Antiplatelet and Anticoagulant Agents in Heart Failure
Current Status and Future Perspectives

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There has been a 3-fold increase in hospital discharges for heart failure (HF) and also significantly increased mortality rate in HF patients in recent years. A major focus of HF research has been in the area of neurohormonal control and resynchronization therapy. There is a great urgency in better understanding the pathophysiology underlying the exceedingly high mortality and a need for exploration of therapeutic strategies beyond those that influence neurohormonal pathways. The decision to treat patients with HF with antiplatelet therapy remains largely influenced by the presence or absence of concomitant arterial disease. Antithrombotic therapy has been shown to be effective in many forms of cardiac disease, including patients with HF and atrial fibrillation. Although it is clear that platelet activation and hypercoagulability are present in HF, and there is evidence that stroke is reduced by warfarin therapy in the HF patient, the available data suggest that the risk of major bleeding overshadows the antithromboembolic benefit in HF patients in sinus rhythm. The utility of oral anticoagulant and/or antiplatelet therapy has never been evaluated in an adequately powered dedicated clinical trial of HF patients in sinus rhythm. In this state-of-the-art paper we explore the evidence for targeting the inhibition of platelet function and coagulation to improve outcomes in the HF patient. (J Am Coll Cardiol HF 2014;2:1–14) © 2014 by the American College of Cardiology Foundation

On the basis of data from National Health and Nutrition Examination Survey 2007 to 2010, an estimated 5.1 million Americans ≥20 years of age have heart failure (HF) (National Heart, Lung and Blood Institute tabulation). One in 9 death certificates (274,601 deaths) in the United States mentioned HF in 2009. There has been a 3-fold increase in hospital discharges for HF since 1979 in the United States (1).

A major focus of HF research has been in the area of neurohormonal control and resynchronization therapy (2). However, venous thromboembolism (VTE), cardioembolic stroke, and sudden death occur in 30% of HF patients and contribute to the observed high overall mortality and morbidity (3). After atrial fibrillation (AF), which accounts for 15% of strokes, HF is the next most frequent associated cardiac condition accounting for 9% of all strokes (4). Although AF significantly increases the risk of stroke, the heightened risk of thromboembolism in HF patients is independent of AF. These observations serve as evidence for a potential “heart failure research paradox” where comparatively less information has been gained from adequately sized prospective investigations of thrombogenicity and antithrombotic therapy in the HF patient. Despite the fact that treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta adrenergic antagonists, and mineralocorticoid receptor antagonists in HF patients has improved outcomes, morbidity or mortality remains particularly high in patients with acute decompensated HF (2). In patients hospitalized for HF, the mortality rate is 4% at 1 month, 18% at 6 months, ∼30% at 12 months, and ∼40% at 38 months (2). These dismal statistics suggest urgency in better understanding the pathophysiology underlying the exceedingly high mortality and a need for exploration of therapeutic strategies beyond those that influence neurohormonal pathways. In this state-of-the-art paper we explore the evidence for targeting the inhibition of platelet function and coagulation to improve outcomes in the HF patient.

Pathophysiology of Arterial Thrombosis in HF
Approximately 70% of patients with HF and left ventricular systolic dysfunction will have ischemic heart disease (5). Nonischemic etiologies will be responsible for the remainder
The Thrombin also activates FXIII to induce and time dependence in the importance of thromboxane A2, remains unknown whether there is interindividual variability left ventricular dysfunction in the HF patient. At present, it The latter mechanism may participate in the progression of generated on ruptured plaques may embolize downstream sclerotic plaque rupture or endothelial denudation. Thrombi of various factors facilitate platelet adhesion and activation. Platelet activation leads to the release of important secondary agonists, thromboxane A2 and adenosine diphosphate (ADP). Thromboxane A2 is produced from membrane phospholipids, and ADP is released from dense granules. Through autocrine and paracrine mechanisms, these 2 locally generated secondary agonists play a critical role in the sustained activation of IIb3 receptors and stable platelet aggregation. Plaque rupture results in tissue factor (TF) exposure at the site of vascular injury and the generation of femtogram amounts of thrombin, the most potent primary platelet agonist. Tissue factor bearing cells come in contact with circulating coagulation factor (F) VII resulting in the autoactivation of FVII to form the TF-FVIIa complex, which in turn activates FX to FXa and FIX to FIXa. FXa initially activates small amounts of thrombin, which in turn activates platelets and also FV and FVIII. Subsequently, the intrinsic FXase (FVIIIa-FIXa) and prothrombinase (FVa-FXa) are formed on the activated platelet surface where large amounts of thrombin are generated by the conversion of prothrombin to thrombin. Plasminogen activator inhibitor-1, released from platelets, depresses fibrinolysis. Thrombin finally catalyzes the conversion of soluble fibrinogen to insoluble strands of fibrin, thereby initiating clot formation (Fig. 1). Thrombin also activates FXIII to induce fibrin polymerization. The final result is a platelet-fibrin clot that mediates normal hemostasis and pathologic thrombosis at the site of atherosclerotic plaque rupture or endothelial denudation. Thrombi generated on ruptured plaques may embolize downstream and occlude the microvasculature resulting in microinfarction. The latter mechanism may participate in the progression of left ventricular dysfunction in the HF patient. At present, it remains unknown whether there is interindividual variability and time dependence in the importance of thromboxane A2, ADP, and thrombin in thrombus generation (6,7).

Occlusive thrombus generation at the site of plaque rupture is dependent on vulnerable blood (hypercoagulability, enhanced platelet function, inflammation) and vulnerable vessel (endothelial dysfunction, and ruptured plaque/denuded endothelium/abnormal anatomy) (Fig. 2). Reduced platelet survival time, increased mean platelet volume, and greater platelet activation and reactivity have been observed in patients with HF (8,9). In addition, elevated levels of β-thromboglobulin, p-selectin, platelet/endothelial cell adhesion molecule-1, and osteonectin as well as increased platelet surface p-selectin and CD40L all serve as further evidence of heightened platelet activation in patients with HF (10–12). High levels of circulating fibrinogen, fibrinopeptide A, and D-dimer have also been demonstrated in patients with HF. In addition, high levels of fibrinogen and D-dimer observed in patients with HF have correlated with disease severity (13). Decreased circulating levels of ADAMTS–13 and increased von Willebrand factor (vWF) were found to be significant predictors of clinical events in patients with HF (14). In addition, a prothrombotic environment in the setting of HF is indicated by increased inflammatory cytokines such as tumor necrosis factor-α and interleukin-1. These factors in turn are associated with increased expression of tissue factor and thrombin generation and decreased thrombomodulin and protein C pathway activation (anticoagulant factors) (15–17). Vulnerable vessel is characterized by decreased antithrombotic factor expression such as nitric oxide, thrombomodulin and increased expression of TF, vWF, and elevated inflammation at the site of plaque rupture. Moreover, a bifurcated and stenotic vessel affects arterial shear and promotes platelet activation (18,19).

Pathophysiology of Venous Thrombosis in HF

Heart failure has been recognized as a prothrombotic or hypercoagulable state. The major components of Virchow’s triad are present in venous thrombosis–vessel wall abnormalities, vulnerable blood, and blood flow abnormalities (Fig. 3) (2). Venous stasis induced by high pressure, a low-flow state, and immobility result in distention of the vessel wall local and local hypoxia, causing ischemia and oxidative stress (18,20,21). The latter mechanisms in addition to neurohormonal activation result in endothelial cell activation. Endothelial activation is characterized by increased expression of adhesion molecules–selectins and decreased production of antithrombotic factor–nitric oxide. These mechanisms promote platelet/monocyte adhesion and activation. Importantly, TF-rich microparticles released from activated endothelial cells and monocytes attach to the expressed adhesion molecules on the endothelium at the site of injured vessel wall (20,22,23). TF initiates the coagulation cascade and, ultimately, fibrin–rich thrombus generation. In this line, increased circulating endothelial adhesion molecules, increased microparticles of endothelial origin, and leukocyte activation have been demonstrated in patients with VTE and HF (22–24). Finally, venous stasis promotes thrombosis by decreased clearance of activated coagulation factors (23).
In patients with HF secondary to coronary artery disease (CAD), ongoing silent or symptomatic ischemia has being associated with HF progression (25). The elderly, women, and those with prior myocardial infarction (MI) are at greatest risk for developing HF. However, a relatively low rate (2% to 4%) of fatal or non-fatal MI has been reported in patients with HF (26,27). In contrast, compared with a 0.1% to 0.5% annual rate of stroke in patients 80 years of age, HF patients have a 1.0% to 3.5% annual rate of stroke, with a possible relationship between low ventricular ejection fraction (LVEF) and stroke risk (28).

Strokes associated with HF have been attributed to multiple etiologies. Concomitant AF is associated with loss of atrial contraction. In the setting of stasis, thrombosis is promoted in the left appendix, and embolization may ensue. In addition, AF is associated with atherosclerosis. Therefore, atheroembolism from nonatrial sources may also explain a heightened risk for stroke. In HF patients in sinus rhythm,
underlying atherosclerosis may play a dominant mechanistic role in stroke occurrence. Among HF patients with stroke, about one-half have been reported to have AF (29). The significant impact of HF on stroke risk in AF patients was suggested in the Stroke Prevention in Atrial Fibrillation Investigators studies (30). The risk may also depend on how HF is defined and whether it is decompensated versus stable (31). Significantly more circulating platelet aggregates were demonstrated in patients with HF compared with normal volunteers by Mehta et al. (32). In the same study, the number of circulating platelet aggregates declined to normal levels following sodium nitroprusside infusion, and there was significantly lower ex vivo epinephrine- and ADP-induced platelet aggregation, which was associated with a 30% decrease in systemic vascular resistance and a 28% increase in cardiac output. The authors suggested that an increase in vascular resistance in certain HF patients may cause an increase in circulating platelet aggregates and that antiplatelet therapy may be beneficial in these patients.

Insight into the heightened risk of stroke and death in HF was gained in the Diet, Cancer and Health study. Among the 51,553 patients without prior HF, 1,239 were identified with incident HF. There was a markedly increased risk of death, and death or stroke (ischemic or hemorrhagic or both) in the first 30 days after presentation with first HF relative to non-HF exposed patients (hazard ratios [HR]: 42.8 and 38.4, respectively). There was attenuation of risk at 30 days to 6 months (HRs: 12.7 and 9.3, respectively) and >6 months (HRs: 4.9 and 4.0, respectively) (33). Warfarin use was associated with a lower risk for death and the composite of death or stroke compared with no warfarin therapy and this effect was more prominent in the first 30 days. Finally, independent predictors for death, stroke, and the composite of death or stroke were previous stroke/transient ischemic attack/transient ischemia (33).

In the Rotterdam study, 7,546 participants ≥55 years old (female = 61%) without a history of stroke were continuously monitored for major events including stroke and HF. At baseline, 233 (3.1%) patients had HF, whereas 1,014 patients developed HF and 827 patients developed stroke during an average follow-up time of 9.7 years. There was a more than 5-fold increase in the risk of ischemic stroke in the first month after HF diagnosis (age- and sex-adjusted HR: 5.79, 95% confidence interval [CI]: 2.15 to 15.62), but the risk decreased over time after 1 to 6 months (age- and sex-adjusted HR: 3.50, 95% CI: 1.96 to 6.25) and after 0.5 to 6 years (HR: 0.83, 95% CI: 0.53 to 1.29) (34).

In the SAVE (Survival and Ventricular Enlargement) trial, 2,231 patients who had LV dysfunction after acute MI were followed for an average of 42 months. The annual rate of fatal and nonfatal stroke was 1.5%, and the 5-year rate of stroke was 8.1%. There was a 2-fold increased risk for stroke in patients with left ventricular ejection fraction (LVEF) ≤28% compared with patients with LVEF of
In this study, lower ejection fraction (for every decrease of 5 percentage points in the ejection fraction there was an 18% increase in the risk of stroke), older age, and the absence of aspirin or anticoagulant therapy were found to be independent risk factors for stroke (35).

Venous Thromboembolism

It has been reported that patients with HF have an increased risk for developing deep vein thrombosis versus those without HF, with adjusted odds ratios (ORs) of 1.47 (95% CI: 1.47 to 1.48) to 2.93 (95% CI: 1.55 to 5.56) (36). Moreover, there is a 10% to 22% risk of venographically-proven VTE in HF patients in the absence of pharmacologic treatment (36,37). In several case-cohort studies, HF patients were found to have a 2- to 3-fold increased risk for VTE compared with patients with other medical conditions. The rate of VTE was 2.7 and 2.1 per 100 patient-years in the V-HeFT (Veterans Affairs Vasodilator-Congestive Heart Failure) I and II trials, respectively, that included both patients in sinus rhythm and with AF (38). In an analysis of the SCD-HeFT (Sudden Cardiac Death-Heart Failure Trial), which excluded all patients with AF at the time of randomization, the rate of thromboembolism was 3.4% over a median follow-up of 45.5 months. A trend toward an increased 4-year Kaplan–Meier rate of thromboembolism with lower LVEF was observed (3.5%, 3.6%, and 4.6% with LVEF 30% to 35%, 20% to 30%, and <20%, respectively) (28).

Antithrombotic Therapy in Patients With HF

The previous evidence suggests that antithrombotic therapy targeting the platelet and/or coagulation may provide beneficial effects in patients with HF, particularly early after presentation. Long-term oral anticoagulant (OAC) therapy is an established major preventive treatment strategy against stroke in patients with AF (5). However, unlike AF, the role of antithrombotic agents in the prevention of stroke in patients with HF and sinus rhythm has been much less investigated. Personalized antithrombotic therapy has been studied in patients treated with coronary stents with the goal of determining a therapeutic window for on-treatment platelet reactivity that optimally prevents ischemic events while avoiding medically-important bleeding (39). Laboratory tests are available that identify high intrinsic thrombogenicity that have been associated with clinical thrombotic events after stenting (40). Similar investigations have never been undertaken to identify the prothrombotic HF patient. Despite the extensive research in the PCI population, the goal of optimal antithrombotic therapy that balances reduction in ischemia and avoidance of bleeding remains elusive in HF patients. Moreover, platelet activation and aggregation, and thrombin formation, are highly interlinked. Optimal target(s) for the inhibition of the effects of thrombin remain unclear; proposed strategies include direct thrombin inhibition, inhibition of the coagulation factors.
upstream from thrombin formation including FXa,FIXa, FVIIa, or FVa, or the platelet thrombin receptor-protease activated receptor-1.

**Antiplatelet Therapy**

Aspirin is chosen in HF based on its role in secondary prevention in patients with atherosclerotic vascular disease. To this date there has been no dedicated randomized trial of antiplatelet therapy in the HF patient. All of the randomized trials have included an anticoagulant arm (see subsequent discussion). In patients with high-risk coronary artery disease, it is well established that simultaneous inhibition of cyclooxygenase-1 with aspirin and the adenosine diphosphate-P2Y_12_ receptor with clopidogrel is associated with a significant reduction in MI (41). However, the efficacy of dual antiplatelet therapy on stroke reduction is uncertain. Adding aspirin to clopidogrel in patients with recent ischemic stroke or transient ischemic attack in the large-scale MATCH trial (Management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke) was not associated with a benefit in reducing major vascular events (RRR [relative risk reduction]: 6.4%, 95% CI: −4.6 to 16.3, p = 0.244). However, the risk of life-threatening or major bleeding was increased by the addition of aspirin to clopidogrel (42). In the ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial), treatment of aspirin (30 to 325 mg/day) with dipyridamole (200 mg twice daily) was associated with a 20% relative risk (RR) reduction in the composite end point of composite of death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complication in patients with transient ischemic attack or minor stroke of presumed arterial origin compared to aspirin alone (43). Similarly, aspirin plus extended release dipyridamole versus clopidogrel was associated with similar incidences of primary endpoint of first recurrence of stroke (HR: 1.01, 95% CI: 0.92 to 1.11) in patients with a recent ischemic stroke in the PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial (44).

A meta-analysis performed by Antithrombotic Trialists’ collaboration of secondary prevention trials demonstrated that aspirin therapy was associated with an 1.5% absolute reduction in serious vascular events (6.7% vs. 8.2% per year, p < 0.0001) and a 20% reduction in total stroke (2.08% vs. 2.54% per year, p = 0.002) and coronary events (4.3% vs. 5.3% per year, p < 0.0001) but a nonsignificant increase in hemorrhagic stroke (45). Treatment failure and pharmacologic limitations associated with clopidogrel therapy fostered the development of more potent P2Y_12_ receptor blockers such as, prasugrel, an irreversible agent, and ticagrelor, a reversibly binding agent. Treatment of patients with acute coronary syndromes (ACS) with the latter agents was more effective than clopidogrel; however, the observed degree of adverse event reduction (~20% relative and ~2% absolute), and significantly greater bleeding remain major concerns (39). Moreover, it is also interesting to note that although more potent P2Y_12_ receptor blockers are more effective than clopidogrel in the overall patient population, in “very high-risk patients” (diabetes mellitus, elderly patients, and those with renal failure, history of MI, stroke, and stent thrombosis), the overall rate of ischemic event occurrence remains very high. In addition, some of these “very high risk” groups are also associated with an increased bleeding risk. The previous limitations highlight the ceiling effect of current dual antiplatelet therapy targeting COX-1 and the P2Y_12_ receptor in high-risk CAD patients and suggest that the residual ischemic event occurrences are mediated by other pathways that are unblocked by current antiplatelet therapy. There is no information available on the outcomes of HF patients treated with either prasugrel or ticagrelor. Thus, the indication for antiplatelet therapy in the HF patients depends upon the presence of concomitant vascular disease.

**Warfarin**

Warfarin (vitamin K antagonist) blocks multiple steps of coagulation by reducing the synthesis of vitamin K dependent coagulation factors. In a meta-analysis of trials involving patients with AF, warfarin therapy was found to be associated with a 64% reduction in stroke and a 26% reduction in all-cause mortality when compared with placebo/control (46). As warfarin is metabolized by the cytochrome P450 isoenzymes, interactions with other drugs that are metabolized by the same cytochrome P450 isoenzymes influence the pharmacokinetics and pharmacodynamics of warfarin. The metabolism and efficacy of warfarin are influenced by liver function, genetic polymorphisms, and alcohol and food consumption (47). The major concern of genetic variability lies within the CYP2C9 and VKORC1 genes that encode proteins involved in the metabolism of warfarin (48,49). Warfarin therapy is associated with a relatively narrow therapeutic window of international normalized ratio (INR) values between 2.0 and 3.0. Insufficient anticoagulation and a subsequent rise in the risk of ischemic strokes are associated with INR values below 2.0, and a higher risk of intracranial bleeding is associated with an INR >4.0 (49,50).

**New Oral Anticoagulants**

Currently known anticoagulants can be classified as parenteral or oral (based on their administration route) or direct or indirect inhibitors (based on their target of action). New OACs have been developed to overcome some of the limitations of warfarin therapy. The direct thrombin inhibitors (“gatrans,” e.g., dabigatran) directly bind to thrombin and block thrombin-induced conversion of fibrinogen to fibrin and the activation of FV, FVII, FIX, and platelets. The latter functions are responsible for the amplification of thrombin generation. Moreover, direct thrombin inhibitors inhibit the activity of fibrin-bound thrombin (51,52).
The inhibition of coagulation protease enzymes responsible for the propagation phase attenuates the generation of thrombin. Anticoagulants have been developed to inhibit FXa (e.g., the DNA aptamer pegnivacogin), FVIIa (TB-402), and FVa/FVIIIa (drotrecogin, a recombinant form of human activated protein C). Recomodulin and solulin are soluble recombinant derivatives of human thrombomodulin. The most widely investigated FXa inhibitors have been rivaroxaban and apixaban. Other FXa inhibitors include edoxaban, oatinixaban, darexaban, betrixaban, and TAK-442. Among the new OACs, dabigatran and apixiban have been shown to be more effective in preventing stroke than warfarin in patients with nonvalvular AF. In addition, lower rates of intracranial bleeding have been reported with apixaban, rivaroxaban, and dabigatran in the latter group of patients. Additional advantages of these new OACs over warfarin include the absence of any reported interactions with food, fewer interactions with other medications, and absence of frequent laboratory monitoring and dose adjustments (51).

Evidence for Antithrombotic Efficacy in HF

In a post hoc analysis of major HF trials associated with reduced ejection fraction and anticoagulant therapy, the annual rate of stroke was between 1.1% and 4.6%. Most of the trials included in the analysis had some patients with AF (53). Clinical trials conducted in the 1940s and 1950 have first assessed the utility of OAC in patients with HF. Many of the patients in these studies also had accompanying AF and valvular disease. Dicumarol therapy, the primary OAC used was associated with reduced thromboembolic event occurrence and death (54–56). However, the relevance of these trials in patients with sinus rhythm, which is more prevalent in current practice, is limited.

In the SOLVD (Studies of Left Ventricular Dysfunction) trial (n = 6,797), antiplatelet therapy was used in 46.3% of patients and was associated with significantly reduced all cause death (adjusted HR: 0.82, 95% CI: 0.73 to 0.92, p = 0.0005) and reduced risk of death or hospital admission for HF (adjusted HR: 0.81, 95% CI: 0.74 to 0.89, p < 0.0001) compared to patients not treated with antiplatelet therapy (57). Interestingly, the observation that the addition of enalapril did not decrease the mortality rate in patients receiving antiplatelet agents, and conversely neither did the addition of aspirin in patients receiving enalapril fueled great controversy about an aspirin–ACE inhibitor interaction (58). Further support for an aspirin–ACE inhibitor interaction arose from the CONSENSUS II (Co-operative New Scandinavian Enalapril Survival Study II) study. Differential effects of the ACE inhibitor enalapril in subgroups defined by use of aspirin at baseline were analyzed. Logistic regression demonstrated that the enalapril–aspirin interaction term was a significant predictor of mortality and was a borderline significant predictor of mortality 30 days after randomization (59).

The ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for the prevention of Vascular Events) program added support for the use of aspirin in HF patients on ACE inhibitor therapy. In over 2,000 patients with a history of HF and AF, there was no evidence of aspirin-related attenuation of ACE inhibitor benefit (60).

In a multivariate analysis of the SOLVD trial, warfarin therapy (n = 861) was associated with a significant reduction in all-cause mortality (adjusted HR: 0.76, 95% CI: 0.65 to 0.89, p = 0.0006) and in the risk of death or hospital admission for HF (HR: 0.82, 95% CI: 0.72 to 0.93, p = 0.0002) compared to warfarin nonuse. The benefit of warfarin therapy was not influenced by the presence of AF, age, ejection fraction, New York Heart Association functional class, or etiology (57).

Randomized Trials of Antithrombotic Therapy in HF

In the WASH (Warfarin/Aspirin Study in Heart Failure) pilot study, 279 patients were randomized to receive no antithrombotic treatment (26%), 300 mg/day aspirin (32%) or warfarin (26%, target INR 2.5) for ~27 months. In this study, ~75% of patients were male, ~60% of patients had ischemic heart disease, and only 4% to 7% of patients had AF. No difference in the primary endpoint of first occurrence of death, nonfatal MI, or nonfatal stroke was observed between the treatment groups. However, compared to warfarin, aspirin treated patients were twice as likely to have a cardiovascular hospitalization or death during the first 12 months follow-up. Aspirin treatment was also associated with significantly more hospitalizations for cardiovascular reasons, especially worsening HF (p = 0.044). Therapy with warfarin and aspirin therapy was associated with a higher rate of minor bleeding, although few overall major hemorrhagic events were reported. The overall study results argued against the benefit of antiplatelet therapy in HF patients to prevent thromboembolic events (Table 1) (61).

The subsequent HELAS (HEart failure Long-term Antithrombotic Study) trial was prematurely terminated after enrolling 197 of an intended 6,500 patients due to slow enrollment. In this trial, 115 patients with ischemic cardiomyopathy were randomized to 325 mg daily aspirin or warfarin (INR 2.0 to 3.0), whereas 82 patients with nonischemic cardiomyopathy were randomized to placebo or warfarin (INR 2.5 to 3.0) for 18.5 to 21.9 months. Similar to the WASH study, there was no difference in the occurrence of the primary composite endpoint between the groups and only warfarin therapy was associated with 7 major hemorrhagic events that were predominantly due to high anticoagulation (62).

In the WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) trial, 1,587 of 4,500 planned patients with symptomatic HF (New York Heart Association functional class II to IV) for at least 3 months were studied. The trial was terminated prematurely due to slow enrollment. These patients were in sinus rhythm with documented LVEF ≤35% and received 162 mg daily aspirin, 75 mg daily clopidogrel (in a double-blind, double dummy fashion), or open label warfarin (target INR 2.5 to 3.0) for a mean
duration of 1.9 years (63). There was no placebo arm in this study. Similar to previous studies, there was no difference in the rate of the primary composite endpoint of first occurrence of death, nonfatal stroke, or nonfatal MI with warfarin versus aspirin therapy (HR: 0.98, 95% CI: 0.86 to 1.12, p = 0.77); with clopidogrel versus aspirin therapy (HR: 1.08, 95% CI: 0.83 to 1.40, p = 0.57); and with warfarin versus clopidogrel therapy (HR: 0.89, 95% CI: 0.68 to 1.16, p = 0.39). There was no difference in mortality between therapies. Warfarin therapy was associated with a reduction in the incidence of stroke (both fatal and disabling) compared to aspirin and clopidogrel (p < 0.02 for both). But, there was significantly increased bleeding in the warfarin group compared to clopidogrel group (n = 30 vs. n = 12, p < 0.01) but not compared to the aspirin group (n = 30 vs. n = 19, p = 0.22). A significant reduction in stroke was observed in patients with ischemic HF (73% of population) where the stroke rates were 0% in warfarin group versus 2.7% in clopidogrel group (p = 0.009) and 1.6% in aspirin group (p = 0.01). Furthermore, significantly increased incidences of hospitalization were observed in patients receiving aspirin compared to warfarin (p < 0.001). The overall evidence from the primary endpoint occurrences and mortality did not support that warfarin is superior to aspirin and that clopidogrel is superior to aspirin in HF patients with ejection fraction ≤35% who are in sinus rhythm (63).

In the largest study to date, the WARCEF (Warfarin versus Aspirin in patients with Reduced Cardiac Ejection Fraction) study, the efficacy of 325 mg daily aspirin versus warfarin therapy (target INR 2.5 to 3.0) was evaluated in a double-blind, double-dummy study design with sham INRs in 2,305 patients in sinus rhythm with LVEF ≤ 35% (64). This trial included a relatively young population (mean age = 61 years) with HF and a mean LVEF of 25%. In this trial, 48% of patients had MI, 43% had ischemic cardiomyopathy, 4% had AF, ~80% of patients were male, and 75% were a non-Hispanic white population. The mean duration of follow-up was 3.5 years. In 34% and 32% of the total follow-up time, patients did not receive the randomized warfarin and aspirin therapy, respectively. There was no control arm in this trial. Similar to slow recruitment problems observed in previous trials, in the WARCEF trial, the enrollment was stopped after 2,305 patients from 11 countries instead of a planned 2,860 patients, reducing the power to test the primary hypothesis from 89% to 69%. The maximum follow-up was extended to 6 years instead of 5 years. There was no significant difference between treatment groups for the occurrence of the primary endpoint of death, ischemic stroke or intracerebral hemorrhage (7.47% vs. 7.93% events per 100 patient-years, respectively; HR: 0.93, 95% CI: 0.79 to 1.10, p = 0.40). In a time-varying analysis using a Cox model, there was a marginal trend in the primary endpoint favoring a benefit with warfarin therapy versus aspirin therapy over time with an HR of 0.89 per year (95% CI: 0.80 to 0.998, p = 0.046) and HR of 0.76 favoring warfarin by year 4 (p = 0.04) (64). As in the WATCH trial, there was a significant reduction in ischemic stroke, 1 of the secondary endpoints, throughout the follow-up period with warfarin therapy compared to aspirin therapy (0.72% vs. 1.36%/year; HR: 0.52, 95% CI: 0.33 to 0.82, p = 0.005) but with significantly greater major hemorrhagic events (5.8% vs. 2.7%; OR: 2.2, 95% CI: 1.42 to 2.47, p < 0.001) (63,64). The reduction in stroke associated with warfarin therapy in patients with HF appeared similar to the reduction in stroke observed in patients treated with warfarin for AF (53). However, the overall stroke rate was lower in the HF population in sinus rhythm. Furthermore, there was no difference in the combined rate of intracranial and intracerebral hemorrhage between warfarin and aspirin therapy (0.8% vs. 0.8%) but the rate of major gastrointestinal hemorrhage was 3 times higher with warfarin therapy compared to aspirin therapy (3.2% vs. 1.4%; HR: 3.0, 95% CI: 1.30 to 4.38, p = 0.008). In contrast to the WATCH and WASH trials, aspirin therapy was not associated with an increased rate of hospitalization (61,63). The lack of an effect of warfarin therapy on death in this HF population in sinus rhythm suggests that the mechanism of death in these patients is not due to thromboembolism but may be mostly due to pump failure or ventricular arrhythmias (65).

In a recently reported subgroup analysis of the WARCEF trial, it was demonstrated that among 32 variables explored for an interaction with treatment, patients <60 years of age had a 37% reduction in the occurrence of the primary endpoint (HR: 0.63, 95% CI: 0.48 to 0.84, p = 0.001) as compared with no benefit observed in patients the ≥60 years of age group. Again, this benefit in patients <60 years of age was mainly driven by a significantly lower mortality rate that was not observed in patients ≥60 years of age. In addition, there was less major bleeding risk with warfarin therapy in the younger cohort (66).

The previous 4 randomized trials have important limitations. Enrollment was largely incomplete and all studies were underpowered to test the proposed hypothesis. Second, heterogeneous drug administration, a variable degree of underlying HF etiology, and varying definitions of the primary composite endpoint were observed. Finally, the WATCH and WARCEF trials did not have a placebo arm to evaluate the actual efficacy of antithrombotic therapy (63,64).

Meta-Analyses of Randomized Trials and Registry Data

In a meta-analysis that included 4,378 patients from the 4 randomized trials of chronic HF and reduced ejection fraction in SR, there was no difference in all-cause mortality (RR: 1.00, 95% CI: 0.88 to 1.13, p = 0.94), HF-related hospitalizations (RR: 1.16, 95% CI: 0.79 to 1.71, p = 0.45), and nonfatal MI (RR: 0.87, 95% CI: 0.63 to 1.21, p = 0.40) between warfarin and aspirin treatments. However, warfarin therapy compared to aspirin therapy was associated with a 41% reduction in all strokes (RR: 0.59, 95% CI: 0.41 to 0.85, p = 0.004) and 52% reduction in fatal and nonfatal ischemic strokes (RR: 0.48, 95% CI: 0.32 to 0.73,
NYHA class IV was counterbalanced by the increased risk of bleeding (67). The overall benefit from warfarin in this population appears counterbalanced by the increased risk of bleeding (67).

Another meta-analysis including the same patient population from the previous 4 randomized trials specifically addressed stroke prevention. The number needed to reduce 1 stroke was 61 and that needed to harm (major hemorrhage) was 34 for warfarin therapy (68). Warfarin did not increase mortality or confer an increased risk of intracerebral hemorrhage compared with aspirin.

The REDINSCOR (Red de investigación clínica y básica en insuficiencia cardíaca) registry included 2,263 patients with ejection fraction ≤35% and sinus rhythm without other anticoagulation indications and 26% of patients were receiving anticoagulation therapy. Anticoagulation therapy was associated with no significant differences in total mortality (14% vs. 12.5%) or stroke (0.8% vs. 0.9%), but was associated with a reduction in the combined endpoint occurrence of cardiac death, heart transplantation, coronary revascularization, and cardiovascular hospitalization in a propensity score–adjusted multivariate analysis (HR: 0.74, 95% CI: 0.56 to 0.97, p = 0.03) (69).

### Potential Role of New Anticoagulants

The new oral anticoagulants have been studied in comparison to warfarin mainly in AF patients and for treatment

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**Table 1: Randomized Antithrombotic Trials in Patients With Heart Failure**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment and Follow-Up</th>
<th>Primary Outcome</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WASH</strong> (Warfarin/Aspirin Study in Heart Failure)</td>
<td>HF: ≤35% LVEF n = 279</td>
<td>Randomized to no antithrombotic therapy, 300 mg aspirin, or warfarin (INR 2.5) Mean follow-up: 27 ± 1 month</td>
<td>Death, nonfatal MI, nonfatal stroke</td>
<td>26% no antithrombotic therapy, 32% aspirin, 26% warfarin</td>
<td>More HF hospitalization with aspirin or warfarin</td>
</tr>
<tr>
<td><strong>HELAS</strong> (HEart failure Long-term Antithrombotic Study)</td>
<td>HF: &lt;35% LVEF and NYHA functional class II to IV n = 197</td>
<td>HF pts were randomized to 325 mg aspirin or warfarin (INR 2–3) n = 115 DCM pts were randomized to warfarin (INR 2.5) or placebo Mean followup: 19 to 21 months</td>
<td>Nonfatal stroke, peripheral or PE, MI, re-hospitalization, exacerbation of HF or death</td>
<td>No significant difference between groups</td>
<td>Low n</td>
</tr>
<tr>
<td><strong>WATCH</strong> (Warfarin and Antiplatelet Therapy in Chronic Heart Failure)</td>
<td>HF &gt;3 months, in sinus rhythm + ≤35% LVEF n = 1,587</td>
<td>Randomized to open label warfarin (INR 2.5–3.0) + double-blind treatment to 162 mg aspirin or 75 mg clopidogrel Mean follow-up: &gt;12 months</td>
<td>First occurrence of death, nonfatal MI, or nonfatal stroke</td>
<td>Warfarin vs. aspirin: HR: 0.98, 95% CI: 0.86–1.12; p = 0.77 Clopidogrel vs. aspirin: HR: 1.08, 95% CI: 0.83–1.40; p = 0.57 Warfarin vs. clopidogrel: HR: 0.89, 95% CI: 0.68–1.16, p = 0.39</td>
<td>Lower stroke rate with warfarin More HF hospitalization with aspirin</td>
</tr>
<tr>
<td><strong>WARCEF</strong> (Warfarin versus Aspirin in patients with Reduced Cardiac Ejection Fraction)</td>
<td>HF: normal sinus rhythm, ≤35% LVEF n = 2,305</td>
<td>Randomized to warfarin (INR 2–3.5) or 325 mg aspirin Mean follow-up: 42 ± 18 months</td>
<td>First occurrence of ischemic stroke, intracerebral hemorrhage, or death for any cause</td>
<td>26.4% vs. 27.5%, HR: 0.93, 95% CI: 0.79–1.10; p = 0.40 Ischemic stroke 2.5% vs. 4.7%, HR: 0.52, 95% CI: 0.33–0.82; p = 0.005 Major hemorrhage 5.8% vs. 2.7%, HR: 2.21, 95% CI: 1.42–3.47, p &lt; 0.001 Hospitalization for HF 20.9% vs. 17.5%, HR: 1.12, 95% CI: 0.998–1.47; p = 0.053</td>
<td>No significant difference between groups. Lower ischemic stroke with warfarin offset by higher major hemorrhage.</td>
</tr>
</tbody>
</table>

CI = confidence interval; DCM = dilated cardiomyopathy; HF = heart failure, HR = hazard ratio, INR = international normalization ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PE = pulmonary embolism.

p = 0.0006, and a 2-fold increased risk of major hemorrhage (RR: 2.02, 95% CI: 1.45 to 2.80, p = 0.0001). Thus, the overall benefit from warfarin in this population appears counterbalanced by the increased risk of bleeding (67).
of and prophylaxis against VTE. In a recent meta-analysis of trials in patients with AF, new oral anticoagulants were 22% more effective in the prevention of stroke compared to warfarin (RR: 0.78, 95% CI: 0.67 to 0.92) and there was a significantly reduced risk of intracranial hemorrhage (RR: 0.49, 95% CI: 0.36 to 0.66) (70). Based on the data from the Danish National Patient Registry, the new anticoagulants were superior to warfarin for net clinical benefit regardless of the risk of bleeding in patients at high risk of stroke—CHADS(2) score ≥1 or CHA2DS2-VASc ≥2. The benefit was more prevalent when stroke risk and bleeding risk were high (71).

**Bivalirudin.** In a pooled analysis of randomized trials of bivalirudin therapy that included 14,258 ACS patients treated with dual antiplatelet therapy, bivalirudin therapy compared with heparin plus glycoprotein (GP) IIb/IIIa inhibitor therapy was significantly associated with lower mortality risk in patients with <35% LVEF (random RR: 0.47, 95% CI: 0.30 to 0.72, p = 0.0004), which was consistent across studies. However, the benefit of bivalirudin therapy was attenuated in patients with ≥35% LVEF (pooled analysis RR: 0.92, 95% CI: 0.72 to 1.17, p = 0.50) (72). Similarly, in the PREMIER (Prospective Registry Evaluating Outcomes After Myocardial Infarctions: Events and Recovery) registry, a 37% RR reduction in in-hospital mortality (p < 0.0001) was reported in patients with HF who were treated with bivalirudin compared to heparin plus a GPIIb/IIIa inhibitor (73). These hypothesis-generating data suggest a potential benefit of direct thrombin inhibition in HF patients in the setting of ACS.

**Dabigatran.** In the RE-LY trial (Randomized Evaluation Long-term anticoagulant therapy), a fixed dose (110 mg or 150 mg twice daily) of dabigatran was compared for noninferiority for the prevention of stroke or systemic embolism versus adjusted-dose warfarin in patients with AF. This trial demonstrated that 110 mg twice daily dose of dabigatran was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage compared with warfarin whereas 150 mg twice daily dose of dabigatran was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage compared to warfarin. Among 4,904 patients enrolled with symptomatic HF, there was no significant interaction with treatment effect with both 100 and 150 mg doses of dabigatran (p for interaction = 0.42 and 0.33, respectively) (74).

**Apixaban.** In the ARISTOTLE trial (Apixaban for Reduction In Stroke and Other Thromboembolic Events in atrial fibrillation), 5 mg twice daily apixaban was superior to warfarin in the prevention of stroke or systemic embolism
and was associated with less major bleeding and lower mortality compared to warfarin (target INR 2.0 to 3.0) in patients with AF. One-third of patients had HF or reduced LVEF in this trial and similar to the RE-LY trial, there was no significant interaction with treatment effect (p for interaction = 0.50) (75).

In the APPRAISE-2 trial (Apixaban for Prevention of Acute Ischemic Events 2), a 5 mg twice daily dose of apixaban in addition to standard antiplatelet therapy was associated with no significant reduction in recurrent ischemic events but an increased incidence of major bleeding events in patients with a recent ACS and at least 2 additional risk factors for recurrent ischemic events. The trial was terminated prematurely for the high bleeding rate in the apixaban arm. In this trial, 28% of patients had HF. There was a 23% reduction in the occurrence of the primary endpoint with apixaban versus placebo (HR: 0.77, 95% CI: 0.58 to 1.02) in patients with HF compared to 5% increase in the occurrence of the primary endpoint in patients without HF (HR: 1.05, 95% CI: 0.86 to 1.29, p for interaction = 0.08) (76).

Rivaroxaban. In the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), rivaroxaban was compared to warfarin for the prevention of ischemic stroke in AF patients; ~60% of the population had HF. Rivaroxaban therapy was noninferior to warfarin for the prevention of stroke or systemic embolism. Major bleeding was similar between the groups and rivaroxaban was associated with less frequent intracranial and fatal bleeding. In a subgroup analysis, there was no significant interaction between treatment with rivaroxaban and the presence of HF (p for interaction = 0.419) (77).

In the ATLAS ACS–TIMI 51 trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51), 2 dose regimens of rivaroxaban (2.5 mg twice daily and 5.0 mg twice daily) were compared with placebo in patients with ACS. Nearly 10% of patients had HF and in this subgroup, rivaroxaban 2.5 mg twice daily dose was associated with a lower rate of occurrence of the primary endpoint compared with placebo (10.1% vs. 16.8%). Although the confidence intervals were wide in the HF group, there was no difference in the first occurrence of treatment-emergent non–coronary artery bypass graft related TIMI major bleeding events. However, in patients without HF, there was no apparent difference in the primary endpoint occurrence between the rivaroxaban group and placebo (5.5% vs. 6.0%). There was higher non–coronary artery bypass graft related TIMI major bleeding (1.4% vs. 0.4%) in the rivaroxaban group (78).

In a small study of patients with acute decompensated HF and patients with New York Heart Association functional class III/IV HF, the pharmacodynamics and pharmacokinetics of rivaroxaban were similar. In patients with functional class III/IV HF treated with placebo, prothrombin fragment 1.2 increased over 7 days whereas rivaroxaban therapy (10 mg once daily) was associated with a reduction in prothrombin fragment 1.2. A nonsignificant reduction in the rate of D-dimer and thrombin-antithrombin complex increase over time was also associated with rivaroxaban therapy (79).

There are only 2 trials undergoing involving treatment with antiplatelet and new oral anticoagulants as given in Table 3.

**Meta-Analysis of New Oral Anticoagulants**

In a recent semisystematic review and meta-analysis of phase III trials (ARISTOTLE, RE-LY, and ROCKET-AF) including 44,563 patients with AF, new OAC treatment was not associated with a significant reduction in stroke and systemic embolism compared with warfarin among patients with HF (n = 21,095, OR: 0.91, 95% CI: 0.78 to 1.06, p = 0.22) but was associated with 24% reduction in patients without HF (OR: 0.76, 95% CI: 0.67 to 0.87, p < 0.0001). The definitions of HF in the 3 trials were not uniform. In the RE-LY trial, HF was defined as ejection fraction <40% by echocardiogram, radionuclide, or contrast angiogram within 6 months, or symptoms of New York Heart Association functional class >II HF within 6 months. In the ROCKET AF trial, the definition included symptoms of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Trials of Antiplatelet Agents and New Oral Anticoagulants in Patients With Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the Study</td>
<td>Patients</td>
</tr>
<tr>
<td>COMMANDER HF</td>
<td>HF (EF ≤40%) + CAD</td>
</tr>
<tr>
<td>NCT01877915 (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Patients With Heart Failure and Coronary Artery Disease)</td>
<td>n = 5,000</td>
</tr>
<tr>
<td>Platelet Inhibition in Patients With Systolic Heart Failure</td>
<td>New York Heart Association functional class III to IV (EF&lt;35%)</td>
</tr>
<tr>
<td>NCT01768400</td>
<td>n = 50</td>
</tr>
</tbody>
</table>
Guidelines

The European and American guidelines for the treatment of patients with AF are presented in Table 4 (80–82). According to the 2012 European Society of Cardiology guidelines, “other than in patients with AF (both HF with reduced and preserved ejection fraction), there is no evidence that an OAC reduces mortality and morbidity compared with placebo or aspirin” (80). A similar view also has been provided by the recent consensus document from the European Society of Cardiology Heart Failure Association and the European Society of Cardiology Working Group on Thrombosis as follows: “Given no overall benefit of warfarin on rates of death and stroke, with an increase in major bleeding—despite the potential for a reduction in ischemic stroke—there is currently no compelling reason to use warfarin routinely for all HF patients in sinus rhythm” (53). The 2009 updated American College of Cardiology/American Heart Association guidelines acknowledged the availability of limited data for the recommendation of OAC use in patients with HF, but it recommends OAC in HF patients with a previous thromboembolic event (82).

Finally, the 2010 Heart Failure Society of America guidelines for HF or systolic dysfunction recommend that “Treatment with warfarin (goal INR 2.0 to 3.0) is recommended for all patients with HF and chronic or documented paroxysmal, persistent, or long-standing AF or a history of systemic or pulmonary emboli, including stroke or transient ischemic attack, unless contraindicated,” and “Antithrombotic therapy is recommended to reduce vascular events in patients with HF and CAD unless contraindicated” (81).

Conclusions

Heart failure is a common clinical problem with a prevalence of 1% to 2% in the general population that is increasing due to the aging population. Despite the heightened risk for stroke and thromboembolism in patients with HF and AF, in patients with systolic HF in sinus rhythm, the level of increased thromboembolic risk is less clear. The decision to treat patients with HF with antithrombotic therapy remains largely influenced by the presence or absence of concomitant arterial disease. Antithrombotic therapy has been shown to be effective in many forms of cardiac disease, including patients with HF and AF. However, the utility of oral anticoagulant and/or antithrombotic therapy has never been evaluated in an adequately powered dedicated clinical trial of HF patients in sinus rhythm. Although it is clear that platelet activation and hypercoagulability are present in HF, and there is evidence that stroke is reduced by warfarin therapy in the HF patient, the available data suggest that the risk of major bleeding overshadows the antithromboembolic benefit in HF patients in sinus rhythm. These findings have been reflected in the guidelines.

The CHADS2 and HAS-BLED risk scores may be helpful to select patients for future studies of antithrombotic therapy in the setting of HF and sinus rhythm. The window
of greatest advantage for antithrombotic therapy may be early after initial presentation, when a markedly increased risk of death, and death or stroke, has been reported. Selecting patients for enrollment may also be facilitated by objective assessments of thrombogenicity using laboratory testing. Thromboelastography is a potential method that determines platelet function in addition to thrombin generation and the viscoelastic characteristics of the platelet-fibrin clot. Large-scale, adequately, powered trials that have refined selection criteria, possible including laboratory testing, will be needed to establish the role of antithrombotic therapy in the HF patient in sinus rhythm.

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REFERENCES

41. Connolly S, Pogue J, Hart R, et al., ACTIVE Writing Group of the
42. Harvey WP, Finch CA. Dicumarol prophylaxis of thromboembolic
43. Cleland JGF, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in
44. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and
46. Hart RG, Pearce LA, Aguilir MI. Meta-analysis: antithrombotic
47. You JJ, Singer DE, Howard PA, Lane DA, et al. American College of
48. Eriksson N, Wadelius M. Prediction of warfarin dose: why, when and
49. Weitz JI. Factor Xa and thrombin as targets for new oral anticoagu-
51. De Caterina R, Husted S, Wallentin L, et al., Coordinating Com-
54. Homma S. Warfarin versus aspirin in patients with reduced cardiac ejec-
56. Grif
60. 2010;121:569–83.
66. Hylek E, Singer D. Risk factors for intracranial hemorrhage in out-
70. Weitz JL. Factor Xa and thrombin as targets for new oral anticoagu-
74. Lip GY, Ponikowski P, Andreotti F, et al., ESC Task Force. Thrombo-
76. Griffith GC, Stragnell R, Levinson DC. A study of the benefi-
80. Hart RC, Tyberg VE, Tori-Pederson C, Lip GY. Net clinical bene-
94. McMurray JJ, Adamopoulos S, Anker SD, et al., ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: theTask Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33 Suppl 1:393.
101. McMurray JJ, Adamopoulos S, Anker SD, et al., ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33 Suppl 1:393.

Key Words: anticoagulant • antiplatelet • heart failure.