Review of: "Mid-wall striae fibrosis predicts heart failure admission, composite heart failure events, and life-threatening arrhythmias in dilated cardiomyopathy"

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Comment to: “Mid-wall striae fibrosis predicts heart failure admission, composite heart failure events, and life-threatening arrhythmias in dilated cardiomyopathy” by Purmah et al.

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In this paper by Purmah et al., the Authors evaluated the prognostic role of mid-wall striae (MWS) fibrosis by late gadolinium enhancement (LGE) imaging in a cohort of 719 patients with dilated cardiomyopathy (DCM), prospectively enrolled at two associated hospitals within a single tertiary care healthcare system. In particular, Authors focused on heart-failure (HF) specific outcome, defined as time to first incident HF admission. The secondary endpoints were a HF-related outcome (HF admission, left ventricular (LV) assist device implantation, cardiac transplantation or all-cause mortality) and an arrhythmic outcome (appropriate implantable cardioverter defibrillator therapy, sudden cardiac death, survived sudden cardiac arrest, or sustained ventricular tachycardia requiring cardioversion). During a median follow-up of almost 3 years, 104 (15%) of patients experienced the primary outcome, and 127 (18%) the secondary outcome. The presence of MWS fibrosis was an independent predictor of the primary outcome (HR 1.65; 95%CI 1.11-2.47), as well as secondary composite HF outcome (HR 1.80; 95%CI 1.26-2.58) and arrhythmic outcome (HR 2.23; 95% CI 1.23-4.03). Interestingly, patients with a LV ejection fraction (LVEF) >35% and MWS fibrosis showed a similar rate of events to those with LVEF ≤35%.

The study is well conducted and focused on a clinically relevant issue. To our knowledge, this is the largest prospective study evaluating a specific HF outcome in non-ischemic DCM. Moreover, it confirms previous knowledge on the prognostic role of myocardial fibrosis in non-ischemic DCM, demonstrating an independent prognostic impact of MWS fibrosis on both HF and arrhythmic-related outcomes. However, some limitations should be acknowledged.

First, the coronary anatomy was not systematically investigated through coronary computed tomography angiography or coronary angiography. This may be relevant considering the median age of the study population (57 years; IQR 47–65),

the prevalence of males (72%) and cardiovascular risk factors (active smoking 19%; hypertension 35%; hyperlipidemia 39%; diabetes mellitus 15%). Although LGE-cardiovascular magnetic resonance is able to identify coronary artery disease as the aetiology of LV dysfunction in new-onset congestive heart failure, the absence of ischemic LGE *per se* does not definitively exclude the presence of underlying significant coronary artery disease [1]. Conversely, the presence of ischemic LGE was found in a significant proportion of patients with non-ischemic DCM [2]. Despite our concern that the absence of a systematic evaluation of coronary anatomy might have misclassified some patients, we agree with the Authors that previous works have demonstrated high diagnostic accuracy of CMR in predicting significant CAD in patients with LV dysfunction [3]. Moreover, the Authors correctly highlighted this point in the limitation section.

A second concern refers to the fibrosis phenotype stratification. Overall, 228 patients (32%) had any LGE abnormality and 178 patients (25% of total population; 78% of LGE positive patients) showed MWS fibrosis. Other reported LGE patterns were sub-epicardial (60; 8% of total population), mid-wall patchy (14; 2% of total population) and diffuse (3; 0.4% of total population). This implies that multiple LGE patterns were present in a not specified proportion of patients. Moreover, the patient allocation to the study groups was based only on the presence of MWS fibrosis. As a consequence, the comparison group included patients without LGE and patients with non-MWS fibrosis patterns (541 patients). In our opinion, this is a questionable choice, since both LGE patterns other than MWS and multiple LGE patterns have been associated with adverse clinical outcomes [4,5]. It would be interesting to analyze the contribution of different LGE patterns on study outcomes, for example including 3 groups (MWS, other LGE patterns and absence of LGE).

Another concern regards the description of the secondary arrhythmic-related outcome. In fact, in the results Authors reported 6 SCD events. However, all these patients had a prior coded arrhythmic event. It is not clear if these patients were censored at the time of the first event.

Finally, Authors reported that 14 patients underwent permanent pacemaker implantation. It would be interesting to know the indications and the characteristics of these patients, since bradyarrhythmias are often associated to specific genetic or inflammatory aetiologies.

Concluding, the results of this study mark some relevant points with potential clinical impact. In particular, the contribution of MWS fibrosis to study endpoints in relationship with LVEF is of utmost importance. Interestingly, Authors reported a similar risk of HF-hospitalization in patients with LVEF >35% and MWS fibrosis compared to those with an LVEF ≤35%. Moreover, MWS fibrosis was independent predictor of events in this subgroup. Conversely, among patients with LVEF ≤35%, MWS fibrosis did not remain significant. This observation provides a useful prognostic marker in patients without severely reduced LVEF, in whom the higher risk of HF translates into the need of tight clinical follow up and tailored therapy.

Last but not least, the results of the secondary arrhythmic outcome analysis showed as MWS fibrosis was independent predictor of events, whereas LVEF was not. This observation confirms previous observations and claim the need of further investigations in the setting of the arrhythmic stratification of DCM patients.

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