Cardiovascular disease is the leading cause of death in most Western societies and is increasing steadily in many developing countries. Aortic diseases constitute an emerging share of the burden. New diagnostic imaging modalities, longer life expectancy in general, longer exposure to elevated blood pressure, and the proliferation of modern noninvasive imaging modalities have all contributed to the growing awareness of acute and chronic aortic syndromes. Despite recent progress in recognition of both the epidemiological problem and diagnostic and therapeutic advances, the cardiology community and the medical community in general are far from comfortable in understanding the spectrum of aortic syndromes and defining an optimal pathway to manage aortic diseases.\(^1\)–\(^13\) This comprehensive review is organized in two parts, with a focus on the etiology, natural history, and classification (with vascular staging) of aortic wall disease in Part I and emphasis on therapeutic management and follow-up in Part II. Both parts may help to better integrate the complexities of acute aortic syndromes.

I. Etiology of Aortic Dissection

All mechanisms weakening the aorta’s media layers via micro apoplexy of the vessel wall lead to higher wall stress, which can induce aortic dilatation and aneurysm formation, eventually resulting in intramural hemorrhage, aortic dissection, or rupture (Table I).

Three major inherited connective tissue disorders are currently known to affect the arterial walls: (1) Marfan’s syndrome, (2) Ehlers-Danlos syndrome, and (3) familial forms of thoracic aneurysm and dissection.

Marfan’s Syndrome

Among hereditary diseases, Marfan’s syndrome (MFS) is the most prevalent connective tissue disorder, with an estimated incidence of 1 in 7000 and an autosomal dominant inheritance with variable penetrance. More than 100 mutations on the fibrillin-1 gene have been identified as encoding for a defective fibrillin in the extracellular matrix, which may affect the ocular, cardiovascular, skeletal, and pulmonary systems, as well as the skin and dura mater. The diagnosis of MFS is currently based on revised clinical criteria of the “Gent nosology.”\(^9\) The Gent criteria pay particular attention to genetic information like MFS in kindreds of an unequivocally affected individual. Moreover, both skeletal and cardiovascular features are major (eg, diagnostic) criteria if ≥4 of 8 typical manifestations are present. Considering, however, borderline manifestations such as the mitral-aortic-skin-skeletal (MASS) phenotype or subtle phenotypic features (“forme fruste”), the molecular analysis of suspected MFS and the delineation of criteria for differentiating other inherited conditions (genotypes) from a Marfan phenotype are attracting interest.\(^14\)–\(^20\) The clinical variety of the MFS is only partially explained by the number of mutations on the fibrillin-1 gene. Genetic heterogeneity and the involvement of a second gene (MFS2) may further add to the broad spectrum of symptoms.\(^20\)

A common denominator of all phenotypic forms of aortic wall disease is the dedifferentiation of vascular smooth muscle cells, not only with classic progression of atherosclerosis and aneurysm formation, but also from enhanced elastolysis of aortic wall components\(^21\)—as shown in a fibrillin-q–deficient animal model.\(^22\) Moreover, enhanced expression of metalloproteinases in vascular smooth muscle cells of the Marfan aorta may promote both fragmentation of medial elastic layers and elastolysis, thus initiating an activated phenotype of smooth muscle cells.\(^23\) In parallel, expression of peroxisome proliferator–activated receptor-\(\gamma\) is upregulated both in smooth muscle cells of MFS aorta and in the presence of cystic medial degeneration and correlates with clinical severity, whereas vascular smooth muscle cell apoptosis is likely to be related to progression of aortic dilatation. Thus, peroxisome proliferator–activated receptor-\(\gamma\) expression might reflect the pathogenesis of cystic medial degeneration and disease progression in the aorta of MFS and non-MFS individuals without any vascular inflammatory response.\(^24\)

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of hereditary connective tissue disorders characterized by ar-
was found in fibroblast cultures. I and III collagen or of fibrillin nor any specific fibrillopathy to that seen in MFS. However, neither abnormalities of types charide-like materials, and cystic medial degeneration similar elastolysis or loss of elastic fibers, deposits of mucopolysaccharide-like materials, and cystic medial degeneration similar to that seen in MFS. However, neither abnormalities of types I and III collagen or of fibrillin nor any specific fibrillopathy was found in fibroblast cultures.

Anulooaortic Ectasia and Familial Aortic Dissection
More than 5 mutations in the fibrillin-1 gene have now been identified in patients presenting with either sporadic or familial forms of thoracic aortic aneurysms and dissection.26,27 Histological examination of the aortic wall reveals elastolysis or loss of elastic fibers, deposits of mucopolysaccharide-like materials, and cystic medial degeneration similar to that seen in MFS. However, neither abnormalities of types I and III collagen or of fibrillin nor any specific fibrillopathy was found in fibroblast cultures.

Abdominal Aortic Aneurysms and Dissection
Careful examination of family pedigrees often reveals both involvement of the abdominal aorta and disease in proximal aortic segments, or other features suggestive of MFS or EDS. Differentiation of familial forms of abdominal aortic aneurysm/dissection from thoracic aortic aneurysms/dissection with an abdominal component is difficult considering that only one mutation within the COL3A1 gene is known.27 In fact, many candidate genes encoding for collagens, fibrillins, fibrillins, microfibril-associated glycoproteins, and matrix metalloproteinases and their inhibitors have been investigated, but no mutation has been identified. Similar pathogenetic processes have been described with coarctation28 and with the bicuspid aortic valve architecture.29

Acquired Conditions
Chronic hypertension affects the arterial wall composition, causing intimal thickening, fibrosis, calcification, and extra-cellular fatty acid deposition. In parallel, the extracellular matrix undergoes accelerated degradation, apoptosis, and elastolysis with hyalinization of collagen. Both mechanisms may eventually lead to intimal disruption, most often at the edges of plaques, as seen in coronary plaque. Intimal thickening increases, which further compromises nutrient and oxygen supply to the arterial wall. Adventitial fibrosis may obstruct vessels feeding the arterial wall as well as small intramural vasa vasorum. Both result in necrosis of smooth muscle cells and fibrosis of elastic structures of the vessel wall, which leads to stiffness and vulnerability to pulsatile forces, creating a substrate for aneurysms and dissections.28–32 In addition to chronic hypertension, smoking, dyslipidemia, and potentially the use of crack cocaine are modulating risk factors.

Inflammatory diseases can destroy the medial layers of the aortic wall and lead to weakening, expansion, and dissection of the aortic wall; autoimmune processes may affect vasa vasorum and promote nutrient deficiency of aortic wall layers.

Iatrogenic aortic dissection is usually associated with invasive retrograde catheter interventions or occurs during or much later after valve or aortic surgery.32–35 Given the morbidity and mortality rates associated with iatrogenic aortic dissection, careful assessment is strongly encouraged in patients with unexplained hemodynamic instability or malperfusion syndromes after invasive vascular procedures or surgery (Table 2).

Finally, pregnancy-related dissection is extremely rare as long as the patient is not affected by connective tissue disease. The putative association of pregnancy and acute dissection may largely be an artifact of selective reporting. Pregnancy is a common condition and may coincidentally occur only with concomitant existence of other risk factors such as hypertension and MFS. Preliminary data from the
malperfusion syndrome by dynamic or static obstruction (from coronaries to iliac arteries), tamponade, or aortic insufficiency. The arbitrary classification of acute, subacute, or chronic dissection seems helpful for neither didactic nor differential therapeutic considerations but may rather be used to describe the individual situation and time span of survival of a given patient. From a pathophysiological point of view, progression of dissection is difficult to predict once a patient with dissection has survived the initial 2 weeks after its inception, although false lumen expansion is likely to develop over time. Several clinical features may be used to roughly estimate late risk, including spontaneous false lumen thrombosis, evidence of persistent communication, and patent false channel.

**Intramural Hematoma**

Aortic IMH is considered a precursor of classic dissection, originating from ruptured vasa vasorum in medial wall layers, and may provoke a secondary tear and communication with the aortic lumen; this process may be initiated by an “aortic wall infarction.” Similar to classic dissection, IMH may extend along the aorta, progress, regress, or reabsorb. The prevalence of intramural hemorrhage and hematoma in patients with suspected aortic dissection, as observed by various modern imaging techniques, seems to be in the range of 10% to 30%. IMH can lead to acute aortic dissection in 28% to 47% of the patients and is associated with aortic rupture in 21% to 47%. Regression is seen in ~10% of patients. Involvement of the ascending aorta is generally considered an indication for expeditious surgery because of the inherent risk of rupture, tamponade, or compression of coronary ostia. Distal IMH may warrant watchful waiting and potentially elective or emergent interventional stent-graft placement (Figure 2).

**Plaque Rupture/Ulceration**

Ulceration of atherosclerotic aortic plaques can lead to aortic dissection or perforation. Noninvasive imaging of aortic ulceration has been improved by tomographic scanning and has shed light on pathophysiology and etiology. The ulcers seem to predominantly affect the descending thoracic aorta, as well as the abdominal aorta, in localized fashion; branch vessel compromise is rare. However, ulcers may penetrate intimal borders, often appearing in nipple-like projection with an adjacent hematoma. Symptomatic ulcers and/or those with signs of deep erosion are more likely to rupture than others.

**III. Natural History**

The natural history of aortic dissection is best outlined prognostically by differentiating between patients with involvement of the ascending aorta and patients with dissection confined to the distal arch and the descending aorta. This distinction is notable not only for the differing risk factors for development of dissection, but also with regard to critical proximal branch vessels and anatomic relationships that affect patient outcomes acutely and chronically by virtue of malperfusion syndrome, syncope, tamponade, or shock.
Type A (Proximal) Dissection

Acute aortic dissection of the ascending aorta is highly lethal, with a mortality rate of 1% to 2% per hour early after symptom onset.\textsuperscript{3,49} Instantaneous onset of severe chest (85%) and/or back (46%) pain are characteristic presenting symptoms; however, abdominal pain (22%), syncope (13%), and stroke (6%) are common.\textsuperscript{3,11–13,66,67} Not surprisingly, contained rupture into the pericardium (pericardial tamponade), involvement of one or more coronary arteries causing acute myocardial ischemia/infarction, or dissection compromising brain perfusion carry a particularly high risk.\textsuperscript{48,51,53} Additionally, aortic valve disruption leading to acute congestive heart failure, extensive aortic involvement as manifested by multiple pulse deficits and/or renal failure, and advanced age also correlate with increased risk.\textsuperscript{8,13,66,69} Other less appreciated risk scenarios for type A dissection include prior cardiac and valvular surgery (15%)\textsuperscript{3,32,34} and iatrogenic dissection occurring during cardiac surgery or cardiac catheterization (5%); iatrogenic aortic dissection carries a mortality rate of 35%, slightly higher than that associated with noniatrogenic dissection (24%).\textsuperscript{33}

Acute type A dissection is a surgical emergency. Medical management alone is associated with a mortality rate of nearly 20% by 24 hours after presentation, 30% by 48 hours, 40% by day 7, and 50% by 1 month. Even with surgical repair, mortality rates are 10% by 24 hours, 13% by 7 days, and nearly 20% by 30 days, as recently documented in the largest registry of aortic dissection, although randomized data are not available (Figure 4). Aortic rupture, stroke, visceral ischemia, and cardiac tamponade or circulatory failure are the most common causes of death.\textsuperscript{8,13,66,69} Present surgical techniques target the ascending aortic tear primarily with replacement or repair of the aortic root and the aortic valve apparatus (if necessary); meanwhile, the remaining false lumen and potential remodeling of the dissected descending aorta currently play a secondary role. Replacement or repair of the ascending aorta does not consistently eliminate flow and pressure from the distal false channel. Fewer than 10% of operated type A dissections have postoperative false lumen obliteration.\textsuperscript{52}

Figure 2. Evolutions of acute IMH of the descending aorta (left) to growing local dissection and formation of an aneurysm on spiral contrast-enhanced CAT scans within 4 months; reconstruction of the dissected aorta and exclusion of aneurysm after interventional stent-graft placement. F/U indicates follow-up.

Figure 3. Observed vs predicted mortality for acute type A aortic dissection based on a risk score. Each risk factor was statistically extracted from retrospective analysis in IRAD and then prospectively confirmed. Both predicted and observed mortality rates in IRAD increase with increasing number and weight of risk factors. Adapted from reference 66.

Figure 4. Thirty-day mortality in 464 patients from the IRAD registry stratified by medical and surgical treatment in both type A and type B aortic dissection. Adapted from reference 3.
Type B (Distal) Dissection
Acute aortic dissection affecting the descending aorta is less lethal than type A dissection but not strikingly different with regard to clinical presentation. Instantaneous onset of severe back (64%) and/or chest (63%) pain are frequently reported symptoms, as is sudden abdominal pain (43%). Stroke is less common (21%), and presentation with an ischemic leg or peripheral ischemic neuropathy is encountered on occasion.<ref>11,13,66,68,69</ref>

Patients with uncomplicated type B dissection have a 30-day mortality rate of 10%<ref>3</ref> (Figure 4). Conversely, those who develop an ischemic leg, renal failure, visceral ischemia, or contained rupture often require urgent aortic repair; their mortality rate is 20% by day 2 and 25% by day 30. Not surprisingly, advanced age, rupture, shock, and malperfusion are the most important independent predictors of early mortality.<ref>11,13,66</ref> Chronic use of crack cocaine seems to predispose patients to acute aortic dissection, with preferred manifestation in the descending aorta.<ref>70,71</ref> Interestingly, and similar to acute myocardial infarction and other cardiovascular conditions, acute aortic dissection follows a chronobiological pattern and exhibits significant circadian and seasonal variations, with onset of dissection preferentially in the morning between 6 and 10 o’clock and in the early afternoon; moreover, the risk of dissection is higher in the cold season (winter and spring) than in the summer.<ref>72</ref> (Figure 5). These observations may have implications for tailoring treatment strategies, such as antihypertensive drugs, to vulnerable periods.

Intramural Hematoma
The natural history of acute IMH continues to be debated. The cardiologic and surgical communities have generally concluded that acute IMH involving the ascending aorta should be managed surgically because of an unacceptably high mortality rate with medical treatment.<ref>41–43,45,46,54,56,73</ref> Studies in Asian patients from Japan and Korea have argued that wall hematoma reflects a more benign condition, in which aggressive medical therapy and serial imaging may allow watchful waiting and avoidance of surgery in some patients.<ref>57,90,74</ref> The reasons for this disparity may relate either to a different gene pool of Asian and white patients or to critical semantic differences. Acute IMH, when first diagnosed, may be a classic subtle aortic dissection that escapes diagnosis on initial imaging but shows on subsequent imaging or re-review of initial studies. A second scenario is the progression of IMH to classic aortic dissection between an initial diagnostic study and an interim follow-up image (Figure 2). Not uncommonly in type B IMH, the findings remain unchanged over time or even reveal evidence of repressure and reabsorption. For acute aortic dissection or IMH involving the ascending aorta, extent and location of aortic involvement and time from onset of symptoms are critically related to outcome.<ref>44–46,56,75</ref> For a patient presenting within a few hours of symptom onset with an unequivocal acute hematoma in the ascending aorta extending toward the coronary ostia or the aortic valve, watchful waiting is far more hazardous than surgical repair. Conversely, in a patient seen beyond 48 hours of symptom onset with a limited IMH near the arch or distally, watchful waiting and medical therapy is an appropriate approach considering currently available data. Given these uncertainties, and until further studies provide more predictive data, many experts recommend definitive aortic repair for acute IMH of the ascending aorta similar to type A dissection, and a less aggressive attitude toward hematoma in the descending aorta similar to type B dissection.

IV. Diagnostic Strategies
Clinical Presentation
The challenge in managing acute aortic syndrome—and especially dissection—is appropriate clinical suspicion and action in pursuing the diagnosis and therapy.<ref>60,76</ref>

Typical features of dissection are the acute onset of chest and/or back pain of blunt, severe, and sometimes radiating and migrating nature. A history of or signs of chronic hypertension are common if obvious signs of connective tissue disorders are absent. Clinical manifestations of acute aortic dissection are often dominated by the pathoanatomic characteristics of specific malperfusion syndrome from dissection-related side branch obstruction. Up to 20% of patients with acute aortic dissection may present with syncope without a history of typical pain or neurological findings.<ref>3,10–13,60,76</ref> Cardiac tamponade may result in hypotension and syncope.<ref>2,62</ref> Syncope may also result from severe pain, obstruction of cerebral vessels, or activation of aortic baroreceptors. After an initial dominance of chest pain, cardiac failure may become the main symptom and is usually related.
Dissection that results from trauma, valve replacement or iatrogenic causes is usually obvious; however, paraplegia may emerge if too many pairs of intercostal arteries are separated from the aortic lumen.

Recurrent abdominal pain, elevation of acute phase proteins, and increase of lactate dehydrogenase are indicators of involvement of either the celiac trunk (observed in ~8%) or the mesenteric artery (in 8% to 13%). Involvement of the renal arteries may result in oliguria or anuria. Further propagation of the dissection will usually result in repetitive bouts of acute pain, often along with a deteriorating clinical picture. Dissection that results from trauma, valve replacement, or iatrogenic causes is usually obvious; however, dissection after aortic (valve) surgery is less frequent and is easily overlooked.

Signs and Symptoms
Pulse deficits on physical examination are important clues and an ominous sign heralding complications and bad outcome (Figure 6); the IRAD registry of patients with acute aortic dissection reported pulse deficits in <20% of patients; pulse phenomena, however, may be transient, including neurological symptoms such as loss of consciousness or ischemic paresis.

A diastolic murmur indicative of aortic regurgitation is seen in 40% to 50% of patients with proximal dissection. Signs of pericardial involvement, jugular venous distension or a paradoxical pulse, should alert caregivers to pursue rapid diagnostic confirmation. Shock may be a presenting sign, resulting from tamponade, coronary compression, acute aortic valve incompetence, or loss of blood and imminent exsanguination.

Up to 30% of patients later found to have aortic dissection are initially suspected to have other conditions, such as acute coronary syndromes, nondissecting aneurysms, pericarditis, pulmonary embolism, aortic stenosis, or even cholecystitis. Consequently, the differential diagnosis of acute aortic dissection should always be considered in patients presenting with unexplained syncope, chest pain, back pain, abdominal pain, stroke, acute onset of congestive heart failure, pulse differentials, or malperfusion syndrome of extremities or viscera (Table 3).

In the current absence of useful specific biomarkers for aortic dissection, interpretation of positive cardiac markers may be even more complex in a scenario of the aortic dissection compromising the coronary ostia.

Initial Diagnostic Steps and Decisions
A routine chest x-ray is abnormal in 60% to 90% of cases of suspected aortic dissection. However, acute dissection (especially type A) can present with a normal chest film, and this may distract physicians from pursuing further imaging. ECG analysis may also be misleading because it may be normal in dissection or very abnormal when ascending dissection causes coronary compromise. Bedside specific biomarkers are not yet in clinical use, although biochemical diagnosis of aortic dissection may become feasible according to studies that have examined the concentrations of soluble elastin compounds or smooth muscle myosin heavy chain in the early hours of aortic dissection. In suspected aortic syndromes, swift noninvasive diagnostic imaging is advised to differentiate conditions requiring immediate action (involvement of the ascending aorta) from less dramatic scenarios. Visualization of an intimal flap separating 2 lumina identifies dissection. If the false lumen is completely thrombosed, central displacement of the intimal flap, calcification, or separation of intimal layers signals chronic dissection rather than mural thrombosis.

In the IRAD, the first diagnostic test used was transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) in 33%, computed tomography (CT) in 61%, magnetic resonance imaging (MRI) in 2%, and angiography in 4%, reflecting the current use of diagnostic resources. As a secondary technique, TTE/TEE was used in 56%. CT in 18%, MRI in 9%, and angiography in 17%. On average, 1.8 methods were used to diagnose aortic dissection. Of the cases in which 3 methods were used, CT was used in 40%, MRI in
30%, and angiography in 21%. Preferred use, availability, and access in the emergency setting may impact the choice of imaging method because overall accuracy for the parameters are similar.\textsuperscript{5,7} Moreover, a high index of suspicion for the problem is more important than the type of test used. If aortic dissection is suspected, patients should be transferred to a center with interventional and surgical back-up. Each institution should establish pathways for diagnosis, early treatment, and eventual transfer to definitive care.

**Detailing of Dissection**

The extent (beginning and end point) of a dissection is described by taking wall thickness and the intimal flap into consideration. Antegrade, retrograde, or delayed flow is identified in the false lumen by Doppler ultrasound, cine tomographic imaging using CT or MR technology or by motion of the flap synchronized to heart beat. With diminishing false lumen flow, thrombus formation may take place, heralded by spontaneous contrast.\textsuperscript{6,81,82} Conversely, noncommunicating aortic dissections cannot always be differentiated from IMH; an acute symptomatology may speak for IMH potentially progressing to full dissection with typical appearance.\textsuperscript{41,42,46,59}

In presence of false lumen flow, the exact location of entries may be instrumental in choosing potential treatment options. New imaging techniques even allow differentiation of antegrade from retrograde dissection. Retrograde dissection with involvement of the ascending aorta and presence of a tear at the aortic isthmus is found in up to 20% of type A (type I) dissections and constitutes an indication for surgery even when initially identified as type B (type III) dissection.\textsuperscript{38}

Plaque ulceration after plaque rupture is typically visualized by TEE, CT, or MRI.\textsuperscript{46,62–65} In case of multiple lesions, each one has to be carefully checked for signs of penetration or rupture, as evidenced by fluid extravasation into the pericardium, pleural space, and/or mediastinum, which often heralds the risk of sudden death from exsanguination.\textsuperscript{56,74} The presence of pericardial fluid around the aortic root is a sign of ongoing penetration or imminent perforation regardless of dissection or IMH. Fluid within the pleural space can be detected by echocardiography, CT, and MRI. The presence of blood in a pleural space is associated with a mortality rate >50%.\textsuperscript{3,4}

Even more challenging is the interpretation of myocardial ischemia or infarction resulting from a dissection flap or from diastolic collapse of the true lumen. Transoesophageal echocardiography can visualize the ostium and proximal part of both coronary arteries. Multislice CT and MRI can now visualize the proximal third of all coronary arteries. Coronary angiography adds little to the decision-making process and should generally be avoided in type A dissection. However, in stable patients, particularly in type B (type III) dissection, coronary angiography via the right radial or brachial artery may add to vascular staging in the chronic phase of the disease.\textsuperscript{82} Contrast-enhanced CT (in spiral and multislice technique) or transoesophageal ultrasound as an extension of conventional echocardiography are key imaging tools for decision-making in the emergency setting with excellent accuracy. Diagnostic pitfalls currently are less of a problem than are delays in the diagnostic pathway. Modern imaging techniques can reliably identify variants of dissection such as IMH, plaque ulceration, or traumatic aortic injury.\textsuperscript{7,46,52}

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**References**
