Reply to the letter regarding the article 'Subclinical systolic dysfunction in genotype-positive phenotype-negative relatives of dilated cardiomyopathy patients: A systematic review and meta-analysis'

We would like to express our gratitude to Dr. Albulushi and colleagues for their interest in our work[1] and for raising insightful questions that allow us to clarify certain concepts. The authors inquire about how we addressed the heterogeneity in global longitudinal strain (GLS) vendor-machine and software across the studies included in our analysis. We acknowledge, as previously stated in the manuscript, that the variability in GLS assessment complicates result interpretation. Ideally, all studies would have employed the same GLS vendor; however, this was not feasible. However, from a meta-analytical standpoint, since both the genotype-positive phenotype-negative (GEN+ PHEN−) and control groups were consistently evaluated with the same GLS vendor within each study, we did not anticipate any significant impact on the meta-analytic computation of the standardized mean difference. Additionally, as none of the included studies used a GLS cut-off to categorize 'GEN+ PHEN−', the heterogeneity in vendors is unlikely to have affected the inclusion/exclusion of subjects in these studies.

Dr. Albulushi *et al.* also inquire whether additional details on how different gene variants specifically affect GLS could be provided. While a gene-by-gene GLS analysis would be ideal, the current lack of published data precludes the establishment of specific genotype–phenotype subclinical associations through GLS in this context, with the exception of the previously discussed association between phospholamban and left ventricular apex post-systolic shortening.

Furthermore, the authors seek our perspective on the implementation of GLS monitoring in routine clinical practice in the setting of GEN+ PHEN− relatives of dilated cardiomyopathy (DCM) patients. From our standpoint, currently the main significance of our work lies in the biological context: individuals traditionally considered PHEN− still exhibit a relative reduction in GLS compared to their GEN− counterparts, indicating a potential early subclinical dysfunction with clinical and prognostic implications yet to be fully defined. Indeed, the study underscores that the concept of a positive phenotype depends on the diagnostic sensitivity and the diagnostic technique used to identify it, supporting the utility of conducting large prospective studies to assess this point. Therefore, before suggesting routine implementation of GLS in this setting, we believe it is necessary to: (1) demonstrate that GEN+ PHEN− relatives with altered GLS are more likely to develop the overt DCM phenotype, and (2) identify a specific GLS cut-off (ideally vendor-machine independent). Should future studies succeed in validating these hypotheses, the routine implementation of GLS in GEN+ PHEN+ relatives may be reasonable and could potentially guide intervention studies to search for pharmacological management strategies useful in preventing the development of overt DCM. In this clinical context, studies are indeed a daunting challenge because they require very long follow-up (for the phenotype to manifest) and, above all, because they involve the pharmacological treatment of apparently healthy and asymptomatic individuals. Currently, the only ongoing study is the EARLY-GENE (NCT05321875), a randomized, placebo-controlled, double-blind clinical trial evaluating the safety and efficacy of early administration of candesartan in preventing the development of DCM in GEN+ PHEN− individuals. Identifying and enrolling potentially higher-risk subjects (e.g. those with subclinical systolic dysfunction) could facilitate the endeavour to identify a preventive strategy.

Finally, Dr. Albulushi *et al.* also raise the question of whether the results can be generalized to other populations, especially those with diverse genetic backgrounds, since our study seems to be based predominantly on data from Taiwanese cohorts. We kindly point out that no study was conducted on Taiwanese cohorts, but rather three Dutch, two from the USA, and one multicentre European. Nonetheless, we believe that our findings are applicable to diverse populations, given the heterogeneous genetic backgrounds in the included studies, except for Taha et al.'s study[2], which exclusively focused on phospholamban mutations.

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References

1. Faggiano A, Gherbesi E, Gnan E, Paldino A, Merlo M, Sinagra G, *et al.* Subclinical systolic dysfunction in genotype-positive phenotype-negative relatives of dilated cardiomyopathy patients: A systematic review and meta-analysis. *Eur J Heart Fail* 2024;**26**: 1097–1099. https://doi.org/10.1002/ejhf.3248
2. Taha K, te Rijdt WP, Verstraelen TE, Cramer MJ, de Boer RA, de Bruin-Bon RHACM, *et al.* Early mechanical alterations in phospholamban mutation carriers: Identifying subclinical disease before onset of symptoms. *JACC Cardiovasc Imaging* 2021;**14**:885–896. https://doi.org/10.1016/j.jcmg.2020.09.030