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SPECIAL EDITION

Controversies in Surgery for Thoracic Aorta

# The IRAD and beyond: what have we unravelled so far?

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**Abstract** Acute aortic dissection is a life-threatening condition associated with high morbidity and mortality rates and a long history of challenges to both diagnose and manage this condition successfully. The International Registry of Acute Aortic Dissection (IRAD) was established in 1996 as a global database to understand this old disease better and improve care for dissection. IRAD initially targeted various areas including etiological factors of dissection, modes of presentation, clinical features, physical findings, imaging, management, and outcomes, and is currently branching out in more specific fields such as endovascular intervention, genetic profiling, and functional imaging. Although presenting symptoms and physical findings have not changed significantly over two decades, the widespread use of computed tomography is standard and has improved the diagnostic pathway. Moreover, more patients are managed with appropriate procedures, such as surgery in type A, and endovascular therapy in subsets of type B aortic dissection. With these ongoing improvements in swift diagnostic work-up and therapeutic care, fewer patients are not getting appropriate treatment and more patients survive once they reach hospital.

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## Introduction

Acute aortic dissection is a life-threatening condition and occurring up to 30 per 100,000 person-year in the elderly (>65 years) population worldwide, in other words, a relatively rare condition [1]. IRAD was established in 1996 as a global database to understand this old disease better and improve care for dissection. IRAD initially targeted various areas including etiological factors of dissection, modes of presentation, clinical features, physical findings, imaging, management, and outcomes, and is currently branching out in more specific fields such as endovascular intervention, genetic profiling and functional imaging.

Since its inception, the IRAD database under the direction of Drs. Eric Isselbacher, Christoph Nienaber, and Kim Eagle was served as a practical resource for data and has contributed to the advancement of managing acute aortic conditions with more than 80 peer-reviewed publications. To date, IRAD has recruited more than 7500 cases in 43 active sites in 12 countries in Europe, the Americas and Asia.

Although presenting symptoms and physical findings have not changed significantly over two decades, noninvasive diagnostics have significantly improved (especially with the use of computed tomography (CT) imaging). Moreover, more patients are managed with surgical and interventional procedures than ever before in particular open surgery in type A and endovascular therapy in type B dissection (Fig. 1). With recent changes in diagnostic imaging and better management, a significant decrease in overall in-hospital and short-term mortality of aortic dissection has also been documented [2].

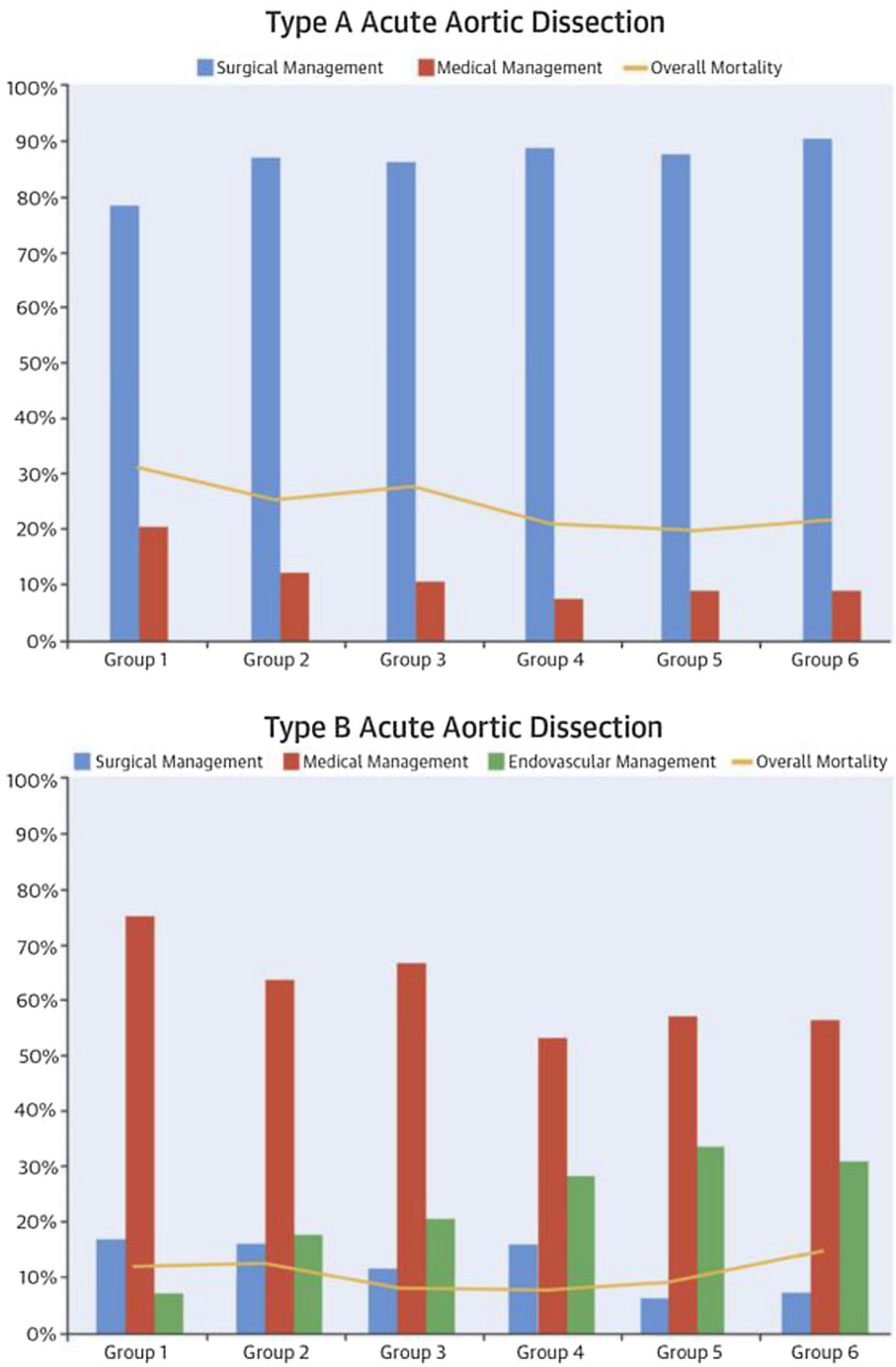


**Fig. 1** Central illustration. Trends in acute aortic dissection over 17 years. Type A ($n = 2952$) and type B ($n = 1476$) acute aortic dissection patients divided into equal-sized groups based on time of enrollment, 1996–2013. Reproduced with permission of Pape et al. [3]

## Demographics

IRAD could show, that 67% of patients presented with type A dissection, and 33% with type B dissection; two-thirds of patients were men, with the average age of 63 years [3]. While there were no indications of a change in the distribution of type A and B aortic dissection over time (17 years), the management of both forms had improved with a higher proportion of up to 90% of proximal dissection subjected to surgical repair, and more than 30% undergoing endovascular management (in addition to customised medication). This observation has been recently supported by demographic data from Japan [4]. Hypertension was the most prevalent risk factor for acute aortic dissection and present in 76.6% of cases [5]. In the elderly population (over 70 years), twice as many hypertensive women than men experienced an acute aortic syndrome [6]. 3.3% of dissection cases were iatrogenic after surgery or

catheter instrumentation [7], while cocaine abuse was recorded in 1.8% [8, 9], and 17% of patients with type A dissection had previous cardiac surgery [10]. In the black population, IRAD found an earlier onset of dissection at 55 years of age, more frequently (52.4%) type B dissection, and a higher proportion of cocaine abuse (12%), hypertension (89.7%) and diabetes (13.2%) [11]. Patients younger than 40 years were more likely to have Marfan's syndrome or a bicuspid aortic valve (59%), rather than affected by hypertension (34%) and atherosclerosis (1%) [12]. Although dilation of the ascending aorta is a well-established risk factor for dissection, the maximum ascending aortic diameters in acute phase averaged at 5.3 cm, and interestingly, 60% of patients had aortic diameters <5.5 cm, and 40% even less than 5.0 cm. Hence, current surgical guidelines for prophylactic thoracic aortic aneurysm repair (<5.5 cm) would miss the majority of patients before they develop a type A dissection [13]. Similarly, only 18.4% of patients with type B aortic dissection had an aortic diameter ≥5.5 cm and in 21% the maximum aortic diameter was <3.5 cm [14, 15]. The occurrence of dissection showed a circadian and seasonal variation, with a peak in the morning and a higher incidence during cold months [16, 17].

## Spectrum of symptoms

A sudden onset of severe chest or back pain continues to be the most frequent symptom. The pain is usually described as sharp, ripping, tearing, knife-like, and typically different from other sensation of chest pain; the abruptness of its onset is the most specific characteristic [18]. Chest pain is more common in patients with type A dissections (79 vs. 63% of type B dissections), whereas back pain and abdominal pain are prone to occur more often in type B dissections (43 and 25% of patients, respectively) [19]. Patients who present primarily with abdominal pain (4.6%) tend to be diagnosed later and have a higher mortality than those with more typical symptoms [20]. However, symptoms of dissection cannot be clearly related to its anatomical location, and the pain often migrates down or up along the dissection. Migrating pain was observed in almost 15% of patients with acute type A dissection and in nearly 20% of those with acute type B dissection; patients with painless dissection (6.3%) often presented with syncope, congestive heart failure or stroke and have a higher mortality [21]. Syncope as a leading symptom was reported in 13% of patients with type A dissection and less than 5% of those presenting with distal dissection; syncope is often associated with life-threatening complications such as cardiac tamponade, obstruction of cerebral vessels or stroke [22]. Hypertension at presentation was more frequent in type B than in type A dissection (70 vs. 36%) [3]. Hypotension (systolic blood pressure <90 mmHg), is seen in >25% of patients and often associated with neurological deficits, altered mental status, myocardial and mesenteric ischaemia, limb ischaemia in 55% of patients; 15% of patients present in a state of shock and are more likely to die in hospital (30.2 vs. 23.9%, $p = 0.007$). Aortic insufficiency is present at the time of presentation in 40% of type A dissections usually with dilatation of the aortic root and annulus, caused by tearing of the annulus or valve cusps, downward displacement of one cusp below the closure line of the valve or interference of the aortic valve with the intimal flap [3, 18], a scenario that can lead to symptoms of heart failure; registry data show that this complication occurs in less than 10% of cases of dissection [23]. A pulse differential at presentation is also an important diagnostic finding and should rise the suspicions of acute aortic dissection; a pulse differential occurs in 30% of patients with type A dissection and 15% in patients with type B dissection, while overt lower limb ischemia is rare [24]. A useful overview of symptoms is given in Table 1 [3, 25].

## Diagnostic modalities and findings

Initial diagnostic imaging is performed by CT techniques in 69% of cases, by echocardiography in 25%, magnetic resonance imaging (MRI) in 4% and aortography in 2–3% [26]. The clear advantage of CT over other imaging modalities is the short time required for image acquisition of the entire aorta and the wide availability [27]. The availability of multi-slice CT imaging has certainly improved over time (in IRAD) and even enhanced the

**Table 1** Main clinical presentations and complications of patients with acute aortic dissection (reproduced from Erbel et al. [25])

| | Type A (%) | Type B (%) |
|---|---|---|
| Chest pain | 80 | 70 |
| Back pain | 40 | 70 |
| Abrupt onset of pain | 85 | 85 |
| Migrating pain | <15 | 20 |
| Aortic regurgitation | 40–75 | NA |
| Cardiac tamponade | <20 | NA |
| Myocardial ischaemia or infarction | 10–15 | 10 |
| Heart failure | <10 | <5 |
| Pleural effusion | 15 | 20 |
| Syncope | 15 | <5 |
| Major neurological deficit (coma/stroke) | <10 | <5 |
| Spinal cord injury | <1 | NR |
| Mesenteric ischaemia | <5 | NR |
| Acute renal failure | <20 | 10 |
| Lower limb ischaemia | <10 | <10 |

diagnostic yield. There is, however, no solid data to show a significantly higher proportion of intramural hematoma (IMH) associated with this trend in IRAD; it is also speculative whether a higher incidence of IMH in Asian countries is a matter of earlier diagnosis or different evolution of dissection. The use of transesophageal echocardiography (TOE) as the first diagnostic imaging modality has come down over time, while transthoracic ultrasound may prove or disprove proximal dissection only. TOE offers more complete and better imaging of the aorta but still misses the abdominal part and is considered semi-invasive in the acute setting. Interestingly, the time to diagnosis of a type A aortic dissection was found to be longer in North America as compared to Europe, which, however, did not result in significant differences in early mortality [28]. Preoperative coronary arteriography is rarely performed in patients with aortic dissection [29] and has no impact on therapeutic management. Some imaging findings also have prognostic value and are useful for improving management strategy, such as pericardial effusion ($p = 0.04$), tamponade ($p < 0.01$), periaortic haematoma ($p = 0.02$), and patent false lumen ($p = 0.08$), all are more frequent in non-survivors [30].

## Biomarkers

Aortic dissection separates the medial layers of the aorta; thus, all biochemical molecular compounds involved in this dissection process would be potential biomarkers, including markers of injury to vascular smooth muscle (smooth muscle myosin), to the vascular interstitium (calponin), to elastic laminae (soluble elastin fragments) of the aorta, and eventually markers of exposure of blood to non-intimal vascular surfaces (D-dimer). Smooth muscle myosin heavy chain concentration peaks very early with aortic dissection followed by a rapid reduction in the first 24 h [31]. Concentration of calponin in the blood is high in both proximal and distal aortic dissection, with a negative predictive value of 84% in the first 24 h [32]. Serum matrix metalloproteinase-9 (MMP-9) is elevated in all anatomical variants of aortic dissection, occurring within 1 h from onset of symptoms in patients with type A and B aortic dissection, but remains high over 2 months of follow-up, suggesting that MMP-9 is also involved in aortic remodelling [33]. Disruption of the elastin lamella is another major pathological feature of acute aortic dissection with elastin degradation products being released into the circulation at the time of presentation [34]. However, most plasma biomarkers, except for D-dimer [3] are not yet available for routine use in emergency rooms [35]. Only the widely used D-dimer cut-off level of 500 ng/mL for ruling out pulmonary embolism can also reliably rule out aortic dissection [36] Other biomarkers of vascular inflammation (C-reactive protein and IL-6) and cardiac stress/damage (troponin and creatine kinases) may fluctuate over time after dissection, but are not specific for aortic dissection.

## Management

### *Proximal aortic dissection*

In proximal aortic dissection involving the ascending aorta, open surgery is the treatment of choice. Today almost 90% of the patients presenting with proximal aortic dissection are managed surgically [3] (Fig. 1). In-hospital mortality of patients with type A aortic dissection came down from 31 to 22%, as a result of better referral and improved surgical techniques [3] (Fig. 2). 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 of them would die by 1 week [19], caused by proximal or distal extension of dissection, heart failure from valvular dysfunction or pericardial tamponade, arch vessel occlusion causing stroke, visceral ischaemia, or rupture resulting in a mortality of about 20% on day 1 and 30% in 48 h. According to IRAD, the interval from diagnosis to surgical intervention is 4.3 h (Q1–Q3, 2.4–14 h) [26]. Not surprisingly, the period was shorter in unstable than in stable patients and major predictors of death, such as tamponade and shock, force the surgeon to accept and operate sooner and sometimes even on moribund patients. The superiority of surgery over conservative treatment even in patients with unfavourable presentations and major comorbidities became evident [37]. In most cases of aortic insufficiency associated with type A aortic dissection, the aortic valve is essentially normal and can often be preserved. According to an IRAD survey standard supra-coronary ascending aorta replacement was performed in 59% patients, while extensive aortic resections involving aortic root replacement were performed in 34% and total arch replacement in 12% of patients [38]. Hypothermic circulatory arrest was used in 92% patients, with antegrade cerebral perfusion in half of all [38]. Recently, endovascular treatment for type A dissection has been reported in some select patients; this approach should not be considered an emerging standard management for many patients as it faces abundant technical and anatomical restrictions [39] but may be useful as a bridging concept to definitive repair (Fig. 3). Nevertheless, 32–50% of patients undergoing open repair of the ascending aorta would be anatomically suitable for endovascular repair [40, 41].

The highest mortality from aortic dissection occurs in the first 48 h after symptom onset [18]; therefore, undelayed diagnosis and decision-making is considered life-saving. Overall in-hospital mortality of distal dissection is hovering around 13%, with most deaths in the first week of medical management (63%).

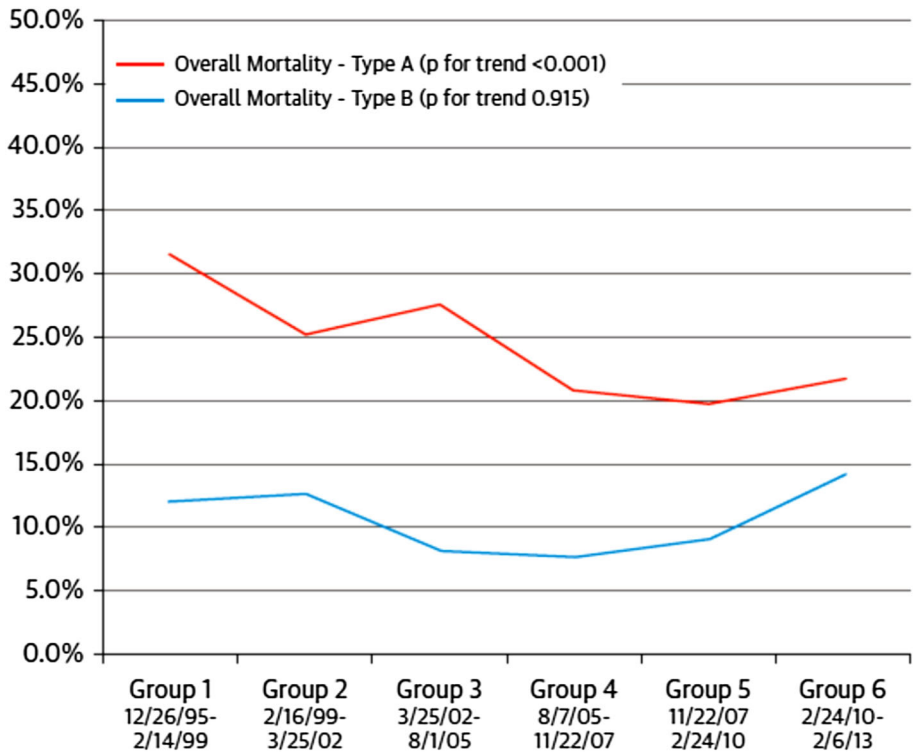


**Fig. 2** Mortality over time by dissection type. Trends in mortality among patients with type A and type B acute aortic dissection over 17 years of IRAD. Reproduced with permission of Pape et al. [3]

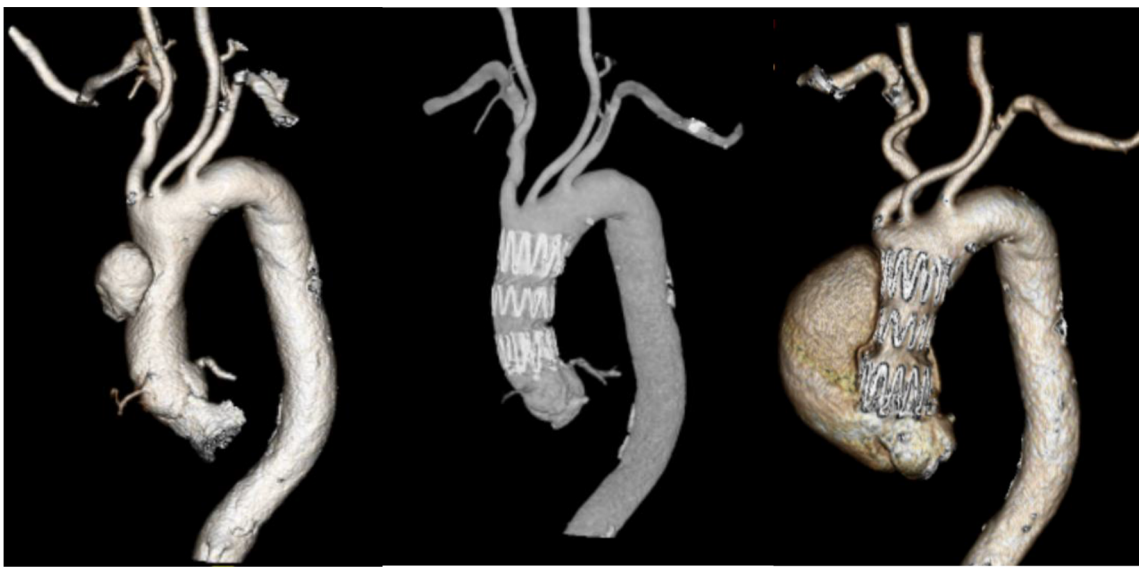

**Fig. 3** From *left* to *right*: 3-dimensional coronal sections of a proximal (type A) aortic dissection before (*left*) and after stent-grafting (*centre*), demonstrating thoracic endovascular aortic repair reconstruction and remodelling of the aorta. 15 months after successful intervention, the follow-up CT scan shows asymptomatic aortic erosion with a new stent-induced entry at the distal end of the stent-graft requiring a high-risk surgical procedure

*Distal aortic dissection*

Over the last two decades, the concept of endovascular management has been introduced and is used currently in 31% of cases, replacing open surgery as the preferred treatment modality for complications of distal dissection [3]. One-third of patients with acute type B dissection present with complications such as malperfusion syndromes, imminent rupture, early expansion, or haemodynamic instability; independent predictors of surgical mortality are age >70 years (OR 4.3) and preoperative shock/hypotension (OR 6.0) [38]. Considering the 33.9%

mortality of open surgery, endovascular treatment with a mortality of 10.6% ($p = 0.002$) has become the new standard of management of at least complicated and high-risk patients with type B dissection [42]. 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 [25] in the setting of complicated, hemodynamically unstable dissection, and with a grade IIA recommendation in so-called uncomplicated, hemodynamically stable patients [43].

## Outcomes analysis

Patients who survived open surgery for type A aortic dissection had a 96.1 and 90.5% survival rate at 1 and 3 years, respectively. Independent predictors of survival do not appear to be influenced by in-hospital risks but rather by pre-existing comorbidities [44]. Conversely, in patients with distal dissection, 3-year survival was only 78%; mortality in type B dissection is clearly associated with complications, such as hypotension/shock (HR 12.5), renal failure (HR 2.5) and pleural effusion on chest X-ray (HR 2.56) [45].

A subgroup of acute type B dissection patients treated by endovascular repair reported a lower death rate (16 vs. 29%, $p = 0.02$) at 5 years compared with patients with medical therapy alone, despite the initially higher risk profile due to the complicated nature of the dissection cases subjected to this therapy [46]. Partial false lumen thrombosis in medically managed type B dissection is found in 33.8% of distal dissection and is considered an independent predictor of death at 3 years (RR 2.7) [47]. Alterations in lifestyle should be recommended in all survivors of aortic dissection regardless of treatment and encouraging loss of weight, smoking cessation and an active lifestyle. Some restrictions, however, may indeed reduce quality of life in some post-dissection patient [48], and clinicians should assess any psychological burden after dissection that may lessen the quality of life of survivors [49] and offer appropriate counselling [50].

Despite their younger age at presentation, patients with Marfan syndrome or other connective tissue diseases have according to IRAD survey a higher mortality with any dissection than non-Marfan or non-syndromic patients [51]. Patients diagnosed at the stage of IMH were frequently older, but presented with similar symptoms than classic dissection. Like classic dissection, IMH is a serious condition when it involves the ascending aorta revealing similar mortality (26.6 vs. 26.5%, respectively) than classic dissection. While the in-hospital mortality of IMH ranges around 4.4%, up to 40% [52] of patients showed an evolution to full dissection on serial imaging.

## Outlook

With growing insight with the process and evolution of aortic dissection, the old distinction between complicated and uncomplicated dissection is becoming blurred as the understanding of the nature of dissection improves, and as pre-emptive endovascular treatment in distal dissection has emerged as a way to prevent late complications [52]. Over the last decade, endovascular approaches have been found useful in the management of distal dissection, particularly to manage complications, such as malperfusion or impending rupture; at the same time, the range of latent complications is growing, including persistent hypertension and pain, or ongoing inflammation. Even in clinically silent "uncomplicated" distal dissection, long-term data suggest nowadays a survival benefit from stent-graft-induced remodelling of dissected aorta. The "pre-emptive concept" is supported by a meta-analysis and two retrospective registries [46, 53, 54]; in particular, observations from IRAD corroborate the late advantage of thoracic endovascular aortic repair beyond 3 years of follow-up [46]. Thus, in anatomically suitable patients with substantial life expectancy, pre-emptive thoracic endovascular aortic repair (TEVAR) could be offered irrespective of clinical presentation of type B dissection to prevent later complications; a change from a complication-specific approach to pre-emptive TEVAR to induce remodelling requires TEVAR to be performed at very low risk and thus suggests that patients with dissection are best to be transferred to tertiary, high-volume aortic centres for high-quality care and surveillance [55–57]. Finally, the description of any given dissection can be individualised by addressing specific features rather than insisting on simple classification systems of the past.

New prospective all-comers registries focused on individualised clinical characteristics and new subgroups with a particular interest in interventional techniques, genetic profiling, and aortic imaging are likely to propel clinical science around the aorta even further.

### Compliance with ethical standards

**Conflict of interest** All the authors have declared no competing interest.

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