# Atrial Fibrillation In Heart Failure: New Directions In Diagnosis, Risk Assessment And Risk Reduction

Dr. Richard J. A. Till, Prof. Martin R. Cowie

*Imperial College London/Royal Brompton Hospital.*

## Abstract

Heart failure and atrial fibrillation are common conditions which frequently co-exist. In patients with established systolic and diastolic dysfunction, atrial fibrillation increases the risk of stroke, mortality and reduces quality of life. Recent advances in implantable device technology have improved the detection of atrial fibrillation and reduced the time to intervention. Rate control remains the mainstay of treatment to improve symptoms in patients with heart failure. Currently evidence does not suggest that the routing use of a rhythm control strategy is beneficial, other than improving symptoms in patients resistant to or intolerant of rate control medications. Atrial fibrillation ablation in heart failure is safe and may be effective in maintaining sinus rhythm. Patients with AF and heart failure have more severe strokes and require longer hospital admissions. Warfarin has traditionally been the drug of choice to reduce the risk of stroke in patients with AF and heart failure, although it use is no longer recommended in patients with heart failure and sinus rhythm. Newer oral anticoagulants offer improved stroke prevention in patients with heart failure albeit at a higher drug cost. Alternative methods of stroke reduction such as left atrial appendage occlusion are emerging, although evidence for their benefit in patients with heart failure has not yet been published.

## Introduction

### Atrial Fibrillation And Heart Failure: A Perspective

Atrial fibrillation remains the most common cardiac arrhythmia and continues to add significantly to worldwide mortality and morbidity. In addition to the reduction in quality of life that occurs due to the symptoms of palpitation, dyspnoea and fatigue, AF significantly increases the risk of stroke. It also reduces life expectancy, is more common with advanced age, and the prevalence continues to increase. In England, data from death certification has shown that atrial fibrillation as a primary cause of death increased by 6.6% per year between 1995 and 2010.[1] The management of the growing burden of atrial fibrillation occurring in ageing populations is a pressing issue for health systems throughout the world.

The prevalence of heart failure in Western populations has been estimated at 1-2%.[2] Heart failure is also more common in older patients. Data from an English population has reported an incidence rate rising from 0.02/1000 population per year in those aged 25-34 to 11.6/1000 population per year in those aged over 85.[3] Heart failure is a complex syndrome involving multiple organ systems. Both conditions share many risk factors, and frequently co-exist. The addition of atrial fibrillation can destabilise patients and balancing the risks and benefits of treatment with antiarrhythmic and antithrombotic therapies in patients with multiple co-morbidities can be challenging for physicians.

The symptoms of heart failure have been observed both in the presence and absence of normal left ventricular function. Heart failure physicians differentiate between 'Heart Failure with Reduced Ejection Fraction' ('HFrEF') and 'Heart Failure with preserved Ejection Fraction' ('HFpEF') depending on the measurement of ejection fraction on echocardiography. The commonest causes of systolic dysfunction in Western populations are ischaemic coronary heart disease and dilated cardiomyopathies. In other regions, conditions such as Chagas' disease and nutritional deficiencies, such as Beri Beri, also feature as causes. Diastolic dysfunction may occur due to hypertrophic and restrictive cardiomyopathies, and is also seen in the context of hypertension, advanced age and diabetes.

### Pathophysiology Of Atrial Fibrillation In Heart Failure

The pathophysiology of atrial fibrillation remains an area of intense scientific interest. The factors affecting the initiation and propagation of AF appear to be multiple and complex. AF and heart failure share many common risk factors, and both may share a common aetiology, for example ventricular and atrial ischaemia.[4] Through rapid ventricular rates, ventricular remodelling and increased left atrial size, atrial fibrillation may itself worsen, or even cause, left ventricular dysfunction.[5]

AF is initiated by 'triggers', usually in the form of ectopic electrical activity. In the otherwise structurally normal heart the pulmonary

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**Corresponding Author:**
Imperial College London/Royal Brompton Hospital
Sydney Street, London SW3 6NP

veins have been considered the main site of origin of such triggers, but ectopic activity originating in other sites such as the superior vena cava, oblique vein of Marshall, coronary sinus and the terminal crest have also been implicated.[6] Following AF initiation, propagation of atrial fibrillation across the atrial myocardium occurs and is thought to adversely affect atrial electrical remodelling, further increasing the likelihood of AF formation and propagation, leading to the concept that 'AF begets AF'.

The association between left atrial dilatation and atrial fibrillation is well established, and is both a consequence of, and cause of, AF.[7] The left atrium, being a thin-walled structure, is unable to compensate for increase ventricular filling pressures by hypertrophy. In the failing heart, where left ventricular filling pressures are elevated either due to systolic dysfunction or impaired relaxation and/or compliance (i.e. diastolic dysfunction) left atrial dilatation occurs.[8] This induces fibrotic changes within the atrial myocardium which, in addition to the electrolyte and neurohormonal disturbances of heart failure and intrinsic myocardial disease, increases the likelihood of initiating and propagating atrial fibrillation. Heart failure may therefore itself be considered pro-arrhythmogenic.

The symptoms of AF are due to rapid ventricular response to atrial fibrillation and the loss of atrial contraction. In the normal heart, the majority of left ventricular filling occurs due to the reduction in left ventricular pressure below left atrial pressure due to myocardial relaxation. Atrial contraction is responsible for a small portion of ventricular filling later in diastole. However, in diastolic dysfunction, the impaired relaxation means that the atrial contraction becomes much more important to ventricular filling. With atrial fibrillation, the atrial contraction is lost. Thus, in patients with HFpEF the onset of atrial fibrillation can be particularly destabilising.

### Characteristics Of Atrial Fibrillation In Heart Failure

Atrial fibrillation is common in patients with heart failure. Multiple studies have demonstrated an association between the two conditions and the prevalence of persistent atrial fibrillation appears to increase with heart failure severity. Data from randomised trials of drugs therapies in heart failure have reported a prevalence of ≤5% in patients with NYHA I symptoms[9] rising to 50% in patients with NYHA IV symptoms.[10] The incidence of paroxysmal AF, which may be unnoticed by patients and therefore not reported, is more poorly understood.

The association between AF and mortality has been investigated for the past 2 decades. The consensus appears to be that AF is an indicator of poor prognosis in heart failure. Despite earlier evidence that did not establish a link between AF in heart failure and premature death,[11] subsequent studies have suggested that AF acts as an independent risk factor for mortality, possibly increasing death rates by 1/3rd.[12] Whether AF or heart failure presents first appears not to matter.[13]

AF in heart failure is associated with clinical decompensation. Around 30% of patients admitted to hospital with acutely decompensated heart failure will be in atrial fibrillation, and where present, AF is associated with a longer hospital stay and a higher inpatient mortality rate.[14,15]

### Economic Costs

The costs of treating the AF and its complications are large and rising. Whist estimates of the costs of AF vary between health systems, the direct costs of managing AF in Europe have been estimated to range from €450-€3000 per patient year.[16] Costs for treating atrial fibrillation in patients with heart failure are higher. An economic analysis of the AF-CHF trial reported that the costs of treating patients with heart failure with either a rate or rhythm control strategy were similar (€18,494 vs. €24,211).[17]

Acute strokes due to AF add additional costs. For example in the German health system, the cost of treating strokes in atrial fibrillation vs non-AF related strokes is estimated at €11,799 per stroke admission vs €8,817.[18] This is presumed to be due to the fact that strokes that occur in AF are more severe than those which occur in sinus rhythm.[19]

Because of the large costs involved in treating the vascular complications of atrial fibrillation and the potential to reduce these by means of anticoagulant therapy, many health systems are attempting to improve case-finding and treatment.

## Diagnosing AF

### Classification Of Atrial Fibrillation

Current guidelines classify AF according to the duration of episodes. Atrial fibrillation may be persistent if episodes last for at least 7 days, or paroxysmal if when less than 7 days. Patients may alternate between the two states; for example, when a patient experiences a new episode of AF that has lasted for a few hours which has been preceded by episodes lasting several weeks. When AF is present for more than 7 days and cardioversion has either failed or will not be attempted, AF is considered permanent.[20]

While persistent or permanent AF is easier to capture on electrocardiography and therefore well represented in clinical trials that assess the benefit of anticoagulation, paroxysmal AF, which by its nature is more difficult to capture, has been less well studied. Many of the earlier trials of warfarin in AF excluded patients with paroxysmal AF altogether.[21,22] Therefore how much AF is required to warrant the risk of anticoagulant therapy is not yet known. The amount of time that a patients spends in AF is frequently referred to as the "AF burden". There are no accepted definitions of a clinically significant burden. Whether or not the total proportion of time in AF, length of individual episodes or frequency or pattern of episodes confer similar risk is still under investigation. In heart failure, as the risk of bleeding is higher than that found in the lone-AF population, a better understanding of the risk posed by an increasing burden of AF is needed to guide oral anticoagulant therapy (OAT).

### Case Finding

Many of the initial observational and cohort studies which reported the prevalence of atrial fibrillation relied on ECG assessment at interval follow-up, either scheduled or on presentation to a physician, for the diagnosis of atrial fibrillation. Whether atrial fibrillation had occurred in the intervening period was not assessed. By this method, the Framingham study[23] reported a 2% incidence of AF over a 22-year follow-up in a population without a history of AF.

The development of atrial fibrillation may not always be associated with symptoms, and therefore the first presentation is often with an acute stroke. In view of the significant potential for reducing morbidity, mortality and health service costs through the use of anticoagulation in atrial fibrillation, much effort has been invested in case finding.

#### Screening Programmes

The results of a randomised, controlled trial of opportunistic vs. systematic screening for AF were reported in 2005.[24] In this study, 15,000 patients ≥ 65 years were randomised to either a control group, or to systematic or opportunistic screening protocols (Figure 1). After 1 year, the results showed that both screening strategies were
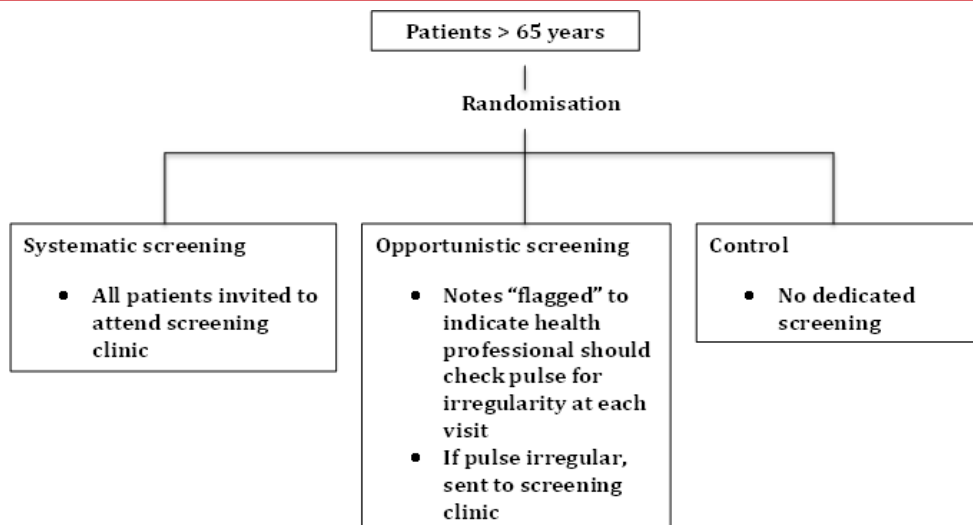
| Figure 1: | Typical,full right sided geometry as drawn by Ensite System |

significantly better than conventional care and were comparable in terms of the number of new cases detected. However, the incremental cost per case detected for systematic screening was approximately 4.5 times higher than for opportunistic screening.

*Population Education And Self-Diagnosis*

With evidence in support of opportunistic pulse screening by physicians, attention in recent years has turned to population-wide education and the promotion of self-detection. Public education is promoted through programmes such has 'Know Your Pulse' in the United Kingdom, and  'Beat Your Odds' in the USA.[25,26] Smart phone applications are also available and promoted by heart disease charities for the self-assessment of cardiac rhythm.[27] The introduction of "wearable health technologies" such as smart watches will offer further opportunities for self-diagnosis and may become an increasingly important source of heart rhythm data.

**Atrial Fibrillation Detection In Heart Failure**

Careful assessment for the development of atrial fibrillation should be part of the routine care for all patients with heart failure. For patients with implantable electrical cardiac devices such as CRT and ICD generators, continuous intra-cardiac rhythm monitoring offers another opportunity for AF diagnosis. Most modern pacemakers and implantable cardioverter-defibrillators are capable of arrhythmia detection and in many instances are also capable of storing and transmitting intracardiac electrograms to the supervising physician. The wireless telemetry of heart rhythm data has been shown to be useful in the diagnosis of atrial fibrillation in a population at higher risk of thromboembolic complications.[28-31]

There is emerging evidence that the incorporation of such technologies into models of device follow-up may improve outcomes by enabling the initiation of OAT at an earlier time than would otherwise occur. In a 2008 study of 166 patients undergoing home monitoring of implanted devices, Ricci et al reported that interventions for newly-detected atrial fibrillation occurred around 5 months earlier than the next scheduled hospital follow-up.[32] Earlier treatment has significant potential to reduce the incidence of stroke in heart failure.

## Treatment Of AF  In Heart Failure

**Treatment Goals: Rate or Rhythm?**

The relative merits of cardioversion to sinus rhythm as opposed to the control of the ventricular rate in patients with atrial fibrillation have been discussed extensively elsewhere.[33-35] Several large studies have failed to demonstrate the superiority of rhythm control over rate control in the reduction of stroke rates or mortality in patients with AF and structurally normal hearts.[36,37]

Similar results have been observed in studies enrolling patients with heart failure.  Several studies have been published over the last decade which looked at the benefits of rate vs. rhythm control in patients with heart failure (Table 1). There appears to be no benefit from a rhythm control strategy in reducing stroke rate, embolisation or death.[38,39] Moreover, maintaining sinus rhythm was difficult, with all studies reporting a high recurrence rate of AF. Rhythm control strategies remains a recommended treatment where symptoms remain despite adequate rate control.[40]

**Pharmacological Treatments Of AF**

*Rate*

Slowing the ventricular rate in atrial fibrillation improves symptoms, but aggressive rate reduction strategies have not been

| Table 1: | Studies of AF treatment strategy (rate vs. rhythm) in patients with heart failure |

| Study | n | Heart failure % | Heart failure criteria | End point(s) | Result for enrolled patients with HF |
|---|---|---|---|---|---|
| STAF[38] | 200 | 55.5% | ≥ NYHA II | Combined: death, cardiopulmonary resuscitation, cerebrovascular event, systemic embolism | No difference between rate or rhythm |
| AF-CHF[39] | 1376 | 100% | ≥ NYHA II; EF ≤ 35% | Time to cardiovascular death | No difference between rate or rhythm |
| CAFÉ-II[40] | 61 | 100% | ≥ NYHA II; systolic dysfunction on echo | NYHA class, 6MWT, LV function, NT-proBNP, QOL | 6MWT and QOL: no difference |
| | | | | | LV function, NT-proBNP, QOL: slight improvement with rhythm control |

| Table 2: | | | Comparison of NOAC trials with respect to participants with heart failure | | |
|---|---|---|---|---|---|
| | Drug | n | Proportion of enrolled patients with heart failure % | Heart failure definition | Result for heart failure group |
| RE-LY[66] | Dabigatran | 18,113 | 32% | LVEF < 40% or NYHA ≥ II | 110mg: Non-inferior |
| | | | | | 150mg: Dabigatran superior |
| ROCKET HF[67] | Rivaroxaban | 14,264 | 62.5% | LVEF ≤ 35% | Non-inferior |
| ARISTOTLE[71] | Apixaban | 18,201 | 44% | LVEF ≤ 40% or symptomatic HF in prior 3 months | Apixaban superior |
| ENGAGE[72] | Edoxaban | 21,105 | 58% | Not stated | Not reported |

shown to be superior to lenient, easier to achieve targets. The RACE II trial,[41] which randomised 614 patients with permanent AF to either lenient (<110 bpm) or strict (<80 bpm) heart rate targets, reported no difference in the reduction of a composite outcome of death from cardiovascular causes, hospitalisation for heart failure, stroke, systemic embolism, bleeding and life-threatening arrhythmic events. For patients with heart failure (47% of patients enrolled) a separate post-hoc analysis of this group has also shown no benefit when a more strict rate-control target was adopted.[42]

### Rhythm

Where rate control is ineffective in reducing the symptoms of atrial fibrillation, rhythm control may be considered. Whilst ineffective at reducing mortality in heart failure,[43] amiodarone is effective in maintaining sinus rhythm.[44] However, the side effects of amiodarone use have meant that there is reluctance to use it for long periods of time.

Dronedarone, a newer antiarrhythmic developed as an alternative to amiodarone, is associated with a significantly higher mortality in patients with heart failure, and is therefore contraindicated in patients with NYHA IV heart failure or recent decompensation.[45]

### Non-Pharmacological Treatments Of AF

### Ablation In Heart Failure

In the past decade, catheter ablation has emerged as a treatment option for patients with symptoms of recurrent atrial fibrillation not amenable to drug therapy. Multiple studies have demonstrated the effectiveness at improving symptoms and the relative safety of this procedure in the structurally normal heart.[46] Patients who undergo catheter ablation often require multiple procedures to obtain satisfactory pulmonary vein isolation, and the procedural complication rate is around 3% and is higher in elderly patients.[47,48] Whilst effective in reducing the symptoms of atrial fibrillation, whether or not catheter ablation reduces stroke risk remains unanswered.[49]

Evidence from randomised trials for the role of catheter ablation in the management of AF in heart failure is emerging. In 2013, Jones et al[50] reported a trial of 52 patients randomised to either catheter ablation or rate control. In this study, there was a significant increase in peak oxygen consumption in the ablation group (+3.07 ml/kg/min; p = 0.018), although the trends towards improvement in 6MWT and EF were not significant. A higher proportion of patients maintained sinus rhythm (92% at 12 months; 72% after single procedure) during follow-up (12 months) compared to other studies comparing rhythm and rate control. The recently reported CAMTAF trial[51] randomised 50 patients with heart failure and persistent atrial fibrillation to receive either catheter ablation or conventional medical therapy. After a 6 month follow-up period, 81% of the patient in the catheter ablation arm were free of AF (vs. 0% in the conventional treatment arm),

demonstrating the potential effectiveness of ablation in restoring sinus rhythm with a similar risk to procedures performed in patients without heart failure.

Ablation for atrial fibrillation in heart failure appears to be effective in maintaining sinus rhythm, albeit with high rates of repeat procedures (around 60-70% in most studies[20]). The case for the role of ablation in reducing stroke risk, hospitalisation and mortality has, however, not been made.

For patients in whom atrial fibrillation ablation is not considered, another option is AV node ablation. The use of radiofrequency energy to disrupt the normal atrio-ventricular conduction at the AV node predates catheter ablation for AF in the left atrium. Although AV node ablation has no effect on fibrillation in the atria, the prevention of conduction of fast atrial rates across the AV node prevents a fast ventricular response. Because of the induction of iatrogenic complete heart block, AV node ablation requires the insertion of an artificial pacemaker prior to the procedure and is therefore often referred to as 'ablate and pace'. Ablate and pace treatment strategies reduce symptoms and improve quality of life.[52] Concerns regarding the introduction of interventricular dyssynchrony in patients with heart failure due to pacing from the right ventricle following AV node ablation has led many physicians to prefer a biventricular device when performing 'ablate and pace'.[53]

### Thromboembolic Risk Stratification And Reduction

### Thromboembolic Risk In Heart Failure

The earliest epidemiological studies on AF and stroke noted the association between the incidence of stroke in AF and heart failure.[54] In the Framingham cohort, the risk of stroke in patients with heart failure was observed to be doubled when atrial fibrillation was present,[55] and the increased risk of stroke in AF when heart failure is present has been observed in multiple studies since.[56,57] AF also predicts mortality in patients with heart failure – new onset AF increases mortality risk in heart failure by 30%[12]. Current guidelines for the assessment of stroke risk in atrial fibrillation incorporate the risk of heart failure as part of the $CHADS_2$/$CHADS_2Vasc$ classification schemes.[58]

How much AF confers a higher stroke risk? The earliest studies of warfarin in AF were designed to enrol patients with persistent AF – patients with paroxysmal AF were either excluded or only included if AF was present at interval follow-up.[59,60] With the advent of continuous cardiac monitoring through implanted electrical heart failure devices, a greater understanding of the risk of differing burdens of AF is starting to emerge. High atrial rates detected by CRT and ICD devices have been shown to be associated with strokes[30], although further work is needed to answer the question of how much AF warrants OAT and whether or not certain patterns of AF confer a higher risk than others.

The use of OAT to prevent thromboembolism in patients in heart failure and sinus rhythm has been studied in several large RCTs. Despite the observation that patients with heart failure have a higher risk of stroke, in those who do not have atrial fibrillation anticoagulation does not reduce the rate of thromboembolism and is no longer recommended routinely.[61-65]

### Novel Oral Anticoagulants In HF

Since the introduction of Dabigatran in 2008, several novel oral anticoagulants ('NOACs') have emerged as potential treatments to reduce the risk of stroke in atrial fibrillation. Based on evidence from RCTs such as RE-LY[66], ROCKET AF[67] and ARISTOTLE[68], NOACs are as either as effective as or superior to warfarin in reducing the risk of stroke and mortality. Whilst the results vary between individual compounds and dosing regimens, most studies report a lower rate of major bleeding on NOACs compared to warfarin. There are no randomised trials comparing NOACs with one another, although indirect comparisons have been attempted.[69] NOACs offer considerable advantages to the patient over older vitamin K antagonists, such as simpler dosing regimens without monitoring, shorter duration of action and fewer drug interactions, albeit at a higher drug cost. NOACs are now recommended as first-line treatment for patients with AF requiring OAT.[70]

For patients with heart failure, the benefits of NOACs appear more mixed. Patients with heart failure were enrolled into all of the trials for NOACs to differing degrees, although in each trial the definition of heart failure was slightly different. Overall, for patients with impaired systolic function and ≥ NYHA II symptoms NOACs are likely to be non-inferior to warfarin in preventing strokes. A summary of the involvement and results of patients with heart failure in NOAC trials is given in table 2.

### Non-Pharmacological Techniques

Occlusion of the left atrial appendage has recently emerged as an alternative to oral anticoagulation for the prevention of stroke in atrial fibrillation. Several devices have been developed to occlude the LAA, such as the PLAATO device (withdrawn due to lack of funding for phase II or III trials), the Amplatzer cardiac plug (St Jude™, on-going trial) and the LARIAT™ (SentreHeart) percutaneous LAA suture device. Currently, the most widely used technique is the WATCHMAN™ device (Boston Scientific). The WATCHMAN is a percutaneously implanted device consisting of a polyester fabric stretched across a self-expanding nitinol frame. Permanently placed in the orifice of the left atrial appendage, the device should prevent the escape of thrombus from within the lumen of the appendage. The efficacy, safety and non-inferiority of the WATCHMAN™ device to warfarin has been demonstrated in the PROTECT-AF trial.[73]

The initial experience with LAA occlusion devices has been to implant the device in patients in whom warfarin is contra-indicated. In heart failure, where the risk of bleeding is higher, this would be beneficial. However, evidence supporting the use of such devices in heart failure patients is, at best, limited - although patients with mild-moderate heart failure were included in the PROTECT-AF study, the trial excluded patients with more severe heart failure (NYHA IV symptoms or an ejection fraction < 30%) and results for patients with heart failure have not yet been separately reported.[73] Comparison of efficacy with novel OATs is also limited.[74]

### Conclusions:

Atrial fibrillation in heart failure is common, and early detection and treatment can reduce the incidence of stroke, improve quality of life and reduce mortality. Modern technologies offer a new opportunity to increase case-finding and reduce the time to first diagnosis, and provide further insight into the risk of paroxysmal atrial fibrillation. Multiple strategies now exist for reducing the risk of stroke and improving the symptoms of atrial fibrillation and heart failure, but the assessment of the risk-benefit balance for individual patients remains complex.

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