Does Lifestyle Impact Risk, Burden, and Symptomatology of Atrial Fibrillation?

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Atrial fibrillation is the most common sustained arrhythmia, affecting 1-2% of the general population and 8% of patients over the age of 80 years.[1] The lifetime risk for development of AF is 26% for men and 23% for women. It is associated with significant morbidity, mortality and cost, but also with an increase in mortality and a six-fold risk of stroke.[2,3] The Framingham heart study showed that AF was associated with a 1.5 to1.9 fold mortality risk after adjustment for the preexisting CV conditions with which AF was related.[4] The Heart and Stroke Foundation estimates that 350 000 Canadians are living with atrial fibrillation, and that this is increasing due to Canada's aging population.[5]

The diagnosis of AF may be made fortuitously, such as through a pulse check, or in the emergency department if the patients presents with symptoms. Severity of symptoms for AF may range from a 'nuisance' feeling of palpitations to debilitating symptoms that do not permit performance of activities of daily living, interfere with normal livelihood and significantly impair exercise tolerance. The most severe symptoms are those resulting in hemodynamic compromise and heart failure, which are associated with poor prognosis and increased mortality.[6] Those that are symptomatic pose the greatest burden to the health care system, often making repeated visits to the emergency room for treatment or repeated hospitalizations due to delayed and limited access to specialist care, to initiate necessary therapies or undergo crucial cardiac investigations. Those that are asymptomatic don't pose as great a burden, at the time of diagnosis, however, are at risk for deleterious consequences if not treated appropriately. The mainstay for therapy for AF is aimed at stroke prevention and control of symptoms due to the arrhythmia itself. The primary mode of therapy is to use rate controlling agents, such as calcium channel blockers or beta blockers, but patients with more symptoms may require rhythm control. In one study, AF was diagnosed by the family physician in 63.2% of events, by an office-based cardiologist in 13.2%, and by hospital-based physicians in 23.9% of cases.[7] Up to a third of patients with AF will present to an emergency department (ED) at some time due to symptoms, representing 3-6% of all medical admissions to hospital.1 Overall, the estimated care costs of hospitalized AF patients are 9 to 23-fold greater than for those without AF.[8]

Most AF care is delivered through family physicians, eventual referral to specialists, but many repeated emergency room visits, or even hospitalizations may have occurred, prior to specialist assessment. Mcdonald et al. reported an 88% increase in ED visits with a primary diagnosis of AF over a 12 year period (1993 to 2004).[9] Of these, 64% were admitted to hospital; this proportion remained constant over the 12 year period. There are few data on the actual costs to the health care system for AF. Khaykin et al. estimated a cost of $4840/patient/year of AF.[10] The distribution of costs are amongst inhospital care, emergency room visits and family physician visits. There are many aspects of AF management that are best managed by those specifically trained to manage AF. It is well documented that there are a number of care gaps in management of AF at the general practitioner level.[11,12] These issues relate to which patients to anticoagulate, when to perform a cardioversion, when to switch from rate to rhythm control, and when to refer for catheter ablation.

Pathophysiology of AF as it relates to cardiovascular risk factors

AF may be due to one of three mechanisms:[13] the initiation and perpetuation of atrial fibrillation requires triggers which start an episode, and an arrhythmogenic substrate which allows it to continue. The triggers typically consist of ectopy which most frequently originate in the pulmonary veins, but extra-pulmonary

vein triggers may also exist in the coronary sinus, superior vena cava or within the body of the left atrium.[14,15] The maintenance of AF, once triggered, is due to changes in atrial structural and electrophysiologic properties. These changes may result from a wide variety of causes including left atrial stretch, structural remodeling leading to atrial fibrosis, as in congestive heart failure.[16] Paroxysms of rapid, consecutive premature atrial contractions, or short paroxysms of AF, can promote further functional changes that can perpetuate AF.[17] The role of the autonomic nervous system in the maintenance of AF has also been extensively studied. The ganglionic plexi are located along the great vessels and in the pericardial fat pads. Scherlag et al. have performed numerous experimental studies demonstrating that activation of the ganglionic plexi at the junctions of the pulmonary vein and atrium may result in conversion of pulmonary vein ectopy to atrial fibrillation.[18] Kistler et al. studied the effect of chronically elevated BP in animal models. It was found that elevated BP was associated with atrial fibrosis, significant conduction abnormalities, shortening of atrial wavelength and increased AF.[19] In both human and animal models, obstructive sleep apnea has been shown to result in increased atrial fibrosis and increased incidence of extra-pulmonary vein triggers.[20] Other clinical factors have been implicated in atrial remodeling and consequent AF, including: increased age, obesity, diabetes and heart failure.

Current Status of Management of AF

Current guidelines suggest that AF treatment should focus on strategies to prevent stroke, and to manage and control heart rate and rhythm.[21,22] AF is known to be a chronic disease. Rarely, patients will have a single episode of AF, but the majority of patients have progressively more episodes, or present with persistent AF. As with all chronic diseases, it cannot be cured but can be controlled with effective treatments, as recommended by the guidelines. Our current health care system was designed to address acute illness, rather than chronic disease. AF often occurs in the setting of other diseases, increasing the complexity in determining appropriate therapies. Lone atrial fibrillation occurs in a very small proportion of patients who present with new onset AF and may not even be a real entity. Most often, AF occurs in the setting of other cardiovascular disease, obesity, diabetes, sleep apnea or a combination of the above. In order to effectively manage AF, a 'holistic' approach is necessary. Appropriate management of hypertension, sleep apnea, obesity etc needs to become part of the mainstay of therapy for AF. The CCS AF guidelines recommendations state: "Underlying causes or precipitating factors for AF including hypertension should be identified and treated."[23] Possible targets for these are included in Table 1.[24]

Lifestyle Modification in AF

There are several facets of lifestyle modification that can be addressed to modify AF and its resultant outcomes. Risk factor modification has been termed the fourth pillar of AF care, with the first three being rate, rhythm and stroke prevention. The presence of risk factors that are known to promote AF are increasing in prevalence in the population: it is likely that the AF epidemic is greater than predicted. The Framingham study evaluated the incidence and prevalence of AF and its risk factors over 50 years.25 In 9511 patients over 50 years of observation, the incidence of AF increased in both men (3.7 vs 13.4 per 1000 person-years) and women (2.5 vs 8.5 per 1000 person-years).

Table 1. Potentially Modifiable Risk Markers/Conditions Associated with AF[24]

Conventional Risk Factors	Emerging Risk Factors	Less Established Risk Factors
Advancing age	Subclinical atherosclerosis	Chronic obstructive pulmonary disease
male	Borderline hypertension	Left atrial dilatation
Coronary artery disease	Chronic kidney disease	Atrial conduction delay/PR interval
hypertension	Subclinical hyperthyroidism	Left ventricular diastolic dysfunction
Heart failure	Inflammation	Left ventricular hypertrophy/diastolic dysfunction
Valvular disease	Elevated natriuretic peptides	Obesity
diabetes	Widened pulse pressure	Genetic factors
Thyroid disease	Excessive endurance exercise	
Obstructive sleep apnea syndrome	Excessive alcohol intake	
	Increased height	
	Increased birth weight	
	Smoking	
	Caffeine intake	
	Ethnicity	

The population attributable risk over time for AF increased due to higher body mass index (BMI) and diabetes. In a further analysis of the Framingham study, the risk profile of patients as it related to the lifetime risk of atrial fibrillation as assessed.[26] In this study 4.6% of patients had an optimal risk profile, defined as no smoking, alcohol consumption within recommended limits, normal body mass index, normotensive, no diabetes, heart failure or myocardial infarction. The lifetime risk of AF was 23.4% with an optimal risk profile, 33.4% with a borderline risk profile and 38.4% with an elevated risk profile (Figure 1).

The diagram in Figure 2 demonstrates the inter-relationship of these facets.

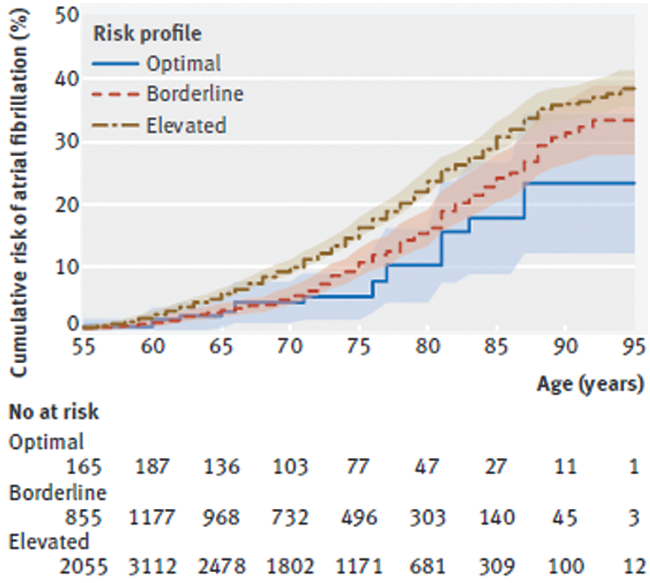

Figure 1. Cumulative risk (%) for development of AF according to risk-factor burden: optimal, borderline or elevated. Shading=95% confidence intervals.[26]

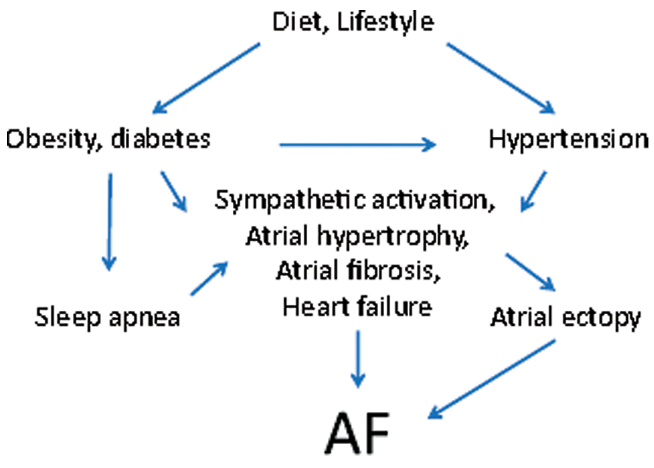

Figure 2. Relationship of cardiovascular risk factors to pathogenesis of AF. Adapted from Van Wagoner et al.[27]

Exercise in AF

Exercise and physical activity have been shown to improve outcomes in patients with cardiac health conditions such as ischemic heart disease, myocardial infarction and congestive heart failure but its effects on AF remain somewhat unclear.[28] Exercise has numerous cardiac effects including reducing heart rate and increasing stroke volume. Chronic exercise can further help protect the myocardium from acute ischemia and improve function in response to cardiac insults such as hypertension, myocardial infarction and general wear and tear associated with aging.[29]

The effects of exercise training on health benefits in AF have been evaluated in two systematic reviews. These studies have demonstrated that exercise can increase exercise capacity, improve quality of life, and provide a mechanism of rate control in AF patients.[30,31] An increase in exercise capacity in AF patients who exercised was demonstrated with increased distances in six-minute walk tests, and increased muscular strength, power and work. Exercise has been shown in some studies to lower resting heart rate by 7 beats per minute and improve heart rate reserve by 15 beats per minute. It should be noted that there are many important parameters to consider when evaluating health outcomes with exercise in AF patients. More work is needed to establish appropriate values for these parameters to maximize beneficial health outcomes.

While many studies have enrolled AF patients in different exercise regimens, only a handful to our knowledge have reported adverse events.[31] An estimated life-threatening adverse event rate of 1 per 209 752 minutes of exercise has been calculated in AF patients. Similarly for non-life-threatening adverse events (e.g., ischemic chest pain, exercise-induced AF), the adverse event rate is estimated to increase to 1 per 9756 minutes of exercise. These studies suggest that exercise is a safe therapy that can be further investigated in AF patients. The significance of this work is highlighted by the fact that patients with AF often present with symptoms of dyspnea, fatigue, palpitations, and decreased exercise capacity. These symptoms not only make it more difficult for patients to exercise, but also reduces their quality of life. Exercise intolerance and sedentary behaviour specifically can drive weight gain and lead to a variety of health issues. The effects of physical activity, as well as physical inactivity ie sedentary behaviour, is unknown in this population. The FIT project examined 64 561 adults without AF from 1991 to 2009 and found that one higher metabolic equivalent during treadmill testing was associated with a 7% lower risk of incident AF, with a stronger relationship amongst obese patients.[32] The CARDIO FIT study found an association between a gain of ≥2 METS pre and post a tailored exercise program to be associated with improvements in AF burden and symptom severity in a single center cohort study. Malmo et al. performed a single center randomized trial in 50 patients demonstrating a positive effect of intense aerobic interval training to reduce

recurrent AF in a population of patients with nonpermanent AF.[33] Although none of these studies provide definitive evidence regarding the benefits of exercise in AF, they do demonstrate that it is reasonable to have patients with AF perform moderate exercise, without the danger of deleterious effects.

Obesity and AF

Two randomized trials have shown reduction of AF and improved quality of life in patients with obesity and in patients with heart failure.[34,35] Abed et al. examined the effect of weight reduction and cardiometabolic risk factor treatment in patients with AF.34 Abed et al. examined the effect of weight reduction and cardiometabolic risk factor treatment in patients with AF and found an improvement in AF-related quality of life in the experimental arm. The LEGACY study was a cohort study that demonstrated weight reduction of ≥ 10% to be associated with a six-fold greater probability of arrhythmia-free survival compared with the those who loss less weight or did not lose weight at all.[36]

Blood Pressure and AF

Hypertension is the most prevalent, independent and potentially modifiable risk for atrial fibrillation.[37,38] The Framingham study revealed that an electrocardiographic diagnosis of LVH increases the risk of AF by more than 3 fold.[39] These changes may be a direct result of increased left atrial stretch resulting from increased pressures on the left side of the heart.

Recent studies have found a direct relationship between the risk of AF and systolic and diastolic BP. Conen et al. evaluated the risk of incident AF in healthy, middle-aged women as it pertains to BP.[40] Over a followup period of 12.4 years, the longer term risk of AF increased as the systolic and diastolic BP increased. Only a systolic BP < 120 mmHg was not associated with an increased HR of developing AF. The primary prevention of AF with antihypertensive therapy has been reported previously. A post-hoc analysis of the Losartan Intervention for Endpoint reduction (LIFE) study found that losartan reduced the incidence of new-onset AF from 10.1 to 6.8 per 1000 patient-years, as compared to atenolol alone; a meta-analysis examining the effect of angiotensin converter enzyme inhibition or angiotensin II receptor blockade on primary prevention of AF in patients with structural heart disease showing similar findings, providing support for the pleotropic effects of these medications.[41,42]

Whether aggressive BP control is of benefit in prevention of AF once it develops remains elusive. Secondary prevention of AF, has not been found to be of benefit using angiotensin converter enzyme inhibition or angiotensin II receptor blockade. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiac Atrial Fibrillation (GISSI-AF) study failed to show any benefit in preventing recurrent AF in a population of AF with paroxysmal or persistent AF.[43] The Atrial Fibrillation Clopidogrel Trial with Irbesartan to Prevent Vascular Events (ACTIVE I) trial also failed to show that the pleotropic effects of angiotensin II receptor blockade had any effect on cardiovascular outcomes in patients with AF.[44]

Parkash et al performed a multicenter, randomized trial examining the effect of an aggressive blood pressure control strategy on recurrent AF after catheter ablation.[45] This study did not find a benefit to reduction in AF with targeting this risk factor in isolation. The study did however demonstrate that patients whose baseline blood pressure was < 140 mm Hg, had a significantly lower recurrence of AF after ablation, as compared to those whose blood pressure was elevated at baseline (45% recurrence for SBP<140 compared to 86% recurrence for SBP>150, p=0.03). Patients older than the age of 61 had a significant benefit to aggressive BP lowering, as compared to younger patients (p for interaction =0.011).

These studies did not find direct benefits to aggressive BP lowering in AF; it remains important, however, to treat this risk factor using the current recommendations from the Canadian Hypertension Education Program guidelines as the target for BP control in AF patients.[46]

Sleep Apnea and AF

Sleep apnea is a disorder of breathing resulting in hypoventilation, hypopneas and apnea during sleep. It is associated with deleterious outcome when left untreated, particularly from a cardiovascular viewpoint.[47] It is known to affect 4% of middle-aged men and 2% of middle-aged women, as a whole. In the setting of concomitant AF, sleep apnea has been found to occur in up to 1 in 5 patients in the ORBIT AF registry.[48] The ORBIT registry also demonstrated in reduction in progression to AF, with no effect on mortality or cardiovascular hospitalization. Obstructive sleep apnea and AF are known to coexist; the risk of AF recurrence is higher in patients who have undergone catheter ablation in patients with obstructive sleep apnea, compared to those patients who do not have it.[49] Systematic reviews have pooled data from cohort studies that support the beneficial effect of sleep apnea treatment on AF, in combination with catheter ablation of AF.[49] In a recent clinical trial, there was no benefit of continuous positive airway pressure therapy on cardiovascular outcomes[50]; the effect of CPAP in AF has been shown to be of benefit in cohort studies but no randomized studies have been performed.

Multifactorial Risk Factor Management

There have been a few studies that have examined the effect of multifactorial risk factor management in patients with AF. The concept here is that treating a single risk factor in isolation may be ineffective, that many patients have multiple risk factors that coexist and overlap to result in further maintenance of AF. Rienstra et al. examined the optimization of heart failure medications, cardiac rehabilitation and aggressive blood pressure control in patients

with AF and heart failure, and demonstrated maintenance of sinus rhythm as measured on a 7 day Holter at one year pf 75% in the intervention group, as compared to 63% in the control group (OR 1.77, p=0.042).[35] Another single center study examined the role of risk factor management concomitantly with catheter ablation for AF. Pathak et al. performed a single center, cohort study that demonstrated that patients who chose to undergo aggressive risk factor modification had a reduction in AF compared to those who did not with an odds ratio of 4.8 (95% confidence interval 2.04-11.4).[51]

Delivery of Lifestyle Modification: Use of Specialized Clinics

How best to deliver lifestyle modification to this population remains an unanswered question. The use of cardiac rehabilitation programs has been traditionally reserved for those with acute coronary syndromes. Expansion of these programs to include AF patients could result in an overload of this resource, required for a different cardiac population. In addition, ensuring delivery of care across geographic boundaries, particularly in Canada is important. Using 'bricks and mortar' programs, this becomes difficult. Specialized AF clinics have garnered significant attention recently. The studies that have been performed are discussed below.

Gillis et al. published their preliminary data from this type of clinic, which showed encouraging results.[52] The clinic accepted 20–40 patients per week for assessment. The time for specialist assessment was brought to 38+/-31 days, as compared to 221+/-774 days in the year prior to the formation of the clinic. The number of emergency department visits and hospitalizations were dramatically reduced, 82% and 56% respectively. Gillis et al. first established their clinic through an innovative fund from their health care region. The results were so positive that funds to permanently establish this clinic were allocated. The Integrated Management to AF study (ICAT-AF) demonstrated that a nurse-led, physician supervised program providing education and management of risk factors (before-after study; n=433) could improve guideline adherence, and improve health outcomes (decreased AF-related ED visits and hospitalizations by 29% in new onset AF.[53] The largest study examining this model of care was performed in the Netherlands. Hendriks et al. demonstrated a reduction in CV mortality in a randomized controlled trial of a nurse-led, physician supervised AF clinic in the Netherlands, as compared to usual care.[54] Cardiovascular death occurred at a rate of 1.1% in the nurse-led care vs. 3.9% in the usual care group (hazard ratio: 0.28; 95% CI: 0.09–0.85; P= 0.025); cardiovascular hospitalization was reduced to 13.5 from 19.1% in the usual care group (hazard ratio: 0.66; 95% CI: 0.46–0.96, P=0.029). The Hendriks study utilized a computer-based algorithm to assist the nurse with the AF care. This computer-based algorithm is costly to apply widely and as such the outcomes observed by the study may not be generalizable.

Multiple prior studies have demonstrated the effectiveness of multidisciplinary care in peri-procedural management. Recent reviews have emphasized the importance of integrated care for heart rhythm disorders. Greater coordination of care with nursing interventions has demonstrated more efficient use of resources,[55] and better coordination of heart rhythm procedures,[56,57] as well as better implementation of other cardiac therapies.[58,59]

In these studies, the observed reduction in primary outcome events may be attributable to several factors including consistency of patient education delivered by a nurse, repeated encounters, improved guideline adherence, particularly in OAC use, as well as risk factor management, resulting in the observed reduction in cardiovascular events. Significant delays in receiving guideline-indicated therapies, specifically appropriate anticoagulation, could lead to adverse cardiovascular outcomes. Based on previously published data, the monthly incidence of stroke with non-valvular AF ranges from 0.23% to 1.5%, depending on CHADS2 score.[60] Given wait times for specialist assessment, whether through a specialized AF clinic or specialist usual care, the incidence of stroke could be reduced by improving anticoagulation at the time of AF diagnosis.

Conclusion

The difficulty arises in how patients with AF and its associated risk factors should be managed. The use of specialized clinics may result in patients receiving care from various specialists, that may lead to multiple and potentially conflicting treatment recommendations. As the complexity of medical problems plaguing an individual patient increases, so does the number of specialty clinics that he/she may be exposed to. This results in greater need for centralization of a patient's care with their family physician. Risk factor management may be improved by a form of integrated care. Using a combination of pharmacologic and non-pharmacologic treatments (ie focus on lifestyle), risk factors that aggravate and trigger AF likely need to become a part of our usual armamentarium of care in AF patients. The most expeditious model of care for AF remains a challenge in our resource-constrained environment, but remains an important focus to improve outcomes associated with AF.

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