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Review

Precision medicine in heritable thoracic aortic disease (HTAD): From molecular mechanisms to genotype-driven risk stratification and timing of intervention

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Abstract

Aim: Heritable thoracic aortic disease (HTAD) accounts for approximately 20-25% of thoracic aortic aneurysm and dissection (TAAD) cases and is a major cause of premature death in young adults.

Methods: We performed a selective synthesis of clinical practice guidelines (ACC/AHA 2022, EACTS/STS 2024), large multicenter cohort studies (Montalcino Aortic Consortium), and molecular mechanism data published between 2019 and 2025.

Results: The advent of next-generation sequencing (NGS) has driven a paradigm shift in HTAD management: from risk assessment based purely on *phenotype* (aortic diameter) to risk stratification based on *genotype* (molecular mutation). Eleven genes now carry sufficient evidence to be included in clinical testing panels, grouped into three pathogenic mechanisms:

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extracellular matrix dysregulation, TGF-β signaling dysregulation, and vascular smooth muscle contractile dysfunction. Prophylactic surgical thresholds are now rigorously individualized by gene, ranging from 4.0 cm (high-risk TGFBR1/TGFBR2, PRKG1) to 5.0 cm (FBN1, TGFB3), replacing the uniform 5.5 cm threshold historically applied to all patients.

Conclusions: This review synthesizes the molecular pathogenesis, gene-specific epidemiologic and prognostic data, and updated prophylactic intervention algorithms per the ACC/AHA (2022) and EACTS/STS (2024) guidelines, providing a practical reference framework for individualizing surveillance and surgical decision-making in patients with HTAD.

Keywords: Heritable thoracic aortic disease, precision medicine, marfan syndrome, loeys-dietz syndrome, vascular ehlers-danlos syndrome, ACTA2, PRKG1, FBN1

INTRODUCTION

For decades, the prophylactic surgical strategy for thoracic aortic aneurysm relied on a single *"gold standard"*: the maximal aortic diameter measured on imaging. Guidelines prior to 2010 typically applied a uniform 5.0-5.5 cm threshold for surgical referral across all patients, regardless of underlying etiology.

However, this one-size-fits-all approach has clearly failed in patients with heritable thoracic aortic disease (HTAD), in whom type A aortic dissection often occurs earlier and at substantially smaller diameters than in degenerative/atherosclerotic thoracic aortic aneurysm. Gene-specific cohort studies show that certain genotypes (e.g., *PRKG1*) can precipitate type A dissection with only minimal aortic enlargement, whereas other genotypes (e.g., *FBN1*) permit safe surveillance to a larger diameter threshold.

The widespread availability of next-generation sequencing (NGS) over the past two decades has enabled identification of the causal mutation in most HTAD families, transforming genetic testing into a tool with dual significance: diagnostic, prognostic and therapeutic[1,3].

This review systematically addresses three pillars of precision medicine in HTAD: (i) molecular pathogenesis; (ii) gene-specific epidemiologic and prognostic data; and (iii) individualized prophylactic intervention algorithms per the 2022 ACC/AHA and 2024 EACTS/STS guidelines.

Figure 1 (next page) summarizes the complete clinical approach to HTAD - from initial clinical suspicion, through genetic testing and cascade family screening, to stratification by the three molecular mechanisms, and finally to the intervention decision made by the multidisciplinary aortic team. The following sections present the supporting evidence for each branch of this algorithm in detail.

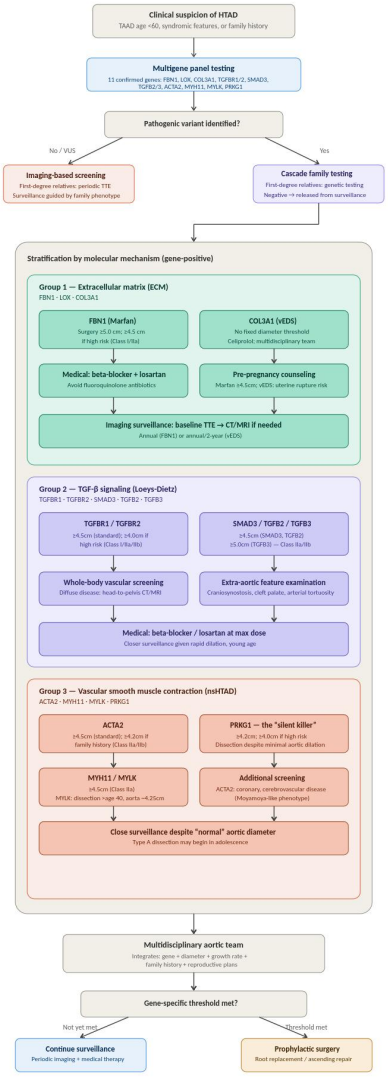

Figure 1. Diagnostic and treatment algorithm for heritable thoracic aortic disease (HTAD): from clinical suspicion to gene-specific individualized intervention. HTAD: heritable thoracic aortic disease; nsHTAD: non-syndromic heritable thoracic aortic disease; TAAD: thoracic aortic aneurysm and dissection; VUS: variant of uncertain significance; TTE: transthoracic echocardiography; CT: computed tomography; MRI: magnetic resonance imaging; ECM: extracellular matrix; TGF-β: transforming growth factor-beta; vEDS: vascular Ehlers-Danlos syndrome; Class I/IIa/IIb: class of recommendation; FBN1: fibrillin-1; LOX: lysyl oxidase; COL3A1: collagen type III alpha 1 chain; TGFBR1/TGFBR2: transforming growth factor-beta receptor type 1/type 2; SMAD3: SMAD family member 3; TGFB2/TGFB3: transforming growth factor-beta 2/beta 3; ACTA2: actin alpha 2, smooth muscle; MYH11: myosin heavy chain 11; MYLK: myosin light chain kinase; PRKG1: protein kinase cGMP-dependent type 1.

MOLECULAR PATHOGENESIS: THREE PRINCIPAL BIOLOGICAL PATHWAYS

The mechanical integrity of the aortic wall depends on a tightly coordinated interaction between the extracellular matrix (ECM) network and vascular smooth muscle cells (VSMC) within the tunica media. Eleven genes have been confirmed by the American College of Medical Genetics and the ACC/AHA as having “strong” to “definitive” evidence for HTAD: FBN1, LOX, COL3A1, TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3, ACTA2, MYH11, MYLK, PRKG1[1,3]. These mutations converge on three principal pathogenic pathways.

Extracellular matrix (ECM) disorders

The prototypical example is *FBN1* (Marfan syndrome), encoding fibrillin-1, the structural glycoprotein of elastic microfibrils; *COL3A1* (vascular Ehlers-Danlos syndrome, vEDS), encoding type III collagen; and *LOX*, encoding lysyl oxidase, the enzyme that catalyzes collagen and elastin cross-linking[1]. Deficiency of these structural proteins directly reduces the elasticity and tensile strength of the aortic wall.

Notably, the mechanism of *FBN1* mutations extends beyond simple structural deficiency: under normal conditions, fibrillin-1 also *sequesters* latent TGF-β complexes within the

extracellular matrix. When fibrillin-1 is deficient, these complexes are abnormally released, producing secondary TGF-β hypersignaling - a mechanism that converges with the primary TGF-β signaling pathway disorders discussed below.

TGF-β signaling pathway disorders

This group includes mutations at the transmembrane receptors (*TGFBR1, TGFBR2*) or downstream intracellular signal transducers (*SMAD3, TGFB2, TGFB3*). A key biological paradox: although these mutations are typically loss-of-function with respect to the receptor, the resulting tissue phenotype is paradoxical compensatory hyperactivation of TGF-β/SMAD signaling in the vessel wall - the mechanism underlying Loeys-Dietz syndrome (LDS). This group is clinically characterized by diffuse vasculopathy (affecting systemic arteries, not the aorta alone), rapid dilation, and aggressive disease progression at a young age, often accompanied by extra-aortic features (bifid uvula/cleft palate, craniosynostosis, arterial tortuosity)[1].

Vascular smooth muscle contractile dysfunction

This group comprises *ACTA2, MYH11, MYLK*, and *PRKG1* - the classic genes underlying non-syndromic HTAD (nsHTAD), i.e., disease without prominent extracardiac manifestations. These proteins (smooth muscle α-actin, myosin heavy chain, myosin light-chain kinase, and cGMP-dependent protein kinase, respectively) all participate directly in the VSMC contractile apparatus. When contractile function is lost, VSMCs switch phenotype from a physiologic *"contractile"* state to a pathologic *"synthetic phenotype"*, leading to medial degeneration and proteoglycan accumulation.

Of particular mechanistic importance: a recurrent gain-of-function mutation in *PRKG1* (c.530G > A, p.Arg177Gln) renders protein kinase G *constitutively active* independent of cGMP binding, causing sustained inhibition of contraction and rendering the thoracic aorta susceptible to dissection even with minimal or absent dilation[1,6].

Convergent mechanism: Mechanotransduction failure

Although initiated by three distinct protein groups, these pathogenic pathways converge on a common final axis: elastic fiber damage → loss of mechanical coupling between elastic fibers and VSMCs (mechanotransduction failure) → compensatory activation of the TGF-β pathway and the renin-angiotensin system (angiotensin II) → VSMC apoptosis → medial degeneration (cystic medial degeneration) → aortic dilation/dissection[4]. This unifying model explains why agents targeting the TGF-β/angiotensin axis (losartan) are effective across multiple genetically distinct subgroups, regardless of whether the primary mutation lies in the ECM, the TGF-β receptor, or the contractile apparatus.

Table 1. Classification of the three pathogenic mechanism groups in HTAD by gene.

Mechanistic group	Genes involved	Principal biological consequence
Extracellular matrix (ECM)	FBN1, LOX, COL3A1	Structural weakening of the aortic wall; FBN1 causes secondary TGF-β hypersignaling
TGF-β signaling	TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3	Excessive compensatory TGF-β/SMAD activation; diffuse, aggressive vasculopathy at young age (LDS)
Vascular smooth muscle contraction (SMC)	ACTA2, MYH11, MYLK, PRKG1	VSMC phenotypic switch to "synthetic" state; medial degeneration; PRKG1 causes dissection with minimal aortic dilation

GENE-SPECIFIC PHENOTYPE AND IMAGING SURVEILLANCE

For non-syndromic HTAD (nsHTAD) caused by *ACTA2, PRKG1, MYH11, MYLK, LOX* mutations, the 2022 ACC/AHA guideline recommends baseline imaging by transthoracic echocardiography (TTE), supplemented by CT/MRI when TTE inadequately visualizes the ascending aorta and aortic arch, followed by annual surveillance if stable[1]. Each gene carries a distinct phenotypic signature that should inform individualized surveillance planning:

Table 2. Gene-specific phenotype and imaging surveillance recommendations (nsHTAD).

Gene	Clinical features	Surveillance implications
ACTA2	Type A or B dissection; root and ascending aortic aneurysm; some pathogenic variants cause occlusive vasculopathy (Moyamoya-like cerebrovascular disease, early coronary artery disease)	Additional screening for coronary and cerebrovascular disease warranted
PRKG1	Type A/B dissection may occur in adolescence without preceding aortic dilation	Close surveillance warranted despite normal aortic diameter; low surgical threshold
MYH11	Type A dissection may occur at diameters < 5.0 cm; may be associated with peripheral arterial disease, patent ductus arteriosus (PDA)	Whole-aorta imaging plus peripheral vascular screening
MYLK	Type A dissection typically after age 40, with minimal aortic dilation (median diameter 4.25 cm)	Intervention should not be deferred solely because diameter has not reached "classic" thresholds
LOX	Aortic root aneurysm; fusiform dilation extending from root to ascending aorta and arch	Imaging must survey the entire aortic arch, not just the root

GENOTYPE-BASED CLINICAL RISK STRATIFICATION: OUTCOMES DATA

Large multicenter cohort studies - most notably the Montalcino Aortic Consortium (MAC), an international registry collecting patient data to construct gene-specific risk models for HTAD[3] - have demonstrated clearly distinct clinical prognoses across genotype groups, sufficient to justify a gene-stratified management strategy.

Risk of subsequent cardiovascular events

In a retrospective study of 518 genetically diagnosed patients (Yagyu *et al.*, National Cerebral and Cardiovascular Center, Japan), patients were stratified by causative gene: Group 1 - *FBN1* (n = 344); Group 2 - *TGFBR1, TGFBR2, SMAD3*, or *TGFB2* (n = 74); Group 3 - *COL3A1* (n = 60); Group 4 - *ACTA2* or *MYH11* (n = 40)[5]. Patients carrying TGF-β signaling pathway variants (Group 2, corresponding to the Loeys-Dietz phenotypic spectrum) had a 2.33-fold higher risk of subsequent cardiovascular events (HR 2.33; 95% CI 1.60-3.38; $p <$ 0.001) compared with the *FBN1* group, after adjustment for age at first event, sex, and diagnostic status (proband versus relative)[5]. The 5-year cumulative event rate in Group 2 was 70.6% (95% CI 56.2-83.7%), compared with 41.5% in Group 1 (log-rank $p < 0.001$)[5].

Risk of visceral vessel rupture and obstetric complications - the COL3A1 paradox

The same study revealed a striking clinical paradox: female patients carrying *COL3A1* mutations (vEDS) had a significantly lower rate of aortic dissection compared with the three other genotype groups among women (3.1% versus 34.2%, 59.0%, and 43.8% for Groups 1, 2, and 4, respectively; $p < 0.001$), whereas no significant between-group difference was observed among men ($p = 0.06$)[5]. This does not imply that COL3A1 is "safer": the true hazard of vEDS lies in rupture of medium-caliber arteries outside the aorta (mesenteric, renal, splenic) and uterine rupture or massive obstetric hemorrhage during pregnancy, through mechanisms independent of aortic diameter[1,10].

Dissection with minimal aortic dilation - the "Silent Killer" phenomenon

The MAC study of 1,028 patients across 7 HTAD genes (Regalado *et al.*, J Am Coll Cardiol 2022) identified statistically significant differences in the risk of first aortic event among the smooth-muscle contractile genes (*ACTA2, MYLK, PRKG1*; $p = 0.002$) and among the Loeys-Dietz spectrum genes (*SMAD3, TGFB2, TGFBR1, TGFBR2*; $p < 0.0001$)[3]. Critically, the cumulative incidence of type A dissection exceeded that of elective aneurysm surgery for *ACTA2, MYLK, PRKG1*, and *SMAD3* - meaning most patients in these groups first present with acute dissection rather than being identified and electively repaired; conversely, *TGFBR2* showed a lower rate of type A dissection than elective surgery, suggesting this group offers a greater "window of opportunity" for detection and intervention before an acute event[3].

A case series from the UTHealth Houston Multidisciplinary Aortic and Vascular Disease Conference, describing two unrelated families carrying the recurrent PRKG1 c.530G > A variant (p.Arg177Gln, also termed p.Arg192Gln), vividly illustrates this phenomenon: multiple individuals experienced acute dissection at very young ages, resulting in five deaths across the two families, including early-onset type A dissection, chronic thoracoabdominal dissection with visceral complications, and a case requiring elective ascending aortic repair despite minimal dilation[6]. This stands as direct evidence for the principle that a "normal" aortic diameter does not equate to safety in patients carrying contractile-gene mutations.

Table 3. Summary of key gene-specific outcomes data.

Metric	Key finding
Risk of subsequent events (*vs.* FBN1)	TGF-β group (LDS): HR 2.33 (95% CI 1.60-3.38; $p < 0.001$)
Aortic dissection in women carrying COL3A1	3.1% *vs.* 34.2-59.0% in the three other genotype groups ($p < 0.001$)
Type A dissection *vs.* elective surgery	Exceeds in ACTA2, MYLK, PRKG1, SMAD3 ($p < 0.002$ to $p < 0.0001$)
Aortic diameter at dissection (PRKG1)	May occur with minimal or no aortic dilation
Aortic diameter at dissection (MYLK)	Median 4.25 cm, typically age > 40 years

GENOTYPE-PHENOTYPE CORRELATION: ACTA2 AS A MODEL FOR PRECISION MEDICINE

Among HTAD genes, *ACTA2* best exemplifies precision medicine at the variant-specific level, not merely the gene level. The location of the mutation within the molecule determines the clinical phenotype, as illustrated by the following groups[11,12]:

•p.Arg179His/p.Arg179Cys (R179H/R179C): causes Smooth Muscle Dysfunction Syndrome (SMDS), with complete penetrance before age 20 for patent ductus arteriosus (PDA) and thoracic aortic disease; accompanied by Moyamoya-like cerebrovascular disease, pulmonary arterial hypertension, congenital mydriasis, and gastrointestinal dysmotility reflecting concurrent visceral smooth muscle involvement[11].

•p.Arg149/p.Arg118: associated with increased risk of early coronary artery disease.

•p.Arg258: associated with early stroke due to occlusive cerebrovascular disease.

A recent breakthrough using CRISPR-Cas9 adenine base editing successfully rescued the SMDS phenotype in a mouse model carrying the *ACTA2* p.Arg179His mutation, restoring aortic VSMC contractile function and preventing aortic dilation/dissection[13]. This represents an important *proof-of-concept* for causal gene-editing therapy in monogenic HTAD, although clinical application remains distant.

INDIVIDUALIZED GENE-SPECIFIC PROPHYLACTIC INTERVENTION ALGORITHM

The convergence of the 2022 ACC/AHA guideline[1] and the 2024 EACTS/STS guideline[9] establishes a surgical algorithm (root replacement or ascending aortic repair) that is rigorously calibrated by gene and additional risk factors, entirely superseding the previous uniform 5.5 cm threshold model.

Marfan syndrome (FBN1)

Underlying medical therapy: beta-blocker or angiotensin II receptor blocker (ARB - losartan) at maximally tolerated dose (Class I, Level of Evidence A); combination of both agent classes is reasonable (Class IIa)[1]. Randomized controlled trials, including the Pediatric Heart Network trial and the trial by Teixido-Tura *et al.*, showed equivalent efficacy of losartan and atenolol in slowing aortic root dilation in Marfan patients[7,8], while a Cochrane systematic review confirmed the benefit of beta-blockade in dissection prevention[18].

Surgical thresholds for aortic root replacement in Marfan syndrome:

• Aortic root diameter ≥ 5.0 cm: surgery is recommended (Class I)

• ≥ 4.5 cm with high-risk features (family history of dissection, growth rate > 0.3 cm/year, severe dilation of the abdominal aorta/branch vessels, or a Marfan patient planning pregnancy): surgery is reasonable (Class IIa)

•Aortic cross-sectional area-to-height ratio ≥ 10 cm^2/m: surgery is reasonable (Class IIa) - this index is particularly useful in patients of unusually small or tall stature, in whom absolute diameter alone may underestimate true risk[1].

Loeys-dietz syndrome (TGF-β gene group)

Surgical thresholds are stratified by specific gene, reflecting differing degrees of malignancy within the same signaling pathway:

Table 4. Prophylactic surgical thresholds by gene - the Loeys-Dietz spectrum.

Gene	High-risk features*	Diameter (cm)	Class
TGFBR1	No	≥ 4.5	I
TGFBR1	Yes*	≥ 4.0	IIb
TGFBR2	No	≥ 4.5	I
TGFBR2	Yes*	≥ 4.0	IIa
SMAD3	—	≥ 4.5	IIa
TGFB2	—	≥ 4.5	IIb
TGFB3	—	≥ 5.0	IIb

*High-risk features for TGFBR1/TGFBR2: a specific pathogenic variant known to be associated with a severe phenotype; small body habitus in TGFBR2-affected women; severe extra-aortic features (craniosynostosis, cleft palate, hypertelorism, bifid uvula, severe arterial tortuosity); family history of dissection; aortic growth rate > 0.3 cm/year. TGFBR1: transforming growth factor-beta receptor type 1; TGFBR2: transforming growth factor-

beta receptor type 2; SMAD3: SMAD family member 3; TGFB2: transforming growth factor-beta 2; TGFB3: transforming growth factor-beta 3; Class: class of recommendation; cm: centimeter.

Vascular ehlers-danlos syndrome (COL3A1)

vEDS represents a uniquely dangerous group, as the aorta and its branch arteries may rupture or dissect even without significant dilation - consequently, no specific diameter threshold is recommended for diameter-based prophylactic surgery[1]. Comprehensive management includes:

• Baseline whole-body MRI or CT angiography (head to pelvis); annual surveillance, or every 2 years if stable.

• Celiprolol (a vasodilating beta-blocker) is the only medicine that with both randomized trial data (the BBEST trial) and long-term observational data (Frank *et al.*, 144 patients followed up to 17 years) demonstrating a clear survival benefit, with a dose-dependent effect (best protection at 400 mg/day, $p = 0.003$)[10].

• Surgery carries substantial complication risk owing to friable vascular tissue prone to tearing during manipulation → intervention decisions should be made by a multidisciplinary aortic team experienced in vEDS.

Non-syndromic HTAD (nsHTAD): ACTA2, PRKG1, MYH11, MYLK

Table 5. Prophylactic surgical thresholds by gene - the smooth-muscle contractile (SMC) group.

Gene	Risk factor**	Diameter (cm)	Class
ACTA2	No	≥ 4.5	IIa
ACTA2	Yes**	≥ 4.2	IIb
MYH11 & MYLK	N/A	≥ 4.5	IIa
PRKG1	No	≥ 4.2	IIb

Gene	Risk factor**	Diameter (cm)	Class
PRKG1	Yes**	≥ 4.0	IIb

**Risk factor: family history of type A dissection with minimal aortic dilation, aortic growth rate ≥0.3 cm/year, or concomitant valvular disease requiring surgery. SMC: smooth muscle contraction; ACTA2: actin alpha 2, smooth muscle; MYH11: myosin heavy chain 11; MYLK: myosin light chain kinase; PRKG1: protein kinase cGMP-dependent type 1; N/A: not applicable; Class: class of recommendation; cm: centimeter.

In HTAD families in whom a causative gene has not been identified (gene-negative or incompletely tested), the clinical phenotype of an affected family member should guide management - including features: aneurysm location, aortic diameter at the time of a relative's dissection, and other vascular features[1].

Considerations before and during pregnancy

Pregnancy increases the risk of aortic dissection through hemodynamic mechanisms such as: increased cardiac output, increased circulating volume and hormonal mechanisms (estrogen/relaxin-mediated changes in vessel wall collagen architecture). Pre-pregnancy prophylactic surgical thresholds are likewise individualized by genotype: Marfan ≥ 4.5 cm (or 4.0 - 4.5 cm if high-risk features are present); LDS due to *TGFBR1/TGFBR2/SMAD3* ≥ 4.0 cm; LDS due to *TGFB2/TGFB3* ≥ 4.5 cm; nsHTAD ≥ 4.5 cm[1]. For vEDS, the predominant obstetric risk is uterine rupture and massive hemorrhage, which does not correlate with aortic diameter; pregnancy risk-benefit counseling should therefore be addressed separately at an experienced center.

FUTURE DIRECTIONS: BIOMECHANICS AND POLYGENIC RISK SCORES

Biomechanical indices beyond transverse diameter

Recent recommendations have begun to highlight the additional value of aortic length and aortic stiffness measured by 4D-flow MRI. In HTAD patients, an aortic length exceeding 11-13 cm or abnormal changes in wall shear stress may predict dissection risk better than transverse diameter alone[4]. This remains an evolving research field, not yet formally incorporated into class of recommendations, but it reflects a broader shift from a two-

dimensional geometric model (diameter) toward a three-dimensional dynamic model (shape, length, flow) in aortic risk assessment.

Polygenic risk scores (PRS)

Approximately 75-80% of thoracic aortic disease cases occur in individuals without evidence of a highly penetrant monogenic mutation[14]. For this group, large genome-wide association studies (GWAS) - including the Million Veteran Program and UK Biobank - have identified dozens of common risk loci, paving the way for polygenic risk scores (PRS)[15,16].

A study in a diverse biobank found that a dissection-specific PRS improved predictive performance beyond clinical factors and aortic diameter alone, with AUROC increasing from 0.676 to 0.723 upon addition of the dissection-PRS[14]. Similarly, the AORTA Gene Score (Pirruccello *et al.*, combining a 1.1-million-variant PRS with clinical factors) explained 35-42% of the variance in ascending aortic diameter across validation cohorts (UK Biobank, All of Us, Framingham Heart Study, Mass General Brigham), with a hazard ratio of 1.58 (95% CI 1.26-1.99) per standard deviation increase in score, representing a substantial improvement over clinical-factors-only models[17]. Although PRS is not yet recommended for routine clinical use, it represents a promising avenue for narrowing the risk-assessment gap in the 80% of patients without an identifiable monogenic mutation.

HOLISTIC MEDICAL MANAGEMENT

Genetic testing and cascade family screening

Per the 2022 ACC/AHA guideline (Class I, LOE B-NR), genetic testing is recommended for patients with aortic root/ascending aneurysm or aortic dissection plus *at least one* of four risk features suggestive of HTAD[1]:

1. Thoracic aortic disease with syndromic features of Marfan, Loeys-Dietz, or vascular Ehlers-Danlos syndrome (tall stature, arachnodactyly, lens dislocation, cleft palate, bifid uvula, hypertelorism, craniosynostosis, arterial tortuosity, thin translucent skin, easy bruising).

2. Early-onset thoracic aortic disease, age < 60 years.

3. Family history of thoracic aortic disease, or peripheral or intracranial arterial aneurysm/dissection in a first- or second-degree relative.

4. Family history of unexplained sudden death at a relatively young age in a first- or second-degree relative.

Once a pathogenic variant is identified in the proband, cascade genetic testing of all at-risk relatives is strongly recommended (Class I)[1]. Relatives carrying the pathogenic variant should undergo aortic imaging by TTE (or CT/MRI if TTE is inadequate); relatives who do not carry a confirmed familial pathogenic variant may be released from costly periodic imaging surveillance[1,3]. When testing identifies a Variant of Uncertain Significance (VUS), this result should not be used to guide clinical management or cascade testing; first-degree relatives still require imaging surveillance (Class I) regardless of the genetic result[1].

A multigene panel encompassing at minimum the 11 genes with strong evidence noted above is the most cost-effective and clinically useful testing strategy, and may be expanded to include genes with moderate or emerging evidence[1,3].

Contraindications and factors to avoid

HTAD patients should avoid high-intensity isometric/anaerobic exercise involving sudden exertional strain (heavy weightlifting, collision or contact sports), as these activities cause acute peak blood pressure surges and increased aortic wall stress.

Fluoroquinolone antibiotics should be avoided when an alternative exists, owing to their mechanism of inhibiting collagen synthesis and increasing matrix metalloproteinase activity within the vessel wall, thereby increasing the risk of aortic aneurysm/dissection - a particular concern in patients with an underlying collagen/ECM defect (FBN1, COL3A1, LOX).

Foundational medical therapy

Beta-blockers and losartan (ARB) are the two pillars of medical therapy shown to slow the rate of aortic root dilation, with the clearest benefit in Marfan and Loeys-Dietz syndromes[7,8,18]. The mechanism of losartan extends beyond blood pressure reduction alone: by blocking the AT1 receptor, losartan reduces SMAD-independent TGF-β activation, thereby acting directly on the molecular pathogenic axis described in Section 2. For vEDS, celiprolol is the preferred agent given its disease-specific long-term survival data[10].

CONCLUSION

The notion that a “normal aortic diameter equals safety” is a dangerous illusion in heritable thoracic aortic disease. Data from multicenter registries demonstrate that dissection risk does not correlate simply and linearly with aortic diameter, but instead depends fundamentally on the underlying molecular etiology -ranging from ECM structural defects, to TGF-β hypersignaling, to loss of vascular smooth muscle contractile function.

Genotype differentiation allows multidisciplinary teams to individualize surveillance strategy, surgical decision-making, and pregnancy counseling, rather than applying a uniform intervention threshold to all patients. Adherence to an intervention algorithm stratified by the biological malignancy of each gene -ranging from a 4.0 cm threshold in high-risk Loeys-Dietz syndrome and PRKG1, to 5.0 cm in Marfan syndrome and TGFB3 - is the practical key to minimizing aortic dissection-related mortality in the HTAD patient population.

Emerging directions - including biomechanical indices (aortic length, wall shear stress) and polygenic risk scores (PRS) - hold promise for narrowing the risk-assessment gap in patients without an identifiable monogenic mutation, further refining the precision medicine framework for thoracic aortic disease.

DECLARATIONS

Availability of data and materials

Data is available on request.

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Conflict of interest

Not applicable.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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