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Position Statement

Canadian Cardiovascular Society Position Statement on the Management of Thoracic Aortic Disease

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ABSTRACT

This Canadian Cardiovascular Society position statement aims to provide succinct perspectives on key issues in the management of thoracic aortic disease (TAD). This document is not a comprehensive overview of TAD and important elements of the epidemiology, presentation, diagnosis, and management of acute aortic syndromes are deliberately not discussed; readers are referred to the 2010 guidelines published by the American Heart Association, American College of Cardiology, American Association for Thoracic Surgery, and other stakeholders. Rather, this document is a practical guide for clinicians managing adult patients with TAD. Topics covered include size thresholds for surgical intervention, emerging thera-

RÉSUMÉ

Cet énoncé de position de la Société canadienne de cardiologie a pour but de donner des perspectives succinctes sur les aspects clés de la prise en charge de la maladie de l'aorte thoracique (MAT). Ce document n'est pas un aperçu complet de la MAT, et les éléments importants de l'épidémiologie, du tableau clinique, du diagnostic et de la prise en charge des syndromes aortiques aigus ne sont délibérément pas discutés; les lecteurs sont invités à consulter les lignes directrices de 2010 publiées par l'American Heart Association, l'American College of Cardiology, l'American Association for Thoracic Surgery et les autres parties prenantes. Ce document est plutôt un guide pratique pour les cliniciens

Thoracic Aortic Aneurysm

Size thresholds for elective thoracic aortic intervention

Thoracic aortic aneurysms are largely asymptomatic until a sudden and catastrophic event, including aortic rupture or dissection, occurs, and is rapidly fatal in a large proportion of patients.[1,2] Elective intervention on the thoracic aorta carries a much lower risk of mortality and morbidity, and prophylactic aortic surgery can be life-saving.

The decision to perform aortic intervention is a balance between risks of natural history of the disease vs the risk of the surgical intervention itself, and any additional long-term risks

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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pies, imaging modalities, medical and lifestyle management, and genetics of TAD. The primary panel consisted of experts from a variety of disciplines that are essential for comprehensive management of TAD patients. The methodology involved a focused literature review with an emphasis on updates since 2010 and the use of Grading of Recommendations Assessment, Development, and Evaluation methodology to arrive at specific recommendations. The final document then underwent review by a secondary panel. This document aims to provide recommendations for most patients and situations. However, the ultimate judgement regarding the management of any individual patients should be made by their health care team.

prenant en charge des patients adultes atteints d'une MAT. Les thèmes couverts incluent les seuils de l'ampleur de l'intervention chirurgicale, les nouveaux traitements, les modalités d'imagerie, la prise en charge médicale et du mode de vie, et la génétique de la MAT. Le premier panel comprenait des experts de diverses disciplines qui sont essentielles à la prise en charge complète des patients atteints d'une MAT. La méthodologie exigeait une revue de littérature ciblée s'appuyant sur les mises à jour depuis 2010 et l'utilisation de la méthodologie GRACE (Grading of Recommendations Assessment, Development, and Evaluation) pour parvenir à des recommandations précises. Le document final était ensuite passé en revue par un second panel. Ce document a pour but de fournir des recommandations pour la plupart des patients et la plupart des situations. Cependant, la décision définitive concernant la prise en charge de chaque patient devrait être prise par l'équipe soignante.

of treatment. The risk of aortic complications is influenced by a number of patient-related factors (eg, family history of aortic disease, history of smoking, etc) and disease-related factors (eg, true vs false aneurysm, bicuspid valve aortopathy, connective tissue disorders, etc) (Table 1). Similarly, the risk of surgical intervention might be significantly influenced by comorbidities (eg, chronic obstructive pulmonary disease, coronary or valve disease, etc.) and anatomy (presence of dissection, aortic arch involvement).

The risk related to intervention is an instantaneous risk whereas the risk of aortic complications accrues over time (eg, 5-year risk of rupture is greater than 1-year risk of rupture). Therefore, it might be acceptable for patients to accept a one-time risk of intervention (eg, 5%) to prevent the long-term consequences of aortopathy (eg, 2%-3% per year). Maximum aortic diameter is the most important predictor of aortic complications. However, because many factors influence the relationship between size and aortic complications, absolute size should not be used in isolation. There are occasionally long-term consequences that deserve consideration, such as minimizing the risk of valve-related complications in patients eligible for aortic valve-sparing or repair surgery. Last, estimates of risk of aortic complications based on natural history studies are not well established in all subsets of thoracic aortic disease (TAD).

The size threshold for considering aortic intervention has decreased successively over recent years, because of substantial reduction in morbidity and mortality for elective procedures. In experienced centres, elective repair of ascending aorta and aortic root aneurysms carries a mortality of 1%. Aneurysms involving the aortic arch and descending thoracic aorta typically carry a greater risk of mortality and neurologic morbidity.

The **I**nternational **R**egistry of **A**ortic **D**issection (IRAD) registry and other data have brought into question the current threshold of aortic diameter of 5.5 cm for ascending aortic aneurysm, because the median diameter of patients presenting with type A and B aortic dissections was significantly less than 5.5 cm.[3,4] With an intervention threshold of 5.5 cm, more than half of type A aortic dissections would not be prevented. However, the number of patients in the general population with aortic diameters between 5.0 and 5.5 cm (and 4.5-5.0 cm) is large, and their annual risk of aortic complications is not well characterized. Even with the low risk of elective aortic replacement, at some level, this number needed to treat would be prohibitively high.

Table 1. Factors determining increased risk of aortic complications and of increased risk of surgical intervention

Factors associated with increased risk of aortic complications	Factors associated with increased risk of surgical intervention
Aortic size	Aortic arch pathology
Connective tissue disorder	Descending thoracic aortic pathology
Family history of aortopathy	Chronic obstructive pulmonary disease
Bicuspid aortic valve	Renal dysfunction
Smoking history	Previous cardiac surgery
Aneurysm related symptoms	Advanced age
Rapid growth (> 0.5 cm/y)	Left ventricular dysfunction
Concomitant aortic valve disease	
Uncontrolled hypertension	

Additional factors might be relevant for risk stratification in some patients.

RECOMMENDATION

1. We recommend that the decision to perform prophylactic aortic intervention should be tailored to the individual patient and incorporate patient-related and disease-related factors (Strong Recommendation, Moderate-Quality Evidence).

Values and Preferences. The important factors influencing the risk of aortic complications and risk of operative intervention are listed in Table 1. When there is uncertainty regarding decision-making, patients should be referred to specialists in the management of TAD for consideration of operative intervention.

Intervention thresholds for thoracic aortic aneurysms

RECOMMENDATION

2. We recommend that surgical intervention be considered for thoracic aortic aneurysms according to the disease etiology and anatomic region affected as indicated in Table 2 (Strong Recommendation, Moderate-Quality Evidence).

Table 2. Recommended size thresholds for intervention for asymptomatic thoracic aortic aneurysms*

	Aortic root	Ascending	Arch	Descending
Degenerative	5.5 cm	5.5 cm	6.0 cm	6.5 cm
Bicuspid aortic valve	5.0-5.5 cm	5.0-5.5 cm	5.5 cm	6.5 cm
Marfan syndrome	5.0 cm†	5.0 cm	5.5-6.0 cm	5.5-6.0 cm
Familial aortopathy	4.5-5.0 cm	4.5-5.0 cm	5.5-6.0 cm	5.5-6.0 cm
Other genetic syndromes‡	4.0-5.0 cm	4.2-5.0 cm	5.5-6.0 cm	5.5-6.0 cm
Undergoing cardiac surgery	—	4.5 cm	—	—

*Size thresholds for intervention should take patient body size into consideration, either empirically or using proposed formulas for adjustment.
†For women anticipating pregnancy, the threshold is 4.1-4.5 cm.
‡Loeys-Dietz, Turner, Ehlers-Danlos.

Certain factors confer increased risk and include (in increasing order of significance): bicuspid aortic valve (BAV) aortopathy, Marfan syndrome, familial thoracic aortic disease, Ehlers Danlos (vascular type), Turner syndrome and in particular, Loeys-Dietz syndrome (LDS). The size threshold for intervention is lower for these conditions. Patient body size is an important variable; a lower threshold may be used in female patients and patients of shorter stature.

Degenerative aneurysms. Patients with degenerative aortic aneurysms do not have connective tissue disorders, familial aortopathy, or BAV aortopathy. They are typically older and have atherosclerotic risk factors, particularly hypertension and smoking. Increased aortic size has been linked to increased risk of dissection, rupture, and death, particularly when the size of the aneurysm exceeds 6.0 cm (7% annual risk of rupture or dissection and 12% annual risk of death).[5] Surgical intervention is recommended at a diameter of 5.5 cm for the ascending aorta. For the descending thoracic aorta, surgical intervention is recommended at a diameter of 6.5 cm.[6]

BAV aortopathy. Patients with BAVs have an increased risk of aortic dilation and molecular and histological changes suggesting an aortopathy independent of valve function.[7,8] The risk of aortic dissection in BAV patients is greater than in the general population but is less than that for patients with Marfan syndrome or other genetic aortopathies.[9] Surgical intervention in this population should be considered when the size of the ascending aorta is between 5.0 and 5.5 cm, accounting for patient size, particularly in the presence of other risk factors.

Marfan syndrome. Marfan syndrome individuals are susceptible to thoracic aortic aneurysms with a greater incidence of aortic dissection.[10,11] However, a low risk of aortic complications is noted in patients with an aortic size < 5.0 cm.[10] For the aortic root and ascending aorta, a size threshold of 5.0 cm is appropriate. For the descending thoracic aorta, a size threshold of 5.5-6.0 cm is recommended. Patients with a family history of premature aortic dissection warrant consideration of surgical intervention at smaller diameters.

Familial thoracic aortic aneurysm. These individuals have 1 or more relatives with thoracic aortic aneurysms with or without a previous history of aortic dissection. Aortic dilation progresses more rapidly in patients with familial aortopathy with a greater risk of aortic complications.[12,13] The threshold for surgical intervention may be guided by the aortic size at which other family members have had aortic complications, if known. If not known, then a size threshold of 4.5-5.0 for the ascending aorta and 5.5-6.0 for the descending thoracic aorta is reasonable.

Non-Marfan genetic aortopathy. A number of genetic disorders including Loeys-Dietz, Turner, and Ehlers Danlos (vascular type) are linked to thoracic aortic aneurysm and dissection. Because of the low prevalence of these syndromes, there is a paucity of data on the risk of aortic complications; it is significantly greater compared with degenerative aneurysms and Marfan syndrome. Patients with LDS have a high risk of aortic dissection at small diameters, leading to limited life expectancy.[14] The threshold for surgical intervention is therefore lower than that for Marfan syndrome. Patients with vascular Ehlers-Danlos syndrome (vEDS) can have a high risk of surgical complication because of poor-quality vascular tissue.

Other considerations

In addition to size thresholds, the following factors deserve careful consideration.

Presence of symptoms. A small subset of patients will present with compressive symptoms, malperfusion, or pain, all of which are associated with poor outcome,[15] and surgical intervention should be considered in all symptomatic thoracic aortic aneurysms, regardless of absolute size.

Pseudoaneurysms. False aneurysms of the thoracic aorta might occur secondary to blunt trauma, before aortic surgery, catheter-based manipulation, or in association with penetrating atherosclerotic ulcers. Rates of aortic rupture for pseudoaneurysms are not well characterized. Surgical intervention might be considered when the total diameter of the aorta (including the native aorta and the false aneurysm) meets the criteria in Table 2 or if the pseudoaneurysm is > 2 cm in maximum diameter.

Rate of growth. Typical growth rate of thoracic aortic aneurysms is 0.1 cm/y. Rapidly growing aneurysms (> 0.5 cm/y increase in diameter) are uncommon but are associated with increased aortic complications.[16] Surgical intervention should be considered in rapidly growing aneurysms regardless of absolute diameter.

Concomitant cardiac surgical procedures. Surgical intervention on the moderately dilated ascending aorta (> 4.5 cm) should be considered in patients undergoing open cardiac surgical procedures because it minimizes the long-term risk of dissection and rupture and avoids a future higher-risk surgery.[17-19] However, other factors including patient age, body size, comorbidities, additional risk of procedure, and life expectancy must be considered in the decision-making process. In some patients, aortic dilation less than the thresholds recommended for surgical intervention might lead to aortic valve insufficiency because of cusp malcoaptation and a

decreased threshold for aortic resection is reasonable to facilitate aortic valve repair.

Indexing for patient size. The normal thoracic aorta is smaller in female and shorter individuals. In these individuals, aortic size index (maximum aortic diameter/body surface area) > 2.75 cm/m^2 is a better predictor of aortic complications.[20] Some investigators have suggested that the ratio between the cross-sectional area of the aorta (at its maximum diameter) divided by the patient's height (m) is another useful method to adjust for differences in body size.[21] Indexed measurements are most useful for female patients and patients with short stature and certain genetic syndromes (eg, Turner syndrome).

Emerging interventions for TAD

Thoracic endovascular aneurysm repair. In contrast to open surgical repair, thoracic endovascular aneurysm repair (TEVAR) involves exclusion of the aneurysm sac with a covered stent. Compared with open surgical repair, TEVAR is associated with a decreased rate of procedural mortality and morbidity,[22,23] but a greater need for reinterventions, and concerns remain regarding long-term outcome and late aneurysm-related mortality.[24]

Although TEVAR is used primarily for the descending thoracic aorta, alternate approaches to aortic arch disease in high-risk candidates include a combination of open and endovascular techniques, depending on anatomic suitability and are described in Supplemental Table S1. Open surgical treatment is the standard of care for the ascending aorta.[25,26] Type B dissections without complications are treated medically,[27] with surgery reserved for complications including malperfusion syndromes (visceral, renal, or limb perfusion), rupture, and rapid expansion. In the IRAD, TEVAR therapy for complicated, acute type B aortic dissections was associated with decreased rate of mortality and complications than open surgical intervention. Results from the STABLE trial suggest this therapy is associated with increased true lumen size, and favourable clinical and anatomic results.[28] TEVAR might therefore offer better outcomes compared with open surgical approaches in complicated cases. For noncomplicated type B dissections, the **In**vestigation of **Ste**nt Grafts in Patients With Type B **A**ortic **D**issection (INSTEAD) trial did not demonstrate any advantage for TEVAR in the short-term.[29,30] However, long-term follow-up demonstrated that TEVAR, in addition to optimal medical treatment, is associated with improved 5-year aorta-specific survival and delayed disease progression.[31]

TEVAR is associated with a number of complications including paralysis and paraperesis. Drainage of cerebrospinal fluid has been shown to improve spinal cord perfusion and function.[32,33] Intraoperative monitoring of motor and sensory evoked potentials to monitor spinal cord function, and improved preoperative imaging to identify critical intercostal arteries to reimplant, are some techniques used to minimize post operative spinal cord ischemia and post operative dysfunction.[34] Stroke, renal failure, and retrograde type A dissection are other potential complications.

Aortic valve preservation and repair. Patients with aortic root aneurysms, with or without associated aortic valve disease have traditionally been treated with composite aortic valve and root replacement with reimplantation of the coronary arteries (Bentall procedure). Although this procedure is effective at treating the aortopathy, patients are left with the long-term risks associated with prosthetic heart valves, which include thromboembolism, structural and nonstructural valve dysfunction, endocarditis, and anticoagulant-related hemorrhage for those with mechanical prostheses.[35] Because many of these patients have morphologically normal aortic valve leaflets, there has been increasing interest in valve-sparing aortic root surgery. Long-term observational cohort studies have demonstrated excellent outcome at > 15 years of follow-up.[36] The concepts, innovations,[37] and techniques[38] in valve-preserving surgery have also been applied in patients with aortic insufficiency and BAVs and associated aortopathy with promising results,[39,40] including a low risk of valve-related complications.[41,42] These benefits are most significant for young patients who are likely to accrue valve-related events over time. The likelihood of valve repair might be a consideration in determining the threshold for aortic replacement in these patients.

RECOMMENDATION

3. We recommend that patients with complex TAD who stand to benefit from these emerging techniques and technologies be referred to teams experienced in these approaches (Conditional Recommendation, Low-Quality Evidence).

The role of imaging in diagnosis and surveillance

Imaging is fundamental for diagnosis and surveillance of TAD. The test chosen should be determined according to the presentation, location, and patient age, with renal dysfunction, local expertise, and access to imaging modalities as additional considerations. Height and weight should be recorded for calculation of body surface area. Strengths and weaknesses of the various imaging modalities are summarized in Table 3. Details on technical aspects of imaging are provided in Supplemental Appendix S1. An overview of imaging modalities is provided in the following paragraphs.

Multidetector computerized tomography. Electrocardiographic-gated scans are useful for imaging the ascending aorta, enabling assessment of the aortic valve and at least the proximal coronary arteries (see Supplemental Appendix S1). After aortic intervention, computerized tomography (CT) is also preferred to detect leaks after the procedure or pseudoaneurysms because echocardiography (ECHO) is often limited by the presence of metallic devices and clips and transesophageal ECHO is semi-invasive and thus not optimal for surveillance.

Currently, external aortic diameters are reported for CT- or magnetic resonance (MR)-derived measurements. ECHO-derived measurements are typically reported as luminal size; this difference is important in the descending thoracic aorta where mural thrombus is more prevalent. Pronounced arterial wall calcifications can lead to underestimation of the lumen size.

Table 3. Advantages and disadvantages of various modalities for thoracic aortic imaging

Modality	Advantages	Disadvantages
Transthoracic echocardiography	• Portable • Readily available • Established role in evaluation of structural cardiac disease	• Limited acoustical access, particularly in obese patients and in patients after surgery • Best for visualization of proximal portion of ascending aorta • Operator-dependent
Transesophageal echocardiography	• Portable • Readily available • Excellent visualization	• Limited visualization of distal ascending aorta • Reduced diagnostic accuracy for intramural hematoma • Operator-dependent
Computed tomography	• Availability • Imaging of aorta, neck vessels, and thorax • Short image acquisition time • Able to define coronary anatomy	• Radiation exposure • Renal insufficiency might require restriction in contrast administration*
Magnetic resonance imaging	• Tissue characterization • No radiation	• Long acquisition time • Cannot be performed in unstable patients or in patients with renal dysfunction,* pacemakers/AICD

AICD, automatic implantable cardioverter defibrillator.
*See Supplemental Appendix S1 for options in patients with mild to moderate renal dysfunction.

Although the potential stochastic risk of radiation exposure decreases significantly when patients reach the fifth decade of life, CT must be used with caution in neonates, children, and young adults in whom the risk of radiation-induced malignancy is the greatest.[43-47]

MR imaging. The avoidance of radiation or iodinated contrast exposure with MR imaging (MRI) is a particularly valuable feature in younger patients and for serial follow-up imaging. Disadvantages include longer scan times, which is a particular issue in the setting of acute chest pain and claustrophobic patients, and issues related to the use of gadolinium contrast agents in renal failure because of concerns regarding nephrogenic systemic fibrosis and implanted cardiac devices. MRI might be particularly helpful in distinguishing mural thrombus from intramural blood in the setting of acute aortic syndromes with early potential being shown by new dual-energy CT techniques.[48,49]

Transthoracic and transesophageal echocardiography

ECHO. Imaging of the aortic root and proximal ascending aorta is part of the standard transthoracic echocardiography (TTE) procedure with images obtained at end diastole.[50,51] Three-dimensional ECHO, particularly combined with transesophageal echocardiography (TEE), has the potential of enhancing diagnostic utility,[52] but its aortic application has been focused on the proximal ascending aorta. TEE is superior to TTE for visualization of the thoracic aorta and has an important role in settings where CT or MR imaging might not be available or feasible, such as the intensive care unit or the operating room. Criteria for TTE/TEE diagnosis of acute aortic dissection are: (1) intimal or dissection flap seen on

Table 4. Screening for patients and family members with genetic aortopathy

Aortopathy	Gene(s) involved	Transmission mode	Part of aorta affected	Screening of family members	Imaging modality
Marfan syndrome	*FBN1*	Autosomal dominant with different phenotypic expression	Asc: ++ Arch: + Desc: +	Clinical: Ghent criteria Genetic: in some cases Imaging: yes	ECHO and CT vs MRI
Loeys-Dietz syndrome	*TGFBR1* *TGFBR2* *SMAD3* *TGFB2*	Autosomal dominant with variable expression	Asc: ++ Arch: + Desc: + *	Clinical: yes Genetic: yes Imaging: yes	ECHO and CT vs MRI
Aneurysm-osteoarthritis syndrome	*SMAD3*	Autosomal dominant	Asc: ++ Desc: + *	Clinical: yes Genetic: yes Imaging: yes	ECHO and CT vs MRI
Ehlers-Danlos type IV	*COL3A1*	Autosomal dominant	Asc: + Desc: + *	Clinical: yes Genetic: yes Imaging: yes	ECHO and CT vs MRI
Bicuspid aortic valve	Likely multiple genes	Complex trait; familial clustering	Asc: ++ Arch: + Desc: −	Clinical: yes Genetic: no Imaging: yes	ECHO and CT vs MRI
Familial thoracic aortic aneurysm	*TGFB2* *TGFBR1* *TGFBR2* *MYH11* *SMAD3* *ACTA2*	Autosomal dominant with reduced penetrance and variable expression	Asc: ++ Arch: + Desc: +	Clinical: yes Genetic: yes Imaging: yes	ECHO and CT vs MRI

++, most common site involvement; +, next common site of involvement; −, not involved; Asc, ascending aorta; CT, computed tomography; Desc, descending thoracic aorta; ECHO, echocardiogram; MRI, magnetic resonance imaging.
*See text for imaging of other vessels.

multiple views; (2) independent motion of the intimal flap; and (3) differential colour flow in true and false lumens.[53] ECHO is operator-dependent, therefore serial examinations should be performed with standardized protocols and by experienced individuals in laboratories with quality assurance processes in place.[51]

Cardiac catheterization and angiography. The main use of angiography is in the evaluation of a suspected aortic syndrome while the patient is undergoing a cardiac catheterization procedure, but it has otherwise been replaced by CT and MR imaging and TEE.

RECOMMENDATION

For acute aortic syndromes:

4. We recommend CT as the preferred initial imaging test (Strong Recommendation, Moderate-Quality Evidence).
5. We suggest TEE as an appropriate alternative in the following situations (Conditional Recommendation, Moderate-Quality Evidence): i. An indeterminate CT examination; ii. When transport to CT is not feasible because of hemodynamic instability; and iii. Intraoperative TEE when a dissection flap is seen on the initial TTE.
6. We suggest MRI for characterizing acute intramural hematomas when CT is equivocal (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. These recommendations are based on cohort studies, overviews, and expert opinion, because there are no contemporary studies that compared diagnostic accuracy of the imaging modalities. A systematic review concluded that TEE, helical CT, and MRI, yield clinically equally reliable diagnostic value for confirming or ruling out aortic dissection.[54] There are no standards for the appropriate phase of the cardiac cycle to evaluate aortic size using CT or MRI, therefore, the phase (diastolic vs systolic) used should be reported to allow for consistent serial measurements to assess interval changes.

RECOMMENDATION

For ongoing aortic surveillance in patients who are candidates for intervention, we suggest:

7. For preoperative planning, the entire thoracic aorta should be imaged using CT or MRI (Conditional Recommendation, Moderate-Quality Evidence).
8. For surveillance after repair in patients without residual aortopathy, the entire aorta should be imaged using CT or MR at least once every 3-5 years after repair (Conditional Recommendation, Low-Quality Evidence).
9. MRI should be considered the first-line test of choice if serial repeat examinations are being considered in an adolescent or in the adult population younger than the age of 50 years (Conditional Recommendation, Low-Quality Evidence).
10. If dilation is established to only involve the root or proximal ascending aorta then TTE serves as a reasonable alternative, with TEE reserved for those with nondiagnostic TTE images (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. To reduce variability, serial aortic imaging should be performed using the same imaging protocols and modality, in the same laboratory. Follow-up studies should be scheduled at 6-12 months after diagnosis, and then every 6 or 12 months thereafter depending on aortic size and the rate of change. In patients with stable dimensions between serial examinations, imaging intervals may be increased.

Medical Therapy and Lifestyle Considerations for Patients With TAD

Antihypertensive therapy

The rationale for antihypertensive therapy is based on mechanistic and animal studies,[55,56] and observational reports linking aortic dissection with hypertension.[57,58] Randomized controlled trials of antihypertensive therapies have not included patients with TAD per se or reported consistently on aortic end points.[59,60] Although summaries of antihypertensive trials support treatment of hypertension when present, they do not offer specific guidance on the management of patients with thoracic aortic aneurysm, dissection, or aortopathy, either for choice of drug therapy or for blood pressure targets.[61-69]

For Marfan syndrome, the available studies report surrogate outcomes, and are limited by small sample size, lack of blinding, and choice of comparator. Small randomized trials of β-blockers or losartan in addition to β-blockers showed lower rates of aortic root dilation, with no difference in other clinical outcomes (Supplemental Table S2). No published trials compare β-blocker monotherapy with angiotensin-converting enzyme (ACE)-inhibitor monotherapy, and in a recent trial of losartan only a subset were taking losartan alone.[70] In other subsets of TAD including BAV, Loeys-Dietz, Ehlers Danlos, and other genetic aortopathies, there are no randomized trials or observational studies.

In patients with chronic aortic dissection, observational reports suggest lower risk for operative repair with β-blocker therapy.[71] In a series of 722 and 579 patients with type A and type B aortic dissections, respectively, β-blockers were associated with improved survival in both groups, and ACE inhibitors were not associated with improved survival.[72] Use of calcium channel blockers was associated with improved survival in type B aortic dissections,[72] and decreased aortic expansion in a smaller cohort of 191 patients with type B aortic dissections.[73] A cohort of 78 consecutive type B aortic dissection cases identified an association between ACE inhibitor use and better survival.[74] Poor blood pressure control ($\geq$ 140/90 mm Hg) has been linked with late mortality.[74,75]

RECOMMENDATION

11. We recommend antihypertensive drug therapy for hypertensive patients with TAD to achieve a goal blood pressure of < 140/90 mm Hg, or < 130/80 mm Hg in those with diabetes, to reduce the risk of myocardial infarction, stroke, heart failure, and cardiovascular death[76] (Strong Recommendation, Moderate-Quality Evidence).
12. We recommend β-blocker or angiotensin receptor blocker therapy for patients with Marfan syndrome to reduce the rate of aortic dilation. If tolerated, we recommend consideration of additional therapy (ACE inhibitor, angiotensin receptor blocker, or β-blocker) for patients with Marfan syndrome to reduce the rate of aortic dilation (Strong Recommendation, Low-Quality Evidence).

Values and preferences. Although there are no randomized trials that support lower blood pressure targets (eg, <120/80 mm Hg), aggressive therapy might be reasonable based on the physiologic rationale and patient-specific factors including type of aortopathy, patient or family history of acute aortic syndrome, or sudden death, aortic aneurysm growth despite medical therapy, or patient preference. To date, there are no randomized trials supporting that monotherapy with a specific agent is superior to others for any form of TAD.

Preventing hypertension and atherosclerosis

Diet and smoking cessation. Standard dietary advice for prevention of hypertension and atherosclerosis and smoking cessation are appropriate for most patients with TAD (Supplemental Appendix S1).

Lipid-lowering therapy. Some observational studies suggest benefit, and many patients with TAD have multiple atherosclerotic risk factors (Supplemental Appendix S1). Lipid-lowering, generally with statin drugs, should be offered according to general guidelines.[77]

Exercise. Aortic dissection has been linked with severe physical exertion due to weight-lifting.[78] The mean aortic diameter of these cases was 4.6 cm, therefore strenuous strength training might be dangerous for patients with TAD. The proposed mechanism is transiently increased blood pressure associated with isometric exercise or Valsalva manoueuvre.[79] Exercise-based cardiac rehabilitation for patients with coronary artery disease has been shown to reduce mortality in randomized controlled trials,[80] and exercise cardiac rehabilitation was found to be safe in a small series of survivors of type 1 aortic dissection.[81]

RECOMMENDATION

13. We recommend that patients with TAD be evaluated for risk for atherosclerotic vascular disease, and that recommendations for ameliorating this risk, whether using endurance exercise, dietary changes, smoking cessation, or medical therapy, be made in accordance with current general guidelines (Strong Recommendation, Low-Quality Evidence).

Values and preferences. Patients and clinicians commonly require guidance with respect to these issues, and basing clinical decisions on the minimal observational data available, or extrapolating results from other populations, is a sensible compromise.

14. We suggest patients with TAD avoid strenuous resistance and isometric exercise (Strong Recommendation, Very Low-Quality Evidence).

Values and preferences. Although the data are minimal, the risks associated with strenuous isometric exercise[78] appear great enough to strongly recommend avoiding this exposure.

Driving. Neither the Canadian Cardiovascular Society Conference nor the Canadian Medical Association (CMA) have made recommendations about fitness for driving in the context of TAD.[82] However, the CMA has recommended that patients with abdominal aortic aneurysm be precluded from driving when the rupture risk exceeds 10% per year. Based the best observational data available, these thresholds of risk occur for thoracic aortic aneurysms > 6.0 cm in the ascending aorta or arch, and > 6.5 cm in the descending aorta. A lower threshold for rupture risk is reasonable for commercial driving.[82]

RECOMMENDATION

15. We suggest that patients with TAD be precluded from private driving if the ascending aorta diameter is > 6.0 cm or the descending aorta diameter is > 6.5 cm, and restricted from commercial driving if the ascending thoracic aorta diameter is > 5.5 cm or the descending thoracic aorta is > 6.0 cm.[83] (Conditional Recommendation, Very Low-Quality Evidence).

Values and preferences. These thresholds are based on the methodology of the CMA and Canadian Cardiovascular Society Consensus Conference on the assessment of the cardiac patient for fitness to drive and fly,[82] and the best available observational evidence. Risk thresholds can be reached at different aortic diameters for different aortopathies. Further studies are required to provide reliable estimates of rupture risk.

16. We suggest that patients return to private driving 6 weeks after and commercial driving 3 months after open aortic repair (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. This practice is in accordance with current recommendations for patients after cardiac valve surgery. Patients undergoing endovascular aortic procedures may resume driving sooner based on assessment by their treating physician.

Pregnancy. Information related to pregnancy in patients with TAD is provided in Supplemental Table S3.

Screening for Family Members of Patients With Genetic Aortopathy

Key features of common genetic aortopathies are described in Table 4.

Marfan syndrome

Marfan syndrome is an autosomal dominant disorder with high penetrance and varying phenotypic expression, which is associated with progressive aortopathy including dilation of the ascending aorta (sinuses of Valsalva) and can lead to dissection (usually type A) or rupture if not repaired surgically.[10] Clinical screening of patients suspected to have Marfan syndrome should be done using the revised Ghent criteria.[84] Routine CT or MRI for definite Marfan syndrome should be initiated in early adulthood or at time of surgery, whichever comes first.

Screening of the first-degree family members is indicated because the transmission rate is 50%. Genetic screening might help to clarify: (1) the nature of the disease; (2) the risk to the patient when the clinical diagnosis is uncertain; (3) to ascertain sporadic cases; or (4) prenatal diagnosis.[85] Imaging in family members suspected to have the disease should include at least a transthoracic echocardiogram to assess the ascending aorta and a baseline CT or MRI scan to assess the entire aorta. When dilation of the ascending aorta is found, a repeat transthoracic ECHO at 6 months should be performed to ascertain the rate of progression. If stable, an annual ECHO should be done thereafter.[86] Any family member who has Marfan syndrome (clinically or genetically determined) with a normal-size ascending aorta, should undergo annual ECHO.[86]

RECOMMENDATION

For Marfan syndrome:

17. We recommend clinical and genetic screening for suspected Marfan syndrome to clarify the nature of the disease and provide a basis for individual counselling (Strong Recommendation, High-Quality Evidence).
18. We recommend echocardiographic screening be performed at diagnosis to measure aortic root and ascending aorta diameters, and repeated 6 months thereafter to determine rate of progression. If aortic diameters remain stable, annual imaging is recommended. If the aortic diameter exceeds 45 mm or if significant deviation from baseline studies occurs, more frequent imaging should be considered (Strong Recommendation, High-Quality Evidence).
19. We recommend that women with Marfan syndrome who want to become pregnant be considered for aortic root and ascending aorta replacement if the diameter reaches 41-45 mm. These women should undergo surgery at centres with expertise in aortic valve-sparing surgery (see *Recommendation 3*) (Conditional Recommendation, Low-Quality Evidence).

LDS

LDS is associated with arterial tortuosity and aggressive, progressive dilation of the ascending aorta; although the aorta at any level can be affected. Cerebral aneurysms are common in LDS. Accompanying craniofacial involvement can include bifid uvula, cleft palate, craniosynostosis, and hypertelorism. It is autosomal dominant with a 50% transmission rate. First-degree family members should undergo clinical and genetic screening. In affected family members, an initial transthoracic echocardiogram is recommended with a repeat at 6 months if aortic dilation is present or at 1 year if the aorta is not dilated.[86] Prophylactic aortic root surgery is recommended in these patients when the ascending aorta reaches 42 mm.[87] An MRI scan from the base of the neck to the pelvis is also recommended every 18-24 months to assess the degree of arterial tortuosity and presence of arterial aneurysms, or more frequently if specific pathology is followed.[88]

BAV

BAV is the most common cardiac malformation with a prevalence of 1%-2% in the general population. BAV is a heritable disorder with a significantly increased recurrence risk in first-degree relatives (5%-30%).[89-93] Although autosomal dominant transmission with reduced penetrance and variable expression has been reported, it is likely a complex genetic trait influenced by several loci. Fifty percent of patients with BAV have an associated aortopathy that can involve the proximal aorta, usually the mid ascending aorta. Some affected family members might not have BAV, but might have aortopathy.[89,94,95] Because of its high risk of recurrence, clinical screening of first-degree relatives is suggested with a transthoracic ECHO to ascertain the presence of BAV and/or ascending aorta dilation. CT scan or MRI might be indicated to completely visualize the ascending aorta and arch.[96] Echocardiographic screening of first-degree relatives in the pediatric age range might be useful.

Familial thoracic aortic aneurysm

Familial thoracic aortic aneurysm (FTAA) is a genetic disease that occurs in "nonsyndromic" patients with aortopathy and a family history of aortic aneurysm. Most FTAA patients demonstrate an autosomal dominant inheritance with decreased penetrance and variable expression. A positive family history for thoracic aortic aneurysm should prompt a search for signs of syndromic disease. To date, a number of genetic mutations have been identified which explain 20% of the FTAA. Imaging of the aorta of first-degree relatives to identify asymptomatic aneurysm is

critical. Transthoracic echocardiogram is recommended, with additional CT scan or MRI if the entire aorta needs imaging.

Aneurysm-osteoarthritis syndrome

Aneurysm-osteoarthritis syndrome is an autosomal dominant trait with aneurysms of the arterial tree, and skeletal and cutaneous anomalies.[97,98] Phenotypic overlap with LDS encompasses hypertelorism and abnormal palate/uvula, and velvety skin. Early-onset osteoarthritis and intervertebral disc degeneration are present. Arterial disease mostly presents as aneurysm of the aortic root, but can also affect the thoracic aorta and the remainder of the arterial tree with an aggressive course.[99] Imaging of the entire vascular tree and genetic testing should be performed in such patients. First-degree relatives of patients with aneurysm-osteoarthritis syndrome should be screened for arterial disease and genetic testing be offered when a causal mutation is identified in the index case.

vEDS

vEDS is an autosomal dominant disorder caused by a mutation in the *COL3A1* gene.[100] The ensuing deficiency in collagen III formation results in connective tissue fragility including aneurysms, arteriovenous fistulae, spontaneous vascular dissections and ruptures, and bowel and uterus ruptures. Patients present with easy bruising, translucent skin, and spontaneous arterial bleeding. Typically, aneurysms involve any medium-to-large-sized muscular artery including branch vessels in the head, neck, thorax, abdomen, and extremities. Dilation of the ascending aorta might occur. Surgical complications are common, with a high rate of procedural mortality.[101] Surgery should be avoided unless a lesion is considered to be imminently life-threatening. Clinical and genetic screening is recommended for first-degree relatives. Widespread imaging modalities should be performed to document anatomy of the entire vascular tree.[100]

Turner syndrome

Turner syndrome is a chromosomal anomaly in which 1 sex chromosome is lacking in a female individual, most commonly in the form of monosomy X (45, X). Salient features are short stature, ovarian failure, and cardiovascular disease. Between 10% and 25% of women with Turner syndrome have BAVs, and approximately 8% have coarctation. The risk of aortic dissection is increased in women with Turner syndrome,[102] and occurs in young individuals at smaller aortic diameters than in the general population or those with other forms of genetically triggered aortopathy. The absence of aortic valve or other cardiac malformations reduces the risk of aortic dissection. Data from the international Turner syndrome aortic dissection registry suggest that individuals with Turner syndrome who are > 18 years of age with an ascending aortic size index > 2.5 cm/m^2 should be considered for aortic surgery to prevent aortic dissection.[103]

RECOMMENDATION

For non-Marfan, genetic forms of aortic disease:

20. We recommend aortic imaging for first-degree relatives of patients with genetic forms of TAD to identify asymptomatic carriers (Strong Recommendation, Moderate-Quality Evidence).
21. We recommend cardiac imaging in adult first-degree relatives of patients with BAV to identify asymptomatic carriers (Strong Recommendation, Moderate-Quality Evidence).
22. We recommend screening for TAD-associated genes in non-BAV aortopathy index cases to clarify the origin of disease and improve clinical and genetic counselling (Strong Recommendation, Moderate-Quality Evidence).
23. We recommend that genetic counselling and testing be offered to first-degree relatives of patients in whom a causal mutation of a TAD-associated gene is identified. We recommend that aortic imaging be offered only to mutation carriers (Strong Recommendation, Low-Quality Evidence).
24. We recommend complete aortic imaging at initial diagnosis and at 6 months for patients with LDS or a confirmed genetic aortopathy (eg, *TGFBR1/2*, *TGFB*, *SMAD3*, *ACTA2*, or *MYH11*) to establish if enlargement is occurring (Strong Recommendation, Moderate-Quality Evidence).
25. We recommend that patients with LDS have whole-body MRI every 18-24 months to assess progression of vascular disease, or more frequently if specific pathology is followed (Strong Recommendation, Moderate-Quality Evidence).
26. We recommend that patients with Turner syndrome should have a complete assessment of cardiac and aortic structures. If normal, repeat imaging should be performed every 5 years. If abnormalities are detected, annual imaging should be performed. In children, annual imaging may be recommended (Strong Recommendation, Moderate-Quality Evidence).

Knowledge Gaps

Most of the epidemiology and natural history of TAD is based on: (1) surgical series from selected populations; (2) retrospective cohorts of acute aortic syndromes; (3) single-centre studies of patients with inherited or degenerative forms of TAD; and (4) extrapolation from non-TAD patients, leaving important knowledge gaps in this patient population.

Future research should be focused on these key knowledge gaps in the pathophysiology, natural history, and treatment of patients with TAD, including but not limited to:

- Contemporary natural history data on the risks of aortic complications.
- Predictors of aortic complications (other than size) in patients with moderate aortic dilation.
- Genetic, epigenetic, and imaging determinants of the development and progression of the various forms of TAD and predictors of acute aortic syndromes.

- Prevalence of TAD in susceptible populations and the role of age in development of disease.
- The efficacy of screening strategies and the psychological, social, and legal consequences of such screening.
- The efficacy of risk factor modification on preventing TAD or attenuating its progression.
- The outcomes and effect of emerging therapies in the management of TAD.

Multidisciplinary Care and Quality Indicators

Comprehensive management of TAD spans multiple disciplines including but not limited to cardiac surgery, vascular surgery, cardiology, genetics, imaging, and adult congenital heart disease. Therefore, care for these patients is best provided in such a multidisciplinary environment and clinics are currently emerging across major cardiac centres in Canada. These might also be an important source of critical natural history data on thoracic aortic pathologies, and facilitate prospective clinical trials and mechanistic studies to help advance care for these patients.

Assessment of quality of care indicators for TAD may include: (1) timely referral for surgery (as per proposed size thresholds); (2) appropriate imaging surveillance; and (3) risk factor management (antihypertensive agents, smoking cessation, etc).

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.02.018.