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Voorrips, Suzanne N.; Daan Westenbrink, B.

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EDITORIAL

Circulating ketone bodies as signals for cardiovascular disease and mortality

Suzanne N. Voorrips and B. Daan Westenbrink *

Department of Cardiology, University Medical Center Groningen (UMCG), University of Groningen, Hanzeplein 1, P.O. BOX 30.001, 9700RB Groningen, the Netherlands

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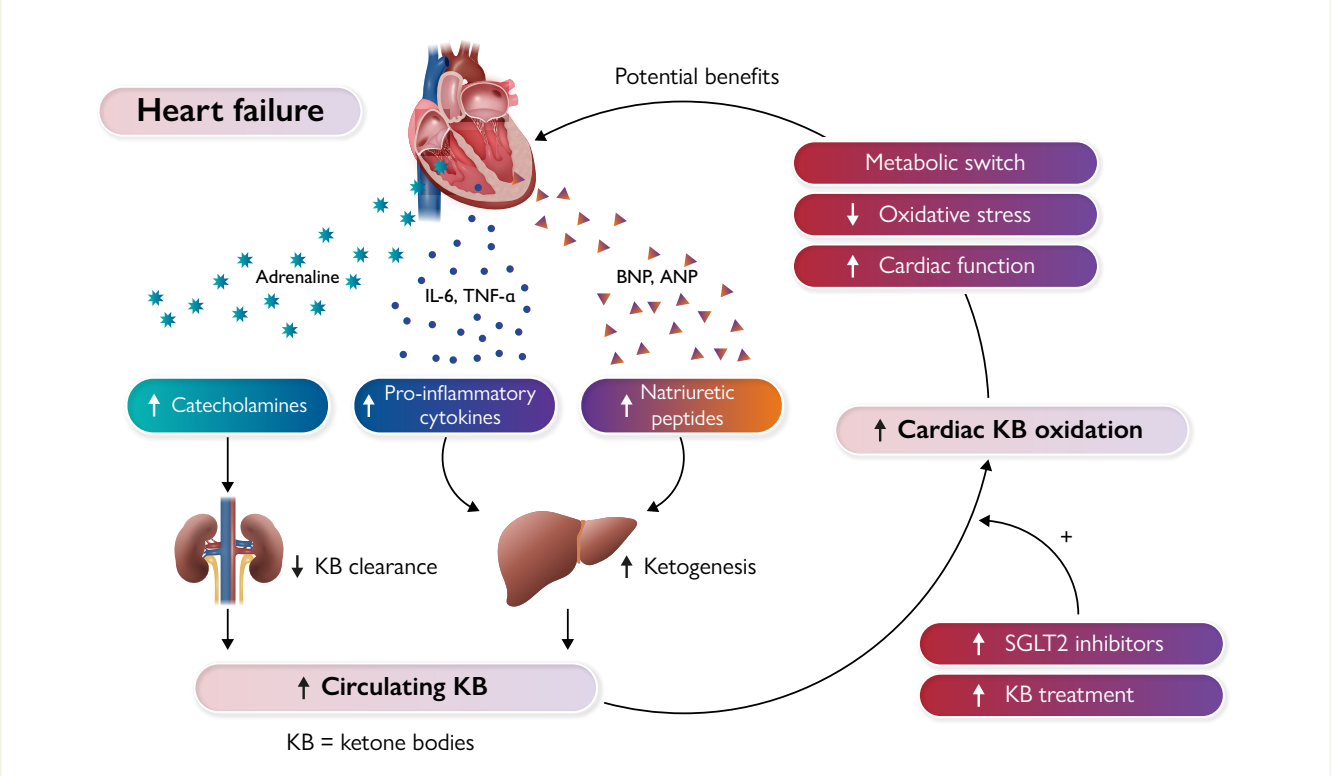
This editorial refers to 'Circulating ketone bodies and cardiovascular outcomes: the MESA study', by E. Shemesh *et al.*, https://doi.org/10.1093/eurheartj/ehad087.

Graphical Abstract



Underlying mechanisms and potential benefits of increased circulating ketone bodies in heart failure. Heart failure is associated with an increase in catecholamines, pro-inflammatory cytokines, and natriuretic peptides, resulting in a decrease in ketone body clearance and an increase in ketogenesis. The consequent elevation in circulating ketone bodies results in an increased cardiac ketone body oxidation. This latter effect is further escalated after ketone body or SGLT2 inhibitor treatment, resulting in potential cardiac benefits in heart failure. Abbreviations: KB, ketone body; SGLT2, sodium–glucose co-transporter 2.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author: Tel: +31 503616161, Email: b.d.westenbrink@umcg.n

Ketone bodies (KBs) are endogenous fuels which are generated by the liver in response to metabolic stress.[1] There are three types of KB, of which β-hydroxybutyrate and acetoacetate can be used to generate ATP, whereas acetone is metabolically inert. While these metabolites provide efficient fuels for the starving body, previously they have primarily been recognized as signals for harm due to their role in the diagnosis of diabetic ketoacidosis. More recently it has been discovered that KBs are also produced under conditions of neurohormonal stress, and circulating concentrations have been found to be increased in a variety of cardiovascular diseases (CVDs).[2] Ketogenesis in CVD is considered to be adaptive, as mice incapable of oxidizing KBs in their heart develop severe heart failure (HF) in response to injury,[3] while treatment with KBs can improve cardiac function.[1,4] While higher concentrations of KBs appear to correlate with the severity of neurohumoral stress, little is known about the association between circulating KBs and the incidence and prognosis of CVD.

In this issue of the *European Heart Journal*, Shemesh *et al*. explored the relationship between circulating KBs and cardiovascular outcomes in the Multi-Ethnic Study of Atherosclerosis (MESA) registry of 6796 healthy individuals.[5] Plasma concentrations of individual KBs were measured at study entry, and subjects were followed up for a mean duration of 13.6 years. The authors assessed correlations between individual and total KB concentrations and various cardiovascular outcomes. Interestingly, the authors observed consistent associations between higher concentrations of both the biologically active KBs β-hydroxybutyrate and acetoacetate as well as total KBs and the incidence of CVD. Associations were consistent for a composite endpoint of myocardial infarction, resuscitated cardiac arrest, stroke and cardiovascular death, and all other CVDs, as well as for the separate endpoints all-cause and CVD mortality. Of note, while there was a significant association between higher KB concentrations and the incidence of HF, the univariate associations between stroke or myocardial infarction were lost after multivariable adjustments. These findings led the authors to conclude that circulating KBs could serve as a biomarker for future CVD.

The authors should be applauded for their diligent study, which provides in-depth evaluation of individual and total KBs, multiple definitions of CVD, and extensive multivariable adjustments. Furthermore, the lucid discussion provides a thorough interpretation of the predictive value of circulating KBs and the explanation of the role in different settings of cardiovascular health and disease.

One of the main strengths of the current analysis is the fact that this is the first study to show a clear association between circulating KBs and the incidence of cardiovascular events in healthy individuals. Furthermore, these conclusions are drawn from a diverse, multiethnic cohort with a predictive value of circulating KBs in both sexes. As Shemesh *et al*. described in their Discussion, there are several preceding studies that did not find an association between KBs and CVD outcome parameters.[5] We previously studied the association between KBs and outcomes in a population of healthy elderly subjects at risk for CVD and detected similar associations between circulating KBs and new-onset HF, showing that the association was stronger in females.[6] In addition, others found an independent association between acetoacetate and incident HF in a population of healthy men.[7] Interestingly, circulating KBs were also markedly increased in patients with an ST-elevation myocardial infarction, and higher concentrations were associated with left ventricular dysfunction after 4 months in these patients.[8] These results substantiate the hypothesis that circulating KBs could function as a biomarker for CVD, although most evidence so far suggested that KB concentrations predicted HF and mortality.[6,7,9,10] This hypothesis can be supported by the fact that circulating KBs were elevated further in the decompensated setting of HF and—when increased—were found to be associated with a higher all-cause mortality after 3 months.[9,11] Of note, in the current analysis, KB concentrations were only significantly associated with the incidence of HF and CVD, and not with the incidence of stroke or myocardial infarction.

Supposedly, evaluating associations between KBs and outcomes in different settings could increase the understanding of the role of KBs in cardio metabolism. Whilst a biomarker for disease, increased KBs could reflect a protective mechanism. In the stable chronic setting of HF, a cardiac shift towards increased cardiac utilization of KBs was shown to have beneficial effects on cardiac function.[4,12,13] Providing an efficient energy source in a setting of decreased mitochondrial function, KB could serve as alternative fuel,[14] not to mention other effects of KBs such as reduction of oxidative stress which could further benefit the failing heart.[15] Furthermore, the authors refer to the hypothesis that the cardio-protective effects of sodium–glucose co-transporter 2 (SGLT2) inhibitors work through a metabolic switch in favour of KBs. Although a mechanistic study proving this mechanism is still lacking, evidence is accumulating that the metabolic switch towards KBs reflects an adaptive response in subjects with or at risk for CVD. Whether treatment with (exogenous) KBs is protective in this setting remains to be established.

As the authors fairly state, the underlying mechanism responsible for the association between KBs and CVD is hard to unravel with an epidemiological study, among other things because KB metabolism can be influenced by many different factors, including diet, physical activity, and various hormones. Although the authors were able to correct for many different variables, including calory intake and physical activity, a mechanistic explanation is difficult to ascertain. Nevertheless, they did find a modest association between increased NT-proBNP levels and KB concentrations. In addition to insulin, a variety of hormones have been shown to influence KB concentrations, including natriuretic peptides and catecholamines.[2] It is possible that similar mechanisms are involved with the associations demonstrated in the current manuscript.

Unfortunately, no repeated measures of circulating KBs were available in the period leading up to the onset of CVD events. This could have given more insights into the role of KBs as a biomarker. Furthermore, the authors stratified their analysis for β-hydroxybutyrate and acetoacetate but did not explore the predictive value of the third ketone body, acetone. While β-hydroxybutyrate is the ketone body with the highest bioavailability, acetone is the breakdown product of acetoacetate and is metabolically inert. Previous literature hypothesized that the 'idle' acetone could therefore be a more suitable reflection of total ketogenesis.[9,11] In this present study, in all models a stronger association for incident CVD events was found for acetoacetate as compared with β-hydroxybutyrate.[5] Considering the difficulties in differentiation between ketogenesis, oxidation, and clearance of KB, analysis of acetone in this cohort could have strengthened the predictive value of KBs in the onset of CVD events even further. Lastly, the authors do not elaborate on the type of HF or left ventricular ejection fraction in this analysis. As the differences in pathophysiological development are becoming more and more apparent over recent years, Flores *et al.* described that an increased concentration of KBs was predominantly associated with HF with reduced ejection fraction and not with HF with preserved ejection fraction.[6] Future studies should focus more on the associations with different HF subtypes to ascertain this hypothesis.

In this work, Shemesh *et al*. amplify the existing proof that KBs could serve as a biomarker for new-onset HF and, moreover, they show how increased circulating levels of KBs can be predictive for other CVDs and

that this association is independent of sex and ethnicity. Mechanistic underpinnings of ketogenesis in cardiovascular disease and whether these findings are protective or pernicious in this setting remain to be established.

Conflict of interest

None declared.

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