Coronary artery disease and dilated cardiomyopathy: Where parallel universes merge

Marco Merlo[1,2]*, Martina Setti[1,2,3], and Gianfranco Sinagra[1,2]

[1]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy; [2]European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart (ERN GUARD-Heart); and [3]Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy

This article refers to 'Assessing the association between genetic and phenotypic features of dilated cardiomyopathy and outcome in patients with coronary artery disease' by R.E. Jones *et al.*, published in this issue on pages 46–55.

Coronary artery disease (CAD) is the leading cause of death worldwide[1], and its prevalence is set to grow with population ageing. As genetic profiling became widely accessible in large-scale research, the incorporation of genetic data with known long-standing cardiovascular risk factors has led to polygenic risk scores (PRS) as tools to improve the prediction of ischaemic disease.[2] On the other hand, dilated cardiomyopathy (DCM) has evolved in its concepts[3] for widespread diagnostic and therapeutic advancements, with the estimation of its prevalence ranging from 1 in 2500 to 1 in 250 individuals.[4] Indeed, in the last decades, cardiac magnetic resonance (CMR) and genetic testing have yielded insight into the complex pathophysiology of DCM, suggesting that 30–40% of DCMs may exhibit a monogenic Mendelian basis. CAD and DCM are structurally and functionally different heart diseases, with secondary aetiologies as the most important exclusion criteria from the DCM definition, bringing us to consider them as parallel and distinct universes. However, clinical practice has taught us idiopathic ventricular dilatation and dysfunction can coexist with important CAD, as DCM patients may develop incident ischaemic heart events, and severe ischaemic ventricular dysfunction is not always entirely explained by obstructive but limited coronary lesions. Moreover, CMR has shown non-ischaemic late gadolinium enhancement (NI-LGE) patterns not related to the territory of a coronary artery also in ischaemic patients, as well as the ischaemic pattern of LGE (subendocardial and transmural) has been reported in DCM without CAD.[5,6] Finally, identifying at-risk individuals who can benefit from tailored preventive interventions in both CAD and DCM is still a field of growing clinical concern.

All these features in CAD and DCM congregate and intersect in the complex interplay between genes and environment. In this issue of the Journal, Jones *et al.*[7] analysed the prevalence and the prognostic implication of genetic (DCM pathogenic genetic variants) and phenotypic (NI-LGE pattern in CMR) features in two independent cohorts of patients with stable CAD: the first included individuals from the UK Biobank (UKB), the second was composed of patients referred to a tertiary centre. The main findings were the following: (i) DCM pathogenic variants in patients with CAD impact left ventricular remodelling and outcomes; (ii) non-ischaemic pattern myocardial scar does not affect prognosis, and no rare genetic basis was found in patients with NI-LGE compared to those without this imaging feature. Moreover, the authors found that these results are mainly driven by titin truncating variants (TTNtv). Emerging evidence demonstrated that putative pathogenic variants in DCM genes, first of all TTNtv, can be present in healthy individuals.[8,9] Also, recent findings suggest additional environmental contributions (i.e. peripartum, alcohol, chemotherapy, inflammation, age) can unmask the deleterious cardiac effects of TTNtv in developing a dilated phenotype, with more adverse phenotypes.[10,11] The study seems to confirm the so-called 'second-hit' phenomenon, as CAD appears as another modifiable insult which potentially impacts a genetically-modified myocardium. On the other hand, pathogenic variants in DCM-associated genes, including TTNtv, do not seem to be the predominant driver of NI-LGE in CAD patients. Considering DCM as a dynamic disease and the more pronounced left ventricular reverse remodelling in TTNtv DCM,[12,13] in future studies, it would be interesting to assess if also CAD patients carrying a TTNtv have a higher rate of reverse remodelling during follow-up.

The authors have to be congratulated for this study opening two main scenarios. First, considering DCM as a monogenic disease is too simplistic, above all when TTNtv variants are involved, genetic

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.3033.

*Corresponding author. Cardiovascular Department, Azienda Sanitaria Universitaria Integrata di Trieste and University of Trieste, Via P. Valdoni 7, Trieste 34149, Italy.
Email: marco.merlo79@gmail.com

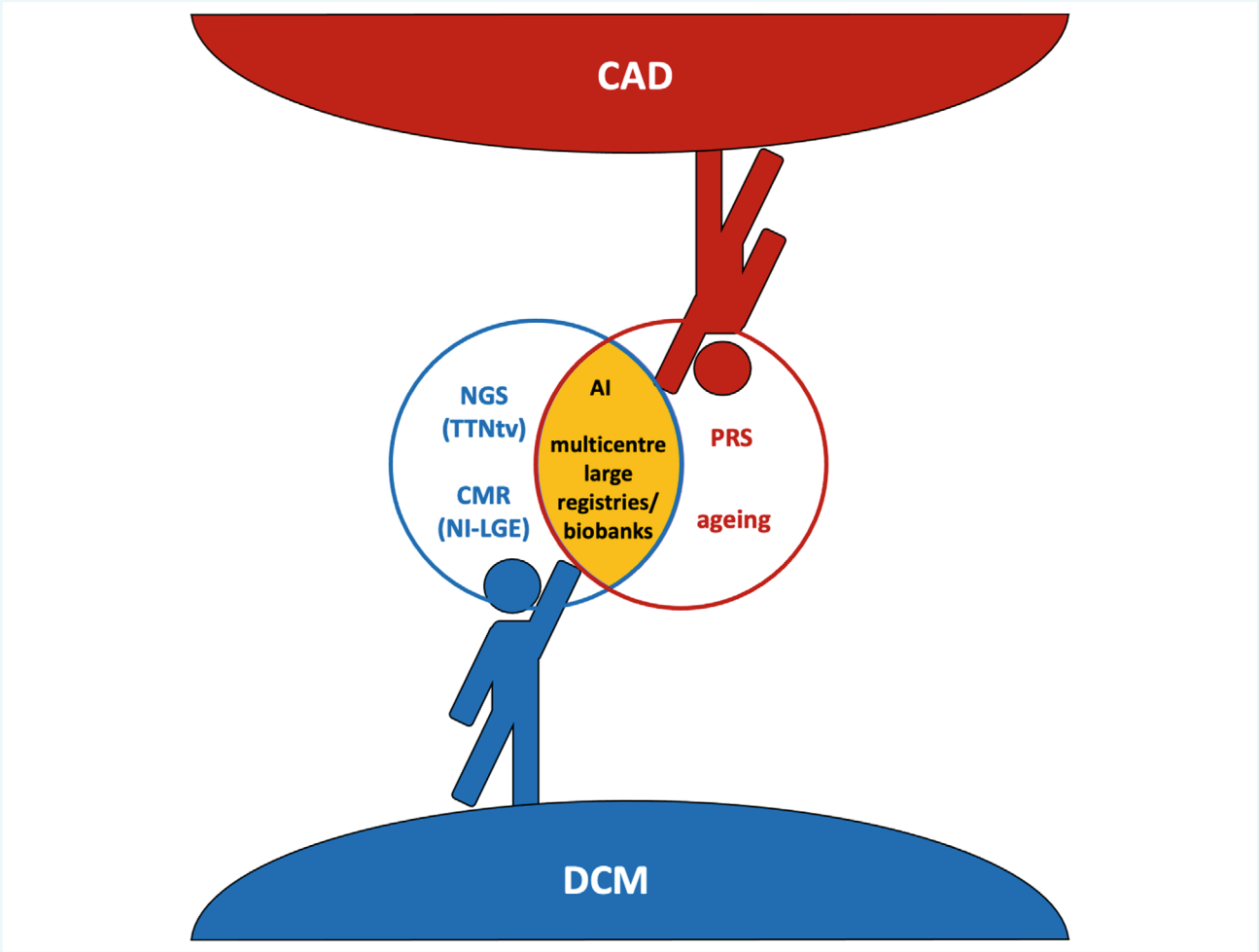

Figure 1 Graphical representation of genetic and phenotypic aspects of two distinct clinical scenarios (dilated cardiomyopathy and coronary artery disease) to reinforce throughout larger multicentre registries/biobanks and artificial intelligence. AI, artificial intelligence; CAD, coronary artery disease; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; NI-LGE, non-ischaemic late gadolinium enhancement; NGS, next generation sequencing; PRS, polygenic risk score; TTNtv, titin truncating variant.

analysis is 'negative' or shows variants of uncertain significance. The additional contribution of environmental modifiers and the possible additive or interactive influence of other genetic variants may exacerbate or attenuate the effect of the Mendelian genetic variant on the phenotype. Just like in CAD, PRS will help us understand deeper the complex genetic architecture as well as risk stratification and outcomes in DCM patients. Second, although the genetic and phenotypic overlap between DCM and other cardiomyopathies is established,[4] clinicians still often consider DCM as a stand-alone disease. The focus of management in DCM patients is centred on heart failure treatment and, in the last decades, arrhythmic risk stratification, considering DCM as a no-CAD by definition. However, in the era of precision medicine, advanced imaging techniques and better treatment options, DCM patients are older at first diagnosis[14] and become much older during extended follow-up. Consequently, the coexistence between DCM and CAD has to be considered and explored, especially in discrepancies in cardiac left ventricular remodelling, to be sure of what disease our patients are facing. For these reasons, the study offers a remarkable melting point between two separate universes, setting the course for the paradigm shift required to manage DCM and CAD patients (*Figure 1*). As a result, the impact of association between these diseases on prognosis and therapeutic strategies should be addressed with future multicentre studies. Indeed, adjusted data that support the correlation between DCM-associated genes and adverse clinical outcomes in CAD are missing in the study, mainly due to the limited number of participants with CAD in the UKB cohort who carry pathogenic variants in DCM genes (only eight individuals).

Finally, the authors stated a strong message about the possibility of applying genetic sequencing to CAD patients with greater left ventricular remodelling. However, DCM pathogenic variants have a low prevalence, approximately 0.5–0.6%, in the UKB cohort of the study. Caution should be maintained before considering genetics extensively in clinical practice in different contexts, such as CAD, due to its costs, accessibility, and all the possible implications for

probands and relatives. Larger multicentre registries and biobanks should help us identify CAD patients with higher pre-test probability to benefit from genetic testing, and artificial intelligence has been proving to play a key role for this purpose.[15]

Conflict of interest: none declared.

References

1. World Health Organization. Cardiovascular Diseases (CVDs). 2022.
2. Patel AP, Wang M, Ruan Y, Koyama S, Clarke SL, Yang X, *et al.*; Genes & Health Research Team; the Million Veteran Program. A multi-ancestry polygenic risk score improves risk prediction for coronary artery disease. *Nat Med* 2023;**29**:1793–1803. https://doi.org/10.1038/s41591-023-02429-x
3. Merlo M, Cannatà A, Gobbo M, Stolfo D, Elliott PM, Sinagra G. Evolving concepts in dilated cardiomyopathy. *Eur J Heart Fail* 2018;**20**:228–239. https://doi.org/10.1002/ejhf.1103
4. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: The complexity of a diverse genetic architecture. *Nat Rev Cardiol* 2013;**10**:531–547. https://doi.org/10.1038/nrcardio.2013.105
5. Almehmadi F, Joncas SX, Nevis I, Zahrani M, Bokhari M, Stirrat J, *et al.* Prevalence of myocardial fibrosis patterns in patients with systolic dysfunction: Prognostic significance for the prediction of sudden cardiac arrest or appropriate implantable cardiac defibrillator therapy. *Circ Cardiovasc Imaging* 2014;**7**:593–600. https://doi.org/10.1161/CIRCIMAGING.113.001768
6. De Angelis G, De Luca A, Merlo M, Nucifora G, Rossi M, Stolfo D, *et al.* Prevalence and prognostic significance of ischemic late gadolinium enhancement pattern in non-ischemic dilated cardiomyopathy. *Am Heart J* 2022;**246**:117–124. https://doi.org/10.1016/j.ahj.2022.01.006
7. Jones RE, Hammersley DJ, Zheng S, McGurk KA, de Marvao A, Theotokis PI, *et al.* Assessing the association between genetic and phenotypic features of dilated cardiomyopathy and outcome in patients with coronary artery disease. *Eur J Heart Fail* 2024;**26**:46–55. https://doi.org/10.1002/ejhf.3033
8. Shah RA, Asatryan B, Sharaf Dabbagh G, Aung N, Khanji MY, Lopes LR, *et al.*; Genotype-First Approach Investigators. Frequency, penetrance, and variable expressivity of dilated cardiomyopathy-associated putative pathogenic gene variants in UK Biobank participants. *Circulation* 2022;**146**:110–124. https://doi.org/10.1161/CIRCULATIONAHA.121.058143
9. Akinrinade O, Koskenvuo JW, Alastalo TP. Prevalence of titin truncating variants in general population. *PLoS One* 2015;**10**:e0145284. https://doi.org/10.1371/journal.pone.0145284
10. Ware JS, Seidman JG, Arany Z. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med* 2016;**374**:2601–2602. https://doi.org/10.1056/NEJMc1602671
11. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, Lunde IG, Wakimoto H, Smith AM, *et al.* Genetic variants associated with cancer therapy-induced cardiomyopathy. *Circulation* 2019;**140**:31–41. https://doi.org/10.1161/CIRCULATIONAHA.118.037934
12. Akhtar MM, Lorenzini M, Cicerchia M, Ochoa JP, Hey TM, Sabater Molina M, *et al.* Clinical phenotypes and prognosis of dilated cardiomyopathy caused by truncating variants in the *TTN* gene. *Circ Heart Fail* 2020;**13**:e006832. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006832
13. Dal Ferro M, Stolfo D, Altinier A, Gigli M, Perrieri M, Ramani F, *et al.* Association between mutation status and left ventricular reverse remodelling in dilated cardiomyopathy. *Heart* 2017;**103**:1704–1710. https://doi.org/10.1136/heartjnl-2016-311017
14. Merlo M, Cannatà A, Pio Loco C, Stolfo D, Barbati G, Artico J, *et al.* Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2020;**22**:1111–1121. https://doi.org/10.1002/ejhf.1914
15. Tayal U, Verdonschot JAJ, Hazebroek MR, Howard J, Gregson J, Newsome S, *et al.* Precision phenotyping of dilated cardiomyopathy using multidimensional data. *J Am Coll Cardiol* 2022;**79**:2219–2232. https://doi.org/10.1016/j.jacc.2022.03.375