Atherosclerosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Editorial

Aortic valve calcification: Time for a sex- and race-based assessment

ARTICLE INFO

Keywords
Aortic valve calcification
Aortic stenosis
Ethnicity
Sex
Epidemiology

In this issue of *Atherosclerosis*, Boakye et al. investigated the sex and race-specific prevalence and extent of aortic valve calcification (AVC) [1]. The authors performed an analysis of the Atherosclerosis Risk in Communities (ARIC) Study, a prospective community-based biracial cohort established in 1987 for the surveillance of determinants of subclinical atherosclerosis and coronary heart disease (CHD) in United States Black and White adults [2]. Specifically, they included 2283 participants (≥75 years old) who reported no history of overt CHD who underwent non-contrast cardiac gated computed tomography scanning at their 7th semi-annual visit (2018–2019). The aim of this analysis was to identify the sex and race burden of AVC and its association with cardiovascular risk factors. Although not universally present, AVC was highly prevalent (44.8%) in this older patient cohort (mean age 80.5 ± 4.3 years old). White men had the highest prevalence (58.2%) followed by Black men (40.5%), White women (38.9%) and Black women (36.8%). The prevalence of AVC increased significantly with age in all race-sex groups. Similar trends were noted when comparing the extent of AVC with the highest median Agaston unit (AU) noted in White men (100.9 AU) followed by Black men (68.5 AU), White women (52.3 AU) and Black women (46.5 AU). This persisted after adjusting for age, education level, study center and atherosclerotic Cardiovascular Disease (ASCVD) risk factors, Moreover, in a fully adjusted model (including race and sex), increasing age, male sex, White race, hypertension, and lipoprotein a (Lp(a)) were all independent predictors of prevalent AVC.

The study presented by Boakye et al. adds to a growing body of literature investigating sex and racial differences in the atherosclerotic processes such as coronary artery calcification (CAC) and extra-coronary calcifications (ECCs) including thoracic aortic wall calcification, mitral valve and aortic valve calcification. Several prior studies have extensively described racial differences in the prevalence and extent of CAC and coronary artery disease (CAD). The earliest study dates back to 1965 when an autopsy study found that White patients had a higher prevalence of calcified lesions in the major coronary arteries compared to their Black counterparts [3]. More recent CT-based studies have confirmed prior conclusions showing that Black patients have a lower prevalence of coronary calcifications as compared to White patients [4,5]. Studies using invasive coronary angiography further confirms this trend reporting a lower prevalence of obstructive disease in Black versus White patients, but higher prevalence of diffuse atherosclerotic plaques among Black patients [4]. An analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) (6814 participants; White n = 2619 and Black = 1898) has also found that White participants had the highest prevalence and extent of coronary calcification even after adjusting for coronary risk factors [6].

Are the results of this analysis expected? Although AVC was initially believed to be the product of a degenerative process, emerging evidence suggests a strong relation between valvular calcification and atherosclerotic risk factors. This is supported by epidemiological studies showing that atherosclerosis and AVC share similar risk factors such as increasing age, male gender, hypertension, dyslipidemia, and smoking [7,8]. This is further reinforced by recent immunohistochemical studies that provide evidence of similar atherosclerosis pathological processes such as inflammatory cell mediated infiltration, lipid deposition, and active calcification [9,10]. As such, AVC looks to be mainly the result of a cascading effects initiated by endothelial valvular damage, leading to an influx of inflammatory cells. This inflammatory response stimulates the activation and differentiation of interstitial cells to osteoblasts culminating in the formation of calcification processes. To that effect, AVC has been strongly associated with CAC [11], CAD [11,12], and carotid stenosis [13] suggesting AVC as a potential marker of atherosclerosis burden and not just an age-mediated degenerative disease. Moreover, the current paper supports these proposed processes as the authors found that hypertension, non-high-density lipoprotein-cholesterol, and Lp(a) to be independently associated with AVC.

The prevalence of AVC depends on the studied cohort and ranged in several population-based studies from 13% in the MESA study to 33% in the Rotterdam study [9,14]. The current study primarily included older

https://doi.org/10.1016/j.atherosclerosis.2022.07.005
Received 26 June 2022; Received in revised form 4 July 2022; Accepted 6 July 2022
Available online 14 July 2022

patients, and thus had higher prevalence of AVC (44.8%) [1]. Additional analysis of the MESA study showed that ethnic differences were also observed regarding ECCs. After adjusting for traditional cardiovascular risk factors and coronary artery calcium, White participants had the highest prevalence of valvular calcifications, AVC included, as compared to Black participants [9]. The current paper further underlines a recurring paradoxical trend, that Black patients have lower prevalence of aortic valve calcification even in the presence of multiple atherosclerotic risk factors [1,15]. It seems that this racial difference is not solely driven by traditional cardiovascular risk factors, a finding mirrored in studies investigating CAC burden [6]. These trends in AVC may bridge our understanding of the racial difference in aortic stenosis (AS), often a product of AVC progression [16,17].

What are the clinical implications of these findings? Recently, AVC score is being used more often in different clinical scenarios to determine whether the patient has severe aortic stenosis. Similar epidemiological studies, including the current paper, have also shown that men have a higher prevalence and burden of AVC compared to women, even among patients with severe aortic stenosis [1,14,18]. AVC is most useful in evaluating AS in patients with discordant echocardiographic/hemodynamic conventional markers (ie: Low-flow low-gradient AS). To that effect, recent European guidelines have encouraged a gender-based interpretation of AVC scores [19]. However, most of the defined thresholds currently used in clinical practice are derived from predominantly white cohorts.

This study suggests that race should be taken into account when assessing patients with suspected severe aortic stenosis and aortic valve calcifications. The current evidence encourages the investigation of sex and race-based cutoffs for optimal use and clinical practice. Given the above, identifying and adopting sex and race-based cutoffs for aortic valve calcifications is important to ultimately delivering personalized and equitable medicine.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] E. Boakye, Z. Dardari, O.H. Obisesan, et al., Sex-and race-specific burden of aortic valve calcification among older adults without overt coronary heart disease: the atherosclerosis risk in communities study, Atherosclerosis (2022), https://doi.org/10.1016/j.atherosclerosis.2022.06.003. https://www.sciencedirect.com/science/article/pii/S0021915022002908.

[2] J.D. Wright, A.R. Folsom, J. Coresh, et al., The ARIC (atherosclerosis risk in communities) study: JACC focus seminar 3/8, J. Am. Coll. Cardiol. 77 (23) (2021) 2939–2959, https://doi.org/10.1016/j.jacc.2021.04.035. https://www.ncbi.nlm.nih.gov/pubmed/34112321.

[3] D.A. Eggen, J.P. Strong, H.C. Mcgill JR., Coronary calcification: relationship to clinically significant coronary lesions and race, sex, and topographic distribution, Circulation 32 (6) (1965) 948–955, https://doi.org/10.1161/01.CIR.32.6.948. http://circ.ahajournals.org/cgi/content/abstract/32/6/948.

[4] M.J. Budoff, T.P. Yang, R.M. Shavelle, D.H. Lamont, B.H. Brundage, Ethnic differences in coronary atherosclerosis, J. Am. Coll. Cardiol. 39 (3) (2002) 408–412, https://doi.org/10.1016/S0735-1097(01)01748-X.

[5] T.C. Lee, P.G. O'Malley, I. Feuerstein, A.J. Taylor, The prevalence and severity of coronary artery calcification on coronary artery computed tomography in black and white subjects, J. Am. Coll. Cardiol. 41 (1) (2003) 39–44, https://doi.org/10.1016/S0735-1097(02)02618-9. https://www.ncbi.nlm.nih.gov/pubmed/12570942.

[6] D.E. Bild, R. Detrano, D. Peterson, et al., Ethnic differences in coronary calcification: the multi-ethnic study of atherosclerosis (MESA), Circulation 111 (10) (2005) 1313–1320, https://doi.org/10.1161/01.CIR.0000157730.94423.4B. http://circ.ahajournals.org/cgi/content/abstract/111/10/1313.

[7] F.C. Marmelo, S.M.F. Mateus, A.J.M. Pereira, Association of aortic valve sclerosis with previous coronary artery disease and risk factors, Arq. Bras. Cardiol. 103 (5) (2014) 398–402, https://doi.org/10.5935/abc.20140136. https://www.ncbi.nlm.nih.gov/pubmed/25229357.

[8] B.F. Stewart, D. Siscovick, B.K. Lind, et al., Clinical factors associated with calcific aortic valve disease, J. Am. Coll. Cardiol. 29 (3) (1997) 630–634.

[9] K. Nasir, R. Katz, M. Al-Mallah, et al., Relationship of aortic valve calcification with coronary artery calcium severity: the multi-ethnic study of atherosclerosis (MESA), J. Cardiovasc. Comput. Tomogr. 4 (1) (2010) 41–46, https://doi.org/10.1016/j.jcct.2009.12.002. https://www.clinicalkey.es/playcontent/1-s2.0-S1934592509006376.

[10] K.D. O'Brien, Pathogenesis of calcific aortic valve disease: a disease process comes of age (and a good deal more), Arterioscler. Thromb. Vasc. Biol. 26 (8) (2006) 1721–1728, https://doi.org/10.1161/01.ATV.0000227513.13697.ac. http://atvb.ahajournals.org/cgi/content/abstract/26/8/1721.

[11] H. Yamamoto, D. Shavelle, J. Takasu, et al., Valvular and thoracic aortic calcium as a marker of the extent and severity of angiographic coronary artery disease, Am. Heart J. 146 (1) (2003) 153–159, https://doi.org/10.1016/S0002-8703(03)00105-4.

[12] L. Sgorbini, A. Scuteri, M. Leggio, W. Gianni, E. Nevola, F. Leggio, Carotid intima–media thickness, carotid distensibility and mitral, aortic valve calcification: a useful diagnostic parameter of systemic atherosclerotic disease, J. Cardiovasc. Med. 8 (5) (2007) 342–347, https://doi.org/10.2459/01.JCM.0000268128.74413.1b. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=01244665-200705000-00007.

[13] Y. Adler, U. Levinger, A. Koren, et al., Relation of nonobstructive aortic valve calcium to carotid arterial atherosclerosis, Am. J. Cardiol. 86 (10) (2000) 1102–1105, https://doi.org/10.1016/S0002-9149(00)01167-X.

[14] D. Messika-Zeitoun, L.F. Bielak, P.A. Peyser, et al., Aortic valve calcification: determinants and progression in the population, Arterioscler. Thromb. Vasc. Biol. 27 (3) (2007) 642–648, https://doi.org/10.1161/01.ATV.0000255952.47980.c2. http://atvb.ahajournals.org/cgi/content/abstract/27/3/642.

[15] Jackson 2 J.B. Wilson, R. Larry, F.E. Ugowe, et al., Racial and ethnic differences in treatment and outcomes of severe aortic stenosis: a review, JACC Cardiovasc. Interv. 13 (2) (2020) 149–156, https://doi.org/10.1016/j.jcin.2019.08.056, https://www.ncbi.nlm.nih.gov/pubmed/31973792.

[16] M.J. Czarny, S.J. Shah, S.P. Whelton, et al., Race/ethnicity and prevalence of aortic stenosis by echocardiography in the multi-ethnic study of atherosclerosis, J. Am. Coll. Cardiol. 78 (2) (2021) 195–197, https://doi.org/10.1016/j.jacc.2021.04.078.

[17] D.K. Patel, K.D. Green, M. Fudim, F.E. Harrell, T.J. Wang, M.A. Robbins, Racial differences in the prevalence of severe aortic stenosis, J. Am. Heart Assoc. 3 (3) (2014), e000879, https://doi.org/10.1161/JAHA.114.000879 n/a, https://onlinelibrary.wiley.com/doi/abs/10.1161/JAHA.114.000879.

[18] S.R. Aggarwal, M. Clavel, D. Messika-Zeitoun, et al., Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis, Circulation. Cardiovascular imaging 6 (1) (2013) 40–47, https://doi.org/10.1161/CIRCIMAGING.112.980052. https://www.ncbi.nlm.nih.gov/pubmed/23233744.

[19] Helmut Baumgartner, Judy Hung, Javier Bermejo, et al., Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the european association of cardiovascular imaging and the american society of echocardiography, J. Am. Soc. Echocardiogr. 30 (4) (2017) 372–392, https://doi.org/10.1016/j.echo.2017.02.009. https://www.clinicalkey.es/playcontent/1-s2.0-S0894731717301335.

Jean Michel Saad, Ahmed Ibrahim Ahmed, Mouaz H. Al-Mallah*
Houston Methodist DeBakey Heart & Vascular Center, United States

* Corresponding author. Medicine and Cardiology, Weill Cornell Medical College, Cardiovascular PET, 6550 Fannin Street, Smith Tower - Suite 1801, Houston, TX, 77030, United States.
E-mail address: mal-mallah@houstonmethodist.org (M.H. Al-Mallah).