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EDITORIAL COMMENT

Realizing the Potential of Metabolomics in Heart Failure

Signposts on the Path to Clinical Utility*

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Heart failure (HF) is a heterogeneous clinical syndrome affecting more than 5 million people in North America alone. In the past decade, we have witnessed significant advances in neurohormonal modulation, electrophysiologic therapies, and mechanical circulation; however, patients with HF still suffer from excess morbidity and mortality on par with many malignancies. How might we stem the tide of the swelling HF epidemic in the 21st century? One way we could address this challenge is by identifying and targeting alternative biological pathways involved in HF pathophysiology. In this issue of *JACC: Heart Failure* Lanfear et al. (1) present data further supporting metabolism as one such pathophysiologic axis on which we should focus in the coming years.

Using targeted metabolomic profiling of plasma in a large cohort of patients with a history of HF and reduced ejection fraction, Lanfear et al. (1) identify significant differences in circulating metabolites among key HF subgroups: diabetics versus nondiabetics, ischemic versus nonischemic HF etiology, African Americans versus other races, and male versus female. Further, plasma metabolite profiles differ significantly by age, as well as by New York Heart Association functional class and 6-min walk distance. Most important, they identify a set of 13 metabolites independently associated with survival. In alignment with prior studies, these metabolites were involved in the tricarboxylic acid cycle (e.g., succinate, α-ketoglutarate, and fumarate), fatty acid oxidation (e.g., long-chain acylcarnitines), and nitric oxide synthesis (e.g., arginine). Overall, these data contribute to an expanding body of literature suggesting that perturbations of these and other key energy-producing pathways mediate HF pathogenesis and progression, and contribute to residual risk beyond neurohormonal, hemodynamic, and electrophysiologic abnormalities (2).

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As the authors acknowledge, however, these data do not identify a new HF biomarker, or clarify mechanisms of HF-associated metabolic impairments. Rather, the strength of this investigation is broader in scope: It constitutes further proof of concept of the potential of metabolism, and metabolomics, as a primary investigative tool for refining phenotypes, improving risk stratification, and identifying novel therapeutic targets in HF. But, how do we begin to realize this great potential? The steps will be many, and the journey will require focus and collaboration from investigators in clinical, translational, and basic arenas. The present article highlights several key principles that can maximize the usefulness of metabolomics investigations in HF. These principles, or signposts, will help to guide us on the path to developing clinically impactful applications of metabolism and metabolomics in the management of HF (**Figure 1**).

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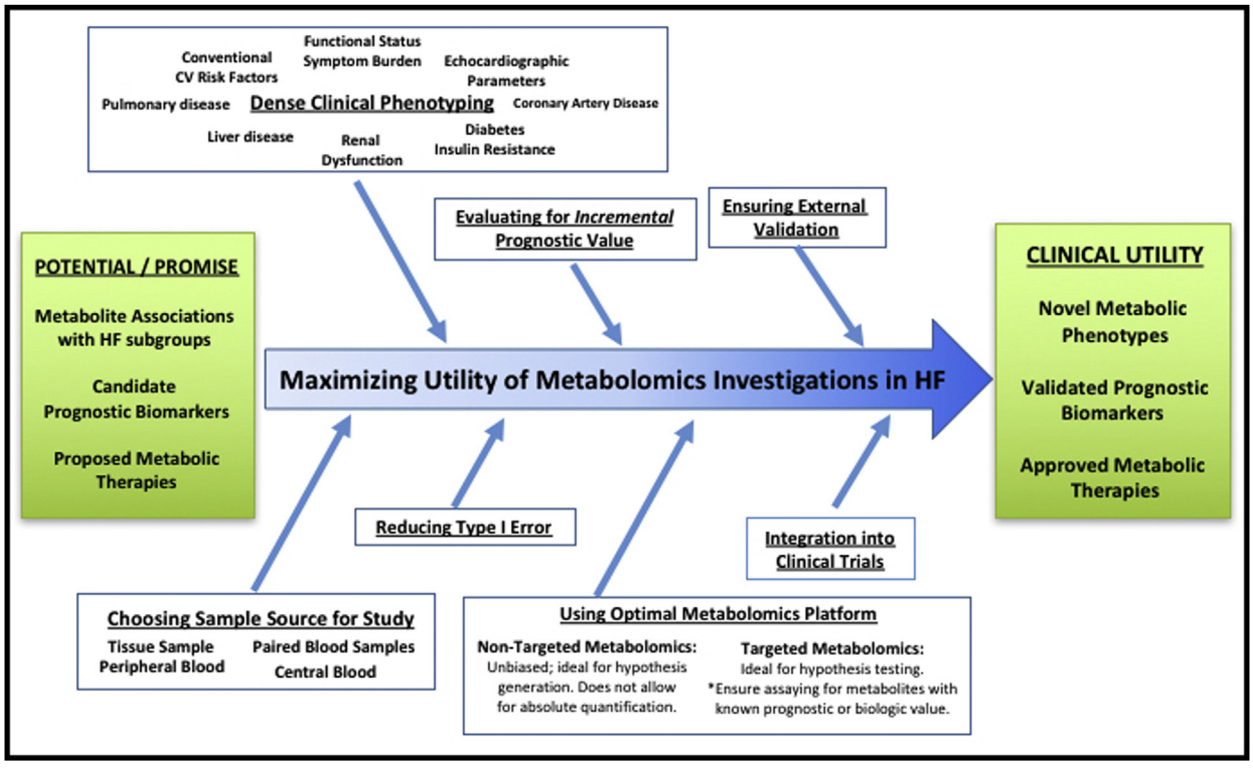
FIGURE 1 Identification and Development of Novel Metabolic Biomarkers and Therapeutics in Heart Failure



Design principles, or signposts, guiding the identification and development of novel metabolic biomarkers and therapeutics in heart failure (HF). CV = cardiovascular.

PERFORMING DENSE CLINICAL PHENOTYPING

The first key principle for metabolomics investigations, and signpost on the journey to clinical usefulness, is dense clinical phenotyping. This is well-exemplified in the study by Lanfear et al. (1); they collected all of the variables included in the validated Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score (3). These variables included age, sex, smoking, presence of diabetes, HF duration, systolic blood pressure, left ventricular ejection fraction, body mass index, New York Heart Association functional class, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or beta-blockers. Additionally, they collected natriuretic peptide measurements on all subjects. Dense clinical phenotyping, as demonstrated in this study, is critical because it improves signal-to-noise ratio, and thereby facilitates detection of key metabolite associations with outcomes or subgroups of interest. Additionally, it enables thorough adjustment in multivariate modeling, and reduces confounding. In fact, circulating metabolite profiles are significantly impacted by a number of clinical measures and their associated comorbidities, such as coronary artery disease (CAD), diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disease (2).

Importantly, Lanfear et al. (1) show that, although attenuated, the 13 metabolite profile remained predictive of mortality even after accounting for the important clinical covariates included in the MAGGIC score. However, the presence or severity of CAD is not adjusted for in this analysis. This omission is critical because several metabolites included in the 13 metabolite panel have been associated with CAD severity in previous studies published by our group, and discriminate ischemic vs. nonischemic etiology of HF in the present study (4). This lack of adjustment for CAD thus complicates interpretation of the mortality results because some of the associations could be primarily related to CAD as opposed to HF per se; nevertheless, the authors should be lauded for their attempts to minimize confounding and show independent association. Finally, although not pursued in