REVIEW ARTICLE

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Blood Coagulation in Patients with Chronic Heart Failure

Evidence for Hypercoagulable State and Potential for Pharmacological Intervention

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Abstract

Incidence data on thromboembolism in patients with heart failure (which may include stroke, peripheral embolism, pulmonary embolism) are limited but provide a general population range from 1–5 cases per 1000 each year, increasing with age to more than 30 cases per 1000 each year among people aged 75 years or older. However, the incidence of thromboembolism varied depending very much on what was being investigated in each of these studies. Data from subgroup analysis of the larger heart failure trials would seem to support this incidence data, although there is very little true epidemiological data and no randomised, controlled trial has been designed to specifically investigate thromboembolism in patients with heart failure.

The pathophysiology of heart failure is complex. There are many well recognised factors which are associated with thrombosis in heart failure patients, such as vascular abnormalities, increased coagulability and impaired blood flow.

In the past 50 years many studies have been performed to investigate if oral anticoagulation is of benefit for the prevention of thromboembolism in patients with heart failure.

The use of warfarin therapy for heart failure patients has been a controversial subject. Warfarin does have a role to play in patients with myocardial infarction and those with atrial fibrillation. Furthermore, in patients with congestive heart failure secondary to coronary artery disease, warfarin reduces the occurrence of

nonfatal myocardial infarction and, therefore, may reduce the chances of progression to heart failure. It has also been shown that warfarin reduces the risk of thromboembolic strokes in patients recovering from myocardial infarction.

At present, there is a lack of randomised data, and the incidence of bleeding complications in patients with heart failure has caused a decrease in the use of oral anticoagulants for the prevention of thrombosis.

This review summarises the incidence, potential mechanism and therapeutic approaches for management of thromboembolism in heart failure.

1. Epidemiology of Heart Failure

During the past 20–30 years, coronary heart disease mortality rates have declined steadily in Western countries.[1,2] Despite the combination of primary preventive measures and improved disease management,[2,3] heart failure remains an important and increasing public health problem.[4-7]Admissions to hospitals because of heart failure seem to be increasing, partly because of an ageing population but also because of the greater survival of patients with coronary heart disease. Substantial healthcare expenditure is required for the management of heart failure, of which hospital costs account for the largest proportion.[7,8]

Clinical research on heart failure has mainly been aimed at identifying better therapies for advanced disease. Although the management of heart failure has improved, there is no clear evidence that therapeutic advances have made any impact on the overall burden of the disease in the community. Broader management strategies are required with vigourous preventive measures and earlier intervention, together with a more comprehensive disease management approach, especially in the elderly population.

Epidemiological data on heart failure vary widely and some cannot be compared, but they do provide a perspective on the size of the problem and are consistent in some respects.[9-11] Incidence data are limited but provide a general population range from 1–5 cases per 1000 each year, increasing with age to more than 30 cases per 1000 each year among people aged 75 years or older.[9,10] Tables I and II show the attributable risk for development of heart failure and the incidence of heart failure by sex and age.

Hospital admissions because of heart failure seem to have increased during the last decade.[5-7] Although admissions have risen, total days of stay in the hospital has decreased because of the average shorter duration of stay.[11] Readmission rates of heart failure patients remain very high, because of inevitable progression of underlying severe disease.

Although the number of deaths due to heart failure has risen generally with the ageing of the population, age-adjusted rates in the elderly have also

Table I. Population attributable risk for development of heart failure (reproduced from Sharpe and Doughty,[12] with permission from Elsevier Science)

Risk factor and sex	Hazard ratio adjusted for age and risk factor (95% CI)	Prevalence (%)	Population attributable risk (%)[a]
Hypertension			
Male	2.07 (1.34–3.20)	60	39
Female	3.35 (1.67–6.73)	62	59
Myocardial infarction			
Male	6.34 (4.61–8.72)	10	34
Female	6.01 (4.37–8.28)	3	13
Angina pectoris			
Male	1.43 (1.03–1.98)	11	5
Female	1.68 (1.23–2.30)	9	5
Diabetes mellitus			
Male	1.82 (1.28–2.58)	8	6
Female	3.73 (2.71–5.15)	5	12
Left ventricular hypertrophy			
Male	2.19 (1.49–3.21)	4	4
Female	2.85 (1.97–4.12)	3	5
Valvular heart disease			
Male	2.47 (1.70–3.60)	5	7
Female	2.13 (1.54–2.94)	8	8

a Defined as 100 × prevalence × (hazard ratio – 1)/prevalence × ([hazard ratio – 1] +1).

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Table II. Incidence of heart failure by age and sex (for those aged 25 years and over) [reproduced from Cowie et al.,[13] with permission from the *European Heart Journal*]

Age (y)	Men			Women			Total		
	population	number of cases	incidence[a]	population	number of cases	incidence[a]	population	number of cases	incidence[a]
25–34	14 042	0	0.00	13 620	1	0.04	27 662	1	0.02
35–44	11 135	3	0.2	10 056	3	0.2	21 191	6	0.2
45–54	9405	4	0.3	8827	1	0.1	18 232	5	0.2
55–64	7408	21	1.7	7157	8	0.7	14 565	29	1.2
65–74	5260	34	3.9	6243	24	2.3	11 503	58	3.0
75–84	2506	41	9.8	4254	42	5.9	6760	83	7.4
85+	537	15	16.8	1435	23	9.6	1972	38	11.6
Total	50 293	118	1.4	51 592	102	1.2	101 885	220	1.3

a Incidence rate expressed as number of cases per 1000 population year.

risen.[11] Over the last 30 years management strategies for myocardial infarction (MI) have improved survival, which has increased the potential for the development of heart failure.

2. Heart Failure and Hypercoagulable States

Patients with chronic heart failure (CHF) are well recognised to be at greater risk of thromboembolism and stroke.[14,15]

The pathophysiology of heart failure is complex. There are many well recognised factors that are associated with thrombosis in heart failure patients, such as vascular abnormalities, increased coagulability and impaired blood flow. Dilated cardiac chambers in heart failure cause poor contractility, low cardiac output and stasis, and this may cause flow abnormalities and predispose to thrombus formation and subsequently thromboembolism. In left ventricular (LV) dysfunction there is both diastolic and systolic bulging resulting in stasis, which predisposes to thrombus formation. Defective endothelial function has been demonstrated in heart failure patients which can be assessed by the measurement of specific markers of endothelial damage, such as von Willebrand factor (vWf), the values of which are abnormal in heart failure patients.[16]

Several studies have shown that patients with CHF have significant levels of circulating platelet aggregates compared with healthy controls. There is reported evidence of elevated levels of β-thromboglobulin (βTBG) in CHF patients.[17,18] The degree of hypercoagulability depends on the severity of heart failure as determined by low ejection fraction or high plasma noradrenaline (norepinephrine) levels.[19] Thompson et al.[20] evaluated haemostatic factors in 3043 patients with documented coronary artery disease and showed that patients with higher baseline levels of fibrinogen, vWf antigen, tissue plasminogen activator antigen, and C-reactive protein had an increased incidence of MI. Lip et al.[16] demonstrated that patients with LV dysfunction had elevated plasma levels of fibrinogen, vWf and D-dimer. Mehta and Mehta[21] also showed increased levels of circulating platelet aggregates in

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heart failure patients. Sbarouni et al.[22] showed increased levels of βTBG and D-dimer as evidence of platelet activation in heart failure patients. Several studies have shown that patients with CHF have increased plasma levels of βTBG, fibrinopeptide A and thrombin anti-thrombin (TAT) complexes, in addition to increased plasma levels of endothelial pro-coagulants, vWf and fibrinolytic products.[17,22]

Elevated levels of coagulation markers may be due to several factors; it is suggested that dilated chambers cause stasis and low cardiac output further promotes formation of fibrin rich clots. Patients with mitral stenosis and atrial fibrillation have been shown to be in hypercoagulable state.[23,24] It has also been reported that even increased sympathetic activity can cause platelet activation as seen in patients with acute MI and mitral valve prolapse.[24,25]

Recent observational data from the Studies of Left Ventricular Dysfunction (SOLVD) and the Veterans Administration Co-operative (V-HeFT) studies suggest that mild to moderate heart failure is associated with an annual stroke risk of 1.5%, but is higher in severe heart failure at almost 4%, compared with a risk of <0.5% in those without heart failure.[26-28] It is possible that the major cause of sudden death in patients with CHF is not arrhythmia but thrombotic vascular occlusion, which means that the state of hypercoagulability is a very significant problem.

3. Thromboembolism in Chronic Heart Failure

3.1 Incidence and Significance

The clinical incidence of thromboembolism in patients with CHF without anticoagulation has been reported to be from 0.9–42.4 events per 100 patient years. Baker and Wright[29] estimated the clinical incidence of thromboembolism after reviewing 11 trials as 1.9 per 100 patient years. Kyrle et al.[30] reported an incidence of 42.4 events per 100 patient years in 38 patients. Where as Fuster et al.[31] from the Mayo clinic reviewed 104 patients with idiopathic dilated cardiomyopathy for 6–20 years and reported the thromboembolic incidence as 3.5 events per 100 patient years.

Data from large scale clinical trials have reported the thrombolic events as ranging from 1.6–2.5 total events per 100 patient years (table III). The V-HeFT investigators[26,28] reported the total number of embolic events in heart failure patients with an ejection fraction of 29.4% as 2.5 and 2.2 per 100 patient year in V-HeFT-1 and V-HeFT-2, respectively. The SOLVD trial[27] included asymptomatic patients and as well as patients in New York Heart Association (NYHA) class II and III CHF, and the total incidence of thromboembolism was reported as 1.6 events per year. An unexpected finding was that women were at increased risk for thromboembolic events compared with men (2.4 events per 100 pa-

Table III. Incidence of thromboembolic events in selected chronic heart failure trials[a]

Study (NYHA class) year	Ejection fraction (%)	No. of patients	Atrial fibrillation (%)	Anticoagulant therapy (%)	Antiplatelet therapy (%)	CVA	PTE	PE	Total thrombi
V-HeFT-1 (II-III), 1986	30.0	632	16	14.5	12.8	1.8	0.3	0.3	2.5
CONSENSUS (IV), 1987	NIP	25.3	50	33.5	?	2.3	NIP	NIP	NIP
V-HeFT-2 (II-III), 1991	29.0	804	14	15.1	30.4	1.8	0.1	0.3	2.2
SOLVD (I-II-III), combined 1991, 1992	26.8	6797	6	13.3	46.4	1.2	0.3	0.2	1.6

a All events expressed as 100 patients years.

CONSENSUS = Co-operative North Scandinavian Enalapril Survival Study; **CVA** = cerebrovascular accident; **NIP** = no information provided; **NYHA** = New York Heart Association functional class; **PE** = pulmonary embolism; **PTE** = peripheral thromboembolism; **SOLVD** = Studies Of Left Ventricular Dysfunction; **V-HeFT** = Veterans Administration Co-operative Study; ? indicates unknown.

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tients years vs 1.8 events per 100 patient years), which may be due to gender differences in the clotting system because of the hormonal variations.[27] In the Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS) –1,[32] the annual incidence of fatal cerebrovascular events were reported as 2.3%. Patients were included with NYHA class IV CHF, which may account for the higher incidence of embolic events. The Acute Infarction Ramipril Efficacy (AIRE) trial recruited patients presenting with symptomatic LV dysfunction after MI and reported the incidence of 1.7% per year of non fatal and fatal strokes.[33] While another study, the Survival and Ventricular Enlargement (SAVE) trial, which included post-MI patients with LV ejection fractions ≤40%, reported an annual rate of 1.5% per year of non fatal or fatal stroke.[34] It was also shown that if there is a 5% decrease in the ejection fraction there is 18% increase in the risk of stroke, which means LV systolic dysfunction is inversely related to stroke.[34]

Several studies suggest that a high incidence of sudden death may be due to fatal systemic thromboembolic events or intra coronary thrombi leading to MI and eventually tachyarrhythmias.[35] An earlier autopsy study[36] in patients with CHF reported a 50% incidence of thromboembolic events. Robert et al.[36] completed an autopsy analysis in patients with dilated cardiomyopathy and found that 60% of patients had systemic or pulmonary embolic events. The reported clinical incidence of thromboemboli in patients with CHF is estimated at 2% per year with the majority being systemic emboli to the cerebrovasculature. Although the rate of clinically evident thromboembolic events may be low, there is evidence of high incidence of clinically occult thromboembolism which may play an important role in the mortality and morbidity of patients with CHF.

3.2 Mechanism

The predisposing factors in the pathogenesis of thromboembolism are hypercoagulability, stasis and injury. The hypercoagulable state in CHF is demonstrated by elevated markers of platelet activity, activation of the coagulation system and abnormal endothelial function. Increased platelet activity as evidenced in CHF is by the formation of greater circulating platelet aggregates and elevated levels of βTBG,[17,18,22] a marker of platelet activation. In addition, activation of the coagulation system in CHF patients has been demonstrated with TAT complex, prothrombin fragments 1 and 2, and increased plasma concentrations of fibrinopeptide A and D-dimer, an index of fibrinolytic activity.[17,37] Neuroendocrine activity occurs via sympathetic and renin angiotensin system resulting in an increased level of norepinephrine and angiotensin II (figure 1). Catecholamines and angiotensin II cause direct increase of the release of vWf.[38-40] tumour necrosis factor, a proinflammatory cytokine which also activates the coagulation system, is also found to be elevated in patients with CHF patients.[41,42]

It has been suggested by different studies that endothelial dysfunction has a role to play in the formation of thrombi, and there are also data to suggest that CHF patients exhibit abnormal endothelial function.[37] The impaired release of endothelium derived nitric oxide (NO) in response to stimuli may contribute to the increased peripheral vasoconstriction which is characteristic of heart failure. This reduced NO may also promote monocyte and platelet adhesion predisposing to thrombosis and thromboembolism.[16,22] Endothelin, which is a vasoconstrictor, is elevated in the CHF patients and, therefore, it may contribute to the formation of thrombi.[43] One of the methods of assessing endothelial damage or dysfunction is vWf.[22]

Patients with severe CHF have diastolic dysfunction because of the dilatation of cardiac chambers. This results in poor myocardial compliance and, therefore, causes impaired ventricular filling and possibly alterations in intracardiac blood flow resulting in stasis, which may be adequate to promote thrombus formation. The factors responsible for stasis are reduced LV systolic function, decreased functional capacity, atrial fibrillation,[44,45] decreased or absent apical flow,[46,47] and increased plasma and blood viscosity.[22] All of these contrib-

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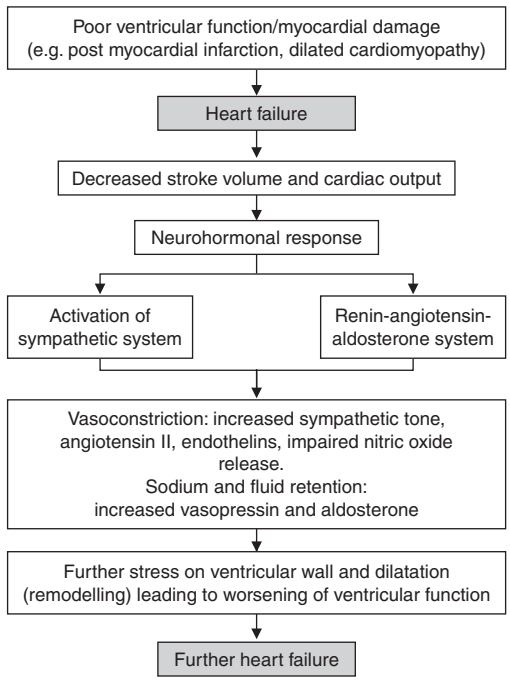

Fig. 1. Neuronal mechanism and compensatory mechanisms in heart failure.

ute to the predisposition of thromboemboli in CHF.[48]

As we know that the majority of thrombi are formed in the apex of the LV, an abnormal reduction or absence of blood flow by Doppler studies have been characterised in those with intracardiac thrombi.[49,50] In the post MI SAVE trial it was found that patients with an ejection fraction <28% had a risk of stroke of 1.86 compared with those with an ejection fraction >35%, which indicates that LV ejection fraction was an independent risk factor for stroke.[34] In the VeHFT trials it was shown that patients with higher ejection fraction had lower thrombolic events but this was not statistically significant.[26,28] There are smaller trials that have shown a definite relationship between the severity of LV systolic dysfunction and emboli.[48]

Segal et al.[44] showed an almost 50% increase in systemic emboli in CHF patients with atrial fibrillation.

There are studies which have shown that injury of the endothelium may help in the formation of thrombosis. As we understand that thrombi in dilated cardiac chambers may be the result of intracavitary stasis and hypercoagulability, so patients with ischaemic heart failure may additionally have endocardial abnormalities which predispose to thrombi formation.[50-52] However, Gottdiener et al.[53] completed a follow up study on 96 patients for 2 years and found that 38 of them developed a mural thrombus. In this study, the presence of a mural thrombus was not different for patients with CHF secondary to ischaemia or dilated cardiomyopathy and, therefore, mural thrombus was not related to the aetiology of the CHF. The presence of mural thrombi was found in 75% of the autopsy reports of the dilated cardiomyopathy patients studied by Roberts et al.[36] Cabin et al.[54] and Katz[55] have suggested that there are two types of mural thrombi, one with a flat surface and the other with a protruding surface. So the latter ones are more likely to embolise than the flat ones because of the larger surface area exposed to the flowing blood. In the case of heart failure, embolisation depends on the contractile ability of the myocardium.[54,55] Mural thrombi developing in is-

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chaemic cardiomyopathy have a lesser chance to embolise because of better contractility in other areas; however, in idiopathic dilated cardiomyopathy because of generalised hypokinesia the contractility is reduced and it has also been seen that the thrombi in these patients tend to be smaller.[46] So the smaller the thrombi the more it is likely to embolise.

4. Anticoagulant Therapy in the Prevention of Thromboemboli

In the last 50 years many studies have been performed to investigate if oral anticoagulation is of benefit for the prevention of thromboembolism in patients with heart failure. There is proven evidence of a hypercoagulable state in heart failure and, therefore, anticoagulant therapy could be beneficial for these patients.

Several studies used warfarin for prevention of thromboembolism in patients with idiopathic dilated cardiomyopathy.[30,31,46] Fuster et al.[31] has suggested that there is a role of anticoagulant therapy in CHF patients. Similarly Kyrle et al.[30] observed no thromboembolic events in 38 patients receiving anticoagulation, although 45% had experienced embolic events before anticoagulation. In this study, 44.7% of the patients not receiving anticoagulation therapy developed emboli. Yokota et al.[46] also concluded that in patients with idiopathic dilated cardiomyopathy oral anticoagulant therapy prevented embolic events without the risk of major haemorrhage.[46]

Large randomised clinical trials have established a role for anticoagulant therapy for primary prevention of thromboembolism in patients with CHF.[56] More recent studies included patients with both ischaemic and idiopathic dilated cardiomyopathy and have shown no benefit with the use of anticoagulant therapy.[28,55,57,58] In addition, in both V-HeFT I and II,[28] the rates of systemic and pulmonary emboli in patients not anticoagulated were similar to those in patients receiving anticoagulants.

The SOLVD trial also reported no benefit from anticoagulant therapy.[32] The analyses by Natterson et al.[58] and Cioffi et al.[57] also came to the same conclusion that there was no benefit of the anticoagulation therapy. In the former trial, 1.2% of the 82 patients receiving anticoagulant therapy experienced emboli, while there were 142 patients who were not on any anticoagulant therapy of whom 3.5% developed emboli.[58] It should be noted that these retrospective analyses were performed using anticoagulant therapy in a non-randomised manner.

One third of deaths in patients with CHF are due to sudden death.[59] In majority of patients the reason is acute coronary thrombosis.[60,61] Yusuf et al.[62] demonstrated that MI and unstable angina both increased the risk of death in patients with CHF. There is a possibility that a subclinical ischaemic event may progress to heart failure and sudden death in this population.[35] Therefore, preventing progression of coronary artery disease and acute coronary syndromes may be of benefit for CHF patients.

Recently the American College of Cardiology/American Heart Association (ACC/AHA)[63] have given a guideline for anticoagulant therapy in patients with CHF stating that atrial fibrillation or a history of thromboembolism are both definite indications for anticoagulation.

4.1 Antiplatelets

The efficacy of aspirin as an antithrombotic agent is well established. It has been proved that aspirin reduces the incidence of MI and death, and also reduces incidence of stroke and death in patients with transient ischaemic attack, unstable angina and atrial fibrillation, and probably also reduces mortality and reinfarction after acute MI.[64,65] In patients with unstable angina, aspirin 75 mg/day halves the rate of MI and death.[66]

There are not many studies regarding use of antiplatelets in patients with CHF. Data analysis from Ve-HFT I and II trials suggest that aspirin/dipyridamole or both may reduce thromboembolic events in heart failure.[26,28] On the other hand, the SOLVD trials found that antiplatelet therapy did not prevent thromboembolic events.[27] The retrospective analysis of the SAVE trial suggests that use of aspirin alone reduced the risk for stroke by 56% and also identified the absence of aspirin therapy as an

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independent risk factor for increased risk of stroke. This protective effect of aspirin was most pronounced in patients with an LV ejection fraction <28% in whom the reduction in the risk of stroke was 66%.[34] In the Stroke Prevention in Atrial Fibrillation Trial (SPAF) 325 mg/day of aspirin reduced the rate of thromboembolic events in patients with atrial fibrillation.[67]

Antiplatelet therapy may result in adverse effects such as systemic haemorrhage or gastrointestinal symptoms such as vomiting, heart burn or abdominal pain.[68] In the United Kingdom Transient Ischaemic Attack (UK-TIA)[69]aspirin trial, where patients were given low dose aspirin (300mg), it was found that 0.9% of patients on aspirin therapy reported with haemorrhagic events compared with 0.4% of those receiving placebo. However, quite a significant number reported minor gastrointestinal symptoms and, thus, 31% of the low-dose aspirin group presented with minor gastrointestinal adverse effects compared with 26% in the placebo group.

An important consideration is the possibility that aspirin may adversely effect the benefit that ACE inhibitors have on reducing mortality in heart failure patients.[69,70] The mechanism for this interaction is not clearly understood. ACE inhibitors block the conversion of angiotensin I to angiotensin II and this results in the synthesis of prostaglandins which produce vasodilatation; however, aspirin therapy may inhibit the synthesis of prostaglandins and there is a possibility that this may effect the benefit of ACE inhibitors in reducing mortality in patients with heart failure.[71]

4.2 Warfarin

The use of warfarin therapy for heart failure patients has been a controversial subject. Warfarin does have a role to play in patients with MI and those with atrial fibrillation. However, as discussed in section 2, recent evidence suggests that patients with LV dysfunction may be in a chronic hypercoagulable state.[22,72]

The majority of earlier studies of warfarin therapy in patients with idiopathic cardiomyopathy showed trends for benefit with oral anticoagulation.[30,31,46] Furthermore, in patients with CHF secondary to coronary artery disease, warfarin reduces the occurrence of non-fatal MI and, therefore, may reduce the chances of progression to heart failure. It has also been shown that warfarin reduces the risk of thromboembolic strokes in patients recovering from MI.[69,70]

However, warfarin therapy in LV dysfunction is controversial. There is lack of randomised data, and clinically evident thrombosis and bleeding complications have all caused a decrease in the use of oral anticoagulants for the prevention of thrombosis in CHF patients. Lip et al.[16] demonstrated that warfarin therapy helped in decreasing the level of D-dimer in patients with LV dysfunction but had no effect on plasma fibrinogen levels. Furthermore D-dimer levels were highest in patients not receiving antithrombotic therapy. Conway et al. demonstrated that prothrombin activation was suppressed with warfarin therapy in those with prothrombin time ratio of >1.5.[73]

Currently, warfarin is administered at a dosage to provide a 'therapeutic range of international normalised ratio (INR)' in patients at risk of thromboembolism. We know from other studies that there is a wide range of hypercoagulability in patients with heart failure. Some patients may require a low dose of anticoagulation, while others may require higher doses of anticoagulation for thromboprophylaxis. The results of Stroke Prevention in Atrial Fibrillation (SPAF-III) and Coumadin Aspirin Reinfarction Study Investigators (CARS) trials suggest that treatment with low intensity anticoagulation therapy does not confer the same benefits as those seen with the standard range of INR (2.0–3.0) obtained with adjusted-dose warfarin.[74]

The SAVE study[34] demonstrated an 81% reduction in total stroke in those treated with warfarin and 56% reduction in those treated with aspirin, while the SOLVD trial[27] where data on warfarin use in 6797 enrolled patients were reviewed, the findings support the use of warfarin in patients whose LV ejection fraction is ≤35%. In contrast, the V-HeFT reported a low incidence of thromboembolism in

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mild to moderate heart failure which was not reduced with warfarin treatment.[28]

In multiple large, randomised trials the risk of major bleeding with oral anticoagulants was observed to be 1.5% when maintaining a therapeutic INR in the range of 2–3.[75]

The SOLVD trial[27] did not have any data regarding noncardiac events and noncardiac deaths with warfarin use, may be because patients with a higher risk, such as those with atrial fibrillation, were on anticoagulation and so the total number of fatal vascular events was small (<2%) and, therefore, cases of pulmonary embolism were taken as sudden death or acute heart failure. In patients recovering from acute MI, warfarin anticoagulation reduces mortality, fatal and non fatal coronary events, pulmonary embolism and stroke when started within 4 weeks from the onset of symptoms.[76] Other studies have suggested a similar reduction in coronary events but not in overall mortality.

The use of warfarin in patients with LV dysfunction is associated with improved survival and reduced mortality. Future randomised clinical trials need to be designed to test the hypothesis that patients with an LV ejection fraction <35% would benefit from warfarin treatment.

4.3 Low Molecular Weight Heparins

In the clinical setting of acute coronary syndromes, low molecular weight heparins (LMWHs) are currently recommended as an alternative to unfractionated heparin (UFH).[77] The LMWHs have a number of advantages over UFH. The antithrombotic response is more predictable, no laboratory monitoring is required, they have a high bioavailability following subcutaneous injection, a longer half-life, no drug interactions, fixed-weight adjusted doses and a lower risk of heparin induced thrombocytopenia (HIT) than UFH.[78] The LMWHs also have a higher affinity for factor Xa (critical in thrombin production) and greater induction of the coagulation inhibitor tissue factor production inhibitor (TFPI). LMWHs also have lower affinity for platelets, which may translate to less microvascular bleeding (table IV).

Table IV. Characteristics of unfractionated heparin and low molecular weight heparin

Unfractionated heparin	Low molecular weight heparin
High molecular weight (15 000)	Low molecular weight (4500–6000)
Low bioavailability (<30%)	High bioavailability (>90%)
Binds to proteins	No protein binding
Short half-life	Long half-life
Low anti Xa:anti IIa ratio	High anti Xa:anti IIa ratio
Significant drug interaction	No drug interaction
Risk of heparin-induced thrombocytopenia	Lower risk of heparin-induced thrombocytopenia
Requires monitoring and dose adjustment	Fixed-dose weight adjusted

There have been large scale clinical trials to evaluate LMWH in treatment of acute coronary syndromes.[79-82] The meta-analysis of two studies showed that the risk of death or MI was 20% lower in enoxaparin treated patients than in the standard heparin treated patients.[83] The recent prophylaxis of Venous Thromboembolism in MEDical Patients with ENOXaparin (MEDENOX) proved the benefit:risk ratio of thromboprophylaxis in immobilised severely ill patients (eg. patients with CHF). Enoxaparin 40mg once daily for 6–14 days reduced the risk of thromboembolism by 63%.[84]

De Lorenzo et al.[85] observed that LMWH therapy significantly decreased plasma levels of D-dimer, TAT complexes and prothrombin fragments 1 and 2, and factor VII activity, whereas protein C was significantly increased in patients with CHF. In this study of LMWH and the coagulation profile in patients with CHF, 100 patients were randomly assigned to one of two groups and started on a dosage of bemiparin sodium 3500 IU/day subcutaneously or placebo (sodium chloride solution 9 g/L) for 5–10 days.[85] After 24 hours, a more apparent decrease of factor VII activity, and plasma prothrombin fragments 1 and 2 and D-Dimer levels was observed in the LMWH than placebo group. In addition, a highly more evident increase of protein C was observed in the LMWH group but in the placebo group there was significant decrease of protein C after 24 hours of randomisation. At discharge, 4–10 days after admission, the increase of protein C was still higher in the LMWH group, and D-dimer and TAT complex

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levels were more likely to have decreased in these patients. Therefore, a prophylactic dose of LMWH once daily resulted in significantly reduced thrombin generation and activity. These data are in accordance with the recent findings of Ernofsson et al.,[86] that showed significant changes of markers of thrombin generation and activity in patients with unstable coronary artery disease treated with LMWH.

In addition, in coronary heart disease patients with mild LV dysfunction, De Lorenzo et al.[87,88] showed evidence of a hypercoagulable state and impaired fibrinolytic activity. This is a subgroup of high-risk patients who may develop thrombotic complications and might benefit from a more aggressive anticoagulant therapy. Therefore, LMWHs might offer benefits in patients with CHF, and prospective, randomised clinical trials are needed to confirm this hypothesis.

5. Conclusions

Anticoagulation with warfarin is frequently used for patients with CHF to prevent systemic embolisation. This practice is based largely on retrospective analyses of referral populations. In an analysis of the major studies, the incidence of arterial thromboembolism ranged from 0.9–5.5 events per 100 patient years, with the largest studies reporting an incidence of 2.0–2.4% per 100 patient years. However, clinical embolic complications were linked to a low ejection fraction, and many physicians currently administer anticoagulation to patients with an ejection fraction <20–25%. Similarly, many physicians will administer anticoagulation in patients with LV dysfunction and an intracardiac thrombus. However, the value of this approach is unclear, except in patients with thrombus after an acute MI.

At present, there is no good evidence for or against the effectiveness of anticoagulation in preventing stroke, arterial or pulmonary embolus in patients with heart failure in sinus rhythm without a history of thrombus or emboli. There are no controlled trials demonstrating the efficacy of routine anticoagulation in other patients with heart failure and normal sinus rhythm, and its use here is questionable. A large randomised trial of warfarin in heart failure patients in sinus rhythm is currently in progress and data from this trial will hopefully help clarify this situation.

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