Thoracic Aortic Aneurysm: Clinically Pertinent Controversies and Uncertainties
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This paper addresses clinical controversies and uncertainties regarding thoracic aortic aneurysm and its treatment. 1) Estimating true aortic size is confounded by obliquity, asymmetry, and noncorresponding sites: both echocardiography and computed tomography/magnetic resonance imaging are necessary for complete assessment. 2) Epidemiology of thoracic aortic aneurysm. There has been a bona fide increase in incidence of aortic aneurysm making aneurysm disease the 18th most common cause of death. 3) Aortic growth rate. Although a virulent disease, thoracic aortic aneurysm is an indolent process. The thoracic aorta grows slowly—0.1 cm/year. 4) Evidence-based intervention criteria. It is imperative to extirpate the thoracic aorta before rupture or dissection occurs; surgery at 5.0- to 5.5-cm diameter will prevent most adverse natural events. Symptomatic (painful) aneurysms must be resected regardless of size. 5) Development of nonsize criteria. Mechanical properties of the aorta deteriorate at the same 6 cm at which dissection occurs; elastic properties of the aorta may soon become useful intervention criteria. 6) Medical treatment of aortic aneurysm. Medical treatment is of unproven value, even beta-blockers and angiotensin-receptor blockers. 7) A genetic disease. Even non-Marfan aneurysms have a strong genetic basis. 8) Need for biomarkers. Virulent but silent, TAA cries out for a biomarker that can predict the onset of adverse events. Pathophysiologic understanding has led to identification of promising biomarkers, especially metalloproteinases. 9) Endovascular therapy for aneurysms. Endovascular therapy has burgeoned, despite the fact that the EVAR-2, DREAM, and INSTEAD trials showed no benefit at mid-term over medical or conventional surgical therapy. We must avoid “irrational exuberance.” 10) Inciting events for acute aortic dissection. Recent evidence shows that dissections are preceded by a specific severe exertional or emotional event. 11) “Silver lining” of aortic disease. Proximal aortic root disease seems to protect against arteriosclerosis. (J Am Coll Cardiol 2010;55:841–57) © 2010 by the American College of Cardiology Foundation

This review of the key issues in thoracic aortic aneurysm disease maintains a clinical focus, calling on basic science as directly needed in addressing topics that arise daily in the care of patients. We call extensively on data reported or currently emerging from the Yale Center for Aortic Disease (with its database including 3,000 patients, 9,000 imaging studies, and 9,000 patient-years of observation), but we supplement liberally with key information from other leading aortic centers.

**Estimating True Aortic Size (and Reconciling Discrepant Reports) Can Be Difficult**

It is important to know the size of the aorta because key decisions regarding management of aortic aneurysms depend on size. However, the question “How big is the aorta?” is not always easy to answer.

The following specific sources of error are encountered regularly in the clinical practice of aortic care.

**Inherent level of resolution of current imaging technologies.** A radiologist may report an increase in size of 1 or 2 mm between the current scan and the previous scan. However, we cannot reliably detect so small a change, be it on echocardiography (echo), computed tomography (CT), or magnetic resonance imaging (MRI). Unlike the precise physical sciences, in clinical aortic size estimation, one cannot have confidence in a measured change of <3 or 4 mm, and even this level of precision requires carefully ascertaining that similar levels of the aorta are being measured.

**Include or exclude the aortic wall itself in a measurement?** There is no consensus on whether the aortic wall should be included or excluded in the aortic diameter, whether the test is made by echo, CT, or MRI. This may make a difference of several millimeters in the calculated measurements. On a noncontrast CT image, for example, it is most comfortable to measure the entire aortic wall, including the lumen and wall; on the other hand, on a contrast image, it may be more comfortable to measure the luminal shadow alone.

**Limitations of specific imaging modalities.** Echocardiographic images of the ascending aorta are often beautifully crisp. However, a transthoracic echocardiogram can only
visualize the proximal several centimeters of the ascending aorta, to just above the sinotubular junction in a patient with good echo windows (Fig. 1). Thus, echo will miss an aneurysm of the mid-portion of the ascending aorta. This may explain, for example, why the transthoracic electrocardiogram may give a reading of 4.3 cm, whereas the CT scan shows 5.4 cm. Each modality is accurate for the portion of the ascending aorta accessible to that type of image. Even transesophageal echo is limited by the interposed tracheal air column and can be “blinded” to the upper portion of the ascending aorta (Fig. 2).

A CT scan with axial images cannot properly evaluate the very proximal portion of the ascending aorta. The entire portion of aorta between the annulus and the coronary arteries usually represents a distance of only 1 or 2 cm. Axial imaging planes may miss an aneurysmal dilation in this location. Also, it can be exceedingly difficult to be certain whether a given axial cut is above or below the aortic valve—a key distinction if one is to take a diameter measurement based on that cut (Fig. 3). Furthermore, it is naïve to believe that the plane of the aortic valve is confined to the plane of the axial images (perpendicular to the longitudinal axis of the body). Even the normal annulus may be skewed. Furthermore, as the ascending aorta elongates, the aortic valve plane is forced into a more vertical orientation, rendering even more difficult the assessment of size on axial images (Fig. 4). In modern CT scanners, reconstructions are done not only in axial, but also in sagittal and coronal planes, but the resolution in the nonaxial reconstructions is often insufficient to permit precise assessment of aortic shape or diameter.

In addition, motion artifact can adversely affect the resolution of CT images of the aorta, producing changes in diameter as great as 7.5% to 27.5%, although technology is improving, especially with gated tomographic angiography (1–3).

MRI is inherently a multiplane modality that can provide meaningful axial, sagittal, and coronal images. Depending on the resolution of a particular set of images, accurate
measurements may be feasible. Oftentimes, however, images are insufficient to permit accurate measurement.

Old-fashioned ascending aortography is exceptional in providing crisp images of the aortic contour. The morphology of the proximal aortic root can be seen beautifully, including the loss of the normal “waist” seen above the coronary ostia in annuloaortic ectasia (Fig. 5). The shape of the aorta is ideally seen angiographically. This can facilitate accurate surgical planning. However, diameter measurement from angiographic images is not always simple to calculate or very accurate, and measurements are more commonly made from echo, CT, or MRI.

**Geometric complexity.** The human aorta is geometrically complex. The ascending aorta is not truly or totally vertical.

The *aortic arch* poses an additional challenge because an axial image through the aortic arch will produce an oblong rather than a circular contour; measuring the long axis of this oblong contour is misleading because this does not represent a true aortic diameter. (See also the following section, The Dilated Thoracic Aorta Grows Slowly, in an Indolent Fashion) The same holds true for any other portion of the aorta that takes a sharp curve, as often happens at the peridiaphragmatic portion. As the aorta dilates, it often elongates as well. The only way that an elongating aorta can “stay in the chest” is by becoming...
tortuous or S shaped. Furthermore, in comparing measurements over time, one can easily be misled by diameters taken from even slightly different longitudinal levels of the aorta. Also, even in a given cross section, the aorta will not be a true circle (Fig. 6). The measured girth may vary depending on which particular geometric diameter is selected. This can be especially true even on good-quality transesophageal echo, which may not “see” all diameters of the aortic annulus and aortic root; asymmetric dilation of 1 sinus, for example, may escape detection.

Knowing the dimension of the aorta is vitally important. As can be seen from the previous descriptions and images, measuring the thoracic aortic is not a mean feat. In some cases, it may be difficult to reconcile discrepant studies or to achieve an ultimate measurement that encompasses the separate “realities” of different imaging modalities.

In comparing serial imaging studies, it is important to avoid the temptation to compare with the previous image. The aneurysmal aorta grows slowly, approximately 1 mm per year on average (4). Thus, looking at closely spaced images may miss even inexorable growth—the way a parent does not notice children growing. Rather, it is imperative to compare with the very first available image, even if it means searching or sending for early studies (5).

It is important to remember as well that size is not the only important imaging criterion; shape matters as well, especially loss of the normal “waist” of the aorta at the sinotubular junction (Fig. 5). Loss of this normal indentation is an indication of intrinsic aortic disease, which should raise attention and concern about future aortic events.

Thoracic Aortic Aneurysm

It is not easy, from an epidemiologic standpoint, to determine whether the apparent increase in number of patients seen with thoracic aortic aneurysm is due to increased detection (reflecting the frequency with which CT scans are ordered in the current era) or to a bona fide increase in the incidence of this disease. Some available evidence suggests the latter (6).

Aneurysm disease is usually silent unless an imaging study happens to have been performed; thus, true incidence is hard to estimate. Lethal thoracic aortic dissections are also often misdiagnosed as myocardial infarctions (7,8).

The most recent data available from the Centers for Disease Control and Prevention indicate that aneurysm disease is the 18th most common cause of death in all individuals and the 15th most common in individuals older than age 65 years, accounting for 13,843 and 11,147 deaths in these 2 groups, respectively (9). Note that aneurysm causes more deaths than human immunodeficiency virus disease. These figures almost certainly represent underestimates of the impact of aortic diseases due to the reasons previously mentioned. Experts have suggested that 30,000 to even 60,000 deaths per year in the U.S. represents a reasonable estimate (10). The incidence of aortic disease is certain to increase as our population ages.
The concept that aortic disease is truly increasing in incidence is based on evidence from geographic regions with stable populations with little out- or in-migration, as studied in Minnesota and Sweden (11,12). Analysis in these regions suggests a true, bona fide increase in the incidence of aortic disease. This is seen clearly in Figure 7.

The Dilated Thoracic Aorta Grows Slowly, in an Indolent Fashion

Although a virulent disease, thoracic aortic aneurysm is an indolent process. The thoracic aorta grows very slowly—at approximately 0.1 cm per year. The descending aorta grows a bit faster than the ascending (Fig. 8). Previous estimates had failed to account for negative observed growth (measurements of any object will vary around the mean) and other statistical complexities, leading to overestimates of actual growth. Dr. John Rizzo of our team developed exponential equations specifically for the purpose of accurately estimating growth rates (13).

In fact, reports of rapid growth of the thoracic aorta are usually reflective of measurement error—specifically, measuring across an oblique portion of the aorta, especially the aortic arch (Fig. 9). The only condition that we have encountered in which the thoracic aorta truly grows rapidly in a short time occurs when there has been an intercurrent aortic dissection; this should be suspected in a circumstance in which the diameter of the aorta truly has grown rapidly.

Evidence-Based Size Criteria for Replacement of the Dilated Aorta Are Now Available

The poor prognosis after realized dissection indicates how critically important it is to intervene before aortic dissection occurs. Our studies of the natural history of the enlarged aorta have defined criteria that predict when dissection and rupture are likely to occur in an enlarged thoracic aorta.

We started by analyzing the lifetime risk of rupture or dissection. Analysis revealed sharp “hinge points” in the aortic size at which rupture or dissection occur. These hinge points are seen at 6 cm in the ascending aorta and 7 cm in the descending aorta (Fig. 10). It is important to intervene before the aorta reaches these hinge-point dimensions. Specifically, as seen in the figure, an individual with thoracic aortic aneurysm incurs a 34% lifetime risk of rupture or dissection by the time that his or her ascending aorta reaches a diameter of 6 cm. As seen in Figure 10, the descending aorta, for inexplicable reasons, does not rupture until a larger dimension.

To calculate yearly growth rates required even more robust data, which have now become available in our database. This analysis reveals that the incidence of rupture, dissection, or death increases in a roughly linear fashion as the aorta grows, reaching maximal levels at an aortic dimension of 6 cm (Fig. 11).

There is something special about the dimension of 6 cm, which we shall see is important mechanically as well as clinically.
These data have permitted us to formulate evidence-based guidelines for surgical intervention for thoracic aortic aneurysms. These guidelines have been widely adopted. The simple fact is that the vast majority of ruptures, dissections, and aneurysm-related deaths can be prevented by preemptive extirpation of the aneurysmal thoracic aorta before the critical dimension of 6 cm is reached. We usually recommend intervention for the ascending aorta at 5.5 cm; we use a criterion of 5.0 cm for patients with Marfan syndrome, bicuspid aortic valve, or family history of aortic dissection (14).

It should be emphasized that these criteria apply to asymptomatic aneurysms.

**Symptomatic aneurysms should be resected regardless of size.** Symptoms are a harbinger of aortic rupture or dissection and must not be ignored. However, symptoms are rare in this disease; only approximately 5% of patients are symptomatic before an acute aortic event occurs. For the other 95% of patients, the first symptom is often death. Ascending aneurysms can produce retrosternal pain that is not exertional in nature, and descending aneurysms can produce interscapular back pain. Attention to these symptoms can be literally lifesaving.

Now, it may be questioned whether 1 set of size criteria for surgical intervention can be applied to all individuals, regardless of body size. In fact, it is indeed appropriate to make body size corrections, especially for very small or very large individuals. Our data now have become so robust that we have been able to determine appropriate criteria for interventions based on an aortic size index, which takes into account both aneurysm size and the patient’s body surface area (Fig. 12).

### Dissections Can and Do Occasionally Occur at Small Aortic Sizes

We have known for some years that dissections do occasionally occur at small aortic sizes (Fig. 11). A recent paper from the International Registry of Aortic Dissection (IRAD) noted that a good number of the aortic dissections in their registry occurred at sizes below our recommended intervention criterion of 5.5 cm (15) (Fig. 13). Insightfully, the IRAD authors recognized the dangers of amending size...
criteria for surgical intervention downward, and they did not recommend any such change for fear of promoting surgical harm in operating on small aortas.

The key to reconciling our observational studies that small aortas pose only a low risk with the IRAD observation of a substantial number of dissections occurring at small

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**Figure 11** Yearly Rates of Rupture, Dissection, or Death Related to Aortic Size

Note that the likelihood of rupture, dissection, or death within the coming year also jumps sharply for aneurysms that reach 6 cm or larger. (The rates indicated for rupture or dissection and for rupture, dissection, or death are lower than the sum of the rates in individual categories because patients with multiple complications were counted only once in the combined categories.) These data underlie the conclusion that aneurysms in the ascending aorta need corrective surgery when the artery balloons to 5.5 cm. Adapted, with permission, from Elefteriades (14). Figure illustration by Rob Flewell.

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**Figure 12** Aortic Size Index Nomogram

sizes lies in recognition of the “at-risk” denominator pool of patients. Our Yale studies present danger rates for patients under observation at our institution with small aortas; indeed, their risk of aortic events, although not zero, is low—too low to justify surgical intervention. For the IRAD patients with dissection, however, these were drawn from the general population at large. Whether the distribution of aortic sizes is normal or paranormal, the number of at-risk patients increases dramatically as one moves toward normal from the largest aortic sizes in the distribution curve (Fig. 14). In fact, it is likely that there are millions of patients in the U.S. with aortas between 4 and 5 cm. One could certainly cause harm by operating prophylactically on all of them. In fact, if one were to divide the numerator of observed dissections in IRAD by a denominator of millions, the observed yearly percentage rate of dissection in the small sizes would be very small. Such interpretation supports, as IRAD concluded, that we maintain our current surgical intervention criteria.

In fact, to this point, we recently tested our intervention algorithm in real time in the real-world setting of our Yale Aortic Center (unpublished data analyzed by Amer Trivedi, 2006). We longitudinally followed patients triaged, based on our algorithm (surgery for symptoms or size <5.5 cm), to observational management (Fig. 15). As a matter of fact, not a single patient triaged to medical therapy died of rupture during follow-up. This is powerful information validating the safety of medical management for small aortic aneurysms. On the other hand, among patients triaged algorithmically to the surgical arm who were too ill for surgery or who refused surgery, the rate of aortic events leading to death was indeed very high, validating surgical therapy for patients meeting the algorithm criterion.

Size is a very helpful criterion, and, beyond symptoms, it is the best intervention criterion in the current state of the art.

Nonsize Engineering Criteria Are Evolving

We performed a detailed engineering analysis on the aortic wall in patients with ascending aortic aneurysms. We did this by epiaortic echo at the time of aortic surgery. A full spectrum of engineering calculations regarding the mechanical properties of the dilated aorta can be determined via measurement of 6 independent variables: aortic pressure in systole and diastole, aortic diameter in systole and diastole, and aortic wall thickness in systole and diastole.

These measurements have shown that as the aorta enlarges, distensibility of the aortic wall decreases, so that by...
approximately 6 cm in size, the aorta becomes a rigid tube (16). The result is that because the aneurysmal aortic wall cannot “stretch” in systole, the full force of cardiac contraction is translated into wall stress. The correlate of this phenomenon is that the enlarged aorta demonstrates a very high wall tension. These findings are shown in Figure 16. The dotted line in Figure 16B represents the ultimate strength of human aorta. As seen in Figure 16B, during episodes of moderate hypertension, part of everyday life, an individual with a 6-cm aorta will “flirt” with the ultimate bursting strength of human aortic tissue. This has clinical consequences that we explore in the following text.

Please note how beautifully the engineering data dovetail with the clinical data. It is at 6 cm that the mechanical properties of the aneurysmal aorta deteriorate markedly. It is precisely at 6 cm that the malignant behaviors of the dilated human aorta—rupture and dissection—commonly become manifest, as discussed previously.

We are currently replicating our intraoperative mechanical measurements with simultaneously accrued transesophageal measurement of mechanical properties. If we can confirm that similarly reliable measurements can be made transesophageally, then mechanical properties may become a clinically relevant parameter. Periodic outpatient calculations of mechanical properties, say distensibility and wall stress, may prove good predictors of rupture and dissection. Thus, mechanical properties may be useful to supplement symptoms and size as criteria for prophylactic aortic intervention.

Recent, preliminary evidence from Europe suggests that similar measurement of mechanical properties can be made by MRI, and that such measurements may demonstrate regions of the aneurysm at high risk of disrup-

tion (17,18). In addition, preliminary studies from Europe also suggest that evidence of enhancement on positron emission tomography may be an indicator of the “activity” of an aneurysm, possibly preceding or predicting rupture (19,20).

**Drug Therapy for Thoracic Aortic Disease Is Largely Unproven**

Is drug therapy effective for the treatment of chronic aneurysms? Patients with chronic aneurysms are often treated with beta-blocking medications to decrease the virulence of the systolic impact on the aortic wall. Of course, hypertension must be controlled in aneurysm patients to limit the disruptive forces on the aortic wall, and this goal in and of itself may involve the use of beta-blockers. The effectiveness of beta-blockers in aneurysm disease, however, is largely unproven and somewhat controversial, but this therapy has become standard practice. One long-duration Johns Hopkins study of a moderate-size group (n = 70) of Marfan patients provides support (21), but there is also reason for doubt regarding this therapy, especially for non-Marfan patients (22,23). Concerns revolve around a number of issues: There is evidence that beta-blockers decrease the elasticity of the aortic wall, already deficient in aneurysmal aortas. There is concern about the side effects of beta-blockers in young people because treatment is often a lifetime decision. Finally, there is concern about a paradoxical adverse impact (increased mortality) in a blinded, randomized, controlled trial of beta-blockers for abdominal aneurysm (24). Nonetheless, we do not object to the current standard practice of prescribing beta-blockers for aneurysm
disease at present because the negative evidence is not yet overwhelming. A great deal of excitement was generated by a recent report by Habashi et al. (25) showing dramatic suppression of aneurysm disease by the angiotensin receptor blocker losartan in an animal model of Marfan syndrome. Clinical trials are under way to investigate this exciting potential avenue of treatment (26,27).

Investigation of other medical treatments has also been performed (23). The antibiotic doxycycline, a matrix metalloproteinase (MMP) inhibitor, has been tested in large-scale clinical trials in abdominal aneurysm patients and shows promise (28,29). Other drugs that hold theoretical promise and have undergone some animal or clinical testing include anti-inflammatory agents (cyclooxygenase inhibitors), statin drugs, immunosuppressants (rapamycin), and angiotensin receptor blockers (losartan) (30,31). None are of proven clinical benefit at this time.

Our findings (see the following text) that acute exertion and emotion can precipitate the onset of acute aortic dissection have led to lifestyle alterations as part of the medical management of aortic aneurysms. In susceptible patients with known chronic aortic enlargement, we advise against heavy weight lifting (32–34) and insist on a job change when heavy lifting is involved. We advise susceptible patients to seek attention when severely emotional personal or family situations arise, so that sedative medications can be prescribed to prevent massive blood pressure spikes. Our findings that acute exertion and emotion often underlie the onset of acute aortic dissection constitute another reasonable rationale for beta-blocker therapy, with the intent of blunting pressure spikes.

Thoracic Aortic Aneurysm Is a Genetic Disease

Marfan syndrome, based on any of a large number of mutations on the fibrillin gene, is a well-known cause of aortic dissection. Patients with Marfan syndrome, if denied surgical intervention, run a 50% risk of the development of aortic dissection during their lifetime. Marfan syndrome accounts for approximately 5% of all cases of aortic dissection.

The genetics of Marfan syndrome have been elucidated for decades. However, Marfan disease explains only approximately 5% of known thoracic aortic aneurysms. The question arises whether genetic abnormalities explain some of the remaining 95% of patients with thoracic aortic aneurysm. The answer is a resounding “yes.”

The Yale database has allowed us to recognize that many patients with aortic dissection do not fit any acknowledged syndrome of collagen vascular disease. In fact, Marfan syndrome and the other named syndromes account for only the “tip of the iceberg” of thoracic aortic aneurysm and dissection. Our studies have indicated a strong genetic component in patients with thoracic aortic aneurysm and dissection among those patients without Marfan syndrome.

Our construction of nearly 500 family trees of patients with thoracic aortic aneurysm or dissection has indicated that 21% of our probands have at least 1 family member with a known aneurysm somewhere in the arterial tree (35,36). The patients with positive family trees showed a higher rate of growth of their aortas and presented at an earlier age, 2 findings that strongly support the influence of an inherent genetic defect of the aortic wall. Our family trees indicate that the predominant method of inheritance is autosomal dominant, but other genetic patterns are expressed as well. The true rate of inheritance is likely much higher than 21%, as many family members may have aneurysms without being aware of their presence.

Our most recent analysis indicates that the location of the aneurysm in the proband has a strong impact on the site at which aneurysms develop in family members (36). Specifically, probands with ascending aortic aneurysm have family members with predominantly ascending aortic aneurysms (Fig. 17). However, probands with descending thoracic aneurysms most commonly have family members with abdominal aortic aneurysms. This analysis fits a concept that aneurysm disease divides itself into 2 entities at the ligamentum arteriosum: above the ligament is 1 disease and...
below the ligament is another (Fig. 18). Above the liga-
mentum, the disease is nonarteriosclerotic, in contradistinc-
tion to below, where arteriosclerosis is abundant.

Genetic Testing for Clinical Purposes Is Still Controversial

The genetics of Marfan syndrome have been fully charac-
terized; any one of hundreds of specific mutations on the 
fibrillin-1 gene can result in the Marfan phenotype. Dr. 
Diana Milewicz has done groundbreaking work on the 
genetics of aneurysm disease, identifying multiple mutations 
responsible for aortic aneurysms occurring in families 
(37–40). These mutations include thoracic aortic aneurysm 
and dissection 1 (which accounts for 20% to 30% of familial 
cases), familial aortic aneurysm 1, transforming growth 
factor-beta receptor 2 (which accounts for 5% of cases), and 
myosin heavy chain 11.

Yet, currently, Marfan syndrome is diagnosed on a clinical 
basis, and the thoracic aortic aneurysm and dissection and 
other mutations remain laboratory tools. Thoracic aortic an-
eurysm is multigenetic; consequently, no easy, comprehensive, 
full aortic genetic screen is currently generally available. Ge-
etic testing is rarely ordered clinically. Researchers in the field, 
however, are eager to accrue additional blood or sputum 
specimens for investigative purposes.

Our own group has undertaken intensive efforts aimed 
toward identifying the specific genetic aberrations that 
underlie these family transmissions of aortic disease, in the 
 hope of developing a widely sensitive genetic screening test 
for thoracic aortic aneurysm. We studied 30,000 ribonucleic 
acid (RNA) expression patterns in the blood of patients 
with thoracic aortic aneurysm and compared them with 
those of control patients. We found that a 41-single 
nucleotide polymorphism panel could discriminate quite 
well between patients with and without aneurysm from a 
blood test alone (Fig. 19) (41).

This “RNA signature” is >80% accurate in determining 
from a blood test alone whether a patient has an aneurysm. 
We hope that this may result in a screening test for family members or even for the general public. This level of 
accuracy far exceeds that of the prostate-specific antigen test 
used for prostate cancer.

In collaboration with colleagues at Celera Diagnostics in 
California, we have also performed genomewide scans for 
deoxyribonucleic acid single nucleotide polymorphisms 
associated with thoracic aortic aneurysm and dissection. We 
have studied >500 Yale patients and their spousal controls 
in this manner. Results are encouraging, with several single 
nucleotide polymorphisms strongly predicting the aneurysm 
disease. Replication studies from our European collection 
sites are currently under way.
Biomarkers for Thoracic Aortic Aneurysm May Be on the Horizon

Thoracic aortic aneurysm is a virulent, potentially lethal disease. It is also a predominantly silent disease. This combination of circumstances cries out for discovery of biomarkers for this disease—blood tests that can detect aneurysms in the general population, monitor the progress of an aneurysm, and predict complications in those patients known to be affected. We recently reviewed the nascent field of biomarkers in aortic diseases, and the cardinal messages of this review are described in the following paragraphs (42) (Table 1).

D-dimer is a byproduct of fibrin degradation and a useful biomarker in acute aortic dissection. D-dimer is 99% sensitive in the detection of acute aortic dissection (43), except perhaps in intramural hematoma. If the D-dimer is not elevated, the patient does not have aortic dissection. However, D-dimer is extremely nonspecific, being elevated in pulmonary embolism and coronary thrombosis, essentially in any state in which thrombosis and thrombolysis proceed. The extent of D-dimer elevation reflects the longitudinal extent of aortic dissection, predicts the mortality of aortic dissection, and differentiates from myocardial infarction. However, because D-dimer elevation occurs after the dissection, it is not useful as a predictor.

MMPs are known to be intimately involved in the pathogenesis of aortic aneurysm and dissection. Their use in the monitoring of aortic disease is in the earliest stages. It has been shown that MMP elevation signals recurrent blood flow in an aneurysm after endovascular therapy (44,45).

Inflammation and collagen degradation are also known to be involved in the pathogenesis of aortic aneurysms. Accordingly, inflammatory markers and indicators of collagen turnover are being investigated as potential biomarkers in aortic diseases. CD4⁺CD28⁻ T cells and elastin peptide are being investigated, in those 2 categories, respectively. Smooth muscle heavy chain myosin has also shown some promise.

We are also hopeful that our RNA signature test, which measures up- and down-regulation of aneurysm-related RNAs, may be a useful marker of aneurysm activity and prove helpful in the detection and monitoring of disease. Ideally, with this RNA panel, we would like to be able biologically to predict rupture and dissection in the long-term course of aneurysm disease (Fig. 19).

Imaging studies have advanced dramatically in depicting the aneurysmal thoracic aorta. Imaging is not enough, however. We need to be able to detect aneurysm disease in the general population. We need to be able to predict the onset of adverse events. Size alone is useful but not ideally

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**Table 1** Potential Biomarkers in Aortic Diseases (for Diagnosis and/or Monitoring)

<table>
<thead>
<tr>
<th>Indicators of ongoing thrombosis</th>
<th>D-dimer</th>
<th>Plasmin</th>
<th>Fibrinogen</th>
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<tbody>
<tr>
<td>Matrix metalloproteinases</td>
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<td>Inflammatory markers</td>
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<td>Cytokines</td>
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<td>CD4⁺CD28⁻ T cells</td>
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<tr>
<td>C-reactive protein</td>
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<tr>
<td>Markers of collagen turnover</td>
<td>Elastin peptide</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td>Endothelin</td>
<td>Hepatocyte growth factor</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Genetic markers</td>
<td>Ribonucleic acid signature</td>
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<td></td>
</tr>
</tbody>
</table>

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**Figure 19** The RNA Signature Test for Thoracic Aortic Aneurysm

In the hierarchical cluster diagram on the left (A), each vertical line represents a patient, and each horizontal line represents an RNA. In the grid (A), the green indicates underexpression and red indicates overexpression (as indicated in C). Note in the diagram on the left (A) how the overexpression and underexpression cluster, depending on phenotype. In the figure on the right (B), note that if all the greens were together and all the reds were together, the test would have been 100% accurate. As it turns out, the overall accuracy was >82%.
sufficient as a predictor. It is hoped that in the future, biomarkers will supplement size in prediction of adverse events and enhance the decision to proceed to pre-emptive surgical extirpation of the aneurysmal human aorta.

**Stent Therapy for Degenerative Aneurysms Is Burgeoning, But It May Be “The Emperor’s New Clothes”**

A complete review of the debate over the effectiveness of stent therapy for thoracic aortic aneurysm (or abdominal aneurysm) is beyond the scope of this article. However, this topic is of such profound importance in the current era that a commentary is appropriate.

Two points deserve emphasis. First, the decision to treat an aneurysm must be made with the same rigor for endovascular therapy as for open surgical therapy. We must balance the intense pressure from departments, hospitals, and industry to perform procedures and use devices with a full understanding of the disease of thoracic aortic aneurysm and a respect for the patient. Although a virulent disease, thoracic aortic aneurysm is an indolent one. As seen in Figure 20, a thoracic aortic aneurysm usually does not take a patient’s life (in asymptomatic patients) until several years after diagnosis (46). In addition, as can be seen in Figure 20, this disease takes life generally when the aneurysms are large (see the line in the graph for aneurysms ≥6 cm). The presence of a small thoracic aneurysm is not a valid indication for endovascular therapy just because stent therapy is available.

Second, the fundamental rationale of endovascular therapy for degenerative aneurysms is questionable (47). Specifically, one may question how a device inside the aorta, and not attached to the aorta, can prevent the enlargement of the aorta. Stents were designed originally to prevent atheroma from encroaching on the lumen of a vessel. In the case of an aneurysm, we are asking the stent to do the opposite: to prevent the outward expansion of the aorta. One would think that any potential restraining device would need to be placed outside, not inside, the aorta. This concern is compounded by the fact that stents for an aortic aneurysm exert a radially directed force, which would be anticipated to encourage outward enlargement of the aorta.

In fact, the generally sparse data available to date that have matured to mid-term or beyond are very discouraging in terms of the effectiveness of endovascular therapy for degenerative aneurysm. (Early “effectiveness” is meaningless because most patients would be alive at 1, 2, or 3 years, even absent any therapy at all, as demonstrated in Fig. 20.) At the recent International Aortic Symposium in Liege, Belgium (48), where the latest midterm data on abdominal aortic aneurysms were presented, the conclusion was frankly that endovascular therapy is not effective, in essence representing “sham” therapy (low risk, no benefit). This was based on data from 3 studies (representing the best scientific evidence available):

1. **EVAR-2 (Endovascular Aneurysm Repair Trial 2).** The EVAR-2 trial compared endovascular aneurysm repair (EVAR) with no specific therapy (medical therapy). The key graph (49) presented in Figure 21 shows no benefit from stent grafting compared to no therapy. (This was a trial for abdominal aortic aneurysms.) The all-cause mortality curves for EVAR and medical therapy are superimposable, as are the curves for aneurysm-related mortality. There is simply no evidence of benefit.

2. **DREAM (Dutch Randomised Endovascular Aneurysm Management).** The DREAM trial compared EVAR with traditional surgical therapy. The midterm follow-up in the DREAM trial found that at 2 years, the survival curves cross, and, from that point on, stent-treated patients have worse survival than surgically treated patients.
patients (50). (This was a trial for AAA.) That is, EVAR shows an early advantage, because surgery has some mortality, but this advantage is lost because EVAR has no durable benefit. (The graph is dramatic. It was shown at the International Aortic Symposium in Liege, Belgium [48].)

3. INSTEAD (INvestigation of STEnt Grafts in Patients With Type B Aortic Dissection). The INSTEAD trial, conducted by the noted authority Professor Neinaber in Germany, investigated stent therapy for patients doing well beyond 2 weeks after uncomplicated type B aortic dissection. The hope was that “tacking down” the dissection flap would lead to later benefit. Contrary to expectations, the INSTEAD trial found severe early mortality and complications subsequent to stent therapy. There was no survival advantage over medical therapy alone. These results were also presented in Belgium, but, as a negative study, have yet to be published.

These extremely discouraging midterm data should raise a serious flag of caution regarding endovascular therapy in the current state-of-the-art for degenerative aneurysms. To borrow a term from the lay economic press, we must avoid “irrational exuberance” in the application of endovascular therapies for degenerative aneurysms.

Further amplifying the need for caution are the recent findings that endovascular therapy exerts a serious emotional toll on patients (who experience extreme anxiety living from scan to scan, in fear of need for ancillary procedures) (51) and that the radiation burden from frequent repeated scans for surveillance of unreliable stents is worrisome (52). The enthusiasm for endovascular therapy must be balanced as well against the tremendous advances in open therapy for thoracic aortic aneurysm, which have set a very high standard of safety and effectiveness for endovascular therapies to surpass or even to equal (53,54).

The Date and Time That Acute Aortic Dissection Occurs Is Not Random

How does aortic dissection pick a specific time to occur? How is it that dissection picks January 4, 2009, at 5:03 PM (the moment that this sentence is being written) to occur? The authors formerly believed that the occurrence of dissection in a susceptible patient was random. They do not think so any longer.

It is interesting that aortic dissection has long been known to occur in circadian and diurnal patterns, with a preponderance of instances in the winter months and in the early morning hours. The reasons behind these patterns are unknown, but these characteristics correlate with the season and time of day when blood pressure is known to be highest.

Studies at Yale have added another interesting dimension to our understanding of the timing of aortic dissection in susceptible individuals. Specifically, we have found that extreme exertion or emotion may precipitate acute aortic dissection (55).

Let us presume that a patient is rendered susceptible to aortic dissection due to his genetic makeup and then consider what factors or forces might precipitate dissection at 1 particular moment in time.

A few years ago, we noticed a cluster of healthy young weight lifters who had presented to Yale with acute ascending aortic dissection and required urgent surgery. We reported this cluster in JAMA (33). We did a biomechanical study on ourselves and found that, during severe weight lifting, we reached blood pressures approaching or exceeding 300 mm Hg (Fig. 22) (32). These are levels of hypertension simply not seen in any type of cardiac care, be it in the coronary care unit or in the cardiothoracic surgical unit. We hypothesized that extreme elevation of blood pressure during lifting was a factor in the cluster of dissections that we had treated in weight lifters. After publication of our original report, we received cases from around the country. We did a follow-up report enumerating 31 similar cases of acute aortic dissection in the setting of weight lifting or severe straining activity (34). Nearly all these dissections occurred in young men with previously unknown moderate aortic enlargement (4 to 5 cm). Based on this evidence, we recommended routine screening of all athletes embarking on weight lifting or other heavy athletic activity. We saw this as the only means to protect these young athletes from needless death. It is interesting and reassuring that the Olympic Committee now requires an echocardiogram for every athlete competing in the Olympics. We would like to see this prescription extended to college and high school athletes.

We subsequently did another study in which we contacted each patient or family member whom we had treated for acute aortic dissection at Yale University. This investigation implicated emotion as well as exertion as an etiologic factor in the acute onset of aortic dissection. Specifically, we found that a majority of patients could recall a specific episode of severe emotional upset (notification of a cancer
diagnosis, losses at the casino, or illness in a loved one) or extreme exertion at the time of their dissection (Fig. 23).

These studies, looking at aneurysm and dissection from multiple viewpoints—clinical, biologic, genetic (mendelian and molecular), mechanical, epidemiologic—permit formulation of the following schema for the onset of acute aortic dissection in a specific individual at a specific time (Fig. 24).

The susceptibility to aortic aneurysm and dissection is set from birth by genetics. The aorta is destroyed over time, at least in part by excess proteolysis by the MMPs. The aorta enlarges as its wall is damaged. As the aorta enlarges, the mechanical properties deteriorate, with loss of distensibility and imposition of excess wall tension. An acute hypertensive event supervenes, usually emotional or exertional, and exceeds the tensile limit of the aortic wall, producing an acute aortic dissection.

A Silver Lining in the Cloud of Aneurysm Disease

Indeed, there is a silver lining in the cloud of thoracic aortic aneurysm disease. This silver lining is protection from arteriosclerosis in patients with ascending aortic aneurysm or dissection.

We noticed, in the course of operating on patients with ascending aortic aneurysm and dissection, that their arteries tended to be arteriosclerosis free. Specifically, the femoral arteries, which are cannulated for cardiopulmonary bypass, are usually soft and pliable, without any arteriosclerotic plaque or even a fatty streak. These are generally pristine arteries, like those of a teenager, despite the patient’s age.

We followed up by analyzing the total body arterial calcium score in patients with and without ascending aortic aneurysm or dissection. We used calcium score as a proxy for arteriosclerosis (Fig. 25). We found that the calcium score was significantly lower in patients with ascending aortic dissection than in age- and sex-matched controls (56). Subsequent to this clinical finding, we identified in the literature molecular biological studies that corroborate that a high MMP state such as aneurysm disease would be expected to show lower arteriosclerotic burden, partly by lysis of developing plaques by the MMPs. MMPs are thought to be proaneurysmal and antiatherogenic (57,58).

Therefore, patients with ascending aortic aneurysm or dissection, although they have a virulent aneurysm disease, seem, in some measure, to be protected from the arteriosclerosis, which is the leading killer of Americans.

Advances in Diagnosis and Treatment Envisioned for the Near Future

One may fairly expect to see the following major advances in diagnosis and treatment of aortic diseases in the relatively near future.

**Figure 23** Precipitating Events for Acute Aortic Dissection

Emotional or exertional events immediately preceding the onset of the pain of acute aortic dissection. Adapted, with permission, from Hatzaras et al. (55).

Figure illustration by Rob Flewell.

**Figure 24** Conceptual Pathway Leading to Acute Aortic Dissection

Overall schematic understanding of how aortic dissection picks a specific time to occur. See “The Date and Time That Acute Aortic Dissection Occurs Is Not Random” section for details.

**Figure 25** “Silver Lining” in Ascending Aneurysm Disease: Protection From Arteriosclerosis

The total body calcium index in patients with ascending aortic aneurysms and dissection as well as in matched controls. Note that male sex (G), hypertension (HTN), smoking, dyslipidemia (Dyslip), diabetes mellitus (DM), and advanced age led to higher calcium scores, as would be expected. Note that ascending aortic dissection (Dis.) and annuloaortic ectasia (AAE) were protective against calcification. Adapted, with permission, from Achneck et al. (56).

Figure illustration by Rob Flewell.
• Population screening will be improved, first by general recognition in the medical community of the familial patterns of aortic disease and then by novel (genetic) mass screening techniques.

• Selection criteria for surgical intervention will go beyond symptoms and size. We anticipate that the following modalities may be applied:
  ○ Biomarkers that indicate impending rupture or dissection may come into play (including potential RNA expression indexes).
  ○ Mechanical properties of the aorta (distensibility and wall tension) may be assessed noninvasively and applied as intervention criteria.
  ○ Imaging modalities (including positron emission tomography) may be found to be predictive of aneurysm “activity” and guide timing of surgery.

• Stent therapies may advance to achieve truly durable results (in contradistinction to currently disappointing lack of effectiveness in preventing death or rupture). This may require paradigm shifts in the design of endovascular prostheses.

• Genetic elucidation of these diseases will advance even further, permitting enhanced understanding of the pathophysiology of aneurysm disease and improved diagnosis.
  ○ Understanding of genetic alterations resulting in aneurysms may suggest avenues to pharmacologic therapy (with conventional drugs designed to short-circuit the mechanism of aneurysm formation and progression). In particular, we look forward to seeing whether the angiotensin receptor blocker drug losartan meets its high expectations.
  ○ Understanding of genetic alterations may ultimately permit gene therapy in children or adults to prevent the development or progression of aortic diseases.

Medical science has done much to tame this virulent disease and to improve the prospects for affected patients in the 100 years since Osler’s famous quote (59) that “There is no disease more conducive to clinical humility than aneurysm of the aorta.” The current advances in genetic and molecular understanding of aneurysm disease are considerable. There is great promise that current scientific techniques will yield additional giant advances, perhaps enabling the playing field from timely surgical “plumbing” interventions (albeit challenging and thrilling) to early recognition and genetic-based prevention of thoracic aortic aneurysms and dissections.

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