Review Article

What are the Thromboembolic Risks of Heart Failure Combined With Chronic or Paroxysmal AF?

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ABSTRACT

Background: Heart failure (HF) and atrial fibrillation (AF) are common disorders that frequently occur together and are associated with an increased risk of thromboembolism. This thromboembolic risk may be reduced by anticoagulation with warfarin but not without introducing new hemorrhagic risks.
Methods and Results: Current guidelines recommend the use of anticoagulation in patients with HF and chronic AF and paroxysmal AF (PAF) that is symptomatic or frequent and prolonged enough to be detected by electrocardiogram. However, the evidence supporting these recommendations is weak and does not take account of research indicating that the prothrombotic risk is higher in more severe HF.
Conclusions: An area not addressed by current guidelines is anticoagulation in patients with HF and short, asymptomatic episodes of AF. These issues need to be resolved with further studies using implanted devices to detect such asymptomatic PAF. (*J Cardiac Fail 2010;16:340–347*)
Key Words: Paroxysmal atrial fibrillation, heart failure, thromboembolism.

Heart failure (HF) and atrial fibrillation (AF) are common disorders, especially in our increasingly elderly population prevalence of HF[1] and AF[2] each reaching 9% amongst those older than 80 years of age.[2] These disorders often occur together, with up to 50% of HF patients also having AF.[3] Thromboembolic events are an important source of morbidity in both conditions. The stroke rates in HF patients in sinus rhythm of ~1%/year[4] and AF patients without HF ~3.3%/year[5] are much greater than the rate of just ~0.2%/year in the general population.[6] Although current AF and HF guidelines recommend the use of anticoagulation in patients with HF and chronic AF or paroxysmal AF (PAF) the advice is not consistent (Table 1).[7–10] For example, although the American Heart Association/American College of Cardiology guidelines advocate formal anticoagulation in all patients with HF and permanent or paroxysmal AF,[8] the European Cardiology Society HF guidelines give no guidance on Paroxysmal AF,[7] and the equivalent American Heart Association/American College of Cardiology/European Cardiology Society AF guidelines only advocate anticoagulation if there as an additional thromboembolic risk factor accompanying HF and permanent or paroxysmal AF (eg, diabetes, hypertension, previous stroke).[10] One reason for this variation is that the evidence supporting these recommendations is weak. A further issue with the current guidelines is that none of them take account of research indicating that the prothrombotic risks are increased in more severe HF. In this review, we will examine the evidence for the risk of thromboembolism in HF being relating to the degree of severity of HF before examining the influence of coexisting chronic and paroxysmal AF. Finally, we will discuss the increasingly recognized phenomenon of asymptomatic paroxysms of AF, another area not addressed by current guidelines.

Thromboembolism in HF

Evidence for Thrombogenic State: Plasma Markers

Through a combination of direct mechanical effects and neurohormonal/cytokine changes, HF produces a prothrombotic state. As detailed in Table 2, many clinical trials have examined this prothrombotic state in HF using plasma markers that assess activation of the individual components of Virkow's triad: clotting cascade, platelets, and endothelium

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Table 1. Summary of Advice from Current HF and AF Guidelines from ACC, AHA, ESC, and ACCP

Guidelines	Management Advice on HF/AF Combination	Management Advice on HF/PAF Combination	Comments on HF Severity	Comments on Asymptomatic AF
ACC/AHA HF[8]	Formal anticoagulation in patients with HF and persistent AF	Formal anticoagulation in patients with HF and paroxysmal AF	None	No comments but mention of need for continued anticoagulation if any history of AF
ESC HF[7]	Anticoagulation recommended in patients with HF and AF especially if previous stroke/TIA	No specific advice for PAF although PAF is mentioned as one of the classifications of AF	Merely that anticoagulation should be given in all patients with LVEF < 35%	No comments
ACC/AHA/ ESC for AF[10]	Formal anticoagulation in AF +HF + 1 other moderate risk factor. Choice of aspirin or anticoagulation if AF + HF alone.	Acknowledges evidence of prothrombotic changes in PAF and advises " select antithrombotic therapy using the same criteria irrespective of the pattern (i.e., paroxysmal, persistent, or permanent) of AF	Definition of risk factor as LVEF < 35% or clinical heart failure	Acknowledgement that "device-based monitoring have revealed that an individual may experience periods of both symptomatic and asymptomatic AF" and "that longer periods of monitoring are needed to detect". No advice on management.
ACCP AF[9]	Anticoagulation recommended in AF and HF + 1 other risk factors. Choice of aspirin or anticoagulation if AF + HF alone.	PAF to be managed in a manner similar to those with persistent AF, basing use of anticoagulants on the presence of risk factors for stroke	Definition of risk factor as moderately or severely impaired LV systolic function and/or heart failure	Acknowledgment that "studies document a high prevalence of asymptomatic PAF" but no specific advice on how to manage. Comment is in PAF section suggesting management should be the same.

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Cardiology Society; ACCP, American College of Chest Physicians; HF, heart failure; AF, atrial fibrillation; PAF, paroxysmal AF.

(Fig. 1).[11-15] In most of these studies, the level of prothrombotic activity was related to the severity of HF/degree of chamber dilatation.[11–13]

Evidence for Thrombogenic State: Clinical Thromboembolism

The influence of HF on clinically detectable thromboembolism is less clear because most large-scale HF trials and registries include patients both with and without AF. Only a couple of trials, namely the Study of Left Ventricular Dysfunction (SOLVD)[16] and Sudden Cardiac Death-HF Trial,[4] have reanalyzed their data to exclude patients with AF or atrial flutter. As detailed in Table 3, both of these studies showed increasing thromboembolic rates with worsening severity of HF. Similarly, the year-long Survival And Ventricular Enlargement trial[17] showed increased stroke rates with worsening HF. However, because this study did not exclude patients with known AF, the risks of thromboembolism from HF alone is not clear because the prevalence of AF also increased with worsening HF (Table 3). It should be noted that this interpretation of worsening HF linking to increased thromboembolic rates could be flawed because not all strokes in HF are due to thromboembolic events, but rather can result from cerebral hypoperfusion during acute decompensation and strokes may result from arthrosclerotic plaque rupture rather than thromboembolism. Indeed, arthrosclerotic risk factors such as diabetes and hypertension are common in HF patients and have been linked to the risk of thromboembolic events.[4]

As well as clinically obvious strokes, a couple of small-scale studies have shown increased rates of subclinical thromboembolism in HF by brain imaging (Table 3).[18,19] In Vogels et al, the presence of total white matter hypodensities and lacunar infracts correlated to the degree of HF as judged by New York Heart Association (NYHA) and left ventricular ejection fraction (LVEF) ($P < .01$),[19] whereas in Schmidt et al, the NYHA status was the same for patients with or without magnetic resonance imaging changes.[18]

Chronic AF in Heart Failure

Often AF and HF go hand in hand; 15% to 20% of patients with AF suffer from HF[20] and 5% to 50% of patients with HF have chronic AF.[3] In patients with HF, the prevalence of AF appears to increase with HF severity as judged by NYHA class. This is highlighted by the variation of AF prevalence in major HF trials; mild HF in SOLVD was associated with an AF prevalence of <5%,[21] whereas severe HF in the Cooperative North Scandinavian Enalapril Survival Study was associated with an AF prevalence of 50%.[22] Similarly, in these trials, AF tended to be associated with worse NYHA class than patients in sinus rhythm (Table 4). Less clear is the relationship between AF prevalence and LVEF. Pai demonstrated a similar incidences of AF in patients with mild (LVEF 41% to 54%), moderate (LVEF 26% to 40%), and severe HF (EF ≤25%).[23]