Heart Failure and Cardiac Events: Is a Consecutive Measurement of Biomarkers a Simple and Practical Approach?

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Heart failure (HF) is common, with a prevalence of approximately 2% in the overall population, and increasing to 5 to 9% in people older than 65 years.[1] This prevalence is likely to increase in relation to an aging population, increasing prevalence of comorbidities or risk factors, and improved survival of postmyocardial infarction.[2] Of note, HF is associated with worse clinical outcomes, including successive hospitalizations, higher risk of mortality, and impaired quality of life.[3,4]

Over the last decade, the role of various biomarkers for understanding underlying pathophysiology, improving risk stratification, or prediction of adverse events in cardiovascular diseases has gained much attention.[5–11] In the clinical setting, specifically in HF, the natriuretic peptides (NPs) (B-type natriuretic peptide [BNP], N-terminal fraction of BNP [NT-proBNP], and midregional proANP) are markers of myocardial stress that have been widely investigated, being predictive of mortality and rehospitalization.[12–14] Similarly, cardiac troponins are markers of myocardial injury that have been observed to be elevated in many HF patients even in the absence of an acute coronary syndrome due to the stress and damage of myofibrillar proteins. Hence, NP and troponins concentrations may help in the diagnosis and prognosis of HF.[15–17]

The prothrombotic state of HF has been well described, whereby the presence of hemostasis, platelets, and endothelial function abnormalities confers an increased risk of thrombogenesis. Hence, some markers associated with thrombogenesis and endothelial dysfunction may be useful in identifying "high-risk" HF patients and have prognostic implications.[14,18]

In this issue of *Thrombosis and Haemostasis*, van den Berg et al investigate some fibrinolytic factors scarcely explored in HF, plasminogen activator inhibitor 1 (PAI-1), tissue-type plasminogen activator (tPA), urokinase-type PA (uPA), and soluble urokinase PA surface receptor (suPAR). In their study, while tPA concentrations were not related with the endpoint of interest, longitudinally measured PAI-1, uPA, and suPAR were strongly associated with adverse cardiac events in patients with chronic HF from the Bio-SHiFT cohort.[19]

Some years ago, a report from the Ludwigshafen Risk and Cardiovascular Health study demonstrated that the tPA/PAI-1 complex concentration had additional prognostic value above and beyond NT-proBNP and was an independent predictor of mortality from all-cause and cardiovascular in patients with HF with preserved ejection fraction.[14] Although these results were derived from a long period of observation (more than 9 years), they are based on baseline measurement of tPA/PAI-1 complex. In fact, one common criticism of biomarker studies is that they measure biomarkers only once, often at baseline, and in highly selected trial cohorts. Nevertheless, as van den Berg et al correctly state in their manuscript, plasma levels of coagulation and fibrinolysis factors vary over time. Even during the same day biomarkers concentrations could be different, due to circadian variability, the hemodynamic state of the patient, and concomitant diseases, which highlights the role of the differential gradient of two measurements.

Thus, how can a baseline measurement of a biomarker predict adverse events many years later? Such an approach is controversial, even when this measurement shows "statistical differences." Indeed, the risk of adverse events is not static, but dynamic. During a follow-up period, this risk is usually modified by aging, incident or changing comorbidities, and changes in drug therapies. Accordingly, biomarkers are also modified, and therefore, in proximity to the adverse event, biomarker levels might be quite "different" from measured baseline levels (►**Fig. 1**).

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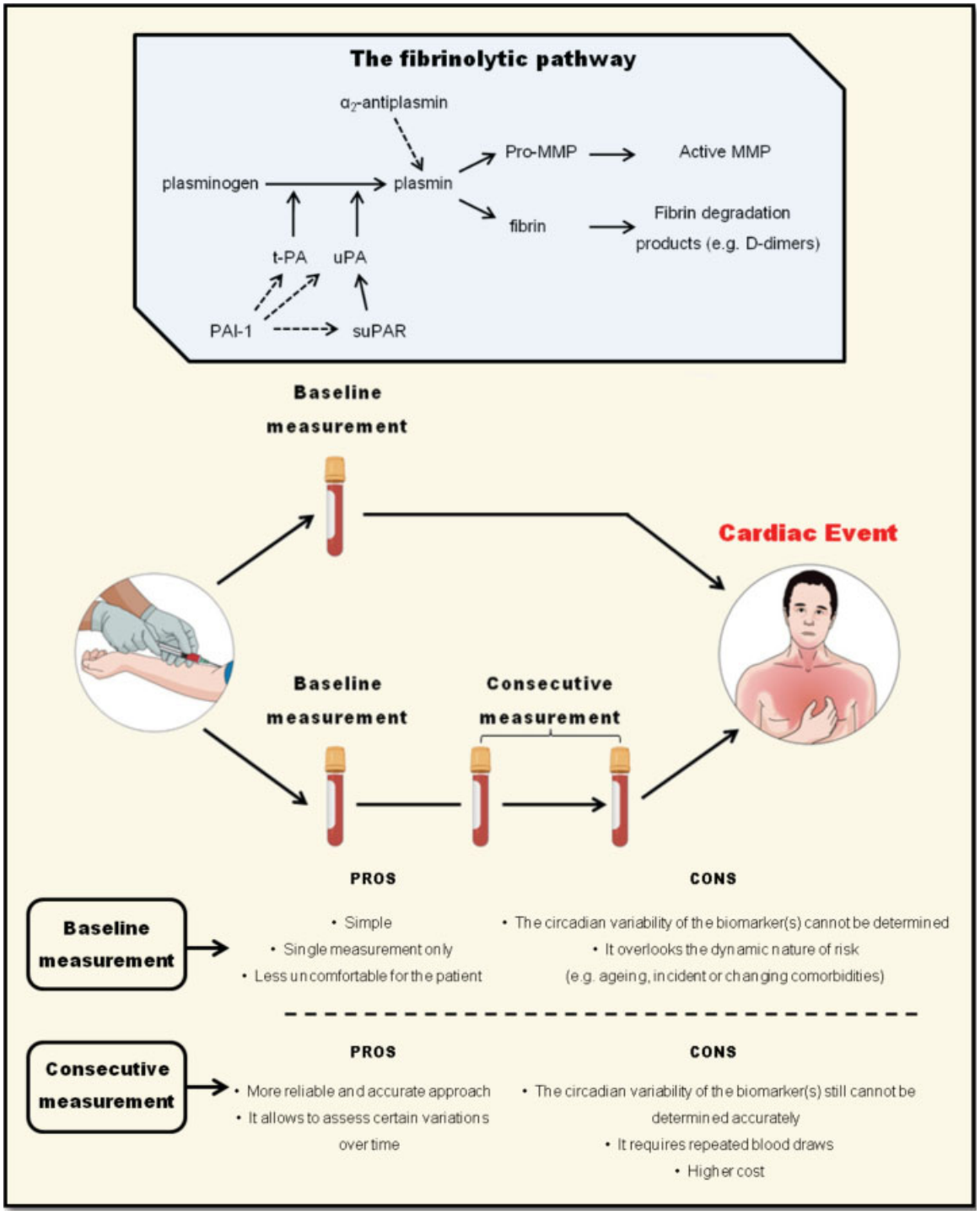

Fig. 1 The fibrinolytic pathway and different approaches for assessing biomarkers. MMP, matrix metalloproteinase; PAI-1, plasminogen activator inhibitor 1; suPAR, soluble urokinase plasminogen activator surface receptor; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator.

For the above reasons, the study by van den Berg et al has important strengths. The study was performed in a prospective and observational real-world cohort, which better reflects real-world clinical practice.[20] Of note, they measured biomarkers every 3 months over more than 2 years, and by using this approach, the authors were able to select the last two measurements prior to the endpoint, that is, closer in time to the adverse event. This provides more reliable and accurate information about the status of biomarkers, and their potential association with the event(s) of interest. Specifically, they demonstrated how important it is to take into account the change in biomarker levels with laboratory follow-up samples, particularly when the aim is to aid in decision making or risk stratification.

Nevertheless, several issues need to be clarified and further investigated. For example, many biomarkers are nonspecific and therefore can be associated with various cardiovascular and noncardiovascular outcomes at the same

time, including thromboembolism, bleeding, decompensated HF, atrial fibrillation, myocardial infarction, renal failure, severe infection, inflammatory disorders, or death. Thus, whether biomarkers are actually related to worse outcomes per se or simply reflect sick patients or sick hearts is still unknown. The inter- and intrapatient variability, use of specific biomarker assays, diurnal variation, influence of concomitant diseases, and drug therapies, as well as access to laboratories in different health care systems, may also hinder the generalizability of using some biomarkers.[21]

In conclusion, it is not just about "statistical significance" but the necessity of practical usefulness. Measurement of biomarkers should also balance costs and daily use in clinical practice since, and importantly, the incremental predictive value of biomarkers over simple clinical factors is only marginal even though multiple biomarkers are added.[22] In busy clinics and emergencies or ward settings, simplicity and practicality matter.

Conflict of Interest
None declared.

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