Heart failure with reduced ejection fraction and monogenic dilated cardiomyopathy: Distinct diseases? Insights from randomized controlled trials

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The genetic component of heart failure with reduced ejection fraction (HFrEF) is traditionally considered as part of the non-ischaemic aetiology. Dilated cardiomyopathy (DCM) has been recognized as the most heterogeneous amongst the classical cardiomyopathy phenotypes, with >250 genes which have been causally related with the disease.[1] However, progresses in knowledge and availability of large international multicentre databases tightened the landscape of genes with solid association with the disease to about 20 genes,[2] which are now considered the basis for creating cardiomyopathy genetic panels in referral centres for the management of these diseases. The largest amount of evidence on genetic DCM indeed derives from the major tertiary care international centres, generating a bias in the quantification of the actual yield of genetic testing, which is reported ranging between 25% and 40% in the largest but still highly selected populations.[3]

In addition to monogenic causality, there are secondary non-ischaemic cardiomyopathy (NICM) cases characterized by a significant background of gene variants, particularly in the titin (*TTN*) gene, challenging traditional paradigms related to alcoholism, chemotherapy, and myocarditis as sufficient causes of non-ischaemic left ventricular systolic dysfunction.[4–6] The classical distinction between primary and secondary forms of DCM should be rather interpreted as a continuum, where the interplay between gene variants and additional myocardial injuries contributes to the development of the disease.

However, the complete understanding of the epidemiological contribution of genetic variants in the general population, especially in unselected HFrEF patients, remains an intriguing challenge. In the UK Biobank, which includes a wide range of individuals aged 40–69 years, 0.4% of participants carried pathogenic or likely pathogenic variants associated with DCM. The most prevalent variants were found in the *TTN* and *MYH7* genes, and the majority of carriers were women. Considering that the estimated prevalence of NICM in the general population is 1:250, with only a small fraction being hereditary, the observed prevalence of genetic variants in DCM seems high for a classic Mendelian model with complete penetrance. Only 3.1% of individuals with DCM-associated gene variants were diagnosed with DCM or heart failure, indicating the low penetrance of these variants in the general population.[7] However, it is important to note that also the general population recruited in Biobank may not be representative of HFrEF patients in the real world, as HFrEF patients are typically in an older stage of life and often have comorbidities that can act as confounders.

To better understand the genetic landscape of common HFrEF patients, randomized controlled trials (RCTs) offer an ideal opportunity, as they provide a controlled population for analysis, minimize confounders and ensure an established and verified diagnosis of heart failure. Additionally, RCTs are the most valuable source of evidence for HFrEF treatments and can thus provide insights into the influence of gene variants on treatment efficacy and tolerability.

A first experience has been derived from a study combining data from two RCTs, the Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality (CHARM)

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and the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trials. These RCTs included patients >60 years old with both ischaemic and non-ischaemic aetiology and, in CHARM, with both reduced and mildly reduced/preserved ejection fraction. 3.4% of patients had pathogenic/likely pathogenic variants, with *TTN* again as the predominant gene involved, and among aetiologies the yield was higher in patients with DCM, but also patients with hypertensive and ischaemic forms of heart failure were found to be carriers of potentially causative variants. Similar findings were obtained in the validation cohort from the UK Biobank.[8]

In this issue of the Journal, the study by Barat *et al.*[9] explored the genetic background in a subgroup of subjects from the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. Compared with the previous study, the authors had the possibility to analyse a more contemporary cohort of patients with exclusively HFrEF. Conducted between 2009 and 2014, the PARADIGM-HF study compared the efficacy of sacubitril/valsartan with the established treatment enalapril in patients with HFrEF. Sacubitril/valsartan, a combination of a neprilysin inhibitor and an angiotensin receptor blocker, showed remarkable superiority over enalapril, leading to a significant reduction in cardiovascular mortality and hospitalizations for heart failure.[10]

These results prompted a paradigm shift in the management of HFrEF, and sacubitril/valsartan became a cornerstone therapy for this condition.[11]

The post-hoc analysis by Barat *et al.*[9] utilized whole-exome sequence data from 1412 HFrEF participants in the PARADIGM-HF trial (defined as the WES cohort). These patients were predominantly white, hypertensive (75%), had ischaemic heart failure (65%), and were overweight (mean body mass index 29 kg/m^2), certainly aligned more with the general population than with a highly selected cohort of NICM patients. A total of 44 genes associated with DCM were divided into three tiers based on the strength of evidence supporting their association with the disease. The analysis focused on rare predicted loss-of-function (pLoF) variants within these genes, prioritizing variants using ClinVar annotations, measures of gene transcriptional output and evolutionary constraint, and pLoF confidence predictions. The prevalence of pLoF variant carriers was reported based on the gene tiers associated with DCM. The study also compared clinical characteristics between carriers and non-carriers but, for statistical reasons, no prognostic comparison was provided, nor familial investigations were available.

The results shed light on the prevalence and clinical characteristics of deleterious pLoF variants in genes definitely or strongly associated with DCM. Approximately 5% of patients in the WES cohort exhibited these variants, which is consistent with previous analyses in the general population and in HFrEF patients from the CHARM and CORONA trials.[8] *TTN* was the almost unique involved gene.

The observation of a similar prevalence of pLoF variants between the general population and HFrEF patients may initially appear as a discrepancy, as one would expect an enrichment of DCM-causing variants in the latter group. However, the clinical characteristics of these variant carriers could provide an explanation since they were younger, had lower ejection fraction and lower body mass index, and were less likely to have an ischaemic aetiology compared with non-carriers.

These findings indicate that mono-genetically determined NICM represents a distinct and relatively rare entity within the HFrEF population of RCTs and is characterized by clinical features that are largely under-represented in patients enrolled in RCTs, including the WES sub-cohort of the PARADIGM-HF trial.[9]

In conclusion, we can confirm the notion that unselected patients with HFrEF from RCTs accurately reflect the genetic landscape of the general population from which they are recruited.

The study by Barat *et al.*[9] adds another piece to the complex puzzle of the genetic susceptibility to heart failure, but once again also reaffirms the complexity of the aetiology behind the vast majority of HFrEF cases. Despite a consistent heritability of the disease, the role of genetics remains secondary, especially in its Mendelian form, in more than 90% of patients enrolled in RCTs on HFrEF. In addition, due to the potential predisposing nature and the low penetrance of pLoF *TTN* variants among older patients, establishing a definite causative role of such genetic variants in the remaining 10% of patients, although probable, is also extremely challenging.

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