Advancing Research on the Complex Interrelations between Atrial fibrillation and Heart Failure: A Report from a National Heart, Lung, and Blood Institute Virtual Workshop

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Abstract

The interrelationships between atrial fibrillation (AF) and heart failure (HF) are complex and poorly understood, yet the number of patients with AF and HF continues to increase worldwide. Thus, there is a need for initiatives that prioritize research on the intersection between AF and HF. This report summarizes the proceedings of a virtual workshop convened by the National Heart, Lung, and Blood Institute to identify important research opportunities in AF and HF. Key knowledge gaps were reviewed and research priorities were proposed for characterizing the pathophysiological overlap and deleterious interactions between AF and HF; preventing HF in persons with AF; preventing AF in individuals with HF; and addressing symptom burden and health status outcomes in AF and HF. These research priorities will hopefully help inform, encourage, and stimulate innovative, cost-efficient, and transformative studies to enhance the outcomes of patients with AF and HF.

Keywords

atrial fibrillation; heart failure; research

Atrial Fibrillation (AF) and Heart Failure (HF)

Atrial fibrillation (AF) and heart failure (HF) are highly prevalent clinical conditions that frequently co-exist.[1–3] It is well known that patients with HF are at increased risk of AF.[1–3] Of the estimated 5.8 million Americans with HF with reduced ejection fraction (HFrEF) or preserved EF (HFpEF), up to 40% develop AF.[1, 4] AF itself can cause HF via different mechanisms.[2, 3] Risk factors are similar for both AF and HF, including advancing age, male sex, tobacco use, alcohol consumption, physical inactivity, sleep disorders, obesity, hypertension, diabetes mellitus, coronary heart disease, and valvular heart disease. In addition, there are underlying genetic predispositions for both conditions.[2, 3] Many have called for better understanding of mechanisms predisposing to AF in HF patients and to HF in AF patients, identifying high risk subgroups of patients with AF or HF for screening and prevention, and detecting and treating asymptomatic or paroxysmal AF early on as a means to prevent AF and HF progression. Many have also called for improved understanding of symptom burden in AF versus HF and the best approaches to utilizing and refining patient-reported outcomes, improving monitoring, and tailoring treatment to patient-specific benefit in order to optimize the quality of care. Therefore, there is a need for a platform that allows discussion and consideration of research priorities that will help address these gaps in knowledge.

Recognizing the importance of AF research, in 2008 the National Heart, Lung, and Blood Institute (NHLBI) convened an expert panel to identify gaps and recommend research strategies focused on improving AF prevention.[5] To build on this prior work, the NHLBI recently launched a series of webinar-based workshops covering different areas in AF. The first virtual workshop in the series focused on catheter ablation of AF.[6] The second workshop, held on August 14, 2019, had an overall theme of advancing research on the complex interrelationship between AF and HF. The webinar provided a platform for the identification of research priorities by covering the following four specific topics in AF and

HF: 1) pathophysiological overlap between AF and HF, 2) prevention of HF in individuals with AF, 3) prevention of AF in individuals with HF, and 4) symptom burden in AF and HF. This report summarizes the content of the webinar. In addition, upon the report's publication, the topic frameworks and recorded webinar will be posted on the NHLBI website.[7]

The Overlapping Pathophysiology Between AF and HF

It is well known that AF can lead to cardiomyopathy and HF via different mechanisms including persistent tachycardia, abnormalities in calcium handling, changes in ion channel expression, irregular ventricular response leading to abnormal excitation-contraction coupling, and neurohormonal activation.[1, 8, 9] Studies have shown that left atrial fibrosis, stretch, and denervation, as well as the downregulation of natriuretic peptides that occur in AF can aggravate both HFrEF and HFpEF.[9–13] However, other causal links between HF and AF likely differ between HFrEF and HFpEF and, as such, should be evaluated differently for these conditions. Neurohormonal activation is more intense with HFrEF and may be further aggravated by the fast heart rate and irregularity of AF.[11–13] In contrast, inflammation that may predispose to AF may initially be more relevant to the metabolic milieu of HFpEF, but immune activation increases with severity of disease in both HFrEF and HFpEF.[14–16]

Tachycardiomyopathy is a type of cardiomyopathy that develops as a result of rapidly conducted AF. Development and resolution of tachycardiomyopathy caused by AF are defined for HFrEF by changes in left ventricular (LV) EF, but a parallel indicator does not exist for HFpEF.[1] HFpEF definitions and staging are further complicated by distinct phenotypes relating to presence or absence of obesity and baseline venous congestion, which worsen diastolic function, exertional dyspnea, and hospitalizations that characterize clinical HFpEF.[1]

AF, obstructive sleep apnea (OSA), and HF cluster together.[17, 18] These three conditions share not only similar risk factors but are influenced by and have effects on neurohormonal activation.[11, 17] Tachycardiomyopathy from AF may reflect not only the direct effect of persistently elevated heart rates but also the adverse effects of sympathetic stimulation. The rapid activation rate and irregularity of ventricular response in AF cause intermittent reduction in diastolic pressure, which, in turn, further activates the sympathetic nerves.[11] Microneurography studies show that muscle sympathetic nerve activity as well as circulating plasma norepinephrine are increased in patients with OSA.[19, 20] Continuous positive airway pressure therapy can attenuate the increased sympathetic tone.[20] It can also improve LVEF in patients with HFrEF.[21] These findings suggest that OSA is a modifiable risk factor for both AF and HF. In addition to beta-blocker therapy, neuromodulation methods that further reduce sympathetic output might provide additional therapeutic benefit in patients with AF and HF with or without OSA.[22–24] Whereas baroreflex activation therapy has been approved for selected patients with HF, recent randomized clinical trials of vagal nerve stimulation in HFrEF did not include patients with chronic AF.[25–27] It remains possible that patients with AF, OSA, and HF may benefit from neuromodulation methods that reduce sympathetic nerve activity.

Current indications and selection of interventions for rhythm control of AF have appropriately mostly focused on improvement of symptoms, which is a top priority.[28–32] However, the potential for "cure" of tachycardiomyopathy elevates the urgency of identification and aggressive treatment of AF in at risk patients, even without compelling current symptoms. Toward that end, the following knowledge gaps were identified:

- A crucial knowledge gap is the risk profile and prevalence of tachycardiomyopathy identified retrospectively by normalization of a reduced EF. This condition appears to be most common in patients without coronary heart disease, particularly those in whom HF appears synchronously or after the onset of AF, and those with little or no ventricular fibrosis detected by late gadolinium enhancement on cardiac magnetic resonance imaging (MRI).[32] The best way to address this gap is to curate a carefully phenotyped cohort of patients undergoing definitive therapy for AF, including baseline cardiac MRI and echo imaging, genetic testing, and serial evaluation to follow changes in LV function/ fibrosis and symptom status.

- Further studies should investigate treatment regimens, including pharmacologic and direct neurohormonal modulation. These interventions should be tested for their role in enhancing recovery from and preventing tachycardiomyopathy in patients at high risk for progression due to a monitored high burden of paroxysmal AF (Figure 1).

- An important priority is the development of medications for treating AF that either do not lead to adverse HF outcomes or can improve HF outcomes.

- Another knowledge gap relates to whether vigilant maintenance of volume balance and optimal left atrial pressures can reduce progression from paroxysmal to persistent AF and improve the outcomes of AF ablation and other rhythm control strategies.

The following prioritized research opportunities were identified:

1. To establish the risk profiles and prevalence of tachycardiomyopathy with complete and partial reversibility of LV dysfunction. This may be best accomplished through a curated cohort of patients with AF and HF in whom the following are characterized: biomarkers, fibrosis on cardiac MRI, cardiac structure on cardiac MRI and echocardiography, genomic (methylation, transcriptomic, proteomic, metabolomic, etc.) and genetic profiles of cardiomyopathy and AF, peak VO2 testing, and patient-reported outcomes before and at 6 and 12 months after ablation, to determine frequency and predictors of meaningful improvement in LV function and outcomes.

2. To conduct a randomized trial of intensive maintenance of volume status vs. usual care to reduce progression of HF and progression of paroxysmal to persistent AF as well as following AF ablation in adults with either HFrEF or HFpEF. Outcomes in both HFrEF and HFpEF would include diastolic function, left atrial volume, and patient-reported symptoms and function, and in HFrEF, LVEF and LV dimensions.

3. To conduct randomized clinical trials of catheter ablation, antiarrhythmic drugs, and prevention in patients with AF and HF. To enhance the feasibility of such trials, pragmatic and other innovative trial designs should be leveraged.

Research to Prevent HF in Individuals with AF

As noted above, AF and HF are closely intertwined, with each condition predisposing to the other.[1–4, 33, 34] The risk of both HFrEF and HFpEF is elevated in patients with AF.[1–4, 33, 34] Notably, the 5-year incidence of HF is nearly twice that of incident stroke after AF diagnosis, yet the clinical focus has been squarely on stroke prevention after AF, whereas little is known about HF prevention in this growing population.[35] There are a number of randomized clinical trials not focused on individuals with AF demonstrating that HF can be prevented among high-risk individuals.[36–38] For example, selected antihypertensive treatments (ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) and HYVET (Hypertension in the Very Elderly Trial)) may prevent the development of HF.[37, 38] Whether such HF preventive strategies are generalizable to individuals with AF has not been established.

Observational studies suggest that traditional modifiable risk factors account for more than half of the population's attributable risk of developing HF among persons with AF, and these may be even more prevalent in HFpEF.[39, 40] This suggests that AF may provide an opportunity to focus preventive efforts with careful attention on known cardiovascular risk factors. For example, initial studies evaluating weight loss and intensive risk factor control in AF patients have reported favorable effects on cardiac structure and function that may reduce incident HF.[41] However, clinical and therapeutic strategies to prevent HF among patients with AF remain largely understudied, and randomized controlled trials should investigate the efficacy of such strategies (**Figure 2**).

With the recognition that incident HF is common among patients with AF, and that HF can be prevented in the context of prior clinical trials in broader populations, the following knowledge gaps were identified:

- There is limited understanding as to whether HF after AF occurs due to shared underlying mechanisms, with a common pathobiology of AF and HF. In contrast, there may also be hemodynamic and other triggers for cardiac remodeling that are specifically driven by AF that make the progression to HFrEF or HFpEF more likely.

- Strategies to identify individuals with AF at highest risk for progression to HF are needed. Whether biomarker or imaging modalities may help risk-stratify individuals in a clinically meaningful way and whether screening will lead to improved outcomes are largely unknown.

- In individuals with AF, the role of intensive cardiovascular risk factor control, such as aggressive hypertension treatment, weight loss strategies, or more targeted therapies in preventing progression to HF has not been well studied.

The following research opportunities were proposed:

1. Mechanistic studies are needed to elucidate the underlying pathobiology of cardiac remodeling, HFpEF, and HFrEF after AF onset.

2. Studies should focus on risk stratification of individuals with AF, and identification of at-risk individuals most likely to develop HFrEF or HFpEF, leveraging clinical, biochemical, imaging, or genomic/genetic data. Through detection of atrial and ventricular fibrosis and accurate measurement of hemodynamics, cardiac MRI specifically may be important in elucidating factors responsible for the development and progression of HF in AF patients.

3. Studies should focus on identifying preventive/therapeutic strategies to effectively reduce the risk of developing HFpEF and HFrEF in AF patients.

Research to Prevent AF in Individuals with HF

Remodeling in HF and the resultant atrial myopathy with impaired left atrial hemodynamics predispose patients with HF to developing AF.[42] AF often develops in patients with HF, possibly with an increasing prevalence from HFrEF to HF with mid-range EF (HFmrEF) to HFpEF.[2, 33, 43–46]. Because of the worse clinical outcomes of patients with HF who develop AF,[2, 33, 47] comprehensive early management of upstream and possibly downstream risk factors may potentially improve mild-to-moderate HF and prevent or delay the onset of AF. [48–51] Restoration of sinus rhythm by ablation therapy in symptomatic paroxysmal or persistent AF and HFrEF may improve outcomes,[29, 30] whereas anti-arrhythmic drugs have more pronounced adverse side effects in HF patients (Figure 3).

While AF onset in HF patients is a discrete event, it could also be an indicator or a trigger of HF deterioration with further impairment of cardiac output and hemodynamics.[52] Patient characteristics significantly differ by HF type; HFpEF patients are generally older, are more likely to be women, and often have heterogeneous comorbidities including hypertension, obesity and diabetes, whereas HFrEF patients are relatively young, and have a higher prevalence of coronary heart disease. This renders the definition of an exact AF-HF phenotype very difficult. Compared with HFrEF, HFpEF is associated with different remodeling and biomarker profiles in AF.[42, 53, 54] In HFrEF, AF appears to be a sign of advanced disease with a more homogeneous elevation of biomarkers indicative of severe cardiac disease; whereas in HFpEF the biomarker pattern is less predictable and reproducible.[53] It is noteworthy that establishing the diagnosis of HFpEF can be extremely difficult in patients with AF given that the 2 conditions have overlapping symptomatology and both can lead to an elevated NT-pro-brain natriuretic peptide (NT-pro-BNP) and echocardiographic markers of diastolic dysfunction (e.g. atrial enlargement).[15]

HF patients tend to have frequent medical encounters, so asymptomatic paroxysmal AF may be detected earlier during routine follow-up compared to patients without HF. Cardiac implantable electronic devices, in particular in patients with HFrEF, may permit early detection of AF, especially of short and asymptomatic episodes.[55] The prognostic significance of short episodes of AF is unclear; however, many clinicians and patients want to know whether an early rhythm control strategy in such patients would help prevent development of clinical AF and progression of HF. Indeed, in patients with a pacemaker or defibrillator enrolled in the ASSERT (Asymptomatic Atrial Fibrillation and Stroke

Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial), progression of shorter to longer episodes of subclinical AF was strongly associated with HF hospitalization.[56] Many patients with HFpEF do not have implantable devices given a lack of clinical indication, and as a result, detection of AF may be delayed. Studies should examine the role of various screening strategies, including both non-invasive and invasive strategies in patients with HFpEF, and at least one such study using implantable loop recorders is underway.[57]

The following knowledge gaps were identified for the prevention of AF in individuals with HF:

- Determination of efficient methods for AF screening (mode, frequency, and duration) in HF patients, including device-detected AF. In randomized controlled trials, it would be important to test whether treating early detected asymptomatic AF in closely followed HF patients can improve event-free survival (HF deterioration/hospitalization, stroke/systemic embolism, dementia/cognitive decline, and mortality).

- Characterization of predictors, ideally modifiable, of AF in HFrEF and HFpEF patients. It is important to focus on different AF subtypes in HFpEF because of the expected increase in prevalence, less knowledge, and high heterogeneity of HFpEF. Defining the role of atrial myopathy in HFpEF and AF is also important.

- Understanding the prognostic significance of brief episodes of subclinical AF and the potential benefit of early interventions.

- Development of animal models of HFpEF with incident AF to investigate causal pathways.

- In-depth phenotyping of HF cohorts with improved non-invasive imaging for atrial structure and function, and atrioventricular interaction. Efforts should better exploit existing and new information from biomarkers, genomics, and genetics,[58] including from atrial tissue specimens. It will be important to integrate data across multiple–omics to simultaneously assess their biological meaning to stratify HF subtypes in relation to AF risk. Machine learning analytic methods should be applied to understand the role of individual comorbid conditions and comorbidity burden in the HF-AF relationship, including clinically rich information from electronic health records.[59] Once these factors are better identified, it will be important to link them with clinically meaningful outcomes.

- Extension of integrated care concepts for HF patients towards prevention, detection, and treatment of AF to improve quality of life and other outcomes. In particular, there is great variability in current management of these comorbid disorders, especially given the lack of evidence in the field, and this variability should be exploited in large, clinically-rich observational registries to link alternative management strategies, adjusting for patient risk, to clinically-important outcomes.

- To prevent AF, HFpEF research in this area should be prioritized, given that the knowledge gaps appear to be much larger in HFpEF than in HFrEF, and as HFpEF prevalence is increasing in an aging population with a high prevalence of obesity and hypertension.

Relevant suggested studies on mechanistic background and clinical questions are outlined in Figure 3.

The following prioritized research opportunities were proposed:

1. In randomized controlled trials, test whether treating early detected AF can improve event-free survival (stroke/systemic embolism, heart failure deterioration/hospitalization, mortality, dementia/cognitive decline) and patient-centered outcomes (quality of life, functional status, frailty). Also, the best treatment for early detected AF should be investigated and may include more aggressive rhythm control with available or novel antiarrhythmic drugs, catheter ablation, or device therapies.

2. Explore existing and deeply-phenotyped HF cohorts to define HF subtypes with a high risk of AF and adverse, clinically-important outcomes based on multi-level information in order to highlight pathophysiological pathways for experimental work-up, improve screening efficiency, and identify targets for prevention. Characterize AF phenotypes that are specific to HFpEF versus HFrEF. .

3. Conduct randomized controlled trials comparing the effectiveness in preventing AF of standard and novel HF treatments (e.g., beta-blockers, cardiac resynchronization therapy) in HFrEF and HFpEF patients.

Research on Symptom Burden in AF versus HF

HF and AF symptoms have substantial overlap, including, shortness of breath, dyspnea on exertion, impaired exercise tolerance, and fatigue. There are also symptoms that are more common in one than the other (e.g. palpitations in AF or edema in HF). AF may also be asymptomatic, and yet it can still result in poor outcomes such as HF and stroke.[60] HF-like symptoms in AF may reflect physiologic effects of AF in an otherwise normal heart, may indicate occult HFpEF,[61] or may represent the interplay of AF and non-cardiac comorbid conditions, which also produce HF-like symptoms.[60] Occult HFpEF or various comorbid conditions may affect the impact of AF treatment on symptoms and quality of life.[60]

Generic health status measures are designed to assess the totality of health in relation to patients' symptoms, function, and quality of life, whereas disease-specific measures seek to more sensitively capture the impact of a given disease on patients' symptoms, function, and quality of life. Whereas there are several disease-specific measures for both AF and HF,[62–64] the interaction of these diseases with disease-specific measures and the impact of treatment on patients' health status need further study to better define the impact of new-onset HF on AF patients' health status and the impact of new-onset AF on HF patients' health status. [65–68] It is important for clinicians to understand what outcomes matter to patients. In addition to "hard" clinical outcomes, patients care about the effects of a given intervention on ability to work, exercise tolerance, cognitive function, and the risk of depression.[69, 70]

Circulating cardiovascular biomarkers, including NT-pro-BNP, have not been helpful in discriminating pure AF-related from HF-related symptoms, predicting outcomes in AF, or predicting success of AF therapies.[71–73] There is a need for better biomarkers that can discriminate HF from AF. New technologies and alternate "biomarkers" including artificial intelligence[74] assisted analysis of ECG or images, and wearable and implantable physiologic monitors may provide the means to predict, detect, and monitor AF, evaluate the impact of AF on physiologic parameters reflective of quality of life, as well as shed light on the pathophysiology of HF and AF.[75] Such technologies may enable better understanding of the trajectory of health status over time, provide insights into potential future interventions, and allow novel clinical trial designs.[75, 76]

The following knowledge gaps were identified:

- Better definition of the impact of AF and AF burden on patient-reported outcomes in HF and vice versa.

- How can we cost-effectively and systematically detect undiagnosed AF in the population in order to determine its impact on quality of life?

- How can we discriminate between symptoms due to AF and symptoms due to occult myocardial dysfunction or comorbidities that may persist/progress after AF onset and therapies and limit the impact of AF therapy on quality of life?

- What novel physiologic biomarkers will enhance assessment of the burden of AF and the impact of AF therapies at the patient and population levels, or are they needed if patient-reported outcomes can adequately measure the burden?

- What combinations of patient-reported outcomes are optimal in monitoring the health status of patients with both AF and HF?

- What roles should patient-reported health status measures have in guiding therapeutic interventions, and can care protocols be developed to better assess the application of emerging treatments to patients?

- How do race, ethnicity, sex, and age impact symptom burden and quality of life in AF and HF?

- What is the variability in symptom control and quality of life across clinical practices in patients with AF and HF and what practice characteristics are associated with the best health status?

- Does symptom burden in AF versus HF vary by geographical location?

The following prioritized research opportunities were proposed (see Figure 4):

1. Determine if disease-specific, patient-reported outcome measures best determine the impact of AF and AF therapy on quality of life in order to define the best endpoints in AF and HF clinical trials, the most appropriate measures of clinical AF care quality, and the most accurate predictors of AF disease trajectory.

2. Study the effects of AF on cardiovascular function and symptoms in a spectrum of AF patients to determine how to discriminate between symptoms due to occult myocardial dysfunction or comorbidities versus AF.

3. Define clinically-important differences in disease-specific patient-reported outcome measures and their associations with age, sex, and race/ethnicity and the variability in health status across practices determining the proportion of this variability that is due to patient (e.g. socio-demographic, socio-economic, clinical comorbidities and disease severity) and practice characteristics (e.g. treatment).

Conclusions:

As the number of patients with AF and HF continues to rise, it is no longer appropriate to only treat these conditions when they are fully manifest. Research efforts should focus on prevention that extends beyond tachycardiomyopathy and target more effective approaches to AF prevention/treatment in HF patients and HF prevention/treatment in AF patients. To that end, developing a better understanding of the mechanisms underlying predisposition to AF in HF patients and to HF in AF patients, and its relationship to clinically-meaningful outcomes is of paramount importance. This understanding applies to both HFpEF and HFrEF, each of which may relate differently to AF. Such understanding should be coupled with identifying high-risk subgroups of patients with AF or HF for screening and prevention and the best modalities for early detection of these conditions. In addition, efforts should enhance understanding of symptom burden in AF versus HF and define the best approach to utilizing patient-reported outcomes clinically and in research. Addressing the knowledge gaps identified in this report will be critically important. Prioritized research opportunities to help address many of the identified knowledge gaps were proposed (Table). It is hoped that this report will propel investigators to conduct research in the area of AF and HF that will provide definitive information and lead to transformative, lasting, and meaningful improvement in clinical care and patient outcomes.

Acknowledgment:

Non-standard Abbreviations and Acronyms:

HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
OSA	obstructive sleep apnea
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
HYVET	Hypertension in the Very Elderly Trial
NT-pro-BNP	NT-pro-brain natriuretic peptide
HFmrEF	heart failure with mid-range ejection fraction
ASSERT	Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial

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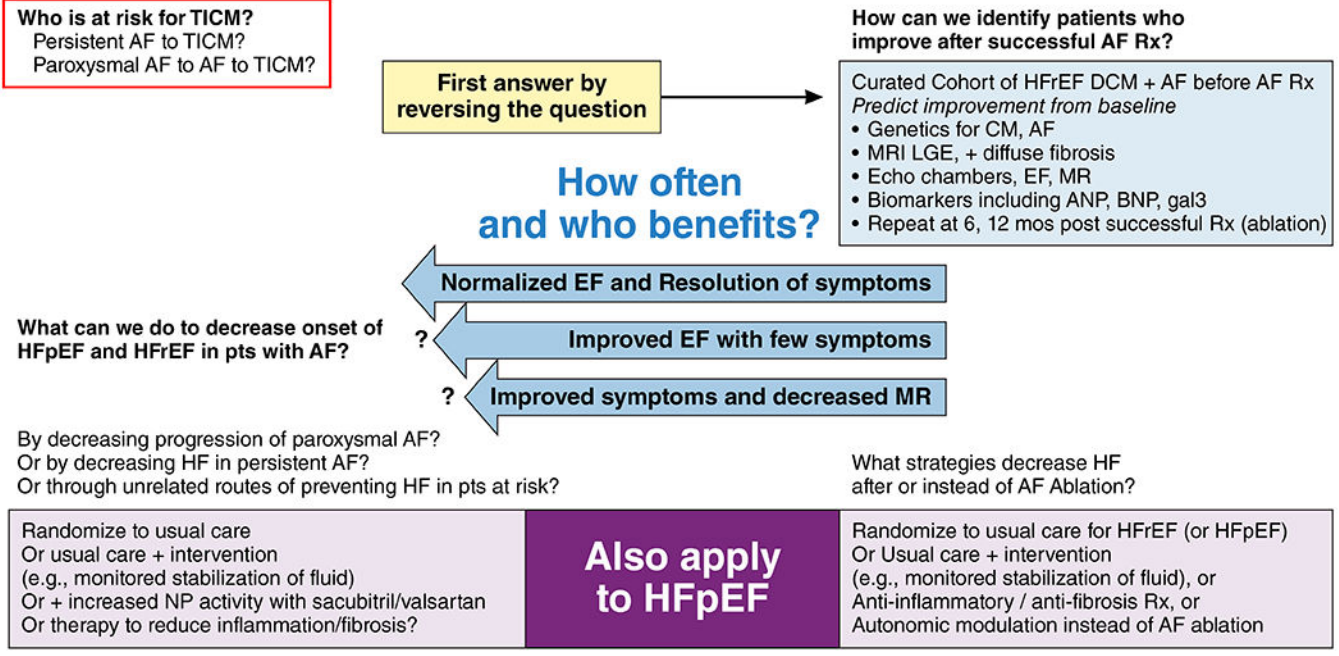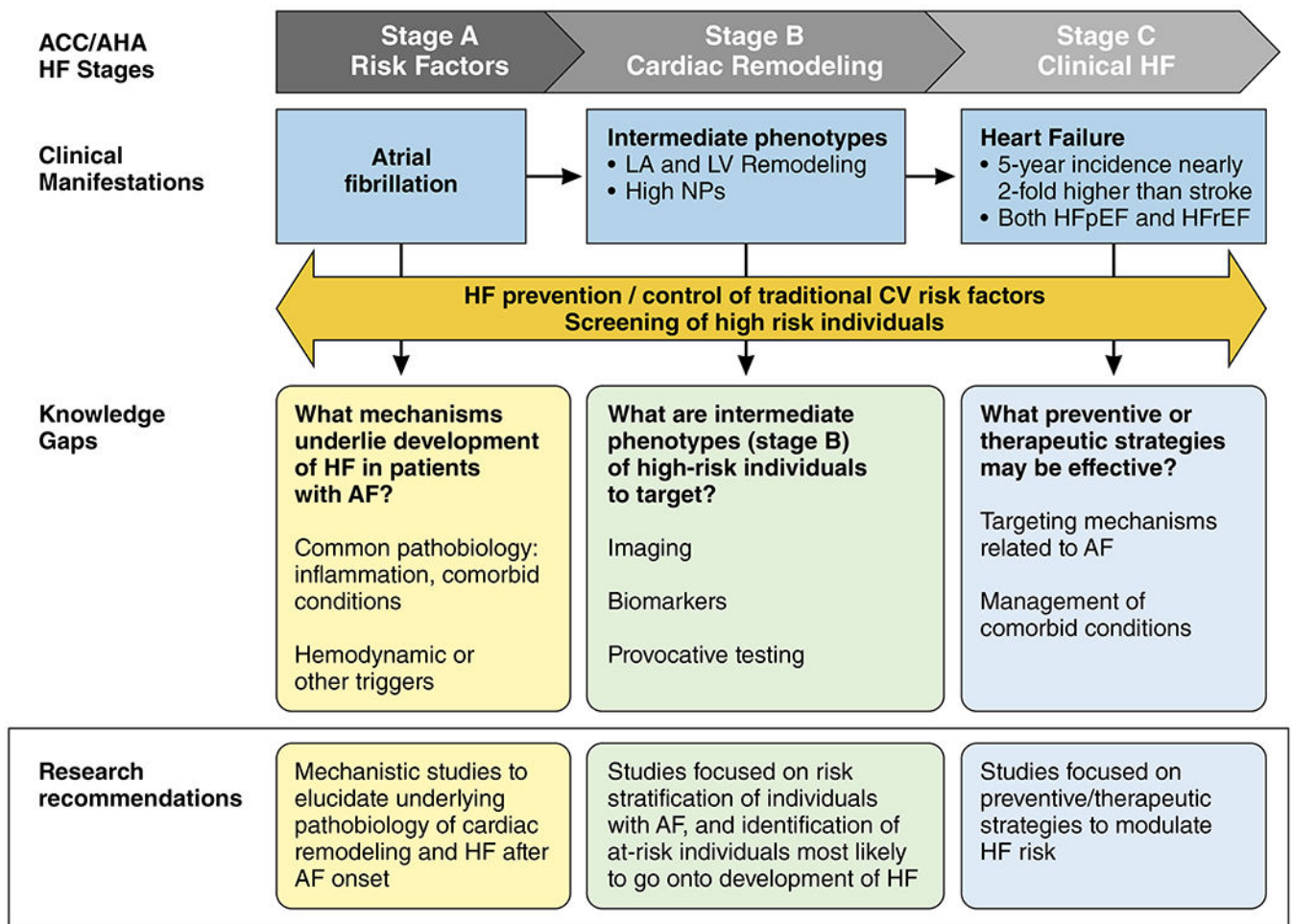
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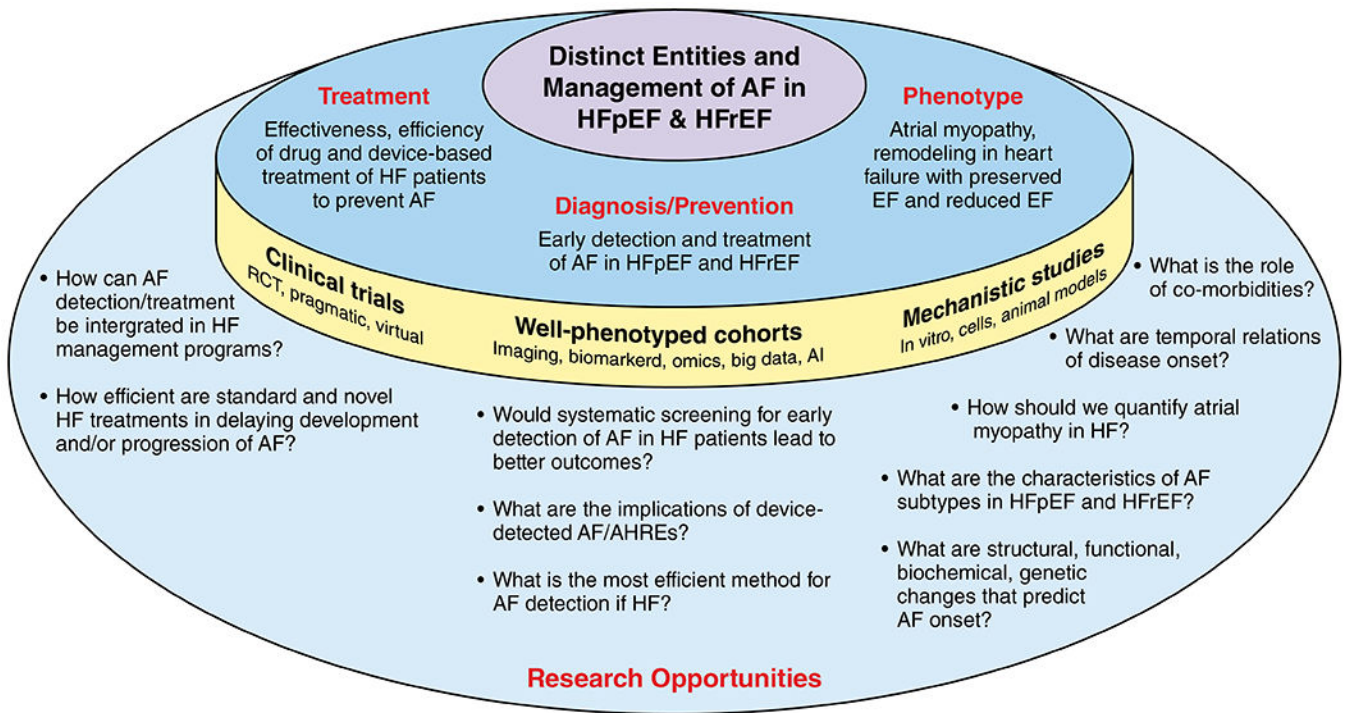Preventing HFpEF and HFrEF in individuals with AF
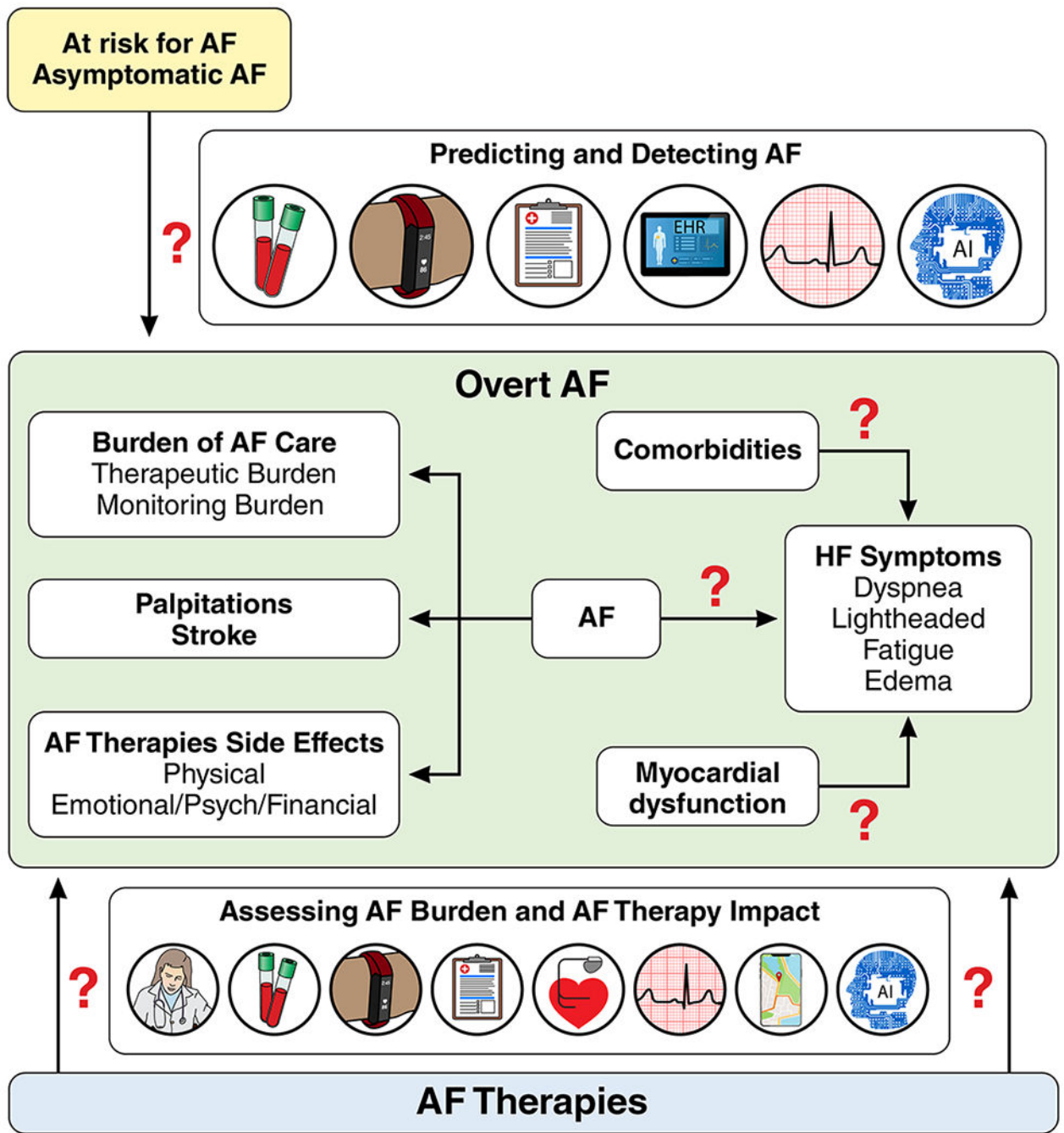
Figure 3:
Preventing AF in patients with HF

Figure 4:
Assessing disease burden in AF.

Table.

Prioritized Research Opportunities for AF and HF

The Overlapping Pathophysiology Between AF and HF
1. To establish the risk profiles and prevalence of tachycardiomyopathy with lesser degrees of reversible LV dysfunction. This may be best accomplished through a curated cohort of patients with AF and non-ischemic HF in whom the following are characterized: biomarkers, fibrosis on cardiac MRI, cardiac structure on cardiac MRI and echo, genomic (methylation, transcriptomic, proteomic, etc.), and genetic profiles of cardiomyopathy and AF, peak VO2 testing, and patient-reported outcomes before and at 6 and 12 months after ablation to determine frequency and characteristics predicting meaningful improvement.
2. To conduct a randomized trial of intensive maintenance of volume status vs. usual care to reduce progression of HF and progression of paroxysmal to persistent AF as well as following AF ablation in adults with either HFrEF or HFpEF. Outcomes would include LVEF and LV dimensions in HFrEF, diastolic function and left atrial volume and patient-reported symptoms and function in both HFrEF and HFpEF.
3. To conduct randomized clinical trials of catheter ablation, antiarrhythmic drugs, and prevention in patients with AF and HF. To enhance the feasibility of such trials, pragmatic and other innovative trial designs should be leveraged.
Research to prevent HF in individuals with AF
1. Mechanistic studies are needed to elucidate the underlying pathobiology of cardiac remodeling, HFpEF, and HFrEF after AF onset.
2. Studies should focus on risk stratification of individuals with AF, and identification of at-risk individuals most likely to develop HFrEF or HFpEF, leveraging clinical, biochemical, imaging, or genomic/genetic data. Through detection of atrial and ventricular fibrosis and accurate measurement of hemodynamics, cardiac MRI specifically may be important in elucidating factors responsible for the development and progression of HF in AF patients.
3. Studies should focus on identifying preventive/therapeutic strategies to effectively reduce the risk of developing HFpEF and HFrEF in AF patients.
Research to prevent AF in individuals with HF
1. In randomized controlled trials, test whether treating early detected AF can improve event-free survival (stroke/systemic embolism, heart failure deterioration/hospitalization, mortality, dementia/cognitive decline) and patient-centered outcomes (quality of life, functional status, frailty). Also, the best treatment for early detected AF should be investigated and may include more aggressive rhythm control with available or novel antiarrhythmic drugs, catheter ablation, or device therapies.
2. Explore existing and new deeply-phenotyped HF cohorts to define HF subtypes with a high risk of AF and adverse outcomes based on multi-level information in order to highlight pathophysiological pathways for experimental work-up, improve screening efficiency, and identify targets for prevention. Characterize AF phenotypes that may be unique in HFpEF versus HFrEF.
3. Conduct randomized controlled trials comparing the effectiveness in preventing AF of standard and novel HF treatments (e.g., beta-blockers, cardiac resynchronization therapy) in HFrEF and HFpEF patients.
Research on symptom burden in AF versus HF
1. Determine if disease-specific, patient-reported outcome measures best determine the impact of AF and AF therapy on quality of life in order to define the best endpoints in AF and HF clinical trials, the most appropriate measures of clinical AF care quality, and the most accurate predictors of AF disease trajectory.
2. Study the effects of AF on cardiovascular function and symptoms in a spectrum of AF patients to determine how to discriminate between symptoms due to occult myocardial dysfunction or comorbidities versus AF.
3. Define clinically-important differences in disease-specific patient-reported outcome measures and their associations with age, sex, and race/ethnicity and the variability in health status across practices determining the proportion of this variability that is due to patient (e.g. socio-demographic, socio-economic, clinical comorbidities and disease severity) and practice characteristics (e.g. treatment).