Imaging and Biomarkers in Acute Aortic Syndromes: Diagnostic and Prognostic Implications

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Abstract: Acute aortic syndrome (AAS) is an emergency and life-threatening condition including aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer and iatrogenic-traumatic aortic injury. An integrated multiparametric approach (clinical history and examination, electrocardiogram, biomarkers and imaging techniques) is recommended in order to make timely and accurate diagnosis, delineate the prognosis, choose the most appropriate therapeutic interventions tailored for the individual patient. Nowadays the best imaging strategy for diagnosing AAS and its complications is a combination of transthoracic echocardiography and computed tomography angiography (CTA). Transesophageal echocardiography tends to be carried out in complicated cases prior to surgical or endovascular therapy, often in the

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Conflict of Interest: The authors declare that they have no conflict of interest.

Curr Probl Cardiol 2021;46:100654
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100654

operating room and under general anesthesia. In this regard, intravascular ultrasound and intraluminal phase array imaging may be implemented during the endovascular procedures depending on operator expertise and cost issues. On the other hand, owing to its intrinsic characteristics, magnetic resonance imaging is an ideal imaging technique for serial measurements in patients at risk of AAS or with chronic dissection. Among biomarkers, D-dimer is the closest to "golden status" (high sensitivity and low negative likelihood ratio). Interestingly, 18fluorodeoxyglucose positron emission tomography/CT is increasingly being used along with specific serologic biomarkers (white blood cells, C-reactive protein, fibrinogen and D-dimer) to detect and monitor vascular inflammation affecting the aorta and systemic arteries. It is expected, in the near future, the development of serologic and imaging biomarkers able to early detect clinically-silent pathologic changes in the aorta wall before (primary prevention) and after (secondary prevention) the acute index event. (Curr Probl Cardiol 2021;46:100654.)

Introduction

Acute aortic syndrome (AAS) is an emergency and potentially life-threatening condition which include aortic dissection (AD), intramural hematoma (IMH), penetrating atherosclerotic ulcer (PAU) and iatrogenic-traumatic aortic injury (TAI) characterized by impairment of aortic wall integrity.[1] These clinical entities are commonly classified as type A and type B AAS depending, respectively, on involvement or not of the ascending aorta regardless of the site of origin (Stanford classification). Recently, a new subtype, non-A-non-B AD has been defined due its unique clinical course as AD involving the aortic arch-either by a primary entry tear in the aortic arch or by retrograde extension of a primary type B AD (Fig 1).[2] The time course is stratified in acute (<14 days), sub-acute (15-90 days) and chronic (>90 days) phases.[1] Presenting symptoms and signs may be heterogenous, nonspecific or, in some cases, absent (painless dissections reported in 5%-6%) requiring a high index of clinical suspicion by the treating physician team. Thus, an integrated multiparametric approach including data derived from

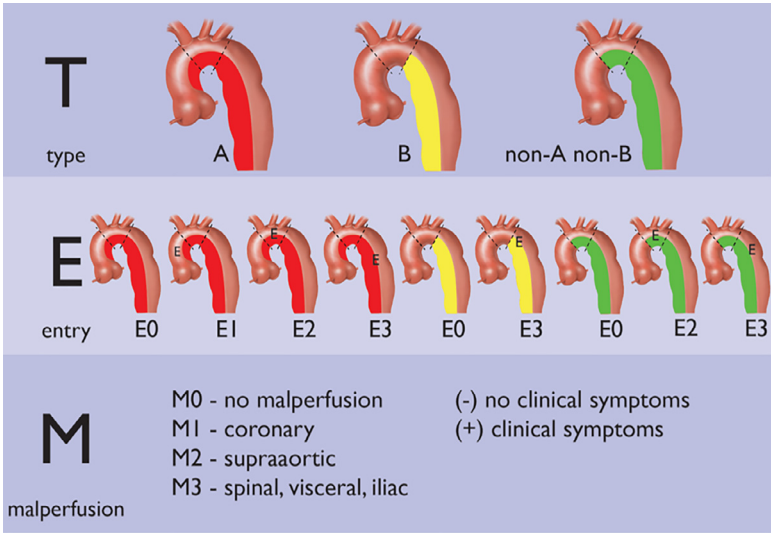

FIG 1. The TEM aortic dissection classification system. Modified from ref.[2]

anamnesis, clinical examination, electrocardiogram, chest X-ray, biomarkers and imaging techniques is recommended in order to make a prompt and accurate diagnosis, delineate the prognosis, choose the most appropriate therapeutic interventions and plan careful follow up (Fig 2).[1,3,4]

The aim of this review is to discuss the advance diagnostic and prognostic role of imaging techniques and biomarkers.

Clinical Features—Imaging

Cardiovascular Ultrasound

Transthoracic echocardiography. Transthoracic echocardiography (TTE) is the most used imaging test in the clinical evaluation of cardiovascular disease and plays an important role in the diagnosis of aortic diseases. Among imaging techniques, echocardiography has the advantage that it can be performed at the patient's bedside, is rapid, without any side effects and without radiation. TTE permits adequate assessment of several aortic segments, particularly the aortic root and proximal ascending aorta and, in most cases, the aortic arch, proximal descending aorta and abdominal aorta (Fig 3A and B). All scanning planes should be used

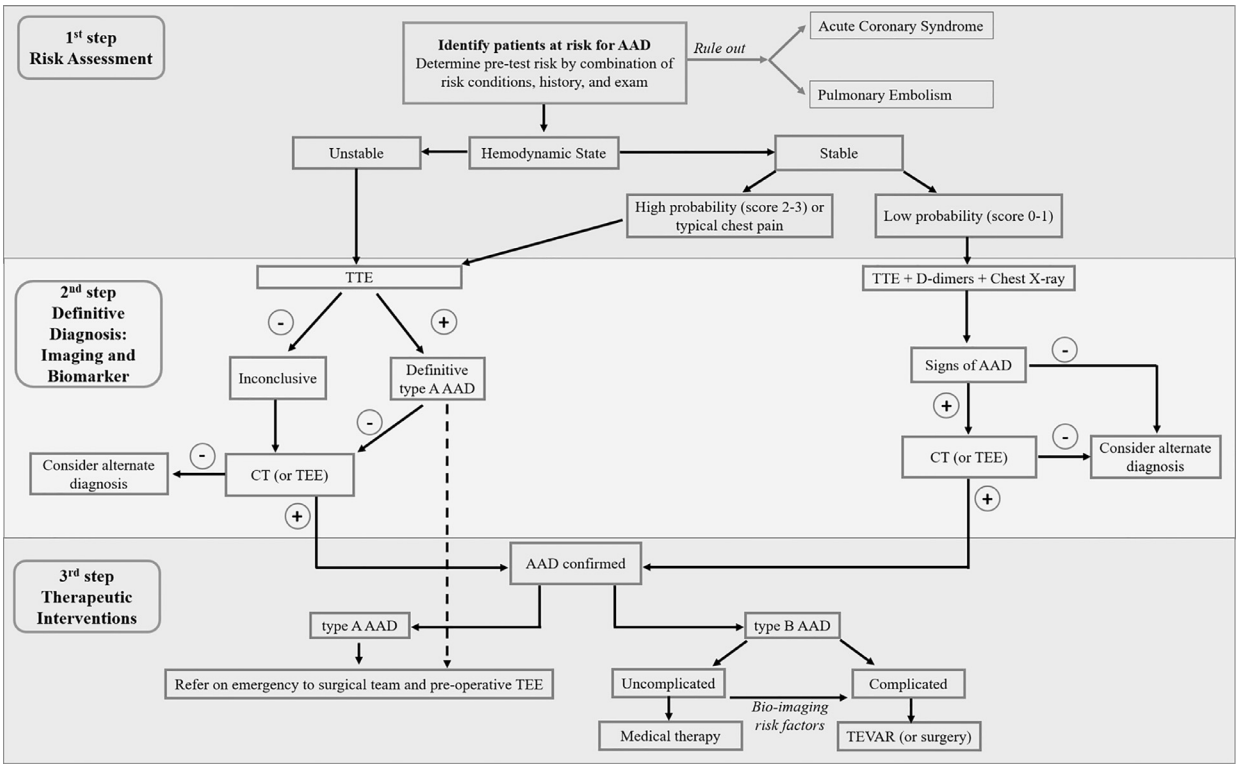

FIG 2. AAS diagnostic algorithm modified from ref.[1,2] Abbreviations: AAD, acute aortic dissection; AAS, acute aortic syndrome; CT, computed tomography; TEE, transesophageal echocardiography; TEVAR, thoracic endovascular aortic repair; TTE, transthoracic echocardiography.

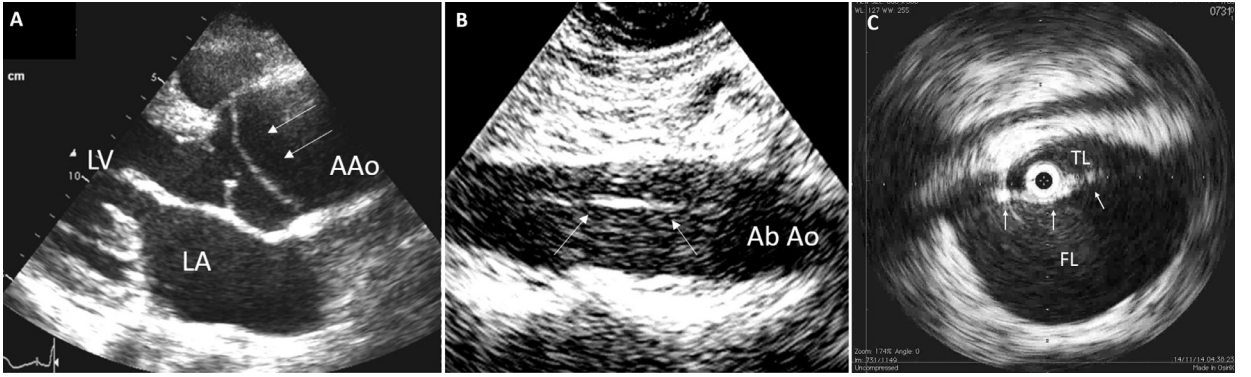

FIG 3. Cardiovascular ultrasound imaging in acute aortic dissection. (A and B) Aortic dissection diagnosed by TTE: (A) Intimal flap (arrows) is visualized in the aortic root; (B) intimal flap (arrows) in abdominal aorta. (C) Descending aorta dissection showed by intravascular ultrasound (IVUS). The intimal flap (arrows) is visualized between FL and true lumen TL. Abbreviations: AAO, ascending aorta; Ab Ao, Abdominal aorta; FL, false lumen; LA, left atrium; LV, left ventricle; TEE, transesophageal echocardiography; TL, true lumen; TTE, transthoracic echocardiography.

including the left and right parasternal long-axis views, suprasternal, 2-chamber and subcostal views. Transthoracic echocardiography has been generally considered limited in the diagnosis of acute aortic dissection (AAD). Older series reported sensitivity levels as low as 57%, which was inadequate for clinical purposes. However, recent advances in echocardiography, including harmonic and contrast imaging, have greatly improved image quality and, consequently increases sensitivity and specificity to 80%.[5,6] In addition, TTE provides dimensions of the aorta, assessment of left ventricular contractility, pericardial effusion, and aortic valve dysfunction. However, intrinsic TTE limitations (ie, restricted echo-windows and thorax deformities) can limit the ability to perform a complete aorta assessment, particularly of the descending thoracic aorta. In fact, TTE is less accurate for type B AAS assessment,[6] particularly in IMH and PAU diagnoses. For this reason, when clinical suspicion is high, a negative TTE does not rule out the diagnosis of AAD and a second imaging test (usually computed tomography angiography [CTA] or transesophageal echocardiography [TEE]) is recommended.

Transesophageal echocardiography. Given the anatomic proximity of the esophagus to the aorta, TEE can overcome many TTE limitations. It has the unique advantage that it can be performed in virtually all clinical settings (ie, emergency room, operating room, and intensive care unit). The sensitivity of TEE for AAD reaches 99% with 89% specificity.[7] Furthermore, the emerging added value of 3-dimensional TEE in terms of guiding therapeutic intervention should also be considereds.[8] TEE is very useful for locating and measuring the size of the primary entry tear. Color Doppler can reveal the presence of multiple small communications between the lumina. TEE provides an easy identification of the true lumen (TL), which may be important before surgery or endovascular treatment. The false lumen (FL) is usually larger and has less flow than the TL. M-mode TEE shows how the intima moves towards the FL at the start of systole by expansion of the TL. Moreover the flap thickness provides information about the acuity of the event, the thinner the flap the most likely is that the AAD is acute. Aortic regurgitation is a common complication, occurring in approximately 40%-76% of patients with type A dissection. TEE is the best technique for defining the mechanisms of aortic regurgitation, which can result in substantial changes in surgical strategy for aortic valve replacement or repair. Furthermore, TEE may provide prognostic information on AAD beyond clinical risk features.[9] In surgically-treated type A AAD, the in-hospital mortality risk increases among patients with pericardial effusion, tamponade, periaortic

hematoma and patent FL while decreasing in the presence of a dissection flap confined to the ascending aorta and complete thrombosis of the FL. However, TEE is semi-invasive, but can cause a rise in systemic pressure from gagging, and adequate sedation and strict blood pressure control are mandatory. The need for 24-hour availability of experienced operators may further limit the emergent accessibility of TEE. Finally, TEE can be limited in visualizing of the distal ascending aorta and proximal arch (blind spot) owing to interposition of the left mainstem bronchus. In recent years, has tended to be carried out in the operating room and under general anesthesia, before surgical or endovascular therapy and monitoring of these procedures.

Intravascular ultrasound and intraluminal phase array imaging. By providing real-time imaging details of aortic disease along with accurate aortic diameter assessment, intravascular ultrasound (IVUS) is considered to be reliable and safe for guiding stent-graft positioning. Intraluminal phase array imaging (IPAI) adding key flow information on aorta side branches may be a useful tool for emergency fenestration. However, the use IVUS and IPAI depending on the availability of local expertise and cost related issues should be taken into account (Fig 3C).[10]

Abdominal ultrasound. In cases of aneurysm/dissection of the abdominal aorta, color Doppler abdominal ultrasound (A-US) provides substantial information regarding potential wall lesions including vessel dimension and flow patterns (TL vs FL). It should be highlighted that population screening for AAA with A-US is recommended in all men >65 years of age, while it may be considered in women >65 years of age with a history of current/past smoking. In the above cohorts or in any case of increased risk for AAA, it is also advised to perform a "quick check" of the abdominal aorta during TTE examination (opportunistic screening for AAA).[11,12]

Computed Tomography Angiography

CTA is the most widely used imaging technique in patients with suspected AAS owing to its high diagnostic accuracy (pooled sensitivity 100%, pooled specificity 98%) and robustness, rapidity and wide availability in virtually all emergency departments.[13,14] Recent improvements in CT technology have increased scan speed, thereby shortening scan times and reducing radiation dose to patients. Diagnosis is usually made on native axial images complemented by multiplanar reconstructions/

reformats (MRP) (Figs 4 and 5). A pulsation artifact in the ascending aorta can often mimic a pseudoflap; this artifact should prevented by using ECG-synchronized acquisitions in analogy of what is required when Cardiac CT is performed. There different methods of ECG synchronization that can minimize or cancel motion artifacts at the level of ascending aorta. In any situation in which an aortic disease is suspected, especially if acute, ECG synchronization with CT is a standard operational requirement. This is true even when a simple aortic dilatation is present because it allows to collect proper measurements that are mandatory for risk stratification and treatment planning. In addition, there are multiple other means and algorithms for the visualization of relevant information in the context of AAS (eg, aneurysms, dissections, thrombi, calcifications and involvement of adjacent structures and parent arteries of the aortic arch) which are mainly: maximum intensity projections, 3D volume-rendering images and, more recently, 3D cinematic rendering.[15,16] High spatial and temporal resolution also permits the evaluation and assessment of fast-moving structures such as aortic root, coronary arteries, cardiac valves (ie, aortic valve) and cardiac chambers; also it can properly visualize pericardial structures and all chest and abdominal structures. The standard protocol includes an unenhanced scan followed by a contrast enhanced CT. Correct CT scan protocols for thoracic aorta assessment include ECG triggering or gating in order to remove motion artifacts related to heartbeat, particularly in the ascending aorta.[17] CT has been proposed as a one-step imaging modality (triple-rule out strategy) to distinguish 3 potential causes of acute chest pain: AAS, pulmonary embolism and coronary artery disease.[18] AAD is characterized on contrast-enhanced images by the intimal flap separating TL and FL. On unenhanced images, intraluminally displaced calcifications adherent to intimal layer may also be visible.[19] The careful administration of intravenous contrast (both volume and injection rate) can avoid streak artifacts in the aorta which may potentially simulate dissection. CT and TEE are more useful than MR for locating and measuring the size of the primary entry tear and secondary communications. In addition, CT is the technique of choice in the diagnosis of aortic trunk involvement which may account for some symptoms secondary to visceral or peripheral ischemia. Two main patterns of branch circulation disorder can be detected using CT: dissection or dynamic obstruction of the intimal flap at the branch ostia. Differentiating the 2 mechanisms has major therapeutic implications. This technique can easily diagnose periaortic hematoma which is associated with increased mortality in type A AAD; a preliminary nonenhanced ECG-synchronized CT scan prior to contrast material administration can

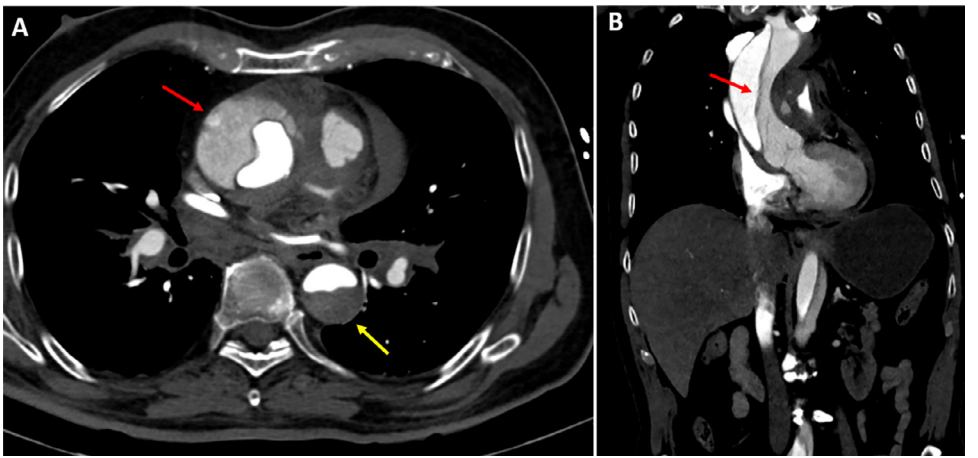

FIG 4. (A) Computed tomography axial view in a patient with a type A aortic dissection. Ascending aorta dissection (red arrow) and descending aorta dissection (yellow arrow); (B) sagittal view of type A dissection extending into the right subclavian artery. (Color version of figure is available online.)

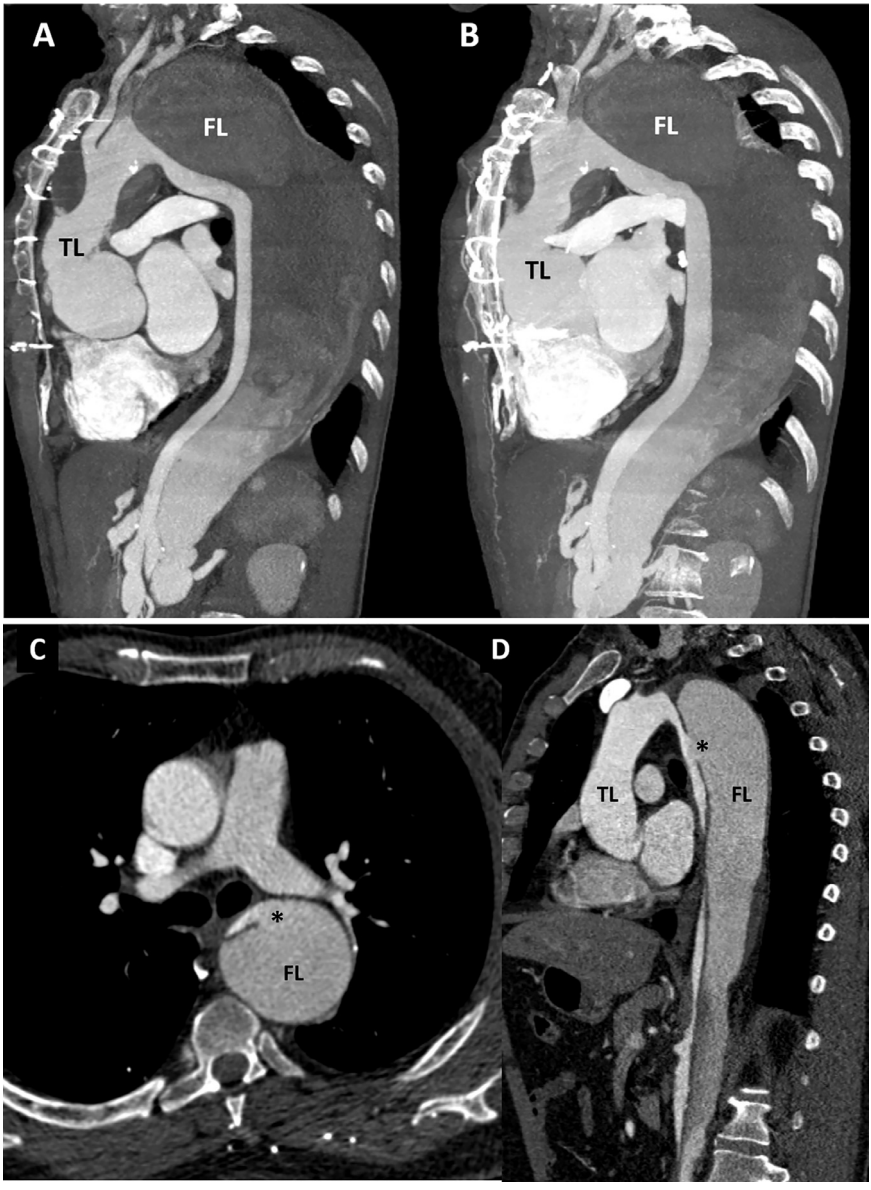

FIG 5. (above) Computed tomography 2D in a sagittal view in a patient with a residual type B aortic dissection (A) and MIP reconstruction (B). (below) Computed tomography 2D reconstruction in a patient with a type B aortic dissection. Image (C) showing an axial reconstruction at the level of the entry tear (*) and image (D) showing a sagittal oblique reconstruction of the aorta. Abbreviations: FL, false lumen; TL, true lumen.

easily detect crescent hyper-density within the thickened wall which corresponds to blood infiltrating the aortic layers. Furthermore, in type B AAD, CT may rapidly detect "high-risk" imaging features (primary entry tear diameter >10 mm, initial total aortic diameter ≥40 mm, FL ≥22 mm, patent FL or partially-thrombosed FL, location of the primary entry tear at the lesser curvature as well as its distance to the left subclavian artery ostium suggesting an unstable disease state (Table 1).[20-35]

Intramural hematoma (IMH) appears on unenhanced CT as high-attenuation crescentic thickening of the aortic wall (Fig 6, A and B). Medially-displaced calcifications can occur, however, unlike AAD, the aortic lumen is rarely compromised and no intimal flap or enhancement of the aortic wall is seen after contrast administration.[36] The combination of unenhanced and contrast-enhanced CT acquisitions increases IMH sensitivity to as high as 96%.[37] Looking carefully at the surface of the aortic lumen, it is almost always possible to detect the intimal tear if the images are technically adequate (ie, ECG synchronization and high resolution reconstructions), especially at the level of the aortic root and ascending aorta.

Penetrating atherosclerotic ulcer (PAU) may have a similar appearance to IMH on precontrast imaging and is often associated with surrounding atherosclerosis. PAU is best detected on contrast-enhanced CT (Fig 6, C). It is characterized by a contrast-filled outpouching beyond the normal countours of the aorta. PAU erodes the aortic wall and reaches the medial

Table 1. High risk imaging features in acute type B AD, IMH and PAU[20,21]

Type B AD	IMH	PAU
Primary ET diameter >10 mm[22]	Maximum aortic diameter >45 mm[28,29]	Periaortic bleeding presence[34,35]
Initial total AD ≥ 40 mm[22]	Wall thickness of involved segment ≥10 mm[30]	Pleural effusion: significant/ progressive[34,35]
FL diameter ≥22 mm[23]	Periaortic hemorrhage presence[28,31]	IMH-associated[34,35]
Patent FL (vs fully thrombosed)[24]	Pleural effusion presence[31,32]	Large initial depth or high growth rate size[34,35]
Partially thrombosed FL[25]	FID:[33]	
Location of the primary entry tear[26]	- Time presentation: acute	
Distance of the primary entry tear to LSA[27]	- Communicating orifice > 3 mm	

Abbreviations: AD, aortic diameter; ET, entry tear; FID, focal intimal disruption; FL, false lumen; IMH, intramural hematoma; LSA, left subclavian artery; PAU, penetrating aortic ulcer.

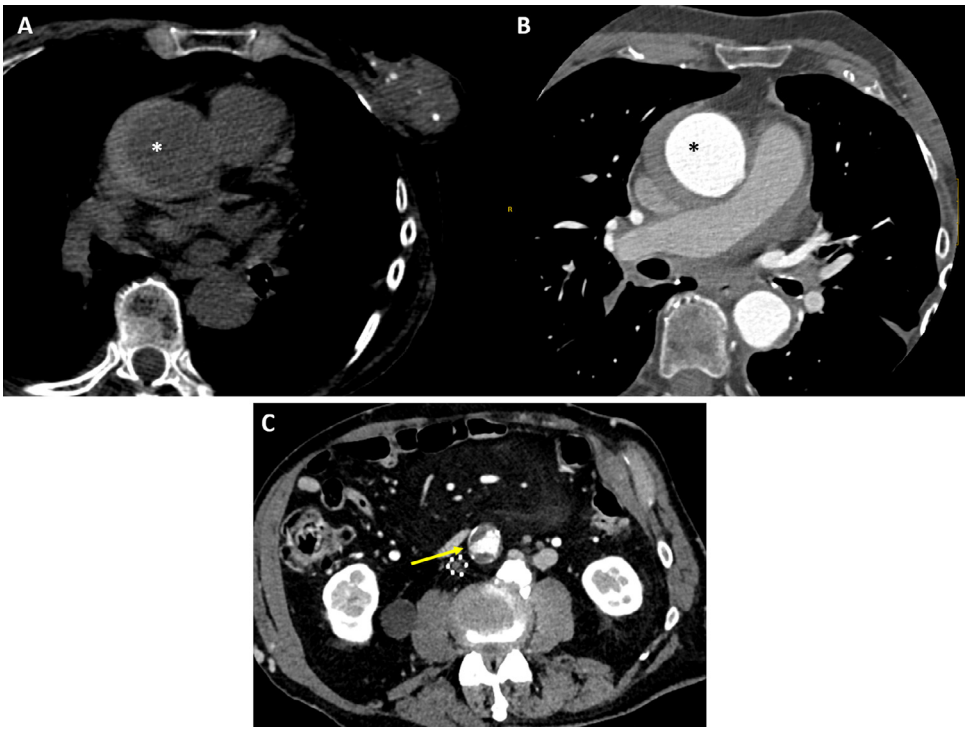

FIG 6. Computed tomography of intramural hematoma and penetrating aortic ulcer. Computed tomography in an axial view in a patient with an intramural hematoma (* showing the bleeding region) before (A) and after (B) the administration of iodine contrast. Of note, the hyperintensity of the aortic wall in the pre-contrast image. (C) Computed tomography in axial view showing ulcerated plaque in the descending aorta.

layer, allowing hematoma formation.[38] New insights into the pathophysiology of PAU may derive from CT tissue characterization of the atherosclerotic plaques to clarify plaque composition in the context of PAU.[39] As for AAD, CT may intercept imaging biomarkers as early predictors of major adverse events.

The main drawbacks of CTA are the administration of iodinated contrast agent, which may cause allergic reactions or acute kidney injury, and the use of ionizing radiation which may limit its use in younger patients and when follow-up is needed.[40] Importantly, CTA is limited by contrast material exposure in the setting of renal dysfunction, even though the amount of contrast material currently required to perform the scan is quite low compared to the past (ie, using state-of- the-art CT technology, 50 ml). Also the radiation dose for CTA with contemporary equipment is significantly reduced as compared to the past due to improved speed of acquisition, low KiloVoltage and iterative reconstructions. Nevertheless, CTA is anyhow mandatory in emergency settings when acute aortic disease is the main suspicion.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MR), with a high spatial (even though lower than CTA) and temporal resolution, provide anatomical, functional, and multiparametric tissue characterization in aortic diseases (sensitivity 97%-100% and specificity 94%-100%).[41] Nonetheless, since the limited availability, complex management of the acute patient inside the scanner, and long scan duration (> 30 minutes), it is not considered the technique of choice in AAS.[18] However, by the absence of ionizing radiation and the possibility to use noncontrast sequences, it is an excellent test in the chronic follow-up after AAS.[42] MR protocols for aortic diseases include black-blood, bright blood, ECG-gated cine, phase-contrast sequences, contrast-enhanced (CE) MR angiography (MRA)[3,18,42-44], and more recently, noncontrast enhanced MRA (with similar accuracy as CE-MRA).[45]

Black-blood sequences provide excellent morphological information on the aortic wall and adjacent structures.[4,46,47] They show the intimomedial flap in AD and the semilunar or concentric wall thickening in IMH. Due to contrast differences between tissues, small IMHs not diagnosed by CT can be detected by MR. In the hyperacute phase of IMH, T_1-weighted images appear isointense (Fig 7) and T_2-weighted hyperintense (Fig 8). However, change from oxyhemoglobin to methemoglobin after 24-72 hours, induces a hyperintense signal in both T_1- and T_2-weighted

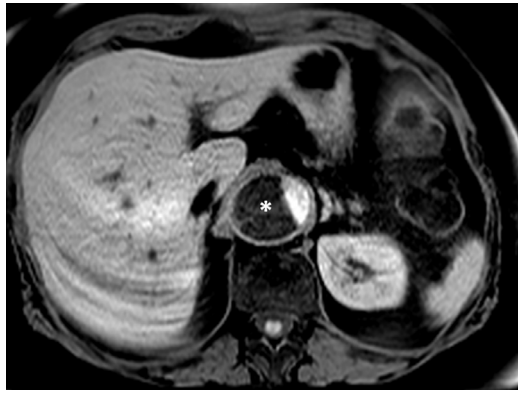

FIG 7. T_1-weigthed turbo spin echo in an axial view in a patient with a type B intramural hematoma. A fat suppression technique is applied to differentiate the intramural hematoma from periaortic fat (* show the presence of signal hyperintensity corresponding to the bleeding region).

images.[18] Moreover, disruption of the intima with an extension to the thickened media associated with intramural hematoma is seen in PAU. The differential diagnosis should be established between atherosclerotic ulcers that penetrate the middle layer and ulcer-like images that develop from a focal intimal disruption or a localized dissection in IMH evolution.

Bright-blood and ECG-gated sequences show spontaneous contrast differences between aorta wall and the brighter blood pool,[4] thus, the aortic vessel can be nicely studied without intravenous contrast injection.[48] Given the ECG-synchronization, these sequences are of choice for the aortic root evaluation, in analogy with the requirements of CTA in these settings. TL and FL can be easily differentiated by flow patterns and anatomic features: the TL shows systolic expansion and unidirectional systolic antegrade flow.[49] Pericardial, pleural, or mediastinal fluid extravasation are signs of imminent rupture.

Phase-contrast sequences can identify aortic regurgitation, entry sites, and differentiate slow flow from thrombus in the FL. They have a promising role in the functional assessment of AD through the quantification of flow in both lumina and the possibility of establishing hemodynamic patterns of progressive dilation risk. An increased FL pressure is associated with FL enlargement and aortic dilation. Indirect signs of high FL pressure include TL compression, partial thrombosis of the FL, and a diastolic retrograde flow in the FL.

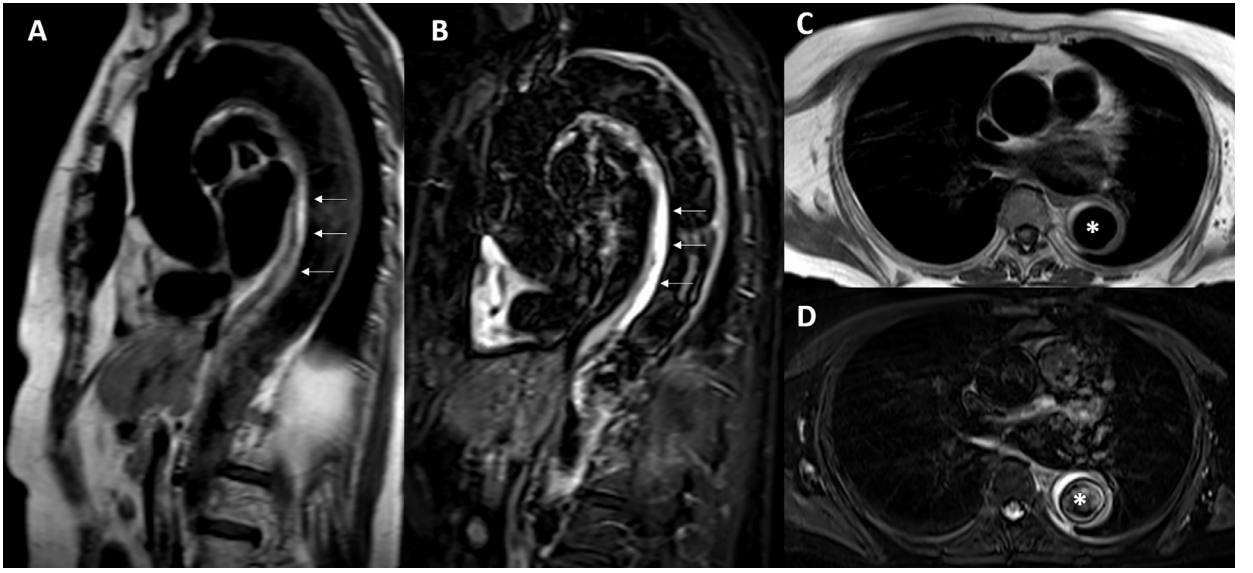

FIG 8. T_1-weigthed turbo spin echo in a sagittal view (A) and axial view (C) in a patients with an intramural hematoma. T_2-weighted turbo spin echo of the same patient and same views (B and D). The arrows and the * show the presence of signal hyperintensity corresponding to the bleeding region. Hyperintensity in T_2-weighted sequences confirm the presence of an intramural hematoma in the hyperacute setting.

CE-MRA offers important 3D anatomical information on both the aorta and main collateral vessels (Fig 9). The acquired images must be re-evaluated by postprocessing maximum intensity projections, MPR and volume rendering reconstructions. In AD, they assess FL patency, degree of lumen thrombosis, aortic diameters, intimal flap, and demonstrate both entry and exit tears.[4,44] Multiphasic time-resolved 3D-MRA images can be obtained with a high temporal and spatial resolution which are important to evaluate flow dynamics in TL and FL as well as to identify entry and exit tears. For planning surgery or endovascular repair, it is useful to demonstrate the course of the flap, entry tear location, FL thrombosis, aortic diameter, and main arterial trunk involvement by postprocessed images. Compared to CT, images provided by MR do not allow to recognize vessel calcification and artifacts produced by certain types of endovascular prosthesis.[7]

In the near future, 4D-flow MR which is able to assess and quantify aortic flow dynamics over time would be able to improve characterization in patients with aortic diseases.

^{18}F fluorodeoxyglucose positron emission tomography/CT

^{18}fluorodeoxyglucose positron emission tomography/CT is increasingly being used along with specific serologic biomarkers (white blood cells, C-reactive protein [CRP], fibrinogen and D-dimer) to detect and monitor vascular inflammation affecting the aorta and systemic arteries, as in the case of noninfectious aortitis and aorta endovascular graft infection (postimplantation syndrome).[50-52] Furthermore PET-CT imaging may be helpful in the setting of AAS to identify patients at higher risk of disease progression, re-intervention during follow-up and death. The combination of increased inflammatory and/ or thrombotic biomarker levels and PET findings may better predict major adverse events than PET alone.[53,54] However, PET imaging remains costly, not widely available and does involve exposure to ionizing radiation.

Role of integrated multimaging in the Hybrid Room—CT, TEE, Angiography, Aortoscopy

The hybrid room setting has become the fundament for modern treatment of AASs as nature and dynamics of the disease may require both-open surgery and endovascular therapy. Acute complicated type A AD is a very good example where- given that the primary entry tear is not located in the ascending but in the descending aorta (retrograde type A

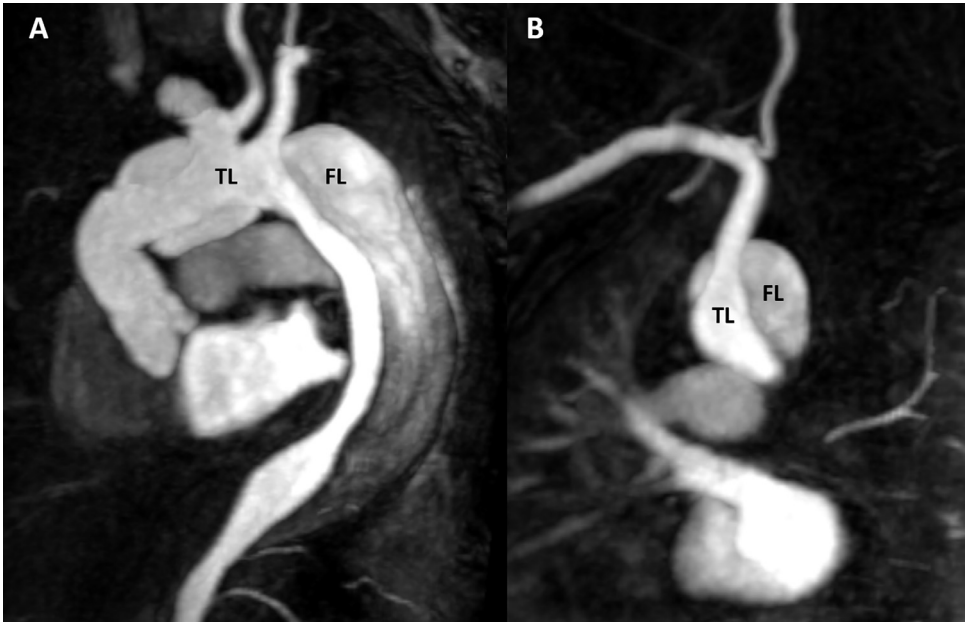

FIG 9. Contrast-enhanced magnetic resonance (MR) angiography of the aorta (MIP reconstruction) in a sagittal view (A) in a patient with a residual type B aortic dissection. Coronal view (B) showing the left subclavian artery arising from the true lumen. Abbreviations: FL, false lumen; TL, true lumen.

AD) more extensive surgery is needed either to surgically resect the primary entry tear or to exclude it from circulation. This diagnosis is established by both CTA and TEE.

The surgical approach of choice in these complex scenarios is most often by application of the so-called frozen elephant trunk technique where a hybrid prosthesis being composed of a stent-graft and a regular Dacron prosthesis is used to replace the ascending aorta and the aortic arch, the stent-graft component stabilizes the dissection membrane in the proximal descending aorta.

Intraoperative aortoscopy to exactly position the stent-graft component in the TL is a very useful tool, in particular in cases where several communications between lumina are present and crossing the membrane with final deployment of the stent-graft component in the FL may have deleterious consequences. In addition, TEE can be very useful for placing a guidewire transfemorally into the TL which is an excellent way to guarantee TL positioning of the stent-graft component.

In case of persistent malperfusion, for example due to large secondary communications between lumina, simultaneous TEVAR can be performed transfemorally and the malperfusion syndrome can be treated timely and effectively before irreversible end-organ injury has occurred.

Clinical Features—Biomarkers

In recent decades, circulating biomarkers have gained an exponential key player role in the diagnostic-prognostic pathways of cardiovascular diseases, namely acute coronary syndrome, venous thromboembolism (VTE), heart failure (HF) and AAS. In AAS, several biomarkers reflecting aortic wall pathophysiologic changes (smMHC, CK-BB, MMPs, sELAF) including inflammatory (CRP, IL-6, Tenascin-C, NT-proBNP) and thrombotic (D-dimer) process as are under investigation. Among these, D-dimer appears to be the closest to acquiring "golden status" (Fig 10).[55,56]

Smooth muscle markers (Table 2)[55-57]

Smooth muscle myosin heavy chain. The smooth muscle myosin heavy chain (smMHC) is released into the bloodstream immediately after the aorta media layer wall lesion, reaching concentrations 20 times higher than baseline and rapidly dropping to normal levels.[58] Thus, smMHC quantification shows a time-dependent AAD diagnostic sensitivity and

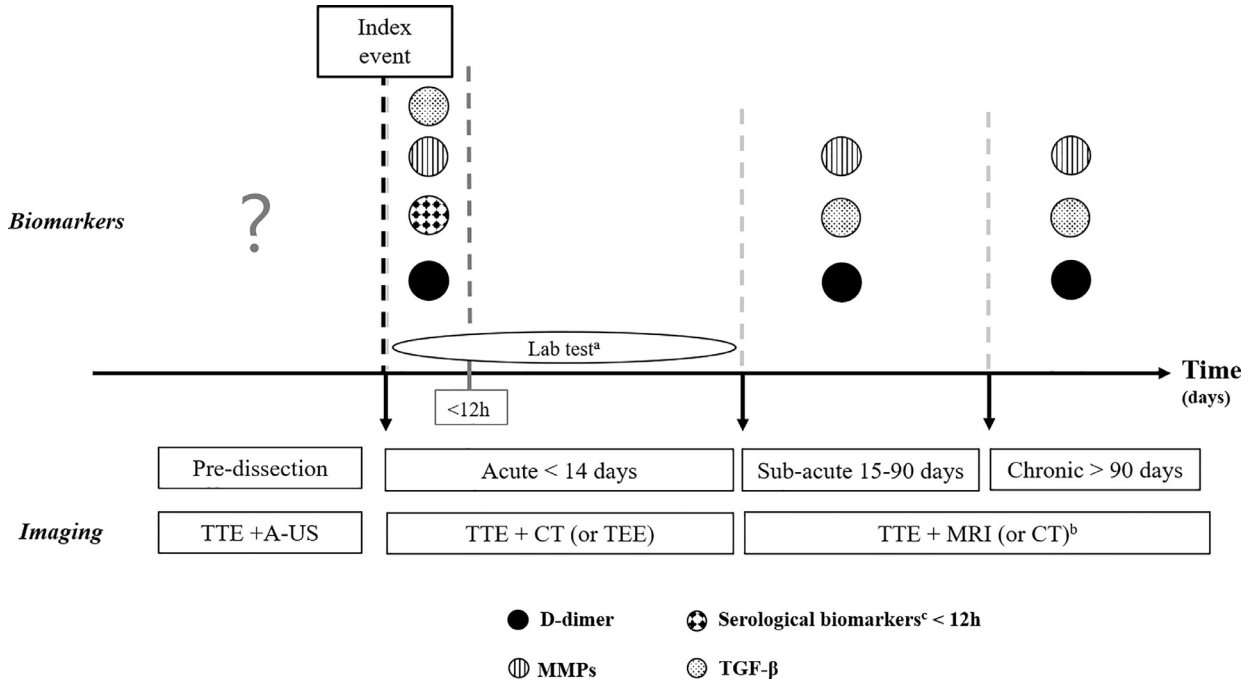

FIG 10. Time course serological biomarkers and imaging in acute aortic syndrome. [a]Laboratory test: Red blood cell count/Hb; white blood cell count; C-reactive protein; IL-6; procalcitonin; creatine kinase; troponin I or T; D-dimer; creatinine; aspartate transaminase/alanine aminotransferase; lactate; glucose; blood gases; BNP/NT-proBNP. [b]During follow-up the patients perform imaging tests at 3, 6, 12 months and subsequently annually. [c]Serological biomarkers: smooth muscle myosin heavy chain; creatine kinase BB-isozyme; calponin. Abbreviations: A-US, abdominal ultrasound; CT, computed tomography; MMPs, matrix metalloproteinases; MR, magnetic resonance imaging; TEE, transesophageal echocardiography; TGF-β, transforming growth factor-β; TTE, transthoracic echocardiography. Modified from Refs.[50,51]

Table 2. Smooth muscle biomarkers of acute aortic syndrome.

Biomarkers	Characteristics	Availability	Clinical implications	Remarks
SM-MHC	Protein present in the aortic media layer.	Experimental	Sensitivity 90%; specificity 97%. Elevation limit in the initial 3-6 h. Restricted time window. Differential diagnosis: type A-AAD vs AMI within 3 h.	Higher levels in proximal vs distal dissection.
CK-BB isozyme	Selective isozyme for smooth muscle and neurological tissue.	Commercial (USA, EU, AP)	Short time window. Peak at 6 h after symptom onset in AAD pts.	Lack of specificity.
Calponin	Troponin counterpart of smooth muscle. The basic isoform is most specific for smooth muscle.	Experimental	Elevated levels in AAD within the first 24 h. Peak at 6 h after symptom onset in type A-AAD pts.	
ET	Peptides produced primarily in the endothelium, having a key role in vascular homeostasis.	Experimental	ET-1 and ET-2 elevation in AAD pts. Higher levels in acute AD vs chronic AD.	

Abbreviations: AAD, acute aortic dissection; AD, aortic dissection; AMI, acute myocardial infarction; AP, Asia-Pacific; CK-BB, creatine kinase BB-isozyme; ET, endhotelin; EU, European Union; pts, patients; SM-MHC, smooth muscle myosin heavy-chain protein; USA, United States of America.
Modified from Refs.[55-57]

specificity. The limited time accuracy window (3-6 hours from onset) restricts its clinical use.[55,56]

Creatine kinase-BB isozyme. CK-BB isoenzyme concentrations were found raised in AAD patients (reflecting aortic smooth muscle damage). In particular, a 7.8-fold CK-BB isoenzyme increase was observed, peaking approximately 6 hours after onset.[59]

Calponin. AAD patients showed both acid and basic calponin elevations within the first 24 hours in of both proximal and distal aortic disease. Conversely, no correlation was detected between neutral calponin and AAD. Moreover, different time-dependent specificity was observed in acid and basic calponin detection. Raised double (acid calponin) and triple (basic calponin) levels were detected in AAD patients, within the first 6 hours after symptom onset. Acid calponin showed high specificity in type A-AAD detection.[57] In particular, Suzuki et al (2008) reported sensitivity of 50% and 53% and specificity of 87% and 73%, respectively, for acidic and basic calponins, within 6 hours with clinical cutoffs of 2.3 ng/ml (acidic) and 159 ng/ml (basic). Calponin presented a long time course (within 1 day) but poor positive predictive value.[57] Currently, calponin assays are not available as point-of-care tests since further refinements are required.

Endothelins. Endothelins are a family of peptides including endothelin-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3). Elevated ET-1/2 concentrations were found in AAD or ruptured aneurysms particularly in the nonsurvival patient cohort, suggesting a potential prognostic value.[60,61]

Extracellular Matrix Markers (Table 3)[55,56]

Matrix metalloproteinases. Matrix metalloproteinases (MMP) are a family of zinc- and calcium-endopeptidases mainly involved in the aortic remodeling process.[55,56,62,63] Increased MMP-9 levels within 1 hour of symptom onset have been observed among patients with type A AAD and type B AAD. Moreover, elevated MMP-9 concentrations were also recorded in the subacute phase (up to 2-month posthospital discharge) of medically-treated type B AA.[64]

Table 3. Extracellular matrix proteins biomarkers of acute aortic syndrome

Biomarkers	Characteristics	Availability	Clinical implications	Remarks
MMPs (MMP-9)	Zinc- and calcium-dependent endopeptidases. Enzymes involved in aortic remodeling process.	Experimental	MMP-9 is elevated in AAD. Increased levels within 1 h from symptoms onset.	MMP-9 may be useful in long term follow-up to monitor aortic remodeling.
sELAF	Soluble fragments due to degradation of elastin that is abundantly present in aortic wall.	Experimental	Sensitivity 64%; specificity 99.8%. Potential diagnostic use within 0.7 h after onset of AAD. Elevation in AAD pts depends on the status of the FL or degree of thrombus formation.	Higher levels in proximal vs distal dissection.
TGF-β	Multifunctional cytokine involved in several pathways.	Experimental	Therapeutic monitoring of aortic remodeling in MFS pts. Elevated in AAD (particularly in type A).	

Abbreviations: AAD, acute aortic dissection; FL, false lumen; MFS, Marfan syndrome; MMPs, matrix metalloproteinases; pts, patients; sELAF, soluble elastin fragments; TGF-β, transforming growth factor-β.
Modified from Refs.[55,56]

Soluble elastin fragments. Soluble elastin fragments (sELAF) could be considered an early diagnostic marker since their circulating levels increased as early as 0.7 hours after AAD symptom manifestation.[65] Of note, patients with thrombosed FL showed no sELAF increase while, in contrast, in patients with perfused FL, sELAF levels remained high for a long period of time (>72 hours).[65]

Transforming growth factor-β. TGF-β is a signaling molecule involved in several pathways. TGF-β can bind to fibrillin-1, an extracellular matrix protein encoded by the FBN1 gene, which is mutated in most Marfan patients. In Marfan patients, fibrillin-1 deficiency results in over-signaling of TGF-β, leading to deregulation of TGF-β bioavailability.[1,66] Suzuki (2011) recently reported elevated TGF-β levels also in AAD patients.[67] In detail, a 2-fold rise was observed in type A patients compared with type B patients, supporting TGF-β as a potential biomarker in the identification of AAD in adult non-MS patients. Moreover, the quantification of circulating TFG-β level could be useful as an aortic remodeling marker. Additional evidence has shown that increasing amounts of circulating TGF-β also occur in patients with larger aortic diameter. However, the true clinical value of TGF-β testing in AAD patients requires further study .

Inflammatory Markers (Table 4)[55,56]

C-reactive protein. CRP is mainly produced in the liver by the stimulation of several cytokines during the acute phase of inflammation. Its levels are related to both the presence and extension of the inflammatory response (nonspecific protein of vascular inflammation). Interestingly, in AAS, CRP plasma levels at hospital admission appear to correlate with adverse long-term adverse events.[68] However, the added clinical value of CRP testing among AAS patients remains uncertain.

Tenascin-C. Tenascin-C (TN-C) (adhesive glycoprotein, constituent of the extracellular matrix) is thought to play a leading role in cardiovascular tissue remodeling, including coronary atherosclerotic plaque, abdominal aortic aneurysm, acute myocardial infarction, myocarditis and VTE.[69-73] In type B-AAD patients, raised TN-C levels have been associated with in-hospital mortality.[74] Conversely, in chronic B-AAD patients, increased TN-C levels may constitute a predictive marker for low risk of aortic lesion extension.[75]

Table 4. Inflammatory biomarkers of acute aortic syndrome.

Biomarkers	Characteristics	Availability	Clinical implications	Remarks
CRP	Nonspecific inflammatory marker produced in the liver.	Commercial (USA, EU, AP)	Monitoring evolution of FL thrombosis. Elevated levels indicate poor prognosis (in type A and B-AAD) ↑ CRP and positive PET uptake in the aortic wall correlate with progression of aortic disease.	Lack of specificity.
IL-6	Originates from the liver after stimulation with cytokines.	Experimental	IL-6 refers to dissection gravity and time after presentation. Inflammatory stages reflect concentration variation.	
TN-C	Adhesive glycoprotein, constituent of the extracellular matrix. Roles in cardiovascular tissue remodeling.	Experimental	Concentrations of fibrin degradation products correlate with TN-C concentrations in acute phase of AD.	In type B-AAD: elevated levels in both acute stage and at hospital's admission predicting in-hospital mortality. ↑ TN-C could induce a protective effect in the chronic AD pts.
NT-proBNP	Inactive form (prohormone) of BNP. Simple and objective assessment of cardiac function.	Commercial (USA, EU, AP)	In type A-AAD powerful of 30-days survival. NT-proBNP and aortic diameter correlation is useful in predicting in-hospital mortality with higher sensitivity.	Possible misinterpretation: higher levels in elderly and renal compromised pts.
sST2	Truncated form of transmembrane ST2 (IL-33 receptor).	Experimental	Elevated levels in AAS.	Modest accuracy for diagnosis of AAS.

Abbreviations: AAD, acute aortic dissection; AAS, acute aortic syndrome; AP, Asia-Pacific; BNP, B-type natriuretic peptide; CRP, C-reactive protein; EU, European Union; FL, false lumen; IL, interleukin-6; IMH, intramural hematoma; NT-proBNP, N-terminal pro-brain natriuretic peptide; PET, positron emission tomography; pts, patients; sST2, soluble suppression of tumorigenesis-2;TN-C, tenascin-C; USA, United States of America.
Modified from Refs.[55,56]

Natriuretic peptides. Natriuretic peptides (NPs) (circulating hormones secreted mainly by cardiac tissues) are well- established diagnostic and prognostic biomarkers in heart failure patients. Interestingly, higher levels of NT-proBNP also appear to be independently associated with in-hospital death in type A-AAD patients. In this regard, higher sensitivity in predicting in-hospital mortality has been demonstrated with the combined use of NT-proBNP levels and aortic diameters.[76]

Soluble suppression of tumorigenesis-2. Soluble suppression of the tumorigenesis-2 (sST2)—truncated form of transmembrane ST2—is a strong independent predictor of outcome in heart failure. A potential diagnostic role in AAS has also been reported.[77]

Thrombotic Markers

D-dimer. D-dimer is a fibrin degradation product (protein fragment) detectable in blood in cases of an active fibrinolysis process (Table 5).[50,53-57,78,79] D-dimer testing is widely used (point-of-care) as a diagnostic and prognostic marker in the clinical arena, namely in VTE, AAD and disseminated intravascular coagulation.[80] A cutoff level of 0.5 mg/L is generally used to rule out PE and can reliably be used to rule out AAD. The IRAD-Bio study demonstrated that D-dimer has high sensitivity (96.6%) and low negative likelihood ratio (0.07) rendering this biomarker suitable for ruling-out AAD within 24 hours of symptom onset.[81] Moreover, D-dimer could be used to rule-in AAD within 6 hours at a cut off level of 1.6 mg/L. Current ESC guidelines on the diagnosis and treatment of aortic diseases have integrated the D-dimer testing in diagnostic work-up of AAD.[1] Specifically, in the event of low clinical probability of AAD, negative D-dimer levels rule out "*de facto*" the diagnosis. On the other hand, an intermediate AAS clinical probability along with a positive (point-of-care) D-dimer test should trigger further imaging tests. D-dimer testing is not recommended in patients with a high AAD clinical probability (risk score 2 or 3). However, it should be highlighted that D-dimer normal value levels may be found in AAS with thrombosed lumen, IMH and PAU.[81]

Prognostic role. Several investigators have demonstrated a significant positive correlation between a substantial increase in D-dimer levels and worse outcome in AAD patients. An increased D-dimer value post thoracic endovascular aortic repair has been shown to be associated with shorter survival.[50] Moreover, a mean D-dimer $\geq$9 mg/L during hospitalization is

Table 5. Diagnostic and prognostic value of D-dimer in acute aortic syndrome

D-dimer
- Fibrin fragment (fibrin degradation product).
- Half-life < 8 h.
- Commercial (USA, EU, AP).

Diagnostic value
- Only biomarker close to golden standard status.
- Possible lack of elevation in the case of thrombosed FL, IMH and PAU.
- Sensitivity 96.6%; specificity 46.6% (cut-off 0.5 mg/L, < 24 h).
- Sensitivity 95.7%; specificity 61.3% (cut-off 0.5 mg/L, < 6 h).
- Integration of ADD-RS=0 or ≤ 1 with D-dimer < 0.5 mg/L shows negligible heterogeneity and consistently high sensitivity across studies, thus supporting reliability for diagnostic rule-out of AAS.[78]
- D-dimer specificity is related to age: ↑ incidence of false positive results in elderly pts.[78]

Prognostic value
- D-dimer levels on admission not predict long-term mortality in AAD pts.
- A mean D-dimer ≥ 9 mg/L during the hospitalization is an independent predictor of in-hospital mortality in ADD and IMH pts. But the prognostic role of D-dimer is not confirmed at 3-year follow-up.[79]
- Increased D-dimer value post TEVAR is associated with decreased in-hospital survival in type B AAD pts.[50]
- Elevated D-dimer value during the follow up may predict partially thrombosed FL and aneurysmal progression in chronic type B AD pts.[53]
- The combination of ^{18}F-FDG PET/CT-positive with the D-dimer level (cut-off 4.8 mg/L) during hospitalization may have better discriminant value of MAE (aorta-related mortality, disease progression and re-intervention) than PET alone during follow-up in AAS pts.[54]

Abbreviations: ^{18}F-FDG, 18F-fluorodeoxyglucose; AAD, acute aortic dissection; AD, aortic dissection; ADD-RS, aortic dissection detection risk score; AP, Asia-Pacific; AASs, acute aortic syndromes; CT, computed tomography; EU, European Union; FL, false lumen; IMH, intramural hematoma; MAE, major adverse events; PAU, penetrating aortic ulcer; PET, positron emission tomography; pts, patients; TEVAR, thoracic endovascular aortic repair; USA, United States of America; ↑, higher.
Modified from Refs.[50,53-57,78,79]

an independent predictor of in-hospital mortality, however, the prognostic role of D-dimer was not confirmed at a 3-year follow-up.[79] This evidence also suggest a potential role of D-dimer as a prognostic marker.

MicroRNA

MicroRNA (miRNA) are short noncoding single-strand RNA of around 22 nucleotides in length which negatively regulate gene expression via mRNA degradation or translational repression.[82] They are involved in numerous cellular processes (development, differentiation, proliferation, apoptosis) related to diseases such state as cancer and neurological and cardiovascular disorders.[83,84] However, to date only limited studies have correlared miRNA deregulated expression

and AAS. Wang et al analyzed miRNA expression in aortic tissues and in plasma samples of AAD patients and control groups.[85] They found 4 miRNA (miR-4313; -933; -1281 and -1238) to be up-regulated both in aortic tissue and in plasma, and concluded that these selected molecules might be potential diagnostic biomarkers for AAD.[85] Further studies are needed to clearly define the diagnostic and prognostic role of miRNA in AAS.

Conclusions

Timely diagnosis and prompt intervention are essential for the clinical outcomes of AAS patients. The best imaging strategy for diagnosing AAS and its complications is currently a combination of TTE and CT. TEE tends to be carried out in complicated cases prior to surgical or endovascular therapy, often in the operating room and under general anesthesia. In this regard, IVUS and IPAI may be implemented during the endovascular procedures depending on operator expertise and cost issues. Owing to its intrinsic characteristics, MR is not suitable in the emergency settings but an ideal imaging technique for serial measurements in patients at risk of AAS and for the follow-up evaluation of chronic dissections; less useful when metallic endoprostesis are in place. For this purpose CTA plays a major role in follow-up. A-US as part of a comprehensive TTE exam may detect an abdominal aorta dissection. Among biomarkers, D-dimer is the closest to "golden status." Multiparametric risk stratification models integrating clinical, laboratory and imaging indexes are on the way, aiming to provide a more appropriate management strategy within the concept of tailored treatment for the individual patient. In the near future, we await the development of serologic and imaging biomarkers able to early detect clinically-silent pathologic changes in the aorta wall before (primary prevention) and after (secondary prevention) the acute index event, in order to better define short and long-term prognosis.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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She focused on ultrasound cardiovascular imaging, including transthoracic and transoesophageal echocardiography from ambulatory to emergency settings, acquiring complete ability also in stress echocardiography.
She completed her professional training with experiences in several aboard cardiology centers of excellence: the Institute of Cardiology of Hôpital Pitié-Salpetriére in Paris, the Intensive Care Unit of Royal Brompton and Harefield Hospital in London and the Interventional Cardiology laboratory of Inselspital in Bern.
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