Commentary

Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry predicting predictors for aortic dissection: a new thought around the corner?

Giacomo Murana[1], Antonio Pantaleo[1], Alessandro Parolari[2], Roberto Di Bartolomeo[1], Davide Pacini[1]

[1]Department of Cardiac Surgery, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [2]Department of Cardiac Surgery, Operative Unit of Cardiac Surgery and Translational Research, I.R.C.C.S. Policlinico San Donato-San Donato Milanese, Milan, Italy

Correspondence to: Prof. Davide Pacini, M.D., PhD. Department of Cardiac Surgery, S. Orsola-Malpighi Hospital, University of Bologna-Alma Mater Studiorum, Via Massarenti n. 9, 40128 Bologna, Italy. Email: davide.pacini@unibo.it.

Submitted Aug 07, 2016. Accepted for publication Aug 10, 2016.
doi: 10.21037/jtd.2016.08.71
View this article at: http://dx.doi.org/10.21037/jtd.2016.08.71

The multicenter prospective National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry collects clinical and biological data from patients with aortic aneurysm and associated genetic conditions, including Marfan syndrome (MFS), Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Turner syndrome, bicuspid aortic valve (BAV), and familial or premature (age <50 years) thoracic aortic aneurysm (TAA) (1). Patient enrollment began in November 2007 and the registry was born with the main objective to compare cross-sectional and longitudinal data on risk factors related to diagnosis, treatment, and outcome among groups of enrolled patients (1). Since then many important findings have emerged regarding the clinical characteristics and management of genetically-induced TAAs and dissections (*Table 1*) (1-8).

In this last paper (9) from the GenTAC registry reported in the *Journal of the American college of cardiology*, the investigators set out to determine the relative risk for aortic dissection (AoD) in patients with TAA including those who previously underwent prophylactic TAA surgery, and then test the relationship between antecedent aortic size and subsequent AoD. BAV (39%) and MFS (22%) were the leading diagnoses among participants (n=1,991). Primary endpoint occurred in 1.6% (n=31) of patients and was assessed during a mean follow-up time of 3.6±2.0 years from baseline evaluation.

The present study raised three interesting points that offer insight for further considerations:

(I) MFS conferred greater relative risk for AoD (after 3 years of follow-up, the cumulative incidence was 6-fold higher in patients with MFS *vs*. the remainder of the population, log-rank P<0.001);

(II) Risk for AoD persisted even after TAA surgery (52% of affected patients had undergone previous aortic graft implantation) and it could occur within native aortic segments proximal or distal to prosthetic grafts;

(III) AoD can occur in at-risk patients even when aortic size is normal or minimally dilated (among patients with type A AoD, only 1 of 9 had an aortic diameter ≥5.0 cm in either the root or ascending aorta).

These findings confirmed that patients with genetically associated TAA remain at risk for AoD in the current era even after controlling for maximal aortic size and even after performing preventive surgical or medical treatments. Probably patients with TAA undergoing aortic grafting represent a high-risk phenotype in terms of intrinsic vascular properties that predispose them to aortic dilation and AoD. Unfortunately, mechanisms remain out of sight and thus many questions remain unanswered.

A recent paper coming from Yan *et al*. investigated the role of the structural cellular components of the aortic wall in the pathogenesis of AoD (10). They could demonstrate an overexpression of the octamer binding protein (Oct4) in the aortic media of AoD patients capable of inducing a phenotype switch of human aortic smooth muscle cells from the contractile to the synthetic type (10). This phenomenon may alter the normal biomechanical properties of aortic media facilitating pathological conditions such as AoD (11). In this way, investigating the mechanisms of AoD has gained an

Table 1 Main contributions by GenTAC registry

First author, year of publication	Journal	No. of patients enrolled in the study	Most frequent aortic pathology (%)	Major findings
Eagle (1), 2009	*American Heart Journal*	500	MFS: 214 (42.8) BAV: 131 (26.2) FTAAD: 70 (14.1)	Illustrated registry design and described baseline characteristics of the population enrolled in the study
Song (2), 2009	*Annals of Thoracic Surgery*	606	MFS: 217 (35.8) BAV: 153 (25.2)	Demonstrated as patients with genetically transmitted TAAs evaluated in tertiary care centers frequently undergo surgical repair. Aneurysm repairs most commonly involved the ascending aorta with distal repairs been less common
Kroner (3), 2011	*American Heart Journal*	2,046	MFS: 576 (28.2) BAV: 504 (24.6)	Defined the second phase of the registry (GenTAC II) including new contributing clinical centers and possibility to use imaging and phenotyping core laboratories
Mendoza (4), 2011	*Annals of Thoracic Surgery*	50	MFS: 12 (24.0) BAV: 21 (42.0)	Established methods for measurement of aortic size supporting the linear dimensions in double oblique plane for imaging evaluation
Song (5), 2012	*Journal of Thoracic And Cardiovascular Surgery*	635	MFS: 635 (100.0)	Emphasized the importance of aortic surveillance and timely elective aortic root aneurysm repair for patients with MFS in order to reduce the occurrence of type A dissection and long-term adverse effects
Holmes (6), 2013	*American Journal of Medical Genetics*	1,449	MFS: 458 (31.6) BAV: 495 (34.2) FTAAD: 219 (15.1)	Explored the effect of gender on aortic events and found women to have reduced prevalence of aortic operations probably due to their smaller absolute aortic diameters
Song (7), 2014	*Journal of Heart And Valve Disease*	788	MFS: 788 (100.0)	Demonstrated that aortic valve-sparing root replacement is performed commonly among the MFS population with durable aortic valve repair at mid-term follow-up
Asch (8), 2016	*Journal of The American College Of Cardiology: Cardiovascular Imaging*	930	MFS: 315 (34.0) BAV: 260 (28.0)	Identified important differences in aortic measurements among multiple imaging modalities (echo/CT/MRI)

GenTAC, Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions; MFS, Marfan syndrome; BAV, bicuspid aortic valve; FTAAD, familial thoracic aortic aneurysm/dissection; TAA, thoracic aortic aneurysm; CT, computed tomography; MRI, magnetic resonance imaging.

increasing interest to reverse the prognosis of these patients.

Another unresolved issue highlighted in the present GenTAC study is the increased incidence of AoD observed in patients using beta-blockers compared with the remaining of the population (62% *vs.* 47%; P<0.001). Beta-blockers are presently considered to be first-line therapy in patients with MFS. However, their benefit is debatable and several observational studies including meta-analyses have reported conflicting results. Probably the small sample (31 patients experienced an AoD) and the lack on standardized medical therapy (50% of the entire population received a beta-blocker) could have influenced this finding; unfortunately, the authors do not provided any comment on this argument.

The only available randomized clinical trial comparing losartan with atenolol in children and young adults with MFS suggested no significant difference in the rate of aortic-root dilatation between the two treatment groups over a 3-year period (12). This topic could propel GenTAC investigators to further analyze medication patterns in order to prevent TAA and dissection.

The GenTAC database method has limitations, which the investigators discuss frankly in this paper.

These regard image data collection performed using various imaging modalities and at different times across GenTAC sites but most importantly there is bias due to the registry enrollment which was skewed toward a more severe group of patients with genetically associated aortopathies with TAA.

In conclusion, AoD is a disease that has a catastrophic impact on a patient's life. Unfortunately, it's relative infrequency and overlapping clinical manifestations because missed diagnosis on delayed initial examination in more than 30% of patient (13). This paper provided us with clever hints to facilitate AoD diagnosis. The take home message in the author's words is that "*patients with genetically associated TAA remain at substantial risk for AoD despite state-of-the-art care and conventional imaging at experienced centers*" and we add "…*but mechanisms are still unknown*". Future endeavors to find genetic variants that might be associated with sporadic dissection could help to anticipate this catastrophic aortic syndrome.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Lei Zhang (Department of Vascular Surgery, Changhai Hospital, Second Military Medical University, Shanghai, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Weinsaft JW, Devereux RB, Preiss LR, *et al*. Aortic Dissection in Patients With Genetically Mediated Aneurysms: Incidence and Predictors in the GenTAC Registry. J Am Coll Cardiol 2016;67:2744-54.

References

1. Eagle KA; GenTAC Consortium. Rationale and design of the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). Am Heart J 2009;157:319-26.
2. Song HK, Bavaria JE, Kindem MW, et al. Surgical treatment of patients enrolled in the national registry of genetically triggered thoracic aortic conditions. Ann Thorac Surg 2009;88:781-7; discussion 787-8.
3. Kroner BL, Tolunay HE, Basson CT, et al. The National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC): results from phase I and scientific opportunities in phase II. Am Heart J 2011;162:627-632.e1.
4. Mendoza DD, Kochar M, Devereux RB, et al. Impact of image analysis methodology on diagnostic and surgical classification of patients with thoracic aortic aneurysms. Ann Thorac Surg 2011;92:904-12.
5. Song HK, Kindem M, Bavaria JE, et al. Long-term implications of emergency versus elective proximal aortic surgery in patients with Marfan syndrome in the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Consortium Registry. J Thorac Cardiovasc Surg 2012;143:282-6.
6. Holmes KW, Maslen CL, Kindem M, et al. GenTAC registry report: gender differences among individuals with genetically triggered thoracic aortic aneurysm and dissection. Am J Med Genet A 2013;161A:779-86.
7. Song HK, Preiss LR, Maslen CL, et al. Valve-sparing aortic root replacement in patients with Marfan syndrome enrolled in the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions. J Heart Valve Dis 2014;23:292-8.
8. Asch FM, Yuriditsky E, Prakash SK, et al. The Need for Standardized Methods for Measuring the Aorta: Multimodality Core Lab Experience From the GenTAC Registry. JACC Cardiovasc Imaging 2016;9:219-26.
9. Weinsaft JW, Devereux RB, Preiss LR, et al. Aortic Dissection in Patients With Genetically Mediated Aneurysms: Incidence and Predictors in the GenTAC Registry. J Am Coll Cardiol 2016;67:2744-54.
10. Yan Y, Tan MW, Xue X, et al. Involvement of Oct4 in the pathogenesis of thoracic aortic dissection via inducing the dedifferentiated phenotype of human aortic smooth muscle cells by directly upregulating KLF5. J Thorac Cardiovasc Surg 2016;152:820-829.e4.
11. Pacini D, Murana G, Pantaleo A. A "muscled" fight against aortic dissection: Knowledge is the key to success. J Thorac Cardiovasc Surg 2016;152:830-1.
12. Lacro RV, Dietz HC, Sleeper LA, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. N Engl J Med 2014;371:2061-71.
13. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA 2000;283:897-903.

Cite this article as: Murana G, Pantaleo A, Parolari A, Di Bartolomeo R, Pacini D. Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry predicting predictors for aortic dissection: a new thought around the corner? J Thorac Dis 2016;8(9):E1093-E1095. doi: 10.21037/jtd.2016.08.71

