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.

In additional patients clinically and genetically diagnosed with different diseases, we identified *HCN4* variants (single nucleotide polymorphisms, modifiers?) with Minor Allele Frequency (MAF) of 0.0017 [p.(Ala62Ser), p.(Pro1117Leu), p.(Gly1169Arg)]; 0.0025 [p.(Glu153Gly)]; 0.0192 [p.(Met1113Val)]; and 0.0109 [p.(Pro883Arg)]. Beyond research, which must explore mechanisms by which genetic variants cause or modify clinical phenotypes, genetic diagnoses can have major impact on patients and families. Missing the right genetic diagnosis can lead to potentially fatal events in families. Assigning an incorrect genetic diagnosis can label healthy family members as being predisposed to develop a disease, or alternatively, can result in overlooking the real cause of disease. On the basis of available evidence and our experience, we are not listing *HCN4* mutations as causing familial thoracic aortic aneurysm, but we remain extremely interested regarding their potential effects on heart rate, conduction disturbances, and arrhythmias, in addition to other potentially related traits when not explained by other causes.

***Eloisa Arbustini, MD**
Valentina Favalli, BME, PhD
Nupoor Narula, MD
Alessandra Serio, MD, PhD
Maurizia Grasso, PhD

*Centre for Inherited Cardiovascular Diseases
IRCCS Foundation
University Hospital Policlinico San Matteo
Piazzale Golgi, 19
27100 Pavia
Italy
E-mail: e.arbustini@smatteo.pv.it

http://dx.doi.org/10.1016/j.jacc.2016.11.073

Please note: This study was supported by Grants European Union INHERITANCE project #241924 and by the Italian Ministry of Health "Diagnosis and Treatment of Hypertrophic Cardiomyopathies" (#RF-PSM-2008-1145809) to Dr. Arbustini, IRCCS Policlinico San Matteo, Pavia; E-Rare Project 2014 - OSM - Dilated Cardiomyopathies to Dr. Serio; and MAGICA (MAlattie GenetIche CArdiovascolari) Onlus Charity. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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. Arbustini E, Narula N, Tavazzi L, et al. The MOGE(S) classification of cardiomyopathy for clinicians. J Am Coll Cardiol 2014;64:304–18.

Apixaban Dosing in Chronic Kidney Disease

Differences Between U.S. and E.U. Labeling

The recent State-of-the-Art Review paper by Lau et al. (1) was exceptional. I commend the authors on presenting a timely and cogent discussion of the pros and cons of antithrombotic therapy in chronic kidney disease (CKD) patients with atrial fibrillation. As the authors point out, even at baseline (i.e., before drug therapy), there is a fine line between thrombosis and bleeding in CKD patients. Consequently, clinicians are often faced with difficult antithrombotic dosing considerations to strike the appropriate balance between efficacy and bleeding.

My specific comment is in regard to the Central Illustration (Proposed Algorithm for Oral Anticoagulant Choices in Patients With Atrial Fibrillation and CKD). For apixaban, at creatinine clearance rate of 15 ml/min to 29 ml/min, the authors recommend an apixaban dose of 2.5 mg twice daily. The collaborating authors, all of whom are from European countries, are correct in their dosing recommendations. This dose, however, illustrates the difference between the U.S.- and European Union (E.U.)-approved labeling. For example, the U.S. Food and Drug Administration-approved label for apixaban (2) states that the 2.5 mg twice daily dose is indicated, not on a specific creatinine clearance rate, but rather when 2 of the following 3 criteria are met (age ≥80 years; body weight ≤60 kg; serum creatinine level ≥1.5 mg/dl [133 μmol/l]). Conversely, the E.U. Summary of Product Characteristics leaflet (3) for apixaban does recommend the 2.5 mg twice daily dose based on a creatinine clearance between 15 ml/min and 29 ml/min.

Thus, clinicians should be aware of the differences in apixaban dosing recommendations between the U.S. and E.U, specifically in patients with compromised renal function. Hopefully this letter provides some clarification. Again, congratulations to Dr. Lau and colleagues for publishing an excellent paper.

***Donald F. Brophy, PharmD, MSc**

*Department of Pharmacotherapy & Outcomes Science
Virginia Commonwealth University
410 North 12th Street
Richmond, Virginia 23298-0533
E-mail: dbrophy@vcu.edu

http://dx.doi.org/10.1016/j.jacc.2016.11.074

Please note: Dr. Brophy has reported that he has no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Lau YC, Proietti M, Guiducci E, Blann AD, Lip GYH. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. J Am Coll Cardiol 2016;68:1452–64.

2. Eliquis [Package insert, p6]. Princeton, NJ: Bristol-Myers Squibb; 2016.

3. Eliquis [Summary of Product Characteristics]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. Accessed September 28, 2016.