authors was used in support of the opposite view; namely, that there is "no strong evidence of a reduction in mortality effect over time" (2).

Dr. Taylor and colleagues state that cardiac rehabilitation is no longer advocated on the basis of a reduction in all-cause mortality. This would be a welcome change. However, in 2011 they claimed that rehabilitation reduced overall mortality by 13%. In their most recent advocacy for cardiac rehabilitation they sought to challenge clinical trial evidence which conflicted with a reduction in all-cause mortality due to rehabilitation (3), and their most recent publication obscures the issue by reporting a "survival benefit" without clarifying its basis (4).

We remain of the view that evidence about the mortality benefits of rehabilitation in patients with coronary heart disease is weakened by an over reliance on secondary research, based on studies of patients with markedly different clinical risks.

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REFERENCES

1. Sheridan DJ, Julian DG. Achievements and limitations of evidence-based medicine. J Am Coll Cardiol 2016;68:204–13.

2. Taylor RS. The RAMIT trial: its results in the context of 2012 Cochrane review. Heart 2012;98:672–3.

3. Dalal HM, Doherty P, Taylor RS. Cardiac rehabilitation. BMJ 2015;351:h5000. http://dx.doi.org/10.1136/bmj.h5000.

4. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016;67:1–12.

A Distinct Cardiomyopathy

HCN4 Syndrome Comprising Myocardial Noncompaction, Bradycardia, Mitral Valve Defects, and Aortic Dilation

We read with interest the review paper by Arbustini and colleagues (1), elegantly highlighting the significance of precise patient and genetic data collection for epidemiology, genotype-phenotype correlation, and management of left ventricular noncompaction cardiomyopathy (LVNC). Aiming at a comprehensive clinical and mechanistic understanding of this complex disorder, an electromechanical overlap syndrome linked to mutations in the pacemaker channel gene *HCN4* requires more detailed recognition. We agree that cautious interpretation is essential when a genetic association is limited to single patients or families, lacking replication. However, contrary to Arbustini et al. (1), simultaneous initial reports appeared in the *Journal* in 2014 (2,3) linking *HCN4* mutations to LVNC. These findings have been extended further by independent groups to accumulate a significant body of evidence for a relevant LVNC sub-entity related to *HCN4* dysfunction (2–5). Despite its recent description, 39 patients (10 families) carrying 7 different *HCN4* mutations have been published to date, indicating higher prevalence of the novel syndrome than previously anticipated. Given the challenging analysis of mechanistic pathways leading to LVNC associated with previously identified mutations, this specific entity is expected to provide valuable novel insights into the complex pathomechanisms underlying LVNC that may include both hereditary and acquired components (1).

We conclude that in patients with a combined clinical phenotype comprising LVNC, sinus bradycardia, mitral valve defects, and/or dilation of ascending aorta, mutations in *HCN4* should be considered. The advanced study of the *HCN4*-related syndrome is required to improve both mechanistic understanding and clinical management of LVNC patients.

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REFERENCES

1. Arbustini E, Favalli V, Narula N, Serio A, Grasso M. Left ventricular noncompaction: a distinct genetic cardiomyopathy? J Am Coll Cardiol 2016;68:949–66.

2. Milano A, Vermeer AMC, Lodder EM, et al. *HCN4* mutations in multiple families with bradycardia and left ventricular noncompaction cardiomyopathy. J Am Coll Cardiol 2014;64:745–56.

3. Schweizer PA, Schröter J, Greiner S, et al. The symptom complex of familial sinus node dysfunction and myocardial noncompaction is associated with mutations in the HCN4 channel. J Am Coll Cardiol 2014;64:757–67.

4. Millat G, Janin A, de Tauriac O, Roux A, Dauphin C. *HCN4* mutation as a molecular explanation on patients with bradycardia and non-compaction cardiomyopathy. Eur J Med Genet 2015;58:439–42.

5. Vermeer AMC, Lodder EM, Thomas D, et al. Dilatation of the aorta ascendens forms part of the clinical spectrum of *HCN4* mutations. J Am Coll Cardiol 2016;67:2313–5.

REPLY: A Distinct Cardiomyopathy

HCN4 Syndrome Comprising Myocardial Noncompaction, Bradycardia, Mitral Valve Defects, and Aortic Dilation

We appreciate the letter by Dr. Schweizer and colleagues as it agrees that cautious interpretation is essential when a genetic association is provisional and limited to single/few patients or families (1). We are in a transition phase of genomic medicine in which Sanger-based sequencing is progressively being substituted by high-throughput massive parallel sequencing of multigene panels or exome sequencing. These novel tools identify many rare or unknown genetic variants. Our use of the MOGE(S) (Morphofunctional Organ Genetic Ethiology Status) nosology system promotes the strategy of "annotation" and supports the need for attention to the combination of phenotypic traits, of the causes of disease and modifiers (2). In our ongoing multigene panel sequencing (n = 599), we found rare variants in the *HCN4* gene (MIM#613123-Brugada Syndrome 8 and MIM#163800-Sick Sinus Syndrome 2), but these were in patients with different genetic diseases causally linked with mutations in disease-specific genes. To date, we have not found *HCN4* variants segregating with left ventricular noncompaction cardiomyopathy, mitral valve prolapse, or aortic aneurysms (**Table 1**).

TABLE 1 Phenotypes, Disease Mutations, and *HCN4* Variants

Phenotype	Disease Gene(s):Mutation(s)	*HCN4*:Variants (MAF:0.0008 - 1:1198 Alleles)	LVNC	MVP	HR (BPM)
HCM	*TPM1*-p.(Arg191X)	p.(Asp2Tyr)	No	No	91
F-TAA	*FBN1*-p.(Gly343Arg)	p.(Ser47Gly) + p.(Pro152Ser)	No	No	73
BAV + F-TAA	*NOTCH1*-p.(Thr194Pro)	p.(Arg68Trp)	No	Yes	71
ACM	*DSP*-p.(Asp472IlefsX13)	p.(Arg82Leu) + p.(Gly112Asp)	No	No	65
F-TAA	*MYH11*-p.(Ile138Asn)	p.(Ser110Gly) + p.(Ser384Ile)	No	No	68
F-TAA	*MYLK*-p.(Arg179Gln)	p.(Glu127Lys)	No	No	74
DCM + AVB in Steinert	*DMPK*-[E2,500-1000CTG] + *TTN*-c.(354 + 1G>A)	p.(Pro145Arg) + p.(Leu1083His)	No	No	58
BAV + TAA	*MYLK*-p.(Ile155Val) + *NOTCH1*-p.(Arg624His)	p.(Val190Ala)	No	No	80
HCM	*MYBPC3*-p.(Arg1271X)	p.(Ile363Met)	No	No	72
SSS with AVB	*PKP2*-p.(Pro627Ser)	p.(Ala485Val)*	Yes†	No	52
ACM	*DSG2*-p.(Thr466Ile)	p.(Val487Met)	No	No	AF
MFS	*FBN1*-p.(Met2263ArgfsX28)	p.(Ser568Thr)	No	Yes	75
LDS4	*TGFB2*-p.(Arg302Cys)	p.(Val673Leu)	No	Yes	65
Lone F-AF	*KCNH2*-p.(Val194Met)	p.(Asn690Ser)	No	No	66
HCM	*JPH2*-c.(1288 + 2_1288 + 15delTAGGGCCAGCCAGG)	p.(Ala787Ser)	No	No	78
DCM + AVB	*LMNA*-p.(Arg343Gln) + *CALR3*-p.(Trp37X)	p.(Pro852Leu)	No	No	82
F-TAA	*TGFB2*-p.(Val207Leu)	p.(Gly953Arg)	No	No	56‡
Conduction disease	*TRMP4*-p.(Ala432Thr) + *DSP*-p.(Cys81Tyr)	p.(Thr993Met)	No	No	72
DCM	*BAG3*-p.(Arg218Gln)	p.(Arg1022Leu) + p.(Arg1069Trp)	No	No	68
ASA-1R + AVB	*LMNA*-p.(Arg397Cys)	p.(Val1065Phe)	No	No	60
F-TAA + L-ICA Diss.	*MYLK*-p.(Arg1204Gln)	p.(Gly1070Asp)	No	No	55‡
DCM	*RBM20*-p.(Arg589Trp)	p.(Gly1077Ser)	No	No	62
DCM	*JPH2*-p.(Arg231Gln)	p.(Ala1098Val)	No	No	72
LDS1	*TGFBR1*-p.(Pro10Thr)	p.(Arg1102His)	No	No	66

*Association with SSS. †Not segregating in the family. ‡Beta blockers.

ACM = arrhythmogenic cardiomyopathy; AF = atrial fibrillation; ASA = atrial septal aneurysm; AVB = atrioventricular block; BAV = bicuspid aortic valve; BPM; beats per minute; DCM = dilated cardiomyopathy; F = familial; HCM = hypertrophic cardiomyopathy; HR = heart rate; IR = Type 1R Olivares-Reyes; LDS = Loeys-Dietz syndrome; L-ICA diss. = left internal carotid dissection; LVNC = left ventricular noncompaction cardiomyopathy; MFS = Marfan syndrome; MVP = mitral valve prolapse; SSS = sick sinus syndrome; TAA = thoracic aortic aneurysm.