



Editorial

Prognostic value of biomarkers of impaired metabolism in heart failure patients with reduced ejection fraction



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 bioadrenomedullin [10], galectin-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 acetoacetate, 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.

Acetoacetate has been proposed as a potential biomarker of HF prognosis [13] and HF severity [13–17]. The major sources of acetoacetate 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 decrease 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 acetoacetate) can be used as reliable biomarkers of HF is not established.

In this issue of IJC Heart & Vasculature Yokokawa and al. proposed acetoacetate 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 acetoacetate levels. There were also no significant differences in acetoacetate levels between HF patients with and without diabetes mellitus. Circulating levels of serum acetoacetate 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 acetoacetate group" and "high acetoacetate 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 acetoacetate group included older patients with a higher NYHA classification, prevalence of hypertension and BNP levels compared to the low acetoacetate group. In a multivariate analysis, circulating acetoacetate 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 acetoacetate did not correlate with cardiac events in the NYHA classes III and IV for unclear reasons. The authors speculate that acetoacetate 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 acetoacetate 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 acetoacetate. In addition, the follow-up period was rather short in order to establish the role of circulating acetoacetate 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 acetoacetate 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.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

References

- [1] A. Aimo, C. Seghieri, S. Nuti, M. Emdin, Building medical knowledge from real world registries: the case of heart failure, *Int. J. Cardiol. Heart Vasc.* 19 (2018) 98–99, <https://doi.org/10.1016/j.ijcha.2018.03.008>.
- [2] X. Du, A. Khamitova, M. Kyhlstedt, S. Sun, M. Sengoele, Utilisation of real-world data from heart failure registries in OECD countries – a systematic review, *Int. J. Cardiol. Heart Vasc.* 19 (2018) 90–97, <https://doi.org/10.1016/j.ijcha.2018.02.006>.
- [3] K. Balakumaran, A. Patil, S. Marsh, J. Ingrassia, C.L. Kuo, D.L. Jacoby, et al, Evaluation of a guideline directed medical therapy titration program in patients with heart failure with reduced ejection fraction, *Int. J. Cardiol. Heart Vasc.* 22 (2019) 1–5, <https://doi.org/10.1016/j.ijcha.2018.10.003>.
- [4] G.M. Rosano, C. Vitale, Metabolic modulation of cardiac metabolism in heart failure, *Card Fail Rev.* 4 (2) (2018) 99.
- [5] M.-L. Cheng, C.-H. Wang, M.-S. Shiao, M.-H. Liu, Y.-Y. Huang, C.-Y. Huang, et al, Metabolic disturbances identified in plasma are associated with outcomes in patients with heart failure, *J. Am. Coll. Cardiol.* 65 (15) (2015) 1509–1520.
- [6] R. Ikegami, I. Shimizu, Y. Yoshida, T. Minamino, Metabolomic analysis in heart failure, *Circ J.* 82 (1) (2018) 10–16.
- [7] J. Schroder, N.D. Mygind, D. Frestad, M. Michelsen, H.E. Suhrs, K.B. Bove, et al, Pro-inflammatory biomarkers in women with non-obstructive angina pectoris and coronary microvascular dysfunction, *Int. J. Cardiol. Heart Vasc.* 24 (2019) 100370, <https://doi.org/10.1016/j.ijcha.2019.100370>.
- [8] M. De Buyzere, D. Gruson, CCA special issue: biomarkers in heart failure Available from: *Clin. Chim. Acta* 443 (2015) 1–2.
- [9] H.K. Gaggin, J.L. Januzzi, Biomarkers and diagnostics in heart failure, *Biochim. Biophys. Acta – Mol. Basis Dis.* 1832 (12) (2013) 2442–2450, <https://doi.org/10.1016/j.bbdis.2012.12.014>.
- [10] M. Arrigo, J. Parenica, E. Ganovska, M. Pavlusova, A. Mebazaa, Plasma bioadrenomedullin is a marker of acute heart failure severity in patients with acute coronary syndrome, *Int. J. Cardiol. Heart Vasc.* 22 (2019) 174–176, <https://doi.org/10.1016/j.ijcha.2019.02.011>.
- [11] A. Salgado-Somoza, L. Zhang, M. Vausort, Y. Devaux, The circular RNA MICRA for risk stratification after myocardial infarction, *Int. J. Cardiol. Heart Vasc.* 17 (2017) 33–36, <https://doi.org/10.1016/j.ijcha.2017.11.001>.
- [12] J. Lommi, P. Koskinen, H. Näveri, M. Härkönen, M. Kupari, Heart failure ketosis, *J. Intern. Med.* 242 (3) (1997) 231–238.
- [13] M. Takahashi, K. Ueda, R. Tabata, S. Iwata, K. Ozawa, S. Uno, et al, Arterial ketone body ratio as a prognostic indicator in acute heart failure, *J. Lab. Clin. Med.* 129 (1) (1997) 72–80.
- [14] F.G. Marcondes-Braga, I.G.R. Gutz, G.L. Batista, P.H.N. Saldiva, S.M. Ayub-Ferreira, V.S. Issa, et al, Exhaled acetone as a new biomarker of heart failure severity, *Chest [Internet]* 142 (2) (2012) 457–466, <https://doi.org/10.1378/chest.11-2892>.
- [15] F.G. Marcondes-Braga, G.L. Batista, I.G.R. Gutz, P.H.N. Saldiva, S. Mangini, V.S. Issa, et al, Impact of exhaled breath acetone in the prognosis of patients with heart failure with reduced ejection fraction (HFrEF). One year of clinical follow-up, *PLoS One* 11 (12) (2016) 1–10.
- [16] J.H. Chung, J.S. Kim, O.Y. Kim, S.M. Kang, G.S. Hwang, M.J. Shin, Urinary ketone is associated with the heart failure severity, *Clin. Biochem. [Internet]* 45 (18) (2012) 1697–1699, <https://doi.org/10.1016/j.clinbiochem.2012.08.013>.
- [17] S.M. Kang, J.C. Park, M.J. Shin, H. Lee, J. Oh, D.H. Ryu, et al, ¹H nuclear magnetic resonance based metabolic urinary profiling of patients with ischemic heart failure, *Clin. Biochem. [Internet]* 44 (4) (2011) 293–299, <https://doi.org/10.1016/j.clinbiochem.2010.11.010>.
- [18] A. Janardhan, J. Chen, P.A. Crawford, Altered systemic ketone body metabolism in advanced heart failure, *Texas Hear Inst. J.* 38 (5) (2011) 533–538.
- [19] I.F. Kodde, J. van der Stok, R.T. Smolenski, J.W. de Jong, Metabolic and genetic regulation of cardiac energy substrate preference, *Comp. Biochem. Physiol. – A Mol. Integr. Physiol.* 146 (1) (2007) 26–39.
- [20] H. Ardehali, H.N. Sabbah, M.A. Burke, S. Sarma, P.P. Liu, J.G.F. Cleland, et al, Targeting myocardial substrate metabolism in heart failure: potential for new therapies, *Eur. J. Heart Fail.* 14 (2) (2012) 120–129.
- [21] P. Puchalska, P.A. Crawford, Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics, *Cell Metab.* 25 (2) (2017) 262–284, <https://doi.org/10.1016/j.cmet.2016.12.022>.
- [22] G. Voros, J. Ector, C. Garweg, W. Droogne, J. Van Cleemput, N. Peersman, et al, Increased cardiac uptake of ketone bodies and free fatty acids in human heart failure and hypertrophic left ventricular remodeling, *Circ. Heart Fail.* 11 (12) (2018) e004953.
- [23] T. Yokokawa, A. Yoshihisa, Y. Kanno, S. Abe, T. Misaka, S. Yamada, et al, Circulating acetoacetate is associated with poor prognosis in heart failure patients, *Int. J. Cardiol. Heart Vasc.* 25 (2019) 100432, <https://doi.org/10.1016/j.ijcha.2019.100432> (in this issue).
- [24] H.K. Gaggin, J.L. Januzzi, Biomarkers and diagnostics in heart failure, *Biochim. Biophys. Acta – Mol. Basis Dis.* 1832 (12) (2013) 2442–2450.

Denisa Corina Ciuculete ^{a,b}

Dobromir Dobrev ^c

G.-Andrei Dan ^{a,b,*}

^a University Hospital Colentina, Bucharest, Romania

^b “Carol Davila” University of Medicine, Bucharest, Romania

^c Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany

* Corresponding author at: University of Medicine “Carol Davila”, Medicine Faculty, Colentina University Hospital, Bucharest, Romania.
E-mail address: andrei.dan@gadan.ro (G.-Andrei Dan)

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