Heart failure (HF) is one of the most severe cardiovascular conditions and is associated with an increased morbidity and mortality [1] and very high treatment costs [2], which could be decreased by proper guideline-recommended medical treatment [3]. Early detection of HF is key and there is an unmet need to implement reliable biomarkers as potential outcome predictors and therapy guiders. The pathogenesis of HF is complex and includes metabolic abnormalities leading to progressive impairment of cardiac and skeletal muscle high-energy phosphate production [4]. A thorough understanding of the cardiac metabolism is mandatory for identifying reliable metabolic biomarkers. Although about 6500 metabolites are considered as potential contributors to maintenance of normal biological functions [5], their precise functional roles have not been clearly defined [6,7]. Until today about 100 biomarkers have been proposed and tested either clinically or experimentally in HF [8], with a only few biomarkers being used clinically.

The most commonly used biomarkers for the diagnosis and prognosis of HF are B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) [9]. Other biomarkers such as plasma adiponectin [10], galecit-3 [9], GDF-11 [8], or MICRA (Myocardial Infarction-associated Circular RNA) [11], among others, have been less well validated in HF. Although there has been an interest in validating metabolic biomarkers such as acetacetate, a member of the ketone bodies group, along with 3-hydroxybutyrate and acetone [12], the clinical use and value of such biomarkers is still limited.

Acetacetate has been proposed as a potential biomarker of HF prognosis [13] and HF severity [13–17]. The major sources of acetacetate in the heart are fatty acids and glucose, while ketone bodies, lactate and amino acids play only a minor role [18,19]. Under normal conditions, the heart covers its energy demands through oxidation of fatty acids in the mitochondria. In the failing heart, an increase in this process is an early event, with a shift toward glycolytic metabolism [20]. Although the uptake of ketone bodies is increased in HF [21], it is unclear whether this is an adaptive or a maladaptive change in metabolism, with some data pointing to potential beneficial effects [22]. It appears that ketone bodies have anti-inflammatory effects, reduce atherosclerosis, sympathetic nervous system activity, oxidative stress, and diminish cellular damage and cardiomyocyte apoptosis [21]. However, whether ketone bodies (including acetacetate) can be used as reliable biomarkers of HF is not established.

In this issue of IJC Heart & Vasculature Yokokawa and al. proposed acetacetate as a potential biomarker to predict the prognosis of HF patients [23]. The study enrolled 615 consecutively hospitalized patients with HF. Patients taking SGLT-2 inhibitors were excluded because of the potential effect on circulating acetacetate levels. There were also no significant differences in acetacetate levels between HF patients with and without diabetes mellitus. Circulating levels of serum acetacetate were measured by an enzymatically using venous blood samples collected at the time of admission, regardless of the prandial state. Subjects were divided into two groups: “low acetacetate group” and “high acetacetate group”. Follow-up data showed that the latter had a worse prognosis pointing to differences in metabolism between those patients. Nonetheless, it is important to stress that the high acetacetate group included older patients with a higher NYHA classification, prevalence of hypertension and BNP levels compared to the low acetacetate group. In a multivariate analysis, circulating acetacetate levels were associated with all cause mortality. Of note the association with cardiac death was present only by the univariate analysis. In addition, the level of acetacetate did not correlate with cardiac events in the NYHA classes III and IV for unclear reasons. The authors speculate that acetacetate acts as a marker of increased oxidation in low degree of HF and as alternative fuel in more severe forms of HF.

In conclusion, although acetacetate might constitute of potential biomarker of HF, it is likely that some factors might have biased the results. For instance the study did not take into account possible changes in treatment or clinical parameters that could have influenced the level of acetacetate. In addition, the follow-up period was rather short in order to establish the role of circulating acetacetate levels in HF. Finally, the added value of using another biomarker for prognosis in HF, in addition or instead of NT-proBNP, remains unclear. Thus, BNP and NT-proBNP remain the gold standard biomarkers in determining the diagnosis and prognosis of HF [24]. Clearly, prospective clinical trials in large patient populations are needed to prove whether acetacetate is a reliable and cost-effective biomarker of HF and validate whether it provides a better prognostic value than conventional biomarkers in the different subpopulations of HF patients.

Funding sources

Dobromir Dobrev: The author’s research work is funded by the National Institutes of Health (R01-HL131517, R01-HL136389, and R01-HL089598 to DD) and the German Research Foundation (Do 769/4-1 to DD).
Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Received 8 November 2019
Accepted 8 November 2019

Available online 19 November 2019