Hereditary thoracic aortic disease: How to save lives

Mary J. Roman, MD,* and Julie De Backer, MD, PhD†

Aortic dissection, particularly that involving the ascending aorta, remains an important (and underestimated) cause of sudden death.4 If aneurysmal dilatation preceding dissection is unrecognized, the availability of preventive elective aortic replacement is moot. In contrast, known aneurysms can be managed with aggressive blood pressure control and lifestyle interventions, monitored with serial imaging, and electively replaced with low surgical morbidity and mortality when the risk of dissection rises. Thus, timely detection of aortic aneurysms is paramount in reducing dissection risk. Aneurysms may be detected incidentally, for example, when an imaging study is performed for an unrelated reason, or when suspected based on the presence of syndromic features of a genetic aortopathy, such as those associated with Marfan syndrome or Loeys–Dietz syndrome.

The importance of family history in determining the risk for aortic aneurysm and dissection, and hence genetic predisposition, is reinforced by 2 recent simultaneous publications that provide population-based estimates of dissection risk when a first-degree relative has suffered an aortic dissection.2,3 The Taiwan study2 was based on data from its National Health Insurance Program that covers over 99% of the population. Almost 24,000 incident dissections occurred between 2000 and 2015. The overall relative risk for aortic dissection was 6.82 in first-degree relatives and remained high (5.05) after elimination of syndromic conditions. Genetic factors accounted for 57% of phenotypic variability. Of note, dissection prevalence was 2- to 3-fold higher in men than in women independent of family history.

The Danish study, performed in another country with universal health care, used registries to identify individuals with aortic aneurysms and dissections.3 Over an average 7-year follow-up, first-degree relatives of these individuals had a hazard ratio (HR) of 6.7 for aneurysm and 9.24 for dissection compared with matched controls. Findings remained significant after exclusion of individuals with Marfan syndrome, bicuspid aortic valve, or hypertension. As in the Taiwan study, male sex was associated with an HR of 2.2 for aneurysm and 1.72 for aortic dissection. In a separate analysis, the authors compared aortic diameters measured by computed tomography scan in parents and offspring in the Framingham Heart Study. The risk of an aortic diameter falling in the highest quartile in an offspring was increased by 2- to 3-fold, depending on the aortic level, if at least one parent had such a finding.3

The strength of both studies lies in the use of robust population-based data to quantify rates of aortic dissection, although individuals who die before hospitalization obviously are not captured. Unfortunately, neither study subdivided dissection according to location. However, to the extent that descending and abdominal dissections are less likely than those involving the ascending aorta to be genetically mediated, family association will only be underestimated. In contrast, aneurysm detection and prevalence estimates are more problematic in the absence of systematic screening, known age-dependent expression, variations in

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measurement location and technique, and the need to account for the importance of age, sex, and body size in defining aneurysmal dilatation. Finally, given the nature of the study design, genetic data were not available.

In broad terms, hereditary thoracic aortic disease (HTAD); other terms for this condition include familial thoracic aortic aneurysm and dissection [FTAAD] and genetic aortopathy) can be classified as syndromic or nonsyndromic, based on the respective presence or absence of extra-aortic manifestations. Although neither of the 2 recent population-based studies provided direct genetic data and both likely underrecognized syndromic conditions, it can be reasonably inferred that most of the familial clustering represented non-syndromic HTAD. Although the presence of Marfan syndrome or bicuspid aortic valve greatly increased the risk for aortic dissection (HR, 65.71 for Marfan syndrome and 16.33 for bicuspid aortic valve in the Danish study; relative risk, 31.92 for Marfan syndrome and 5.88 for bicuspid aortic valve in the Taiwan study), these groups constituted a small minority of the populations. Unfortunately, owing to the usual absence of non-aortic phenotypic features, nonsyndromic HTAD is more likely to present with aortic dissection in the proband.4,5

To the extent that early recognition may not be a feasible strategy, particularly in nonsyndromic families, the “second line” of defense falls on healthcare providers treating those with known aneurysms and dissections, particularly cardiologists and cardiothoracic surgeons. A proband is the first member of a family in whom HTAD is detected and should serve as the stimulus for genetic diagnostics in the patient in parallel with screening of first-degree relatives. HTAD is inherited in an autosomal dominant manner; however, nonsyndromic types may have variable penetrance, especially in females,6 and age-dependent expression. Spontaneous variants account for approximately 25% of patients with Marfan syndrome; spontaneous variant rates in other conditions are not well characterized.

Because HTAD dissections usually occur earlier than those associated with hypertension and atherosclerosis, genetic testing is more likely to be informative when the proband is young (age <60 years).8 However, before concluding that a degenerative cause is present in an older individual, one must ensure that the patient does not have syndromic features and that familial involvement is not present. Preventive screening with dedicated imaging for aneurysm in all first-degree relatives should be undertaken (Figure 1). Because aneurysm expression may be age-dependent, an initial normal imaging study should be repeated in 5 years.8 If a pathogenic variant is identified in the proband and absent in a first-degree relative with a normal initial imaging study at screening, further surveillance imaging can be discontinued. A comprehensive list of genes implicated in HTAD is provided in Table 1. An appreciation of the potential phenotypic features in these families is equally critically important.

The major syndromic aortopathies may be diagnosed or strongly suspected based on clinical features, with confirmation by detection of a monogenic pathogenic variant (Table 2). Diagnostic criteria for the prototypical Marfan syndrome have been established9; cardinal features include the presence of aortic root dilatation and ectopia lentis. If one of these cardinal features is absent, then the diagnosis requires definite family history or a (likely) pathogenic variant in the gene coding for fibrillin1 (FBNI), or a high systemic score (≥7) based on the weighted presence of characteristic phenotypic features (ie, arachnodactyly, pectus deformity, hind foot deformity, spontaneous pneumothorax, dural ectasia, scoliosis, striae, dolichocephaly [typical facies], severe myopia, and mitral valve prolapse). Bedside application of diagnostic criteria is greatly facilitated by use of the smartphone app Marfan Dx, which is also available on the Marfan Foundation website (https://www.marfan.org/dx/home).

Medical management of Marfan syndrome includes treatment with beta blockers or angiotensin receptor blockers to reduce the rate of aortic growth,10 avoidance of contact and competitive sports and isometric forms of exercise to decrease dissection risk, surveillance imaging, and timely referral for elective aortic root replacement. In the absence of rapid growth (3.5 mm per year) or a family history of aortic dissection at a small aortic diameter, a threshold of 5.0 cm for surgical referral is recommended.11 Safe and effective replacement of the ascending aorta has made type B dissection more common than type A dissection in patients receiving optimal management.11 Type B dissections may occur more commonly after elective root replacement,12 possibly owing to altered flow dynamics related to the rigid proximal conduit or to a more severe phenotype. Analyses of genotype–phenotype correlations indicate that individuals with variants that lead to haploinsufficiency have a more severe aortic phenotype than those resulting in a dominant negative effect.13

Loeys–Dietz syndrome was recognized as a separate HTAD in 2005 with overlapping phenotypic features of Marfan syndrome (other than ectopia lentis) but with several distinguishing characteristics.14 The initial description attributed the syndrome to mutations in transforming growth factor (TGF)-β receptors (TGFBR1 and TGFBR2) resulting in abnormal TGF-β signaling. Subsequently, additional genes coding for TGF-β ligands (TGFβ2 and TGFβ3) and intracellular components (SMAD2 and SMAD3) of the TGF-β signaling pathway have been added as causes of the Loeys–Dietz phenotype.15 Additional bedside or historical diagnostic features include hypertelorism (widely spaced eyes), bifid uvula, cleft palate, and clubfoot. Patients with SMAD3 mutations may have an additional syndromic feature of early-onset osteoarthritis.16
Medical management of patients with Loeys–Dietz syndrome is largely like that of Marfan syndrome, although similar randomized controlled trials of pharmacologic therapies have not been performed. The initial descriptions of the syndrome suggested a more aggressive aortic phenotype than that seen in Marfan syndrome; subsequent, more robust natural history data in patients harboring TGFBR1 or TGFBR2 pathogenic variants led to the recommendation for elective root replacement at smaller diameters (≤45 mm depending on gene, extra-aortic features, and sex).
TABLE 1. Causal genes in hereditary thoracic aortic disease

<table>
<thead>
<tr>
<th>Gene</th>
<th>Related syndromic entity (when applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes encoding components of the extracellular matrix</td>
<td></td>
</tr>
<tr>
<td>COL3A1, procollagen type III α1</td>
<td>Vascular Ehlers–Danlos syndrome</td>
</tr>
<tr>
<td>FBN1, fibrillin-1</td>
<td>Marfan syndrome</td>
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<tr>
<td>LOX, lysyl oxidase</td>
<td></td>
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<tr>
<td>MEAP5, microfibrillar-associated protein 5</td>
<td></td>
</tr>
<tr>
<td>BGN, biglycan</td>
<td>Meesler–Loeys syndrome</td>
</tr>
<tr>
<td>THSD4, ADAMTS-like 6 protein</td>
<td></td>
</tr>
<tr>
<td>Genes encoding proteins involved in the TGF-β pathway</td>
<td></td>
</tr>
<tr>
<td>TGFBR1, TGF-β receptor type 1</td>
<td>Loeys–Dietz syndrome</td>
</tr>
<tr>
<td>TGFBR2, TGF-β receptor type 2</td>
<td></td>
</tr>
<tr>
<td>SMAD2, Mothers against decapentaplegic Drosophila homolog 3</td>
<td></td>
</tr>
<tr>
<td>SMAD3, Mothers against decapentaplegic Drosophila homolog 3</td>
<td></td>
</tr>
<tr>
<td>TGFBR3, TGF-β3</td>
<td>Dental abnormalities and short stature</td>
</tr>
<tr>
<td>LTBP3, latent TGF-β-binding protein</td>
<td></td>
</tr>
<tr>
<td>Genes encoding components of the vascular smooth muscle contractile apparatus</td>
<td></td>
</tr>
<tr>
<td>ACTA2, SM α-actin 2</td>
<td>SM cell dysplasia syndrome</td>
</tr>
<tr>
<td>MYH11, SM myosin heavy chain</td>
<td></td>
</tr>
<tr>
<td>MYLK, myosin light chain kinase</td>
<td></td>
</tr>
<tr>
<td>PPKG1, protein kinase cGMP-dependent type 1</td>
<td></td>
</tr>
<tr>
<td>Other genes</td>
<td></td>
</tr>
<tr>
<td>FOXE3, Forkhead box E3</td>
<td>HTAD with bradycardia and left ventricular noncompaction</td>
</tr>
<tr>
<td>MAT2A, methionine adenosyltransferase IIα</td>
<td></td>
</tr>
<tr>
<td>HCN4, hyperpolarization-activated cyclic nucleotide-gated channel 4</td>
<td></td>
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</tbody>
</table>

The left column lists genes in italics with the proteins they encode. In the right column, syndromic entities are listed when applicable. Variants in practically all genes have been reported in patients with nonsyndromic HTAD. TGF, transforming growth factor; SM, smooth muscle; HTAD, hereditary thoracic aortic disease.

However, emerging data providing a more thorough description of the phenotypic spectrum of the different genotypes indicate that SMAD3 pathogenic variants are associated with a later onset of aortic dissections and elective surgeries compared to those with TGFBR1 or TGFBR2 variants.18

Vascular Ehlers–Danlos syndrome (VEDS), due to pathogenic variants in the collagen III gene (COL3A1), includes aortic aneurysm and dissection, as well as, more importantly and less predictably, nonaortic arterial aneurysms and dissections.19,20 Other typical features include hollow organ rupture (uterine, colonic) and spontaneous pneumothorax. Unfortunately, these phenotypic features may manifest as sudden catastrophes that prompt diagnosis, unless a family history is already known and family screening has been performed. Bedside clues to the underlying diagnosis include an almond-shaped facies with thin lips, translucent skin with easily visible venous patterns, easy bruising, and acrogeria (premature aging of the skin on hands and feet).

The vasodilating beta blocker celiprolol was shown to limit complications in a European population of VEDS patients.21 However, issues with study design have limited widespread acceptance of these findings, and a more rigorous treatment trial is needed. Owing to the unpredictable progression of vascular disease, as well as technical difficulties associated with surgical repair, surveillance imaging is critical, with surgical interventions generally tailored to individual circumstances.

Identification of underlying genetic variants allows further classification based on putative pathogenic mechanisms for both syndromic and nonsyndromic conditions (Table 1).6,8,22 Over the past 2 decades, the genetic underpinnings of nonsyndromic HTAD have been identified, and their natural and clinical histories are in the process of more robust characterization. Of note, the pathogenic variants associated with syndromic conditions also may be causative of aortic disease in nonsyndromic as well as sporadic HTAD.22,23 Current commercially available genetic aortopathy panels screen for most pathogenic variants discussed in
TABLE 2. Syndromic hereditary thoracic aortic diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene(s)</th>
<th>Diagnosis/phenotypic features*</th>
</tr>
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<tbody>
<tr>
<td>Marfan syndrome</td>
<td>FBN1</td>
<td>Aortic root aneurysm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectopia lentis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic score (≥7 required for cardinal feature): arachnodactyly (3); pectus carinatum, hind foot deformity, spontaneous pneumothorax, dural ectasia (all 2); scoliosis or kyphosis, reduced elbow extension, pes planus, striae, dolichocephaly, pectus excavatum, severe myopia, mitral prolapse (all 1)</td>
</tr>
<tr>
<td>Loeys-Dietz syndrome</td>
<td>TGFB1</td>
<td>Aortic root aneurysm</td>
</tr>
<tr>
<td></td>
<td>TGFB2</td>
<td>Similar systemic features, as above, other than ectopia lentis</td>
</tr>
<tr>
<td></td>
<td>SMAD2</td>
<td>Cleft palate, bifid uvula*</td>
</tr>
<tr>
<td></td>
<td>SMAD3</td>
<td>Clubfoot*</td>
</tr>
<tr>
<td></td>
<td>TGFBI</td>
<td>Hypertelorism*</td>
</tr>
<tr>
<td></td>
<td>TGFBI</td>
<td></td>
</tr>
<tr>
<td>Vascular Ehlers–Danlos syndrome</td>
<td>COL3A1</td>
<td>Medium-sized artery aneurysms and dissections*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hollow organ rupture: uterus, colon*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spontaneous pneumothorax</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin: translucent, easy bruising, acrogeria*</td>
</tr>
</tbody>
</table>

*Indicates those features that are relatively specific to the syndrome (ie, nonoverlapping).

this article; however, as many as 70% to 80% of families with HTAD will not have a known pathogenic variant.4,6

Bicuspid aortic valve (BAV) is commonly associated with aortic aneurysm and is hereditary in a small percentage (<10%), with first-degree relatives exhibiting BAV and/or aortic aneurysm.24 Interestingly, male family members are more likely than female family members to have BAV, similar to the male predominance of BAV in general. Genes associated with BAV include some specific genes (NOTCH1, GATA5, SMAD6, LOX, ROBO4, and TBX20), in addition to genes related to HTAD (TGFB1, TGFB2, TGFB3, ACTA2, and MAT2A).

Patients with pathogenic variants in the ACTA2 gene affecting smooth muscle integrity frequently present with acute aortic dissection.5 Lysyl oxidases are involved in cross-linking of elastin and collagen fibers; pathogenic variants in the LOX gene have been found to cause aortic root fusiform aneurysms extending to the ascending aorta and dissections of the ascending but not the descending aorta.25 Individuals with pathogenic variants in the gene encoding myosin light chain kinase (MYLK) frequently present with aortic dissection, because clues to an underlying aortopathy are not present. Although not all affected family members have aortic aneurysms, aortic size following dissection is not always enlarged, making management decisions for elective aortic surgery complicated.26

Families in whom HTAD is identified require multidisciplinary teams for optimal care. For example, conditions such as Marfan syndrome require coordinated care between ophthalmology, orthopedics, pediatrics, rehabilitation medicine, and maternal-fetal medicine, in addition to cardiology and cardiothoracic surgery. Vascular surgeons are a critical part of the team managing VEDS patients. Genetic counseling is important for all families with HTAD, especially in the context of family planning. In addition, genetic counselors will aid the interpretation of genetic testing results. Although known pathogenic variants are relatively straightforward, a negative study or variant of uncertain significance (VUS) requires additional discussion.27 Gene discovery is ongoing, and pathogenic variants may be identified in the future in certain families, necessitating a strategy for retesting. A VUS in HTAD genes is found more frequently in HTAD families,5 suggesting that some variants should ultimately be reclassified when disease association is confirmed.

Preventive screening for HTAD usually applies to specific clinical situations, as discussed above. However, thanks to technical progress in genetic testing, leading to a much higher throughput at lower costs, screening strategies at the population level are being undertaken. The creation of large biobanks offers the potential to set up large-scale genetic screening in populations whose clinical phenotype will be less well defined. This strategy is also called the “genotype-first” approach. Care needs to be taken with ethical issues, and people need to be informed appropriately. Results from studies applying this approach have already indicated utility in the identification of undiagnosed cases of Marfan syndrome, the ultimate goal in preventing potentially lethal complications.28

Taking population genetics even further, genome-wide association study results, combined with large aortic imaging datasets, can be used to design polygenic risk scores. These may enable the identification of even larger groups of asymptomatic individuals at risk for aneurysm or dissection and also facilitate the prioritization of potential
TABLE 3. Knowledge gaps in hereditary thoracic aortic diseases

- The underlying genotype is unknown for the vast majority of nonsyndromic hereditary thoracic aortic diseases.
- The full spectrum of natural and clinical histories is lacking.
- Randomized controlled trials of pharmacologic therapies are lacking in non-Marfan conditions.
- Imaging strategies based on natural histories of various conditions need to be devised.
- Thresholds for elective aortic replacement surgery need to be established based on dissection risk in different genotypes.
- Refinement of techniques is needed to avoid significant aortic regurgitation following valve-sparing root replacement.
- Causes of type B dissection following elective ascending aortic surgery need to be elucidated.

References

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Key Words: aortic aneurysm, aortic dissection, heritable aortic disease
Commentary: Multidisciplinary teamwork and precision medicine for thoracic aortic disease save lives

Marion A. Hofmann Bowman, MD, and Kim A. Eagle, MD

Aortic dissection remains among the most morbid and mortal conditions and occurs often in a dramatic fashion, with ripping chest pain, syncope, or sudden death and takes patients by great surprise in an untimeliest manner. What if we could prevent aortic dissection? What if we could identify patients at greater risk for aortic dissection and truly practice preventive medicine?

In this issue of the Journal, Drs Mary Roman and Julie De Backer¹ provide a contemporary review on aortic aneurysm due to heritable aortopathy and make a compelling case to initiate screening of all first-degree relatives. Dissection of the thoracic aortic often occurs in patients with genetic variants in genes predisposing to aortic disease, such as genes encoding for vascular smooth muscle, extracellular matrix, or signaling pathways. Rarely, as in the case of Marfan syndrome or Loeys–Dietz syndrome, do the carriers of such variants show any syndromic findings, hence aortic dissection can be the first manifestation of the disease. Indeed, whole-genome sequencing on unselected patients with thoracic aortic dissection revealed in approximately 10% of cases the presence of a pathogenic variant.¹ This study and others confirms the seminal findings by Biddinger and colleagues² 25 years ago, that up to 20% of individuals with thoracic aortic aneurysms and dissection who do not have a known syndrome (eg, Marfan syndrome, vascular Ehlers–Danlos syndrome, Loeys–Dietz syndrome) have a family history of thoracic aortic disease. Indeed, a recent population-based study in Denmark³ confirmed that first-degree relatives of individuals with aortic aneurysms and dissections had a hazard ratio of 6.7 for aneurysm and 9.2 for dissection over an average 7-year follow-up compared with matched controls. The risk was particularly high if a sibling or parent younger than the age of 50 years was affected by aortic disease.

Surgical treatment for aortic dissection has improved substantially, leading to a significant reduction in mortality and morbidity over the last decade.⁵,⁶ However, the surgeon can have an even larger impact on the health of his or her patients and their families by referring patients with aortic dissections to an “aortic clinic,” a multidisciplinary team of experts in vascular medicine, cardiology, and genetic counselors with the recommendation to initiate genetic testing if appropriate.⁷

The review by Roman and De Backer in this issue of the Journal provides a step-by-step tutorial on risk assessment, including appropriateness for genetic testing. By identifying other family members who could be at increased risk for aortic dissections, patients have the chance to lower their risk by a variety of measures with strict treatment of hypertension, surveillance aortic imaging, lifestyle changes aimed at reducing vascular risk factors as the cornerstones of personalized care, and timely referral for elective surgical repair of aneurysms. Recent data by our group showed a 30% increase in frequency of aortic type A dissection during the months with high community influenza prevalence, raising the question of whether influenza infection could be
Hofmann Bowman and Eagle

Interdisciplinary aortic team
personalized care & screening of first degree relatives
- clinical genetic testing
- aortic (and branch vessel?) imaging
- hypertension and lipid management
- referral for elective aortic surgery
- tobacco and cocaine cessation
- patient education for exercise restrictions
- patient education for symptoms
- maternal-fetal medicine for perinatal care
- management for secondary prevention
- influenza vaccine
- other cardiovascular diagnostic and treatment

FIGURE 1. Multidisciplinary collaboration and specialized care in an “aortic center” are important to improve outcome and individualized risk assessment for family members of patients with aortic dissections. With the advance of genetic testing and international registries, we are in an area of personalized medicine to save lives.

a modifiable risk factor for aortic dissection. Until we have further data, we would like to propose that the annual flu vaccine should become part of the toolbox used in the care for patients with aortic disease. In summary, after recovery from aortic dissection, which is in large part due to timely and skillful surgery, patients benefit from an interdisciplinary and multispecialty care in an aortic center that addresses the many aspects of cardiovascular health (Figure 1).

References

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Commentary: Thoracic aortic disease: One step closer to precision medicine

Teng C. Lee, MD, and Tom C. Nguyen, MD

Despite recent advances in management, aortic dissection and rupture continue to be life-threatening conditions. More than 60% of individuals are not diagnosed before

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CENTRAL MESSAGE

Screening family members with thoracic aortic disease may allow the detection of otherwise asymptomatic disease and the planning of appropriate prophylactic surgery based on size and specific pathogenic genetic variants.
of Cardiovascular Disease. Among those who survive to undergo repair, mortality and morbidity are still very high. Therefore, the best prevention is identification of asymptomatic but at-risk individuals.

The etiology of aortic dissection is multifactorial, involving both physiologic and anatomic factors. It is commonly known that aneurysms result in dissection/rupture. We have traditionally used aortic diameter as a criterion for prophylactic repair; however, up to 40% of patients who experienced dissection and were listed in the International Registry of Aortic Dissection database had an aortic dimension <5 cm. This is especially prevalent in patients who have syndromic hereditary thoracic aortic diseases (HTAD). Recent publications have espoused the value of other predictors of dissection/rupture, such as aortic length and its surrogate, aortic volume. Regardless of which anatomic criteria is better, the majority of patients with dissection/rupture have no knowledge of their aortic size. A recent commentary in the Journal stressed the importance of screening and better primary prevention with hypertension management. Without screening, even the best therapy would be moot. Societal guidelines for screening are confusing and have not been updated since 2010. The US Preventive Services Taskforce still does not have any guideline on screening for thoracic aortic disease.

Thoracic aortic aneurysm and dissection (TAAD) has a strong genetic component compared to abdominal aortic aneurysm. A recent systematic review by Mariscalco and colleagues revealed that 33% of first-degree relatives and up to 24% of second-degree relatives also have HTAD. In the current issue of the Journal, Roman and De Backer highlight the importance of family history in HTAD and advocated for cascade screening to allow for timely referral for elective aortic surgery to save lives. Their premise is based on 2 recent large population-based estimates of dissection risks in first-degree relatives who have sustained an aortic dissection, showing that their overall relative risks are extremely high.

In their algorithm of screening, Roman and De Backer use a phenotype-first approach with imaging and clinical evaluation of all first-degree relatives. Genetic screening and counseling are advocated only if HTAD is found. Some others favor a genotype-first approach and obtain imaging only if a pathogenic variant is found. There are pros and cons to each approach.

Over the past 2 decades, our understanding of the genetic basis of HTAD has advanced significantly, and the number of known pathogenic variants continues to increase yearly. Currently, more than 30 genes have been associated with HTAD. The aortopathy working group of the Clinical Genome Resource (ClinGen) evaluated 53 candidate genes selected from the literature and summarized the cumulative evidence as of 2018 for 11 genes that cause highly penetrant HTAD. Currently, only approximately 30% of familial nonsyndromic HTAD are attributable to known pathogenic variants. These can be detected through various types of available aortopathy panel testing. With decreasing costs of genetic testing and next-generation sequencing technologies, whole exome and whole genome sequencing are becoming more common. Although whole exome sequencing is tempting as it provides us with a lot of data, we must be careful about how to interpret and use these data. Genetic counselors must be available as part of the team that relay the information to the patient and their family members. Even if a pathologic variant is identified, the presentation in each individual could be substantially different due to variable penetrance. Insurance coverage for such tests is also inconsistent. The consequences of the information obtained are unclear, because the Genetics Information Non-Discrimination Act in the United States, which provides protection against genetic discrimination by health insurers and employers, does not provide protection against genetic discrimination for life insurance, disability insurance, and other long-term care insurance.

In recent years, with the work done by the GenTAC Alliance and the Montalcino Aortic Consortium, our understanding of genotype–phenotype interactions has improved significantly. Different pathogenic variants present differently, and certain genes, such as MILK, can result in aortic dissection with minimal aortic enlargement. Another recent study looking at SMAD3 pathogenic variants show that different variants are associated with different ages at presentation of aortic complications.

In summary, as we move toward identifying more family members with HTAD via cascade screening, and as we improve our understanding of different genotype–phenotype interactions among different pathogenic variants, we will be able to move closer to the holy grail of precision medicine.

References

Commentary: How to save and improve the lives of families with heritable aortic diseases

Michelle Keir, MD, MSc, R. Scott McClure, MD, SM, and Paul W. M. Fedak, MD, PhD

As our understanding of the genetics underlying heritable aortic disease (HAD) grows, so too does the complexity increase with respect to managing this growing population. In this issue of the Journal, Roman and De Backer review the contemporary management of HAD, outline the minefield of knowledge gaps facing clinicians, and propose a reasonable pathway forward. The concise recommendation for family screening of first-degree relatives for those with aortic dissection under age 60 years is a clear wayfinder for the multidisciplinary teams managing these patients and their families.

The greatest strength of the offered discourse is the excellent summary of known genetic variants for HAD and their clinical implications. Staying informed about the myriad of genetic advancements is a daunting task. This focused review highlights the importance of geneticists in the care paradigm of aortic disease. In the flurry of acute management of aortic dissection, the focus is on reducing morbidity and mortality for the affected patient.
and the foundational nature of a robust family history easily can be forgotten or dismissed. We are reminded by the authors to avoid a myopic focus on the immediate surgical task at hand, as it could cost us many more future lives than the single life that we are trying to save in the moment.

In the past, a binary evaluation for those with aortic dissection, Marfan or non-Marfan, was the standard of care. First-degree relative screening using advanced imaging and genetic phenotyping were isolated events. Family members were triaged into discrete categories, either affected or not affected. Roman and De Backer remind us of how this simple approach lacks precision and depth, and encourage us to challenge our assumptions. They emphasize the importance of longitudinal care for affected families, given that variants of unknown significance can become significant over time.

Will this proposal be feasible and provide value? Genetic testing is becoming more accessible and efficient, but the complex challenge of managing patients in resource-poor settings remains an unsurmountable barrier. Advocating for longitudinal imaging screening of first-degree relatives is laudable, but the cost-effectiveness of screening needs more consideration.

A diagnosis of HAD is a life-changing event. Individuals are forced to confront their own mortality while simultaneously managing the stress and grief that comes from supporting a family member with a complication from a heritable disease. The impact of psychological distress on adherence to treatment and long-term follow-up should be a research priority moving forward. For example, expert consensus led us to counsel women with Loeys–Dietz syndrome that their average life expectancy was 26 years, and that pregnancy carried a high risk of severe complications. Longitudinal cohort studies and data from wider genetic testing efforts have now informed us that these estimates and recommendations were likely too conservative. Counseling has since changed, and we must now confront the real-world implications of past recommendations on affected women. As such, more precise screening and management of families with heritable aortopathy is needed. Future research should assess the cost-effectiveness, psychological burden, and feasibility of the proposed management strategy.

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