Management of acute aortic dissection

Christoph A Nienaber, Rachel E Clough

A new appraisal of the management of acute aortic dissection is timely because of recent developments in diagnostic strategies (including biomarkers and imaging), endograft design, and surgical treatment, which have led to a better understanding of the epidemiology, risk factors, and molecular nature of aortic dissection. Although open surgery is the main treatment for proximal aortic repair, use of endovascular management is now established for complicated distal dissection and distal arch repair, and has recently been discussed as a pre-emptive measure to avoid late complications by inducing aortic remodelling.

Published **Online** February 6, 2015 http://dx.doi.org/10.1016/S0140-6736(14)61005-9

University Heart Centre Rostock, University of Rostock, Rostock, Germany (C A Nienaber MD); **and King's College London, Cardiovascular Imaging Department, Lambeth Wing St Thomas, London, UK** (R E Clough MD)

Correspondence to: Dr Christoph A Nienaber, Heart Centre Rostock, Department of Internal Medicine I, University of Rostock, Rostock 18055, Germany **christoph.nienaber@med.uni-rostock.de**

Introduction

Continuing demographic changes in developed countries will affect the prevalence of acute and chronic aortic disorders, and move the specialty into the focus of specialised care in dedicated aortic centres. In this Seminar, we will review improved imaging, operative, and endovascular strategies for aortic dissection, both in diagnostic and therapeutic management. Here, we focus on developments since the 2008 Seminar in *The Lancet*.[1]

Epidemiology

Hospital studies suggest an incidence of acute aortic dissection of about three cases per 100 000 per year, which is half the incidence of symptomatic aortic aneurysm.[2,3] Swedish population-based studies with high rates of post-mortem examination identified 4425 cases in 8·7 million people, giving an annual incidence of 3·4 per 100 000.[2] Studies in Olmstead County, MN, USA,[4] and Hungary[5] estimate the annual incidence of aortic dissection at between 2·9 and 3·5 per 100 000. Epidemiological studies of aortic dissection could underestimate the true incidence because data are derived from retrospective registries in specialised centres, rely on correct hospital coding, and might not include deaths before hospital admission.[6–12]

An analysis from the International Registry of Acute Aortic Dissections (IRAD) reported a mean age at presentation of 63 years and a male predominance of 65%, yielding an incidence of 16 per 100 000 in men.[6,13–15] Although women were less frequently affected (7·9 per 100 000), their outcome was worse because of delayed diagnosis and atypical symptoms.[16] A contemporary prospective population-based analysis of individual patient data showed similar age and sex distributions as earlier studies, but the incidence of acute dissection was higher (six per 100 000) compared with incidence in hospital-based reports, probably because of inclusion of deaths before hospital admission and improved diagnostic vascular imaging.[17] The selection of patients who survived successful transfer to hospital could account for lower in-hospital mortality in this study compared with population-based IRAD data.

Pathophysiology

The pathophysiology of acute aortic dissection is diverse and affected by histopathology and genetic components. Most cases develop without aneurysmal degeneration and therefore factors other than ectasia (vessel dilation) predispose to acute dissection with intimal tearing, which is commonly preceded by medial degeneration or cystic medial necrosis.[18,19] The dissection propagates in an antegrade and retrograde manner due blood flow within the aortic wall. Complications such as tamponade, aortic valve insufficiency, and malperfusion occur when the aortic side branches are involved.[20] Thrombi might form in the false lumen, indicating continuing inflammation, which might start further necrosis and apoptosis of smooth muscle cells and degeneration of elastic tissue as seen with enhanced fluorodeoxyglucose (FDG) uptake on PET scan.[21] The importance of inflammation is shown by the increased risk of rupture in patients with inflammatory disorders (polyarteritis nodosa, Takayasu's disease, Behçet's syndrome, etc), and the effect of diabetes mellitus on the pathogenesis of dissection needs further assessment.[22–24]

History and presentation

Contributing factors are diverse, and arterial hypertension and known connective tissue diseases are the most common risk factors. The most frequent presentation is sudden-onset severe chest or back pain without evidence of myocardial ischaemia. A recent history of strenuous exercise or use of drugs (such as cocaine or amphetamines) followed by severe chest or

Search strategy and selection criteria

We comprehensively searched PubMed and the Cochrane Library databases with the terms "acute", "aortic", and "dissection" for papers published in the past 5 years (last search in July 2013). The articles were categorised with relevance to epidemiology, pathophysiology, predisposing factors, classification systems, diagnostic imaging, prognostic features, biomarkers, management and immediate outcome, and follow-up. We largely selected publications from the past 3 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified with this search strategy and selected those we judged to be relevant. We gave more weight to randomised controlled trials and meta-analyses than to evidence of a lesser quality, such as case series. Review articles have been cited to provide the reader with additional details and references.

back pain is highly suggestive of acute aortic dissection; affected patients often have a sudden onset of pain that is the worst they have ever experienced, and that migrates from chest to lower back. Not infrequently, initial neurological signs coexist with the pain, ranging from transient or permanent central nervous symptoms, including syncope, to various spinal signs such as paraparesis or paraplegia. Proximal dissection is suggested by new-onset aortic regurgitation, pericardial effusion, or accompanying myocardial ischaemia.

Predisposition

Hypertension is the most prevalent risk factor for acute aortic dissection and is present in up to 75% of cases.[25] Other risk factors include smoking, direct blunt trauma, and drugs (cocaine and amphetamines).[26] A detailed analysis of deaths confirmed that poor blood pressure control was an important risk factor in acute dissection; treatment-resistant hypertension might reflect increased aortic stiffness or other pathophysiological mechanisms that lead to the development of acute aortic syndromes.[1,5,17]

Panel 1: **Contributing disorders for aortic dissection**

- Long-term arterial hypertension
- Smoking
- Dyslipidaemia
- Cocaine, crack cocaine, or amphetamine use
- Connective tissue disorders
  - Hereditary disorders
    - Marfan's syndrome
    - Loeys-Dietz's syndrome
    - Ehlers-Danlos syndrome
    - Turner's syndrome
  - Hereditary vascular disease
    - Bicuspid aortic valve
    - Coarctation

Vascular inflammation

- Autoimmune disorders
  - Giant-cell arteritis
  - Takayasu's arteritis
  - Behçet's disease
  - Ormond's disease
- Infection
  - Syphilis
  - Tuberculosis

Deceleration trauma

- Car accident
- Fall from height

Iatrogenic factors

- Catheter or instrument intervention
- Valvular or aortic surgery
  - Side-clamping, cross-clamping, or aortotomy
  - Graft anastomosis
  - Patch aortoplasty

Improved primary prevention, particularly aggressive management of hypertension and smoking cessation, might reduce the incidence of aortic dissection, but resistant hypertension is a challenge. Circadian variations and seasonal frequency variations for aortic dissection have been recorded, with incidence peaking in the morning during winter.[6,13] The most common causes of traumatic aortic dissection or rupture are traffic accidents or deceleration trauma.[27] Panel 1 lists the most common contributing disorders for aortic dissection.

Genetic risk

Hereditary traits linked to aortic syndromes are usually autosomal dominant and affect younger patients (table). About 20% of cases are associated with a genetic disorder resulting in altered connective tissues (Marfan's syndrome, Turner's syndrome, type 4 Ehlers-Danlos syndrome), smooth muscle contraction, or pathological cell signalling (Loeys-Dietz's syndrome). In Marfan's and Loeys-Dietz's syndromes, common mutations are located in either the fibrillin gene (*FBN1*) or the TGF-β receptor 2 gene (*TGFBR2*) respectively. Both these syndromes often present with aortic dissection or aneurysm.[28,29] S100A12 protein is significantly upregulated in human type A aortic dissection, and *SMAD3* locus frameshift mutation causes 2% of familial thoracic aortic dissection.[30,31] The most common non-syndromic

	Function	Clinical manifestation (OMIM number)
Ascending aorta		
FBN1	Microfibrils, elastogenesis, TGF-β bioavailability, and smooth muscle cell phenotype	Marfan's syndrome (154700)
EFEMP2	Fibulin 4, elastic fibres	Cutis laxa autosomal recessive IIA (219200)
Thoracic aorta		
FBN1	Microfibrils, elastogenesis, TGF-β bioavailability	Marfan's syndrome (154700)
TGFBR1, TGFBR2, TGFB	Signalling domain of TGF-β receptor	Loeys-Dietz syndrome (609192)
MYH11	Smooth muscle cell contraction	Familial thoracic aortic aneurysm with patent ductus arteriosus (132900)
ACTA2	Smooth muscle cell contraction	Familial thoracic aortic aneurysm (611788)
COL3A1	Type III collagen, altered extracellular matrix fibres	Ehlers-Danlos vascular type IV (130050)
Aorta and other arteries		
SLC2A10	Decreased GLUT10 protein in TGF-β pathway	Arterial tortuosity syndrome
Aorta		
SMAD3	Impaired TFG-β signal transmission	Syndromic form of aortic aneurysm and dissection

OMIM=Online Mendelian Inheritance in Man.

Table: **Monogenic disorders that cause acute aortic dissection by site and gene**

mutation associated with aortic dissection is located on *ACTA2*, the smooth muscle cell actin gene. The association between mutations in genes encoding the contractile apparatus of vascular smooth muscle cell and aortic dissection suggests that smooth muscle cell tone and function have an important role in the response of the aortic wall to stress. Furthermore, both annulo-aortic ectasia and bicuspid aortic valve have a genetic basis and are known to predispose to aortic dissection.[24]

Classification systems

Investigators have classified aortic dissection temporally and in terms of anatomical location. Temporally, acute dissection is defined as within 2 weeks of symptom onset and chronic dissection as longer than 2 weeks. This classification was based on survival estimates of patients treated in the 1950s. Many patients present with complications beyond 2 weeks and so this definition has been revised recently.[32] The new classification system by Booher and colleagues[33] has four time domains: hyperacute (<24 h), acute (2–7 days), sub-acute (8–30 days), and chronic (>30 days).

Anatomically, acute aortic dissection can be classified according to the site of the intimal tear or the part of the aorta affected irrespective of the position of tear. Anatomic classification using the DeBakey and Stanford systems drives decisions about surgical and non-surgical management (figure 1). For the purposes of classification, the ascending aorta refers to the part of the aorta proximal to the brachiocephalic artery and the descending aorta refers to the aorta distal to the left subclavian artery. The DeBakey classification system categorises dissections on the basis of the origin of the intimal tear and the extent of the dissection, and the Stanford system divides dissections according to whether the ascending aorta is involved (type A) or not (type B) involved (panel 2). PENN ABC is a more recent classification for distal dissection that focuses on the evolution of complications in type B aortic dissection. It is a simple clinical framework to describe previously unrecognised signs of complications that can indicate high risk of mortality so that the individual risk of a given patient can be accurately assessed.[34]

The DISSECT system is a mnemonic-based classification system designed to divide patients into subsets according to anatomical involvement, with relevance for endovascular management.[35] This approach addresses previously omitted elements such as location of primary entry tear, clinical symptoms, and false lumen patency. The DISSECT mnemonic communicates fundamental anatomical and clinical features to select between medical management, open surgical repair, or endovascular interventions.[36] The classification has six elements: duration of dissection (D) less than 2 weeks, 2 weeks to 3 months, and more than 3 months from initial symptoms; intimal tear location (I) in the ascending aorta, arch, descending, abdominal, or unknown; size of the aorta (S); segmental extent (SE); clinical complications (C) such as aortic valve compromise, tamponade, rupture, and branch malperfusion; and thrombosis (T) of the false lumen and the extent.

On first impression, DISSECT can seem complex and unwieldy; nonetheless, it considers all major prognostic elements.[37] The duration of dissection might need revision to capture the plasticity of the aorta (for about 90 days after dissection) and its ability to remodel after endovascular treatment. In future, classification will involve functional characteristics (such as metabolic evidence of continuing inflammation), and haemodynamic and tissue biomechanic parameters.

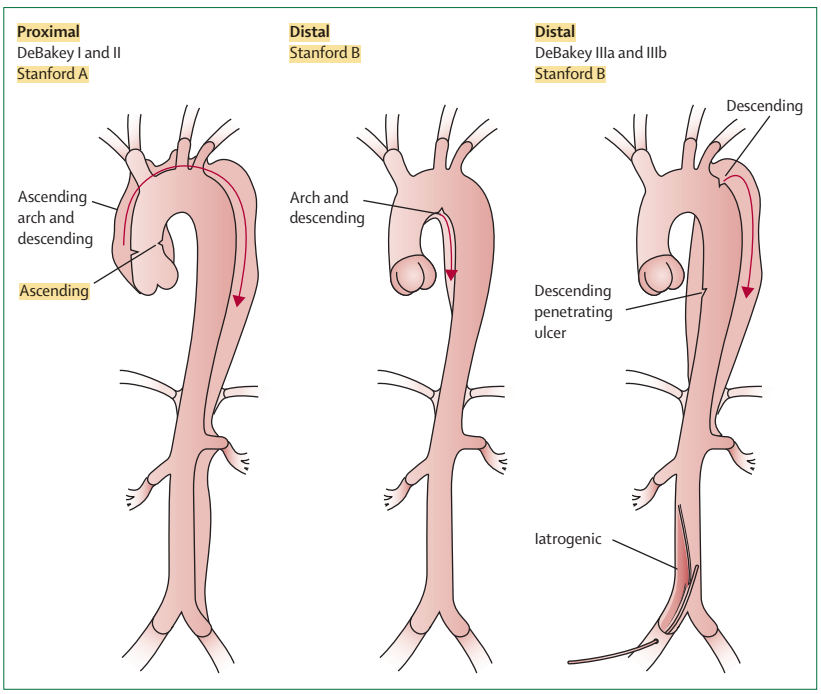

Figure 1: **Anatomical classification of aortic dissection**
Aortic dissection described by the DeBakey and Stanford classifications.

Panel 2: Traditional classification systems

DeBakey

- Category I: Dissection tear in the ascending aorta propagating distally to include at least the aortic arch and typically the descending aorta
- Category II: Dissection tear only in the ascending aorta
- Category III: Dissection tear in the descending aorta propagating most often distally
- Category IIIa: Dissection tear only in the descending thoracic aorta
- Category IIIb: Tear extending below the diaphragm

Stanford

- Type A: All dissections involving the ascending aorta irrespective of the site of tear
- Type B: All dissections that do not involve the ascending aorta; note that involvement of the aortic arch without involvement of the ascending aorta in the Stanford classification is labelled as type B

Diagnostic imaging

Imaging studies of aortic dissection have important goals, including confirmation of diagnosis, classification of the dissection, localisation of tears, and assessment of both extent of dissection and indicators of urgency (eg, pericardial, mediastinal, or pleural haemorrhage). The main diagnostic imaging modalities currently in use are CT, transthoracic echo (TTE), transoesophageal echo (TOE), and MRI. Contrast-enhanced CT angiography is mainly used because it is widely available, fast, and non-invasive.[38] It provides information about cardiac, vascular, and intrathoracic anatomy. A study of the pooled diagnostic accuracy of imaging techniques in patients with suspected thoracic aortic dissection showed a higher positive likelihood ratio for MR techniques compared with TOE and CT, although the pooled sensitivities (98–100%) and specificities (95–98%) were comparable between CT, MRI, and TOE.[39] These results indicate that all three imaging techniques yield clinically reliable results to confirm or rule out thoracic aortic dissection.

Early imaging in emergency departments

CT

Most emergency departments have a CT scanner located nearby for rapid imaging of unstable patients. Once the examination is done, prompt interpretation is mandatory to allow immediate triage decisions. Remote reading might be less expensive for 24 h cover, but on-site personnel with experience in advanced imaging are preferred. Multi-detector helical CT is used worldwide with various protocols to evaluate non-specific acute chest pain. Accordingly, the choice of an optimised CT examination should be individualised according to clinical presentation. Imaging without contrast should be used first to detect haemorrhage and haematomas because displacement of intimal calcification within the aortic lumen is a typical finding in dissection. The triple rule-out protocol has been described as the one-stop CT examination for chest pain designed to differentiate acute coronary syndrome, pulmonary embolism, and acute aortic dissection. Despite some limitations,[40] future triple rule-out protocols might have potential to reduce the time for patient triage, the number of diagnostic tests, emergency department costs, and radiation exposure to the patient.[41] Frequent diagnostic challenges for assessment of aortic dissection, especially in the ascending aorta, are motion artifacts that can mimic imaging findings suggestive of type A aortic dissection; these can be overcome by electrocardiogram (ECG)-gating. It is expected that the triple rule-out protocol will become more widely used in patients with non-specific acute chest pain because it can be done with lower radiation exposure using 128-slice dual-source CT.[42]

See Online for video

TTE

A high clinical index of suspicion after a negative result from the first diagnostic study might warrant subsequent imaging. In haemodynamically unstable patients, TTE is favoured because it is portable, rapid, and allows access to the patient during image acquisition. However, TTE is operator-dependent and has limitations imposed by the narrow acoustic window and overlying lungs, which obstruct views to the proximal ascending aorta and arch and result in poor image quality. Focused cardiac ultrasound (FOCUS) compared with comprehensive ultrasound protocols can be useful for time-sensitive assessment and can evaluate aortic root size, valvular function, and the presence of a dissection.[43,44]

TOE

TOE offers more complete imaging of the aorta than does TTE, and has improved image quality and spatial resolution for better assessment of the primary entry tear, secondary communications, and true lumen compression. These parameters, as well as dynamic colour flow pattern and flap movement, can have prognostic implications. The ultrasound probe can be left in place for intraprocedural monitoring.

MRI

MRI can combine anatomical and functional information in one examination and provide comprehensive evaluation of aortic dissection. Contrast-enhanced MR angiography (CE-MRA) is commonly used to evaluate the aorta before and after treatment and has short scan time and high tissue contrast. Gadolinium-based contrast agents are preferred because they are less nephrotoxic than iodinated agents used with CTA. Adverse reactions such as nephrogenic systemic fibrosis occur very rarely. Time-resolved MR angiography (MRA) provides additional information and includes images to assess flow dynamics. Rapid acquisition of MRA sequences allows sequential visualisation of true and false lumen, and can be synchronised with the ECG. Although image acceleration techniques have improved MR scan times, MRI is typically slower than CT imaging. With better availability, MRI will be more widely used.

Predictors of outcome

Signs

Recurrent pain or refractory hypertension are signs of extending dissection or impending rupture.[45] Multiple logistic regression analysis of IRAD data showed that refractory pain or hypertension was an independent predictor of in-hospital mortality (odds ratio [OR] 3·3). Age of 70 years or older (OR 5·1) and absence of chest pain on admission (OR 3·5) were also predictors of death, with aortic rupture as the most common cause. Advances in imaging might provide incremental information to identify patients at high risk of adverse events and help to select patients for more aggressive treatment (figure 2, video).[46]

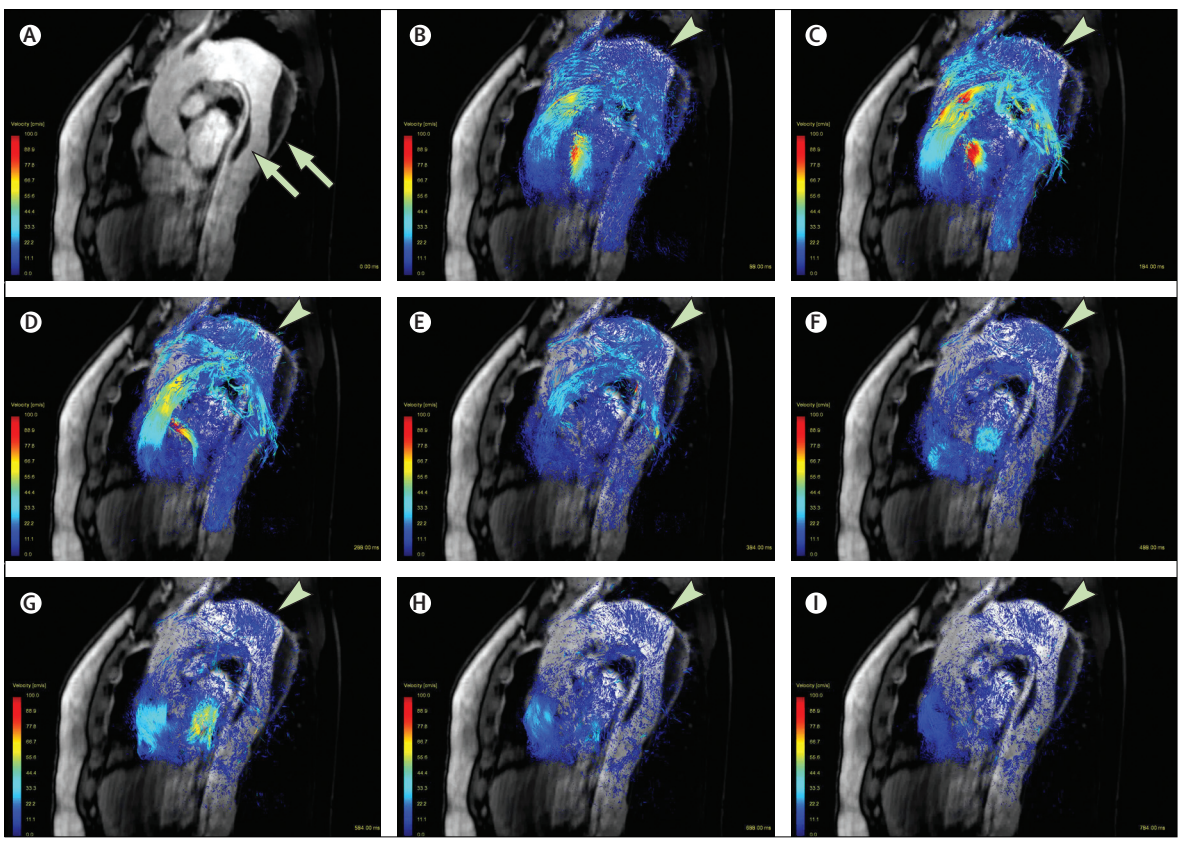

Figure 2: **Morphological and 4D functional MRI**
MRI combining anatomical and functional information. The anatomical image (A) shows dissection of the descending thoracic aorta, with areas of false lumen thrombosis defined (arrows). (B) to (I) show 4D phase contrast images from sequential phases of the cardiac cycle, in the same patient and as in (A). Helical flow (flow perpendicular to the predominant direction of flow) is seen in the false lumen (arrow heads), which has been suggested as a marker of accelerated false lumen aneurysm formation (video).

Anatomy

IRAD revealed that complications of dissection are more common in patients with an aortic diameter of 5·5 cm or greater; these patients have about a four times greater in-hospital mortality than those with a diameter smaller than 5·5 cm.[47,48] Moreover, a false lumen diameter of 22 mm or larger on initial CT imaging predicts aneurysm formation with 100% sensitivity and 76% specificity;[49] true lumen compression is related to poor clinical outcome.[50,51] True lumen dimensions are difficult to assess because they change with the cardiac cycle and depend on tortuosity, spiral flap distribution, and intimal flap mobility. Multiple false lumens are an independent predictor of aortic-related death (hazard ratio [HR] 5·6).[52] Hybrid imaging techniques such as PET combined with CT (PET-CT) identify local inflammation in the aortic wall, another potential identifier of instability and poor outcome.[53]

The status of the false lumen is important because patients with complete thrombosis have good outcomes, whereas those with a patent false lumen have an increased risk of aortic expansion and death; patency of the false lumen and age older than 70 years have been shown to predict late mortality.[54,55] Regression analysis showed that independent risk factors for partial false lumen thrombosis were visceral branches arising from the false lumen (OR 10·1), re-entry tears (30·7), and the maximum diameter of the abdominal aortic false lumen (1·3).[56] Partial thrombosis of the false lumen predicted post-discharge mortality (relative risk 4·0) either through increases in intraluminal pressure by occlusion of outflow or via local inflammation.[56,57] Poor contrast in the false lumen might be due to low flow rather than thrombus. An MRI technique has been developed to provide flow-independent assessment of false lumen thrombus volume using a blood-pool agent.[58]

Haemodynamics

The haemodynamic implications of a patent false lumen cannot be directly measured with morphological imaging; thus, dynamic variables such as flow pattern in the true and false lumens assessed with use of echocardiography or MRI can have prognostic value. MRI enables comprehensive evaluation of flow in both lumens and through entry tears using 4D-phase contrast imaging. Preliminary results suggest that these methods can identify patients at risk of aortic

expansion.[59] Similarly, assessment of intra-aortic flow with ultrasound showed that patients with an entry tear of 10 mm or more in diameter had a higher incidence of dissection-related events than had those with an entry tear less than 10 mm (HR 5·8); this measure had a sensitivity of 85% and a specificity of 87% for prediction of aortic complications during follow-up.[60] The median aortic growth rate in patients with an entry tear of 10 mm or more was significantly higher than in patients with an entry tear smaller than 10 mm. Phantom studies (bench-top flow phantoms) have shown that the larger the intimal tear (in the proximal aorta), the greater the tendency for true lumen collapse;[61] similarly, systolic pressure was lower in the false lumen with decreases in tear size in computational models.[62–64] The number of entry tears connecting true and false lumens might also have a role,[65] with aortic expansion occurring earliest in patients with a single communication less than 5 cm away from the left subclavian artery.

Biomarkers

D-dimer and fibrin degradation products

Dissection is a disease of the aortic medial layer; thus the search is continuing for biomarkers that will show injury to vascular smooth muscle (smooth muscle myosin), vascular interstitium (calponin), elastic laminae (soluble elastin fragments) of the aorta, and exposure of blood to non-intimal vascular surfaces (D-dimer). At present, only D-dimer has a clinically relevant role in the setting of suspected aortic dissection.[66] D-dimer is a fibrin degradation product, generated after fibrinolysis of a thrombus. Assays and cutoff levels can be used to evaluate pulmonary embolism and acute aortic dissection with a cutoff value of 0·5 µg/mL compared with controls. D-dimer has a sensitivity of 97% and a specificity of 47%, implying that a negative D-dimer test can probably exclude the diagnosis of acute dissection.[66] D-dimer analysis has sufficient predictive value to guide the need for further imaging. Lower concentrations are present in patients with a thrombosed false lumen, shorter dissection lengths, and those of younger age.[67]

Fibrin degradation products can be assayed rapidly and inexpensively and might therefore be a useful marker in acute aortic dissection.[68] Concentrations of fibrin degradation products are significantly higher in acute aortic dissection compared with acute coronary syndromes, and are highly predictive of acute dissection with sensitivity of 98% and specificity of 54% at a cutoff value of 2·05 µg/mL and a negative predictive value of 97%.[68] Analysis also showed that increased concentrations of fibrin degradation products were highly predictive of partial thrombosis of the false lumen (complete thrombosis and patency did not show a similar effect). Concentrations of fibrin degradation products correlate with tenascin C concentrations in the acute phase of aortic dissection.[69]

Smooth muscle myosin heavy chain

Smooth muscle myosin is a major component of smooth muscle. In acute dissection, investigators noted peak concentrations at initial testing with a rapid reduction in the first 24 h, whereas patients with acute coronary syndromes did not have any increase in smooth muscle myosin heavy chain.[70] The titres were higher in proximal compared with distal dissection, which may show differential expression of the protein along the aorta.

Matrix metalloproteinase-9

Matrix metalloproteinases are a group of important extracellular matrix enzymes involved in the balance between synthesis and degradation of the aortic wall. Particularly, subunit matrix metalloproteinase-9 (MMP-9) is raised in aortic dissection. MMP-9 released from angiotensin II-stimulated neutrophils initiates acute aortic dissection in the preconditioned aorta.[71] Raised concentrations of MMP-9 occur within 1 h from onset of symptoms in patients with type A and B aortic dissection, and in type B dissection stay increased until 2 months of follow-up, suggesting that MMP-9 is also involved in vascular remodelling.[72] Matrix metalloproteinases might be useful not only for rapid detection but also for long-term follow-up.

Elastin degradation products

Elastin lamellar disruption is a major pathological feature in acute aortic dissection and elastin degradation products are released into the circulation at the time of presentation. With a cut-off point for positivity of three standard deviations higher than the mean in healthy individuals, the positive predictive value is 94% and negative predictive value is 98%.[73] Soluble elastin fragment concentrations remained raised for up to 72 h after presentation.

Calponin

Calponin is a troponin counterpart of smooth muscle. Concentrations of calponin in the blood are increased in both proximal and distal aortic dissection, with a negative predictive value of 84% in the first 24 h.[74] Its positive predictive value is poor, so this biomarker might be useful as part of a biomarker array at presentation but further development is needed.

Transforming growth factor-beta (TGFβ)

Transforming growth factor-beta (TGFβ) concentrations are raised in patients with acute aortic dissection.[75] TGFβ might be a surrogate biomarker to assess aortic expansion after dissection and could therefore be used to predict the risk of rupture and the need for repair. Findings that inhibitors of the renin-angiotensin system can act directly on dysregulation of TGFβ to affect aortic remodelling have led to new possibilities for treatment.[76,77]

Management and outcomes

Acute dissection involving the ascending aorta needs swift open surgical repair, although in some cases, hybrid approaches or endovascular interventions can be used.[35] Conversely, acute dissection confined to the descending aorta is treated medically unless complicated by organ or limb malperfusion, progressive dissection, extra-aortic blood collection (impending rupture), intractable pain, uncontrolled hypertension, or early false lumen expansion (figure 3).[24,49,60,78] The distinction between complicated and uncomplicated dissection is becoming blurred as understanding of the nature of dissection improves, and pre-emptive endovascular treatment in distal dissection is emerging as a way to prevent late complications.[79]

The highest mortality from aortic dissection occurs in the first 48 h after symptom onset; therefore, immediate diagnosis is lifesaving. The annual incidences for acute aortic dissection is low: 440 per 100 000 for acute coronary syndrome, 69 per 100 000 for pulmonary embolism, and three to four per 100 000 for acute aortic dissection.[80,81] This low incidence explains the delayed diagnosis; only 39% of patients are diagnosed by 24 h after symptom onset.[82] Variables associated with delay included female sex (HR 1·73), transfer from a primary hospital (3·3), fever (5·1), and a normal blood pressure (2·45).[83] Time from diagnosis to treatment was significantly associated with non-white race (2·25) and history of previous cardiac surgery (2·81). Imaging every patient with symptoms would be prohibitive, but selective prompt use of imaging can be lifesaving. A risk score derived from the recent guidelines is highly sensitive (96%) for the detection of aortic dissection at initial presentation.[46]

Initial management of acute dissection aims to limit propagation by control of blood pressure and reductions in the change in pressure over time (dP/dt), ideally in intensive care units. Reduction of pulse pressure to maintain sufficient end-organ perfusion is a priority; intravenous β-blockade is the first-line treatment. Labetalol, with both α-blockade and β-blockade, lowers both blood pressure and dP/dt, and opiate analgesia attenuates sympathetic release of catecholamines. Drugs should be adjusted to achieve a systolic pressure of 100–120 mm Hg and a heart rate of 60–80 beats per min, which often needs a polydrug approach.[84,85] Further management (open surgical or endovascular intervention) depends on the site of the tear, evidence of complications (persisting pain, organ malperfusion, etc), and disease progression on serial imaging.

Patients with acute type A dissection who do not receive treatment die at a rate of 1–2% per h during the first day and almost half die by 1 week.[80] Death is caused by proximal or distal extension of dissection, valvular dysfunction, pericardial tamponade, arch vessel occlusion causing stroke, visceral ischaemia, or rupture

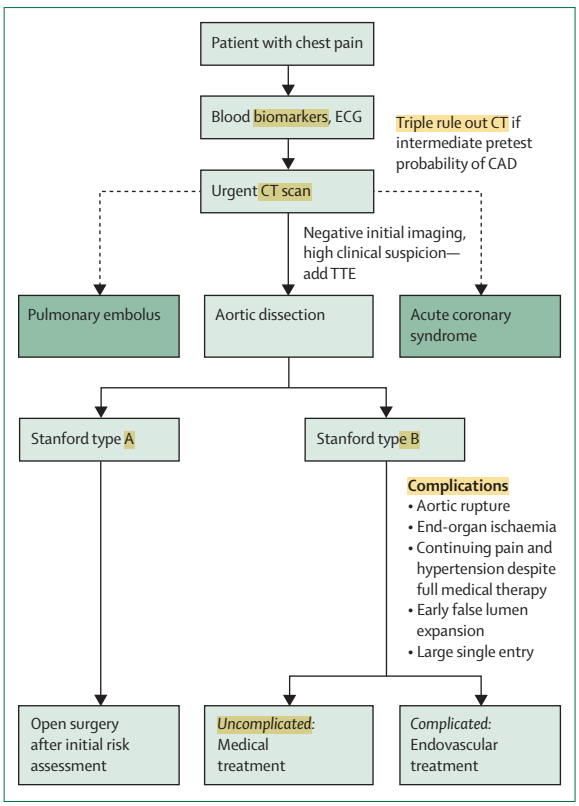

Figure 3: **Management flow chart for aortic dissection**
ECG=electrocardiogram. TTE=transthoracic echocardiogram. CAD=coronary artery disease.

resulting in a mortality of about 20% on day 1 and 30% in 48 h. Swift surgical treatment aims to remove the entry into the false lumen and reconstitute the aortic true lumen with a synthetic interposition graft with or without reimplantation of the coronary arteries. In addition, restoration of aortic valve competence by valve-sparing techniques is important; this is often done by re-suspension of native valve and is preferred to replacement.[24,86,87] Operative 30-day mortality for ascending aortic dissections at experienced centres (involving selective cerebral vessel perfusion) is between 10% and 35%.[15,87,88] In a propensity-matched retrospective analysis, survival rates in patients with acute type A dissection were 91% (SD 2) after 30 days, 74% (3) after 1 year, and 63% (3) after 5 years.[15] Thus, early open surgery is advocated and offers a durable solution. Recently, endovascular treatment for type A dissection has been reported in some patients; this approach should not be considered current standard management and has unique anatomical restrictions.[89] Nevertheless, 32–50% of patients undergoing open repair of the ascending aorta would be anatomically suitable for endovascular repair.[90,91]

Endovascular repair for dissection of the descending thoracic aorta was introduced in 1999 and is now established because of the excess mortality of open

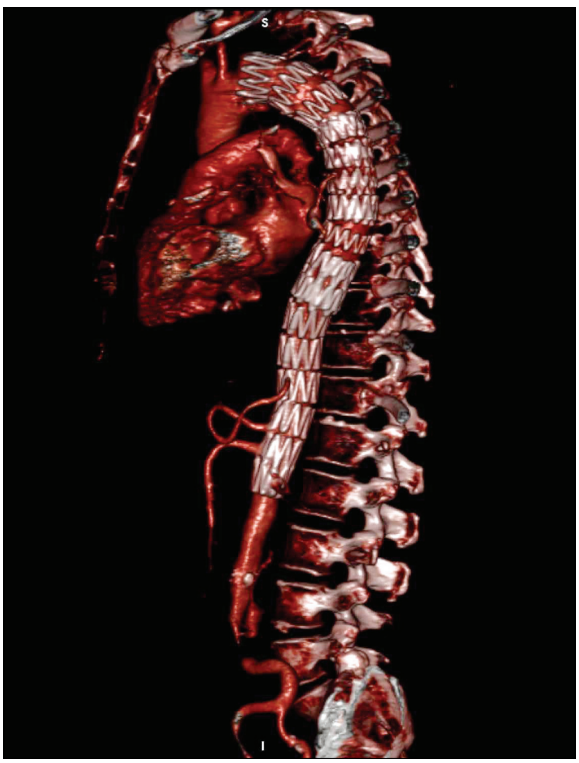

Figure 4: **Follow-up after thoracic endovascular aneurysm repair for type B dissection showing aortic remodelling**
Reconstruction of a CT angiogram showing a completely reconstructed and remodelled thoracic and abdominal aorta 3 years after type B dissection given thoracic endovascular aneurysm repair with distal bare stent extension in the subacute phase. Note the reabsorption of any residual false lumen and the unobstructed side branches of the abdominal aorta.

repair.[14,92] Open surgical repair requires single-lung ventilation, left heart bypass, profound hypothermia, and cerebrospinal fluid drainage and has been replaced by endovascular repair with a grade IA recommendation.[21,93,94] In patients with malperfusion, outcomes with open surgery were unpredictable and the risk of irreversible spinal cord injury and death ranged from 14–67%.[80,95] In-hospital mortality rates are 17% with open surgery, supporting the need for a shift towards endovascular management as first-line treatment in patients with complicated type B dissection (figure 4).[80,96,97] If malperfusion of a branch vessel persists, then branch vessel stenting or the PETTICOAT (provisional extension to induce complete attachment) technique can be used with open bare-metal stents to correct residual distal malperfusion.[98,99] The 30-day mortality point-estimate of 10·8% for endovascular treatment of complicated dissection with rupture and end-organ ischaemia is similar to the mortality in medically treated uncomplicated patients.[100] Complications of endovascular repair include peri-intervention stroke and retrograde dissection.[101,102] A meta-analysis of outcomes for endovascular treatment of acute type B aortic dissections reported an in-hospital mortality of 9·0% and a low rate of major complications (stroke 3·1%, paraplegia 1·9%, conversion to type A dissection 2·0%, bowel infarction 0·9%, and major amputation 0·2%); aortic rupture occurred in 0·8% of patients over 20 months. The authors concluded that endovascular treatment of (complicated) acute type B dissection is a therapeutic option with favourable initial outcomes; long-term data for outcome and remodelling are awaited.[88,102] Results from observational studies suggest that thoracic endovascular aortic repair (TEVAR) improves survival in complicated distal dissection.[97] In patients with connective tissue disease, remodelling is less successful and endovascular strategies are discouraged.[103–105]

According to findings from large registries, in-hospital mortality is 32% for individuals treated with surgery, 7% for those managed with endovascular techniques, and 10% for those treated by medical management alone ($p<0·0001$).[2,80,106,107] About 60% of late deaths beyond 5 years result from rupture of the false lumen, and long-term false lumen patency often leads to aneurysmal aortic dilatation. Previously accepted indications for surgical intervention, such as refractory pain, malperfusion, expansion more than 1 cm per year, and a diameter of 5·5 cm or more, are now indications for TEVAR in chronic type B dissections. There is clear observational evidence that depressurisation and shrinkage of the false lumen are beneficial, and placement of the stent-graft to cover the primary tear promotes false lumen thrombosis and remodelling of dissected aorta. Although not standard care for retrograde dissection and arch pathology, TEVAR has been used to treat retrograde extension into the ascending aorta because coverage of the entry site is needed to induce remodelling and healing.

2-year data from the INSTEAD trial showed no difference in all-cause mortality between patients treated with best medical therapy plus stent-graft and those treated with best medical therapy alone.[108,109] However, long-term outcome data support endovascular scaffolding (with stent-graft) for initially uncomplicated type B dissection due to prevention of late complications and cardiovascular death;[79] pre-emptive TEVAR, if provided at very low risk, is increasingly being used for initially uncomplicated dissection.[110–112] At 5-year follow-up for INSTEAD-XL, aortic rupture, progression of disease, and vascular mortality was tempered by pre-emptive TEVAR in the subacute phase of dissection (figure 5).[79] The pre-emptive concept is supported by a meta-analysis and two retrospective registries;[110–112] in particular, observations from IRAD corroborate the late advantage of TEVAR beyond 3 years of follow-up.[111] Thus, in anatomically suitable patients with substantial life expectancy, pre-emptive TEVAR should be offered irrespective of clinical presentation to prevent late complications. This change from a complication-specific approach to pre-emptive TEVAR suggests that patients with

dissection should be transferred to tertiary, high-volume, aortic centres for high-quality care.[113–115]

Long-term follow-up and outlook

The 10 year survival of patients with acute dissection ranges from 30–60%.[87,116,117] Aortic dissection is a systemic problem with the entire aorta and its branches predisposed to dissection, aneurysm formation, and rupture. Systemic hypertension, older age, aortic size, and the presence of a patent false lumen are all predictors of late complications.[45,118] Therefore, anti-impulse drugs, including β blockers, are needed to minimise aortic wall stress and surveillance is necessary to detect progression, re-dissection, or aneurysm formation. Regular assessment of the entire aorta should be done after discharge from endovascular or open treatment; imaging findings of progressive diameter increase, aneurysm formation, and haemorrhage at surgical anastomoses or stent-grafted sites need prompt attention. The observation that both hypertension and aortic expansion or dissection are common after discharge justifies an aggressive follow-up strategy; even renal denervation is feasible and should be considered in some patients to lower sympathetic drive.[119] As a result of increases in scientific interest, outcomes for patients treated for acute aortic dissection have improved. However, clinical pathways of efficient streamlined care, similar to in acute coronary syndrome or stroke, have not yet been implemented. Emerging serum biomarkers might soon allow easier identification of patients with acute aortic dissection. Finally, continued enthusiasm and further technical improvement will eventually improve management of the low-incidence, high-impact disorder of acute aortic dissection.

Conclusion

With improved understanding of predisposition and genetic risk, acute aortic dissection might soon become predictable and, to some degree, preventable. The description of any given dissection can be individualised by addressing specific features rather than using simple classification systems of the past. Those features are derived from non-invasive imaging algorithms applied during diagnostic work-up in the emergency department; biomarkers will probably be used to help to select patients even sooner, but these might not be ready for routine use yet with the exception of D-dimer, which has a useful negative predictive value. Endovascular approaches are established in the management of distal dissection, particularly to prevent complications, such as malperfusion or impending rupture; at the same time, the range of latent complications is growing, including persistent hypertension and pain or inflammation. Even in clinically silent uncomplicated distal dissection, long-term data suggest survival benefit from stent-induced remodelling of dissected aorta. Eventually, patients will be best cared for in dedicated centres that provide surgical and interventional skills and offer lifelong surveillance.

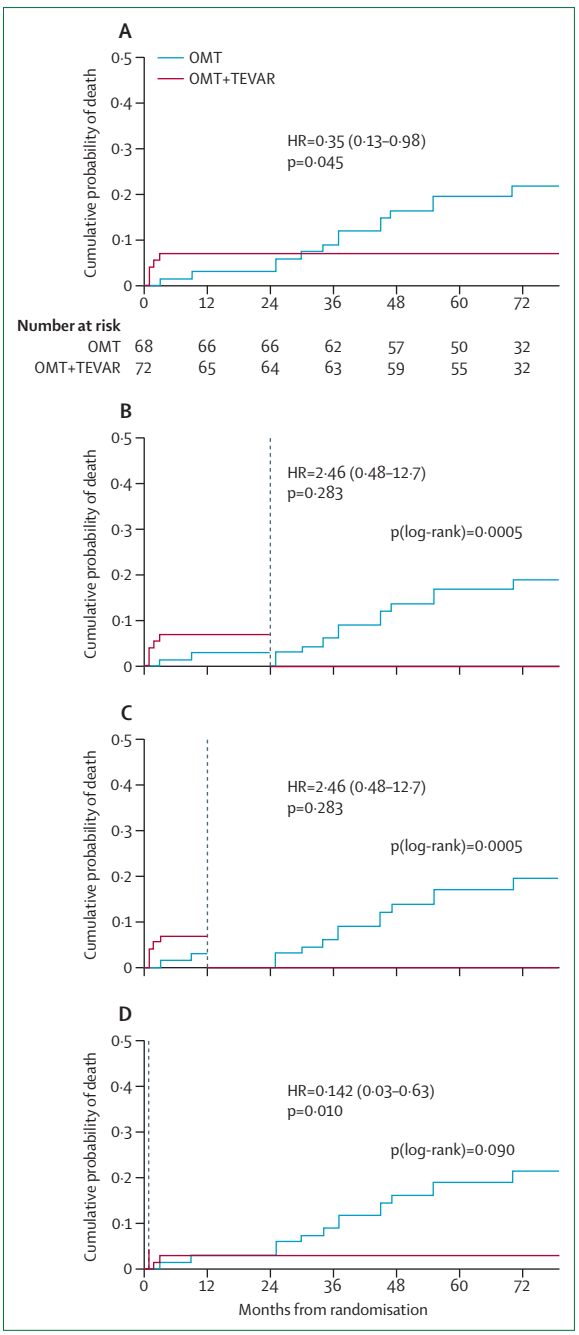

Figure 5: **Cardiovascular mortality from INSTEAD-XL trial**
Kaplan-Meier estimates of aorta-specific mortality (A) and landmark analysis with the breakpoint at 24 months (B), 12 months (C), and 1 month (D) after randomisation to the end of the trial for individuals given optimum medical therapy and those given optimum medical therapy plus thoracic endovascular aortic repair. After 2 years of follow-up, mortality was lower with thoracic endovascular aortic repair than with optimum medical therapy alone.[79,108] HR=hazard ratio. OMT=optimum medical therapy. TEVAR=thoracic endovascular aortic repair. Used with permission of Oxford University Press.

References

1 Golledge J, Eagle KA. Acute aortic dissection. *Lancet* 2008; **372:** 55–66.
2 Olsson C, Thelin S, Ståhle E, Ekbom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation* 2006; **114:** 2611–18.
3 Acosta S, Ogren M, Bengtsson H, Bergqvist D, Lindblad B, Zdanowski Z. Increasing incidence of ruptured abdominal aortic aneurysm: a population-based study. *J Vasc Surg* 2006; **44:** 237–43.
4 Clouse WD, Hallett JW Jr, Schaff HV, et al. Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture. *Mayo Clin Proc* 2004; **79:** 176–80.
5 Mészáros I, Mórocz J, Szlávi J, et al. Epidemiology and clinicopathology of aortic dissection. *Chest* 2000; **117:** 1271–78.
6 Mehta RH, Manfredini R, Hassan F, et al, for the International Registry of Acute Aortic Dissection (IRAD) Investigators. Chronobiological patterns of acute aortic dissection. *Circulation* 2002; **106:** 1110–15.
7 Collins JS, Evangelista A, Nienaber CA, et al, for the International Registry of Acute Aortic Dissection (IRAD). Differences in clinical presentation, management, and outcomes of acute type A aortic dissection in patients with and without previous cardiac surgery. *Circulation* 2004; **110** (suppl 1)**:** II237–42.
8 Suzuki T, Mehta RH, Ince H, et al, and the International Registry of Aortic Dissection. Clinical profiles and outcomes of acute type B aortic dissection in the current era: lessons from the International Registry of Aortic Dissection (IRAD). *Circulation* 2003; **108** (suppl 1)**:** II312–17.
9 Ramanath VS, Oh JK, Sundt TM 3rd, Eagle KA. Acute aortic syndromes and thoracic aortic aneurysm. *Mayo Clin Proc* 2009; **84:** 465–81.
10 Feldman M, Shah M, Elefteriades JA. Medical management of acute type A aortic dissection. *Ann Thorac Cardiovasc Surg* 2009; **15:** 286–93.
11 Thrumurthy SG, Karthikesalingam A, Patterson BO, Holt PJ, Thompson MM. The diagnosis and management of aortic dissection. *BMJ* 2012; **344:** d8290.
12 Office for National Statistics. National Population Projections. National population projections by age and sex for the UK and constituent countries. http://www.statistics.gov.uk/hub/population/index.html (accessed July 1, 2013).
13 Manfredini R, Boari B, Gallerani M, et al. Chronobiology of rupture and dissection of aortic aneurysms. *J Vasc Surg* 2004; **40:** 382–88.
14 Trimarchi S, Nienaber CA, Rampoldi V, et al, for the IRAD Investigators. Role and results of surgery in acute type B aortic dissection: insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 2006; **114** (suppl)**:** I357–64.
15 Tsai TT, Evangelista A, Nienaber CA, et al, and the International Registry of Acute Aortic Dissection (IRAD). Long-term survival in patients presenting with type A acute aortic dissection: insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 2006; **114** (suppl)**:** I350–56.
16 Nienaber CA, Fattori R, Mehta RH, et al, and the International Registry of Acute Aortic Dissection. Gender-related differences in acute aortic dissection. *Circulation* 2004; **109:** 3014–21.
17 Howard DP, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM, for the Oxford Vascular Study. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. *Circulation* 2013; **127:** 2031–37.
18 Roberts CS, Roberts WC. Aortic dissection with the entrance tear in the descending thoracic aorta. Analysis of 40 necropsy patients. *Ann Surg* 1991; **213:** 356–68.
19 Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. *Am J Cardiol* 1984; **53:** 849–55.
20 Nienaber CA, Powell JT. Management of acute aortic syndromes. *Eur Heart J* 2012; **33:** 26–35b.
21 Sakalihazan N, Nienaber CA, Hustinx R, et al. Tissue Inflammation (by PET imaging) and serologic Activity in the Evolution of Chronic Aortic Dissection. *Eur Heart J Cardiovasc Imaging* (in press).
22 Prakash SK, Pedroza C, Khalil YA, Milewicz DM. Diabetes and reduced risk for thoracic aortic aneurysms and dissections: a nationwide case-control study. *J Am Heart Assoc* 2012; published online April 24. DOI:10.1161/JAHA.111.000323.
23 Nienaber CA. Diabetes mellitus and thoracic aortic disease: are people with diabetes mellitus protected from acute aortic dissection? *J Am Heart Assoc* 2012; **1:** e001404.
24 Hiratzka LF, Bakris GL, Beckman JA, et al, for the American College of Cardiology Foundation, and the American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, and the American College of Radiology, and the American Stroke Association, and the Society of Cardiovascular Anesthesiologists, and the Society for Cardiovascular Angiography and Interventions, and the Society of Interventional Radiology, and the Society of Thoracic Surgeons, and the Society for Vascular Medicine. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. *Catheter Cardiovasc Interv* 2010; **76:** E43–86.
25 Baguet JP, Chavanon O, Sessa C, et al. European Society of Hypertension scientific newsletter: hypertension and aortic diseases. *J Hypertens* 2012; **30:** 440–43.
26 Cregler LL. Aortic dissection and cocaine use. *Am Heart J* 1992; **124:** 1665.
27 Richens D, Kotidis K, Neale M, Oakley C, Fails A. Rupture of the aorta following road traffic accidents in the United Kingdom 1992–1999. The results of the co-operative crash injury study. *Eur J Cardiothorac Surg* 2003; **23:** 143–48.
28 Attias D, Stheneur C, Roy C, et al. Comparison of clinical presentations and outcomes between patients with TGFBR2 and FBN1 mutations in Marfan syndrome and related disorders. *Circulation* 2009; **120:** 2541–49.
29 Nienaber CA, Von Kodolitsch Y. Therapeutic management of patients with Marfan syndrome: focus on cardiovascular involvement. *Cardiol Rev* 1999; **7:** 332 41.
30 Das D, Gawdzik J, Dellefave-Castillo L, et al. S100A12 expression in thoracic aortic aneurysm is associated with increased risk of dissection and perioperative complications. *J Am Coll Cardiol* 2012; **60:** 775–85.
31 Regalado ES, Guo DC, Villamizar C, et al, for the NHLBI GO Exome Sequencing Project. Exome sequencing identifies *SMAD3* mutations as a cause of familial thoracic aortic aneurysm and dissection with intracranial and other arterial aneurysms. *Circ Res* 2011; **109:** 680–86.
32 Steuer J, Björck M, Mayer D, Wanhainen A, Pfammatter T, Lachat M. Distinction between acute and chronic type B aortic dissection: is there a sub-acute phase? *Eur J Vasc Endovasc Surg* 2013; **45:** 627–31.
33 Booher AM, Isselbacher EM, Nienaber CA, et al. The IRAD classification system for characterizing survival after aortic dissection. *Am J Med* 2013; **126:** 730. e19–24.
34 Augoustides JG, Szeto WY, Woo EY, Andritsos M, Fairman RM, Bavaria JE. The complications of uncomplicated acute type-B dissection: the introduction of the Penn classification. *J Cardiothorac Vasc Anesth* 2012; **26:** 1139–44.
35 Liu JC, Zhang JZ, Yang J, et al. Combined interventional and surgical treatment for acute aortic type A dissection. *Int J Surg* 2008; **6:** 151–56.
36 Dake MD, Thompson M, van Sambeek M, Vermassen F, Morales JP, for the DEFINE Investigators. DISSECT: a new mnemonic-based approach to the categorization of aortic dissection. *Eur J Vasc Endovasc Surg* 2013; **46:** 175–90.
37 Clough RE, Taylor PR. A new classification system for aortic dissection. *Eur J Vasc Endovasc Surg* 2013; **46:** 191.
38 Cigarroa JE, Isselbacher EM, DeSanctis RW, Eagle KA. Diagnostic imaging in the evaluation of suspected aortic dissection. Old standards and new directions. *N Engl J Med* 1993; **328:** 35–43.
39 Shiga T, Wajima Z, Apfel CC, Inoue T, Ohe Y. Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: systematic review and meta-analysis. *Arch Intern Med* 2006; **166:** 1350–56.
40 Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *Cardiovasc Comput Tomogr* 2010; **4:** 407. e1–33.

41 Ketelsen D, Fenchel M, Thomas C, et al. Estimation of radiation exposure of retrospective gated and prospective triggered 128-slice triple-rule-out CT angiography. *Acta Radiol* 2011; **52:** 762–66.

42 Rogers IS, Banerji D, Siegel EL, et al. Usefulness of comprehensive cardiothoracic computed tomography in the evaluation of acute undifferentiated chest discomfort in the emergency department (CAPTURE). *Am J Cardiol* 2011; **107:** 643–50.

43 Shah BN, Ahmadvazir S, Pabla JS, Zacharias K, Senior R. The role of urgent transthoracic echocardiography in the evaluation of patients presenting with acute chest pain. *Eur J Emerg Med* 2012; **19:** 277–83.

44 Meredith EL, Masani ND. Echocardiography in the emergency assessment of acute aortic syndromes. *Eur J Echocardiogr* 2009; **10:** i31–39.

45 Trimarchi S, Eagle KA, Nienaber CA, et al, for the International Registry of Acute Aortic Dissection (IRAD) Investigators. Importance of refractory pain and hypertension in acute type B aortic dissection: insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 2010; **122:** 1283–89.

46 Rogers AM, Hermann LK, Booher AM, et al, for the IRAD Investigators. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the international registry of acute aortic dissection. *Circulation* 2011; **123:** 2213–18.

47 Trimarchi S, Jonker FH, Hutchison S, et al. Descending aortic diameter of 5.5 cm or greater is not an accurate predictor of acute type B aortic dissection. *J Thorac Cardiovasc Surg* 2011; **142:** e101–07.

48 Booher AM, Isselbacher EM, Nienaber CA, et al, for the International Registry of Acute Aortic Dissection (IRAD) Investigators. Ascending thoracic aorta dimension and outcomes in acute type B dissection (from the International Registry of Acute Aortic Dissection [IRAD]). *Am J Cardiol* 2011; **107:** 315–20.

49 Song JM, Kim SD, Kim JH, et al. Long-term predictors of descending aorta aneurysmal change in patients with aortic dissection. *J Am Coll Cardiol* 2007; **50:** 799–804.

50 Immer FF, Krahenbuhl E, Hagen U, et al. Large area of the false lumen favors secondary dilatation of the aorta after acute type A aortic dissection. *Circulation* 2005; **112** (I suppl)**:** 1249–52.

51 Fattouch K, Sampognaro R, Navarra E, et al. Long-term results after repair of type A acute aortic dissection according to false lumen patency. *Ann Thorac Surg* 2009; **88:** 1244–50.

52 Sueyoshi E, Nagayama H, Hayashida T, Sakamoto I, Uetani M. Comparison of outcome in aortic dissection with single false lumen versus multiple false lumens: CT assessment. *Radiology* 2013; **267:** 368–75.

53 Kato K, Nishio A, Kato N, Usami H, Fujimaki T, Murohara T. Uptake of 18F-FDG in acute aortic dissection: a determinant of unfavorable outcome. *J Nucl Med* 2010; **51:** 674–81.

54 Jonker FH, Trimarchi S, Rampoldi V, et al, and the International Registry of Acute Aortic Dissection (IRAD) Investigators. Aortic expansion after acute type B aortic dissection. *Ann Thorac Surg* 2012; **94:** 1223–29.

55 Bernard Y, Zimmermann H, Chocron S, et al. False lumen patency as a predictor of late outcome in aortic dissection. *Am J Cardiol* 2001; **87:** 1378–82.

56 Qin YL, Deng G, Li TX, Jing RW, Teng GJ. Risk factors of incomplete thrombosis in the false lumen after endovascular treatment of extensive acute type B aortic dissection. *J Vasc Surg* 2012; **56:** 1232–38.

57 Lansman SL, Hagl C, Fink D, et al. Acute type B aortic dissection: surgical therapy. *Ann Thorac Surg* 2002; **74:** S1833–35; discussion S1857–63.

58 Clough RE, Hussain T, Uribe S, et al. A new method for quantification of false lumen thrombosis in aortic dissection using magnetic resonance imaging and a blood pool contrast agent. *J Vasc Surg* 2011; **54:** 1251–58.

59 Clough RE, Waltham M, Giese D, Taylor PR, Schaeffter T. A new imaging method for assessment of aortic dissection using four-dimensional phase contrast magnetic resonance imaging. *J Vasc Surg* 2012; **55:** 914–23.

60 Evangelista A, Salas A, Ribera A, et al. Long-term outcome of aortic dissection with patent false lumen: predictive role of entry tear size and location. *Circulation* 2012; **125:** 3133–41.

61 Chung JW, Elkins C, Sakai T, et al. True-lumen collapse in aortic dissection: part I. Evaluation of causative factors in phantoms with pulsatile flow. *Radiology* 2000; **214:** 87–98.

62 Tsai TT, Schlicht MS, Khanafer K, et al. Tear size and location impacts false lumen pressure in an ex vivo model of chronic type B aortic dissection. *J Vasc Surg* 2008; **47:** 844–51.

63 Karmonik C, Bismuth J, Shah DJ, Davies MG, Purdy D, Lumsden AB. Computational study of haemodynamic effects of entry- and exit-tear coverage in a DeBakey type III aortic dissection: technical report. *Eur J Vasc Endovasc Surg* 2011; **42:** 172–77.

64 Cheng Z, Riga C, Chan J, et al. Initial findings and potential applicability of computational simulation of the aorta in acute type B dissection. *J Vasc Surg* 2013; **57** (suppl)**:** 35S–43S.

65 Tolenaar JL, van Keulen JW, Trimarchi S, et al. Number of entry tears is associated with aortic growth in type B dissections. *Ann Thorac Surg* 2013; **96:** 39–42.

66 Suzuki T, Distante A, Zizza A, et al, for the IRAD-Bio Investigators. Diagnosis of acute aortic dissection by D-dimer: the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) experience. *Circulation* 2009; **119:** 2702–07.

67 Hazui H, Nishimoto M, Hoshiga M, et al. Young adult patients with short dissection length and thrombosed false lumen without ulcer-like projections are liable to have false-negative results of D-dimer testing for acute aortic dissection based on a study of 113 cases. *Circ J* 2006; **70:** 1598–601.

68 Nagaoka K, Sadamatsu K, Yamawaki T, et al. Fibrinogen/fibrin degradation products in acute aortic dissection. *Intern Med* 2010; **49:** 1943–47.

69 Nozato T, Sato A, Hirose S, et al. Preliminary study of serum tenascin-C levels as a diagnostic or prognostic biomarker of type B acute aortic dissection. *Int J Cardiol* 2013; **168:** 4267–69.

70 Suzuki T, Katoh H, Watanabe M, et al. Novel biochemical diagnostic method for aortic dissection. Results of a prospective study using an immunoassay of smooth muscle myosin heavy chain. *Circulation* 1996; **93:** 1244–49.

71 Kurihara T, Shimizu-Hirota R, Shimoda M, et al. Neutrophil-derived matrix metalloproteinase 9 triggers acute aortic dissection. *Circulation* 2012; **126:** 3070–80.

72 Wen D, Zhou XL, Li JJ, Hui RT. Biomarkers in aortic dissection. *Clin Chim Acta* 2011; **412:** 688–95.

73 Shinohara T, Suzuki K, Okada M, et al. Soluble elastin fragments in serum are elevated in acute aortic dissection. *Arterioscler Thromb Vasc Biol* 2003; **23:** 1839–44.

74 Ranasinghe AM, Bonser RS. Biomarkers in acute aortic dissection and other aortic syndromes. *J Am Coll Cardiol* 2010; **56:** 1535–41.

75 Suzuki T, Trimarchi S, Sawaki D, et al. Circulating transforming growth factor-beta levels in acute aortic dissection. *J Am Coll Cardiol* 2011; **58:** 775.

76 Matt P, Schoenhoff F, Habashi J, et al. Circulating transforming growth factor-beta in Marfan syndrome. *Circulation* 2009; **120:** 526–32.

77 Brooke BS Habashi JP, Judge DP, et al. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med* 2008; **358:** 2787–95.

78 Tsai TT, Nienaber CA, Eagle KA. Acute aortic syndromes. *Circulation* 2005; **112:** 3802–13.

79 Nienaber CA, Kische S, Rousseau H, et al, for the INSTEAD-XL trial. Endovascular repair of type B aortic dissection: long-term results of the randomized investigation of stent grafts in aortic dissection trial. *Circ Cardiovasc Interv* 2013; **6:** 407–16.

80 Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA* 2000; **283:** 897–903.

81 Abcarian PW, Sweet JD, Watabe JT, Yoon HC. Role of a quantitative D-dimer assay in determining the need for CT angiography of acute pulmonary embolism. *AJR Am J Roentgenol* 2004; **182:** 1377–81.

82 Klompas M. Does this patient have an acute thoracic aortic dissection? *JAMA* 2002; **287:** 2262–72.

83 Harris KM, Strauss CE, Eagle KA, et al, and the International Registry of Acute Aortic Dissection (IRAD) Investigators. Correlates of delayed recognition and treatment of acute type A aortic dissection: the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 2011; **124:** 1911–18.

84 Suzuki T, Isselbacher EM, Nienaber CA, et al, for the IRAD Investigators. Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). *Am J Cardiol* 2012; **109:** 122–27.

85 Lu Q, Feng J, Zhou J, et al. Endovascular repair of ascending aortic dissection: a novel treatment option for patients judged unfit for direct surgical repair. *J Am Coll Cardiol* 2013; **61:** 1917–24.

86 Coady MA, Ikonomidis JS, Cheung AT, et al, and the American Heart Association Council on Cardiovascular Surgery and Anesthesia and Council on Peripheral Vascular Disease. Surgical management of descending thoracic aortic disease: open and endovascular approaches: a scientific statement from the American Heart Association. *Circulation* 2010; **121:** 2780–804.

87 Svensson LG, Kouchoukos NT, Miller DC, et al, and the Society of Thoracic Surgeons Endovascular Surgery Task Force. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. *Ann Thorac Surg* 2008; **85** (suppl)**:** S1–41.

88 Lai DT, Robbins RC, Mitchell RS, et al. Does profound hypothermic circulatory arrest improve survival in patients with acute type A aortic dissection? *Circulation* 2002; **106** (suppl 1)**:** I218–28.

89 Nordon IM, Hinchliffe RJ, Morgan R, Loftus IM, Jahangiri M, Thompson MM. Progress in endovascular management of type A dissection. *Eur J Vasc Endovasc Surg* 2012; **44:** 406–10.

90 Sobocinski J, O'Brien N, Maurel B, et al. Endovascular approaches to acute aortic type A dissection: a CT-based feasibility study. *Eur J Vasc Endovasc Surg* 2011; **42:** 442–47.

91 Moon MC, Greenberg RK, Morales JP, et al. Computed tomography-based anatomic characterization of proximal aortic dissection with consideration for endovascular candidacy. *J Vasc Surg* 2011; **53:** 942–49.

92 Parker JD, Golledge J. Outcome of endovascular treatment of acute type B aortic dissection. *Ann Thorac Surg* 2008; **86:** 1707–12.

93 Estrera AL, Miller CC 3rd, Huynh TT, et al. Preoperative and operative predictors of delayed neurologic deficit following repair of thoracoabdominal aortic aneurysm. *J Thorac Cardiovasc Surg* 2003; **126:** 1288–94.

94 Safi HJ, Estrera AL, Miller CC, et al. Evolution of risk for neurologic deficit after descending and thoracoabdominal aortic repair. *Ann Thorac Surg* 2005; **80:** 2173–79, discussion 2179.

95 Nienaber CA, Zannetti S, Barbieri B, Kische S, Schareck W, Rehders TC, and the INSTEAD study collaborators. Investigation of stent grafts in patients with type B Aortic Dissection: design of the INSTEAD trial--a prospective, multicenter, European randomized trial. *Am Heart J* 2005; **149:** 592–99.

96 Wilkinson DA, Patel HJ, Williams DM, Dasika NL, Deeb GM. Early open and endovascular thoracic aortic repair for complicated type B aortic dissection. *Ann Thorac Surg* 2013; **96:** 23–30.

97 Nienaber CA, Kische S, Ince H, Fattori R. Thoracic endovascular aneurysm repair for complicated type B aortic dissection. *J Vasc Surg* 2011; **54:** 1529–33.

98 Lombardi JV, Cambria RP, Nienaber CA, et al. Prospective multicenter clinical trial (STABLE) on the endovascular treatment of complicated type B aortic dissection using a composite device design. *J Vasc Surg* 2012; **55:** 629–40.e2

99 Canaud L, Patterson BO, Peach G, Hinchliffe R, Loftus I, Thompson MM. Systematic review of outcomes of combined proximal stent grafting with distal bare stenting for management of aortic dissection. *J Thorac Cardiovasc Surg* 2013; **145:** 1431–38.

100 White RA, Miller DC, Criado FJ, et al, for the Multidisciplinary Society for Vascular Surgery Outcomes Committee. Report on the results of thoracic endovascular aortic repair for acute, complicated, type B aortic dissection at 30 days and 1 year from a multidisciplinary subcommittee of the Society for Vascular Surgery Outcomes Committee. *J Vasc Surg* 2011; **53:** 1082–90.

101 Ullery BW, McGarvey M, Cheung AT, et al. Vascular distribution of stroke and its relationship to perioperative mortality and neurologic outcome after thoracic endovascular aortic repair. *J Vasc Surg* 2012; **56:** 1510–17.

102 Williams JB, Andersen ND, Bhattacharya SD, et al. Retrograde ascending aortic dissection as an early complication of thoracic endovascular aortic repair. *J Vasc Surg* 2012; **55:** 1255–62.

103 Eid-Lidt G, Gaspar J, Meléndez-Ramírez G, et al. Endovascular treatment of type B dissection in patients with Marfan syndrome: mid-term outcomes and aortic remodeling. *Catheter Cardiovasc Interv* 2013; **82:** E898–905.

104 Nordon IM, Hinchliffe RJ, Holt PJ, et al. Endovascular management of chronic aortic dissection in patients with Marfan syndrome. *J Vasc Surg* 2009; **50:** 987–91.

105 Marcheix B, Rousseau H, Bongard V, et al. Stent grafting of dissected descending aorta in patients with Marfan's syndrome: mid-term results. *JACC Cardiovasc Interv* 2008; **1:** 673–80.

106 Olsson C, Granath F, Stahle E. Family history, comorbidity and population-based case-control study. Heart 2013; **99:** 1030–33

107 Fattori R, Tsai TT, Myrmel T, et al. Complicated acute type B dissection: is surgery still the best option?: a report from the International Registry of Acute Aortic Dissection. *JACC Cardiovasc Interv* 2008; **1:** 395–402.

108 Nienaber CA, Rousseau H, Eggebrecht H, et al, and the INSTEAD Trial. Randomized comparison of strategies for type B aortic dissection: the INvestigation of STEnt Grafts in Aortic Dissection (INSTEAD) trial. *Circulation* 2009; **120:** 2519–28.

109 Ulug P, McCaslin JE, Stansby G, Powell JT. Endovascular versus conventional medical treatment for uncomplicated chronic type B aortic dissection. *Cochrane Database Syst Rev* 2012; **11:** CD006512.

110 Patterson B, Holt P, Nienaber C, Cambria R, Fairman R, Thompson M. Aortic pathology determines midterm outcome after endovascular repair of the thoracic aorta: report from the Medtronic Thoracic Endovascular Registry (MOTHER) database. *Circulation* 2013; **127:** 24–32.

111 Fattori R, Montgomery D, Lovato L, et al. Survival after endovascular therapy in patients with type B aortic dissection: a report from the International Registry of Acute Aortic Dissection (IRAD). *JACC Cardiovasc Interv* 2013; **6:** 876–82.

112 Jia X, Guo W, Li TX, et al. The results of stent graft versus medication therapy for chronic type B dissection. *J Vasc Surg* 2013; **57:** 406–14.

113 Nienaber CA. Influence and critique of the INSTEAD Trial (TEVAR versus medical treatment for uncomplicated type B aortic dissection). *Semin Vasc Surg* 2011; **24:** 167–71.

114 Clough RE, Mani K, Lyons OT, et al. Endovascular treatment of acute aortic syndrome. *J Vasc Surg* 2011; **54:** 1580–87.

115 Chikwe J, Cavallaro P, Itagaki S, Seigerman M, Diluozzo G, Adams DH. National outcomes in acute aortic dissection: influence of surgeon and institutional volume on operative mortality. *Ann Thorac Surg* 2013; **95:** 1563–69.

116 Gaul C, Dietrich W, Friedrich I, Sirch J, Erbguth FJ. Neurological symptoms in type A aortic dissections. *Stroke* 2007; **38:** 292–97.

117 Gilon D, Mehta RH, Oh JK, et al, and the International Registry of Acute Aortic Dissection Group. Characteristics and in-hospital outcomes of patients with cardiac tamponade complicating type A acute aortic dissection. *Am J Cardiol* 2009; **103:** 1029–31.

118 Akin I, Kische S, Ince H, Nienaber CA. Indication, timing and results of endovascular treatment of type B dissection. *Eur J Vasc Endovasc Surg* 2009; **37:** 289–96.

119 Divchev D, Turan G, Rehders T, Nienaber CA. Renal sympathetic denervation in patients with aortic dissection. *J Interv Cardiol* 2014; **27:** 334–39.