Editorial

The current evidence on diagnosis and treatment of acute aortic syndrome

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In their article titled "Acute Aortic Dissection and Intramural Hematoma: A Systematic Review" Mussa *et al.* highlight the important evidence on diagnosis and treatment of acute aortic syndrome (AAS) (1). AAS describes the presentation of patients with one of a number of life threatening aortic pathologies, including aortic dissection (AD), intramural hematoma (IMH), and penetrating atherosclerotic ulcer (PAU). Several studies and meta-analyses have discussed the management of AAS (2-4). Mussa *et al.* analyzed many studies involving large numbers of patient, and provided new insights; 82 studies with a total of 57,311 patients were included. The information is of great use in the management of AAS. However, the optimal treatment of patients with AAS is still unclear, due to selection bias and the paucity of randomized trials. Only two randomized clinical trials (RCTs) (5,6) were identified, and the remaining 80 were observational cohort studies.

The acute onset of thoracic pain with severe hypertension should raise suspicion for AAS. In the review, 50–81% of patients were males, with ages ranging from 60 to 70 years. The most common risk factor for AD is hypertension, which was observed in 45–100% of patients. Other risk factors include a smoking history, chronic renal insufficiency, chronic obstructive pulmonary disease, and stroke or transient ischemic attack. Although few studies have accurately determined the incidence of AAS, AD is the most common form of AAS, followed by IMH and PAU. A recent analysis of AD reported an incidence of 15 per 100,000 patient-years (7).

The diagnosis of AAS can be made using imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and transesophageal echocardiography (TEE). The ideal diagnostic tool in AAS should have high sensitivity and specificity, and should provide assessment of anatomical aspects for use in management. Early diagnosis and accurate radiological classification is associated with improvement of clinical outcomes in AAS. In the analysis of eligible articles, the sensitivities of CT and MRI for diagnosis of AAS were 100% and 95–100%, respectively. Although MRI provides detailed anatomic information comparable to that of CT, it is limited by availability and long scan times. The authors also reviewed the diagnostic value of TEE. TEE has considerable potential for the diagnosis of AAS. However, TEE does not visualize the aortic arch or abdominal aorta well. These imaging modalities have their advantages and limitations. This important aspect has been reviewed by Macura *et al.* in detail (8).

Mussa *et al.* came to the conclusion that the lack of studies prevents any suggestions regarding the diagnostic use of serologic biomarkers to improve outcomes. To the best of our knowledge, their review included only limited

Table 1 Sensitivity and specificity of D-dimer for acute aortic syndrome

Publication	No. of studies	No. of patients	Threshold (μg/mL)	Acute aortic syndrome		Acute aortic dissection	
				Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Mussa *et al*. 2016 (1)	6	876	>0.5–0.7	51.7–100.0	32.8–89.2	51.7–100.0	32.8–89.2
Watanabe *et al*. 2016 (9)	12	833/1,994*	>0.5	NA	NA	95.2	60.4

*, based of 833 acute aortic dissection patients and 1,994 non-acute aortic dissection patients. NA, data were not available.

amounts of data on D-dimer. In their analysis, D-dimer was 51.7–100% sensitive and 32.8–89.2% specific among six studies (n=876). We recently reported the diagnostic accuracy of D-dimer for acute AD (9). Based on 833 acute AD subjects and 1,994 non-acute AD subjects constituting 12 studies that used a cutoff value of 500 ng/mL (*Table 1*), the sensitivity was 0.952 [95% confidence interval (CI), 0.901–0.978], the specificity was 0.604 (95% CI, 0.485–0.712), the positive likelihood ratio was 2.4 (95% CI, 1.8–3.3), and the negative likelihood ratio was 0.079 (95% CI, 0.036–0.172). Sensitivity analysis using data from three high-quality studies almost replicated these results. We confirmed that D-dimer >500 ng/mL moderately increases the possibility of acute AD.

Mussa *et al.* discussed treatment recommendations, which were similar to those in current societal guidelines. Initial medical management is recommended for all patients to control pain and blood pressure (level 1, grade C). Stanford type A AD requires immediate open surgical repair (level 1, grade B). For type A AD, medical management alone reduced short-term mortality. Therefore, medical management was reserved for advanced age, significant comorbidity, patient refusal, or death prior to planning of surgery. However, the 30-day mortality rate was still low (13–17%) with surgical intervention. A delay between symptom onset and emergency department arrival may result in a poor outcome with surgical treatment. Although endovascular approaches have gained wide acceptance, they remain under investigation for type A AD.

Thoracic endovascular aneurysm repair (TEVAR) is currently recommended for patients with type B AD with complications such as aortic rupture or malperfusion syndrome. For type B AD, Mussa *et al.* reported a 30-day mortality rate of 0–27% for medical treatment, 13–17% for open surgical procedures, and 0–18% for TEVAR. Moreover, they reviewed two important RCTs comparing medical therapy with TEVAR in patients with uncomplicated type B AD (2,3). The ADSORB trial compared medical therapy with TEVAR in an RCT of 61 patients with uncomplicated acute type B AD (5). The primary end-point was a combination of incomplete/no false lumen thrombosis, aortic dilatation, or aortic rupture at 1 year. Remodeling with thrombosis of the false lumen and reduction of its diameter was induced with a stent graft. In the INSTEAD-XL trial, 140 patients with uncomplicated acute type B AD were randomized (6). Although TEVAR was associated with better outcomes than medical treatment alone for aorta-specific mortality at 5-year analysis, all-cause mortality was not significantly different. There are a number of potential benefits with the use of TEVAR to treat aortic pathology. However, selection bias exists for uncomplicated type B AD; thus, the best treatment choice is still controversial.

IMH typically occurs in patients with severe atherosclerotic disease. Complicated IMH is associated with progression to dissection. Fewer than 10% of cases will resolve spontaneously (10), whereas 16–47% will progress to dissection (11). Therefore, complicated IMH should be treated with an open surgical procedure if type A, and TEVAR if type B. Most patients with uncomplicated type B IMHs are stable or regress with medical therapy. Mussa *et al.* analyzed the 30-day mortality rate of patients with IMH. Six studies used medical treatment (mortality rates: 4–19%), three studies used open surgical treatment (mortality rates: 11–24%), and four studies used TEVAR (mortality rates: 0–6%).

AAS is one of the most acutely life-threatening conditions (12). In emergency care patients, a rapid diagnosis of AAS can be life-saving. The concept of AAS was developed to enable the early identification and definitive treatment of patients with thoracic pain with an aortic origin (13). The systematic review revealed the current evidence on diagnosis and treatment of AAS. However, it should also be interpreted with some caution. The authors do not support the use of serologic biomarkers in the diagnosis of AAS. However it is sometimes difficult

to perform imaging as an initial diagnostic test because of the limited resources available at a facility, the presence of metallic implants in a patient, and the risks of anaphylaxis and acute kidney injury. Thus, we conducted a meta-analysis including both case-control and cohort studies that could provide sufficient data concerning both sensitivity and specificity of D-dimer for acute AD. D-dimer has very good overall accuracy.

As Mussa *et al.* noted, most studies included in their review were limited to cohort studies with only short-term data. Data should be collected over a longer period. Although RCTs are the gold standard for the evaluation of treatments, they are difficult to perform because the clinical setting of AAS is that of an uncommon and high-risk emergency. Much evidence is provided by their review. However, the proper treatment of patients with AAS remains controversial, and further studies are required. With increasing knowledge and better management strategies, the outcomes of AAS will improve.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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