

What is the appropriate approach to prevention of thromboembolism in heart failure?

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Summary

Many studies suggest a higher incidence of thromboembolic syndromes such as stroke, peripheral arterial thrombosis and pulmonary embolism in patients with heart failure (HF), particularly those with left ventricular systolic dysfunction. As a result, some clinicians have chosen to treat patients with HF with anticoagulants as primary prevention against thromboembolic events. However, this practice is not well-supported by scientific data. Retrospective analyses of large HF trials have yielded contradictory results and randomised trials designed to specifi-

cally address this question have been under-populated and under-powered. As a result, there is no general consensus among professional societies in either recommending or advising against anticoagulants in HF. We hope that ongoing clinical trials, WARCEF in particular, will yield results that will guide clinicians in deciding for or against routine use of anticoagulants in HF.

Keywords

Heart, stroke/prevention, thrombosis, cardiology

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Introduction

Intracavitary cardiac thrombosis is an important clinical problem which can contribute to the incidence of stroke, peripheral arterial thrombosis and pulmonary embolism in the case of right-sided cardiac thrombosis. Many studies suggest a higher incidence of thrombosis and thromboembolic syndromes in patients with heart failure (HF), particularly those with left ventricular systolic dysfunction. As a result, many clinicians have chosen to treat patients with HF with anticoagulants as primary prevention against thromboembolic events. However, this practice is not well-supported by scientific data. In addition, there is no general consensus among professional societies in either recommending or advising against anticoagulants in HF. In this article, we will discuss the physiologic underpinnings of thrombogenesis in HF, explore the epidemiologic data associating thromboembolism with heart failure and review the data supporting or refuting the use of anticoagulants in HF. In addition, we will review official recommendations from professional societies and discuss ongoing clinical trials which may provide us with additional information.

Mechanisms of thrombogenesis in heart failure

Thrombosis is precipitated by a combination of stasis, endothelial injury and hypercoagulability commonly known as “Virchow’s

triad” (1). Stasis of blood in areas of cardiac akinesis or dyskinesia can lead to thrombus formation. Stasis of blood triggers activation of the coagulation system, leading to fibrin formation which is the predominant pathogenic mechanism in thrombus formation. Stasis is presumed to be the major contributor to thrombosis in atrial fibrillation in the setting of reduced blood flow out of the left atrial appendage. Stasis can occur in a ventricle with either global or segmental dysfunction and may also be present in a patient with or without overt congestive heart failure. The three conditions most commonly associated with blood stasis are dilated cardiomyopathy, anterior myocardial infarction and left ventricular aneurysm.

The endocardium is the endothelium of the cardiac chambers and as such is critical in the role of intracavitary thrombus formation in patients with heart failure. Kapur et al. demonstrated that acute elevation of left atrial pressure inhibits production of atrial thrombomodulin (2). This results in downregulation of endocardial thrombomodulin expression, ultimately increasing local thrombin production. These investigators found that the targeted restoration of atrial thrombomodulin expression with adenovirus-mediated gene transfer successfully reduced thrombin levels. Additional experiments revealed that thrombomodulin downregulation is caused by the paracrine release of transforming growth factor- β from cardiac connective tissue in response to mechanical stretch. These findings suggest that an increased left atrial pressure commonly seen in HF adversely affects endocardial function and is a potentially important contributor to thrombus formation (in the

presence or absence of atrial fibrillation). Little is currently known about the role of the left ventricular endocardial role in thrombosis. More research into this important contributing factor leading to thrombosis in human heart failure is needed.

HF patients demonstrate higher levels of circulating fibrinogen, fibrinopeptide A and D-dimer (3–5). These abnormalities are most pronounced in patients with severe heart failure as determined by high plasma norepinephrine concentration or low ejection fraction (4). Higher levels of angiotensin and endothelin commonly seen in HF patients increase levels of Von Willebrand Factor (VWF) (6). In addition, ADAMTS13, a protease which cleaves VWF is decreased in HF patients, thereby increasing circulating VWF. Decreased ADAMTS13 and increased circulating VWF were found to be significant predictors of clinical events in HF (7). Decreased levels of nitric oxide increase endothelial monocyte and platelet adhesion, potentially leading to in situ-thrombosis (8, 9). A study examining plasma markers of endothelial damage, dysfunction and activation in patients with acute and chronic HF found that levels of VWF, soluble thrombomodulin (an index of endothelial damage/dysfunction) and soluble E-selectin (an index of

endothelial activation) were significantly higher in patients with acute and chronic HF when compared to controls (8). Tissue factor, a procoagulant, can be increased by tumour necrosis factor α and interleukin 1, both of which are raised in heart failure (10, 11). Elevated tPA (tissue plasminogen activator) antigen levels have been shown to be an independent predictor of prognosis in chronic stable heart failure patients (12). C-reactive protein can directly increase tissue factor and induce expression of other cytokines further potentiating a pro-thrombotic milieu (13, 14). A recently completed study of patients at the University of Utah with class C heart failure showed levels of tissue factor 2.9 times greater than controls (15). These observations strongly suggest a link between inflammation and thrombosis in heart failure. Finally, increased blood viscosity potentiated by diuretic therapy may increase aggregation of red cells and potentiate thrombogenesis (16).

Once a thrombus forms, the clinical significance is mainly related to its potential for embolism. Thrombi that form in areas of the heart which are isolated from normal blood flow may have a lower propensity toward embolisation. One such example would be left ventricular aneurysm (see Fig. 1).

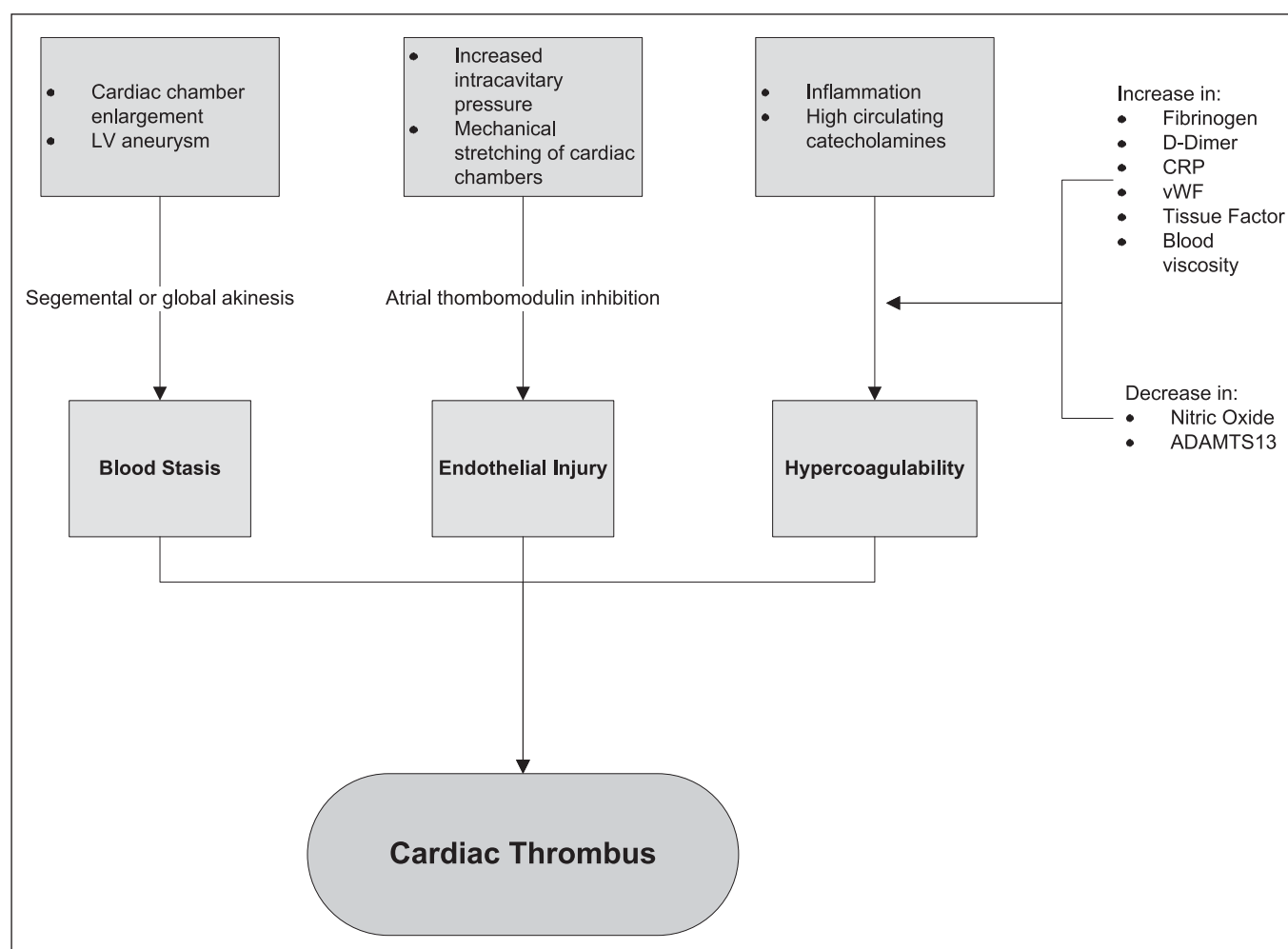


Figure 1: Pathophysiology of cardiac thrombogenesis.

Epidemiology of thromboembolism in heart failure

The risk of thromboembolic events (TE) (stroke, pulmonary and peripheral thromboembolism) in patients with chronic HF has not been well-defined. The analyses that currently exist are from population-based studies and post-hoc analyses of large HF treatment trials (► Table 1). Many of these studies included patients with atrial fibrillation (AF). This is problematic because of the well-described increase in risk of thromboembolism and benefit of anticoagulants in patients with AF independent of HF (17). Most did not specify thromboembolism as an endpoint. In addition the use of precise scales to detect stroke significantly increases the detection of subtle neurologic events (18) and few if any heart failure trials used precise scales to assess for neurologic events.

The belief that HF (in the absence of AF) is associated with an increased risk of TE is based on several observations. Many patients who present with stroke or TE are found to have depressed left ventricular function (19). In addition, retrospective analyses report a yearly incidence of thromboembolism of 1.0%–4.5% in HF patients. In the population-based Framingham Heart Study (20), the relative risk of stroke in individuals with HF compared to those without HF was 4.1 for men and 2.8 for women. However, many of these individuals had concurrent AF. In published HF trials, annual stroke rates between 1.3% and 3.5% have been reported. Again however, almost all of these analyses included patients with AF. A recent analysis of patients in New York Heart Association (NYHA) class II and III HF without AF reported thromboembolic rates of only 1% per year (21).

Similarly, several studies have attempted to identify potential risk factors for the development of stroke or thromboembolism. Other than ejection fraction (EF), a prior thromboembolic event

and possibly the presence of a pedunculated thrombus, these analyses have shed little light on potential risk factors and have provided results which have been difficult to interpret. In a retrospective analysis of the Study of Left Ventricular Dysfunction (SOLVD) trials (24), the annual rate of thromboembolic events was 2.4% in women and 1.8% in men (after excluding patients with AF). Lower EF was associated with higher thromboembolic event rates in women but not in men. In addition, women with lower EF were observed to have a higher risk of pulmonary embolism. In an analysis of the Survival and Ventricular Enlargement (SAVE) Trial (26), the overall risk of stroke was 8.1% at five years. The only independent risk factors for stroke were left ventricular (LV) function, older age and non-use of aspirin or anticoagulants. The risk of stroke was found to be twice as high in patients with EF<28% vs. EF>28%. Every decrease in EF of 5% was associated with an 18%-increase in stroke risk. This analysis of angiotensin-converting enzyme (ACE)-inhibitors versus placebo in post-myocardial infarction patients did not exclude patients with AF and only looked at stroke events. In a more recent analysis of patients with moderately severe HF and an EF≤ 35%, who participated in the Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT), the four-year rate of thromboembolic events was 3.5% with EF 30–35%, 3.6% with EF 20–30%, and 4.6% with EF <20%. These data were extrapolated to signify 0.9%, 0.9% and 1.2% annual rates, respectively (21). Patients with AF at the time of randomisation were excluded from this analysis. The annual rate of thromboembolic events was approximately 1%. Hypertension at the time of randomisation and the greatest reduction in EF were both independent predictors of TE. No other measured variables were significant in terms of outcome.

In the Northern Manhattan Study (NOMAS) (► Table 2), 270 patients hospitalised in a single center with initial occurrence of is-

Table 1: Thromboembolism data from major heart failure trials.

Trial	N	Follow-up (years)	AF(%)	CVA (% per year)	Pulmonary TE (% per year)	Peripheral TE (%per year)
V-HeFT-I (22)	632	2.3	15	1.8	0.3	0.3
Consensus (23)	253	0.5	50	4.6	NR	NR
V-HeFT-II (22)	804	2.6	15	1.8	0.3	.08
SOLVD (24)	6797	3.3	6	1.2	0.3	0.3
CIBIS-II (25)	2647	1.3	1.4	NR	NR	NR
SCD-HEFT (21)	2114	4	0	2.64/	0.3	0.3

Table 2: Left ventricle (LV) function in stroke patients and control subjects (NOMAS [27]).

	Stroke patients, n (%)	Control subjects, n (%)	Unadjusted OR (CI)*	Adjusted OR (CI)
Normal LV function	205 (75.9)	274 (95.1)		
LV dysfunction				
● Any degree	65 (24.1)	14 (4.9)	6.21 (3.39–11.37)	3.92 (1.93–7.97)
● Mild	29 (10.7)	7 (2.4)	5.54 (2.38–12.89)	3.96 (1.56–10.0)
● Moderate/severe	36 (13.3)	7 (2.4)	6.87 (3.00–15.75)	3.88 (1.45–10.39)

*95% CI; adjusted for age, gender, atrial fibrillation, diabetes mellitus, arterial hypertension, hypercholesterolaemia, current smoking, coronary artery disease, clinical CHF, and LV mass index. CI, confidence interval; LV, left ventricle; OR, odds ratio.

chaemic stroke were compared to 288 age, gender and race-matched controls (27). Systolic function was measured in these patients and categorised as normal (EF>50%), mildly reduced (EF 41–50%), moderately reduced (EF 31–40%), or severely decreased (EF≤30%). Decreased EF was found to be strongly associated with ischaemic stroke even after adjusting for other stroke risk factors. Left ventricular dysfunction of any severity was more frequent in stroke patients (24.1% in stroke vs 4.9% in controls $p<0.0001$). Moderate or severe left ventricular dysfunction was also more common in stroke patients versus controls (13.3% vs 2.4% $p<0.001$).

In another study, the rate of recurrent stroke was 9–10% per year in heart failure patients, suggesting that a previous stroke confers a high risk of recurrence (28). In yet another study, the presence of intracardiac thrombus was identified in one-half of patients with neurological events. Patients with thrombus had a significantly higher rate of thromboembolism (5.3%/year) (29). Together, these studies suggest an association between stroke and the presence and degree of systolic dysfunction.

When evaluating epidemiologic data on stroke in heart failure it is important to bear in mind that not all cerebrovascular events are thrombogenic in origin and that not all cerebral infarcts cause clinical events. For example, in situ-atherothrombosis is an important cause of cerebrovascular accident and although ostensibly unrelated to heart failure may be more common in patients with coronary atherosclerosis. In addition, alterations in cerebral blood flow which occur from reduced cardiac output may contribute to or cause neurologic events. Chronic HF (CHF) patients frequently manifest neurological abnormalities with dizziness and memory problems, suggesting altered brain perfusion. In a study of twelve patients with NYHA functional class III and IV, cerebral blood flow (CBF) was found to be significantly reduced compared with healthy control subjects ($n=12$) (30). In another study of 52 patients with advanced non-ischaemic cardiomyopathy, CBF was 19% less in patients with CHF than in controls (31).

Conversely, patients with HF (particularly those with concomitant atherosclerotic heart disease) may have cerebral infarcts without symptoms. This may cause the incidence of neurologic events in HF to be underreported. There is abundant data that cerebral infarctions may be clinically silent. Busing et. al. (32), prospectively evaluated patients undergoing diagnostic and interventional cardiac catheterisation with magnetic resonance imaging studies be-

fore and after the procedure. These investigators found that 15% of patients had new silent cerebral infarctions (SCI), with no association between EF and risk of cerebral infarction, a much higher rate than observed for symptomatic stroke following cardiac catheterisation, which is reported as 0.11. Similarly patients who have undergone coronary artery bypass grafting, have a high incidence of SCI (33), and patients with manifest vascular disease were found to have a 17% incidence of asymptomatic stroke (34).

Evidence for and against the use of anticoagulants in heart failure

Until recently, there have been no randomised controlled trials to help guide physicians in the use of warfarin for embolic prevention in HF patients in normal sinus rhythm. Unfortunately, the controlled trials that exist have suffered from poor recruitment and have not been sufficiently powered to make definitive conclusions.

Retrospective analyses of large HF trials have yielded conflicting results. In SOLVD and SAVE, there was suggestion that warfarin was beneficial in HF patients (24, 26). On the other hand, analyses of V-HeFT and SCD-HeFT data have suggested no benefit to the use of anticoagulants in HF. In SOLVD, anticoagulant treatment with warfarin was associated with a statistically significant decrease in mortality, death and hospitalisation for HF, but the benefit was not from decreased risk of thromboembolic events. Warfarin had a 24% overall relative risk reduction for all-cause mortality (24). The SAVE trial demonstrated an 81% reduction in stroke risk in patients treated with anticoagulation (26).

In contrast, no significant difference in TE was found when comparing patients treated with anticoagulation versus those not treated in the V-HeFT trial data (Veterans Affairs Vasodilator-Heart Failure Trials) (22). In the analysis of the SCD-HeFT data, warfarin use was not associated with reduced risk of TE (21). Unfortunately, the value of these analyses is limited since anticoagulation use was not randomised or controlled, data was collected retrospectively, and endpoints were not pre-defined or standardised.

The EPICAL study was a prospective, observational, community-based HF study undertaken in the French community of Lorraine primarily designed to evaluate the effect of angiotensin con-

Trial	N	Intervention	Outcomes	Comment
WASH (36)	279	Warfarin (INR 2.5) VS.ASA (300 mg)		Underpowered, signal of increased HF hospitalisations in ASA group
WATCH (37)	1,587	Warfarin vs. ASA(162.5 mg) vs. Clopidogrel (75 mg).		Underpowered, signal of increased HF hospitalisations in ASA group
HELAS (38)	197	Ischaemic-ASA or warfarin Non-ischaemic-warfarin or placebo	Stroke, embolisation, infarction, hospitalisation, exacerbation of heart failure, all cause death	Underpowered

Table 3: Trials examining the role of anticoagulation in heart failure patients.

verting enzymes on HF mortality. All patients with severe HF in every hospital were enrolled. Inclusion criteria included EF < 30% or cardiomegaly (cardiothoracic ratio > 60%) and hospitalisation for severe HF (stage III or IV) manifesting hypotension, peripheral oedema or pulmonary congestion. Over a one year period, 417 patients were included. A post-hoc analysis of this study revealed that use of oral anticoagulants and/or aspirin were associated with better five-year survival (35).

More recently, three randomised controlled trials have been attempted to determine the optimal preventive therapy for TE in patients with systolic heart failure (► Table 3). WASH (The Warfarin/Aspirin Study in Heart Failure) was a small pilot study designed to address the question of whether medical therapy with either aspirin or warfarin in HF patients affects clinical outcome (36). The study included 279 patients with LV systolic dysfunction and EF < 35%. It was an open label, randomised, placebo-controlled study with three arms: warfarin (international normalised ratio [INR] target 2.5), aspirin, 300 milligrammes and placebo. Patients with an absolute indication or contraindication to aspirin or warfarin were excluded. No significant difference in combined primary endpoints of all cause mortality, non-fatal myocardial infarction (MI), and non-fatal stroke was found (26% with placebo vs. 32% with aspirin vs. 26% with warfarin). However, patients on warfarin did have fewer hospitalisations for CHF (freedom from hospitalisation was 48% with placebo vs. 47% with aspirin vs. 64% with warfarin). It is important to note that this small pilot study was not powered to make conclusive statements.

The WATCH study (The Warfarin and Antiplatelet Therapy in Chronic Heart Failure) randomised 1587 patients with heart failure and EF < 30% (37). It was a randomised, blinded, non-placebo controlled study with three arms: warfarin (target INR 2.5), aspirin and clopidogrel. Unfortunately, WATCH was terminated early because of poor recruitment and was therefore underpowered to make any definitive conclusions. Nevertheless, there was a strong trend favoring warfarin over aspirin in the incidence of non-fatal stroke (0.7% vs 2.1%) and there was significantly less hospitalisation in the warfarin group (16.1 % with warfarin vs 22.2 % with aspirin vs 18.3 % with clopidogrel). However, this was offset by a significantly higher bleeding rate in the warfarin group (5.5 % vs 3.6 % vs 2.5 % warfarin, aspirin, clopidogrel, respectively).

HELAS (Heart Failure Long-Term Anticoagulation Study) (38) was a randomised, double blinded, placebo controlled trial of 197 patients with NYHA class II-IV heart failure and EF ≤ 35%. Patients with known ischaemic heart disease were randomised to aspirin 325 mg daily vs. warfarin. Patients with idiopathic dilated cardiomyopathy were randomised to warfarin vs placebo. Patients with active ischaemia, atrial fibrillation, mitral valve disease, hypertrophic cardiomyopathy, known LV thrombi, contraindication to aspirin or warfarin, and uncontrolled hypertension were excluded. Those who developed AF were withdrawn from the analysis. Primary endpoints were non-fatal stroke, peripheral or pulmonary embolism, myocardial infarction, re-hospitalisation, and exacerbation of HF or death from any cause. Overall, the event rate was very low with an incidence of TE of 2.2 per 100 patient years. No difference was observed between aspirin and warfarin in the is-

chaemic cardiomyopathy group, while there was a trend toward benefit of warfarin versus placebo in the non-ischaemic cardiomyopathy group (8.9 events per 100 patient years with warfarin vs. 14.8 events per 100 patient years with placebo). Unfortunately, this study also suffered from enrolment problems, preventing statistically significant conclusions.

The ongoing Warfarin Aspirin Reduced Cardiac Ejection Fraction (WARCEF) trial is a double-blinded, multi-center, international study of patients with EF < 35% and NYHA classes I-IV which compares rates of all-cause mortality, stroke and intracranial haemorrhage in patients receiving aspirin or warfarin (39). Recruitment for this trial is ongoing.

The major adverse effects of warfarin are related to its potential for haemorrhage. Previous studies of major bleeding in patients on long-term warfarin have reported ranges between 2–3 events per 100 patient years. In the Stroke Prevention in Atrial Fibrillation Investigators trial (SPAF) the risk of major bleeding was 2.3% per 100 patient years (40). A more recent study was designed to assess the rates of thromboembolism and bleeding in an ambulatory cohort of patients with atrial fibrillation. Of 425 patients enrolled in this study, 40% had concomitant HF and the overall event rate of major bleeding was 2.6% over 2 years (41). In another recent study of patients over 65 years of age with AF who were newly initiated on warfarin, the aggregate rate of major haemorrhage was 7.2% per 100 person years and significantly higher for those patients over 80 years old (13.08% in patients aged 80 or older vs. 4.75% for patients less than 80 years old). Given the aging population and the growing number of elderly patients with HF, this study underscores the importance of considering the potential risks of anticoagulation (42).

Integrative recommendations

None of the relevant professional societies have recommended the routine use of warfarin in heart failure patients. However, the degree to which they have expressed ambivalence about its use has varied. The most definitively negative recommendation comes from the American Society of Chest Physicians who state: “In patients with CHF due to a nonischemic etiology, we recommend against the routine use of aspirin or oral vitamin K antagonists” (43). Most societies have abstained from making a definite recommendation and have instead simply pointed to the lack of available evidence. The European Society of Cardiology states that “there is little evidence to show that antithrombotic therapy modifies the risk of death or vascular events in patients with heart failure” (44). The American College of Cardiology and American Heart Association states that “The usefulness of anticoagulation is not well established in patients with heart failure who do not have atrial fibrillation or a previous thromboembolic event” (45). The European Stroke Initiative (46) has no specific recommendations for primary or secondary stroke prevention in patients with cardiomyopathy who are in sinus rhythm. The Heart Failure Society of America has the least negative recommendation and states that “warfarin may be considered in patients with an EF < 35%” (47).

In consideration of the significant potential for major bleeding and the absence of any definitive randomised trial data supporting its use, routine use of warfarin anticoagulation in all patients with HF cannot be recommended unless there exists a concomitant indication for its use.

Unfortunately, even after a thorough review of the existing literature, it is difficult to make any definitive conclusions about the long-term risk/benefit of warfarin use for the prevention of thromboembolic events in patients with HF. The majority of the data we have is from retrospective analyses with inherent limitations and the randomised controlled data is flawed by poor recruitment and under powering. The ongoing Warfarin Aspirin Reduced Cardiac Ejection Fraction (WARCEF) trial is a double blinded multi center, study of patients with EF <35%, NYHA I-IV, comparing rates of all cause mortality, stroke and intracranial haemorrhage in patients receiving aspirin or warfarin (39). Ideally all patients with EF < 35% in sinus rhythm should be screened for randomisation into the WARCEF trial. In the absence of definitive data we consider warfarin anticoagulation in patients with 1) an ejection fraction less than 20% (based on Freudenberger et al. [21]) 2) a prior stroke with reduced left ventricular function, based on NOMAS (27) or the presence of a pedunculated thrombus in the left or right ventricle. This must be weighed carefully against the risk of bleeding in the patient based on age and concomitant therapy. Those who are not receiving warfarin should be placed on aspirin. At present, we believe there is insufficient evidence to warrant treatment with dual antiplatelet therapy and warfarin in those who have undergone recent stent placement. We eagerly await completion of the WARCEF trial to help guide us in these important issues affecting a large number of patients.

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