Tailored therapy for heart failure: the role of biomarkers

Kai C. Wollert*

Division of Molecular and Translational Cardiology, Department of Cardiology and Angiology, Hannover Medical School, D-30625 Hannover, Germany

This editorial refers to ‘Galectin-3 predicts response to statin therapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)’ 1, by L. Gullestad et al., on page 2290

The key process leading to heart failure (HF) is cardiac remodelling in response to chronic disease stresses. Several pathways, including those that regulate cardiomyocyte hypertrophy and processes that take place outside the cardiac myocyte, e.g. in the vasculature and extracellular matrix, play important roles in the remodelling process. Moreover, non-cardiac pathologies, such as renal dysfunction, anaemia, and skeletal myopathy, may develop in concert with left ventricular remodelling and contribute to the functional impairment in HF. Thus, HF, truly a syndrome rather than a disease, has many distinct subtypes. The heterogeneity of the HF syndrome implies that therapies have to be tailored to the individual patient to optimize the benefits and minimize the risks of a given drug or device.

European Society of Cardiology (ESC) guidelines recommend using New York Heart Association (NYHA) class, left ventricular ejection fraction, and QRS width to guide most treatment decisions in chronic HF. The degree of tailoring achieved with these recommendations is low, and, today, most HF patients are prescribed the same medications. The main virtue in monitoring BNPs may be to prevent therapeutic complacency and encourage continued efforts to maximize treatment. Measurement of BNPs cannot inform specific treatment decisions, however, which would represent the next evolutionary step towards tailored therapy for HF (Figure 1). The elegant study by Gullestad and colleagues moves us closer to that goal. The authors measured galectin (Gal)-3 in plasma samples from a subgroup of 1492 patients enrolled in CORONA and observed an interaction between Gal-3 concentration at baseline and benefit from rosuvastatin therapy. Among patients with below median plasma Gal-3, rosuvastatin reduced the risk of the primary endpoint (HR 0.65; 95% CI 0.46–0.92), whereas no benefit was observed in patients with above median Gal-3 (HR 1.07; 95% CI 0.79–1.45; P-value for interaction = 0.036). Should Gal-3 be used to select HF patients for statin therapy?

Gal-3 is a 29–35 kDa carbohydrate-binding protein that shuttles between the cytoplasm and nucleus and that can be secreted into biological fluids. Because of its expression in inflammatory cells and direct profibrotic effects, Gal-3 is thought to represent a ‘link’...
between inflammation and fibrosis. The circulating concentrations of Gal-3 are elevated in patients with HF and associated with disease severity and prognosis. The incremental prognostic value of Gal-3 beyond clinical variables and N-terminal pro B-type natriuretic protein (NT-proBNP) is uncertain however. Differential lipid-lowering effects of rosuvastatin were not observed in patients with different Gal-3 levels in CORONA, and the question of why low plasma concentrations of Gal-3 should identify a subgroup of patients who benefit from rosuvastatin remains unresolved. Answering this question will require a better understanding of the disease pathways reflected by Gal-3 which may provide fresh insight into HF pathophysiology and the lipid-independent mechanisms of action of statins.

The study by Gullestad and colleagues needs to be put in perspective with two previous reports from the CORONA Study Group showing that patients with high levels of high-sensitive-C-reactive protein or low levels of NT-proBNP benefitted from rosuvastatin in terms of a significant reduction of the primary endpoint. From a statistical perspective, searching for subgroups is known to be a dangerous exercise, with a high possibility of finding false positives. The general opinion is that if subgroups are going to be examined they should be defined a priori and that post-hoc data mining may lead to unreliable results, particularly if the newly identified interactions are not immediately biologically plausible. The biomarker studies from CORONA should therefore be considered hypothesis-generating and will not lead to changes in our current use of statins in HF, even more so since a directional interaction with statin therapy (benefit in one group vs. harm in another) has not been observed.

Advances in HF management will require a more comprehensive understanding of the heterogeneity of the HF syndrome at the cellular, organ, and organism levels. Plasma biomarkers, along with imaging and genetic testing, might be used to define HF subtypes responding differently to specific therapeutic interventions. It is hoped that with an improved understanding of the disease pathways reflected by plasma biomarkers, new treatment targets will emerge. Some plasma biomarkers may be developed as ‘companion biomarkers’ to identify patients with the greatest benefit from a (new) therapeutic intervention. This may result in a shift from risky ‘one size fits all’ HF mega-trials to smaller and smarter trials focusing on biologically defined subpopulations where the expected benefit from a new treatment is largest. Pursuing this path, we may ultimately prove Voltaire (1694–1778) wrong in his assertion that ‘Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing’.

Conflict of interest: Research funding from and licensing contract with Roche Diagnostics.

References

A 17-year-old girl was referred to our Unit for resistant hypertension (180/110), despite full-dose treatment with amlopidine, ramipril, and hydrochlorothiazide. Physical examination showed an abdominal bruit and the absence of the pedal pulse; thigh and leg muscles were normally developed. Angio-computed tomographic (angioCT) scanning revealed hypoplasia of the suprarenal portion of the aorta (5 mm diameter) that was normal in the infrarenal portion (12 mm diameter). The hypoplasia caused obstruction of the celiac trunk and of the superior mesenteric artery; at that level, the vascularization was warranted by the hypertrophy of the Riolano arcade through the inferior mesenteric artery that had a 7 mm diameter. The vascularization of the iliac–femoral axis was warranted by collateral circles on the thoraco-abdominal wall connecting the internal mammary arteries and the epigastric arteries, both markedly hypertrophic. We made a diagnosis of mid-aortic syndrome, a rare congenital disease of unknown aetiology, characterized by narrowing of the abdominal aorta and stenosis of its major branches. Symptoms depend on the severity of the lesions and the organ perfused by arteries originating from the narrowed aorta. Severe to malignant renovascular hypertension can result in heart and/or renal failure; leg claudication is frequently associated. Treatment is aimed at blood pressure control, renal function preservation, and surgery delay until adulthood. Surgical reconstruction is the preferred strategy. The patient received a by-pass between the thoracic descending aorta and the infrarenal abdominal aorta with reimplantation of the renal arteries and of the superior mesenteric artery and a by-pass between the prosthesis and the splenic artery. Six months after surgery, the patient is normotensive under ramipril 5 mg; angioCT scanning shows normal function of the by-pass and dramatic reduction in collateral circles.