Update on the Therapeutic Strategy of Type B Aortic Dissection

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Stanford type B aortic dissection (TBAD) is a life-threatening disease. Current therapeutic guidelines recommend medical therapy with aggressive blood pressure lowering for patients with acute TBAD unless they have fatal complications. Although patients with uncomplicated TBAD have relatively low early mortality, aorta-related adverse events during the chronic phase worsen the long-term clinical outcome. Recent advances in thoracic endovascular aortic repair (TEVAR) can improve clinical outcomes in patients with both complicated and uncomplicated TBAD. According to present guidelines, complicated TBAD patients are recommended for TEVAR. However, the indication in uncomplicated TBAD remains controversial. Recent results of randomized trials, which compared the clinical outcome in patients treated with optimal medical therapy and those treated with TEVAR, suggest that preemptive TEVAR should be considered in uncomplicated TBAD with suitable aortic anatomy. However, these trials failed to show improvement in early mortality in patients treated with TEVAR compared with patients treated with optimal medical therapy, which suggest the importance of patient selection for TEVAR. Several clinical and imaging-related risk factors have been shown to be associated with early disease progression. Preemptive TEVAR might be beneficial and should be considered for high-risk patients with uncomplicated TBAD. However, an interdisciplinary consensus has not been established for the definition of patients at high-risk of TBAD, and it should be confirmed by experts including physicians, radiologists, interventionalists, and vascular surgeons. This review summarizes the current understanding of the therapeutic strategy in patients with TBAD based on evidence and expert consensus.

Key words: Acute aortic dissection, Management, Medical therapy, Surgery, TEVAR

Introduction

Acute aortic dissection (AD) is a life-threatening disease, and its prompt and precise diagnosis is essential for proper management. Current therapeutic guidelines for AD recommend that patients with acute AD involving the ascending aorta, known as Stanford type A, should be treated surgically\(^1\)\(^-\)\(^3\). In contrast, patients with AD not involving the ascending aorta (Stanford type B) are treated medically unless they have fatal complications. Most uncomplicated patients with type B AD (TBAD) have favorable short-term prognosis with medical therapy. However, aorta-related adverse events occur during the chronic stage, which worsen the long-term prognosis. Recent advances in thoracic endovascular aortic repair (TEVAR) can improve clinical outcome in patients with both complicated and uncomplicated TBAD, which may affect therapeutic strategy in patients with TBAD. This review summarizes the present recommended therapeutic strategy based on the current evidence and expert consensus\(^4\)\(^,\)\(^5\).

TBAD: Classic AD and Aortic Intramural Hematoma

As described above, TBAD is defined as AD not involving the ascending aorta. The affected part of the aorta includes the arch, descending, and/or abdominal aorta. Clinically, TBAD is subdivided according to false lumen status, as the prognosis differs significantly. Tsai et al. divided TBAD into three categories according to false lumen thrombosis: patent, partially thrombosed, and completely thrombosed\(^6\). Of these, AD with com-
Optimal Medical Therapy for TBAD

All patients with TBAD should be initially managed with medical therapy to reduce hemodynamic stress to the aortic wall and avoid fatal complications. In particular, blood pressure control is crucially important to avoid both acute adverse events and chronic aortic dilatation. In acute settings, intravenous calcium-channel blockers, nitroglycerin, and beta-blocking agents should be initiated to lower the systolic blood pressure to 100-120 mmHg. Among these antihypertensive drugs, beta-blocking agents are highly recommended to reduce heart rate and dp/dt. During the chronic phase, current guidelines suggest blood pressure control below 140/90 (US and European guidelines) with lifestyle changes and adequate use of antihypertensive drugs. However, limited evidence is available about which drugs are beneficial for patients with chronic aortic dissection. Previous studies suggested that beta-blocker therapy could improve clinical outcome.

Fig. 1. Variations of Stanford type B aortic dissection

A: Classic aortic dissection or communicating aortic dissection. Apparent longitudinal blood flow is observed in the false lumen. B: Ulcer-like projection develops during clinical course in patients with aortic IMH. In the JCS guideline, this type is designated as ULP-type dissection. C and D: IMH or non-communicating dissection. In C, the patient has thrombosed false lumen and tear but without blood flow. In D, the patient has thrombosed false lumen without tear nor blood flow. ULP, ulcer-like projection; IMH, intramural hematoma.
in patients with type B aortic dissection. However, observational data from the International Registry of Aortic Dissection reported that beta-blocker has no significant clinical benefit, whereas calcium-channel blocker is associated with improved outcome in patients with TBAD. Although several studies failed to demonstrate the efficacy of beta-blocker therapy, one observational study revealed that tight heart rate control improves clinical outcome in patients with TBAD. This study suggested the importance of heart rate control rather than the use of beta-blocker. Further studies are warranted to clarify the optimal medical therapy in patients with TBAD.

**Treatment for Patients with Complicated TBAD**

Although patients with TBAD tend to have a more stable in-hospital course than patients with type A AD, a considerable proportion of patients with TBAD suffer from fatal complications. Complicated TBAD is defined by the presence of at least one of the following: aortic rupture, persistent or recurrent pain, uncontrolled hypertension despite full medication, and early aortic expansion and malperfusion in cerebral, spinal, visceral, renal, or peripheral vascular territories. These complications are considered to be a major cause of early mortality in patients with TBAD. Afifi et al. reported that the early mortality rate of patients with complicated TBAD is significantly higher than that of patients with uncomplicated TBAD (2.6% versus 16.1%, respectively). TEVAR is considered to be effective for treatment of patients with complicated TBAD. Several studies confirmed the improvement in clinical outcome with TEVAR in patients with complicated TBAD. Currently, several meta-analyses report favorable short and mid-term results in patients with complicated TBAD treated with TEVAR. Given these results, TEVAR is considered as the gold standard for complicated TBAD, and current guidelines recommend TEVAR for patients with complicated TBAD as Class I indications. Although TEVAR is beneficial for complicated patients, those with visceral malperfusion have poorer prognosis. A previous study reported that patients with visceral ischemia have a high risk of mortality and that mortality rates are similar after surgical and endovascular management. These results suggest that early diagnosis and intervention for visceral ischemia seem to be crucial.

**Watchful Waiting Strategy with Open Surgery or TEVAR for Patients with Uncomplicated TBAD**

The results of open surgical repair of the descending aorta have improved over the last decades, but in-hospital mortality for patients with TBAD remains about 25–50%. The National Survey of Japanese Association for Thoracic Surgery in 2014 including 1039 institutions revealed that the 30-day mortality rates of patients who underwent surgical therapy for acute TBAD including replacement of the arch, descending aorta, and thoracoabdominal aorta for acute AD are 31.3%, 9.8%, and 27.3%, respectively. Considering the relatively high mortality and morbidity, open surgery is delayed until patients with TBAD show dilatation of the affected aorta. Current guidelines recommend surgical intervention for patients with aortic diameter ≥ 55-60 mm. According to the same survey in Japan, the 30-day mortality rates of patients who underwent open surgery for chronic TBAD including replacement of the arch, descending aorta, and thoracoabdominal aorta for chronic aortic dissection are 8.1%, 5.3%, and 5.1%, respectively. By contrast, the 30-day mortality rate of patients with chronic TBAD who underwent TEVAR is 1.9%. Elective aortic graft replacement or TEVAR performed by experienced operators carries a low risk of morbidity or mortality. Considering the relatively low mortality rates with open surgery and TEVAR, watchful waiting strategy in TBAD seems to be rational. However, this strategy has several disadvantages. First, lifelong monitoring is necessary to prevent late aorta-related adverse events. The risk of incomplete follow-up is also present. Second, the degeneration of the aortic wall and extensive aortic enlargement may make aortic intervention more complicated and difficult with time.

**Current Outcomes of Patients with Uncomplicated TBAD**

Several observational studies reported the natural history of TBAD. The investigators of the International Registry of Acute Aortic Dissection (IRAD) reported that the 3-year mortality rates in patients who are treated medically, surgically, or with endovascular therapy and discharged alive with TBAD are 22.4%, 17.2%, and 23.8%, respectively. Other investigators from the US and European countries demonstrated a similar 5-year all-cause mortality rate of 19.3 to 23.4% in patients with uncomplicated TBAD. On the other hand, several centers in Japan demonstrated a relatively lower 5-year all-cause mortality rate.
effectiveness of TEVAR in INSTEAD trial. In this study, patients who underwent preemptive TEVAR have favorable aortic remodeling. TEVAR, which can close primary entry tear into false lumen, could induce false lumen thrombosis and aortic remodeling. The study concludes that preemptive TEVAR should be considered to improve late outcome in uncomplicated TBAD with suitable aortic anatomy. The results of these randomized trials have a large clinical impact on TBAD management and encourage preemptive TEVAR in early disease stage.

Fig. 2 shows a representative case of successful TEVAR in a young patient with TBAD. However, the benefit of TEVAR is not apparent until 2 years after therapy in the INSTEAD-XL trial, which raised several issues about management of TBAD. The first issue is identifying which patients with uncomplicated TBAD should undergo TEVAR. The trial suggested the importance of patient selection for TEVAR. The second issue is the unclear optimal timing of TEVAR and open surgery. Currently, the best timing of preemptive TEVAR may be considered as 3-6 months after the onset of TBAD. However, the benefit of TEVAR is not apparent until 2 years after therapy in the INSTEAD-XL trial, which raised several issues about management of TBAD. The first issue is identifying which patients with uncomplicated TBAD should undergo TEVAR. The trial suggested the importance of patient selection for TEVAR. The second issue is the unclear optimal timing of TEVAR and open surgery. Currently, the best timing of preemptive TEVAR may be considered as 3-6 months after the onset of TBAD. TEVAR is more effective in subacute phase than in chronic phase because the aorta dilates more severely and the intima becomes less elastic with time. Desai et al. reported that severe complications, including retrograde type A AD, are more common in early-acute (within 48 hours from presentation) and delayed-acute (48 hours to 14 days) than in subacute (14 days to 6 weeks). This study showed that the 30-day mortality rates of early-acute, delayed-acute, and subacute are 12.7%, 6.8%, and 0%, respectively. In contrast, delayed timing of more than 3 months might
lead to degeneration of the aortic wall, which hampers aortic remodeling after TEVAR. Moreover, considering the clinical outcomes of open surgery, it might be better to observe and wait until the affected aorta shows significant enlargement in patients with unsuitable aortic anatomy for TEVAR that may lead to serious complications. Further studies are required to determine the optimal timing of TEVAR.

**Predictors for Aortic Events in Patients with TBAD: Toward the Best Practice**

Considering the limited results of randomized trials, a complication-specific approach, instead of endovascular surgery for all patients with TBAD, remains reasonable. For this purpose, identifying high-risk patients with TBAD who benefit from preemptive TEVAR is crucial. Several risk factors including clinical and imaging parameters have been shown to be associated with early disease progression in patients with TBAD. Table 1 summarizes the clinical and imaging predictors of aortic events in patients with TBAD.

**Anatomical Imaging**

An aortic diameter of more than 40 mm is a simple and useful predictor for future aorta-related events. Another important predictor is a false lumen diameter of more than 22 mm. In addition, assessment with transesophageal echocardiography showed that entry tear of more than 10 mm in diameter and proximal entry location are predictive for aorta-related adverse events. Similarly, several morphological parameters of the true and false lumen, such as elliptic configuration of the true lumen and fusiform shape in longitudinal aorta, have been reported to be predictive. These studies suggested that a partially thrombosed false lumen should be carefully followed up with close imaging surveillance. However, Sueyoshi et al. reported that patients with partial thrombosis have worse prognosis than patients with patent or complete thrombosis. Similarly, Trimarchi et al. reported that patients with partial false lumen thrombosis show higher aortic growth rate than patients with other types of false lumen. These studies suggested that a partially thrombosed false lumen should be carefully followed up with close imaging surveillance.

### Table 1. Predictors of adverse aortic events in patients with uncomplicated type B aortic dissection

<table>
<thead>
<tr>
<th>Predictor</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>46) 61)</td>
</tr>
<tr>
<td>White race</td>
<td>15)</td>
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<tr>
<td>Heart rate ≥ 60/min</td>
<td>16)</td>
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<tr>
<td>Marfan syndrome</td>
<td>44)</td>
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<tr>
<td>Without calcium channel blockers</td>
<td>6)</td>
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<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
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<tr>
<td>FDP level ≥ 20 µg/mL on admission</td>
<td>58)</td>
</tr>
<tr>
<td>Peak CRP level ≥ 9.61 mg/dL</td>
<td>59)</td>
</tr>
<tr>
<td><strong>Imaging findings</strong></td>
<td></td>
</tr>
<tr>
<td>Aortic diameter ≥ 40 mm during acute phase</td>
<td>41) 42)</td>
</tr>
<tr>
<td>Patent FL</td>
<td>41) 50) 51)</td>
</tr>
<tr>
<td>Partially thrombosed FL</td>
<td>6)</td>
</tr>
<tr>
<td>FL diameter of the proximal descending aorta ≥ 22 mm on initial imaging</td>
<td>43)</td>
</tr>
<tr>
<td>Sac formation in partially thrombosed FL</td>
<td>46)</td>
</tr>
<tr>
<td>One entry tear</td>
<td>49)</td>
</tr>
<tr>
<td>FL or intimal tear located at the inner curvature</td>
<td>46)</td>
</tr>
<tr>
<td>An elliptic configuration of the TL</td>
<td>46)</td>
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<tr>
<td>Ulcer-like projection</td>
<td>11) 51)</td>
</tr>
<tr>
<td>Fusiform index ≥ 0.64</td>
<td>45)</td>
</tr>
<tr>
<td>Large entry tear (≥ 10 mm) located in the proximal descending aorta</td>
<td>44)</td>
</tr>
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FDP, fibrinogen degradation product; FL, false lumen; TL, true lumen; CRP, C-reactive protein.
IMH and Ulcer-like Projection

In comparison with patients with patent or partially thrombosed false lumen, those with TBAD having closed and thrombosed false lumen, which are identical to IMH and characterized by the absence of intimal tear and continuous flow communication, have different clinical features and outcomes\(^\text{10, 50}\). We previously reported that patients with type B IMH have better short- and long-term prognoses than patients with classic AD\(^\text{51}\). Two important clinical features of IMH may contribute to achieve better clinical outcome. First, patients with IMH have less opportunity of branch occlusion and subsequent malperfusion. Previous studies reported that less fatal complications due to branch ischemia occur in patients with type B aortic IMH\(^\text{10, 51}\). This may contribute to the improvement in short-term mortality. Second, thrombosed false lumen may regress and frequently resolve during clinical course\(^\text{41, 52}\). In other words, aortic remodeling occurs more frequently in patients with IMH. These clinical features may be associated with better clinical outcome, but not all IMH patients have favorable prognosis. Patients with ulcer-like projection (ULP), which indicates the flow communication between the true and false lumen, have been reported to be a strong risk factor for future aorta-related events\(^\text{11, 53}\). This is similar to the finding that partial thrombosis of the false lumen is a risk factor of adverse aortic events. Since ULP can be regarded as one large entry into partially thrombosed false lumen, it has a similarity with the abovementioned morphological risk factors, such as partial thrombosis, sac formation, and large and/or one entry. Thus, these findings suggest that partial false lumen thrombosis due to even small flow communication may lead to adverse outcomes, whereas complete thrombosis may invoke remodeling and improve outcomes. TEVAR, which can close and reduce false lumen blood flow inducing complete thrombosis, might be beneficial for patients with partial false lumen thrombosis.

Functional Imaging

Multiple detector computed tomography imaging provides detailed morphology of the affected aorta. However, it does not reveal the functional information of hemodynamics and flow pattern in both the true and false lumen. Magnetic resonance imaging and
Echocardiography enable comprehensive evaluation of flow pattern in both lumens and entry. Clough et al. demonstrated that four-dimensional phase-contrast magnetic resonance imaging can help visualize and quantify flow characteristics in patients with AD and that stroke volume, velocity, distal dominant entry tears, and helical flow are related to the rate of aortic expansion.

Another possible functional imaging modality that can predict clinical outcome in patients with AD is positron emission tomography (PET). PET imaging is based on the distribution of the glucose analogue 18F-fluorodeoxyglucose (18F-FDG), which is taken up with high affinity by hypermetabolic inflammatory cells. The combined anatomic and metabolic information of 18F-FDG-PET/computed tomography has shown potential in the imaging of aortic wall instability and underlying inflammation in aortic disease. A previous preliminary study reported that the greater uptake of 18F-FDG is significantly associated with rupture and progression in patients with AD.

**Laboratory Findings**

Several biomarkers have been reported to be predictive for adverse aortic events. First, fibrinogen degradation product (FDP) level ≥ 20 µg/mL at admission is associated with aortic growth. However, since FDP level is not measured easily in emergency room, it might not be widely available in many institutions. On the other hand, several studies revealed that peak CRP level is a strong predictor in patients with TBAD. The serum CRP level is widely available and can be a less-invasive marker for identifying high-risk patients. However, since CRP is a non-specific marker, its usefulness might be limited by the fact that it reflects not only the extent of the aortic dissection, but also concomitant inflammatory diseases, such as pneumonia.

**Conclusion**

The optimal treatment of TBAD remains controversial. TEVAR should be recommended for patients with complicated TBAD. Although optimal medical therapy with aggressive blood pressure lowering is essential for patients with uncomplicated TBAD, we have to consider whether they should be treated with preemptive TEVAR to improve clinical outcomes. High-risk patients should be monitored closely, particularly in the first 6 months and referred for endovascular repair when significant aortic dilatation is observed. If patients have a stable course without aortic dilatation, optimal medical therapy and timely surgery are recommended. With this watchful waiting approach, surveillance with regular radiological imaging is essential.

The ultimate goals are patient survival and better quality of life. We should consider carefully the risks and benefits of optimal medical therapy, TEVAR, and open surgery in each patient and determine the treatment strategy by properly balancing them.

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**Disclosures**

The author has no conflict of interest to disclose.

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