Differences in Arterial Events in Vascular Ehlers-Danlos, Loeys-Dietz, and Marfan Syndrome

BACKGROUND: Heritable thoracic aortic disease is due to altered genes that confer a highly penetrant risk for thoracic aortic aneurysm and dissection, and a subset of these genes also cause aneurysms and dissections of peripheral arteries beyond the aorta. Arterial aneurysms, dissections, and ruptures are associated with pathogenic variants (PVs) in COL3A1, which is responsible for vascular Ehlers-Danlos syndrome, but arterial events are rare in Marfan syndrome due to PVs in FBN1, and poorly characterized in Loeys-Dietz syndrome due to PVs in the transforming growth factor (TGF)-β pathway genes.

OBJECTIVES: This study sought to define the relative risk of arterial and aortic events in individuals with PVs in FBN1, COL3A1, and TGF-β pathway genes.

METHODS: The Montalcino Aortic Consortium provided a retrospective cohort of 1,780 individuals with PVs in COL3A1 (n = 125), FBN1 (n = 1028), and the TGF-β pathway genes (TGFBR1, n = 137; TGFBR2, n = 168; SMAD3, n = 196; TGFB2, n = 126). Arterial events were defined as dissections, ruptures, or aneurysms in arteries beyond the aorta requiring open or endovascular repair, and aortic events were defined by aortic dissections or repair of an aortic aneurysm.

RESULTS: Arterial events were identified in 83 individuals, with the highest prevalence in COL3A1 (20.8%), followed by TGFBR2 (7.7%), TGFBR1 (7.3%), TGFB2 (6.4%), SMAD3 (5.6%), and FBN1 (1.5%). Kaplan-Meier curves identified significant gene differences, with COL3A1 having the most and earliest arterial events when compared with TGF-β genes and FBN1. For TGF-β genes and FBN1, aortic events were significantly earlier and more penetrant than arterial events, whereas this difference was not present with COL3A1. Sex impacts arterial events; males with COL3A1 had earlier and more arterial events compared with males with TGF-β genes, and these differences were not observed in females. Arterial events in FBN1 cases occur primarily in men.

CONCLUSIONS: There are significant gene- and sex-specific differences in the prevalence and age of onset of arterial events associated with these heritable thoracic aortic disease genes, highlighting the importance of tailored counseling and surveillance based on the causative gene. Furthermore, smoking cessation and hypertension control should be emphasized in these patients to reduce the risk of arterial events.