

Thromboembolism and Antithrombotic Therapy in Patients With Heart Failure in Sinus Rhythm

Current Status and Future Directions

Luca Bettari, MD; Mona Fiuzat, PharmD; Richard Becker, MD; G. Michael Felker, MD; Marco Metra, MD; Christopher M. O'Connor, MD

Heart failure (HF) represents a major and growing public health problem because of its prevalence, incidence, morbidity, mortality, and economic costs. The prevalence of HF is 2% to 3% of the general population.¹ Five million Americans are affected, with >550 000 cases diagnosed each year.² The mortality rate from severe HF remains >60% within 5 years of diagnosis, and 50% of hospitalized patients with HF require readmission within 6 months of discharge. In the US estimated costs amount to > \$35 billion per year.³

Although several therapies (eg, β -blockers, angiotensin-converting enzyme [ACE] inhibitors, and cardiac resynchronization therapy) have been proven effective in improving HF outcomes, many unanswered questions about optimal treatment remain. One area of ongoing uncertainty is the appropriate role for antithrombotic therapy in patients with HF. Observational data suggest that patients with HF have an increased venous thromboembolism (VTE) risk (deep venous thromboembolism [DVT], pulmonary embolism [PE], peripheral arterial thromboembolism, and stroke).⁴ These epidemiological findings are supported by multiple mechanisms that can contribute to a hypercoagulable state in patients with HF. Despite this increased risk of VTE, the role of antithrombotic therapy remains unclear. In this article, we provide an overview of epidemiology, pathophysiology, clinical trial data, and therapeutic recommendations for prevention of thromboembolism in HF.

Search Strategy

We searched PubMed for articles published between 1958 and 2010 using the following search terms: *epidemiology of heart failure, thromboembolism and heart failure, thrombogenesis and heart failure, anticoagulation in heart failure, antiplatelet agent and heart failure, aspirin and heart failure, bleeding risk and anticoagulation, and aspirin and angiotensin-converting enzyme inhibitors*. We also studied abstracts from national and international cardiovascular meetings to identify unpublished studies using the key words *anticoagulation* and *dilated cardiomyopathy*.

Epidemiology

Data from published observational studies and secondary analyses of randomized controlled trials (RCTs) indicate that patients with HF have a higher risk for VTE than the general population.

Observational Cohorts

DVT and PE

Several case-cohort studies have shown that HF is associated with a 2- to 3-fold increased risk of DVT and PE compared with other medical conditions.⁵ Retrospective analyses report an annual VTE incidence of 1.0% to 4.5% in patients with HF.⁶ In RCTs of thromboprophylaxis in hospitalized patients with HF followed for 90 days, DVT rates ranged from 4.0% to 14.6%.^{7,8} The Prophylaxis in Medical Patients With Enoxaparin trial evaluated VTE incidence in hospitalized patients with (n=353) and without (n=749) HF during a follow-up of 14 days after discharge and found that 15% of patients with HF not treated with enoxaparin developed VTE.⁹ Beemath et al,⁴ using data from the National Hospital Discharge Survey, found an increased risk of VTE in hospitalized patients with HF compared to those without HF, with a relative risk of 2.15 for PE and 1.21 for DVT. Darze et al¹⁰ found that 9% of patients with HF admitted to the coronary care unit developed PE during their hospital stay and that 44% of those patients had concomitant DVT.

Stroke

The annual rate of stroke in the general population is 0.1% to 0.5% at age 80 years, whereas in the HF population, it is 1.0% to 3.5%, with a possible relationship between low left ventricular ejection fraction (LVEF) and stroke risk.¹¹ In the Northern Manhattan Study, 270 patients hospitalized with initial occurrence of ischemic stroke were compared with 288 matched controls. Decreased LVEF of any severity was found to be associated with ischemic stroke, even after adjusting for other risk factors ($P<0.0001$).¹²

LV Thrombi

There is an increased risk for LV thrombus formation in HF. LVEF is the most important risk factor for thrombus forma-

Received October 21, 2010; accepted January 25, 2011.

From the Section of Cardiovascular Diseases, University of Brescia, Brescia, Italy (L.B., M.M.), and Duke Clinical Research Institute, Durham, NC (L.B., M.F., R.B., G.M.F., C.M.O.).

Correspondence to Luca Bettari, MD, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC 27705. E-mail luca_bettari@yahoo.it

(*Circ Heart Fail.* 2011;4:361-368.)

© 2011 American Heart Association, Inc.

Circ Heart Fail is available at <http://circheartfailure.ahajournals.org>

DOI: 10.1161/CIRCHEARTFAILURE.110.959957

Table 1. VTE Incidence in HF RCTs

RCT	No. Patients	LVEF, %	AF, %	VTE, %/y	Anticoagulants-Antiplatelet Agents, %	Follow-Up, y	Considerations
SOLVD	6378	31	0	2.1	9–46	3.3	Higher VTE in women with lower LVEF No lower VTE with warfarin Lower VTE with aspirin
SAVE	2231	31	10	1.5	28–14	3.5	Higher VTE with lower LVEF and older age Lower VTE with warfarin or aspirin
V-HeFT I	642	30	16	2.7	19–13	2.3	Higher VTE with lower LVEF and peak $\dot{V}O_2$ No higher VTE with AF No lower VTE with warfarin Lower VTE with aspirin
V-HeFT II	804	29	15	2.1	21–27	2.6	Higher VTE with lower LVEF and peak $\dot{V}O_2$
SCD-HeFT	2114	25	9	3.4	28–59	3.8	No higher VTE with AF No lower VTE with warfarin or aspirin Higher VTE with lower LVEF and hypertension No lower VTE with warfarin

Data are provided as means. AF indicates atrial fibrillation; HF, heart failure; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; SAVE, Survival and Ventricular Enlargement; SCD-HeFT, Sudden Cardiac Death-Heart Failure Trial; SOLVD, Studies of Left Ventricular Dysfunction; V-HeFT, Veterans Affairs Vasodilator-Congestive Heart Failure Trials; $\dot{V}O_2$, oxygen consumption; VTE, venous thromboembolism.

tion, whereas severe mitral regurgitation may have a protective effect by decreasing blood stasis.¹³ Notably, up to 30% of patients with HF may have evidence of intracardiac thrombi on echocardiography, but their presence may not be predictive of systemic embolism, and anticoagulation has not been associated with a clear VTE reduction.¹⁴ Studies suggest an increased embolic risk associated with LV thrombi, especially when they protrude into the LV cavity and are associated with apical aneurysm or are mobile.¹⁵

Retrospective Analyses of RCTs

In the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment cohorts, VTE annual incidence (stroke, PE, and peripheral emboli) in patients with HF (LVEF <35%) in sinus rhythm was 2.4% and 1.8% in women and men, respectively. Multivariate analysis found that lower LVEF was associated with VTE risk only in women, with a 53% increased risk rate for every 10% LVEF reduction.¹⁶

In the Veterans Affairs Vasodilator-Congestive Heart Failure Trials (V-HeFT I and II), which included both patients in sinus rhythm and with atrial fibrillation (AF), VTE incidence was 2.7 and 2.1 per 100 patient-years in V-HeFT I and II, respectively. Notably, 15% of the patients had AF, but this was not independently associated with VTE increase. These analyses also revealed that individuals experiencing VTE have greater HF severity (lower peak oxygen consumption [$P<0.03$ and $P<0.001$] and lower LVEF [$P=0.1$ and $P=0.07$ in V-HeFT I and II, respectively]).⁶

The Survival and Ventricular Enlargement (SAVE) trial enrolled 2231 patients with LV dysfunction after myocardial infarction (MI). The VTE annual rate (fatal and nonfatal stroke) was 1.5%. The estimated 5-year rate of stroke was 8.1%, with a 2-fold increase in stroke risk in patients with LVEF $\leq 28\%$ and an 18% stroke risk increase for every 5% LVEF reduction.¹⁷

In an analysis of the Sudden Cardiac Death-Heart Failure Trial, which excluded all patients with AF at the time of

randomization, 3.4% of the 2114 patients experienced VTE. A trend toward an increase in incidence of embolic complications with lower LVEF was observed (3.5%, 3.6%, and 4.6% with LVEF 30% to 35%, 20% to 30%, and <20%, respectively). Overall, the 4-year survival analysis found that VTE rate was 4.0%, with an annual incidence of 1%.¹¹ VTE incidence in HF RCTs is summarized in Table 1.

Pathophysiology

The mechanisms leading to increased VTE risk in HF are multifactorial and relate to the Virchow Triade (abnormal blood constituents, blood flow, and vessel wall), which defines a hypercoagulable state¹⁸ (Figure 1). Blood constituent abnormalities are due to platelet and thrombin activation, which result in abnormal coagulation and increased plasma viscosity. In HF, there is evidence of reduced platelet survival time, increased mean platelet volume, and greater platelet activation.¹⁹ Patients with HF demonstrate high levels of circulating fibrinogen, fibrinopeptide A, and D-dimer determined by high plasma norepinephrine concentration or low LVEF.²⁰ Higher levels of angiotensin and endothelin commonly seen in patients with HF increase levels of von Willebrand factor (VWF). Elevated tissue plasminogen activator antigen levels have been shown to be an independent predictor of prognosis in patients with chronic stable HF. C-reactive protein levels can directly increase tissue factor and induce expression of cytokines with prothrombotic properties.²¹ Moreover, patients with HF show increased plasma concentration of β -thromboglobulin, platelet-bound P-selectin, platelet/endothelial cell adhesion molecule-1, platelet surface P-selectin, CD40L, and osteonectin. Thrombin activity has 2 highly sensitive markers that are fibrinopeptide A and thrombin-antithrombin III complexes.²² An increase in these factors is associated with increased VTE risk. Patients with HF also show high levels of fibrinogen and D-dimer, which correlate with the severity of the disease, and decreased levels of ADAMTS-13, a protease that cleaves VWF,²³ thereby increasing circulating VWF. Indeed, de-

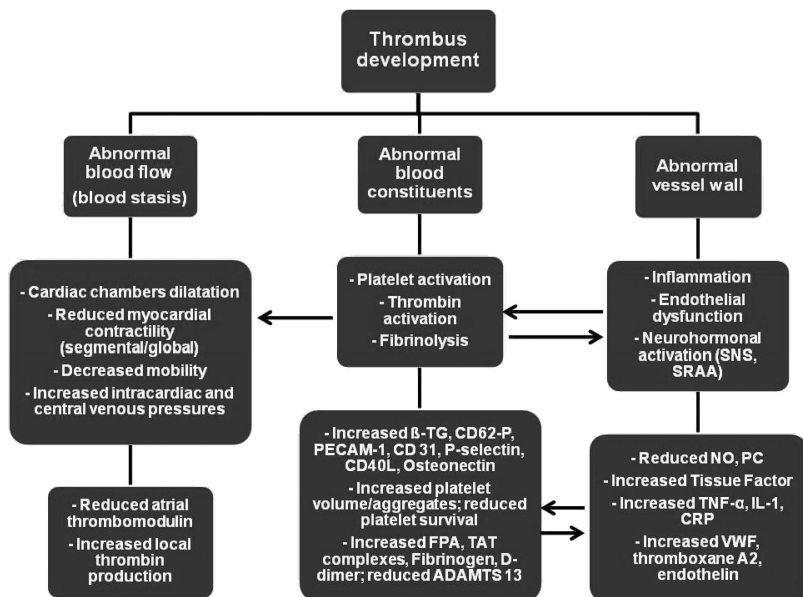


Figure 1. Hypercoagulable state and thrombogenesis. β -TG indicates β -thromboglobulin; CD31, endothelial cell adhesion molecule; CD62-P, platelet-bound P-selectin; CRP, C-reactive protein; FPA, fibrinopeptide A; IL-1, interleukin-1; NO, nitric oxide; PC, prostacyclin; PECAM-1, platelet cell adhesion molecule-1; SNS, sympathetic nervous system; SRAA, renin-angiotensin-aldosterone system; TAT, thrombin-antithrombin III; TNF- α , tumor necrosis factor α ; VWF, von Willebrand factor.

creased ADAMTS13 and increased circulating VWF were found to be significant predictors of clinical events in HF.²⁴

Blood flow abnormalities are due to blood stasis because of the dilatation of cardiac chambers, reduced myocardial contractility, increased intracardiac and central venous pressures, and immobility due to severe HF. Chronic impairment of blood flow leads to tissue hypoperfusion and related ischemic metabolic changes that, in turn, support the development of permanent oxidative stress leading to the activation of platelets, leukocytes, and endothelial cells and production of proinflammatory cytokines.²⁵ Because the endothelium is oxygenated directly by the blood in the vessel lumen, endothelial cells are particularly sensitive to ischemia. Recent studies have shown that ischemia induces expression of the adhesion molecule P-selectin on endothelial cells, which, subsequently, stimulates leukocytes to infiltrate the ischemic vessel wall and upregulate tissue factor expression on their surfaces.²⁶ Moreover, downregulation of thrombomodulin at the endothelial surface, mediated by interleukin-1 and tumor necrosis factor α , decreases the natural anticoagulant protein C effects.²⁷ Additionally, increased plasma concentrations of tumor necrosis factor α and interleukin-1 inhibit the endogenous fibrinolytic system, resulting in inadequate fibrin removal and possibly thrombosis. The increase of intracardiac and central venous pressures inhibits the release of atrial thrombomodulin, resulting in an increase in local thrombin production.²⁸ Kapur et al²⁸ demonstrated that acute elevation of left atrial pressure inhibits production of atrial thrombomodulin, resulting in downregulation of endocardial thrombomodulin expression and thus increasing local thrombin production.

Vessel wall abnormalities are due to inflammation, endothelial dysfunction, and neurohormonal activation. Endothelial dysfunction with decreased levels of nitric oxide causes increased monocyte and platelet adhesion. Tissue factor, a procoagulant, can be increased by tumor necrosis factor α and interleukin-1, which have been shown to be higher in HF.

Activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, which is fundamental to the development and progression of HF, is characterized by increased release of catecholamines, angiotensin II, and aldosterone. These directly influence the metabolism and function of endothelial cells, decreasing nitric oxide bioavailability and prostacyclin production, and increase VWF release, thromboxane A2, and endothelin, which may contribute to increased peripheral vasoconstriction, exacerbation of vessel wall ischemia, and promotion of thrombogenesis.²⁹

Taken together, these data strongly suggest an extensive cross-talk between inflammatory and coagulation pathways. Additionally, they provide a link between inflammation and thrombosis in HF, making HF a prothrombotic condition.

Evidence for Antithrombotic Therapy in HF

Retrospective Analyses

In a post hoc analysis of the SOLVD trials, warfarin was associated with a reduction of all-cause mortality, risk of death, and HF hospitalization ($P=0.0006$). However, there was no reduction in the incidence of VTE.¹⁴ Likewise aspirin was associated with a decrease in all-cause mortality ($P=0.0005$), risk of death, and HF hospitalization, and these effects were significant in the placebo but not in the enalapril group. Aspirin also was associated with lower VTE incidence, which was statistically significant in women, with a 53% relative risk reduction ($P=0.03$).³⁰ In V-HeFT I and II, which included patients either in sinus rhythm or with AF, anticoagulation had no protective effect on VTE. Indeed, the VTE incidence was higher in patients treated with warfarin than in those without anticoagulant therapy ($P=0.01$). In V-HeFT I, a trend toward VTE reduction was observed in patients treated with aspirin compared with those not treated with antiplatelet therapy ($P=0.07$), but these associations were not present in the V-HeFT II ($P=0.48$).⁶

Thus, anticoagulants or antiplatelet agents did not show a clear benefit in survival and VTE risk in retrospective analyses of HF RCTs. Different results have been shown in

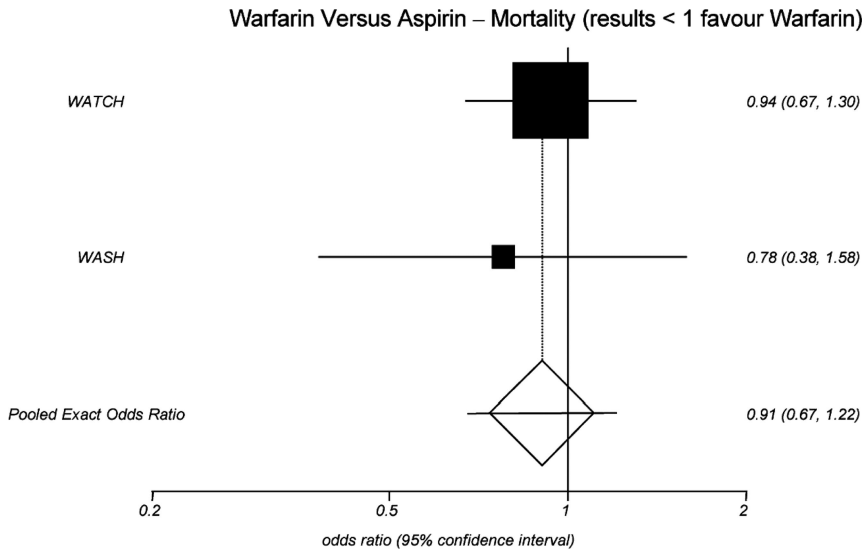


Figure 2. Meta-analysis of randomized controlled trials comparing warfarin with aspirin on death, myocardial infarction, and stroke in patients with heart failure. WASH indicates Warfarin/Aspirin Study in Heart Failure; WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart Failure. Reprinted with permission from Cleland et al.³³ Copyright © 2004 Oxford University Press.

post-MI trials. In the SAVE trial, warfarin use was associated with an 81% reduction in the stroke risk ($P=0.001$), and patients taking aspirin had a 56% lower incidence of stroke after MI, with the protective effect more evident in patients with LVEF $<28\%$ ¹⁵ (Table 1). One important caveat to retrospective analyses of warfarin therapy is that they do not systematically collect or monitor adequacy of anticoagulation (ie, time with a therapeutic international normalized ratio [INR]), making prospective studies of warfarin critical for understanding efficacy and safety.

Prospective RCTs

To date, 3 multicenter RCTs have investigated the safety and efficacy of antithrombotic therapy in HF. The Warfarin/Aspirin Study in Heart Failure (WASH) was an open-label trial with 3 arms that compared no antithrombotic therapy, aspirin (300 mg/d), or warfarin (target INR, 2.5) in 279 patients with HF (LVEF $<35\%$) in sinus rhythm. The primary end point was the composite of death, nonfatal MI, and nonfatal stroke. There was no significant difference in the primary end point among the study groups. The mean INR throughout the follow-up period was 2.3. Over a mean follow-up of 27 months, there was a trend toward worse outcomes (cardiovascular hospitalization, especially worsening HF) among patients randomized to aspirin ($P<0.044$). The incidence of minor bleeding was greater in the aspirin and warfarin groups compared with the no antithrombotic treatment group ($P<0.033$). A trend toward increased systolic blood pressure was observed with aspirin. Overall, the study did not demonstrate superiority of warfarin over no antithrombotic therapy for any primary or secondary measure. Warfarin was generally associated with more favorable outcomes and fewer serious adverse events (except for minor bleeding events) than either aspirin or no antithrombotic therapy. Because of a low rate of enrollment, the study was terminated prematurely and, thus, was not powered to make conclusive statements.³¹

In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) study, 1587 patients with HF (LVEF $<35\%$) in sinus rhythm were randomized to either open-label

warfarin (target INR, 2.5) or double-blind, double-dummy treatment with either aspirin (162 mg/d) plus placebo or clopidogrel (75 mg/d) plus placebo. The primary outcome was the time to first occurrence of death, nonfatal MI, or nonfatal stroke. Among baseline characteristics, the only intergroup difference that reached statistical significance was the prevalence of diabetes, which was highest in the warfarin group (38%) and lowest in the clopidogrel group (31%). The mean INR was 2.6. No differences were found among the 3 study groups with regard to the primary outcome. However, warfarin was associated with fewer nonfatal strokes than aspirin or clopidogrel. More patients randomized to aspirin were hospitalized for worsening HF ($P<0.02$) compared with the warfarin group. Major and minor bleeding events were higher in the warfarin group than in the clopidogrel group ($P<0.01$ and $P<0.025$, respectively) and the aspirin group ($P=0.22$ and $P=0.054$, respectively). Thus, the WATCH trial did not show that warfarin is superior to aspirin or that clopidogrel is superior to aspirin with regard to reduction of major cardiovascular event rate. The higher number of patients with diabetes in the warfarin group, with their higher risk, could have confounded the effectiveness of warfarin with regard to VTE reduction. As with WASH, the WATCH study was stopped prematurely because of a low rate of enrollment and, therefore, lacked power to make conclusive statements.³²

A meta-analysis of the data from WATCH and WASH studies found a modest trend in favor of lower mortality rate with warfarin compared with aspirin and suggested that a substantial difference in mortality or vascular events cannot be excluded (Figure 2); however, these findings are driven primarily by WATCH results because of its much larger sample size relative to WASH (1587 versus 279). A potentially important observation was an increased rate of hospitalizations in the aspirin group compared with warfarin group, which suggests a possible negative interaction between aspirin and ACE-inhibitors.³³

The Heart Failure Long-Term Antithrombotic Study was conducted in 197 patients with HF (LVEF $<35\%$) in sinus rhythm. Patients with ischemic heart disease were random-

Table 2. RCTs on Antiplatelet vs Anticoagulation Therapy in HF

RCT	No. Patients	Therapy	End Points	Results/Considerations
HELAS*	197	IHD: warfarin (INR, 2–3) vs aspirin (325 mg) DCM: warfarin (INR, 2.5) vs placebo	Death, stroke, re-MI Rehospitalization, PE, HF exacerbation	Trend toward benefit with warfarin in IHD
WASH*	279	Warfarin (INR, 2–3) vs aspirin (300 mg)	Death, MI, stroke	More HF hospitalization with aspirin More major bleeding with warfarin
WATCH*	1587	Warfarin (INR, 2–3) vs aspirin (162.5 mg)/clopidogrel (75 mg)	Death, MI, stroke	More HF hospitalization with aspirin More major bleeding with warfarin Fewer strokes with warfarin
WARCEF	2860 (target)	Warfarin (INR, 2.5–3) vs aspirin (325 mg)	Death, stroke	

DCM indicates dilated cardiomyopathy; HELAS, Heart Failure Long-term Antithrombotic Study; IHD, ischemic heart disease; INR, international normalized ratio; MI, myocardial infarction; PE, pulmonary embolism; WARCEF, Warfarin Aspirin Reduced Cardiac Ejection Fraction; WASH, Warfarin/Aspirin Study in Heart Failure; WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart Failure. Other abbreviations as in Table 1.

*No significant difference—underpowered.

ized to receive either aspirin (325 mg/d) or warfarin (target INR, 2 to 3). Patients with dilated cardiomyopathy were randomized to receive either warfarin (target INR, 2.5) or placebo. Primary end points were nonfatal stroke, PE, MI, rehospitalization, HF exacerbation, or all-cause death. Patients with dilated cardiomyopathy were younger, were more likely to be women, and had lower LVEF and larger LV end-diastolic and end-systolic volume compared with those with ischemic heart disease. Baseline medication did not differ markedly between groups. The incidence of primary end points was not different between the groups; however, there was a trend toward benefit for warfarin over placebo in the dilated cardiomyopathy group. During 2 years of follow-up, the event rate was very low. This study also was underpowered to make definitive conclusions.³⁴

Taken together, these 3 RCTs show that VTE is rare in patients with HF in sinus rhythm regardless of treatment. Although they suggest a possible benefit of warfarin, all these studies were underpowered to provide definitive evidence.

The Warfarin Aspirin Reduced Cardiac Ejection Fraction is a multicenter, randomized, double-blind trial in patients with HF (LVEF <35%) in sinus rhythm (target, 2860 patients) designed to test the primary null hypothesis of no difference between warfarin (target INR, 2.5 to 3) and aspirin (325 mg/d) in 3- to 5-year event-free survival for the composite end point of death or stroke. Secondary analyses will compare warfarin and aspirin for reduction of all-cause mortality, ischemic stroke, and MI balanced against the risk of intracerebral hemorrhage and focus on women and blacks and will compare warfarin and aspirin for prevention of stroke alone.³⁵ Recruitment is ongoing. RCTs on antithrombotics in HF are summarized in Table 2.

Does Aspirin Adversely Influence Outcomes in HF?

Previous analyses and RCTs have suggested a potential untoward effect of aspirin on HF hospitalizations. Prostaglandins, which cause vasodilation of the afferent arterioles of the glomeruli, are negatively affected by aspirin. Moreover, an interaction between aspirin and ACE-inhibitors is possible. One potential mechanism is that aspirin may inhibit prostaglandin synthesis, blunting the vasodilator effects of ACE-

inhibitors.³⁶ This has led to the hypothesis that aspirin is harmful in HF.

In addition to the RCTs previously described, untoward effects of aspirin have been suggested by other studies. In SOLVD, antiplatelet agents were associated with an 18% reduction in all-cause mortality ($P=0.0005$). This beneficial effect was seen especially in women, who had a 53% reduction in VTE risk ($P=0.03$) compared with only 23% in men ($P=0.06$).¹⁴ However, a potential interaction between antiplatelet therapy and enalapril was detected, with patients taking antiplatelet therapy and randomized to enalapril experiencing no mortality benefit. Similarly, in the Cooperative New Scandinavian Enalapril Survival Study II, patients receiving aspirin experienced a significant increase in mortality with enalapril treatment ($P=0.047$), whereas those not receiving aspirin experienced no effect.³⁷

A recent analysis of the Organized Program to Facilitate Life-Saving Treatment in Hospitalized Patients With Heart Failure registry did not find any statistically significant association between the combination of aspirin and ACE-inhibitors or angiotensin-II receptor blockers and adverse effects on intermediate postdischarge outcomes.³⁸ Similarly, an analysis from the Candesartan in Heart failure-Assessment of Reduction in Mortality and Morbidity program failed to show an interaction between aspirin administration (4246 patients [55.9%]) and the effects of candesartan compared with placebo on cardiovascular event rates (hazard ratio for the primary outcome in the patients receiving aspirin, 0.81; 95% CI, 0.72 to 0.90; hazard ratio in the others, 0.81; 95% CI, 0.72 to 0.91). There was also no interaction between aspirin and candesartan with regard to discontinuation of the study drug because of adverse reactions. The authors concluded that there seems to be no significant modification of the benefit of candesartan on cardiovascular mortality and morbidity outcomes or safety by concomitant use of aspirin in patients with chronic HF.³⁹

A retrospective, systematic review of 6 long-term RCTs on HF treatment with ACE-inhibitors (SAVE, Trandolapril Cardiac Evaluation, Acute Infarction Ramipril Efficacy, SOLVD, and Heart Outcomes Prevention and Evaluation) did not show any significant differences in the major clinical outcomes in the presence or absence of aspirin administra-

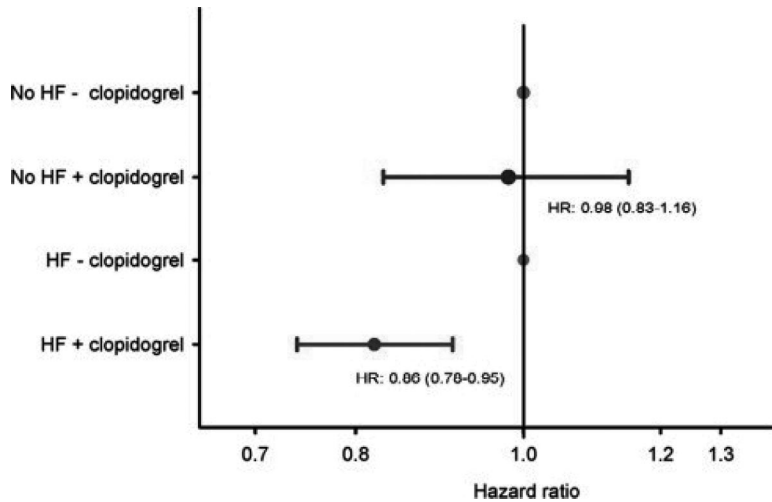


Figure 3. Hazard ratios for death according to clopidogrel. HF indicates heart failure; HR, hazard ratio. Reprinted with permission from Bonde et al.⁴² Copyright © 2010 Elsevier.

tion.⁴⁰ A Cochrane systematic review of trials of antiplatelet agents versus control or anticoagulants for patients with HF in sinus rhythm found no evidence to recommend routine use of aspirin to prevent thromboembolism and a possible adverse interaction with ACE-inhibitors. Moreover, when compared with aspirin, there was some evidence to indicate superior effects of warfarin with regard to hospitalizations.⁴¹ However, these analyses are limited by several factors: retrospective nature of the studies, antiplatelet agent use not having been randomized, the insufficient number of either VTE or patients enrolled, and the 3 RCTs to date being terminated prematurely and being underpowered to give definitive recommendations. Therefore, we lack conclusive data with regard to the impact of different antiplatelet agents on outcomes in patients with HF.

Can Clopidogrel Positively Influence Outcomes in HF?

Therapy with clopidogrel has been demonstrated to inhibit platelet indexes independently of HF etiology, New York Heart Association functional class, or LVEF. Notably, Bonde et al⁴² recently demonstrated with the National Patient Register of 56 994 first-documented MIs in Denmark a significant positive impact of clopidogrel on mortality in patients with HF after MI (5050) (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; $P=0.002$) (mean follow-up of 1.5 years) (Figure 3). Although these observational data raise an interesting hypothesis about the potential role for clopidogrel in HF, such a concept would need to be evaluated in a prospective RCT.

Current Guidelines and Practical Recommendations

The European Society of Cardiology guidelines¹ state that there is no proven role for anticoagulation in HF. However, anticoagulants have been demonstrated to be more effective than antiplatelet agents in reducing the risk of stroke; thus, they are the preferred agents in patients with >1 moderate risk factor (eg, LVEF $\leq 35\%$, age ≥ 75 years, hypertension, diabetes mellitus) and for primary VTE prevention in patients with HF and AF and without any additional risk factors. With respect to antiplatelet agents, the guidelines state that (1) they

are not as effective as anticoagulants in reducing VTE risk in patients with AF, (2) the risk of HF hospitalization has been shown to be significantly greater in aspirin-treated than in warfarin-treated patients, and (3) there is no evidence that antiplatelet agents reduce atherosclerotic risk in HF.

The American College of Cardiology/American Heart Association guidelines² state that anticoagulation should be considered in patients with HF who have experienced a previous VTE or who have paroxysmal or persistent AF, in patients with underlying disorders that may be associated with an increased VTE risk, or in patients with familial dilated cardiomyopathy and a history of VTE in first-degree relatives. With regard to antiplatelet agents, the guidelines state that they should be used for MI and prevention of death in patients with HF with known coronary artery disease. However, they also state that the role of aspirin in HF has not been established, and concerns have been raised that it may attenuate the hemodynamic and survival benefits of ACE-inhibitors. Current guidelines are summarized in Table 3.

Table 3. Guidelines for Antithrombotic Therapy in HF

Society	Recommendations	Evidence
ACC/AHA, 2009	Anticoagulants in patients with HF and paroxysmal or persistent AF or previous VTE	I-A
	Antiplatelet agents for MI and death prevention in patients with HF and CAD	I-B
	Anticoagulants in patients with underlying disorders that may be associated with increased VTE risk (eg, amyloidosis) and in patients with familial DCM and history of VTE in first-degree relatives	IIb-B
ESC, 2008	Anticoagulants for patients with >1 moderate risk factor (age ≥ 75 years, hypertension, LVEF $\leq 35\%$, diabetes mellitus)	I-A
	Aspirin or vitamin K antagonist for primary VTE prevention in patients of HF with AF without additional risk factors	I-A

ACC/AHA indicates American College of Cardiology/American Heart Association; CAD, coronary artery disease; ESC, European Society of Cardiology. Other abbreviations as in Tables 1 and 2.

Unanswered Questions and Future Directions

Several aspects of the pathophysiology of HF could explain VTE predisposition seen in this patient population. However, estimates of the incidence of VTE in patients with HF have varied widely. Additionally, appropriate management strategies to mitigate the risk of VTE remain uncertain for many groups of patients with HF. Three RCTs evaluating the use of antithrombotic therapy in ambulatory patients with HF have been inconclusive, and another RCT is ongoing. Patients at high risk for VTE, such as those with AF, previous VTE, LV thrombi, and underlying conditions predisposing to VTE, should be considered for antithrombotic therapy.

Antiplatelet therapy with aspirin remains an area of controversy and debate. For patients with nonischemic cardiomyopathy, there does not appear to be a role for the routine use of aspirin. For patients with HF and coronary artery disease, a more individualized approach should be considered, potentially using aspirin in those with recent coronary events, procedures, or current angina but not necessarily in those with a distant history of MI. In patients with advanced HF and coronary artery disease, especially if they require frequent hospital admissions despite optimal medical therapy, an alternative antithrombotic agent to aspirin should be considered.

Thus, it is difficult to make decisions about the administration of antithrombotic therapy to patients with HF. Moreover, a large number of alternative anticoagulants and antiplatelet agents currently are being developed (eg, direct thrombin inhibitors, factor Xa inhibitors, thrombin receptor antagonists, thromboxane receptor antagonists), and they may require a reassessment of the role of these agents in HF. RCTs are needed to specifically address the advantages and disadvantages of each antithrombotic regimen (efficacy, bleeding risk, costs) for the different clinical conditions associated with HF.

Disclosures

Dr Fiuzat is a consultant and shareholder of ARCA Biopharma, Inc, and a consultant for Roche Diagnostics and Forest Laboratories. Dr Richard Becker is a consultant for BMS, Boehringer-Ingelheim, Merk, Takeda, and Daiichi-Sankyo. Dr Felker is a consultant for Roche Diagnostics, Amgen, Otsuka, Corthera, Cytokinetics, and Geron. Dr O'Connor is a consultant for Forest Laboratories, Roche Diagnostics, Amgen, Medpace, Hoffman La-Roche, Trevena, Actelion, GE Healthcare, Merck Pharmaceuticals, and Medtronic. Drs Bettari and Metra have no conflicts to disclose.

References

- Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellems I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;29:2388–2442.
- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko

- PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in Collaboration With the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391–e479.
- Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;29:117:e25–e146.
- Beemath A, Stein PD, Skaf E, Al Sibae MR, Alesh I. Risk of venous thromboembolism in patients hospitalized with heart failure. *Am J Cardiol*. 2006;98:793–795.
- Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the SIRIUS study. *Arch Intern Med*. 2000;160:3415–3420.
- Dunkman WB, Johnson GR, Carson PE, Bhat G, Farrell L, Cohn JN; the V-HeFT VA Cooperative Studies Group. Incidence of thromboembolic events in congestive heart failure. *Circulation*. 1993;87(suppl VI):VI-94–VI-101.
- Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation*. 2004;110:874–879.
- Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, Turpie AG, Egberts JF, Lensing AW. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ*. 2006;332:325–329.
- Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Olsson CG, Turpie AG. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness. Analysis of the MEDENOX study. *Arch Intern Med*. 2004;164:963–968.
- Darze ES, Latado AL, Guimarães AG, Guedes RA, Santos AB, de Moura SS, Passos LC. Incidence and clinical predictors of pulmonary embolism in severe heart failure patients admitted to a coronary care unit. *Chest*. 2005;128:2576–2580.
- Freudenberger RS, Hellkamp AS, Halperin JL, Poole J, Anderson J, Johnson G, Mark DB, Lee KL, Bardy GH; SCD-HeFT Investigators. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation*. 2007;115:2637–2641.
- Hays AG, Sacco RL, Rundek T, Sciacca RR, Jin Z, Liu R, Homma S, Di Tullio MR. Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. *Stroke*. 2006;37:1715–1719.
- Kalaria VG, Passanante MR, Shah T, Modi K, Weisse AB. Effect of mitral regurgitation on left ventricular thrombus formation in dilated cardiomyopathy. *Am Heart J*. 1998;135(2 pt 1):215–220.
- Falk RH, Foster E, Coats MH. Ventricular thrombi and thromboembolism in dilated cardiomyopathy: a prospective follow-up study. *Am Heart J*. 1992;123:136–142.
- Stratton JR, Resnick AD. Increased embolic risk in patients with left ventricular thrombi. *Circulation*. 1987;75:1004–1011.
- Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. *J Am Coll Cardiol*. 1998;31:419–425.
- St John Sutton M, Pfeffer MA, Moye L, Plappert T, Rouleau JL, Lamas GA, Rouleau J, Parker JO, Arnold MO, Sussex B, Braunwald E. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation*. 1997;96:3294–3299.
- Davis CJ, Gurbel PA, Gattis WA, Fuzaylov SY, Nair GV, O'Connor CM, Serebruany VL. Hemostatic abnormalities in patients with congestive heart failure: diagnostic significance and clinical challenge. *Int J Cardiol*. 2000;75:15–21.
- O'Connor CM, Gurbel PA, Serebruany VL. Usefulness of soluble and surface bound P-selectin in detecting heightened platelet activity in patients with chronic heart failure. *Am J Cardiol*. 1999;83:1345–1349.

20. Yamamoto K, Ikeda U, Furuhashi K, Irokawa M, Nakayama T, Shimada K. The coagulation system is activated in idiopathic cardiomyopathy. *J Am Coll Cardiol*. 1995;25:1634–1640.
21. Jug B, Vene N, Salobir BG, Sebestjen M, Sabovic M, Keber I. Prognostic impact of haemostatic derangements in chronic heart failure. *Thromb Haemost*. 2009;102:314–320.
22. De Lorenzo F, Saba N, Kakkar VV. Blood coagulation in patients with chronic heart failure: evidence for hypercoagulable state and potential for pharmacological intervention. *Drugs*. 2003;63:565–576.
23. Alehagen U, Dahlstrom U, Lindahl TL. Elevated D-dimer level is an independent risk factor for cardiovascular death in out-patients with symptoms compatible with heart failure. *Thromb Haemost*. 2004;92:1250–1258.
24. Molvarec A, Rigó J Jr, Böze T, Derzsy Z, Cervenak L, Makó V, Gombos T, Udvardy ML, Hársfalvi J, Prohászka Z. Increased plasma von Willebrand factor antigen levels but normal von Willebrand factor cleaving protease (ADAMTS13) activity in preeclampsia. *Thromb Haemost*. 2009;101:305–311.
25. Paulus WJ. Cytokines and heart failure. *Heart Fail Monit*. 2000;1:50–56.
26. Closse C, Seigneur M, Renard M, Pruvost A, Dumain P, Belloc F, Boisseau MR. Influence of hypoxia and hypoxia-reoxygenation on endothelial P-selectin expression. *Thromb Res*. 1997;85:159–164.
27. Nawroth PP, Stern DM. Modulation of endothelial cell hemostatic properties by tumor necrosis factor. *J Exp Med*. 1986;163:740–745.
28. Kapur NK, Deming CB, Kapur S, Bian C, Champion HC, Donahue JK, Kass DA, Rade JJ. Hemodynamic modulation of endocardial thromboreistance. *Circulation*. 2007;115:67–75.
29. Chong AY, Freestone B, Patel J, Lim HS, Hughes E, Blann AD, Lip GY. Endothelial activation, dysfunction, and damage in congestive heart failure and the relation to brain natriuretic peptide and outcomes. *Am J Cardiol*. 2006;97:671–675.
30. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Warfarin anticoagulation and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol*. 1998;31:749–753.
31. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, Prentice C, Ford I, Trainer A, Poole-Wilson PA. The Warfarin/Aspirin Study in heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J*. 2004;148:157–164.
32. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafri SM, Krol WF, O'Connor CM, Schulman KA, Teo K, Warren SR; WATCH Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation*. 2009;119:1616–1624.
33. Cleland JG, Ghosh J, Freemantle N, Kaye GC, Nasir M, Clark AL, Coletta AP. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-LIPIDS and cardiac resynchronization therapy in heart failure. *Eur J Heart Fail*. 2004;6:501–508.
34. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK; HELAS Investigators. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. *Eur J Heart Fail*. 2006;8:428–432.
35. Pullicino O, Thompson JL, Barton B, Levin B, Graham S, Freudenberger RS; WARCEF Investigators. Warfarin versus aspirin in patients with reduced cardiac ejection fraction (WARCEF): rationale, objectives, and design. *J Card Fail*. 2006;12:39–46.
36. Blais C Jr, Drapeau G, Raymond P, Lamontagne D, Gervais N, Venneman I, Adam A. Contribution of angiotensin-converting enzyme to the cardiac metabolism of bradykinin: an interspecies study. *Am J Physiol*. 1997;273:H2263–H2271.
37. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction. Subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol*. 1997;15:115–119.
38. Levy PD, Nandyal D, Welch RD, Sun JL, Pieper K, Ghali JK, Fonarow GC, Gheorgiade M, O'Connor CM. Does aspirin use adversely influence intermediate-term postdischarge outcomes for hospitalized patients who are treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers? Findings from Organized Program to Facilitate Life-Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2010;159:222–230.
39. Chang SM, Granger CB, Johansson PA, Kosolcharoen P, McMurray JJ, Michelson EL, Murray DR, Olofsson B, Pfeffer MA, Solomon SD, Swedberg K, Yusuf S, Dunlap ME; CHARM Investigators. Efficacy and safety of angiotensin receptor blockade are not modified by aspirin in patients with chronic heart failure: a cohort study from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur J Heart Fail*. 2010;12:738–745.
40. Teo KK, Yusuf S, Pfeffer M, Torp-Pedersen C, Kober L, Hall A, Pogue J, Latini R, Collins R; ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet*. 2002;360:1037–1043.
41. Lip GY, Gibbs CR. Antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm: a Cochrane systematic review. *QJM*. 2002;95:461–468.
42. Bonde L, Sorensen R, Fosbøl EL, Abildstrøm SZ, Hansen PR, Kober L, Schramm TK, Bretler DM, Weeke P, Olesen J, Torp-Pedersen C, Gislason GH. Increased mortality associated with low use of clopidogrel in patients with heart failure and acute myocardial infarction not undergoing percutaneous coronary intervention: a nationwide study. *J Am Coll Cardiol*. 2010;55:1300–1307.

KEY WORDS: heart failure ■ thromboembolism ■ anticoagulants ■ platelet aggregation inhibitors

Thromboembolism and Antithrombotic Therapy in Patients With Heart Failure in Sinus Rhythm: Current Status and Future Directions

Luca Bettari, Mona Fiuzat, Richard Becker, G. Michael Felker, Marco Metra and Christopher M. O'Connor

Circ Heart Fail. 2011;4:361-368

doi: 10.1161/CIRCHEARTFAILURE.110.959957

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2011 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circheartfailure.ahajournals.org/content/4/3/361>

An erratum has been published regarding this article. Please see the attached page for: </content/4/5/e19.full.pdf>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Heart Failure* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at: <http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Heart Failure* is online at: <http://circheartfailure.ahajournals.org/subscriptions/>

Correction

In the article, “Thromboembolism and antithrombotic therapy in patients with heart failure in sinus rhythm: current status and future directions,” by Bettari et al, which appeared in the May 2011 issue of the Journal (*Circ Heart Fail* 2011;4:361–368), an incorrect reference was cited.

On page 362, this sentence should read, “Overall, the 4-year survival analysis found that VTE rate was 4.0%, with an annual incidence of 1%.¹¹ This sentence cites the correct reference.

The online version of the article has been corrected. The authors regret this error.

DOI: 10.1161/HHF.0b013e31822f88cd