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EDITORIAL COMMENT

Distal Aorta: The Next Frontier in Managing Marfan Syndrome Aortic Disease*

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Over the past 3 to 4 decades, the underpinnings, manifestations, and optimal treatment for ascending aortic disease in Marfan syndrome have been substantially clarified. The clinical and genetic associations have been described and updated. An evidence-based approach to both medical and preventive treatment and optimal prophylactic surgery has been developed. As a result, a patient with Marfan syndrome living today has a remarkably better chance for long-term survival than a similar patient living just a few decades ago. This chapter in cardiovascular science and the translation of science into practice is a shining example of how patient outcomes can experience historic improvements through scientific collaborations and financial investments in research teams.

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In this issue of the *Journal*, den Hartog et al. (1) offer a superb description of current-day evaluation and treatment of aortic disorders in Marfan syndrome, and they point us toward the next critical steps in further advancing outcomes for this unique population. In a Dutch registry study, they examined treatment and outcomes of a large cohort of patients with Marfan syndrome (>600), with the goal of describing long-term distal aortic complications and potential predictors of type B aortic dissection. The results of their study are both important and practice informing. Given the size of the cohort, extent of follow-up, and use of modern genetic and imaging strategies, the investigators provide a set of observations that all clinicians caring for patients with Marfan syndrome should know. We offer these in no particular order of importance.

First and foremost, Marfan syndrome is a disorder affecting the ascending aorta. In this cohort of 646 subjects, 46 patients had ascending dissections before first imaging, 141 underwent proximal aortic repair to prevent aortic dissection and/or rupture before the study period, and 53 underwent prophylactic ascending aortic repair during the study period. Consequently, just 2 patients experienced ascending aortic dissections during the study period. In other words, 240 of 646 subjects (37%) required aortic repair to prevent ascending aortic dissection, while only 2 patients (0.3%) experienced it during their time of care in dedicated aortic clinics at Dutch centers of excellence. The remarkably successful outcomes in these patients illustrate how far we have come in urgent management, preventive medical therapy, careful patient surveillance, and prophylactic surgery in subjects with Marfan syndrome prone to ascending aortic disease.

Second, Marfan syndrome is also a disorder affecting the descending aorta. In this cohort, the rate of descending aortic dissection, even while receiving excellent medical therapy with beta-adrenergic blockers (and, for some, the angiotensin II receptor blocker losartan), occurred at a rate of 1.5% per year. Subjects at higher risk were not easy to identify. Although an increased rate of descending aortic dissection was observed in patients with prior aortic repair (hazard ratio: 2.1; 95% confidence interval: 1.2 to 3.8; $p = 0.010$) and those with larger than normal (≥27 mm in diameter) proximal descending aortas (hazard ratio: 2.2; 95% confidence interval: 1.1 to 4.3; $p = 0.020$), in truth, only about one-half of the dissection cohort had prior ascending aortic repair, and only one-half had proximal descending aortas larger than normal. This finding is sobering. One might jump to the conclusion that if a patient had

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both of these clinical factors, perhaps prophylactic distal aortic intervention might be considered on top of best medical therapy to prevent subsequent type B aortic dissection. However, even in the best of hands, such surgery carries a combined risk for death, paraplegia, and other morbidity (2) that makes this a tricky decision. Also, unlike type A or ascending aortic dissection, mortality from type B dissection is substantially lower (3), so the decision about "preventive" surgery in this instance is much less secure than it is for ascending aortic disease. Unlike many other types of aortic disease, the role of endovascular interventions for the purpose of either treating or preventing distal aortic dissection remains controversial in patients with Marfan syndrome (4).

Third, optimizing the use of novel imaging markers to predict outcomes and inform practice is an emerging science. For clinicians, it seems logical that aortic distensibility and/or segment-by-segment alterations in aortic geometry might identify patients at greater risk for future aortic dissection. This study observed that aortas with less distensibility on dynamic imaging or those exhibiting an aortic hump within a dilated segment were at higher risk on univariate analysis, but these findings did not remain significant on multivariate analysis. It is possible that the sample size was too small to clarify whether such measures add significant prognostic information to established variables (such as aortic size) as major predictors of risk. It remains possible that future study of these and other novel variables, such as computational methods that can map shear stress and wall hemodynamic status, could improve our ability to identify patients at risk for aortic events (5).

Fourth, best medical therapy for the prevention of aortic dissection and/or rupture in Marfan syndrome continues to evolve. Some data has suggested that adding the angiotensin II receptor blocker losartan to beta-blocker therapy may reduce risk compared with beta-blocker therapy alone (6), and this study suggests a potentially significant risk reduction in distal disease as well. However, recent literature raises caution in making inferences about treatment effects absent large randomized trials. Despite preliminary data suggesting that angiotensin II receptor blockers may be more effective than beta-blockers in reducing progression of aortic root dilation in Marfan syndrome, a recent trial of 608 children and young adults with Marfan syndrome randomized to losartan versus atenolol observed no differences in aortic root dilation (7). Without randomized trial data, the role of angiotensin II receptor blockers in distal aortic disease in Marfan patients remains unclear.

Fifth, genetic testing is far from perfect. In this study, an *FBN1* mutation was found in just over 80% of subjects tested. It is important for clinicians to note that this does not mean the patients did not have Marfan syndrome. Rather, the typical sensitivity of commercial screening for *FBN1* mutations in individuals with a clear Marfan phenotype is nowhere near 100% (8). Some subjects will have deletions or duplications and may therefore simply not "show up" on standard testing. In addition, in this study, *FBN* genetic positivity did not appear to be a predictor of better or worse outcomes.

For clinicians, the paper by den Hartog et al. (1) is important. It calls to mind that distal aortic disease is not uncommon in Marfan syndrome and should be sought out by careful follow-up and imaging. Although only a dilated proximal descending aorta and prior aortic repair were independently associated with type B aortic dissection, the study offers hope that in time, we will be able to better predict who is likely to dissect distally, with the further notion that randomized treatment trials may illuminate the best strategy for specific cohorts. We have come a long way, but many questions remain.

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