MD	Impact of Life-Style Modification On Ablation Outcome in Atrial Fibrillation	Recruiting	•Atrial Fibrillation •Obesity	Procedure: radiofrequency catheter ablation	Study Type: Observational	Texas Cardiac Arrhythmia Research Foundation	Study Start: 8/ 2014 Study Completion: 12/2022	•Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, Texas,	Randomized? (says case-control in another area) pilot; AF recurrence following ablation; single center; n=50
NCT02602457 PI: Jennifer L Reed, PhD	Exercise Training in Patients With Atrial Fibrillation (OPPORTUNITY Study)	Active, not recruiting	•Atrial Fibrillation	Behavioral: moderate intensity continuous exercise training •Behavioral: high-intensity interval training	Study Type: Interventional	Ottawa Heart Institute Research Corporation	Study Start: 11/ 2015 Study Completion: 10/ 2022	•University of Ottawa Heart Institute, Ottawa	Randomized; n=108; single center; QOL and exercise capacity

NCT Number	Title	Status	Conditions	Interventions	Characteristics	Sponsor/Collaborators	Dates	Locations	Design
NCT03910192 PI: Paul Ritvo, Ph.D	Mindfulness to Reduce Ambulatory Hypertension in Atrial Fibrillation	Recruiting	Atrial Fibrillation •Hypertension •Mindfulness •Cardiovascular Risk Reduction	•Behavioral: Mindfulness-based coaching 16-week mindfulness-based protocol focused on home-based & weekly group practice of mindfulness meditation & mindful movement. personal Coaching support; •Comparator: Behavioral: Dietary cardiovascular risk reduction coaching	Study Type: Interventional	•York University •Southlake Regional Health Centre	Study Start: March 14, 2017 Study Completion: 12/ 31/2019	Southlake Regional Health Centre, Newmarket	Randomized; n=50; two centers; nighttime systolic BP and daytime systolic BP
NCT03103854 PI: Avinash Pandey	Novel Strategies to Improve Cardiometabolic Status and Adherence to Exercise Regimens in Patients at High Risk for Cardiovascular Disease	Unknown status	•Diabetes Mellitus, Type 2 •Myocardial Infarction •Coronary Artery Disease •AF •Heart Failure	Behavioral: BURST physical activity •Behavioral: Text Message Reminders •Behavioral: Moderate Intensity Continuous Training	Study Type: Interventional	Cambridge Cardiac Care Centre	Study Start: January 1, 2014 Study Completion: December 31, 2019	•Cambridge Cardiac Rehab, Cambridge	Randomized; n=500; HbA1C at 12 months; single center

NCT Number	Title	Status	Conditions	Interventions	Characteristics	Sponsor/Collaborators	Dates	Locations	Design
NCT03724383 PI: Teddi Orenstein Lyall, MD	Atrial Fibrillation Lifestyle Project	Unknown status	Atrial Fibrillation Paroxysmal	•Behavioral: Risk Factor Management Consult •Behavioral: Diet Classes •Behavioral: Stress Management Classes •Other: Exercise Classes •Other: Home based exercise program	Study Type: Interventional	•Teddi Orenstein Lyall •Vancouver Coastal Health •Vancouver Coastal Health Research Institute •University of British Columbia	Study Start: September 6, 2018 Study Completion: April 2020	**British Columbia, Canada** •Richmond Hospital Cardiac Rehabilitation, Richmond •Richmond Health Services, Richmond •Garratt Wellness Centre, Richmond, •Richmond Cardiology Clinic, Richmond •Gordon and Leslie Diamond Health Care Centre, Vancouver •Live Well Clinic, Vancouver •St. Paul's Healthy Heart Program	Randomized; n=80; several centers in Vancouver, BC; outcome changes in frequent of AF on 48 h Holter, QOL
NCT04511520 No contacts	Efficacy of Personalized Exercise Program and Trimetazidine in Rehabilitation of Patients After RFA of AF	Completed	Atrial Fibrillation Paroxysmal	•Other: Physical training program •Drug: Trimetazidine	Study Type: Interventional	•National Research Center for Preventive Medicine •National Medical Research Center for Therapy and Preventive Medicine	Study Start: July 2013 Study Completion: April 2017		Randomized; n=72; AF recurrence; unknown where recruitment occurred
NCT01523145 **See Table S1** Risom[109] PIs: Signe S Risom, RN, MSc; Selina K Berg, MScN, PhD.; Ann-Dorthe O Zwisler, MD, PhD; Jesper H Svendsen, MD, DMSc	CopenHeartRFA - Integrated Rehabilitation of Patients Treated for Atrial Fibrillation With Radio Frequency Ablation	Completed	•Atrial Fibrillation	Behavioral: Rehabilitation •Other: Control Group	Study Type: Interventional	•Rigshospitalet, Denmark •Copenhagen Trial Unit, Center for Clinical Intervention Research	Study Start: 12/2011 Study Completion: 1/ 2016	•Rigshospitalet, Copenhagen, Denmark	Randomized; n=210; PeakVo2; two centers in Denmark

NCT Number	Title	Status	Conditions	Interventions	Characteristics	Sponsor/Collaborators	Dates	Locations	Design
NCT03068169 Balsam *Cardiol J* 2018 Design paper[121] PIs: Renata Główczyńska, PhD; Paweł Balsam, PhD; Piotr Lodziński, PhD; Marcin Grabowski, PhD	Biomedical Shirt-based ECG Monitoring	Unknown status	•ECG Monitoring 120 patients after PVI for AF		Study Type: Observational	Medical University of Warsaw	Study Start: June 15, 2017 Study Completion: December 31, 2018	**Warsaw, Mazowieckie, Poland** •Department of Pediatric Cardiology and General Pediatrics, Medical University of Warsaw •Department of Clinical Nursing, Medical University of Warsaw •Pawe# Balsam	Observational; recurrence of atrial tachyarrhythmia using an ECG shirt

Unless otherwise noted, Studies Listed in Table S2 have no results available

Search: https://www.clinicaltrials.gov/ct2/results?term=cardiac+rehabilitation&cond=Atrial+Fibrillation