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REVIEW ARTICLE

Antithrombotic therapy in patients with chronic heart failure: rationale, clinical evidence and practical implications

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Summary. Chronic heart failure (CHF) is traditionally associated with increased risk of thromboembolic complications. Key features of CHF pathophysiology, such as impairment of intracardiac hemodynamics, peripheral blood flow deceleration, neuroendocrine activation, chronic oxidative stress and proinflammatory changes, could explain the predisposition to thromboembolism. However, conclusive epidemiologic data on thromboembolic event incidence in CHF are lacking. Furthermore, the place of antithrombotic therapy in CHF management is still uncertain. Apart from established indications for warfarin (e.g. atrial fibrillation and previous embolic events), there is no robust evidence to support administration of vitamin K antagonists to other patients with CHF, particularly to patients in sinus rhythm. The role of aspirin in preventing thromboembolism in these patients is also controversial. Large randomized trial data on the effectiveness and risks of warfarin and aspirin use in CHF patients with sinus rhythm are forthcoming. This article provides a brief overview of the epidemiologic and pathobiological background of thromboembolism in CHF, and discusses the up-to-date clinical evidence on antithrombotic therapy in detail.

Keywords: aspirin, chronic heart failure, thromboembolic events, warfarin.

Introduction

Chronic heart failure (CHF) is an increasingly prevalent clinical condition and serious societal problem, affecting approximately 2% of the population [1]. In 2005, the estimated costs of CHF management in the USA alone reached 27.9 billion dollars [1]. The Framingham Heart Study found that the lifetime risk of CHF development at age 40 years for both men and women was 1 in 5 [2]. In the preceding decade, the rate of death caused by CHF had increased by more than 7% [1]. It is estimated that 1-year mortality in severe cases of congestive CHF is as high as 30–50% [3].

Patients with CHF are thought to have an increased risk of vascular thrombotic events. In the context of Virchow's classic thrombogenesis triad, pathophysiologic features of chronic CHF could explain the predisposition of these patients to suffer vascular thrombotic events [4]. The most common cause of CHF is coronary artery disease [5], and the incidence of carotid, renal and peripheral atherothrombotic disease is also known to be higher in CHF patients than in the general population [6]. Therefore, antithrombotic therapy such as aspirin (acetylsalicylic acid) or vitamin K antagonists (VKA) is not uncommonly prescribed to patients with CHF. However, there is no conclusive epidemiologic evidence that the incidence of clinically significant vascular thrombotic events associated with CHF is high. Furthermore, robust evidence that antithrombotic therapy is beneficial for these patients is absent.

This article aims to provide a brief overview of the epidemiology and pathobiology of thromboembolism in CHF, and to discuss in detail the up-to-date evidence for the usefulness of antithrombotic therapy in this setting. The problem of anticoagulation in acutely ill or non-ambulant CHF patients is out of the scope of this review.

Epidemiologic sketch of thromboembolism in CHF

The risk of vascular thrombotic events in patients with CHF is poorly defined. However, the data from published observational studies indicate that patients with CHF have a higher risk of vascular thrombotic events than the general population. Whereas in the latter the annual incidence of venous thromboembolism is about 0.1% (although it rises exponentially with age and reaches 0.5% at age 80 years) [7], in patients with CHF the figures for systemic and cerebral thromboembolism incidence found by two prospective observational studies were 2.7 and 1.7 per 100 patient-years, respectively [8,9]. In a population of CHF patients awaiting cardiac transplantation, arterial embolic events during the mean follow-up period of 301 days occurred in 3% [10].

Observational analyses of data collected prospectively in large clinical trials also provide relevant data regarding the

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rates of vascular thrombotic events in CHF. A retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials database ($n = 6378$) found that the annual incidence of vascular thrombotic events (including strokes, pulmonary emboli and peripheral emboli) in patients with left ventricular dysfunction and sinus rhythm was 2.4% in women and 1.8% in men [11]. Multivariate analysis found that the decline in ejection fraction (EF) was associated with vascular thrombotic event risk in women [relative risk (RR) per 10% (EF) decrease 1.53, 95% CI 1.06–2.20, $P = 0.02$], but not in men [11]. Quite similar levels of vascular thrombotic event risk were reported in the retrospective analyses of the Veterans Affairs Vasodilator-CHF Trials (V-HeFT I and II), which included patients in sinus rhythm and those with atrial fibrillation: 2.7 and 2.1 per 100 patient-years in V-HeFT I and II, respectively [12]. These analyses also revealed that individuals experiencing vascular thrombotic events had a lower peak for exercise oxygen consumption ($P < 0.03$ in V-HeFT I and $P < 0.001$ in V-HeFT II) and a lower mean EF ($P = 0.1$ in V-HeFT I and $P = 0.07$ in V-HeFT II). Approximately the same rates of vascular thrombotic events (fatal and non-fatal strokes) were reported in an analysis of the data on 2231 patients with left ventricular dysfunction after acute myocardial infarction (MI) who participated in the Survival and Ventricular Enlargement trial (SAVE): 1.5% of stroke per year of follow-up [13]. The estimated 5-year rate of stroke was found to be 8.1%, and independent predictors of increased stroke risk in this patient population were decreased EF and older age. A recent systemic literature review of published reports from 24 prospective or retrospective observational studies on vascular thrombotic events in CHF found a wide range of estimated vascular thrombotic event prevalence, from 3% to 50%, whereas vascular thrombotic event incidence estimates ranged from 1.5 to 3.5 per 100 patient-years [14].

The presence of chronic systolic dysfunction has now been established as an independent risk factor for thromboembolic stroke in patients with non-valvular atrial fibrillation [15]. Unlike in the general population, in patients with CHF atrial fibrillation was not found to be an independent risk factor for vascular thrombotic events, including stroke [12,13]. Thus, it might be possible that the most important risk factors for vascular thrombotic events and stroke in this patient population are pathologic changes of CHF *per se*. Furthermore, compared to controls, patients with CHF were reported to suffer more severe strokes and had a higher stroke-associated mortality rate [16]. Brain magnetic resonance imaging studies revealed that more than 30% of patients with ischemic and non-ischemic CHF/systolic dysfunction had developed asymptomatic thromboembolic strokes [17]. Thus, the incidence of strokes and probably of other vascular thrombotic events in these patients might be higher than would be expected from the published reports.

Sudden cardiac death, often resulting from acute vascular thrombosis, is not uncommon among CHF patients. In individuals diagnosed with CHF, sudden cardiac death occurs at six to nine times the rate in the general population [1]. An analysis of autopsy data from 171 patients with chronic CHF who participated in the Assessment of Treatment with Lisinopril and Survival study found that the incidence of fresh coronary thrombus or ruptured plaque approached 33% [18]. Myocardial ischemia was detected in the majority of cases among 29 cardiac arrests in hospitalized patients with CHF [19]. It has been demonstrated that both acute MI and unstable angina are independent risk factors for death in patients with congestive heart failure [20].

The presence of left ventricular mural thrombi may increase the risk of systemic embolization. In patients with acute MI, the presence of intraventricular thrombi has been documented to significantly increase the risk of stroke or systemic thromboembolism [21]. In patients with CHF, however, the relationship between the presence of intracardiac thrombi and vascular thrombotic event risk has not been unequivocally demonstrated [8–11,22–24]. Possible explanations for such discrepancies might be the biophysical 'properties' of intracardiac thrombi as well as the patterns of remodeling and contractility of the failing left ventricle, which in part might depend on CHF etiology [25,26]. With regard to the latter, this hypothesis remains unproved, as studies have reported the same annual stroke rate (3.5%) for patients with ischemic and non-ischemic etiology of CHF [27].

To conclude this brief overview, the available evidence on vascular thrombotic event rates does not indicate that clinically significant thromboembolism risk in CHF is high. However, the available epidemiologic data mainly originate from observational studies and retrospective analyses of large CHF trials. The overall risk of vascular thrombotic events in patients with CHF, particularly in those with sinus rhythm, has not been studied in a homogeneous population group.

Pathobiological background of thromboembolism in CHF

The mechanism leading to vascular thrombotic events in CHF is multifactorial and includes embolization from intracardiac thrombi, systemic arterial or venous thrombosis and/or embolization, as well as acute coronary or cerebral thrombogenesis *in situ*.

The key pathologic features of CHF are deceleration of blood flow, impairment of intracardiac hemodynamics, and stasis of blood in peripheral vascular beds. Among the main factors responsible are dilated cardiac chambers, atrial fibrillation, decreased myocardial compliance and poor contractility, increased blood viscosity and hypercoagulability, and decreased exercise capacity [28,29].

Chronic impairment of blood flow leads to tissue hypoperfusion and related ischemic metabolic changes that, in turn, support the development of permanent oxidative stress and activation of platelets, leukocytes and endothelial cells [30]. Because the endothelium is primarily oxygenated and perfused directly by the blood in the vessel lumen, endothelial cells are particularly sensitive to hypoxic/oxidative insult [31]. Recent animal studies have shown that ischemia promotes rapid expression of the adhesion molecule P-selectin on endothelial

cells [32]. P-selectin then binds to its main ligand, P-selectin glycoprotein ligand-1 (PSGL-1), which is constitutively present on leukocytes [33]. Subsequent to this interaction, leukocytes infiltrate the 'ischemic' vessel wall, upregulate tissue factor expression on their surfaces, and release tissue factor-bearing microparticles [33,34]. These microparticles expose both PSGL-1 and tissue factor; therefore, they can deliver procoagulant material (tissue factor) directly onto 'ischemic' sites of the vessel wall or 'disseminate' it through the circulation, thus initiating reactions in the coagulation cascade [33,35].

Cardiac overload, myocardial ischemia and peripheral tissue hypoxia in CHF stimulate the production of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6 [30,36]. Numerous clinical studies have reported on elevated levels of proinflammatory cytokines and/or their cytokine receptors in patients with CHF [37]. Apart from promoting adverse left ventricle remodeling, further deterioration of contractile function, and induction of striated muscle cachexia, proinflammatory cytokines may substantially contribute to the acceleration of coagulation reactions [36]. Experimental studies have demonstrated that *in vivo* expression of tissue factor on circulating mononuclear cells is dependent on IL-6 [38]. Other reports have demonstrated that down-regulation of thrombomodulin at the endothelial surface, mediated by IL-1β and TNF-α, results in the abrogation of natural anticoagulant protein C effects [39]. Increased plasma concentrations of TNF-α and IL-1β have been reported to affect the endogenous fibrinolytic system, resulting in its complete inhibition, and as a consequence in inadequate fibrin removal and the possibility of microvascular thrombosis [40]. Evidence is accumulating at present that extensive 'cross-talk' between inflammatory and coagulation pathways might be relevant for pathologic changes and the progression of many vascular disorders, including chronic CHF. Binding of activated coagulation proteases or anticoagulant proteins and components of the plasminogen system to their specific cell receptors on mononuclear cells or endothelial cells may affect proinflammatory cytokine production, resulting in the modulation of their subsequent effects, such as induction of myocardial apoptosis, cardiac hypertrophy and fibrosis [41].

Activation of the sympathetic and renin–angiotensin–aldosterone systems in CHF is accompanied by increased release of catecholamines, angiotensin II and aldosterone into extracellular fluid. It is well established that these substances can directly influence the metabolism and function of endothelial cells, resulting in reduced bioavailability of nitric oxide and prostacyclin production, and an increase in the release of von Willebrand factor, thromboxane A_2 and endothelin, which may contribute to increased peripheral vasoconstriction, further 'exacerbation' of vessel wall ischemia, and the promotion of thrombogenesis [42,43].

Many publications have reported platelet laboratory abnormalities that predispose to thrombogenesis in association with CHF: high mean platelet volume, reduced platelet survival, and increased levels of plasma platelet factor 4, β-thromboglobulin, soluble and platelet P-selectin, platelet CD40L and platelet aggregates [44,45]. Numerous studies have found that patients with CHF have increased plasma viscosity and elevated concentrations of the proteins involved in thrombinofibrinogenesis and fibrinolysis (fibrinogen, coagulation factors VII and VIII, thrombin–antithrombin complexes, prothrombin fragments 1 + 2, fibrinopeptide A, D-dimer and others) [28,44,46]. It has been shown that markers of thrombin activity in patients with dilated and hypertrophic cardiomyopathy are significantly related to parameters of cardiac chamber dilatation and 'stiffening' [47]. Studies have also reported that therapy with low molecular weight heparin and warfarin leads to significant suppression of enhanced coagulation reactions in patients with congestive CHF and ischemic left ventricular dysfunction [48,49].

Antithrombotic therapy in CHF: evidence from clinical studies

Despite the possibility that pharmacologic control of hypercoagulability and platelet activation could be beneficial for patients with CHF, the evidence for this from early and more recent clinical studies is not conclusive.

Data from non-randomized studies

Until recently, the clinical data on the use of antithrombotic therapy for vascular thrombotic event reduction in patients with CHF was largely 'obtainable' from *post hoc* analyses of CHF trials. However, several early prospective non-randomized studies in patients with CHF (which mostly included patients with valvular heart disease) have also been published [50–52]. These studies demonstrated that VKA anticoagulation was more efficacious than control for the reduction of all-cause mortality.

Several *post hoc* analyses of the vascular thrombotic event data, collected in prospective randomized clinical trials of other antithrombotic treatments in the CHF population, have been published. Although thromboembolic outcomes were not specifically defined in these studies as endpoints, the retrospective analyses, nevertheless, provide some relevant information on the impact of antithrombotic therapy on clinical outcome in patients with CHF.

A retrospective analysis of the data from the SAVE trial (2231 patients after acute MI with left ventricular dysfunction) found 81% and 56% reductions in stroke risk with administration of warfarin and antiplatelet therapy, respectively (RR 0.19, 95% CI 0.13–0.27 for warfarin; RR 0.44, 95% CI 0.29–0.65 for antiplatelet therapy) [13]. The absence of warfarin or antiplatelet therapy was found in this observational analysis to be an independent risk factor for stroke.

The findings of the Observations in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (n = 253) indicated that non-randomized, long-term warfarin administration to patients with severe CHF was associated with a 40% decline in the mortality rate [53]. The most common cause of death in the CONSENSUS was the exacerbation of CHF rather than documented vascular thrombotic events.

In V-HeFT I ($n = 642$), the use of neither warfarin nor antiplatelet therapy was associated with a significant reduction in the incidence of vascular thrombotic events, whereas V-HeFT II ($n = 804$) showed an even higher incidence of vascular thrombotic events associated with warfarin therapy compared to no VKA treatment (4.9 events per 100 patient-years vs. 2.1 events per 100 patient-years, $P < 0.01$), and again reported no effect of antiplatelet therapy on vascular thrombotic event rate [12]. In both V-HeFT studies, the overall rate of vascular thrombotic events was reported as 'low', and the presence of atrial fibrillation was not associated with the risk of vascular thrombotic events.

In a multivariate cohort analysis of the data from SOLVD for 6797 patients, antiplatelet and VKA therapy were each associated with a significant reduction in all-cause mortality [for warfarin, adjusted hazard ratio (HR) 0.76, 95% CI 0.65–0.89; for antiplatelet therapy, adjusted HR 0.82, 95% CI 0.73–0.92] and death or hospitalizations for CHF (for warfarin, adjusted HR 0.82, 95% CI 0.72–0.93; for antiplatelet therapy, adjusted HR 0.81, 95% CI 0.74–0.89), although warfarin use, in contrast to antiplatelet therapy, was not associated with a reduction in the total number of vascular thrombotic events [54,55]. Both antithrombotic approaches were associated with significant reductions in the risk of sudden death.

A *post hoc* analysis of the data on 427 patients with advanced CHF who participated in the Promotion of Reperfusion in Myocardial Infarction Evolution-II (PRIME-II) trial showed that both antiplatelet therapy and VKA improved the prognosis in patients with advanced CHF (for antiplatelet therapy, HR 0.62, 95% CI 0.40–0.97, $P = 0.04$; for VKA, HR 0.60, 95% CI 0.43–0.83, $P < 0.01$) [56].

An analysis of the population-based database The Epidemiologie de l'Insuffisance Cardiaque Avancée en Lorraine ($n = 417$) also found that administration of antithrombotic therapy (VKA or aspirin) to patients with severe CHF was associated with a better prognosis: 5-year survival rates were 40.4% in patients on antithrombotic therapy and 31% in patients without this treatment [57].

Randomized prospective clinical studies

Three randomized prospective clinical studies, recruiting patients with both ischemic and non-ischemic CHF, have been conducted recently [58–62] (Table 1).

One of the studies, aiming to define the optimal approach to antithrombotic therapy in the context of CHF, specifically when patients are in sinus rhythm – Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) – randomized 1587 patients with CHF or left ventricular dysfunction to warfarin, aspirin or clopidogrel [58–60]. The study showed no difference between the effects of these regimens on mortality, MI, or stroke. However, the hospitalization rate because of CHF deterioration was lower with warfarin treatment than with antiplatelet treatment, although the rate of major bleeding was higher. The trial was terminated early because of poor recruitment, and was therefore underpowered to detect

Table 1 Randomized controlled trials evaluating antithrombotic therapy in patients with heart failure in sinus rhythm

Trial	Patients, *n*	Antithrombotic regimens	Primary endpoint	Results: primary endpoint	Results: hospitalizations	Major bleeding
WATCH [58,59]	1587	Warfarin (target INR 2–3) vs. AT (blinded aspirin 162.5 mg or clopidogrel 75 mg)	Composite: death/MI/stroke	NS difference between the groups: 20.5% vs. 21% vs. 19.8% for aspirin, clopidogrel and warfarin, respectively	16.1% vs. 22.2% vs. 18.3% for warfarin, aspirin and clopidogrel, respectively (warfarin vs. aspirin $P = 0.01$)	5.6% vs. 3.6% vs. 2.5% for warfarin, aspirin and clopidogrel, respectively (warfarin vs. clopidogrel $P = 0.012$)
WASH [61]	279	Warfarin (target INR 2–3) vs. aspirin 300 mg vs. no ATT	Composite: death/MI/stroke	NS difference between the groups: 26% vs. 32% vs. 26% for no ATT, aspirin and warfarin, respectively	48% vs. 47% vs. 64% for no ATT, warfarin and aspirin, respectively (warfarin vs. aspirin $P = 0.044$)	4, 1 and 0 bleedings for warfarin, aspirin and no ATT, respectively (warfarin vs. no ATT $P = 0.028$)
HELAS [62]	197	IHD: warfarin (target INR 2–3) vs. aspirin 325 mg DCM: warfarin (target INR 2.5) vs. placebo	Any event: death, stroke, (re)MI, (re)hospitalization, PE, peripheral embolism, exacerbation of heart failure	NS difference between the comparison arms: 14.9% vs. 15.7% vs. 14.8% vs. 8.9% for IHD-A, IHD-W, DCM-P and DCM-W, respectively	3.2% vs. 2.4% vs. 5.9% vs. 4.4% for IHD-A, IHD-W, DCM-P and DCM-W, respectively	0% vs. 4.8% vs. 0% vs. 4.4% for IHD-A, IHD-W, DCM-P and DCM-W, respectively

A, aspirin; AT, antiplatelet therapy; ATT, antithrombotic therapy; HELAS, heart failure long-term antithrombotic study; IHD, ischemic heart disease patients; DCM, dilated cardiomyopathy patients; INR, International Normalized Ratio; MI, myocardial infarction; NS, non-significant; P, placebo; PE, pulmonary embolism; W, warfarin; WASH, warfarin–aspirin study in heart failure; WATCH, warfarin and antiplatelet therapy in chronic heart failure.

differences between the three arms. As the study had no placebo arm, it was not clear if any treatment was more effective than no antithrombotic intervention.

The Warfarin/Aspirin Study in Heart Failure (WASH), where 279 patients with CHF in sinus rhythm were subjected to long-term anticoagulation with warfarin or placebo or aspirin, also provided no evidence that either of the antithrombotic regimens was effective or safe [61]. There was no difference in the primary endpoint of death, non-fatal MI or non-fatal stroke between the three arms. However, as in WATCH, patients on warfarin had fewer hospitalizations for CHF than those on aspirin or on placebo. The incidence of minor hemorrhages was greater in the aspirin and warfarin groups than in the placebo group. A meta-analysis of the data from the WATCH and WASH studies found a weak trend in favor of a lower mortality rate with warfarin than with aspirin [odds ratio (OR) 0.91 (0.67–1.22)] [60].

Recently, the results of the Heart Failure Long-term Antithrombotic Study (HELAS), comparing the efficacy and safety of warfarin against placebo and against aspirin, were published [62]. The study recruited 197 patients with ischemic and non-ischemic (dilated cardiomyopathy) CHF in sinus rhythm. Patients with ischemic etiology were randomized to 2 years of therapy with warfarin or aspirin, whereas those with cardiomyopathy were randomized to therapy with warfarin or placebo. During 2 years of follow-up, the incidence of embolic events per 100 patient-years was 2.2, with no significant difference in the primary endpoint between the groups. No peripheral or pulmonary embolism was reported. Echocardiographic follow-up showed an overall increase in left ventricular EF from 28.2 ± 6% to 30.3 ± 7% ($P < 0.05$), which was significant in patients with dilated cardiomyopathy, but not in patients with ischemic CHF. Like WATCH, this study was terminated prematurely, because of poor enrollment; therefore, its findings should be interpreted with caution.

To summarize the results of three recent randomized controlled studies addressing the issue of justification of antithrombotic therapy for CHF patients in sinus rhythm: (i) the results do not suggest that the incidence of vascular thrombotic events can be reduced by antithrombotic therapy; (ii) the studies reported a relatively low rate of vascular thrombotic events; and (iii) WATCH and HELAS were terminated prematurely, and thus did not reach the predesigned statistical power.

It is anticipated that sound data and, hopefully, compelling evidence will soon become available from an ongoing major randomized clinical trial. This is a multicentre double-blind clinical trial, the Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) study, recruiting 2860 patients with left ventricular EF < 30% who do not have established indications for warfarin (such as atrial fibrillation) [63]. Randomizations are to aspirin (325 mg day^{-1}) and warfarin [target International Normalized Ratio (INR) 2.75] arms, and the primary endpoint is a composite outcome of death or ischemic or hemorrhagic stroke occurring during a 3–5-year period after randomization.

Specific considerations

Warfarin anticoagulation

The existing evidence is strong enough to justify the prophylactic use of warfarin only for CHF patients who have previously suffered vascular thrombotic events and for those with atrial fibrillation. A number of randomized clinical studies have shown that warfarin reduces the risk of stroke in patients with atrial fibrillation [15]. A significant proportion of participants in these studies (10–25%) represented patients with CHF. For these patients, anticoagulation with warfarin appeared to be superior to anticoagulation with aspirin in reducing the stroke rate. With regard to CHF patients in sinus rhythm, data supporting the use of warfarin are limited. A recent Cochrane systematic review did not find any evidence to support routine administration of warfarin for CHF patients in sinus rhythm [64].

Warfarin administration should be considered in the presence of intraventricular thrombi following acute MI. Although the evidence from clinical studies suggests that at least a few months of anticoagulation is desirable for post-MI patients with echocardiographically detectable thrombi, no conclusive supporting data are available for CHF patients with intracardiac thrombi who are not MI sufferers [65].

When considering VKA therapy for CHF patients, it is important to judge the potential bleeding risks. These patients often present with variable hepatic congestion and multiple comorbidities, so control of anticoagulation can be challenging, and, thus, unpredictable drug interactions and hemorrhagic complications are very likely to occur.

Recent recommendations on CHF management state that 'in the absence of definitive trials, it is not clear how anticoagulation should be prescribed in patients with CHF' [65]. The use of VKA therapy (with INR 2–3) is most justified for CHF patients with atrial fibrillation [65]. In patients with sinus rhythm, the only situations in which to consider VKA anticoagulation are severely depressed left ventricular systolic function, previous vascular thrombotic events (and underlying disorders associated with increased vascular thrombotic event risk, e.g. amyloidosis), and cases when the presence of intracardiac thrombi cannot be excluded [65].

Antiplatelet agents

The positive role of antiplatelet therapy, mainly aspirin, in preventing atherothrombotic events in different groups of patients with various vascular risks, including patients with CHF, has been suggested by the results of a large meta-analysis, the Antithrombotic Trialists' Collaboration [66], although there is criticism of these findings [67].

Some of the trials investigating the benefits of angiotensin-converting enzyme (ACE) inhibitors in CHF patients have reported unfavorable effects of concomitant use of aspirin. The SOLVD found that survival was not improved with aspirin administration in the group of patients concomitantly receiving

enalapril [55]. In the CONSENSUS II, patients on a combination of aspirin and enalapril had a significantly increased mortality rate in comparison to those patients who received enalapril only, but not aspirin [68]. The most common pathophysiologic explanation of the possible adverse interactions between aspirin and ACE inhibitors is the counteraction between their effects on the production of vasodilating prostaglandins [69]. Despite being plausible, the adverse clinical interactions between aspirin and ACE inhibitors have not been demonstrated so far in a robust clinical study. Nevertheless, the most recent guidelines of the European Society of Cardiology on CHF management state that 'there is little evidence to support the concomitant treatment with an ACE inhibitor and aspirin in heart failure' [70]. Probably, more clinical studies are needed to resolve this question. In the meantime, the wider use of clopidogrel (an antiplatelet agent with a different mechanism of action from aspirin) may circumvent the anticipated problems with aspirin for CHF patients receiving ACE inhibitors. A large randomized trial has reported that clopidogrel is at least as safe, and more effective, than aspirin in the secondary prevention of strokes, recurrent coronary events and cardiovascular deaths in a variety of patients with different clinical presentations of atherosclerosis, including patients with CHF [71]. No prospective study has been conducted to specifically evaluate clopidogrel or other antiplatelet agents (such as dipyridamol) in patient with CHF, so routine administration of these medications remains at the discretion of the attending physician.

In this respect, the evidence for the benefits of antiplatelet therapy for CHF patents is even less conclusive than it is for VKA anticoagulation. Considering the high incidence of atherosclerotic disease as a cause or comorbid condition in CHF, it is anticipated that future studies will address this question. In the meantime, the practical guidelines on the management of CHF [65,70,72] recommend aspirin administration only for the purposes of secondary prevention of atherothrombotic events and for patients with atrial fibrillation in situations when warfarin is contraindicated. Special attention should be paid to the facts that patients with CHF, compared to the general population, appear to be more prone to major gastrointestinal bleeding and renal impairment with aspirin use, and that these complications of aspirin therapy are dose-dependent.

Conclusions

The pathophysiology of CHF could explain the predisposition of patients with this condition to experience thrombosis and thromboembolic complications. However, conclusive epidemiologic data on vascular thrombotic event incidence in CHF are lacking. The available data indicate that the risk of vascular thrombotic events in clinically stable patients is relatively low. Retrospective analyses of large CHF studies differ in their results with regard to reduction of vascular thrombotic event risk with antithrombotic therapy. Three recent prospective randomized studies did not prove that either warfarin anticoagulation or antiplatelet therapy is effective or safe in CHF patients with sinus rhythm, although the premature termination of two of these studies precluded any definite conclusions concerning the potential of antithrombotic therapy to reduce the incidence of vascular thrombotic events in this setting. Another large trial comparing warfarin and aspirin in patients in sinus rhythm and with reduced left ventricular systolic function is currently underway.

Thus, the routine administration of antithrombotic therapy for all CHF patients cannot be justified at the present time. However, for patients with a high risk of vascular thrombotic events, such as those with atrial fibrillation, previous vascular thrombotic events, left ventricular thrombi, underlying conditions predisposing to vascular thrombotic events, and, probably, severely compromised systolic function, VKA anticoagulation should be used. There is also no evidence to substantiate the routine use of antiplatelet therapy to reduce the incidence of vascular thrombotic events in CHF patients who are in sinus rhythm; however, for secondary prophylaxis of atherothrombotic events, aspirin prescription is justifiable.

Because of the absence of definitive studies, it is difficult for physicians to make decisions about the administration of antithrombotic therapy to patients with CHF. Therefore, not only prospective randomized trials are needed, but also more recommendations and guidelines from professional bodies, which should specifically address the advantages and disadvantages of each antithrombotic regimen (including efficacy, bleeding and other adverse event risk, costs and convenience of use) for the different clinical scenarios and comorbid conditions associated with CHF.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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