Chapter 6
Medical Treatment in Chronic Aortic Dissection

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Introduction

Acute aortic syndrome (AAS) is a life-threatening disease which includes classic acute aortic dissection, intramural haematoma and penetrating atherosclerotic aortic ulcer (trauma of the aorta may also be considered) sharing common physiopathological mechanisms (disruption of media), clinical characteristics and therapeutic challenges [1, 2].

Thoracic aortic dissections may be classified anatomically according to the origin of the intimal tear (DeBakey System) or whether the dissection involves the ascending aorta regardless the site of origin (Stanford System) [2] (Fig. 6.1, 6.2, and 6.3). Furthermore, it is termed acute when presentation occurs within 2 weeks, sub-acute within 2–6 weeks, and chronic more than 6 weeks after symptom onset [1].

Given the high risk of complications and non-specific symptoms and signs AAS requires a high clinical index of suspicion. Prompt diagnosis and appropriate therapeutic

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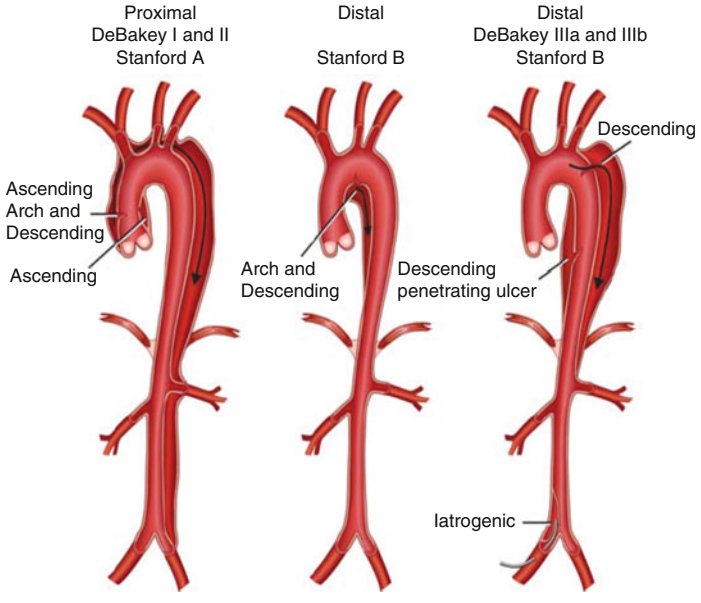

FIGURE 6.1 DeBakey and Stanford classification of aortic dissection. The DeBakey classification system categorizes dissections based on the origin of the intimal tear and the extent of the dissection: *Type I*: Dissection originates in the ascending aorta and propagates distally to include at least the aortic arch and typically the descending aorta. *Type II*: Dissection originates in and is confined to the ascending aorta. *Type III*: Dissection originates in the descending aorta and propagates most often distally. *Type IIIa*: Limited to the descending thoracic aorta. *Type IIIb*: Extending below the diaphragm. The Stanford classification system divides dissections into two categories, those that involve the ascending aorta and those that do not. *Type A*: All dissections involving the ascending aorta regardless of the site of origin. *Type B*: All dissections that do not involve the ascending aorta. Note involvement of the aortic arch without involvement of the ascending aorta in the Stanford classification is labeled as Type B (Reproduced with permission from Nienaber et al. [1])

interventions are paramount to enhance survival [1, 3]. However, after the acute phase, AAS persist with a high risk of re-dissection, aneurysm formation, and/or rupture.

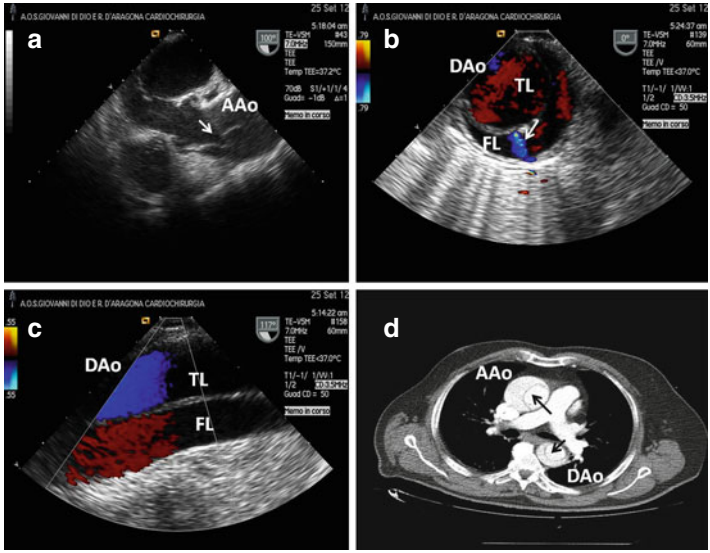

FIGURE 6.2 Chronic Stanford A aortic dissection in 68 years old man with history of hypertension and chest pain occurred 2 months before hospital admission. (**a**) Transesophageal echocardiography (TEE) in long axis view demonstrating intimal flap (see *arrow*) in ascending aorta (*AAo*). (**b**) and (**c**) TEE in short and long axis view respectively of the descending aorta (*DAo*) showing anterior true lumen (*TL*) and posterior false lumen (*FL*); note a distal small intimal tear (**b**, see *arrow*). (**d**) Computed tomography of the aorta: intimal flap (see *black arrows*) in both ascending and descending tract can be appreciated

Long-Term Outcomes

The 10-year survival rate of patients with an aortic dissection may range from 30 to 60 % [1, 4–14]. Among 303 consecutive cases with TA-AAD enrolled in the International Registry of Acute Aortic Dissection (IRAD) (90.1 % managed surgically vs 9.9 % medically), survival for patients treated with surgery was 96.1 % ± 2.4 % and 90.5 % ± 3.9 % at 1 and 3 years versus 88.6 % ± 2.2 % and 68.7 % ± 19.8 % without surgery (mean follow-up overall, 2.8 years) [12] (Fig. 6.4).

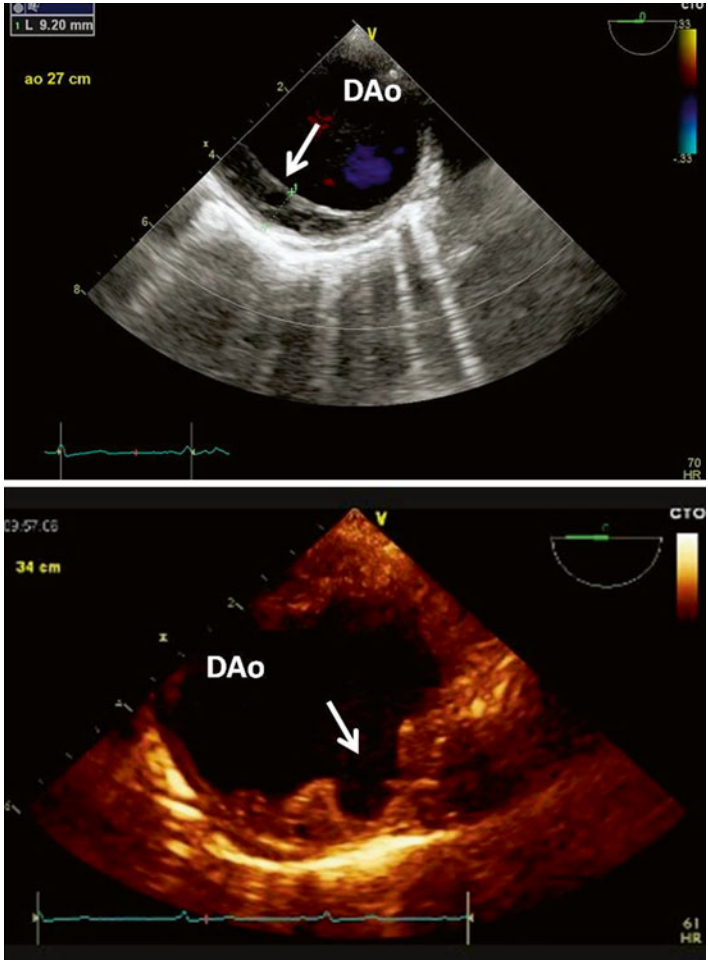

FIGURE 6.3 *Top*: TEE short axis view of the DAo. Note the abnormal thickness of posterior wall do to chronic intramural haematoma. *Bottom*: Penetrating ulcer of atherosclerotic plaque can be clearly appreciated as an incidental finding in a patient with history of hypertension and diabetes mellitus

History of atherosclerosis and previous cardiac surgery were identified as independent predictors of follow-up mortality [12]. On the other hand, 3-year survival for type B aortic

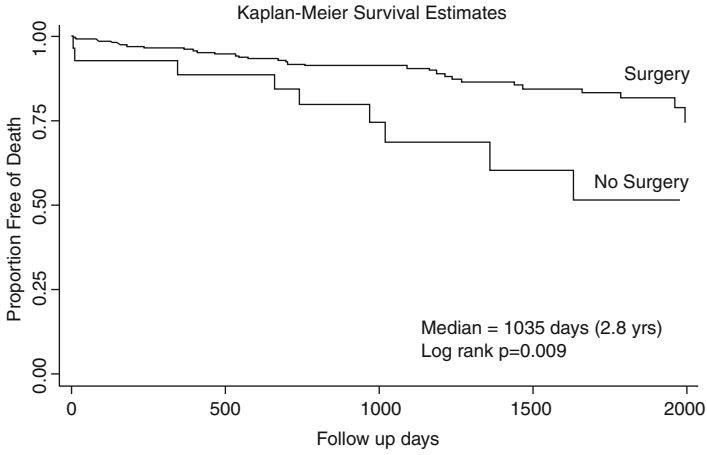

FIGURE 6.4 Unadjusted Kaplan-Meier survival curve stratified by in-hospital management from date of hospital discharge. This figure shows the survival curves estimated by the Kaplan-Meier method stratified by in-hospital management. The unadjusted survival rate at 1 year was 96.1 % ± 2.4 % and 88.6 % ± 12.2 % for surgery versus medical treatment, respectively, with further separation of the curves at 3 years with survival rates of 90.5 % ± 3.9 and 68.7 % ± 19.8 (median 2.8 years, log rank P = 0.009) (Reproduced with permission from Tsai et al. [12])

dissection patients (n = 242) treated medically, surgically, or with endovascular therapy was 77.6 ± 6.6 %, 82.8 ± 18.9 %, and 76.2 ± 25.2 %, respectively (median follow-up 2.3 years) [13] (Fig. 6.5). In that series, independent predictors of follow-up mortality included female sex, history of aortic aneurysm, history of atherosclerosis, in-hospital renal failure, pleural effusion on chest radiograph, and in-hospital hypotension/shock [13]. Some clinical predictors of complications, such as Marfan syndrome [15–17], age [17, 18], chronic obstructive pulmonary disease [17] or atherosclerotic disease have been reported [19]. In addition, maximum descending aorta diameter [12, 17, 20–22], true lumen compression or large false lumen diameter, partial false lumen thrombosis and the presence of a large proximal entry tear [23] are predictors of mortality and the need for surgical/endovascular treatment.

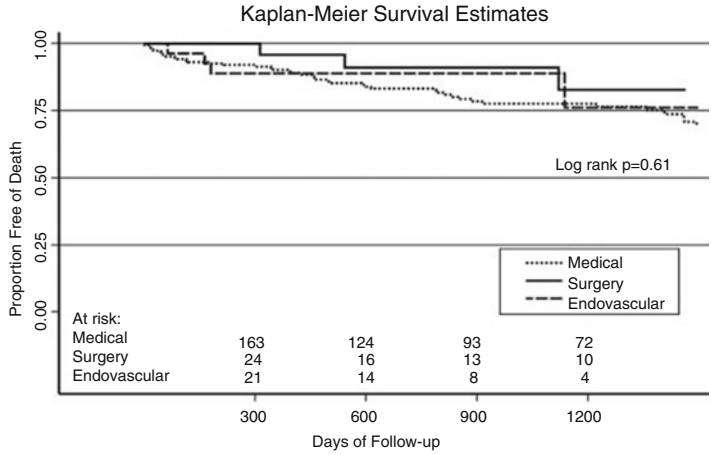

FIGURE 6.5 Unadjusted Kaplan-Meier survival curve stratified by in-hospital management. This figure shows the survival curves estimated by the Kaplan-Meier method stratified by in-hospital management. The unadjusted survival rate at 1 and 3 years for patients discharged from the hospital alive was 90.3 ± 4.3 % and 77.6 ± 6.6 % for medical therapy alone, 95.8 ± 8.0 % and 82.8 ± 18.9 % for surgery, and 88.9 ± 11.9 % and 76.2 ± 25.2 % for endovascular treatment (median 2.3 years, log-rank P = 0.63) (Reproduced with permission from Tsai et al. [13])

Patent false lumen in descending aorta segments after surgical treatment of type A dissection is frequent (64–90 %) [18, 24, 25]. Suboptimal connection of the distal part of the graft implanted in ascending aorta to the true lumen or presence of secondary tears may account for the persistence of flow into the distal residual false lumen after complete surgical resection of the primary entry tear. Long-term outcome of aortic dissection with patent false lumen in descending aorta presents a higher risk of complications in type B than in type A dissections, particularly after 3 years of evolution. The expansion rate of the chronic dissected aorta is not particularly well characterised, but ranges between 0.1 and 0.7 cm per year.

Evangelista et al. investigated the long-term clinical and morphological evolution of 50 IMH. In the first 6 months, total IMH regression was observed in 14 and progression to aortic

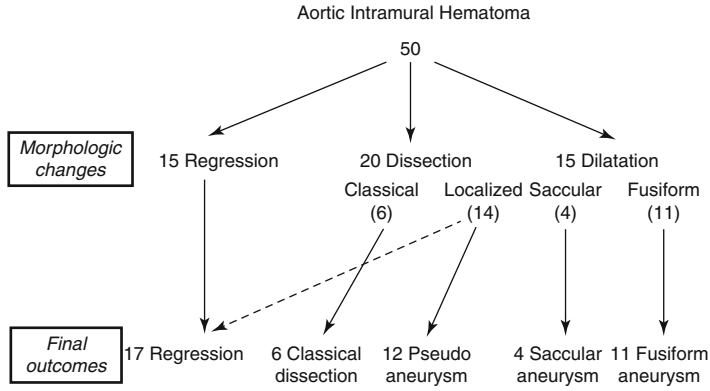

FIGURE 6.6 Different evolution patterns of IMH from morphological changes to final outcomes (Reproduced with permission from Evangelista et al. [14])

dissection in 18 patients; in 14 of these, the dissection was localised, and 12 later developed pseudoaneurysm. At the end of follow-up (mean: 45 ± 31 months), the IMH had regressed completely without dilatation in 17 patients (34 %), progressed to classical dissection in 6 (12 %), evolved to fusiform aneurysm in 11 (22 %), evolved to saccular aneurysm in 4 (8 %), and evolved to pseudoaneurysm in 12 (24 %) [14] (Fig. 6.6). Multivariate analysis showed an independent association between regression and smaller maximum aortic diameter and between aneurysm formation and atherosclerotic ulcerated plaque and absence of echolucent areas in IMH [14].

After discharge, all AAS patients need close clinical and imaging follow-up and excellent blood pressure control (minimise aortic wall stress) along with specific life style recommendations in order to prevent major complications [2, 26, 27].

Imaging Surveillance

The patient with AAD demands careful clinical and imaging monitoring by a specialised aorta team in order to detect signs of aortic expansion/dissection, aneurysm formation,

Table 6.1 Relative strengths of imaging modalities for acute aortic syndromes

	TTE	TEE	MRI	CT
Imaging factors				
Comprehensive aortic assessment	+	++	+++	+++
Tomographic (3D reconstruction)	–	–	+++	+++
Functional	+++	+++	++	+
Tissue characterization	–	–	+++	+++
Clinical factors				
Portability	+++	++	–	–
Patient access/monitoring	+++	+++	+	++
Rapidity	++	++	++	+++
Non-contrast	+++	+++	+	+
Radiation exposure	+++	+++	+++	+

leakages at anastomosis/stent sites, and malperfusion [2, 28]. Computed tomography (CT) and magnetic resonance imaging (MRI) providing a comprehensive evaluation of the aorta represent ideal tools for serial imaging [2, 26] (Table 6.1).

MRI, although not widely available, should be considered the technique of choice. In fact, it provides tomographic-3D reconstruction, tissue characterisation and functional assessment. It entails no radiation exposure and minimises the risk associated with the use of gadolinium – based contrast agents (excellent safety profiles). However, gadolinium-based contrast agents are contraindicated in patients with advanced renal impairment (glomerular filtration rate <30 mL/min) owing to risks of nephrogenic systemic fibrosis. MRI is prohibited in patients with ferromagnetic and/or magnetically-activated implants (including most cardiac pacemakers, defibrillators) and image artifact can interfere with the assessment of vascular stents [26–29].

Current guidelines recommend: (a) regular outpatient visits and imaging at 1, 3, 6, 9 and 12 months post-dissection and

Table 6.2 Imaging follow-up of aortic pathologies after repair or treatment

Pathology	Interval	Study
Acute dissection	Before discharge, 1 month, 6 months, yearly	CT or MR, chest plus abdomen TTE
Chronic dissection	Before discharge, 1 year, 2 to 3 years	CT or MR, chest plus abdomen TTE
Aorticroot repair	Before discharge, yearly	TTE
AVR plus ascending	Before discharge, yearly	TTE
Aorticarch	Before discharge, 1 year, 2 to 3 years	CT or MR, chest plus abdomen
Thoracicaortic stent	Before discharge, 1 month, 2 months, 6 months, yearly or 30 days[a]	CXR, CT, chest plus abdomen
Acute IMH/ PAU	Before discharge, 1 month, 3 months, 6 months, yearly	CT or MR, chest plus abdomen

Adapted from Erbel et al. [27]
AVR indicates aortic valve replacement, *CT* computed tomographic imaging, *CXR* chest x-ray, *IMH* intramural hematoma, *MR* magnetic resonance imaging, *PAU* penetrating atherosclerotic ulcer, *TTE* transthoracic echocardiography
[a]US Food and Drug Administration stent graft studies usually required before discharge or at 30-day CT scan to detect endovascular leaks. If there is concern about a leak, a predischarge study is recommended; however, the risk of renal injury should be borne in mind. All patients should be receiving beta blockers after surgery or medically managed aortic dissection, if tolerated

annually thereafter, depending on aortic size and the patient's clinical condition (hypertension and aortic expansion/dissection are common early after discharge), and (b) to utilise for each patient the same modality at the same institution so that similar images can be compared side by side [2, 27] (Table 6.2).

Studies have suggested detection of increased FDG uptake (marker of active inflammation) by positron emission

tomography (PET)/CT may help to differentiate acute from chronic AAD. The combination of PET/CT and vascular/aortic biomarkers that reflect remodelling (e.g. transforming growth factor α [TGF-α]) may have potential risk prediction value during the following of AAS patients [30–32]. In addition, plasma MMP levels might also be used in long-term follow-up to monitor aortic remodelling [30, 33]. However, further studies are needed to explore potential clinical applications of biomarkers in chronic aortic dissection [30].

Medical Treatment (Table 6.3)

Optimal Blood Pressure Control

Hypertension represents one of the key causative factors of AAS [2, 34]. Patients with AAS often require the combination of at least two drugs to achieve blood pressure and heart rate control [35]. On the basis of the data from patients with Marfan's syndrome, long-term beta blockade (negative inotropic and chronotropic effects, lower blood pressure and decreased dp/dt) is usually recommended in patients with aortic dissection to maintain blood < 120/80 mmHg and heart rate < 60 bpm (first line) [2, 36–39]. Genoni et al. reported improved survival in patients treated with beta-blockers 1685 in the chronic phase of aortic dissection [40]. That study observed an 80 % freedom from aortic events at a mean of 4.2 years in patients on beta-blockers, in comparison with 47 % freedom from aortic events in patients treated with other anti-hypertensive agents. The efficacy of other antihypertensive drugs has not been demonstrated in patients with chronic type B aortic dissection although they have a role in maintaining the patient's blood pressure at the appropriate level. Long-acting rather than short acting beta-blockers should be preferred to reduce side effects and increase compliance. Observational studies suggest similar or better benefits in aortic dissection when compared with other antihypertensive agents [11, 41]. Guidelines recommend progressive uptitration

Table 6.3 Medical treatment and lifestyle goals in the follow-up of patients with chronic aortic syndrome [2]

Medical treatment
1. Optimal blood pressure < 120/80 mmHg and heart rate < 60 bpm control
First line: beta-blockers
Second line: ACE inhibitors or ARB
Third line: calcium channel blockers (long-acting dihydropyridine)
2. Lipid lowering therapy: target of LDL cholesterol less than 70 mg/dL
Lifestyle goals
Low-fat and low-salt diet
Achieve an ideal body weight
Smoking cessation (special programs, and/or pharmacotherapy, including nicotine, replacement, buproprion, or varenicline may be useful)
Avoid cocaine or other stimulating drugs such as methamphetamine
Avoid strenuous physical activities, isometric exercise, pushing, or straining that would require a Valsalva maneuver
Avoid contact sports that can cause sudden stress or trauma to the thorax, (e.g. competitive football, ice hockey, or soccer etc.)
Mild aerobic exercise and daily activities are not restricted
Adherence to medical treatment

ACE angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers

of dosage to achieve a blood pressure 135/80 mmHg in usual patients and 130/80 mmHg in those with Marfan syndrome [42, 43], Several studies have suggested that between 40 and 70 % of late deaths in patients with chronic aortic dissection

are non-aorta related and due to comorbid diseases, mainly heart disease and stroke [15, 44], thus implying that cardiovascular risk factors should be thoroughly assessed in this group. Interestingly, cigarette smoking seems not to affect the expansion and rupture rate of chronic type B aortic dissection, although its detrimental role in cardiovascular risk is well established. Although their role in the incidence of late aortic complications has not been demonstrated, cardiovascular risk-reduction measures (such as cholesterol treatment, antiplatelet therapy, management of hypertension and smoking cessation) is advisable for patients with chronic dissections to reduce the incidence of late cardiovascular death.

Shores et al. among 70 adolescent/adult patients with classic Marfan syndrome [32 treated with propanolol vs 38 untreated (control), open label randomised trial] demonstrated that the mean slope of the regression line for the aortic root dimensions which reflect the rate of dilatation was significantly lower in the beta-blocker group than in the control group (0.023 vs. 0.084 per year, $p < 0.001$; average of 10 years follow-up) [37] (Fig. 6.7). Furthermore, long-term use of β-blockers appears to be associated with reduced progression of aortic dilatation, incidence of hospital admissions, as well as incidence of late dissection-related aortic procedures in acute type B aortic dissection patients [11, 40–45].

Additional (not optimal control) or alternative (beta-blocker intolerance) agents for blood pressure control are ACE inhibitors and angiotensin receptor blockers (second line) [46]. In this regard, Groenink et al. [47] among 233 adults (47 % female) with MFS [multicentre, open-label, randomised controlled trial to either losartan ($n = 116$) or no additional treatment ($n = 117$)] demonstrated that losartan treatment reduced the aortic root dilatation rate (as assessed by MRI) after 3 years of follow-up. Following prophylactic aortic root replacement, losartan treatment reduced the dilatation rate of the aortic arch [47]. Ahimastos AA et al., in a randomised, double-blind, placebo-controlled trial of 17 patients with Marfan syndrome [8 mg/day of perindopril ($n = 10$) or placebo ($n = 7$) for 24 weeks in adjunct to standard beta – blocker therapy], showed that perindopril reduced

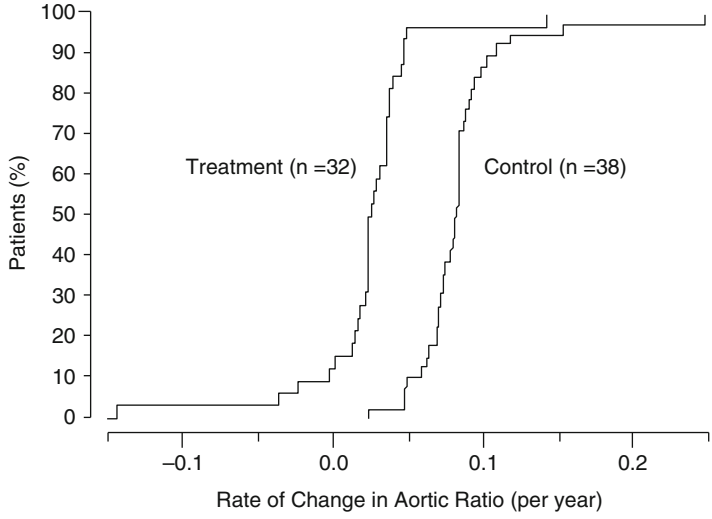

FIGURE 6.7 Empirical distribution functions of the rate of change in the aortic ratio, according to Study Group. The height of each curve at any point shows the proportion of patients with values at or below the value given on the x axis. There is little overlap between the two groups (Reproduced with permission from Shores et al. [37])

both aortic stiffness and aortic root diameter possibly through attenuation of TGF-signalling [48].

Long-acting CCB (reduced reflex tachycardia compared to short-acting) may be considered in addition to an adequate beta-blockade to reach optimal blood pressure control (third line) [2, 49, 50]. Interestingly, Suzuki et al., by analysing 1,301 patients with AAD from IRAD (722 type A AAD vs 579 type B AAD, median follow-up 26.0 months, interquartile range: 12.0–48.0), showed the use of CCB to be associated with improved survival in type B patients (OR 0.55, 95 % confidence interval 0.35–0.88, $p=0.01$), whereas β-blockers improved outcome only in type A patients (OR 0.47, 95 % confidence interval 0.25–0.90, $p=0.02$) [39]. However, data need to be confirmed by RCTs to determine the effects of single medications on the long-term outcome of a different spectrum of aortic disease and define the best medical treatment [51].

Lipid-Lowering Therapy

Patients with atherosclerotic thoracic aortic disease, with or without dissection, should be considered a coronary risk equivalent and treated with statins to achieve a target of LDL cholesterol less than 70 mg/dL. In fact atherosclerosis in any non-coronary vessel significantly increases the risk of MI and stroke (greater than 20 % event rate in 10 years) [2, 52, 53].

Anticoagulation

The degree of false lumen thrombosis in type B aortic dissection or after surgical repair of acute DeBakey type I aortic dissection can predict long-term outcomes. However, there are currently no evidence-based recommendations for anticoagulation. In a retrospective observational study [54] of 136 patients with acute DeBakey type I aortic dissection who underwent surgical repair, the early-anticoagulation group had a higher proportion of completely patent false lumens and lower partial thrombosis than the no-anticoagulation group. Mean segmental aortic growth rate was significantly lower in the early-anticoagulation group than in the no-anticoagulation group (2.9 ± 1.3 and 4.5 ± 2.8 mm/year, $p = 0.01$). Overall survival and aorta-related repeat procedure-free survival were significantly better with early anticoagulation than with no anticoagulation ($p < 0.05$). However, other studies are required to confirm these results. Regarding the risk of anticoagulation in acute intramural haematoma, there is a lack of evidence since only case reports with a disparity effect have been reported [55]. Imaging techniques such as transoesophageal echocardiography or computed tomography are fundamental in the diagnosis of intramural haematoma, assessment of cardioembolic risk and in the follow-up of the evolution of intramural haematoma, which facilitates therapeutic management. Although no established recommendation exists on anticoagulation in aortic intramural haematoma, individual risk-benefit assessment of anticoagulation

and follow-up with imaging techniques are essential to elect the most appropriate therapeutic management.

Lifestyle Recommendations (Table 6.3)

American Heart Association Guidelines for the diagnosis and management of thoracic aorta disease recommend for these patients clear lifestyle targets such as regular aerobic exercise, blood pressure, cholesterol and body weight control, avoid tobacco and cocaine or other stimulating drugs that may trigger aortic catastrophes. In this regard, a stepwise strategy for smoking cessation is recommended (the 5 A's are Ask, Advise, Assess, Assist, and Arrange) including a dedicated programme and specific pharmacotherapy (nicotine replacement, buproprion, or varenicline) [2, 56–60].

Isometric exercise and Valsalva manoeuvre remain contraindicated, being associated with substantial and sudden increase in mean arterial pressure as observed during the lifting of heavy weights. It is also recommended to avoid sports that may cause thoracic stress or trauma [2].

Finally, the importance of adherence to medications, especially beta-blockers and other antihypertensive drugs [2, 60], should be emphasized.

Interdisciplinary Expert Consensus for Treatment of Chronic Type B Aortic Dissection

A recent interdisciplinary expert consensus of cardiovascular, vascular and interventional specialists delineated specific recommendations and related algorithms for the treatment of acute and chronic type B aortic dissection. They confirmed that patients with uncomplicated chronic type B dissection should undergo strict blood pressure control, as stated above in to avoid false lumen dilatation and reduce wall stress [61].

On the other hand, complicated cases (defined by recurrence of symptoms, aneurysmal dilation (total aortic diameter > 55 mm) or a yearly increase (>4 mm) in aortic diameter) should be considered for TEVAR or, if contraindicated, open surgery repair. In this regard, it should underline that open surgery repair carries a higher rate of early mortality than TEVAR. Imaging surveillance and life-style goals remain key steps, irrespective of the type of therapeutic intervention.

Conclusions

Patients with AAS, regardless of the initial therapeutic interventions, deserve long term clinical monitoring by a dedicated team to include imaging surveillance, optimal blood pressure control, lipid lowering and specific life-style targets.

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