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Proteomics for understanding progression to heart failure in chronic kidney disease. Promising but still not there.

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After a long period during which there was a steep rise in the number of publications mainly focusing on risk prediction and the effect of cardiovascular (CV) disease medications on individual biomarkers, we are seeing the emergence of proteomics technologies assaying thousands of blood protein levels at once. This is occasionally combined with other “multiomics”, and more sophisticated data science is transitioning biomarker clinical research to the higher level of disease phenotyping, mechanistic investigations, and discovery of new drug targets.

In this Journal’s issue, Dubin et al.¹ investigated novel circulating proteins associated with progression to heart failure (HF), running a proteomic bioassay of over 5000 unselected proteins in existing cohorts of almost 3000 patients at risk of developing HF, because of the co-existence of chronic kidney disease (CKD). They were able to describe novel individual protein risk factors for HF, some of which are druggable targets. They also showed that that multi-protein risk models have better discrimination for incident HF than the classical clinical risk models. Interestingly, a 4-variable model including N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) high-sensitivity cardiac troponin T (hs-cTnT), albuminuria, and estimated glomerular filtration rate (eGFR) that was developed and validated in the Chronic Renal Insufficiency Cohort (CRIC) study provided similar (or superior) accuracy compared to the 48-protein model proposed by Dubin et al. to predict HF, atherosclerotic and kidney outcomes.² However, Dubin et al.¹ did not perform direct comparisons of their multiproteomic models with this simple biomarker-driven 4-variable model using widely available laboratory values.

While the use of proteomics for the prediction of incident HF is important for targeting patients with the highest need for preventive therapies, this is not the main interest of using “omics” since these more complex models rarely add prognostic value to simpler models using strong prognosticators such as NT-proBNP, hs-cTnT, albuminuria and eGFR.² However, multiproteomic model development may be a more useful exercise when it identifies modifiable risk factors and potential drug targets.

Mitigating clinical risk factors, such as hypertension, the strongest attributable risk factor of HF is already robustly evidence-based, with a sharp decline in incident HF being associated with controlling blood pressure. Still, beyond, and independent from blood pressure control, additional benefits are likely mediated by interference with key mechanisms of progression to HF, such as the antifibrotic effects of renin angiotensin system inhibitors or mineralocorticoid receptor antagonists (MRAs),^{3,4} or through mechanisms yet to be fully understood of sodium-glucose transporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP1-RA) in patients with diabetes, CKD, obesity and high CV risk.⁵ Ironically, identification of HF prevention strategies has benefited from serendipitous findings more than from mechanistically-driven hypotheses.

We may be still a long way from personalised prevention of HF, based on biomarker stratification and mechanistic phenotyping. Indeed, the predictive value of the proteomic score described by Dubin et al.¹ does not add sufficient prognostic information to be useful for routine population screening. Improving BP control in all patients with hypertension and the use of guideline directed medical therapy is still the highest priority to prevent HF in patients with CKD.

An original approach to the work of Dubin et al.¹ is the selection of cohorts with some degree of CKD, because of the expected high rate of progression to HF. This is highly beneficial because of the consubstantial nature of HF and CKD as diseases frequently stemming from common risk factors, developing through similar mechanisms, frequently coexisting and reciprocally aggravating, and warranting therapy with similar medications.⁶

Along with some focus on CKD, Dubin et al.¹ also investigated the influence of left ventricular ejection fraction (LVEF) in patients with HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF) as possible distinct phenotypes. Although not definitive, largely because of lack of power with a low number of progressors to HFrEF and HFpEF, the results did not show sufficiently distinct proteomic profiles of predisposition to the respective EF based types of HF. Given that most drugs used for the treatment of patients with HF appear to be beneficial across a broad spectrum of ejection fractions, and that there is no evidence that strategies for prevention of HF may differ for HFrEF and HFpEF, the findings of no strong differential mechanistic proteomic predictors of HFrEF and HFpEF give credit to the obsolescence of EF-based stratification of HF.⁷

The use of proteomics for mechanistic investigation of diseases is a tempting exercise, and proteomic investigation of progression to HF has attracted recent attention.⁸ Although, it is too early to draw consistent conclusions across recent studies, convergent evidence points to the critical role of extracellular matrix (ECM), fibrosis, oxidative stress, and inflammation as causal pathways leading to HF. Further causal analysis of data collected by Dubin et al.¹ may help in exploring the implication of these findings. It is notable that many ECM proteins were identified in the heart as well as the vascular extracellular matrix, which could reflect the biology underlying a causative association between HF and hypertension, which was present

in almost all patients in the study cohort. It is likely that these very proteins and others more specific to the kidney are also implicated in the progression to HF and concomitant decline in kidney function. Fibrosis, a consequence of systemic inflammation is the most common feature of progression of HF and CKD in hypertension and metabolic diseases. An intriguing finding of the work of Dubin et al.¹ is that hepatic fibrosis ranked highest in Ingenuity Pathway Analysis. This may point to fibrosis as an overarching mechanism, common to HF, CKD, diabetes and metabolic dysfunction-associated steatotic liver disease (MASLD), which frequently coexist as part of a cardio-metabolism-kidney-liver syndrome.⁹

Causal inference using Mendelian randomisation is a valuable tool to characterise the causal relationship between an exposure and an outcome. In the work of Dubin et al., applying it after multiple appropriate adjustments, revealed six proteins with potentially causal associations, four of which are currently druggable targets: Fc fragment of IgG receptor IIb (FCG2B), Insulin-like Growth Factor Binding Protein-3 (IGFBP3), Carbonic anhydrase 6 (CAH6), and Asialoglycoprotein receptor1 (ASGR1).¹ Interestingly, two of these four proteins (FCG2B and IGFBP3) are directly linked to the insulin-growth factor that is responsible for several anabolic processes previously related to HF.^{10, 11} Another protein that has been previously related to the effect of SGLT2 inhibitors is CAH6 (carbonic anhydrase 6), the levels of which are increased with SGLT2 inhibitor treatment.¹⁰ Lastly, ASGR1 may play a role in the degradation of glycoproteins important for cardio-renal-metabolic diseases. Additionally, ASGR1 has been considered a target for liver-specific drug delivery.¹²

Druggability, refers to the likelihood of a target being effectively modulated by drug-like agents, however it takes more than druggability alone to make a good target. While these proteins are plausible targets for preventing HF and are familiar to CV researchers, other

reports using a similar approach (whether in incident or prevalent HF cohorts), point to different plausible druggable targets.^{13, 14} Such striking variations in the druggable targets identified with similar proteomics and Mendelian randomisation studies indicate that further research is needed to improve reproducibility of findings among apparently similar studies.

Clinical proteomics research is full of pitfalls. Dubin et al.¹ exerted laudable caution, using large sample size, separate derivation and validation cohorts, a tight level of false discovery rate, correction for multiplicity, multivariable models, interaction testing, functional enrichment with Gene Ontology and Ingenuity Pathway Analysis, two-sample Mendelian Randomisation utilising available databases and external validation of the protein findings in ARIC, as well as incident HF central adjudication, and protein assay quality control. Still, substantial unknown potential confounders may not be accounted for. Data science, statistics and computational methods are fast evolving fields. The reproducibility of proteomic assays has been recently questioned.¹⁵ There is variation in the quantitative measurements for many proteins across aptamer-based (used in the work by Dubin et al.¹), proximity-extension immunoassays and for correlations of these highly multiplexed technologies with targeted immunoassays. No matter how sophisticated the technique for assessing proteomic biomarkers, measuring circulating extracellular biomarkers will only be remotely indicative of intracellular mechanisms. Finally, Gene Ontology is used for data interpretation to provide functional annotation to proteins. Primarily developed in oncology, the current Gene Ontology annotation needs to be updated specifically for human proteins involved in CV processes, which may help in the more accurate identification of CV relevant proteomics signatures and druggable biotargets.

Dubin et al.¹ must be praised for their work advancing the field of clinical proteomics. Still, future refinements are expected in this field, integrating proteomics with multiomics data. Trial sponsors must be encouraged to provide access to major clinical trials data and bio-samples, since trial data, although potentially lacking generalisability, are usually of more optimal quality. Major unmet needs such as integrating the multi-organ dimension of cardio-renal-liver-metabolism disease, developing enrichment methods for targeted clinical trials, validation of surrogate endpoints which may substitute for hard outcomes and finally fulfilling the gestalt of personalised cardio-renal-metabolism medicine are exciting areas of investigations which may be significantly advanced with omics biomarker research

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Data availability statement

No new data were generated or analyzed in support of this research.

Author contributions

All co-authors contributed to conceptualization, drafting and approval of the manuscript, and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of interest disclosures

Zannad: Consulting fees from Applied Therapeutics, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Boston Scientific, Cardior Pharmaceuticals, Cereno Scientific, Cellprothera, CVRx, Merck, Novartis, Pfizer, and Servier; is the Co-founder of cardiorenal and Founder of CVCT.

Ferreira: Grants or contracts from AstraZeneca and Novartis; and consulting fees from Abbott.

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