

## THE PRESENT AND FUTURE

### STATE-OF-THE-ART REVIEW

# Thoracic Aortic Aneurysm and Dissection



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#### ABSTRACT

Aortic dissection is the most devastating complication of thoracic aortic disease. In the more than 250 years since thoracic aortic dissection was first described, much has been learned about diseases of the thoracic aorta. In this review, we describe normal thoracic aortic size; risk factors for dissection, including genetic and inflammatory conditions; the underpinnings of genetic diseases associated with aneurysm and dissection, including Marfan syndrome and the role of transforming growth factor beta signaling; data on the role for medical therapies in aneurysmal disease, including beta-blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors; prophylactic surgery for aneurysm; surgical techniques for the aortic root; and surgical and endovascular management of aneurysm and dissection for different aortic segments. (J Am Coll Cardiol 2014;64:1725-39) © 2014 by the American College of Cardiology Foundation.

Aortic dissection is the most devastating complication of thoracic aortic disease. In population-based studies, the annual incidence ranged from 6 cases per 100,000 in a British study (1), to 9.1 per 100,000 in women or 16.3 per 100,000 in men in a Swedish study that included national healthcare registry diagnoses and autopsies for all out-of-hospital deaths (2). The first reported case was King George II of Great Britain, who died in 1760 of pericardial tamponade due to acute dissection of the ascending aorta, although the term “aortic dissection” was not coined for another 40 years (3). Since then, much has been learned about risk factors for dissection, including aneurysmal disease and genetic disorders, like Marfan syndrome, that increase risk for both aneurysm and dissection. An animal Marfan syndrome model and later studies of patients with Marfan syndrome provided data

for medical therapies to limit aneurysm growth. Surgical therapies for aneurysm and dissection were initially developed in the 1950s and have steadily improved since then. More recently, endovascular techniques and devices were developed to treat aneurysms and dissections of the descending thoracic aorta.

#### AORTIC SIZE, ANEURYSM, AND DISSECTION

**AORTIC SIZE.** Normal aortic diameter varies by age, sex, and modality (4,5), increasing with age and body surface area (Figure 1). At a given age, men typically have larger aortas than women. Echocardiography, computed tomography (CT) with contrast, and cardiac magnetic resonance (CMR) with gadolinium measure the internal diameter of the aorta, whereas noncontrast CT and CMR generally measure

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**ABBREVIATIONS  
AND ACRONYMS**

- ACC** = American College of Cardiology
- AHA** = American Heart Association
- EACTS** = European Association for Cardio-Thoracic Surgery
- EAPCI** = European Association of Percutaneous Cardiovascular Interventions
- ESC** = European Society of Cardiology
- TEVAR** = thoracic endovascular aneurysm repair
- MMP** = matrix metalloproteinase
- TGF** = transforming growth factor

the **external diameter**. Thus, measurements differ by the aortic wall **thickness**, usually **0.2 to 0.4 cm (4-8)**.

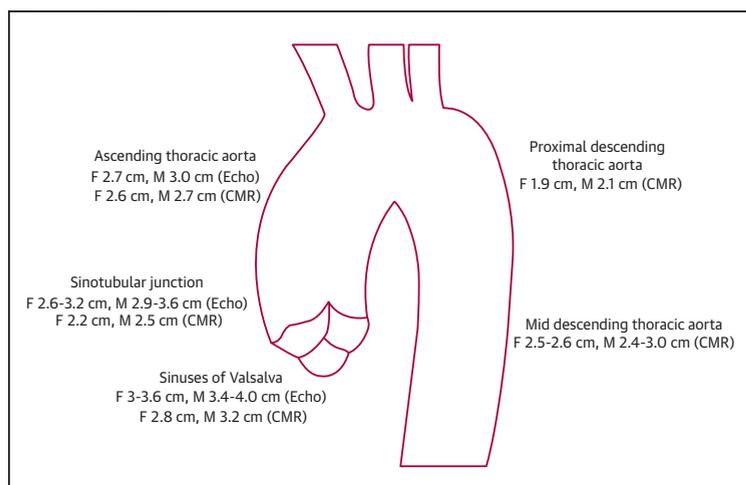
**AORTIC ANEURYSM.** An aneurysm is a permanent, localized arterial dilation to **more than 50% of the normal diameter**. The histopathology of some aortic aneurysms involves **medial degeneration** (formerly called cystic medial necrosis), characterized by **elastic fiber loss** from the **medial layer**, loss of vascular smooth muscle cells, and proteoglycan deposition. Altered microribonucleic acid expression is implicated in **increased activity of matrix metalloproteinase (MMP)-2 and -9 (9,10)**, which **lyse elastic fibers** and break down the extracellular matrix. The media within the aneurysm is also remodeled, with **smooth muscle cells oriented randomly, instead of in organized layers parallel to the aortic lumen**. Transforming growth factor (TGF)- $\beta$ , a regulatory cytokine expressed by arterial wall vascular smooth muscle cells, modulates MMP activity. In a mouse aortic aneurysm model, disrupting TGF- $\beta$  signaling prevented aneurysm formation (11). There are 2 TGF- $\beta$  signaling pathways, and both play roles in aneurysm formation (12,13). In the canonical pathway, TGF- $\beta$  binds at the cell surface to its type I or type II receptors. The complex phosphorylates Smad2 or Smad3, resulting in Smad4 recruitment and nuclear translocation, and Smad-dependent gene transcription. In the noncanonical pathway, TGF- $\beta$  phosphorylates extracellular signal-regulated kinase (ERK), Jun N-terminal kinase, and p38.

**Medial degeneration** may (at least initially) occur as an **adaptive response to wall stress** in the aortic dilation zone. Per **Laplace's law**, **wall tension (T) equals pressure (P) multiplied by radius (R)**, or **T = PR**. **Aneurysm formation increases wall tension**, causing further expansion of the aneurysmal segment. As the aorta enlarges, it loses distensibility. When the tensile limit is reached, dissection may occur, but aneurysms can occur without dissection, and dissections can occur without aneurysms.

**AORTIC DISSECTION.** Dissection involves **disruption of the medial layer**, with **intramural hemorrhage** leading to **propagation** (especially when the intimal layer is also disrupted) and **tracking of blood** within the **media**. Two commonly used classification schemes are used for thoracic aortic dissection: the **DeBakey scheme** categorizes dissections by the **site of origin**; and the **Stanford scheme** categorizes dissections by **involvement of the ascending aorta (Central Illustration)**. In the DeBakey classification, dissections **originating in the ascending aorta** are **subdivided** into those that propagate to the **aortic arch (type I)** and those **confined to the ascending aorta (type II)**, as opposed to those that **originate in the descending aorta (type III)**, regardless of whether they propagate distally or retrograde. The **Stanford scheme** is divided into **type A dissections**, which involve the **ascending aorta**, and **type B dissections**, which do **not**, regardless of point of origin (14).

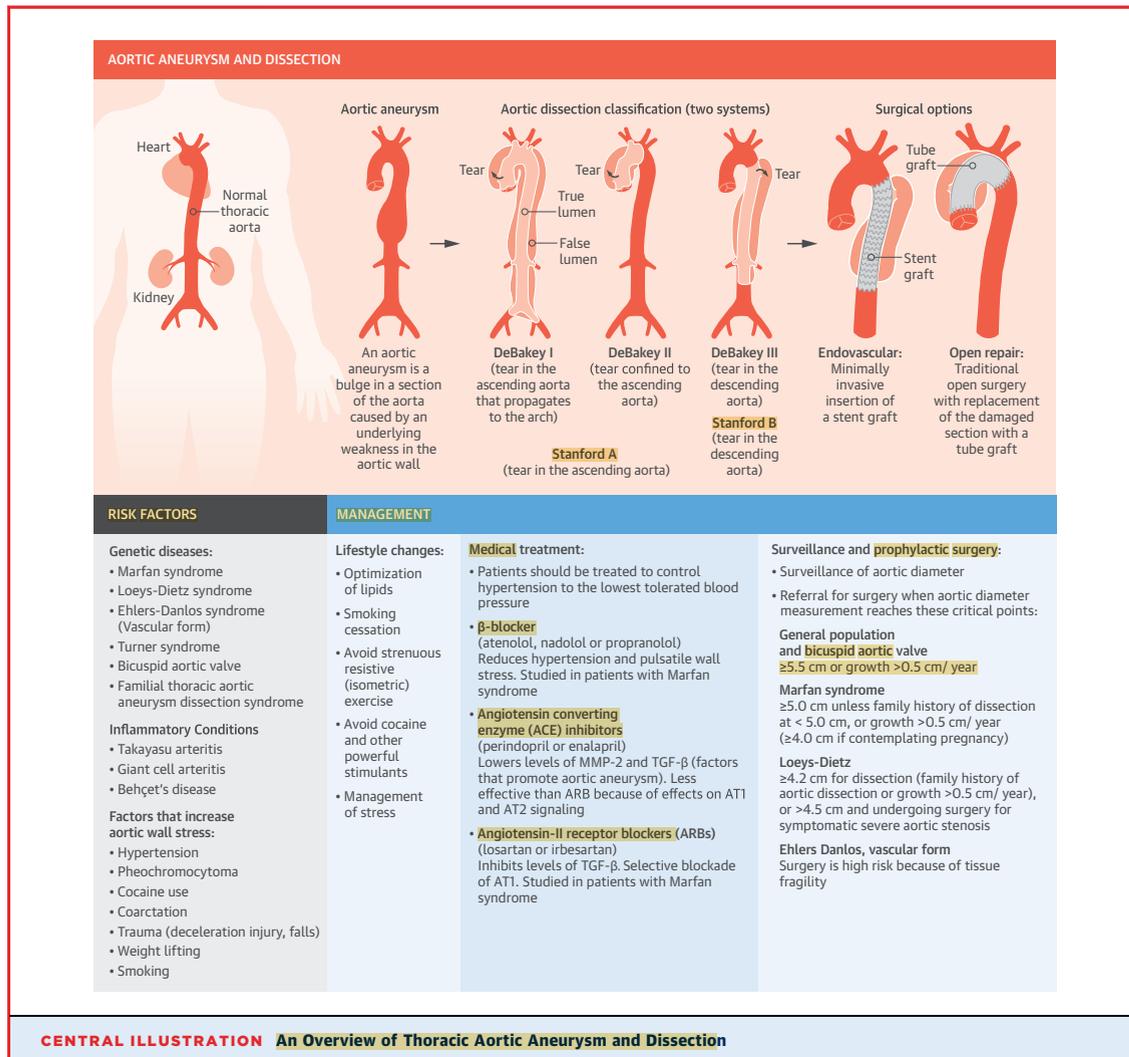
**RISK FACTORS FOR AORTIC DISSECTION**

**Clinical aortic dissection risk factors** fall into **2 broad categories**: conditions that **contribute to medial degeneration** and those that **increase aortic wall stress**. Conditions associated with **medial degeneration** include **Marfan syndrome**, **Loeys-Dietz syndrome**, the vascular form of **Ehlers-Danlos syndrome**, **inflammatory diseases of the aorta**, **Turner syndrome**, **bicuspid aortic valve**, and **familial thoracic aortic aneurysm and dissection syndrome**. The most common condition that increases **wall stress** is **hypertension**, present in more than **two-thirds** of patients with aortic dissection. Other conditions implicated in dissection are likely mediated by hypertension, including **pheochromocytoma**, **cocaine use (15)**, and **coarctation**. **Physical trauma** can increase **wall stress** and cause dissection, as in **weightlifting**, **deceleration injury** in motor vehicle accidents, or **falls (16,17)**. **Smoking** also increases dissection risk, likely by affecting TGF- $\beta$ . **Prior cardiac surgery** may increase the risk of dissection and complications. On the basis of International Registry of Acute Aortic Dissection (IRAD) data, **15%** of patients with dissection had **prior cardiac surgery (18)**,



**FIGURE 1 Normal Sizes for Aortic Segments by Sex and Imaging Modality (6-8)**

CMR = cardiac magnetic resonance; Echo = echocardiography; F = female; M = male.



and black patients with an acute dissection were more likely to present with a type B dissection, were younger, were more likely to have hypertension and prior cocaine use, and were less likely to have bicuspid aortic valves or prior aortic cardiac surgery than white patients (19).

**GENETIC DISORDERS ASSOCIATED WITH MEDIAL DEGENERATION. Marfan syndrome.** Marfan syndrome results from mutations in the FBN-1 gene encoding fibrillin-1, a large glycoprotein deposited in extracellular matrix microfibrils, including at the periphery of elastic fibers in the medial layer of the ascending aorta. Fibrillin-1 regulates the cytokine transforming growth factor-β type II receptor (TGFβR2) (20). Normal fibrillin-1 inhibits TGF-β; TGF-β levels are elevated in Marfan patients, leading to increased MMP activity and extracellular matrix breakdown (21). In patients with a family history of Marfan syndrome, the diagnosis can be made when

either of 2 cardinal features is present: ectopia lentis or aortic root aneurysm. Without a family history, both cardinal features are required. Without these features, diagnosis is based on the revised 2010 Ghent nosology, which assigns points for common systemic correlates, together with genetic testing for fibrillin gene mutations. Aortic aneurysm and dissection are the most life-threatening Marfan syndrome manifestations (22).

**Loeys-Dietz syndrome.** Loeys-Dietz syndrome is characterized by the triad of: arterial tortuosity and aneurysms; orbital hypertelorism (widely-spaced eyes); and bifid uvula or cleft palate. It results from mutations in TGF-β receptors 1 or 2, and diagnosis is confirmed by genotyping. In the largest study of Loeys-Dietz patients (n = 90), 98% had aortic root aneurysms. The mean age at death was 26 years (range 0.5 to 47 years) due to thoracic aortic dissection (67%), abdominal aortic dissection (22%), and intracerebral bleeding (7%) (23).

### The vascular form of Ehlers-Danlos syndrome.

The vascular form of Ehlers-Danlos syndrome is characterized by: easy bruising; thin skin with visible veins; characteristic facial features; and rupture of arteries, the uterus, or intestines. Diagnosis requires genetic testing to identify a defect in the COL3A1 gene, encoding type III collagen. The median survival is 48 years, with most deaths due to dissection or rupture of arteries in the thorax or abdomen, often without aneurysms. Because these patients have such fragile tissue, bleeding, wound dehiscence, poor wound healing, fistulae, and adhesions complicate surgical repair of aortic dissections (24).

**Bicuspid aortic valve.** *Bicuspid aortic valve* is the most common congenital abnormality affecting the aorta, occurring in 1% to 2% of the population. Bicuspid valves are classified by their anatomic appearance (25). Type 0 or true bicuspid valves have no raphe and 2 equally-sized leaflets. More commonly, type I bicuspid valves have a single raphe, usually between the right and left coronary cusps. Less commonly, the right and noncoronary cusps are fused. The raphe's position may create reproducible flow patterns that lead to aortic aneurysm development (26). Patients with bicuspid valves are at increased risk for ascending aortic aneurysm, dissection, and valvular aortic stenosis and regurgitation (27,28).

**Turner syndrome.** *Turner syndrome* is characterized by the absence of one X chromosome in a phenotypic female (45X). Patients commonly have short stature and ovarian failure. Less commonly, patients have cardiac anomalies, including bicuspid aortic valve, aortic coarctation, and aortic dilation, and these patients are at increased risk of dissection. Over 90% of dissection cases in Turner syndrome had hypertension or structural disease (29,30).

**Familial thoracic aortic aneurysm and dissection syndrome.** Between 11% and 19% of patients referred for surgery with thoracic aortic aneurysm or dissection have first-degree relatives with either aneurysm or dissection, suggesting a familial syndrome without specific identifiable genetic defects. Mutations were identified in: TGF $\beta$ R2, similar to Loeys-Dietz syndrome; smooth muscle cell-specific myosin heavy chain 11, a protein involved in smooth muscle cell contraction, where the dissections are associated with patent ductus arteriosus; and ACTA2, encoding smooth muscle-specific  $\alpha$ -actin, also involved in vascular smooth muscle cell contraction (4).

**INFLAMMATORY CONDITIONS ASSOCIATED WITH AORTIC ANEURYSM AND DISSECTION.** Aortic medial disease-associated vasculitides include Takayasu arteritis, giant cell arteritis, and Behçet's disease.

Takayasu and giant cell arteritis are both T cell-mediated panarteritides affecting the vasa vasora in the adventitia and extending inward, with inflammation resulting in either destruction, leading to aneurysm formation, or fibrosis, leading to stenosis. Takayasu arteritis has Asian predominance and 10:1 sex predominance for women. Giant cell arteritis, or temporal arteritis, predominantly affects females of Northern European ancestry over age 50 years (31). Behçet's disease is characterized by oral mucosal ulcers and 2 of the following features: genital ulcers; uveitis; retinal vasculitis; or skin lesions. Behçet's disease affects the aorta infrequently, but can be associated with lymphocytic, histiocytic, eosinophilic, and giant cell infiltration around the vasa vasora, with media disruption leading to aneurysm formation or aortic root necrosis (4).

### MANAGEMENT OF AORTIC ANEURYSM AND DISSECTION

The first step in management of patients with aortic aneurysm is risk factor control to slow the expansion rate and reduce the risk of dissection or rupture. Patients should be treated to control hypertension to the lowest tolerated blood pressure, to optimize lipids, and for smoking cessation, as smokers have twice the aneurysm expansion rate of nonsmokers and higher dissection rates (32). Patients should be cautioned to avoid strenuous resistive (isometric) exercise, such as heavy weightlifting, cocaine, and other powerful stimulants, and to manage stress as best they can. Life stressors can lead to acute hypertension and abrupt wall pressure changes over time (dp/dt), dramatically affecting aneurysm expansion and increasing dissection risk. Patients with aortic aneurysms who become pregnant require close monitoring of aortic diameter and strict blood pressure control.

**MEDICAL TREATMENT WITH  $\beta$ -BLOCKERS.** In the 1960s, using Tygon tubing as a model for aortic dissection, Wheat et al. (33) showed that dissection was initiated and propagated by hypertension and pulsatile wall stress increasing dp/dt.  $\beta$ -blockers decrease both (34), and this was proposed as the mechanism by which propranolol decreased dissection in a turkey model of aortic aneurysms (35).  $\beta$ -blockers may also prevent dissections by preventing the acute hypertensive response to emotional or exertional events (16).

On the basis of ex vivo and animal data,  $\beta$ -adrenergic inhibition was studied in an open-label, randomized trial of 70 Marfan patients: 32 were treated with propranolol at a dose titrated to a heart rate

below 100 beats/min during exercise or an increase in systolic time interval of 30% (mean dose 212 mg); 38 patients in the control arm were untreated. Despite greater aortic diameter in the propranolol arm at baseline (34.6 cm vs. 30.2 cm), the mean slope of the aortic ratio was 0.023 cm/year in the treatment group, compared with 0.084 cm/year in the control group ( $p < 0.001$ ) (Figure 2) (36).

In a retrospective study of 155 children with Marfan syndrome, despite greater dilation of the aorta at the level of the sinuses of Valsalva (29.7 mm vs. 27.3 mm), those who had taken a  $\beta$ -blocker (predominantly atenolol, less frequently nadolol or propranolol) displayed a small but statistically significant decrease (0.16 mm/year;  $p < 0.05$ ) in the aortic expansion rate compared to untreated controls (37).

On the basis of these and other small studies,  $\beta$ -blocker use for thoracic aortic aneurysms became standard for Marfan patients and common in patients with other forms of thoracic aortic aneurysms. However, a meta-analysis of 802 Marfan patients from 5 nonrandomized trials and 1 randomized trial found no difference with  $\beta$ -blocker use in rates of aortic dissection or rupture, cardiovascular surgery, or death. Using a fixed effects model,  $\beta$ -blockers appeared to cause harm (38). There are also concerns that  $\beta$ -blockers might decrease aortic elasticity and regarding potential side effects during long-term therapy in young people (5).

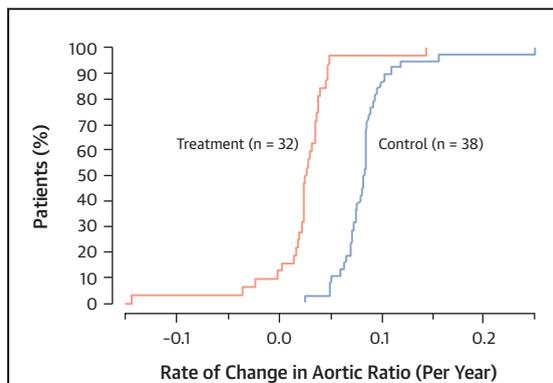
Seminal trials of  $\beta$ -blockers for thoracic aortic aneurysm were limited to Marfan patients. Although thoracic aneurysms arising in a variety of disease states may exhibit medial degeneration, Marfan patients have greater aneurysm expansion dissection, which occurs at smaller aortic diameters than in those

with other conditions, suggesting differences in pathophysiology, tissue integrity, or disease severity (39). Thoracic and abdominal aortic aneurysms are also distinct histologically, with abdominal aneurysms showing an inflammatory infiltrate, apoptosis of vascular smooth muscle cells, extracellular matrix fragmentation, and more frequent and extensive atherosclerosis (40). Two randomized trials of patients with abdominal aortic aneurysms showed no benefits for  $\beta$ -blockers, and many tolerated treatment poorly (41,42).

Although the role of  $\beta$ -blockers in preventing aortic dissection has not been elucidated, once dissection has developed, they have a clearer role in management. Among 1,301 patients with acute aortic dissection in the IRAD database (722 type A and 579 type B),  $\beta$ -blocker administration was associated with improved survival, driven mainly by improvement in those with type A dissections (43).

**ANGIOTENSIN-II RECEPTOR BLOCKERS.** Angiotensin-II receptor blockers (ARBs) inhibit TGF- $\beta$  through selective angiotensin-II receptor AT1 blockade, with no effect on AT2. Mice heterozygous for the Marfan syndrome fibrillin-1 C1039G mutation displayed greater aortic expansion than wild-type mice. When mice with the mutation were treated with propranolol, they displayed slower aortic root expansion than placebo-treated mice, but greater expansion than wild-type mice, whereas treatment with losartan resulted in the same aortic diameter, rate of aortic root expansion, aortic wall thickness, and elastic fiber architecture as wild-type mice, suggesting that losartan corrected the aortic morphology changes associated with this Marfan syndrome model (11). However, losartan's beneficial effect on aneurysm growth requires intact AT2 signaling, and may be due to indirect ERK inhibition (12).

Brooke et al. (44) reviewed the records of 18 pediatric Marfan patients who had received ARB therapy for over a year (17 losartan and 1 irbesartan) while also taking  $\beta$ -blockers. Prior to ARB therapy, the mean aortic root expansion rate was 3.54 mm/year; after ARB therapy, the expansion rate slowed to 0.46 mm/year ( $p < 0.001$ ). There was no significant blood pressure reduction, suggesting another mechanism for this effect (44). A prospective nonrandomized study with 20 pediatric patients found that losartan decreased aortic root size, and suggested that the benefit increased when therapy was started at an earlier age (45). The recently published COMPARE (COzaar in Marfan patients Reduces Aortic Enlargement) trial was a randomized, multicenter, open-label study that enrolled 233 patients (of 330 planned) and randomized 116 to losartan and 117 to no additional



**FIGURE 2** Rates of Change in Aortic Ratio for Marfan Patients Treated With Propranolol Versus Placebo

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treatment. Most were taking  $\beta$ -blockers. Over 3 years of follow-up, aortic root dilation was 0.77 mm in the losartan group, compared with 1.35 mm in the control group ( $p = 0.014$ ). The percentage of participants with a stable aortic root over the 3-year study period was 50% in the losartan group and 31% in the control group ( $p = 0.022$ ), with a number-needed-to-treat of 5.3 patients. The benefit on aortic root size did not appear related to the blood pressure reduction (46).

While intriguing, ARBs' benefits in Marfan patients are not conclusive. Several trials to evaluate losartan in patients with thoracic aneurysms are underway, including the Pediatric Heart Network study comparing the effects of atenolol and losartan on aortic root growth over 3 years, which completed its planned enrollment (47,48), and the Ghent Marfan Trial, which will evaluate losartan versus placebo in 174 Marfan patients taking  $\beta$ -blockers (49).

#### ANGIOTENSIN-CONVERTING ENZYME INHIBITORS.

In a randomized, double-blind, placebo-controlled trial of 17 Marfan patients who were taking  $\beta$ -blockers, 24 weeks of perindopril resulted in smaller aortic root diameters, and lower levels of MMP-2 and TGF- $\beta$  (50). Angiotensin-converting enzyme (ACE) inhibitors block angiotensin I conversion to angiotensin II upstream of the site of action of ARBs, which selectively block the AT1 receptor but not the AT2 receptor. In a mouse Marfan syndrome model, at equivalent doses, the ACE inhibitor, enalapril, was less effective at reducing aortic root growth than losartan ( $p < 0.0001$ ). This may be due to a protective effect of AT2 signaling on aneurysms in Marfan syndrome, specifically through AT2 receptor-mediated ERK 1/2 inhibition. However, ACE inhibitors block AT2 as well as AT1 signaling (12). The benefit of enalapril in the mouse model was comparable to that of propranolol in an earlier study by the same group (11).

**OTHER PHARMACOLOGICAL APPROACHES.** In a retrospective analysis of 649 patients with thoracic aortic aneurysm, 147 patients taking statins were compared to 502 who were not. After 3.6 years, fewer patients taking statins reached the composite endpoint of death, aortic rupture, dissection, or repair, but aneurysm diameter was not affected (51). In a retrospective analysis of 1,560 patients with aortic aneurysms, the 369 (24%) taking statins had lower rates of dissection rupture, death related to surgery, or requirement for surgery for those with aneurysms of the ascending aorta, aortic arch, and descending aorta, but not for aneurysms of the aortic root (52). In mice, doxycycline prevented aneurysm formation through MMP-2 and MMP-9 inhibition;

human studies suggested some benefit for abdominal aortic aneurysms, but the results are insufficient to support clinical recommendations for this line of therapy (39,53,54).

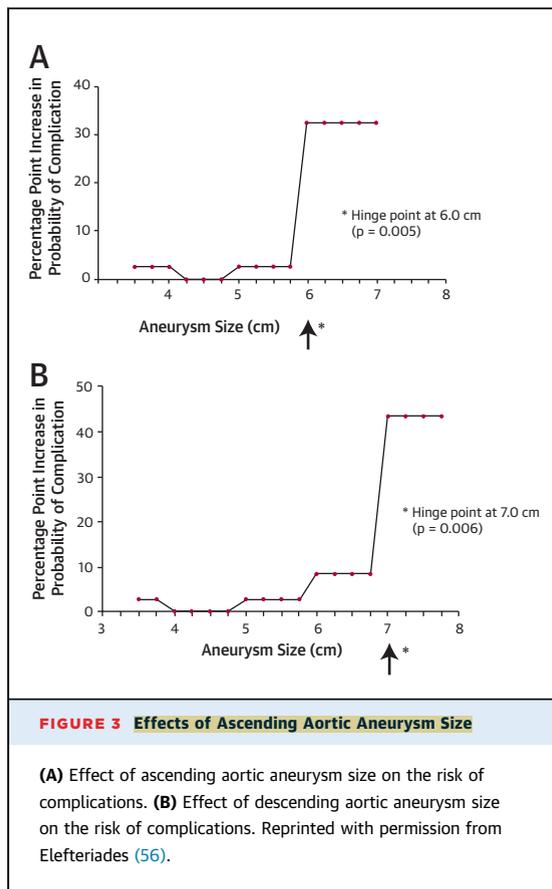
#### SURVEILLANCE AND PROPHYLACTIC SURGERY

Management of patients with aortic aneurysms includes surveillance of aortic diameter and, when it reaches a critical point, referral for surgery. Regardless of aortic dimensions, symptomatic patients should be referred for surgery. In asymptomatic patients, the size of aneurysm is the main determinant of the need for intervention.

Gott et al. (55) described 675 Marfan patients who underwent aortic root replacement at 10 surgical centers between 1968 and 1996. The 30-day post-operative mortality was 1.5% for those undergoing elective repair ( $n = 455$ ), 2.6% for urgent repair ( $n = 117$ ), and 11.7% for emergent repair ( $n = 103$ ). Compared to elective repair, the hazard ratio (HR) for death with urgent repair was 3.33 (95% confidence interval [CI]: 1.14 to 9.79;  $p < 0.025$ ) and for death with emergent repair the HR was 7.40 (95% CI: 2.84 to 19.30;  $p < 0.001$ ). For 103 patients undergoing emergent aortic root replacement within 24 h of surgical consultation, the indications were acute dissection ( $n = 73$ ), chronic dissection ( $n = 9$ ), chest pain, aneurysm diameter  $>7$  cm, or New York Heart Association functional class III or IV symptoms. Among 202 patients with acute or chronic dissection, nearly one-half had aortic diameters  $\leq 6.5$  cm. Thirty-day mortality after acute aortic dissection was 9.1%. The authors concluded that surgery should be undertaken electively when the aortic root diameter is "well below" 6.5 cm to reduce surgical mortality (55).

Elefteriades et al. (56-58) found that the risk of rupture or dissection increased sharply with aortic diameters  $>6$  cm at the ascending aorta and  $>7$  cm in the descending aorta (Figure 3). At these dimensions, the likelihood of aneurysm rupture or dissection was 31% for those with ascending aortic aneurysms and 43% for aneurysms of the descending aorta. Above these critical dimensions, the risk of death associated with surgery (2.5% ascending and 8% for descending aortic aneurysms) was exceeded by the risk of complications related to aortic rupture, dissection, or death (14.1%) (Figure 4) (56-58).

Several professional societies, including the American College of Cardiology (ACC), American Heart Association (AHA), American Association for Thoracic Surgery, and American College of Radiology,

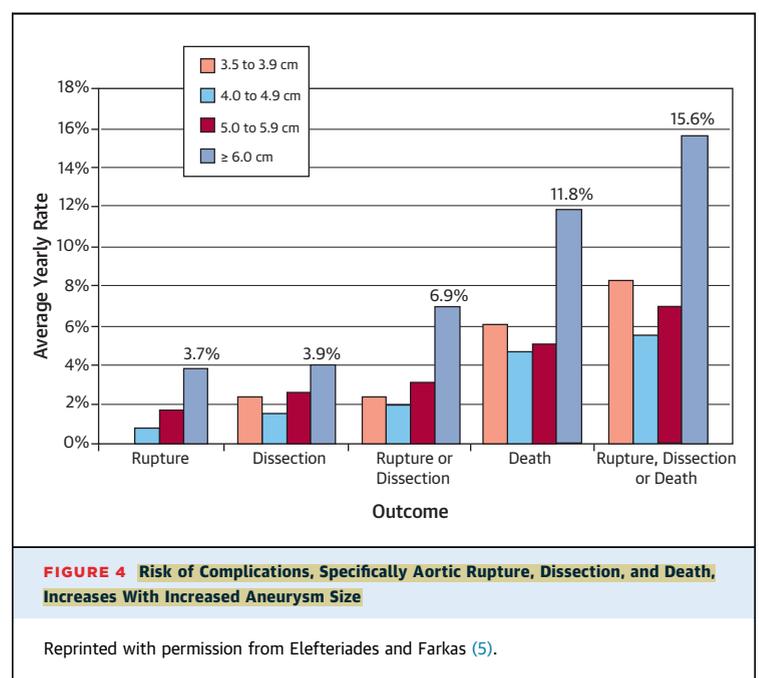


agree on a **5.5 cm threshold for surgical referral for patients with dilated aortic roots**, on the basis of the relative risks of surgical complications, rupture, dissection, and death (4,11). This cutoff will not invariably avoid dissection at smaller diameters. IRAD investigators found that the mean ascending aortic diameter was 5.3 cm in 591 patients with type A dissections between 1996 and 2005; 349 (59%) patients had diameters <5.5 cm. Independent predictors of dissection at diameters <5.5 cm included history of hypertension, radiating pain, and advanced age. The overall 27% mortality rate was unrelated to aortic diameter (59) (Table 1).

For a **bicuspid aortic valve with dilated aortic root**, the 2014 ACC/AHA guidelines for valvular disease recommend surgical referral when the aortic root is **5.5 cm or larger**, similar to recommendations for patients without a bicuspid valve (Class I, Level of Evidence: B). For a bicuspid valve with an additional risk for dissection (family history or rapid growth), there is a Class IIa recommendation for surgery when the aortic root is 5.0 cm (Level of Evidence: C) (60). Previous valvular disease guidelines from 2008 and the thoracic aorta guidelines used a cutoff of 5.0 cm, even in the absence of an additional risk factor (4,61). Prior

to release of the updated valvular disease guidelines, there was considerable discussion about the appropriate cutoff for surgical referral for a bicuspid aortic valve (27,62-64). In defending the new guidelines' higher cutoff of 5.5 cm, the authors cite the low rates of dissection with bicuspid valves, the paucity of data regarding the degree of aortic dilation at which the dissection risk substantively increases, and the variability in aortic level (sinus of Valsalva vs. ascending aorta) at which dilation occurs with bicuspid valves (60).

Marfan patients should undergo echocardiography at diagnosis to assess the aortic root and ascending aorta, then a follow-up echocardiogram after 6 months. If aortic root diameter is stable, patients should have annual imaging until the diameter reaches  $\geq 4.5$  cm or changes significantly, when more frequent imaging is advised (Class I, Level of Evidence: C). Patients with Loays-Dietz syndrome should have complete aortic imaging at diagnosis and after 6 months (Class I, Level of Evidence: C). If stable, they should undergo yearly CMR from the cerebrovascular circulation to the pelvis (Class I, Level of Evidence: B). Patients with mutations that predispose to aortic aneurysm formation and/or dissection should have complete aortic imaging at diagnosis and 6 months later (Class I, Level of Evidence: C). Patients with Turner syndrome should undergo imaging to exclude bicuspid aortic valve, coarctation, or dilation of the ascending aorta. If initial imaging is normal and there are no other risk



**TABLE 1 Recommendations for Referral to Surgery by Disease and Aortic Root Diameter**

| Population                                      | Aortic Root Diameter at Which Referral for Surgery Is Recommended   |
|---|---|
| General (4)                                     | $\geq 5.5$ cm ascending aorta or growth $>0.5$ cm/yr (Class I, Level of Evidence: C)  |
| Marfan syndrome (4)                             | $\geq 5.0$ cm ascending aorta, unless family history of dissection at $<5.0$ cm, or growth $>0.5$ cm/yr or $\geq 4.0$ cm and contemplating pregnancy (Class IIa, Level of Evidence: C)  |
| Loeys-Dietz syndrome (4)                        | $\geq 4.2$ cm by transesophageal echocardiogram (internal diameter) or $\geq 4.4$ to 4.6 cm by CT or CMR (external diameter) (Class IIa, Level of Evidence: C)  |
| Bicuspid aortic valve (4,60)                    | Per 2014 ACC/AHA valvular disease guidelines:<br>$>5.5$ cm (Class I, Level of Evidence: B)<br>$>5.0$ cm with a risk factor for dissection (family history of aortic dissection or growth $>0.5$ cm/yr) (Class IIa, Level of Evidence: C)<br>$>4.5$ cm and undergoing surgery for symptomatic severe aortic stenosis or regurgitation (Class IIa, Level of Evidence: C)<br>Per 2010 ACC/AHA thoracic aortic disease guidelines:<br>$\geq 5.0$ cm (Class I, Level of Evidence: C) |
| Plan for aortic valve repair or replacement (4) | $>4.5$ cm (Class I, Level of Evidence: C)   |

ACC = American College of Cardiology; AHA = American Heart Association; CT = computed tomography; CMR = cardiac magnetic resonance.

factors for dissection, imaging should be repeated every 5 to 10 years. If initial imaging is abnormal, reimaging is indicated based on clinical developments (Class I, Level of Evidence: C).

**PREDICTING DISSECTION.** Diseases of the thoracic aorta may be clinically silent until dissection becomes an emergency. Surveillance of high-risk populations and prophylactic surgery decreased the frequency of dissection, but these events are still too common and catastrophic. Several biomarkers were investigated for earlier detection of events that may precede aortic dissection, including MMP and TGF- $\beta$  levels (65). Microribonucleic acid expression and MMP activity measurements may elucidate distinctive profiles associated with thoracic aorta diseases (9,10). For dissection, these include C-reactive protein, calponin (a troponin counterpart of smooth muscle), and D-dimer, although these have not been studied prospectively. In a meta-analysis of 11 studies that included 349 patients, D-dimer had a pooled sensitivity for dissection of 94% and specificity of 40% to 100%. These markers remain investigational, and current guidelines do not recommend biomarker use in routine clinical practice (4).

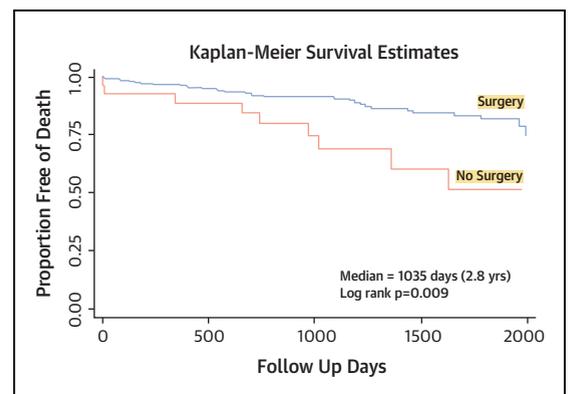
Sensitivity and specificity approach 100% for diagnosis of aortic dissection by CT and CMR imaging, but these figures presuppose clinical suspicion. To improve diagnosis, the IRAD investigators formulated a risk prediction tool that incorporates high-risk

conditions (e.g., Marfan syndrome), certain features of the presenting symptoms (abrupt onset of severe or tearing quality pain), and clinical findings (shock, new murmur of aortic regurgitation) into a score to stratify patients into low-, intermediate-, or high-risk groups (66).

**SURGICAL MANAGEMENT FOR TYPE A DISSECTION**

Mortality associated with acute unoperated type A aortic dissection has been estimated at 1%/h to 2%/h during the first 48 h. Hence, all patients with type A dissection should be considered for urgent surgical repair. In the IRAD database, in-hospital mortality for patients managed surgically was 27%, compared with 56% for those managed medically (Figure 5) (67). For those surviving to hospital discharge, 1-year survival was 96% in the surgery group versus 89% in the medical group, and was 91% after surgery versus 69% at 3 years. In multivariable analysis, predictors of long-term mortality were a history of atherosclerosis (relative risk: 2.17; 95% CI: 1.08 to 4.37; p = 0.03) and previous cardiac surgery (relative risk: 2.54; 95% CI: 1.16 to 5.57; p = 0.02) (68).

Uncertainty surrounds the appropriateness of surgical management in certain populations, such as those older than age 80 years, with neurological injuries, presenting late after the onset of dissection, and with prior cardiac surgery. While 1 study suggested that patients  $>80$  years of age have poor outcomes (69), another comparing patients younger or older than 80 years of age found no difference in survival (70). In an analysis of 936 patients in IRAD, one-third were over 70 years of age and 63 were 80 years of age or older; the rate of surgical repair



**FIGURE 5 Kaplan-Meier Survival Curves for Type A Dissections in Surgical Versus Nonsurgical Groups**

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decreased with age, and surgical mortality increased with age >70 years. There were not enough patients >80 years of age to permit conclusions about a mortality benefit with surgery, and the authors recommend considering surgery in all patients, regardless of age (71).

In single-center reports, surgical repair for type A dissection was performed in the setting of stroke, without neurologic decline (72,73). Similarly, IRAD analyses point to improved outcomes for surgical management of patients who present with acute type A dissection and stroke. In an analysis of 1,873 patients, 87 (4.7%) presented with stroke and 54 (2.9%) with coma. With stroke, mortality was 76% with medical management and 27% with surgical management (p < 0.001), and with coma, mortality was 100% with medical management and 44% with surgical management (p < 0.001). Logistic regression analysis pointed to improved survival with surgery after brain injury (odds ratio: 0.058; p < 0.001). Five-year survival rates for patients presenting with stroke and coma were 23.8% and 0% with initial medical management versus 67.1% and 57.1% with surgery (log rank, p < 0.001), respectively (74). In a later analysis of 2,202 IRAD patients with acute type A dissection over a 16-year period, 132 (6%) presented with stroke. These patients were older, had higher rates of hypertension and atherosclerosis compared to those who did not present with stroke, were more likely to present with shock (13.8% vs. 7%; p = 0.005), and more likely to have aortic arch vessel involvement (68% vs. 37%; p < 0.001), but less likely to undergo surgical repair (73.5% vs. 85.4%; p < 0.001). In-hospital mortality was 42.4% for patients with stroke, compared to 24.1% for patients without stroke (p < 0.001). Among stroke patients, 5-year mortality was 100% for those managed medically and 22.1% for patients managed surgically (75).

In a single-institution study of 195 patients with type A dissection, 93 (47%) presented more than 48 h after the onset of symptoms. There was no difference in long-term survival after 41.8 months among those surviving the initial phase of management (76). It is important to recognize the inherent selection bias when analyzing those patients who survive the initial 48 h without surgical intervention (67,68).

Although some reports suggested that prior aortic valve surgery might protect against complications of type A dissection, specifically aortic regurgitation or involvement of the right coronary artery in the dissection, other reports implicated prior cardiac surgery as increasing operative risk. Prior surgery should not delay treatment of a type A dissection (77,78).

## ROLE FOR SURGERY OR ENDOVASCULAR REPAIR FOR ANEURYSM AND DISSECTION

The role for endovascular versus open repair differs on the basis of the aortic segment containing the lesion. Aneurysms or dissections of the ascending aorta are treated surgically. There is a role for endovascular repair in the descending thoracic aorta, with U.S. Food and Drug Administration (FDA)-approved devices for aneurysm and complicated dissection (79). Endovascular approaches avoid the pain and recovery time from thoracotomy and the risks of aortic clamping, but their use may be limited in patients with inadequate landing zones for stent placement, excessive aortic dilation, inadequate vascular access, and severe aortic atherosclerosis, which would increase the risk for embolism. There are also considerably more long-term data for open repair (4).

### 1. ASCENDING AORTA ANEURYSM AND DISSECTION.

Open repair is the standard of care for patients meeting the criteria outlined in Table 1. However, there is controversy in the treatment approach to the aortic root. Myriad options exist (Table 2), and appropriate treatment centers on the normality of the aortic sinuses. In older patients, the disease process is usually effacement at the sinotubular junction. A tube graft replacement above the sinuses, including the proximal portion of the aortic arch, should be used. These operations are reproducibly done, with only modest hypothermia and low risk of death or stroke (80).

In patients with proximal disease of the aortic root, attention to aortic valve integrity is essential. The modified Bentall procedure, where a composite valve and graft is used to replace the entire aortic root, is the standard of care for these patients. However, many options for composite biological grafts now exist, including a bioprosthetic valve sewn into a Dacron graft, or use of the porcine xenograft Freestyle (Medtronic, Freely, Minnesota) composite valve graft (81). In the last decade, there has been intensive

TABLE 2 Surgical Options for Ascending Aorta Repair

| Surgical Procedure            | Description of the Procedure   |
|-------------------------------|--|
| Bentall (115-118)             | Total aortic root replacement with a composite valve graft consisting of a Dacron aortic root and a prosthetic aortic valve (either bioprosthetic or mechanical), with reimplantation of the coronary arteries |
| Yacoub (root remodeling) (83) | Dacron aortic root with a scalloped design   |
| David (valve sparing) (82)    | Native aortic valve is reimplanted into a Dacron aortic graft and coronary arteries are reattached   |
| Ross procedure (119)          | Pulmonary valve autograft is placed in the aortic valve position, and a homograft valve replaces the pulmonary valve   |
| Aortic homograft (120)        | Consists of aortic valve and ascending aorta   |

interest in valve-sparing aortic root replacement, which allows treatment of the aortic root aneurysm and reimplantation of the aortic valve in both bicuspid and trileaflet valve patients (82). Another valve-preserving option involves remodeling the aortic root in order to recreate the sinuses of Valsalva and sinotubular junction (83). **Patients presenting with type A dissection should be offered immediate surgery.** There is **no role for medical stabilization prior to surgery.** Pre-operative coronary angiography should not be performed routinely; this **delays surgical repair and increases the risk for aortic rupture (84).** Moreover, surgeons are **unlikely to perform coronary artery bypass grafting in the setting of a type A dissection and the risk of wire misadventure in a dissected aorta is not insignificant.** The **primary goal of type A dissection surgery is not to entirely eliminate the dissection, but to emerge with a live patient.** Only in DeBakey **type II** cases can the **dissection be completely eliminated.** In **most patients, there will be persistent downstream dissection with patent false lumen in the descending and abdominal aorta.** The ascending aorta is replaced from the sinotubular junction to the undersurface of the aortic arch. If the aortic root is involved, the operation may be extended proximally to address pathologic or aneurysmal aortic sinuses. There is **little role to expand the operation to include full transverse arch replacement, as this increases operative risk without eliminating all diseased tissue.**

There is **no role for endovascular repair of ascending aortic aneurysms or type A dissections (85,86).**

**2. AORTIC ARCH ANEURYSM AND DISSECTION.** The aortic arch was the **last aortic section to be successfully replaced surgically, due to the difficulty of maintaining perfusion of the head, neck, and upper extremities.** From the 1950s through 1970s, high mortality and neurologic morbidity rates with surgical arch replacement **improved with the introduction of deep hypothermic circulatory arrest (87)** followed by advances in intraoperative cerebral perfusion (88,89). In a retrospective analysis of 347 patients who underwent surgical aortic arch replacement from 1993 to 2007, 95 underwent total arch replacement with **hypothermia and circulatory arrest.** For those who **also received selective antegrade cerebral perfusion, mortality was 6% compared to 34.6% for those who did not, and stroke occurred in 6% versus 19.2%.** Elective cases were even safer, with a mortality rate of 2.7% and strokes in 5.4% (89).

Current guidelines provide Class IIa recommendation for **open surgical repair of the aortic arch.** For

proximal arch disease, **partial arch replacement and ascending aorta repair are recommended.** Total arch replacement is reasonable for acute dissection when the arch is aneurysmal or there is extensive destruction; for aneurysms that involve the entire arch; for chronic dissection with arch enlargement; and for distal arch aneurysms that involve the proximal descending thoracic aorta. Repair is also recommended for arch diameter **>5.5 cm** in asymptomatic, low-risk patients with isolated degenerative or atherosclerotic aneurysms (4).

Although endovascular stent grafts are not FDA-approved for arch aneurysms, and randomized data are lacking, **endovascular or hybrid procedures (combined endovascular and vascular surgery procedures) are increasingly used for patients at high surgical risk due to age or medical comorbidities.** One type of **hybrid procedure involves extra-anatomic bypass, either carotid-carotid or carotid-subclavian, to permit a stent graft to cover the origin of the carotid artery (90).** Hybrid procedures for the aortic arch also include “**debranching**” procedures, where **affected arch vessels are sequentially surgically anastomosed to a Dacron graft, effectively removing the branches from the aortic arch (91).** Because of **high morbidity and mortality, these procedures are reserved for patients at high surgical risk.**

**3. DESCENDING THORACIC AORTA ANEURYSM AND DISSECTION.** The descending thoracic aorta extends from after the arch to proximal to the celiac axis. For saccular aneurysms or degenerative or traumatic aneurysms of the descending thoracic aorta **exceeding 5.5 cm, endovascular stent-grafting should be considered.** The guidelines recommend **open surgical repair for chronic dissection in the setting of a connective tissue disorder and a descending thoracic aortic diameter >5.5 cm. (Class I, Level of Evidence: B) (4,92).** Citing the absence of randomized trial data, the 2010 ACC/AHA guidelines **do not address the relative efficacy of open versus endovascular repair for the descending thoracic aorta.** The authors note the FDA approval of stent grafts for aneurysm repair (TEVAR) on the basis of observational data without long-term durability data (4).

The Society of Thoracic Surgeons Endovascular Surgery Task Force consensus document **recommends against endovascular stent grafting in asymptomatic descending aortic aneurysms <5.5 cm because the surgical risk of roughly 5% exceeds the risk of aneurysm rupture or dissection (92).** Similarly, a 2012 position statement from the European Association for Cardio-Thoracic Surgery (EACTS), European Society

of Cardiology (ESC), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) recommended endovascular repair in asymptomatic patients when maximal aneurysm diameter is 5.5 cm or growth rate exceeds 0.5 cm over 6 months. The authors acknowledged that this cutoff might be too conservative for older patients with comorbidities or not conservative enough in other patients (93). Elefteriades (56) suggested that a 6.5 cm cutoff for the descending aorta may present a more accurate “hinge point,” after which the risk of complications increases steeply (56).

Multicenter, prospective, nonrandomized trials with control groups that included historical controls evaluated 3 endovascular devices for descending thoracic aortic aneurysms, all of which had high successful device placement rates: Gore TAG (W. L. Gore & Associates, Inc., Flagstaff, Arizona), Medtronic Talent (Medtronic, Minneapolis, Minnesota), and Cook Zenith TX2 (Cook Medical, Bloomington, Indiana). The endovascular groups had less morbidity in all 3 trials, the Gore device had lower aneurysm-related mortality at 5 years, and the Medtronic device had lower aneurysm-related and all-cause mortality at 1 year (94-97).

In the INSTEAD (Investigation Of Stent Grafts in Patients with type B Aortic Dissection) trial, patients with chronic (>14 days), uncomplicated type B dissection were randomized to elective stent-graft placement with medical therapy (n = 72) or to medical therapy alone (n = 68). Patients were enrolled between 2 and 52 weeks after dissection. There was greater favorable aortic remodeling in the endovascular arm compared to medical therapy, but no differences between the groups in all-cause or aortic mortality at 1 or 2 years (98,99). At 5 years, the TEVAR group had lower aorta-specific mortality and less disease progression, but only using a retrospective “landmark” analysis (100). IRAD patients who underwent TEVAR for type B dissections had lower 5-year mortality compared to patients treated medically (15.5% vs. 29.0%; p = 0.018), but these observational data may reflect selection and referral biases (101).

Despite limited data, the Gore TAG, Medtronic Talent, and Cook Zenith TX2 stent grafts were recently FDA-approved for descending thoracic aorta dissections, and there are at least 4 devices with new, unique features that are being evaluated in clinical trials (4,102-104). For patients with acute uncomplicated type B aortic dissection, 90% survive with medical therapy aimed mostly at control of hypertension; therefore, uncomplicated type B dissections should be treated medically (67,105).

The EACTS/ESC/EAPCI 2012 position statement and a multidisciplinary panel of European experts recommended TEVAR only for complicated type B dissections. This panel identified persistent pain, refractory hypertension, malperfusion, and signs of rupture, hypotension, or shock as acute complications. Subacute and chronic complications included: aortic diameter  $\geq 5.5$  cm; diameter increase  $>4$  mm; refractory hypertension; recurrent malperfusion; or recurrent symptoms (106). In recommendations for acute or chronic type B dissections, the FDA and a multidisciplinary subcommittee that included the Society for Vascular Surgery, American Association for Thoracic Surgery, Society of Thoracic Surgeons, and the Society for Interventional Radiology, agreed to limit the definition of “complicated” dissection to rupture, impending rupture, or distal malperfusion. Using data collected from investigational device exemption clinical trials between 2000 and 2008, the investigators identified 99 patients with complicated type B dissections on the basis of these criteria. The mortality rate was 10.8% at 30 days and 29.4% at 1 year. At 30 days, rates of stroke, renal failure, and paralysis were each 9.4%. Based on these data, the FDA and SVS/AATS/STS/SIR recommend TEVAR for complicated type B dissections (79).

**4. THORACOABDOMINAL AORTIC ANEURYSM AND DISSECTION.** Thoracoabdominal aneurysms extend from the descending thoracic aorta into the abdomen and/or involve the upper abdominal aorta. They are classified by Crawford type: type I extend from the level of the left subclavian artery to the renal arteries; type II, the most difficult to repair, extend from the level of the left subclavian artery to the aortoiliac bifurcation; type III start at or distal to T6 and affect the lower part of the descending thoracic aorta and the abdominal aorta; and type IV involve the abdominal aorta below the diaphragm (107).

Open repair for thoracoabdominal aneurysms, first performed in the late 1950s, was complicated by spinal cord ischemia and paraplegia, and impaired blood flow to celiac, superior mesenteric, and renal arteries with subsequent renal failure. Morbidity and mortality have since decreased with improvements in surgical technique and spinal cord protection, specifically hypothermic cardiopulmonary bypass; monitoring somatosensory-evoked or motor-evoked potentials to evaluate spinal cord perfusion; cerebrospinal fluid drainage to increase spinal cord perfusion pressure; maintaining increased arterial blood pressure; pressure-controlled perfusion of the celiac, superior mesenteric, and renal arteries so that

they are **continuously perfused** during aortic cross clamping; and **prevention of post-operative hypotension**. However, complication rates remain **high** (107-111).

Crawford **II** lesions are **only** treated with **open** surgical repair. For **other Crawford** lesions, open surgical repair is the gold standard; **hybrid** procedures have been performed in patients at high surgical risk, as they carry significant morbidity and mortality (107,112-114). The **guidelines** recommend **surgical** repair of **thoracoabdominal aneurysms** when diameter **>6.0 cm**, or less with Marfan syndrome or other connective tissue disorders (Class I, Level of Evidence: C). **Surgical repair** is also **recommended** when there is **end-organ ischemia** or significant celiac, superior mesenteric, or renal artery atherosclerosis (Class I, Level of Evidence: B) (4).

## CONCLUSIONS

Thoracic aortic aneurysms occur in the setting of medial degeneration, most commonly due to increased aortic wall stress from hypertension and, less commonly, to genetic and inflammatory conditions or prior cardiac surgery. The most feared complication is dissection. On the basis of small

studies of Marfan patients, medical therapy with  $\beta$ -blockers and/or ARBs is reasonable to reduce the rate of aneurysm growth for patients with thoracic aortic aneurysms. Serial, noninvasive imaging should be used to follow patients with thoracic aortic aneurysms, with referral for surgical repair generally indicated when the aneurysm reaches a critical diameter on the basis of location and etiology. In the future, serological biomarkers may be developed and validated for diagnosis and prediction of aortic rupture or dissection. **Type A dissection is an emergency, and all patients with this condition should be assessed for urgent surgery**, with which survival beyond the hospital phase is excellent out to at least 3 years. There is a role for **endovascular repair** of the **descending** thoracic aorta and a potentially expanding role for stent-graft interventions in patients with thoracic aneurysmal diseases, either as an alternative to or in conjunction with open surgical interventions.

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**KEY WORDS** aortic aneurysm, cardiac surgical procedures, endovascular procedures, Marfan syndrome, risk factors, transforming growth factor beta