

# Evaluating the benefits of home-based management of atrial fibrillation: current perspectives

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**Abstract:** Atrial fibrillation (AF) is the most common arrhythmia worldwide, leading to an extensive public health and economic burden. The increasing incidence and prevalence of AF is due to the advancing age of the population, structural heart disease, hypertension, diabetes, and thyroid disease. The majority of costs associated with AF have been attributed to the cost of hospitalization. In order to minimize costs and decrease hospitalizations, counseling on modifiable risk factors contributing to AF has been strongly emphasized. With the release of novel oral anticoagulants bypassing the need for anticoagulant bridging or laboratory monitoring, post-discharge nurse-led home intervention, and novel methods of heart rate monitoring, home-based AF management has reached a new level of ease and sophistication. In this review, we aimed to review modifiable risk factors for AF and various methods of home-based management of AF, along with their benefits.

**Keywords:** atrial fibrillation, home-based management, epidemiology, risk factors

## Introduction

Atrial fibrillation (AF) is notoriously known as the world's most common sustained arrhythmia. Its rising incidence and prevalence has led to a major evolving economic and public health burden. As the rising costs are mostly attributed to hospitalizations, the ground has been set for studies aiming to optimize outpatient management of AF. In this review, we reviewed methods of attenuating modifiable risk factors to prevent AF and various methods of home-based management once AF manifests.

## Definition

AF, the most common cardiac arrhythmia, is characterized by an irregularly irregular rhythm. On the surface electrocardiogram (ECG), AF manifests as an absence of P waves, as a presence of fibrillary waves, and as a ventricular rate that may range between 90 beats per minute and 170 beats per minute, with an irregular R–R interval. The classification of AF according to the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society guidelines is as follows<sup>1</sup>:

- paroxysmal AF: AF that terminates spontaneously or with intervention within 7 days of onset. Episodes may or may not recur with variable frequency;
- persistent AF: AF that is sustained for >7 days of onset;
- long-standing persistent AF: persistent AF that lasts for >12 months in duration;
- permanent AF: clinical situation in which the patient and clinician agree not to pursue rhythm control strategy;

- non-valvular atrial fibrillation (NVAf): AF in the absence of rheumatic mitral stenosis, bioprosthetic or mechanical heart valve, or mitral valve repair; and
- valvular AF: AF in the presence of mitral stenosis, artificial heart valve(s), or mitral valve repair.

## Epidemiology

AF is an evolving worldwide economic and public health burden. A systematic review of 184 studies conducted revealed that 33.5 million people had AF in 2010, with 5 million new people being diagnosed annually.<sup>2</sup> Studies have clearly demonstrated AF's rising incidence with advancing age. During 2010, in men and women, respectively, the incidence rates (per 100,000 person-years) were estimated to be 77.5 (95% confidence interval [CI] 65.2–95.4) and 59.5 (95% CI 49.9–74.9).<sup>2,3</sup> In the US alone, the incidence of AF has been projected to double from 1.2 million cases in 2010 to 2.6 million cases by 2030.<sup>4</sup>

The population prevalence of each of the risk factors for AF is increasing, as there are increases in life expectancy and advances in medical therapy. Given the increase in incidence, AF prevalence is projected to increase from 5.2 million cases in 2010 to 12.1 million cases by 2030.<sup>4</sup> During 2010, in men and women, respectively, the prevalence per 100,000 population was 596.2 (95% CI 558.4–636.7) and 373.1 (95% CI 347.9–402.2).<sup>2</sup> In the Anticoagulation and Risk Factors in Atrial Fibrillation study, the prevalence of AF in the general population was reported to be 0.5%–1%, and increasing prevalence was strongly associated with increasing age. The prevalence for individuals <55 years old was 0.1%, while for those ≥80 years old was 9%.<sup>5</sup> Similar to its incidence, prevalence of AF is consistently higher in men than in women across the majority of the study cohorts in most age groups. There is a concealed burden of asymptomatic and transient arrhythmias (i.e. sub-clinical paroxysmal AF) in the general population, which may account for underestimation of prevalence of AF.<sup>6</sup>

## Cost

The largest source of health care costs associated with AF is hospitalizations. Additional factors for the increasing cost include emergency department (ED) visits, outpatient anticoagulation management, and increasing trend for disposition to skilled nursing facilities.<sup>7</sup> Emergency hospitalizations for AF with concurrent decompensated congestive heart failure (CHF), stroke, or pulmonary disease are associated with greater costs. Meanwhile, female gender and Caucasian population had been associated with lower AF-related health care costs.<sup>8,9</sup> Long-term nursing home care for patients represents a concealed part of costs associated with AF. This represents

a major economic burden on the health care system, indicating the importance of studies to prevent hospitalizations and decrease thromboembolic events in the home setting.

## Goals

This review aims to provide a comprehensive description of modifiable risk factors for primary and secondary prevention of AF along with advances in home-based surveillance methods and management.

## Modifiable risk factors

Multiple modifiable and non-modifiable risk factors have been described in the literature, which contribute in the development of AF.<sup>10,11</sup> Certain lifestyle changes addressed toward modifiable risk factors have been shown to prevent AF and decrease recurrence. These modifiable risk factors include hypertension (HTN), diabetes mellitus (DM), obstructive sleep apnea (OSA), alcohol intake, chronic strenuous exercise, caffeine intake, obesity, and CHF.<sup>11–15</sup>

## Hypertension

HTN is the most commonly known risk factor associated with the development of AF.<sup>16</sup> Atrial remodeling secondary to renin–angiotensin–aldosterone system (RAAS) is one proposed mechanism underlying the development of AF.<sup>17</sup> Systolic blood pressure (SBP) and diastolic blood pressure (DBP) have both been implicated in the development of AF as well as increased mortality in patients with AF.<sup>18,19</sup> A recent study on patients enrolled in Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial revealed that patients with AF have a “U-shaped” relation between blood pressure (BP) and all-cause mortality (ACM) or adverse outcomes.<sup>20</sup> The nadir SBP and DBP resulting in the lowest ACM were found to be 140 mmHg and 78 mmHg, respectively. The risk of ACM increased by 3.9-fold in the group with SBP <110 mmHg and by 1.9-fold in the group with SBP >160 mmHg ( $p < 0.001$ ). The group with SBP <110 mmHg had a greater mortality than the group with SBP >160 mmHg (hazard ratio [HR] 3.9,  $p < 0.001$ ). The risk of ACM increased by 3.9-fold in the group with DBP <60 mmHg and by 1.8-fold in the group with DBP >90 mmHg. The group with DBP <60 mmHg had a greater ACM compared to the group with DBP >90 mmHg (HR 3.9,  $p < 0.001$ ).<sup>19</sup>

Gender differences in the correlation of SBP and DBP with incident AF have been reported. Recently, a women's health study evaluated ~34,000 women for incident AF based on SBP and DBP. Data from this study suggested that

SBP was a better predictor of incident AF than was DBP. However, the study still concluded that elevation in either SBP or DBP significantly increased the long-term risk of AF. SBP >140 mmHg was associated with an HR of 1.7. In comparison, DBP >90 mmHg was associated with an HR of 1.5. For each measure, the risk increased significantly with increased BP readings, with a greater rise in risk seen in elevated SBP than DBP.<sup>21</sup> A Norwegian study evaluating ~2000 males followed over 35 years revealed that men with baseline SBP  $\geq$ 140 mmHg had a 1.60-fold (95% CI 1.15–2.21) risk of developing AF and those with upper normal SBP (128–138 mmHg) had a 1.50-fold (95% CI 1.10–2.03) risk of AF, when compared to those individuals with SBP <128 mmHg. Furthermore, in this cohort, baseline DBP  $\geq$ 80 mmHg increased the risk of incident AF 1.79-fold (95% CI 1.28–2.59) compared with DBP <80 mmHg.<sup>22</sup> In addition, elevated SBP has been associated with AF recurrence, especially in patients with compromised left ventricular ejection fraction (LVEF)  $\leq$ 40%. In patients with LVEF  $\leq$ 40%, the adjusted mean proportion of time spent in AF was 17.2% if SBP was <120 mmHg, 15.4% for SBP 120–140 mmHg, and 24.0% for SBP >140 mmHg ( $p=0.025$ ).<sup>23</sup>

Despite the proposed mechanism of developing AF being atrial remodeling via activity from the RAAS,<sup>17</sup> inhibition of this axis with the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) has led to conflicting results in the prevention or treatment of AF. Two HTN trials, Losartan Intervention for End Point Reduction in Hypertension (LIFE) and Valsartan Antihypertensive Long-Term Use Evaluation (VALUE), showed a beneficial effect of ARBs on the development of new-onset AF. The LIFE trial showed that patients randomized to receiving losartan had new-onset AF occurring in 6.6 per 1000 person-years compared to 10.1 per 1000 person-years in patients randomized to receive atenolol (relative risk [RR] 0.67, 95% CI 0.55–0.83,  $p<0.001$ ). Patients receiving losartan remained in sinus rhythm longer than those receiving atenolol despite similar reduction in BP (1809 $\pm$ 225 vs. 1709 $\pm$ 254 days from baseline,  $p=0.057$ ). The VALUE trial demonstrated a significant benefit of valsartan over amlodipine in terms of new-onset AF incidence. The incidence was 3.67% with valsartan compared to 4.34% with amlodipine (HR 0.843, 95% CI 0.713–0.997,  $p=0.0455$ ). Additionally, the incidence of persistent AF was 1.35% in the valsartan group compared to 1.97% in the amlodipine group (HR 0.683, 95% CI 0.525–0.889,  $p=0.0046$ ).<sup>24</sup> A meta-analysis of 11 studies including 56,308 patients demonstrated that ACEIs and ARBs decreased RR of AF by 28% only in the setting of

left ventricular hypertrophy and systolic dysfunction (95% CI 15%–40%,  $p=0.0002$ ). This benefit was not portrayed in patients with HTN.<sup>25</sup> Conversely, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation trial failed to demonstrate any reduction in the incidence of AF between the valsartan group vs. placebo group.<sup>26</sup> In addition, a meta-analysis of 4040 patients demonstrated that while ACEI showed significant benefit in preventing AF recurrences, ARBs did not.<sup>27</sup> Additional trials with a larger sample size and strict follow-up schedule to recognize AF episodes are required to settle these discrepancies.

## Diabetes mellitus

While multiple trials have shown an association between Type 2 diabetes mellitus (T2DM) and AF, this finding is not unanimous among all studies. Up to 20% of AF patients have co-existing DM.<sup>28</sup> After 4.2 years of follow-up, the VALUE trial revealed that compared to patients without T2DM, patients with new-onset T2DM had significantly higher rates of new-onset AF and persistent AF.<sup>29</sup> T2DM with concomitant AF has been shown to increase risk of death and cardiovascular (CV) events. Approximately 850 patients with T2DM and concomitant AF in the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN-MR Controlled Evaluation study had an increased risk of CV death, heart failure, stroke, and 61% greater risk of ACM.<sup>30</sup> Another recent population-based study has shown that persistent uncontrolled T2DM poses a cumulative risk of AF initiation and there is a 3% higher risk of AF every year with persistent T2DM. The same study demonstrated that compared to patients without T2DM, patients with T2DM had an increased odds ratio (OR) for developing AF with increasing hemoglobin A1c (HbA1c) levels. The OR with an average HbA1c  $\leq$ 7 was 1.06 (95% CI 0.74–1.51), for HbA1c >7 but  $\leq$ 8 was 1.48 (1.09–2.01), for HbA1c >8 but  $\leq$ 9 was 1.46 (1.02–2.08), and for HbA1c >9 was 1.96 (1.22–3.14). This advocates that strict long-term glucose control may play a significant role in decreasing incidence of new-onset AF.<sup>31</sup>

Despite the abovementioned studies, the association between AF and T2DM is debatable because of various studies failing to demonstrate any significant association between the two entities.<sup>32</sup> In 2009, data analysis from the Framingham Heart Study did not show any statistically significant association between AF and T2DM.<sup>33</sup> This may have been due to the fact that the primary goal of the study was not to evaluate the association between AF and T2DM but to develop a risk stratification score to predict absolute risk of AF. Another population-based cohort study using the

UK's General Practice Research Database failed to reveal any association between AF and T2DM; however, the population size of individuals with T2DM was small ( $n=73$ ) compared to the overall study group with AF ( $n=1035$ ).<sup>34</sup> Similarly, a study consisting of 1739 patients showed that the adjusted OR was 2.0 (95% CI 0.9–4.7) in patients with T2DM, suggesting no statistically significant association. However, this finding barely missed statistical significance secondary to the small T2DM cohort, widening the CI.<sup>35</sup> Although it is impossible to completely explain these discrepancies between the studies, possible reasons include insufficient sample size and failure to adjust for co-morbidities (obesity, heart failure, HTN). Furthermore, the primary goal of many of these studies was not to specifically study the effects of T2DM.

### Obstructive sleep apnea

AF and OSA show a significant association, independent of CHF, HTN, and body mass index (BMI).<sup>36</sup> The exact mechanism for OSA's association with AF has yet to be determined. The suggested mechanisms include: 1) atrial and pulmonary venous stretch leading to increased transmural pressure that may result in atrial and pulmonary vein dilation<sup>37</sup>; 2) atrial remodeling leading to voltage reduction, widespread or site-specific conduction abnormalities, and increased interval of sinus node recovery<sup>38</sup>; 3) elevated levels of inflammatory markers such as C-reactive protein<sup>39</sup> and interleukin-6<sup>40</sup>; 4) higher levels of serum amyloid<sup>41</sup>; and 5) enhanced vagal activation via negative tracheal pressure during obstructive events.<sup>42</sup>

A recent study conducted at a sleep clinic evaluating 6841 patients for OSA revealed that independent predictors of AF included apnea/hypopnea index (AHI)  $>5$ /hour and time with oxygen saturation  $<90\%$ .<sup>43</sup> In addition, it has also been shown that response to antiarrhythmic drug (AAD) therapy depends on severity of OSA. A study including 61 patients with symptomatic AF being treated with AAD therapy who underwent overnight polysomnography revealed that patients with severe OSA were less likely to respond to AADs when compared to those with milder OSA (39% vs. 70%,  $p=0.02$ ). The patients who did not respond to AAD therapy had a higher AHI compared to those who responded ( $34\pm 25$  vs.  $22\pm 18$  events/hour,  $p=0.05$ ).<sup>44</sup> Patients with OSA have also been shown to pose a greater risk of AF recurrence even after pulmonary vein isolation (PVI).<sup>45</sup> In fact, the presence of severe OSA has been shown to be an independent risk factor for AF ablation failure.<sup>46</sup>

The use of continuous positive airway pressure for OSA leads to lower rates of AF recurrence (irrespective of under-

going PVI), improved control of heart rate (HtR), and lower progression to permanent AF when compared to untreated patients.<sup>47,48</sup>

### Alcohol intake

Alcohol-induced arrhythmias were initially described in 1978 by Ettinger et al,<sup>49</sup> terming alcohol-related AF as "holiday heart syndrome." This syndrome was seen in healthy individuals who consumed large amounts of alcohol and presented with AF, typically following holidays or on weekends. Since then, numerous studies have demonstrated that alcohol intake predisposes to the development of arrhythmias.<sup>50</sup> A standard alcoholic drink contains 12–15 g of ethanol. A recent meta-analysis showed that compared to individuals who do not consume alcohol, men consuming 24 g, 60 g, and 120 g of ethanol daily had AF-related RRs of 1.08, 1.44, and 2.09, respectively. For women, the corresponding RRs were 1.07, 1.42, and 2.02.<sup>51</sup> A large study evaluating the risk of AF specifically in women revealed that consumption of two or more drinks per day was associated with a significantly increased risk of AF, with an HR of 1.60 (95% CI 1.14–2.27) after adjusting for multiple covariates.<sup>52</sup> The Framingham Heart Study demonstrated that individuals consuming  $>36$  g/day (approximately more than three drinks) had a significantly increased risk of AF.<sup>53</sup> A meta-analysis by Kodama et al<sup>54</sup> also showed a direct relationship between alcohol dose and future AF, with an 8% increase in AF risk for every 10 g increase in alcohol daily dose.

The impact of light alcohol consumption on the development of AF is still unclear. The beneficial effects of small doses of alcohol for CV disease prevention, not related to AF, have been reported.<sup>55</sup> It is reasonable to counsel patients to consume only low doses of alcohol (i.e. one drink per day). In patients with high risk of developing AF, a reasonable recommendation could be to keep alcohol intake very low (less than one drink per day) or abstaining from it altogether.

### Physical activity (PA) and cardiopulmonary fitness

PA and exercise have demonstrated beneficial effects on CV health.<sup>56,57</sup> Despite this, there is also an increased risk of AF in military personnel and elite athletes, thought due to participation in endurance exercise.<sup>13</sup> This is consistent with other small studies that also demonstrated a relationship between AF and high-intensity PA or occupational PA.<sup>58–60</sup> The pathogenesis proposed for this phenomenon includes autonomic dysregulation as a result of sympathetic/parasympathetic mismatch, increase in left atrial size or atrial stretch in the

setting of exercise-induced left ventricular hypertrophy, atrial fibrosis, myocardial injury, or transient inflammation due to excessive PA. Trigger factors, such as atrial ectopy, sports supplements, and illicit drug use, added to their baseline genetic predisposition are also implicated.<sup>58,59,61</sup>

A study conducted on 1950 middle-aged males followed over 19.5 years to evaluate the relationship between cardiorespiratory fitness (CRF) and incident AF revealed decreasing rates of incident AF with higher levels of CRF. It was only individuals with very high CRF who showed a modest increase in AF rates, but overall the AF rates were significantly lower than those with minimal CRF. These data suggest a nonlinear relationship between higher levels of CRF and AF.<sup>62</sup> A study conducted by Calvo et al<sup>63</sup> showed that with increased hours of vigorous exercise per year, there was a significantly increased risk of AF (OR=3.88), whereas high amounts of moderate activity were protective (OR=0.38). Another study on 36,513 Swedish women followed over a 12-year period revealed that the risk of AF decreased with increasing levels of leisure-time PA (RR 0.85, 95% CI 0.75–0.95 for  $\geq 4$  hours/week vs.  $< 1$  hour/week) and walking/bicycling (RR 0.81, 95% CI 0.72–0.92, for  $\geq 40$  minutes/day vs. rarely), suggesting that moderate PA is associated with a decreased risk of AF.<sup>64</sup> A recent study conducted by Faselis et al on 5962 veterans from the VA Medical Center in Washington DC over an 8.3-year follow-up period demonstrated that the risk of developing AF was 21% lower for each one metabolic equivalent task (MET) increase in exercise capacity, signifying an inverse relation with physical fitness. Compared to the least-fit individuals (4.9 METs $\pm$ 1.1), HRs were 0.80, 0.55, and 0.37 for moderately fit individuals (6.7 METs $\pm$ 1.0), fit individuals (7.9 METs $\pm$ 1.0), and very fit individuals (9.3 METs $\pm$ 1.2), respectively.<sup>14</sup>

Overall, studies suggest that high-intensity and frequent endurance exercise carry an increased risk of AF, while maintaining CRF with light-to-moderate PA reduces risk of AF. Based on these results, it is not unreasonable to encourage patients to be physically active and exercise due to benefits in overall CV health outweighing the risk of AF and to avoid excessive endurance exercise regimens.

## Caffeine intake

Contrary to the popular belief that coffee consumption seems to precipitate AF, there is significant evidence to suggest that drinking moderate amounts of coffee and tea in fact decreases occurrence of AF.<sup>65–68</sup> In 1976, Klatsky et al conducted an observational study following 130,000 patients in the Kaiser Permanente health system. This study

revealed that consumption of four or more cups of coffee per day (about 360 mg of caffeine) was associated with an 18% reduction in the risk of being hospitalized for arrhythmias, including AF.<sup>69</sup> Another large prospective study following 33,638 healthy women over 14.4 years did not show any association between caffeine intake and AF up to 656 mg/day.<sup>70</sup> A recent meta-analysis of six prospective cohort studies with 228,465 individuals showed AF risk reduction with caffeine consumption (RR 0.90; 95% CI 0.81–1.01,  $p=0.07$ ). Additionally, a subgroup analysis demonstrated a greater reduction in the risk of AF with high doses of caffeine intake compared to low doses of caffeine intake (16% vs. 11%). For every 300 mg/day increment in habitual caffeine intake, AF incidence decreased by 6%.<sup>71</sup>

In conclusion, studies indicated that there is no associated risk between caffeine intake and AF development. In fact, caffeine consumption may actually decrease the risk of AF, and its habitual use should not be discouraged.

## Obesity

The association between AF and obesity has been well established, regardless of the presence or absence of metabolic syndrome.<sup>72,73</sup> Childhood large body habitus and weight gain during the second to fourth decades are both independently associated with AF development.<sup>74</sup>

The proposed mechanisms for AF's relationship with obesity include left atrium (LA) enlargement, a known precursor of AF,<sup>75</sup> and electrostructural remodeling, associated with spontaneous and persistent AF.<sup>76</sup> Obesity is an independent predictor of left ventricular diastolic dysfunction, in all age groups,<sup>77,78</sup> predisposing to alterations in LA size, which is a known risk factor for the development of AF.<sup>79,80</sup> Additionally, pericardial fat has been associated with the presence, symptom burden, chronicity, and recurrence of AF.<sup>81,82</sup>

A meta-analysis of 16 studies including 123,249 individuals demonstrated that obese individuals had an increased risk of developing AF compared to non-obese individuals (RR 1.49, 95% CI 1.36–1.64).<sup>83</sup> A large community-based cohort study revealed a 4% increase in AF risk per one unit increase in BMI, in both genders.<sup>84</sup>

Obesity predisposes to the progression of paroxysmal AF to persistent or permanent AF. A cohort study of 3248 patients demonstrated that after adjusting for age and gender, BMI independently predicted the progression to permanent AF (HR per BMI unit 1.04, 95% CI 1.03–1.06,  $p<0.0001$ ).<sup>85</sup> Compared with normal BMI, obesity (BMI $>30$ ) and severe obesity (BMI $>35$ ) were associated with an increased risk for progression of AF (HR 1.54, 95% CI 1.2–2.0,  $p=0.0004$  and

1.87, 95% CI 1.4–2.5,  $p < 0.0001$ , respectively). Progression of AF from paroxysmal AF to persistent or permanent AF has been associated with higher rates of stroke, myocardial infarction (MI), hospital admission, morbidity, and mortality.<sup>86</sup>

Risk factor management (RFM) associated with coronary artery disease (CAD), as per AHA/ACC guidelines, has been associated with improved long-term success of AF ablation. Patients with a BMI  $\geq 27$  kg/m<sup>2</sup> and  $\geq 1$  CAD risk factor who were offered RFM in addition to AF ablation experienced significantly less AF frequency, duration, and symptoms, when compared to those without RFM ( $p < 0.001$ ).<sup>87</sup> Weight loss is always encouraged to attenuate risk factors for AF such as HTN, T2DM, and OSA. The compound effect of RFM on CAD and weight reduction has been associated with a greater reduction in AF symptom burden and severity when compared to RFM alone.<sup>88</sup>

Evidence suggests that a dose-dependent reduction in AF burden is achieved with weight loss and avoidance of weight fluctuations. A study conducted on 1415 patients with a BMI  $\geq 27$  kg/m<sup>2</sup> and symptomatic paroxysmal or persistent AF revealed that a reduction in body weight  $>10\%$  was found to be associated with a sixfold (95% CI 3.4–10.3,  $p < 0.001$ ) greater probability of arrhythmia-free survival when comparing to those individuals who lost  $<9\%$  body weight. Weight fluctuation of  $\geq 5\%$  reduced the benefits with a twofold increased risk of AF recurrence (95% CI 1.0–4.3,  $p = 0.02$ ).<sup>89</sup>

## Congestive heart failure

CHF and AF are known to frequently co-exist. The prevalence of AF in CHF patients ranges from 5% to 50%, depending on the New York Heart Association's classification of severity of CHF.<sup>90</sup> Their co-existence has shown to result in increased hospitalization, longer hospital stays, and increased overall mortality.<sup>15</sup> The proposed pathogenesis for developing AF in CHF includes electrophysiologic abnormalities, such as prolonged atrial refractory period and increase in repolarization heterogeneity. In addition, hemodynamic and mechanical changes, such as atrial tissue stretch due to elevated atrial pressure and volume and neurohormonal effects of RAAS, are also implicated.<sup>90,91</sup> AF has also been shown to induce CHF through tachycardia-mediated cardiomyopathy, reduced cardiac output, and neurohormonal activation. Development of CHF leads to a vicious cycle, with one leading to the other.<sup>15</sup>

Rate and rhythm control are two effective treatments for AF; however, treatment of AF in CHF with rhythm control has not been shown to have a mortality benefit.<sup>92</sup> According to the AFFIRM trial, routine rhythm control does not reduce the

rate of death from CV causes, as compared to the rate control strategy.<sup>15,92</sup> Amiodarone and dofetilide are commonly used AADs for rhythm control of AF in CHF and are associated with symptom and quality of life improvement<sup>93</sup>; however, studies have been conflicting regarding their overall benefits due to proposed higher risk of ACM.<sup>94</sup> The AF-CHF trial on the other hand showed that individuals with both CHF and AF had no differences in mortality or worsening of CHF when comparing rate control to rhythm control strategies.<sup>95</sup> Targeting mechanisms involved in AF development (i.e. atrial fibrosis, cardiac remodeling) with upstream medical therapy such as ACEIs or ARBs and beta blockers has shown beneficial results in reducing incidence of AF.<sup>15</sup> Routine follow-up with a cardiologist should be encouraged to check for medication compliance and monitor for evidence suggesting cardiac resynchronization therapy or catheter-based ablation for AF is indicated, as both have shown to preserve LV function and decrease AF burden.<sup>15,90</sup>

Multiple studies have shown that comprehensive nurse-led home and/or clinic-based management programs kept more patients with CHF out of the hospital and alive as compared to those with usual follow-up.<sup>96</sup> Individuals with home-based management had a significant 60%–70% reduction in recurrent admissions and hospital stays as compared to usual care. Individuals not involved in the nurse-led CHF management program also had a decline in social and physical outcomes. Thompson et al emphasized to tailor care to each patient's individual needs in CHF management for better health outcomes, highlighting why these programs have higher success rates. Since both AF and CHF are associated with a higher prevalence in populations with HTN, DM, obesity, and ACS,<sup>90</sup> it is vital to effectively control these conditions through medication compliance and lifestyle management. This includes monitoring for weight fluctuations and taking pre-emptive action on early signs of decompensated CHF (i.e. taking higher dose of diuretics).

## Preventing AF with chronic medical therapy

It is still controversial as to which, if any, methods can prevent the occurrence of AF. As there are proven risk factors, as discussed earlier, preventing these known risk factors alone may be effective in the prevention of AF.<sup>12</sup> Evidence from multiple studies has substantiated that ACEIs/ARBs are more likely to have an impact on primary, but not on secondary, prevention of AF.<sup>12,26,97</sup> There are certain circumstances, such as following coronary artery bypass grafting or MI and in patients with heart failure, where beta blockers were shown

to decrease incidence of AF (up to 27%).<sup>12</sup> Studies of other drugs, such as aldosterone antagonists and statins, have been inconclusive as to their roles in prevention.<sup>97</sup>

## Home-based AF management HtR monitoring

The simple act of patients' monitoring their own HtR may allow detection of otherwise asymptomatic AF and may allow the patient–physician dyad to follow the response to AF treatment. HTN is often associated with the development of AF, and many patients with HTN monitor their BP at home. Utilizing a practice that patients already perform on a regular basis to additionally monitor for arrhythmias holds much potential. Many studies have been conducted worldwide with modified home BP machines that utilize an algorithm to detect AF, which has been shown to nearly replicate the accuracy of an ECG diagnosis of AF.<sup>98</sup> These algorithms have been shown to have >90% sensitivity and >80% specificity with one assessment alone, while the sensitivity and specificity increased with three readings to >96% and >89%, respectively.<sup>99–101</sup> It should be noted that certain algorithms were better able to differentiate between various irregular rhythms, and there were also some non-AF arrhythmias that were incorrectly diagnosed as AF.<sup>101</sup>

A Finnish study of older adults assessed motivation and ability to palpate their own pulse.<sup>102</sup> After instruction, the patients were instructed to keep a diary of their pulse findings, including any irregularities. Significant independent factors for success of both learning and motivation were high cognitive function (MMSE >24), computer usage at home, higher education level, independence with daily activities, and a lower HtR. While pulse palpation was less specific, this study detected new AF in 2% of participants, 75% of whom were asymptomatic.<sup>102</sup> This further demonstrates the importance of monitoring in the absence of symptoms. As with any home screening method, an abnormal result without the immediate consultation of a physician may be alarming for some patients.

The yield of a single ECG for the diagnosis of new-onset AF in elderly population >75 years of age is only 1%,<sup>103</sup> whereas a 14-day Holter monitor produced 7% new diagnoses, and simple palpation of a pulse has yielded 17% irregular pulses in 30 days.<sup>102</sup> Many episodes of AF are asymptomatic, including patients who were previously symptomatic<sup>104</sup> and especially those who underwent prior ablation,<sup>105</sup> making detection of AF recurrence in these patients a diagnostic challenge. Making the diagnosis is vital, as episodes as short as 6 minutes have been shown to increase the risk of

thromboembolism and stroke may be the first manifestation of AF that had previously been asymptomatic.<sup>105,106</sup>

Extended monitoring may be used to improve diagnostic accuracy as compared to self-monitoring or sporadic assessment. For example, the newly available adherent monitoring patch is a wire-free device that when stuck to a patient's chest allows for continuous monitoring for up to 14 days. During an episode, patients also have the ability to activate a button that associates symptoms with the rhythm at that moment in time.<sup>107</sup> Some devices can be worn for up to 30 days and perform real-time analysis of the ECG that is uploaded to a portal where the prescribing physicians can access the data.<sup>108</sup> While still inconclusive, it seems the research has been pointing toward the benefit of these longer monitoring devices. Rosenberg et al<sup>105</sup>, found that the adherent patch was superior to a 24-hour Holter monitor.<sup>108</sup> Conversely, Lobodzinski<sup>108</sup> stated that adherent patches have not been shown to be superior to other available methods and also brought into perspective the possibility of artifacts throughout the testing period. Turakhia et al<sup>109</sup> proved that these monitors are useful in the detection of paroxysmal AF and that with a median usage of 7 days, 99% of the recordings were analyzable.

Recurrences of AF often occur within the first week following conversion to normal sinus rhythm.<sup>105</sup> However, 5-minute snapshot ECG recordings were not found to be predictive of a 24-hour period of HtR; instead, it appeared that 6-hour recordings, especially if done in the morning, better assessed the overall HtR and rhythm.<sup>106</sup> With 30 days of ambulatory ECG loop recordings after a cryptogenic stroke, AF was detected in almost 10% of more patients than would have been found with just a 24-hour ECG monitor.<sup>110</sup> Oral anticoagulation was also prescribed to significantly more patients in the group monitored for 30 days, assisting with secondary prevention of stroke. The time to AF recurrence is often inversely proportional to the disease burden, and in those with a low burden, recurrence may not occur early,<sup>108,109</sup> making long-term monitoring vital.

While occasional ECG monitoring, Holter monitors, and monitoring patches allow for progressively longer monitoring times, they still may miss cases in which AF burden is very low. Implantable loop recorders can be utilized for several years and have an algorithm for AF/AFL/AT based on the variability of R–R wave.<sup>111</sup> These longer-term devices have been found to detect AF more often than wearable devices (23% vs. 14%) in an elderly population with cryptogenic stroke.<sup>112,113</sup> The detection rates were found to be as high as 30% in 180 days vs. only 5% in <72 hours. The median time to detection was 84 days after a cryptogenic stroke.<sup>112,114</sup>

Mobile cardiac outpatient telemetry (MCOT) is a mobile ECG that can be worn in everyday life. It transmits data instantly whenever a cardiac event occurs. To evaluate the benefits of MCOT, a study on >200,000 patients from the Truven database, an employer database with 2.8 million insured patients with CV disease, was conducted. From this population, 14,000 patients used MCOT, 54,000 patients used an event monitor, and 163,000 patients used a Holter monitor. The MCOT was found to have a significantly higher diagnostic yield of 61% for arrhythmias compared to the event monitor and Holter, at 23% and 24%, respectively.<sup>115</sup>

### Pill in the pocket (PiP)

Many antiarrhythmic medications have significant side effects that patients may find intolerable. For those with episodic AF and structurally normal hearts, the PiP strategy can be useful. In PiP, patients take a single dose of flecainide or propafenone when a symptomatic arrhythmia occurs.<sup>116</sup> Both these class IC drugs work promptly and with high efficacy.

A cohort study including 268 patients with recent onset AF (<48 hours) assessed the safety and efficacy of the PiP strategy in patients without existing conduction abnormalities, structural heart disease, CHF, electrolyte disturbances, collagen vascular disease, or thromboembolic disease. This study revealed that patients who successfully converted to sinus rhythm and experienced no side effects after taking flecainide or propafenone orally in the ED were able to resolve their symptoms with the PiP at home within 2 hours 94% of the time. Among the 163 patients who experienced recurrences after the first successful outpatient treatment with the PiP method, this approach was successful 84% of the time in resolving subsequent symptoms of arrhythmia. The most serious side effect found was transient AFL with rapid ventricular rate. Over the 15±5 months follow-up period, the number of ED visits and hospitalizations were significantly lower than prior to the year prior.<sup>116</sup> Another study on 122 patients with similar inclusion criteria investigated whether successful conversion to sinus rhythm and tolerance to intravenous administration of flecainide or propafenone in the ED had the ability to predict safety of PiP approach after discharge. After follow-up of 11±4 months, 94% of the patients successfully treated their arrhythmia episodes, though adverse events such as presyncope, syncope, and sinus arrest occurred in four patients (5%) during the first treatment. This led to premature termination of the study with the conclusion being drawn that successfully converting to sinus rhythm and tolerance to intravenous administration of propafenone or flecainide do not predict safety of the PiP approach.<sup>117</sup> The differences in these studies may be attributed to the differences in the levels

of 5-hydroxy propafenone, a metabolite of propafenone with strong pharmacologic activity causing PR interval and QRS duration prolongations. These effects are seen only with oral administration of propafenone due to higher serum levels of 5-hydroxy propafenone seen with oral administration than intravenous administration.<sup>118</sup> However, oral or intravenous administration of flecainide exhibits comparable results.<sup>119</sup> Collectively, this evidence may explain why the patient's response to intravenous administration of these drugs could not predict the safety of the PiP approach.

In the UK, a cost-effectiveness analysis was carried out on 12 RCTs in which drugs to treat paroxysmal AF were used.<sup>120</sup> The results indicated that the PiP approach is slightly less effective and less costly than the continuous AAD therapy, with incremental cost-effectiveness ratio (ICER) of £45,916 per quality-adjusted life year (QALY). A similar finding was seen when comparing the PiP approach to in-hospital treatment (ICER of £12,424 pounds per QALY). Greater cost-effectiveness was seen for men >65 years and women >70 years for the PiP approach than the continuous AAD therapy.

### Home-based warfarin monitoring

A major component of AF management is stroke prevention. The most widely used anticoagulant is warfarin, which is effective but can be challenging to use. Despite warfarin dosing being frequently monitored and adjusted based on fluctuating international normalized ratio (INR) levels from changes in diet, metabolism, and drug interactions, in practice the INR may not be within the therapeutic range (TTR) close to 50% of the time.<sup>121</sup> In a study conducted in the US by Matchar et al,<sup>122</sup> testing the INR at home with point of care kits was shown to achieve a higher time in TTR as well as increase patients' quality of life at no higher cost than office- or hospital-based INR monitoring. However, there were slightly more incidents of minor bleeding episodes in the self-monitoring group. Another study conducted in the UK found that self-monitoring could save hundreds of dollars per year per patient.<sup>123</sup> Multiple studies have found that home monitoring results in less mortality, thromboembolic events, and major strokes, likely due to greater TTR.<sup>123,124</sup>

### Novel oral anticoagulants (NOACs)

For >50 years, the only available anticoagulant that had been shown to be effective in reducing the risk of stroke in those with AF was warfarin. Warfarin's efficacy is tempered by the need for periodic INR monitoring, sometimes frequent dose adjustments, and drug–drug interactions. In recent years, however, the NOACs have emerged to allow



often superior risk reduction while offering many lifestyle benefits to patients with NVAf. Often, dosages do not need to be adjusted or regularly monitored, and the NOACs have fewer drug and food interactions. However, for most, there are no specific reversal agents; additionally, the efficacy and safety profile is still being determined. The US Food and Drug Administration (FDA)-approved NOACs include the direct factor Xa (FXa) inhibitors edoxaban, rivaroxaban, and apixaban and the direct thrombin inhibitor dabigatran.<sup>125,126</sup>

Cardiology societal guidelines recommend dabigatran as a useful alternative to warfarin for stroke prevention. In the seminal study comparing two doses of dabigatran (110 mg, 150 mg) and warfarin, dabigatran was found to significantly reduce the number of strokes, especially hemorrhagic strokes.<sup>125,127</sup> The rate of major hemorrhage was similar between warfarin and dabigatran. Similar to some of the other NOACs, more gastrointestinal (GI) bleeding was found.<sup>127</sup> Dabigatran was also compared to home management of warfarin, and no significant differences in outcomes were found.<sup>124</sup> Dabigatran is the first NOAC to have a specific reversal agent. This has set a major platform for ongoing trials assessing safety and efficacy of potential agents that have a role in reversing the remaining approved NOACs.

There are three NOAC-specific reversal agents in development: 1) idarucizumab; 2) andexanet alfa; and 3) ciraparantag (PER977). Of these three, only idarucizumab, a monoclonal antibody that binds to neutralize dabigatran with high affinity and specificity, is FDA approved. In the RE-VERSE AD study, patients who had overt, uncontrollable, life-threatening bleeding and received intravenous idarucizumab had hemostasis restored at a median time of 11.4 hours. Patients who required surgery or invasive procedure that could not be delayed for >8 hours had normal intraoperative hemostasis. One thrombotic event occurred in a patient in whom anticoagulation was not resumed within 72 hours after idarucizumab infusion.<sup>128</sup>

Andexanet alfa is a recombinant, modified human FXa decoy protein that sequesters and subsequently attenuates the anti-FXa activity of direct and indirect FXa inhibitors, including apixaban, rivaroxaban, edoxaban, and enoxaparin. Two parallel Phase III trials to assess its safety and efficacy, called the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXa Inhibitors Apixaban (ANNEXA-A) and Rivaroxaban (ANNEXA-R), revealed reversal of anticoagulant activity of apixaban and rivaroxaban in older healthy adults after intravenous bolus, and these effects were sustained if the patient received infusion after the bolus.<sup>129</sup> However, it is important to note that these trials assessed the efficacy and safety of andexanet alfa in healthy individuals and not

patients who were actively bleeding or requiring emergent surgery. Currently, the ANNEXA-4 Phase IIIb–IV study is evaluating the efficacy and safety of andexanet alfa in patients with FXa inhibitor-associated major bleeding.

Ciraparantag, or PER977, is a synthetic, small, water-soluble, non-specific reversal agent for heparins and NOACs.<sup>130</sup> Ciraparantag exerts its anticoagulation reversal effects by binding to heparins and NOACs through noncovalent hydrogen bonding, thus preventing them from binding to their endogenous targets.<sup>131</sup> Ciraparantag is currently being investigated in Phase II trials.<sup>132,133</sup> Ciraparantag has been investigated in healthy human volunteers. In a Phase I/II dose-ranging cohort trial, 40 healthy individuals who were treated with ciraparantag had reversal of enoxaparin's impact on whole blood clotting time (WBCT) within 20 minutes of administration of a 100-mg dose and within 5 minutes of administration of a 200-mg dose. There was no rebound anticoagulation or signs of procoagulant effect. Ciraparantag was also investigated in a double-blind, placebo-controlled, dose-escalation trial involving 80 healthy volunteers taking edoxaban. Edoxaban administration increased WBCT by 37% over the baseline value. The participants who received intravenous ciraparantag 100 mg, 200 mg, or 300 mg had their WBCT decreased to within 10% above the baseline value within 10 minutes and remained in that window for 24 hours. The patients who did not receive ciraparantag reached their WBCT to within 10% above the baseline value in 12–15 hours. Ciraparantag did not have procoagulant effects. The only adverse events reported were headache, taste distortion, and mild perioral and facial flushing.<sup>133</sup> Similar to ANNEXA-A and ANNEXA-R trials, these trials did not assess the efficacy and safety of ciraparantag in patients who were actively bleeding or requiring emergent surgery.

Overall, the FXa drugs were shown to decrease the rate of thromboembolic events, intracranial bleeds, and hemorrhagic strokes but with more GI and minor bleeds.<sup>125,134</sup> When compared to warfarin, edoxaban had a lower rate of stroke at high doses (60 mg, which was given to those with a CHADS<sub>2</sub> score of 4–6). Rivaroxaban also showed noninferiority compared to warfarin for stroke prevention.<sup>134</sup> For patients in whom vitamin K antagonists were unsuitable, aspirin was compared to apixaban and was clearly shown to be superior in reducing the risk of stroke by half without any further increase in bleeding.<sup>125</sup>

## Post-discharge nurse-led home intervention

Outpatient follow-up monitoring and education may be useful for reducing morbidity and mortality related to AF. For

example, one ongoing multidisciplinary home follow-up program carried out by cardiac nurses, termed standard versus atrial fibrillation-specific management strategy (SAFETY), included home visits and a Holter monitor 7–14 days post discharge in hopes of optimizing AF management.<sup>135,136</sup> The level of surveillance was adjusted based on the level of risk, cardiac function, and patient need. The patients continued to be managed with their antiarrhythmic, antiplatelet, and anticoagulant medications and remained followed by their general practitioner and cardiologist. Using SAFETY, patients had almost one-third less hospital admissions for heart failure, thromboembolism, bleeding, or cardiac-related death.<sup>135–137</sup> Stewart et al<sup>136</sup> found that although there were more days alive and out of the hospital in the SAFETY group, this trend reversed after 2 years. It is postulated that readmissions to the hospital decreased due to the increased surveillance, allowing arrhythmias to be diagnosed and treated before they would progress to critical conditions.

## Conclusion

AF is the most common arrhythmia worldwide leading to extensive public health and economic burden. With its increasing incidence and prevalence, optimizing health by minimizing modifiable risk factors may alone prove to be effective in primary and secondary prevention of AF. Home-based AF management options have shown benefits in terms of early diagnosis of AF, leading to reduction in cost, hospital readmissions, stroke, and mortality. However, most of these findings have revealed conflicting results, and additional studies are required to justify their routine use.

## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

Dr Morin and Dr Lavie have received speaker's honoraria from Boehringer-Ingelheim, and Dr Lavie also from Pfizer and Bristol Myers Squibb. The other authors report no conflicts of interest in this work.

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