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Editorial

Soluble fibrin monomer complex as a candidate sentinel for adverse events in patients with heart failure

The hypercoaguable state in patients with heart failure is of great clinical importance and the decision to initiate anticoagulation to manage thrombotic risk in this population of patients is a big challenge [1]. A small number of trials have specifically addressed this issue in patients with heart failure with reduced ejection fraction (HFrEF, ≤35%) and normal sinus rhythm, i.e. without concomitant atrial fibrillation: (i) the Warfarin/Aspirin Study in Heart Failure (WASH) [2] and (ii) the Heart Failure Long-Term Antithrombotic Study (HELAS) [3], both comparing warfarin and aspirin versus placebo, (iii) the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial compairing open-label warfarin with double-blinded aspirin or clopidogrel [4], and (iv) the Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm (WARCEF) trial [5], examining warfarin versus aspirin. Despite some significant differences in terms of ischemic stroke in some subpopulations, none of the studies could demonstrate a clear benefit of warfarin. Accordingly, the use of anticoagulation in patients with heart failure and sinus rhythm without a prior thromboembolic event or known cardioembolic source is not warranted and listed as evidence class III (no benefit and may cause harm) in the current ACC/AHA Heart Failure Guidelines [6].

Given the strong association between heart failure and thrombosis-driven adverse events, clotting-related biomarkers are increasingly used to monitor thromboembolic risk and predict outcome in heart failure patients. The focus in this context is primarily on indices of fibrinolysis, the dissolution of the stable fibrin clot by plasmin. When blood coagulation is triggered and thrombin is activated, the fibrinogen precurser is cleaved by thrombin to sequentially generate fibrin monomers and polymers that constitute the loose, still-soluble, thrombus. The clot is then stabilised by the thrombin-activated transglutaminase factor XIII in the final step of thrombosis (coagulation state). Fibrinolysis is co-activated with coagulation to counterbalance thrombus formation and generate fibrin degradation products that are cleared from the circulation. In this context, plasminogen is activated to plasmin by tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), alternatively by the contact system encompassing the activated coagulation factors FXIa and FXIIa and kallikrein. Both tPA and uPA are bound and inhibited by the serpins plasminogen activator inhibitors PAI1 and PAI2, where PAI1 is the most relevant representative [7,8].

In patients with heart failure and preserved ejection fraction (HFpEF), the tPA/PAI1 complex has been identified as a significant and independent predictor of death from cardiovascular and all causes [9]. More recently, the Bio-SHIFT study showed strong associations between longitudinally-measured PAI-1, uPA and soluble urokinase PA surface receptor (suPAR), and adverse cardiac events during heart failure progression [10]. Intruigingly, elevated suPAR seems to distinguish ischemia-driven heart failure from heart failure of non-ischemic causes [11]. Another fibrinolysis marker emerging as an independent sentinel predicting adverse outcome and death from all causes in patients with heart failure, is D-dimer [12–15]. D-dimer is a fibrin degradation product generated in the final stage of clot dissolution, and as such, its presence essentially indicates that thrombus formation has occurred and fibrinolysis has been initiated. It is therefore intuitive that patients showing elevated D-dimers indicative of a recent thrombotic event have a poorer prognosis. Clearly, there remains an unmet clinical need for sentinel biomarkers of the pre-coagulant state, before thrombus formation occurs.

In this journal, Yoshihisa and colleagues [16] have revisited the soluble fibrin monomer complex (SFMC) as a predictive biomarker in patients with heart failure. SFMC resides at the sidelines of the very early stages of the coagulation/fibrinolysis cascade, between the sequential formation of fibrin polymers from monomers. In the past, SFMC, a complex of fibrinogen with fibrin monomers, has been measured to detect disseminated intravascular coagulation (DIC) in malignancy and other pathologies, to confirm thrombotic complications in pregnancy and to monitor hypercoagulation in patients with atrial fibrillation or recent myocardial infarction. D-dimer testing has largely replaced SFMC in these diagnostic contexts, but its ability to reflect a pre-coagulant state, and hence predict an imminent thromboembolic event before it occurs, perhaps calls for a renaissance of SFMC.

Yoshihisa and colleagues [16] stratified 723 patients with decompensated heart failure according to SFMC at discharge. The highest tertile significantly and independently predicted major cardio- and cerebrovascular events (MACCE) and all-cause mortality. The predictive ability of SFMC withstood correction for prothombotic comorbidities such as atrial fibrillation, prior stroke, and peripheral artery disease, and was not influenced by the type of oral anticoagulant or the use of antiplatelet agents. SFMC was determined by latex immunoturbidity coupled with a coagulometer. Immunoturbidimetry implements a classical antigen-antibody reaction to generate particle aggregates which can be measured optically in a photometer. The technique allows for quantification of serum proteins not detectable with conventional clinical chemistry methods. The application of this assay in the present study to

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determine SFMC in heart failure patients represents an innovative approach to repurpose a standard clinical diagnostic tool for early detection of thromboembolic risk, before the event has taken place. In the past, SFMC has been assessed by various techniques, which are too complex, time-consuming or insensitive for point-of-care testing, or utilise kits specifically designated for research-use only. The value of the study by Yoshihisa and colleagues [16] is therefore at least two-fold: the authors leverage SFMC from a largely underestimated biomarker to a powerful index of imminent thromboembolic risk, and then validate the immunoturbidity assay for point-of-care testing in patients with heart failure.

One question that arises in this context is whether SFMC is a bystander sentinel or an active participant in heart failure-associated complications and their prevention. A hemostatic shift towards a net pro-coagulant state increases both the risk of thromboembolism and can also cause direct cellular demage. Certain proteases of the activated coagulation cascade, such as thrombin and activated factors X, VII and XII, can activate a family of G-protein coupled receptors termed protease-activated receptors (PAR). The four PAR1-4 described to date are widely expressed in many cells and tissues, are dynamically regulated in response to pathological conditions, and control diverse cellular functions associated with e.g. inflammation, oxidadative stress, matrix remodeling, apoptosis and autophagy [17–20]. Whether or not fibrin-containing moieties such as FDP or SFMC can bind and thus modify PAR activation by proteolytic agonists is an intruiging question, which should be addressed in subsequent studies. Circulating FDP compete with full-length fibrinogen for thrombin binding, therefore preventing conversion to fibrin and thus interfering with clot stabilisation. Conceivably, FDP and perhaps also SFMC may act as a thrombin sink, limiting the extent of thrombin-triggered PAR activation. Future basic research should shed light into the possible (in)direct cellular effect of SFMC.

In summary, the study by Yoshihisa and colleagues in this journal [16] puts the spotlight on SFMC as an independent biomarker of adverse outcome in patients with heart failure, and raises the possibility that SFMC may constitute a sentinel for a prevailing pre-coagulant state, allowing for early detection of an imminent thromboembolic event before it clinically occurs.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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