Thrombotic Complications in Heart Failure:
An Under-Appreciated Challenge

Running title: Shantsila et al.; Thrombosis in heart failure

Eduard Shantsila, PhD1; Gregory YH Lip, MD1,2

1University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 2Thrombosis Research Unit, Dept of Clinical Medicine, Aalborg University, Aalborg, Denmark

Address for Correspondence:
Gregory YH Lip, MD
University of Birmingham Centre for Cardiovascular Sciences
City Hospital
Birmingham, B18 7QH
United Kingdom
Tel: +44 121 507 5080
Fax: +44 121 554 4083
E-mail: g.y.h.lip@bham.ac.uk

Journal Subject Codes: Thrombosis:[172] Arterial thrombosis, Heart failure:[11] Other heart failure

Key words: Editorial, thrombosis, heart failure
Advances in pharmacological and devices therapy have greatly improved prognosis in patients with systolic heart failure. Despite this congestive heart failure still bears a very grim prognosis, particularly in patients with more advances stages of the disease that are so frequently seen on hospital wards.

Which pathogenic pathways may need to be addressed to improve prognosis in heart failure? The current treatment of this condition is primarily focused on performance of the heart itself, and aims to inhibit unfavorable cardiac remodeling (e.g., amelioration of impact of activated catecholamine and renin-angiotensin-aldosterone systems), optimization of cardiac hemodynamics (e.g., cardiac resynchronization therapy) and prevention of life threatening arrhythmia (e.g., insertion of implantable defibrillators). However, accumulating evidence suggests that thrombotic complications may play a major role in morbidity and outcomes in heart failure patients, especially as the cardiac ‘targets’ (largely neurohuneral) are being better managed.

The two major thrombotic sources in heart failure are related to atrial fibrillation (AF) and venous thromboembolism (VTE). Whilst oral anticoagulation in HF with known AF is well established and highly successful the role of oral anticoagulation in heart failure without documented AF is controversial and is not recommended for routine use at present.

Heart failure is undoubtedly associated with a significant prothrombotic shift, which predisposes to thrombi formation both within cardiac chambers (particularly in AF) and blood vessels. Endothelial damage/dysfunction is a hallmark of heart failure irrespective of any etiology.¹ It has been related to severity of heart failure and its presence is consistently linked to poor prognosis. Although most studies focused on arterial endothelial dysfunction, venous dysfunction is also present in heart failure and it is likely to contribute to prothrombotic state.
seen in this condition. Blood stasis in edematous legs with a background of poor mobility and increased pulmonary pressure clearly predisposes to venous thrombosis. Moreover it has been demonstrated that subjects with heart failure have increased blood levels of prothrombotic molecules, such as fibrinogen and von Willebrand factors.

Clinical data indicate significant impact of thrombosis in heart failure, which is unrelated to documented AF or coronary events. Venous thromboembolism is common in patients with heart failure, both admitted with acute decompensation and in those with relatively stable course of the disease. The risk of this potentially life-threatening complication in acute heart failure varied considerably between different studies, but is could affect over a quarter of patients with acute heart failure if anticoagulants are not used.

Several risk factors predictive of VTE and pulmonary embolism in heart failure have been reported but their prognostic value for the occurrence of de-novo venous thrombosis remains unclear. For instance, VTE risk is associated with presence of right ventricular dysfunction, which may simply reflect previous, often undiagnosed episodes of pulmonary embolism. A documented link between history of VTE and immobilization and new VTE episodes upon admission with acute HF may indicate the presence of a chronic prothrombotic state but does not explain the excess of thrombotic complications in heart failure. Indeed, one in ten patients with heart failure develops VTE upon admission to an intensive therapy unit despite adequate thromboprophylaxis, more frequently that it would have been expected in acutely ill patients without heart failure.

The contribution of VTE towards overall mortality in heart failure is not to be neglected. One prospective analysis has demonstrated that pulmonary embolism could be the primary cause of death in 3 to 10% of heart failure patients. Moreover, pulmonary embolism is frequently
missed in subjects with heart failure, which can mask symptoms and features of right ventricular strain.\textsuperscript{4} A meta-analysis of 32 trials of angiotensin converting enzyme inhibitors in heart failure patients identified pulmonary embolism as one of five main causes of death.\textsuperscript{5} Indeed, postmortem studies in people suffering from heart failure show an incidence of pulmonary embolism of up to 32%\textsuperscript{6}.

Heart failure itself is also a strong independent prognosticator of death in patients with VTE. In the Worcester Venous Thromboembolism Study, 17.5\% of the participants had previous history of heart failure.\textsuperscript{7} Also, the presence of heart failure in patients with VTE was related to 3-fold higher risk of in-hospital death.

Undiagnosed ‘silent’ AF is another, often under-recognised cause of thrombotic complications in heart failure. Silent AF is common in heart failure, which can be picked up by screening and would (partly) address the substantial underutilization of oral anticoagulants for stroke prevention in AF.\textsuperscript{8} In patients with acute myocardial infarction, which is a major cause of heart failure, silent AF was 3-fold more common than symptomatic AF (16\% vs 5\%, respectively) despite prompt revascularization and a relatively short duration of ECG monitoring.\textsuperscript{9} Of note, in-hospital heart failure and mortality were markedly higher in silent AF group when compared with patients without AF.

In the Heart and Soul Study, the CHADS\textsubscript{2} score was not only significantly predictive of future ischemic strokes in non-AF patients with coronary artery disease, but its predictive power was comparable to that expected in AF patients.\textsuperscript{10} It is possible that some participants had undetected AF, but all patients with CHADS\textsubscript{2} score 5-6 would be expected to have associated heart failure.

In this issue of \textit{Circulation}, Mebazaa and colleagues demonstrate that heart failure
severity discriminates patients who are particularly high risk of VTE. The study highlights yet again that frequency of VTE remains high despite meticulous anticoagulation in accordance with current guidelines. The study shows that more severe heart failure, either established based on clinical grounds (i.e., New York Heart Association functional class III-IV) or by high NT-proBNP levels is associated with increased risk for VTE. Of note, whilst NT-proBNP was independently predictive of VTE risk short-term only, higher D-dimer concentrations maintained independent prognostic values both short-term and long-term. More importantly, this study suggests that the link between heart failure severity and VTE risk can be disrupted by prolonged administration of a non-Vitamin K antagonist oral anticoagulant (NOAC), rivaroxaban.

A large Danish prospective epidemiological cohort study of patients with incident cases of heart failure without history of AF has demonstrated that heart failure represents a major risk factor for stroke and death, particularly within the first month of heart failure diagnosis, therapy with VKAs was associated with a significant reduction in the rate of outcomes. Ten-year follow up of participants from the large population-based cohort Rotterdam Study confirms the strong association between heart failure and the risk of stroke, with the risk of ischemic stroke being 5-fold increased during the first month following HF diagnosis.

Available controlled studies have not proven a survival benefit of the VKAs in heart failure without AF and current consensus does not recommend routine treatment with oral anticoagulants in this category of patients. In the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) study of heart failure patients without AF, and whilst treatment with warfarin did not reduce the rates of the primary outcome, it did almost halve the frequency of ischemic stroke. Similarly, warfarin was associated with lower rate of stroke compared to aspirin or clopidogrel in the Warfarin and Antiplatelet Therapy in Chronic Heart Failure
(WATCH) trial.\textsuperscript{16}

Although establishment of cut-off values and optimal strategies for VTE prophylaxis was beyond the scope of the work by Mebazaa et al.\textsuperscript{11} the study clearly points towards particular utility of rivaroxaban in patients with more severe heart failure for prevention of both short-term or medium-term VTE risks. Although clinical signs alone appear to be sufficient to identify patients with more severe forms of heart failure who may benefit from more (intense?) protection from VTE, measurement of NT-proBNP levels may provide support for decision making. However, the clinical and financial gains of testing NT-proBNP solely for assessment of VTE risk remain controversial. High D-dimer levels remained predictive of increased VTE risk up to end of the study treatment and may thus provide incremental value for both short-term or medium-term VTE risk prediction. In contrast to NT-proBNP, which is merely a marker of heart failure severity, D-dimer levels might better estimate overall prothrombotic risks, both attributed to heart failure severity and to other prothrombotic factors. Indeed, more data will be needed to confirm this association and to find out optimal cut-off values for more vigorous efforts at thromboprophylaxis.

Current knowledge on the NOACs to mitigate the prothrombotic risk in heart failure without known AF is limited. However the potential of these agents in heart failure is evident from studies in non-valvular AF.\textsuperscript{17,18} In the subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial\textsuperscript{19} the composite endpoint of stroke, systemic embolism or death was highest in patients with heart failure with systolic left ventricular impairment as compared to patients with heart failure and preserved ejection fraction or participants without heart failure. However, apixaban had similar efficacy irrespectively of heart failure status. Also the efficacy of rivaroxaban compared to warfarin was
similar in patients with heart failure and without heart failure in the Rivaroxaban Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial.\textsuperscript{20} The Randomized Evaluation of Long-term anticoagulant therapy (RE-LY) trial of dabigatran included 4904 patients with symptomatic heart failure.\textsuperscript{21} Although heart failure patients had higher mean CHADS\textsubscript{2} score there was no significant interaction between the two tested dabigatran doses and presence of symptomatic heart failure in relation to the primary outcome. Importantly the NOACs showed similar risk of major bleedings in patients with or without heart failure. The findings that a NOAC, rivaroxaban, can be of particular benefit for VTE prophylaxis in heart failure are rather promising. However, data from randomised trials specifically devoted to this high risk population would be required to provide robust evidence for their routine clinical use. The study by Mebazaa et al.\textsuperscript{11} gives an excellent justification for such a randomized trial.

In the view of new data demonstrating that patients with severe heart failure are likely to benefit from oral anticoagulation, using the NOACs in a clinical trial testing this possibility would be highly desirable. The study by Mebazaa et al.\textsuperscript{11} indicates that inclusion of blood biomarkers such as D-dimers may a useful addition to the study design to identify patient with particularly high thrombotic risk. Any such new study would certainly target the prothrombotic risks in heart failure, related to both silent AF and/or VTE.

\textbf{Conflict of Interest Disclosures:} Dr. Lip is a consultant for Bayer, Medtronic, Sanofi, BMS/Pfizer, Daiichi-Sankyo and Boehringer Ingelheim, and has been a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo and Medtronic. Dr. Shantsila does not report any conflicts.
References:


Thrombotic Complications in Heart Failure: An Under-Appreciated Challenge
Gregory YH Lip and Eduard Shantsila

Circulation. published online June 26, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2014/06/26/CIRCULATIONAHA.114.011353

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 is online at:
http://circ.ahajournals.org//subscriptions/