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Acute aortic syndrome (AAS) is a pathologic designation referring to a group of life-threatening cardiovascular diseases, including acute aortic dissection (AAD) and two vasculopathic variants, namely intramural hematoma and aortic ulcer. Aortic dissection, which can be categorized according to its involvement of the ascending thoracic aorta or lack thereof (i.e., Stanford Type A versus B dissections), causes separation of the layers or "tunicae" of the aorta, resulting in the creation of second channel or a "false lumen." This false lumen can extend and potentially disrupt blood flow to major branching arteries and the visceral structures they perfuse. This could be further complicated by acute thrombosis of the false tract and potential rupture of the aorta itself, which has high rates of fatality. Although precise epidemiological rates for AAS and its subtypes remain somewhat unclear, a nationwide cohort study conducted between 1987 and 2002 revealed a substantial increase in thoracic aortic disease incidence by 52% and 28% among men and women, respectively.

AAS typically presents with sudden onset, "thunderclap" or migratory chest, back, and/or abdominal pain, as well as a myriad of perfusion-related deficits, including syncope, focal neurologic deficits, and hemodynamic instability. Yet the incidence is rare, and related symptoms are variable. AAS often mimics cardiovascular disease states far more prevalent and familiar in the Emergency Department (ED). Chest and back pain, for example, can mimic acute coronary

syndrome (ACS) and pulmonary embolism (PE), while sudden extremity numbness or weakness can imitate a stroke.

Although AAS is emphasized as a "must-not-miss" diagnosis, given its incredibly high risk of complications and mortality, nearly 14-39% of cases are misdiagnosed. From the onset of dissection, approximately 40% of patients have an immediate fatal outcome for Stanford Type A dissections (i.e., those involving the aortic arch and which often require surgical repair), with a subsequent increase in mortality of 1-2% per hour while alive. For all cases of AAS, this culminates to approximately 33% mortality after 24 hours and drastically rises to 50% after 48 hours. Therefore, delayed diagnosis increases mortality and morbidity.

Unfortunately, current diagnostic measures struggle to address the time-sensitive nature of this pathology, nor can they reliably determine which patient populations are at risk. This places the burden of diagnosis solely on emergency medicine (EM) physicians and their clinical suspicion, as they are without validated, evidence-based metrics to substantiate or refute a potential case of AAS. Current gold-standard imaging modalities, namely CT angiogram and MRI have limited availability, are more costly, increase length of stay, and can be associated with other risks such as contrast-related kidney injury or anaphylaxis.

Additional clinical tools and markers have since been proposed to assist with the rapid diagnosis/ruling out of AAS. First inspired by the original 2010 AHA guidelines for managing aortic disease, the aortic dissection detection risk score (ADD-RS) emerged as a potential clinical tool to guide clinicians in a manner similar to other pathologies, such as the HEART Score for ACS and Wells Criteria for PE. This three-point system focuses on evidence-based, high-risk, predisposing demographics (i.e., Marfan syndrome, aortic stenosis), clinical features, and objective perfusion deficits (neurologic deficits, hemodynamic instability). Upon initial

evaluation, the ADD-RS was shown to have a sensitivity of 95.7-100%. However, one downfall is that the ADD-RS cannot sufficiently discriminate between cases in low-prevalence patient populations. Subsequently, biomarkers and laboratory tests, specifically the D-dimer, have been evaluated to supplement or replace clinical scoring systems, given their availability and objective nature. Other standard lab tests, including troponins, creatinine kinase, and lactate, have also been evaluated, but to a lesser extent.

D-dimer, a fibrin blood clot degradation product, has been studied extensively for thrombotic-related events such as ACS, PE, and AAS. Positive levels have been linked to all three of these major cardiovascular pathologies. However, its elevation has also been documented in acute or hyper-inflammatory states such as rheumatic disease, trauma, pregnancy, and recent surgical procedures. As a result, the serum D-dimer test alone has limited value in positively identifying AAS and should not be used solely to make a definitive diagnosis. However, the negative D-dimer biomarker result, which has already been widely accepted as an exclusionary principle for PE and deep-vein thrombosis, has shown promise in its utility to potentially rule out AAS as well. Originally proposed by Suzuki et al. in 2009, a negative D-dimer was shown to have a sensitivity of 95.7% with a negative likelihood ratio of 0.07 for AAS at the standard < 500 ng/dL threshold, similar to the risk stratification cutoff for PE. Even an age-adjusted D-dimer yielded similar results. Additional studies have investigated other potential threshold values between ACS and AAS, as well as Stanford Type A versus B dissections. Furthermore, a recent meta-analysis of 16 clinical studies found that D-dimer levels have excellent diagnostic value for AAS due to high pooled sensitivity (0.96 (95% CI 0.91–0.98)). As a result, the D-dimer has been recognized by the European Society of

Cardiology for its clinical importance in the potential ruling-out of AAS, per their 2014 guidelines.

Recent work by Nazerian et al. has since attempted to combine results of the ADD-RS scoring system and D-dimer into a singular clinical algorithm to rule out AAS in the ED. Their study enrolled 1,860 patients (≥ 18yrs old) across 6 European medical centers who presented with acute onset chest, abdominal, or back pain ≤ 14 days. (i.e., duration of the acute period of AAS). They found the combined results of ADD-RS < 1 + D-dimer < 500 ng/mL to yield a high sensitivity (Sn 98.5%) and a high negative predictive value (NPV 99.7%) to rule out AAS. Since then, meta-analyses reaffirmed these results with a high pooled sensitivity (Sn 98.9-100%). Despite these promising results, no prospective multicenter clinical trials have replicated or externally validated this scoring system. Furthermore, the original study cohort had an abnormally high AAS prevalence (13%), questioning the external generalizability. In addition, less than half (46.8%) of the enrolled patients underwent gold-standard confirmatory imaging.

Overall, the ADvISED Trial Algorithm by Nazerian et al. has shown promise for EM physicians and provides an evidence-based method for ruling out AAS in the ED. However, prospective validation of this algorithm incorporating broadened clinical features of AAS is still needed. Also, further refinement of the D-dimer threshold could enhance this clinical tool's sensitivity and negative predictive value. Such testing and refinements could lead to a rapid, easy, and objective diagnostic algorithm to rule out AAS in the emergency room. The hope for EM providers is to have a clinical decision-making tool that can safely rule out AAS and greatly reduce the need for diagnostic imaging.

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