ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3421

INVITED EDITORIAL

Reverse cardiac remodelling: VICTORIA for inflammation and cardiac metabolism

Matthew M.Y. Lee[1]*, Alberto Aimo[2,3], and Antoni Bayés-Genís[4,5,6]

[1]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; [2]Health Sciences Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy; [3]Cardiology Department, Fondazione Toscana Gabriele Monasterio, Pisa, Italy; [4]Heart Failure Clinic and Cardiology Service, University Hospital Germans Trias i Pujol, Badalona, Spain; [5]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; and [6]CIBERCV, Instituto de Salud Carlos III, Madrid, Spain

This article refers to 'Biomarker profiles associated with reverse ventricular remodelling in patients with heart failure and a reduced ejection fraction: Insights from the echocardiographic substudy of the VICTORIA trial' by J. Tromp *et al.*, published in this issue on pages xxx.

'Continuous improvement is better than delayed perfection'.
Mark Twain.

Cardiac structure and function may change over time reflecting the balance between ongoing cardiomyocyte injury and the beneficial effects of disease-modifying therapies.[1] A decline in left ventricular ejection fraction (LVEF) and an increase in left ventricular (LV) volumes, known as adverse remodelling (AR), is associated with worse prognosis. Conversely, recovery from LV dysfunction and dilatation, called reverse remodelling (RR), is usually characterized by improved symptoms, better quality of life, and lower risk of hospitalization or death.[1]

Following disease trajectories over time is crucial, as RR has become increasingly common with advances in treatment for heart failure (HF) with reduced ejection fraction (HFrEF), leading to HF with improved ejection fraction (HFimpEF). Cardiac remodelling, defined based on imaging findings, is accompanied by changes in laboratory values reflecting the severity of cardiac dysfunction and its impact on other organs and tissues through various mechanisms (hypoperfusion, activation of neurohormonal axes, and pro-inflammatory pathways). The relationship between cardiac remodelling and changes in biomarkers remains poorly explored.[1]

Prior studies have reported biomarker changes associated with RR in HFrEF. In the PROVE-HF study, reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) correlated with improvements in LVEF, LV end-systolic volume index (LVESVI), left atrial volume index, and E/e' at 12 months.[2] Similarly, in the GUIDE-IT trial, LV volume reductions and LVEF recovery were proportional to the decrease in NT-proBNP.[3] PROTECT also showed that NT-proBNP could serve as a non-invasive indicator of cardiac structure and function in HFrEF.[4] A biomarker-assist score (ST2-R2 score), including soluble suppression of tumorigenesis-2, was developed to predict RR and mortality.[5]

In VICTORIA, a phase 3 randomized placebo-controlled trial, the oral soluble guanylate cyclase stimulator vericiguat reduced the primary composite outcome of HF hospitalization (HFH) or cardiovascular death in 5050 patients with LVEF <45% and a high risk of new HFH.[6] An echocardiographic substudy in 419 patients showed significant improvements in LV structure and function over 8 months in both vericiguat and placebo groups.[7]

This current analysis of VICTORIA reports on biomarker profiles associated with RR in 419 patients with HFrEF over 8 months (*Figure 1*).[8] RR, defined as >5% absolute increase in LVEF or a >15% relative decrease in LVESVI, was seen in nearly half of patients (49%). The remainder (51%) showed no change or worsening of LVEF or LVESVI between baseline and 8 months. AR was defined as >5% absolute decrease in LVEF or a >15% relative increase in LVESVI. HFimpEF was defined as LVEF ≤40% at baseline with ≥10% point increase in LVEF and second LVEF measurement at 8 months >40%.[8] A total of 92 circulating protein biomarkers were collected at baseline and 8 months. Using weighted co-expression network analysis, clusters of highly correlated biomarkers were identified based on their temporal changes. The relationship between these clusters and remodelling was then assessed.

What are the key findings? First, all tested biomarkers at baseline did not predict future RR. Second, reductions in biomarkers associated with inflammation, LV wall stress, and cardiac metabolism – especially NT-proBNP, growth differentiation factor-15 (GDF-15), insulin-like growth factor-binding protein 1 (IGFBP1) and 7 (IGFBP7), chitinase-3-like protein 1 (CHI3L1), tumour necrosis factor ligand superfamily member 13B (TNFSF13B), osteoprotegerin (OPG), cathepsin D – were observed in patients who experienced RR, but not in those who did not, after adjustment for possible confounders. Third, no biomarker clusters or individual biomarkers were associated with AR or HFimpEF after correction for confounders.[8]

As for possible study limitations, less than 10% patients from VICTORIA were included in this analysis, and the cohort included

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.3397.

*Corresponding author. School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow G12 8TA, UK. Tel: +44 141 3302000, Email: matthew.lee.2@glasgow.ac.uk

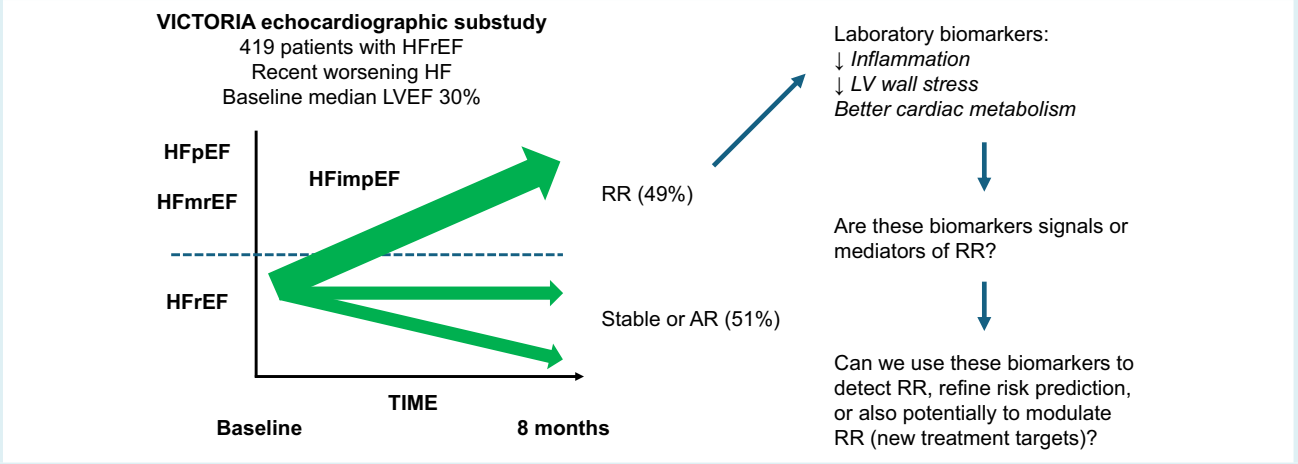

Figure 1 Biomarker profiles associated with reverse remodelling (RR) in the VICTORIA echocardiographic substudy. AR, adverse remodelling; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.

just 27% of women, which may limit result generalizability. The assessment of remodelling was performed concurrently with changes in biomarkers, rather than using changes in biomarkers as predictors of future remodelling and final outcomes. Possible confounding factors when exploring cardiac remodelling include patient demographics, comorbidities, concurrent medications, genetic predispositions, baseline LVEF and LVESVI, measurement variability, and study design and methodology. Furthermore, only one follow-up time interval at the arbitrary time-point of 8 months was studied. Even the definition of RR was just one of many proposed criteria for RR.[9]

In this study, RR was observed on the background of HF therapy including 76% of patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 16% on angiotensin receptor–neprilysin inhibitors, 95% on beta-blockers, 79% on mineralocorticoid receptor antagonists, and 12% having a biventricular pacemaker.[8] Sodium–glucose cotransporter 2 (SGLT2) inhibitors have also been shown to promote RR in HFrEF.[10,11] However, only 15 patients were on SGLT2 inhibitors, as the VICTORIA trial was conducted before SGLT2 inhibitors became a pillar of HFrEF treatment.

Future studies should examine biomarker profiles over time according to aetiology, HF duration, and rhythm (sinus rhythm vs. atrial fibrillation). For example, shorter HF duration and non-ischaemic aetiology are predictors of RR, while genetic or familial cardiomyopathies are less likely to recover.[12] Beyond LVESVI and LVEF, future studies could assess other LV parameters (wall thickness, mass, strain, diastolic function) and other cardiac chambers (left atrium, right heart) and utilize cardiac magnetic resonance (e.g. the absence of late gadolinium enhancement predicts RR).[12]

The interplay between biomarkers and RR, from association to cause–effect relationships, is investigated through dedicated mechanistic studies, potentially identifying new risk predictors. If biomarkers not only signal but also contribute to cardiac remodelling, they could serve as new treatment targets. For instance, the GARDEN-TIMI 74 (NCT05492500) trial is assessing ponsegromab, a monoclonal antibody directed against GDF-15, in patients with HFrEF and elevated baseline GDF-15.

If reduced inflammatory activation and improved cardiac metabolism partially mediate RR, anti-inflammatory therapies and treatments that enhance cardiac metabolism become highly interesting for inducing RR in HFrEF. In the DREAM-HF trial, mesenchymal precursor cell therapy, which has anti-inflammatory properties, increased LVEF at 12 months compared to sham controls, especially in patients with inflammation.[13] Furthermore, the SGLT2 inhibitor empagliflozin has been shown to promote RR in HFrEF,[10,11] as well as to reduce inflammatory biomarkers.[14]

Changes in biomarkers closely linked to the remodelling process and predictive of outcomes could serve as surrogate endpoints in HFrEF clinical trials.[15] Serial biomarker monitoring could guide the timing and frequency of clinical and imaging assessments. Several key questions remain: How many biomarkers are needed for optimal prediction of RR? Does a biomarker-guided strategy improve patient outcomes? Will such a strategy be cost-effective? How feasible is assessing biomarker profiles (single biomarkers, multiple biomarkers, biomarker panels, proteomic, and other multi-omics data) in clinical practice and research?

Overall, this analysis of VICTORIA provides novel insights by demonstrating that RR is associated with reductions in biomarkers associated with inflammation, wall stress, and dysregulated cardiac metabolism. These findings suggest potential targets for new HF therapies. What remains uncertain is whether these are signals or mediators of RR, as these associations may not imply causation. Future studies should define whether we can use these biomarkers to detect RR, refine risk prediction, or also potentially to modulate RR.

Conflict of interest: M.M.Y.L. has received research grants through his institution, the University of Glasgow, from AstraZeneca, Boehringer Ingelheim and Roche Diagnostics; is a member of a Trial Steering

Committee for Cytokinetics, and Clinical Endpoints Committee for Bayer. All other authors have nothing to disclose.

References

1. Aimo A, Gaggin HK, Barison A, Emdin M, Januzzi JL Jr. Imaging, biomarker, and clinical predictors of cardiac remodeling in heart failure with reduced ejection fraction. *JACC Heart Fail* 2019;**7**:782–794. https://doi.org/10.1016/j.jchf.2019.06.004
2. Januzzi JLJ, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, *et al.*; PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA* 2019;**322**:1085–1095. https://doi.org/10.1001/jama.2019.12821
3. Daubert MA, Adams K, Yow E, Barnhart HX, Douglas PS, Rimmer S, *et al.* NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFrEF. *JACC Heart Fail* 2019;**7**:158–168. https://doi.org/10.1016/j.jchf.2018.10.014
4. Weiner RB, Baggish AL, Chen-Tournoux A, Marshall JE, Gaggin HK, Bhardwaj A, *et al.* Improvement in structural and functional echocardiographic parameters during chronic heart failure therapy guided by natriuretic peptides: Mechanistic insights from the ProBNP Outpatient Tailored Chronic Heart Failure (PROTECT) study. *Eur J Heart Fail* 2013;**15**:342–351. https://doi.org/10.1093/eurjhf/hfs180
5. Lupón J, Gaggin HK, de Antonio M, Domingo M, Galán A, Zamora E, *et al.* Biomarker-assist score for reverse remodeling prediction in heart failure: The ST2-R2 score. *Int J Cardiol* 2015;**184**:337–343. https://doi.org/10.1016/j.ijcard.2015.02.019
6. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, *et al.*; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;**382**:1883–1893. https://doi.org/10.1056/NEJMoa1915928
7. Pieske B, Pieske-Kraigher E, Lam CSP, Melenovský V, Sliwa K, Lopatin Y, *et al.*; VICTORIA Study Group. Effect of vericiguat on left ventricular structure and function in patients with heart failure with reduced ejection fraction: The VICTORIA echocardiographic substudy. *Eur J Heart Fail* 2023;**25**:1012–1021. https://doi.org/10.1002/ejhf.2836
8. Tromp J, Lam CSP, Alemayehu W, deFilippi CR, Melenovský V, Sliwa K, *et al.*; VICTORIA Study Group. Biomarker profiles associated with reverse ventricular remodelling in patients with heart failure and a reduced ejection fraction: Insights from the echocardiographic substudy of the VICTORIA trial. *Eur J Heart Fail* 2024. https://doi.org/10.1002/ejhf.3397 Published online ahead of print 30/07/24.
9. Aimo A, Fabiani I, Vergaro G, Arzilli C, Chubuchny V, Pasanisi EM, *et al.* Prognostic value of reverse remodelling criteria in heart failure with reduced or mid-range ejection fraction. *ESC Heart Fail* 2021;**8**:3014–3025. https://doi.org/10.1002/ehf2.13396
10. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, *et al.* Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation* 2021;**143**:516–525. https://doi.org/10.1161/CIRCULATIONAHA.120.052186
11. Omar M, Jensen J, Ali M, Frederiksen PH, Kistorp C, Videbæk L, *et al.* Associations of empagliflozin with left ventricular volumes, mass, and function in patients with heart failure and reduced ejection fraction: A substudy of the Empire HF randomized clinical trial. *JAMA Cardiol* 2021;**6**:836–840. https://doi.org/10.1001/jamacardio.2020.6827
12. Aimo A, Vergaro G, González A, Barison A, Lupón J, Delgado V, *et al.* Cardiac remodelling – Part 2: Clinical, imaging and laboratory findings. A review from the Study Group on Biomarkers of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2022;**24**:944–958. https://doi.org/10.1002/ejhf.2522
13. Perin EC, Borow KM, Henry TD, Mendelsohn FO, Miller LW, Swiggum E, *et al.* Randomized trial of targeted transendocardial mesenchymal precursor cell therapy in patients with heart failure. *J Am Coll Cardiol* 2023;**81**:849–863. https://doi.org/10.1016/j.jacc.2022.11.061
14. Requena-Ibáñez JA, Santos-Gallego CG, Rodriguez-Cordero A, Vargas-Delgado AP, Mancini D, Sartori S, *et al.* Mechanistic insights of empagliflozin in nondiabetic patients with HFrEF: From the EMPA-TROPISM study. *JACC Heart Fail* 2021;**9**:578–589. https://doi.org/10.1016/j.jchf.2021.04.014
15. Bayes-Genis A, Aimo A, Jhund P, Richards M, de Boer RA, Arfsten H, *et al.* Biomarkers in heart failure clinical trials. A review from the Biomarkers Working Group of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2022;**24**:1767–1777. https://doi.org/10.1002/ejhf.2675