Advances in pharmacologic and device 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 advanced stages of the disease, who 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 (eg, amelioration of impact of activated catecholamine and renin-angiotensin-aldosterone systems), optimization of cardiac hemodynamics (eg, cardiac resynchronization therapy), and prevention of life-threatening arrhythmia (eg, insertion of implantable defibrillators). However, accumulating evidence suggests that thrombotic complications may play a major role in morbidity and outcomes in patients with heart failure, especially as the cardiac targets (largely neurohumoral) are being better managed.

The 2 major thrombotic sources in heart failure are related to atrial fibrillation (AF) and venous thromboembolism (VTE). Although oral anticoagulation in heart failure 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 cause. It has been related to severity of heart failure, and its presence is consistently linked to poor prognosis. Although most studies have focused on arterial endothelial dysfunction, venous dysfunction is also present in heart failure, and it is likely to contribute to the 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 a significant impact of thrombosis in heart failure, which is unrelated to documented AF or coronary events. VTE is common in patients with heart failure, in both those admitted with acute decompensation and in those with a relatively stable course of the disease. The risk of this potentially life-threatening complication in acute heart failure varied considerably between different studies, but it could affect more than 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 the presence of right ventricular dysfunction, which may simply reflect previous, often undiagnosed episodes of pulmonary embolism. A documented link between the history of VTE and immobilization and new VTE episodes on admission with acute heart failure may indicate the presence of a chronic prothrombotic state but does not explain the excess of thrombotic complications in heart failure. Indeed, 1 in 10 patients with heart failure develops VTE on admission to an intensive therapy unit despite adequate thromboprophylaxis, more frequently than would have been expected in acutely ill patients without heart failure.

The contribution of VTE toward 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 patients with heart failure. Moreover, pulmonary embolism is frequently missed in subjects with heart failure, which can mask symptoms and features of right ventricular strain. A meta-analysis of 32 trials of angiotensin-converting enzyme inhibitors in patients with heart failure identified pulmonary embolism as 1 of 5 main causes of death. Indeed, postmortem studies in people experiencing heart failure show an incidence of pulmonary embolism of ≤32%. 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 a previous history of heart failure. Also, the presence of heart failure in patients with VTE was related to a 3-fold higher risk of in-hospital death.

Undiagnosed silent AF is another, often under-recognized 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 underuse of oral anticoagulants for stroke prevention in AF. 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% versus 5%, respectively) despite prompt revascularization and a relatively short duration of ECG monitoring. Of note, in-hospital heart failure and mortality were markedly higher in the silent AF group when compared with patients without AF.

In the Heart and Soul Study, the CHADS2 score was not only significantly predictive of future ischemic strokes in non-AF patients with coronary artery disease, but its predictive power was comparable with that expected in patients with AF. It is possible that some participants had undetected AF, but all of the patients with a CHADS2 score of 5 to 6 would be expected to have associated heart failure.

In this issue of Circulation, Mebazaa et al demonstrate that heart failure severity discriminates patients who are particularly high risk of VTE. The study highlights yet again that the frequency of VTE remains high despite meticulous anticoagulation in accordance with current guidelines. The study shows that more severe heart failure, either established on the basis of clinical grounds (ie, New York Heart Association functional class III to IV) or by high N-terminal pro-B natriuretic peptide (NT-proBNP) levels is associated with an increased risk for VTE. Of note, whereas NT-proBNP was independently predictive of VTE risk in the short term only, higher n-dimer concentrations maintained independent prognostic values both in the short and long terms. 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 epidemiologic cohort study of patients with incident cases of heart failure without a 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, and therapy with vitamin K antagonists 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 after heart failure diagnosis.

Available controlled studies have not proven a survival benefit of the vitamin K antagonists 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 study of heart failure patients without AF, although 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 a lower rate of stroke compared with aspirin or clopidogrel in the Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial.

Although the establishment of cutoff values and optimal strategies for VTE prophylaxis were beyond the scope of the work by Mebazaa et al, the study clearly points toward particular use of rivaroxaban in patients with more severe heart failure for the prevention of 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 n-dimer levels remained predictive of increased VTE risk up to the 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, n-dimer levels might better estimate overall prothrombotic risks, both attributed to heart failure severity and to other prothrombotic factors.

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 nonvalvular AF. In the sub-analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, the composite end point of stroke, systemic embolism, or death was highest in patients with heart failure with systolic left ventricular impairment as compared with patients with heart failure and preserved ejection fraction or participants without heart failure. However, apixaban had similar efficacy irrespective of heart failure status. Also, the efficacy of rivaroxaban compared with 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 trial. The Randomized Evaluation of Long-Term Anticoagulant Therapy trial of dabigatran included 4904 patients with symptomatic heart failure. Although patients with heart failure had higher mean CHADS2 scores, there was no significant interaction between the 2 tested dabigatran doses and the presence of symptomatic heart failure in relation to the primary outcome. Importantly, the NOACs showed similar risk of major bleeding in patients with or without heart failure. The findings that an NOAC, rivaroxaban, can be of particular benefit for VTE prophylaxis in heart failure are rather promising. However, data from randomized 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 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 indicates that the inclusion of blood biomarkers such as n-dimers may be a useful addition to the study design to identify patients with particularly high thrombotic risk. Any such new study would certainly target the prothrombotic risks in heart failure related to silent AF and/or VTE.
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 reports no conflicts.

References

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