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KEY ISSUES IN DIAGNOSING AND TREATING ACUTE AORTIC SYNDROMES: RESULTS FROM THE METROPOLITAN AREA OF BOLOGNA NETWORK

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PART II

ACUTE HEART FAILURE IN PATIENTS WITH ACUTE AORTIC SYNDROME: PATHOPHYSIOLOGY AND CLINICAL-PROGNOSTIC IMPLICATIONS

ABSTRACT

Background: Survival of patients with Acute Aortic Syndrome (AAS) may relate to the speed of diagnosis. Diagnostic delay is exacerbated by non classical presentations such as myocardial ischemia or acute heart failure (AHF). However little is known about clinical implications and pathophysiological mechanisms of Troponin T elevation and AHF in AAS.

Methods and Results: Data were collected from a prospective metropolitan AAS registry (398 patients diagnosed between 2000 and 2013).

Troponin T values (either standard or high sensitivity assay, HS) were available in 248 patients (60%) of the registry population; the overall frequency of troponin positivity was 28% (ranging from 16% to 54%, using standard or HS assay respectively, p = 0.001). Troponin positivity was associated with a twofold increased risk of long in-hospital diagnostic time (OR 1.92, 95% CI 1.05-3.52, p = 0.03), but not with in-hospital mortality. The combination of positive troponin and ACS-like ECG abnormalities resulted in a significantly increased risk of inappropriate therapy due to a misdiagnosis of ACS (OR 2.48, 95% CI 1.12-5.54, p = 0.02).

Patients with AHF were identified by the presence of dyspnea as presentation symptom or radiological signs of pulmonary congestion or cardiogenic shock. The overall frequency of AHF was 28 % (32% type A vs. 20% type B AAS, p = 0.01). AHF was due to a variety of pathophysiological mechanisms including cardiac tamponade (26%), aortic regurgitation (25%), myocardial ischemia (17%), hypertensive crisis (10%). AHF was associated with increased surgical delay and with increased risk of in-hospital death (adjusted OR 1.97 95% CI1.13-3.37,p=0.01).

Conclusions: Troponin positivity (particularly HS) was a frequent finding in AAS. Abnormal troponin values were strongly associated with ACS-like ECG findings, in-hospital diagnostic delay, and inappropriate therapy. AHF was associated with increased surgical delay and was an independent predictor of in-hospital mortality**.**

INTRODUCTION

Definition

Acute aortic syndromes (AAS) are defined as emergency conditions with similar clinical characteristics involving the aorta (1). There is a common pathway for the various manifestations of AAS that eventually leads to a breakdown of the intima and media. This may result in intramural haematoma (IMH), penetrating aortic ulcer (PAU), or in separation of aortic wall layers, leading to aortic dissection (AD). AD is defined as disruption of the medial layer provoked by intramural bleeding, resulting in separation of the aorticwall layers and subsequent formation of a TL and an FL with or without communication. In most cases, an intimal tear is the initiating condition, resulting in tracking of the blood in a dissection plane within the media. This process is followed either by an aortic rupture in the case of adventitial disruption or by a re-entering into the aortic lumen through a second intimal tear.

Pathology and classification

Acute aortic syndromes occur when either a tear or an ulcer allows blood to penetrate from the aortic lumen into the media or when a rupture of vasa vasorum causes a bleed within the media. The inflammatory response to blood in the media may lead to aortic dilation and rupture. Figure 1 displays the Stanford and the DeBakey classifications.

The Stanford type A and DeBakey I and II variants involve the ascending aorta, whereas type B dissection (DeBakey III) involves the descending aorta only (1).

Acute AD (<14 days) is distinctfrom sub-acute (15–90 days), and chronic aortic dissection (>90days).

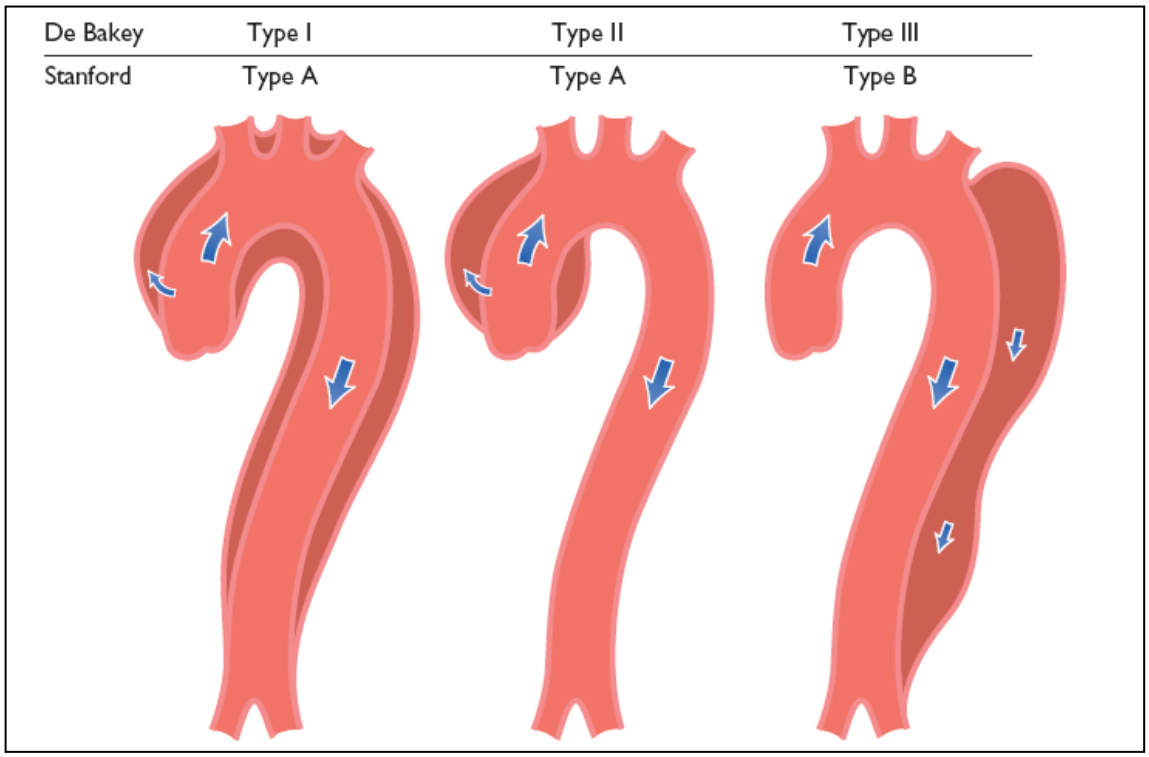


Figure 1: Classifications of aortic dissection (Stanford and De Bakey).

Epidemiology

Up-to-date data on the epidemiology of AD are scarce. In the Oxford Vascular study, the incidence of AD is estimated at six per hundred thousand persons per year (2). This incidence is higher in men than in women and increases with age (3). The prognosis is poorer in women, as a result of atypical presentation and delayed diagnosis. The most common risk factor associated with AD is hypertension, observed in 65–75% of individuals, mostly poorly controlled. In the IRAD registry, the mean age was 63 years; 65% were men (4). Other risk factors include pre-existing aortic diseases or aortic valve disease, family history of aortic

diseases, history of cardiac surgery, cigarette smoking, direct blunt chest trauma and use of intravenous drugs (e.g. cocaine and amphetamines).

Clinical presentation and complications

Chest pain is the most frequent symptom of acute AD. Abrupt onset of severe chest and/or back pain is the most typical feature. The pain may be sharp, ripping, tearing, knife-like, and typically different from other causes of chest pain; the abruptness of its onset is the most specific characteristic. The most common site of pain is the chest (80%), while back and abdominal pain are experienced in 40% and 25% of patients, respectively. Anterior chest pain is more commonly associated with Type A AD, whereas patients with Type B dissection present more frequently with pain in the back or abdomen. The clinical presentations of the two types of AD may frequently overlap. The pain may migrate from its point of origin to other sites, following the dissection path as it extends through the aorta. Although any pulse deficit may be as frequent as 30% in patients with Type A AD and 15% in those with Type B, overt lower limb ischaemia is rare (1).

Aortic regurgitation may accompany 40–75% of cases with Type A AD (1,5). After acute aortic rupture, aortic regurgitation is the second most common cause of death in patients with AD. Patients with acute severe aortic regurgitation commonly present with heart failure and cardiogenic shock.

Aortic regurgitation in AD includes dilation of the aortic root and annulus, tearing of the annulus or valve cusps, downward displacement of one cusp below the line of the valve closure, loss of support of the cusp, and physical interference in the closure of
the aortic valve by an intimal flap.

Pericardial tamponade may be observed in 20% of patients with acute Type A AD. This complication is associated with a doubling of mortality (6).

Myocardial ischaemia or infarction may be present in 10–15% of patients with AD and may result from aortic FL expansion, with subsequent compression or obliteration of coronary ostia or the propagation of the dissection process into the coronary tree (1). In the presence of a complete coronary obstruction, the ECG may show ST-segment elevation myocardial infarction. Also, myocardial ischaemia may be exacerbated by acute aortic regurgitation, hypertension or hypotension, and shock in patients with or without pre-existing coronary artery disease. This may explain the observation that approximately 10% of patients presenting with acute Type B AD have ECG signs of myocardial ischaemia.

Overall, comparisons of the incidence of myocardial ischaemia and infarction between the series and between Types A and -B aortic dissection are challenged by the lack of a common definition. In addition, the ECG diagnosis of non-transmural ischaemia may be difficult in this patient population because of concomitant left ventricular hypertrophy, which may be encountered in approximately one-quarter of patients with AD. Both troponin elevation and ECG abnormalities, which may fluctuate over time, may mislead the physician to the diagnosis of acute coronary syndromes and delay proper diagnosis and management of acute AD.

Congestive heart failure in the setting of AD is commonly related to aortic regurgitation. Although more common in Type A AD, heart failure may also be encountered in patients with Type B AD, suggesting additional aetiologies of heart failure, such as myocardial ischaemia, pre-existing diastolic dysfunction, or uncontrolled hypertension. Notably, in the setting of AD, patients with acute heart failure and cardiogenic shock present less frequently with the characteristic severe and abrupt chest pain, and this may delay diagnosis and treatment of AD. Hypotension and shock may result from aortic rupture, acute severe aortic regurgitation, extensive myocardial ischaemia, cardiac tamponade, preexisting left ventricular dysfunction, or major blood loss.

Large pleural effusions resulting from aortic bleeding into the mediastinum and pleural space are rare, because these patients usually do not survive up to arrival at hospital. Smaller pleural effusions may be detected in 15–20% of patients with AD, with almost equal distribution between Type A and Type B patterns, and are believed to be mainly the result of an inflammatory process (1).

Pulmonary complications of acute AD are rare, and include compression of the pulmonary artery and aortopulmonary fistula, leading to dyspnoea or unilateral pulmonary oedema, and acute aortic rupture into the lung with massive haemoptysis.

Syncope is an important initial symptom of AD, occurring in approximately 15% of patients with Type A AD and in ,5% of those presenting with Type B. This feature is associated with an increased risk of in-hospital mortality because it is often related to life-threatening complications, such as cardiac tamponade or supra-aortic vessel dissection. In patients with suspected AD presenting with syncope, clinicians must therefore actively search for these complications (1).

Neurological symptoms may often be dramatic and dominate the clinical picture,masking the underlying condition. They may result from cerebral malperfusion, hypotension, distal thromboembolism, or peripheral nerve compression. The frequency of neurological symptoms in AD ranges from 15–40%, and in half of the cases they may be transient. Acute paraplegia, due to spinal ischaemia caused by occlusion of spinal arteries, is infrequently observed and may be painless and mislead to the Leriche syndrome. The most recent IRAD report on Type A AD described an incidence of major brain injury (i.e. coma and stroke) in 10% and ischaemic spinal cord damage in 1.0% (7). Upper or lower limb ischaemic neuropathy, caused by a malperfusion of the subclavian or femoral territories, is observed in approximately 10% of cases. Hoarseness, due to compression of the left recurrent laryngeal nerve, is rare.

Mesenteric ischaemia occurs in 5% of patients with Type A AD (8). Adjacent structures and organs may become ischaemic as aortic branches are compromised, or may be affected by mechanical compression induced by the dissected aorta or aortic bleeding, leading to cardiac, neurological, pulmonary, visceral, and peripheral arterial complications. End-organ ischaemia may also result from the involvement of a major arterial orifice in the dissection process. The perfusion disturbance can be intermittent if caused by a dissection flap prolapse, or persistent in cases of obliteration of the organ arterial supply by FL expansion. Clinical manifestation is frequently insidious; the abdominal pain is often non-specific, patients may be painless in 40% of cases; consequently, the diagnosis is frequently too late to save the bowel and the patient. Therefore, it is essential to maintain a high degree of suspicion for mesenteric ischaemia in patients with acute AD and associated abdominal pain or increased lactate levels. The presence of mesenteric ischaemia deeply affects the management strategy and outcomes of patients with Type A AD; in the latest IRAD report, 50% of patients with mesenteric malperfusion did not receive surgical therapy, while the corresponding proportion in patients without this complication was 12%.

Laboratory testing

In patients admitted to the hospital with chest pain and suspicion of AD, few laboratory tests are required for differential diagnosis or detection of complications. If D-dimers are elevated, the suspicion of AD is increased. Typically, the level of D-dimers is immediately very high, compared with other disorders in which the D-dimer level increases gradually. D-dimers yielded the highest diagnostic value during the first hour. If the D-dimers are negative, IMH and PAU may still be present; however, the advantage of the test is the increased alert for the differential diagnosis (9). Since AD affects the medial wall of the aorta, several biomarkers have been developed that relate to injury of the vascular endothelial or smooth muscle cells

(smooth muscle myosin), the vascular interstitium (calponin, matrix metalloproteinase 8), the elastic laminae (soluble elastin fragments) of the aorta, and signs of inflammation (tenascin-C) or thrombosis, which are in part tested at the moment but have not yet entered the clinical arena.

Diagnostic imaging in acute aortic dissection

The main purpose of imaging in AAD is the comprehensive assessment of the entire aorta, including the aortic diameters, shape and extent of a dissection membrane, the involvement in a dissection process of the aortic valve, aortic branches, the relationship with adjacent structures, and the presence of mural thrombus (9).

Computed tomography, MRI, and Transoesophageal echocardiography (TEE) are equally reliable for confirming or excluding the diagnosis of AAD. However, CT and MRI have to be considered superior to TEE for the assessment of AAD extension and branch involvement, as well as for the diagnosis of IMH, PAU, and traumatic aortic lesions. In turn, TEE using Doppler is superior for imaging flow across tears and identifying their locations. TEE may be of great interest in the very unstable patient, and can be used to monitor changes in-theatre and in post-operative intensive care.

Diagnostic work-up

The diagnostic work-up to confirm or to rule out AD is highly dependent on the a priori risk of this condition. The diagnostic tests can have different outputs according to the pre-test probability. In 2010, the ACC/American Heart Association (AHA) guidelines (10)

proposed a risk assessment tool based on three groups of information - predisposing conditions, pain features, and clinical examination - and proposed a scoring system that considered the number of these groups that were involved, from 0 to 3 (Figure 2). The

IRAD reported the sensitivity of this approach, but a validation is not yet available (1). The presence of 0, 1, 2, or 3 groups of information is associated with increasing pre-test probability, which should be taken into account in the diagnostic approach to all AAS. The diagnostic flow chart (Figure 3) proposed by current European Society of Cardiology (ESC) Guidelines on aortic disease (1) combines the pre-test probabilities (Figure 2) according to clinical data, and the laboratory and imaging tests, as should be done in clinical practice in emergency or chest pain units.

High-risk conditions	High-risk pain features	High-risk examination features
• Marfan syndrome (or other connective tissue diseases) • Family history of aortic disease • Known aortic valve disease • Known thoracic aortic aneurysm • Previous aortic manipulation (including cardiac surgery)	• Chest, back, or abdominal pain described as any of the following: - abrupt onset - severe intensity - ripping or tearing	• Evidence of perfusion deficit: - pulse deficit - systolic blood pressure difference - focal neurological deficit (in conjunction with pain) • Aortic diastolic murmur (new and with pain) • Hypotension or shock

Figure 2 Clinical data useful to assess the a priori probability of acute aortic syndrome

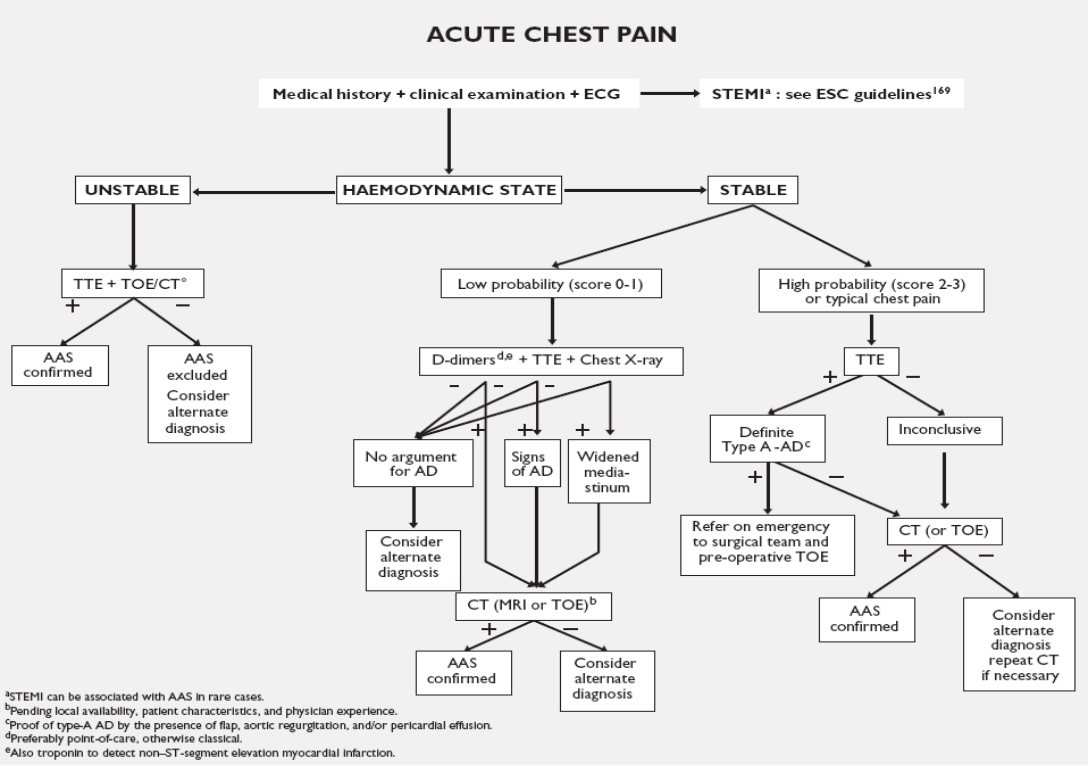


Figure 3 Flowchart for decision-making based on pre-test sensitivity of acute aortic syndrome proposed by ESC Guidelines on aortic disease (1).

Treatment

In type A Aortic dissection, surgery is the treatment of choice (1). Despite improvements in surgical and anaesthetic techniques, perioperative mortality (25%) and neurological complications (18%) remain high. However, surgery reduces 1-month mortality from 90% to 30%. The advantage of surgery over conservative therapy is particularly obvious in the long-term follow-up. Based on that evidence, all patients with TypeAAD should be sent for surgery; however, coma, shock secondary to pericardial tamponade, malperfusion of coronary or peripheral arteries, and stroke are important predictive factors for post-operative mortality. The superiority of surgery over conservative treatment has been reported, even in patients with unfavourable presentations and/or major comorbidities.

Patients with uncomplicated Type B AD receive medical therapy to control pain, heart rate, and blood pressure, with close surveillance to identify signs of disease progression and/or malperfusion (1). Repetitive imaging is necessary, preferably with MRI or CT.

Thoracic endovascular aortic repair (TEVAR) is the treatment of choice in complicated acute Type B AD (1). The objectives of TEVAR are the closure of the 'primary' entry tear and of perforation sites in the descending aorta. The blood flowis redirected into the TL, leading to improved distal perfusion by its decompression. This mechanism may resolve malperfusion of visceral or peripheral arteries. Thrombosis of the FL will also be promoted, which is the initiation for aortic remodelling and stabilization.

The term 'complicated' means persistent or recurrent pain, uncontrolled hypertension despite full medication, early aortic expansion, malperfusion, and signs of rupture (haemothorax, increasing periaortic and mediastinal haematoma). Additional factors, such as the FL diameter, the location of the primary entry site, and a retrograde component of the dissection into the aortic arch, are considered to significantly influence the patient's prognosis (1).

Nowadays, surgery is rare in cases of complicated Type B AD, and has been replaced largely by endovascular therapy (1).

For optimal repair of acute Type A AD in respect of long-term results—including risk of late death and late re-operation—the following points need to be addressed. In most cases of aortic insufficiency associated with acute Type A dissection, the aortic valve is essentially normal and can be preserved by applying an aortic valvesparing repair of the aortic root. Alternatively, given the emergency situation, aortic valve replacement can be performed. In any case, it is preferable to replace the aortic root if the dissection involves at least one sinus of Valsalva, rather than perform a supracoronary ascending aorta replacement only. The latter is associated with late dilation of the aortic sinuses and recurrence of aortic regurgitation, and requires a high-risk re-operation (1). Various techniques exist for re-implantion of the coronary ostia or preservation of the ostia of the coronary arteries. A current topic of debate is the extent of aortic repair; ascending aortic replacement or hemiarch replacement alone is technically easier and effectively closes the entry site but leave a large part of the diseased aorta untreated. Patients with visceral or renal malperfusion in acute Type A AD often have their primary entry tear in the descending aorta. These patients might profit from extended therapies, such as 'frozen elephant trunk' repair in order to close the primary entry tear and decompress the TL. The importance of intraoperative aortoscopy and of immediate post-operative imaging—ideally in a hybrid suite—to reconfirm or exclude the effectiveness of therapy, is obvious. In contrast, more extensive repair, including graft replacement of the ascending aorta and aortic arch and integrated stent grafting of the descending aorta ('frozen elephant trunk') as a one-stage procedure is technically more challenging and prolongs the operation, with an increased risk of neurological complications, but offers the advantage of a complete repair, with a low likelihood of late re-intervention (1). If the dissection progresses into the supra-aortic branches, rather than the classic 'island' technique, end-to-end grafting

of all supra-aortic vessels may be considered, using individual grafts from the arch prosthesis. There is still controversy over whether surgery should be performed in patients with TypeA AD presenting with neurological deficits or coma. Although commonly associated with a poor post-operative prognosis, recovery has been reported when rapid brain reperfusion is achieved, especially if the time between symptom onset and arrival at the operating room is < 5 hours.

One major factor influencing the operative outcome is the presence of mesenteric malperfusion at presentation. Malperfusion syndrome occurs in up to 30% of patients with acute AD. Visceral organ and/or limb ischaemia is caused by dynamic compression of the TL, due to high-pressure accumulation in the FL as the result of large proximal inflow into the thoracic aortic FL and insufficient outflow in the distal aorta. Malperfusionmay also be caused by extension of the intimal flap into the organ/peripheral arteries, resulting in static 'stenosis-like' obstruction. In most cases, malperfusion is caused by a combination of dynamic and static obstruction; therefore, surgical/hybrid treatment should be considered for patients with organ malperfusion (1).

As regards Type B AAS, future studies will have to better clarify whether uncomplicated forms benefit from immediate TEVAR treatment.

Key issues in the contemporary management: diagnostic delay and misdiagnosis

AAS may be rapidly fatal without early diagnosis and appropriate management. Symptoms, signs, electrocardiograms (ECGs), and chest X-rays lack sensitivity and specificity. Diagnosis is therefore not immediate; definitive confirmatory investigation may not available in the emergency room (ER), and the varied presentation allows the diagnosis to be missed, misdiagnosed, or overlooked in up to 40% of cases, sometimes only being established at post-

mortem (11,12). Acute type A dissection is highly lethal, but a rapid diagnosis may allow life-saving surgical repair. Untreated mortality may approximate 1% to 2%/h following symptom onset with the majority of patients succumbing within 30 days. Surgical repair transforms the high mortality risk to a greater than 70% survival chance in the short term. This survival advantage of surgery continues in the longer term with outcomes vastly superior to those achieved by conservative management (12).

For all AAS, reduction in overall patient mortality might be best achieved by shortening the time from symptoms to treatment. Notwithstanding several recommendations and guidelines, the evidence suggests that definitive management is delayed for several hours while diagnostic evaluation is completed (12). Approximately 75% of patients with acute dissection have their initial diagnosis made in a non specialist hospital (13). The time from initial symptoms to hospital presentation is approximately 1 to 2 h, but the time to diagnosis varies considerably. Fifty percent of patients have a time to diagnosis of > 6 h in Europe and >15 h in the U.S.; 75% of patients have diagnostic times > 3 to 4 h (13). In type A dissection, the time duration between presentation and definitive management is >12 h in the majority of patients and has been reported as being >24 h in 20% to 50% in some series (14). Patients presenting with atypical symptoms are at increased risk of in-hospital mortality, which may be related to diagnostic delay, prolonging the institution of treatments that may affect the disease's natural history, particularly dissection propagation (12). Delays in instigating blood pressure control in type B dissection may be > 24 h after the initiating event, a period during which the natural history of the dissection is defined. Therefore, the prognostic significance of accelerating diagnosis is evident.

Diagnostic delay is exacerbated by nonclassical presentations that do not evoke clinical suspicion such as painless malperfusion phenomena, dyspnea due to heart failure or pleural effusion, acute coronary syndrome– like ECG, limb ischemia, or abdominal pain, all of which

are associated with longer in-hospital diagnostic times (15). The challenge is therefore to accurately diagnose the condition as early as possible. The primary presentation of AAD to the ER is most commonly an elderly male, with hypertension and sudden onset chest pain, and the much more common acute coronary syndrome is an important differential diagnosis (12). In addition, the recent introduction of high sensitivity troponin (Tn) assay has determined an increase of the number of patients with abnormal Tn levels also in absence of a final diagnosis of myocardial infarction (16); therefore, an ACS misdiagnosis in patients with AAS may be even more frequent in the contemporary era. Any lack of suspicion of AAD will fail to trigger investigation, delaying diagnosis. In the absence of a rapid, accurate, and readily available diagnostic test, the current diagnosis of AAD requires definitive imaging such as computed tomography (CT), transesophageal echocardiography (TEE), or magnetic resonance imaging (MRI) (1), but the use of each investigation is based on an index of clinical suspicion, and each incurs a further logistical delay in patient management (12). Myocardial ischemia has the diagnostic advantages of the ECG and troponin estimation, allowing risk stratification and emergency treatment. AAS have no such rapidly available diagnostic tools (12).

However, the higher and early mortality of these conditions appeals for improved physician awareness of possible presentations of AAS, in order to reduce diagnostic times, misdiagnosis, inappropriate therapy, and improve outcome.

PART I TROPONIN T ELEVATION IN ACUTE AORTIC SYNDROMES: FREQUENCY AND IMPACT ON DIAGNOSTIC DELAY AND MISDIAGNOSIS

Background

Acute aortic syndromes (AAS) are a life-threatening cardiovascular emergency with a mortality rate of up to 1%/hour (17); hence, prompt diagnosis and initiation of appropriate management are of paramount importance. However, AAS presentation often mimics acute coronary syndromes (ACS) leading to a number of imaging and laboratory investigations, including serum troponin evaluation, which might be expected to impact the promptness of treatment. Despite troponin assay being part of the diagnostic work up in many cases of AAS, little is known about frequency and clinical implications of troponin elevation in this condition. The available studies addressing this issue are small in size and lead to conflicting results (18-20). Regrettably, the largest available AAS registry (IRAD) has not focused on this topic (4,21). In particular, it is unknown whether the finding of elevated troponin in these AAS patients may initially mislead into considering the patient a possible ACS case, which might have potentially deleterious consequences in terms of delaying surgical treatment, and/or exposing the patient to unnecessary (or potentially harmful) therapies and procedures.

Aims

Using data from a prospective metropolitan network AAS registry, our study was aimed to describe the frequency of troponin elevation, to define the clinical and instrumental profile of patients with this finding, and to explore the impact on the time to diagnosis and on outcome.

Methods

Setting and Patients

Our registry (AESA, Archivio Elettronico Sindromi Aortiche acute) includes data from all consecutive patients referred to our Institution between 2000 and 2013 who received a final diagnosis of spontaneous AAS. The S. Orsola-Malpighi University Hospital is the referral centre for AAS treatment in a metropolitan hospital network that covers Bologna and its surroundings (catchment area approximately 1.000.000 people). The database contains comprehensive demographical, clinical, instrumental, laboratory findings of the patients at first hospital contact (either spoke or hub), as well as treatment and outcome details. The following relevant diagnostic time intervals are also recorded: 1) symptoms onset to presentation at any hospital; 2) hospital presentation to final AAS diagnosis; 3) global diagnostic delay (symptoms onset to final AAS diagnosis at any hospital); surgical delay (final diagnosis to entry in the operating room). As in IRAD registry, data concerning the different delays were prospectively collected during the initial phases of hospitalization (21). The "time of final diagnosis" was defined as the time when the first demonstration of the aortic lesion was documented on an imaging examination and recorded.

Patients with symptoms onset >14 days at hospital presentation were not included in the registry. AAS (aortic dissection, penetrating ulcer and intramural hematoma) were defined according to the Stanford classification (22).

In all cases (presenting at either a hub or a spoke centre) the diagnosis was confirmed by a multidisciplinary team that included a cardiologist, heart surgeon, and cardiovascular radiologist.

The local ethics committee approved the study.

Definitions

Cardiac troponin testing was performed according to the standard protocol used in chest pain units (blood samples taken at presentation and after 3, 6 and 12 hours, or until a correct diagnosis of AAS was reached). Until 2010 standard cardiac troponin T (cTnT) test was used (Troponin T Elecsys, fourth generation; Roche Diagnostics GmbH, Mannheim, Germany), which has since been replaced by high sensitivity (HS)-cTnT assay (Troponin T HS Elecsys; Roche Diagnostics GmbH, Mannheim, Germany). For the standard cTnT test the analytical limit of detection (LoD) and the URL are both 10 ng/L, and the 10% CV cut-off value is 30 ng/L. The diagnosis of troponin positivity using standard cTnT testing was made in the presence of at least one value of cTnT > 30 ng/L (10% CV cut-off).

The HS-cTnT assay has an analytical LoD of 3 ng/L, the URL is 14 ng/L and the 10% CV cut-off is 13 ng/L. When HS-cTnT was used, the diagnosis of troponin positivity was made in the presence of at least one value of HS-cTnT > 14 ng/L (URL).

According to current guidelines, electrocardiogram (ECG) was considered to be acute coronary syndrome (ACS)-like in the presence of ≥ 1 of the following characteristics: 1) ST-segment elevation in two contiguous leads with the cut-point ≥ 0.1 mV in all leads other than leads V2-V3, where the cut- point is ≥ 0.2 mV; 2) horizontal or down-sloping ST-segment depression ≥ 0.05 mV in two contiguous leads; 3) T-wave inversion ≥ 0.1 mV in two contiguous leads (23).

Shock was defined as sustained hypotension (systolic blood pressure <90 mm Hg for >30 minutes), accompanied by clinical signs of peripheral/cerebral hypoperfusion (24). We used standard definition of cardiac tamponade (25).

Severe and moderate-to-severe aortic regurgitation at transthoracic/transesophageal echocardiography were considered hemodynamically significant. Pleural effusion was diagnosed by chest x-ray or CT scan. Pericardial effusion was diagnosed by

transthoracic/transesophageal echocardiogram, CT scan, or magnetic resonance imaging. Periaortic hematoma was diagnosed by transthoracic/transesophageal echocardiogram, CT, or magnetic resonance imaging (26).

Study design and statistical analysis

To explore the clinical impact of troponin and other possible determinants the following endpoints were considered: in-hospital mortality, in-hospital diagnostic delay, and a composite endpoint represented by the combination of in-hospital delay, coronary angiography, antithrombotic therapy (the latter two representing unnecessary/deleterious consequences of an initial diagnosis of ACS). To identify particularly long diagnostic times we used 75^{th} percentile of in-hospital delay as cut-off (15).

To evaluate the possible impact of a positive troponin finding on in-hospital delay and on the composite endpoint, the overall registry population was assessed in a logistic regression analysis and patients with positive troponin were compared to patients with negative or unavailable troponin (i.e., in whom management could have not been possibly influenced by the notion of troponin positivity).

To identify predictors of in-hospital mortality and of surgical mortality in patients with Stanford A, we considered only the subgroup tested for troponin; patients with positive were compared to patients with negative assay.

Categorical data were expressed as proportions, and continuous variables reported as mean±SD or median and interquartile range (IQR), as appropriate. Chi-square test for categorical variables was used to compare groups. Two-tailed Student *t* test was used to compare normally distributed continuous variables. Comparison of non-normally distributed variables was performed using the Mann-Whitney U test.

Non correlated variables with $p < 0.2$ at the univariable analyses were included in the multivariable analysis. Model discrimination was assessed by c-statistic, and model calibration was assessed by Hosmer-Lemeshow statistic.

A p value <0.05 in the two-tailed tests was considered significant. All analyses were performed with the STATA/SE 12.1 software for Windows (StataCorp LP, College Station, Texas, USA).

Results

Study Population

During the study period 398 patients received a final diagnosis of spontaneous AAS (Stanford type A 258; Stanford type B 140) and were entered into the AESA Registry. Their main characteristics are reported in Tables 1A and 1B. Presentation with cardiac tamponade, shock, significant aortic regurgitation, and ACS-like ECG findings was more common in patients with type A AAS. On the other hand, patients with type B AAS had higher systolic blood pressure and more frequently complained of back or abdominal pain.

Routinely performed troponin test results were available for 248 patients (62%) including 171 (69%) tested with the standard troponin assay and 77 (31%) with HS test. Epidemiological, clinical, instrumental and outcome findings of the patients with/without troponin availability were comparable (Supplementary Tables 1A and 1B, Supplementary Tables 2A and 2B).

Frequency and profile of patients with troponin T positivity

The overall frequency of troponin T positivity was 28% (70/248), with no difference between type A (50/167, 30%) and type B (20/81, 25%, $p = 0.47$). The proportion of patients with positive troponin T was higher among those tested by HS assay (42 of 77, 54% vs. 28 of 171, 16%, $p = 0.001$) (Table 2).

Baseline clinical and instrumental characteristics of patients according to Troponin T results are shown in Tables 3A and 3B. Troponin positivity was more frequently associated with ACS-like ECG findings.

Risk factors for diagnostic delay and misdiagnosis

In the entire registry median global diagnostic delay was 307 (Q1-Q3, 108 - 900) minutes. Median pre-hospital and in-hospital delays were 90 (Q1-Q3, 50 - 210) minutes and 166 (Q1-Q3, 90-353) minutes, respectively. Regarding in-hospital diagnostic delay, 297 patients had a diagnostic time < 75^{th} percentile (corresponding to 353 minutes) while 101 had a longer delay. With respect to troponin results, in-hospital diagnostic delay was 210 (Q1-Q3, 103-829) in patients with evidence of troponin positivity, and 177 (Q1-Q3, 100-342) in patients with negative troponin values (p = 0.042).

Risk factors for late in-hospital diagnosis (> 75^{th} percentile, 353 min) are reported in Table 4. By multivariable analysis troponin positivity was significantly associated with an approximately twofold increased risk of longer in-hospital delay (OR 1.92, 95% CI 1.05-3.52, p = 0.03), compared to negative/unavailable troponin. Excess risk for in-hospital diagnostic delay was also related to dyspnoea and pleural effusion, while systolic blood pressure < 90 mmHg and back pain were associated with an earlier recognition of AAS. The risk predicted by the model was well correlated with the observed events (76.4 % of correct classification, c-statistic = 0.71, Hosmer-Lemeshow goodness-of-fit p = 0.63).

Risk factors for the composite endpoint of late in-hospital diagnosis and inappropriate treatments due to a misdiagnosis of ACS are reported in Table 5. By multivariable analysis ACS-like ECG was associated with a twofold increased risk (OR 2.12, 95% CI 1.26-3.59, p = 0.005). Excess risk was also related to dyspnoea and pleural effusion and syncope, while

systolic blood pressure < 90 mmHg ,pulse deficit, and back pain were associated with a reduced risk.

The effect of the interplay between troponin data and ECG findings on diagnostic delay and inappropriate treatments are summarized in Figure 1. The combination of positive troponin and ACS-like ECG resulted in a significantly increased risk of both late in-hospital recognition (OR 2.34, 95% CI 1.05-5.18, p = 0.03), and of composite endpoint (in-hospital delay, coronary angiography, antithrombotic therapy) (OR 2.48, 95% CI 1.12-5.54, p = 0.02).

Risk factors for mortality

Considering the overall population of the Registry, 85.6 % (221/258) of type A patients underwent surgical treatment. In the remaining 37 cases surgery was not performed due to advanced age, comorbidity, patient refusal, or death. Sixty-six of 140 type B patients underwent endovascular (n = 51) or surgical (n = 15) treatment due to thoracic/abdominal underperfusion, uncontrolled hypertension, or impending rupture of the false lumen.

Surgical mortality was 20.4% (45/221) in type A and 15.2% (10/66) in type B. Global in-hospital mortality was 26.3% (68 of 258) in type A and 13.6% (19 of 140) in type B.

In the subgroup of 248 patients tested for troponin the association between this biomarker and mortality was assessed in conjunction with other plausible risk factors (Table 6 and 7). Table 6 shows the results of univariable and multivariable analysis of risk factors for global in-hospital mortality. Pleural effusion, age, shock, dyspnoea, Stanford type A, and ACS-like ECG abnormalities were associated with increased in-hospital mortality, whereas only pleural effusion, age, dyspnoea, and shock were confirmed as independent predictors after multivariable analysis. The risk predicted by the model was well correlated with the observed events (79.7 % of correct classification, c-statistic = 0.74, Hosmer-Lemeshow goodness-of-fit p = 0.482). Of note, frequency of troponin positivity was not significantly different between

patients who survived and those who died (26% vs. 35.7%, p = 0.21, Supplementary Table 5) (unadjusted OR 1.63, 95% CI 0.86-3.10, p = 0.13).

Univariable and multivariable analysis of risk factors for in-hospital mortality of Type A patients who underwent surgical intervention are shown in Table 7. Only ACS-like ECG, pleural effusion and age were independently associated with surgical mortality. In particular, troponin positivity (either standard or HS) was not an incremental risk factor .

DISCUSSION

This is the first study to focus on plasma troponin evaluation -including HS troponin assay- in a large cohort of patients with AAS. The main results of our analysis are that troponin is abnormal in a large proportion of cases (up to 54% using the HS assay), which may lead to a relevant in-hospital diagnostic delay.

The study population of our series is comparable to that of the IRAD registry; in particular with regard to age (mean value in our registry 66.7 yrs compared to 63.1), male prevalence (67% vs. 65%), and ratio between Stanford types A and B (1.84 vs.1.65). Frequency and distribution of signs and symptoms at presentation was also similar to the IRAD registry (27). Notably, the frequency of findings classically considered "pathognomonic" of AAS (i.e., migratory pain, pain plus pulse deficit or pain plus cerebrovascular accident) was relatively rare (Table 1A), and patients with type A AAS more frequently showed hypotension, shock, pericardial effusion, aortic regurgitation. Plaque ruptures / ulcerations were more common in Type B. As in IRAD, about one fourth of the patients had an ACS-like ECG at presentation (27).

Troponin positivity was found in 28% of our population, ranging from 16% using the standard troponin assay, to 54% using the more recent HS assay (Table 2). The small

previous studies that included information regarding standard troponin in AAS, reported a positivity ranging from 11% (19) to 23% (18). The high prevalence of positive HS troponin in our study cannot be compared to any published series.

Although our study was not aimed to investigate the pathophysiology of troponin release, our registry offers some insights into the potential mechanisms. Since troponin is not a constituent of the aortic wall (28), the abnormal troponin increase during AAS is reasonably the consequence of myocardial injury. Notably, troponin elevation was more frequently associated with ACS-like ECG abnormalities (41,4% vs. 21.9 %, p = 0.003). However only 9/70 patients (13%) with positive troponin presented with a typical ST-elevation suggestive of true myocardial infarction, initially leading the patient to the cath lab for a primary angioplasty in 3 patients and to intense antithrombotic therapy in 6 patients (Supplementary Table 4). More in general, 4 out of 10 patients studied with TOE had a clear anatomic obstruction of at least one coronary artery due to coronary dissection (2 patients) or diastolic apposition of the flap to the ostium (2 patients). In the remaining cases the mechanism, albeit undefined, is probably multifactorial including acute pressure overload, acute volume overload (aortic insufficiency) and shock in patients with or without pre-existing coronary disease (Figure 2). Notably, although more frequent in type A, troponin elevation occurred also in type B AAS independently of age, gender and clinical history of the patients (Table 3).

One of the main findings of our study is the association between troponin positivity and delayed diagnostic time. Indeed, patients with troponin elevation reach the correct diagnosis of AAS more than two hours later (median values) than patients without this finding, and this extra time was predominantly due to the in-hospital phase (Table 3B). This “delay effect” was amplified in case of concomitant association with ACS-like ECG abnormalities (Figure 1). Notably, the concomitant presence of troponin elevation and ACS-like ECG abnormalities

also increases the probability of inappropriate management (coronary angiography or intense antithrombotic treatment) due to a misdiagnosis of ACS. In addition to troponin positivity, pleural effusion and dyspnoea as presentation symptom were the other independent variables associated with an incremental delay in our study. Probably these findings at presentation lead the physician to embrace an immediate diagnosis of ACS (or pneumonia-associated pleuritis). Comparison with the largest study (21) on the causes of the diagnostic delay is not immediate, since the IRAD Registry considered only patients with Stanford type A, and it did not include troponin in the predictive model of the delay. Differently from IRAD, in our registry neither female gender nor pain characteristics at presentation had a clear confounding or facilitating effect on diagnosis. Differences in sample size, geographic distribution and cut-off values adpopted for delays may explain the differences between the two registries.

In-hospital mortality of our patients (overall = 21,8%, surgically treated type A = 20,4%, medically treated type A = 62,1%, type B = 12,2%) was similar to that observed in the IRAD registry (27). In keeping with IRAD findings, age, shock (and pleural effusion and dyspnoea in our study) were confirmed as independent predictors of in-hospital mortality.

Despite the strong effect on diagnostic delay and on potentially catastrophic treatments (Figure 1), troponin positivity (either standard or HS) was not a statistically significant incremental risk factor for in-hospital mortality in medically as well as surgically treated patients. It should be emphasized, however, that ACS-like ECG abnormalities were associated with increased risk of in-hospital mortality, especially for type A surgically treated patients. Therefore it could be speculated that only a significant level of myocardial damage (relevant enough to determine ischaemic ECG changes) is able to affect short-term outcome. Further analyses are needed to explore a possible prognostic effect of troponin positivity on long-term outcome.

LIMITATIONS

Our prospective registry refers to a single hub center operating in a rather densely populated urban area with a long-lasting hub & spoke organization. So the findings regarding hospital arrival times cannot be generalized to more challenging geographic settings. Unavoidably, this registry included only patients who reached a final diagnosis of AAS and could not consider (or include) the patients that never received a diagnosis of AAS, or had a post-mortem diagnosis. In our registry, encompassing a 13-year period, troponin assay was performed more often in recent cases. However the profile of patients with/without available troponin are strictly comparable regarding epidemiological and morphologic characteristics, use of imaging techniques and outcome (Supplementary Tables 1A and 1B). Although troponin assay was available only in 60% of the overall population, we decided to investigate the effect of troponin on diagnostic delay and misdiagnosis by comparing patients with positive troponin with the remaining patients (negative or unavailable assay), assuming that only the knowledge of positive result can lead the physician towards a misdiagnosis of ACS.

Table 1.A Baseline clinical characteristics in overall study population and according to Stanford type.

VARIABLE	OVERALL (n=398)	Type A (n=258)	Type B (n=140)	P value
Patients' characteristics				
Age (yrs), mean ± SD	66,7 ± 13,3	66,5 ± 13,4	66,9 ± 13,7	0.476
Men	266 (66,8%)	166 (64,3%)	100 (71,4%)	0.186
Hypertension (history)	304 (76,4%)	193 (74,8%)	111 (79,3%)	0.378
Anti-hypertensive therapy	263 (66,1%)	169 (65,5%)	94 (67,1%)	0.827
Marfan syndrome	7 (2,1%)	4 (1,8%)	3 (2,5%)	0,977
Bicuspid aortic valve	9 (2,3%)	7(2,7%)	2 (1,4%)	0.638
Aortic coarctation	1 (0,3%)	1 (4,5%)	0 (0%)	0,756
Known thoracic aortic aneurysm	20 (5,0%)	13 (5,0%)	7 (5,0%)	0.823
Re-dissection	6 (1,5%)	3 (1,4%)	3 (2,1%)	0.737
Previous stroke	22 (5,5%)	15 (5,8%)	7 (5,0%)	0.913
Coronary artery disease (history)	28 (7,0%)	20 (7,7%)	8 (5,7%)	0.580
Clinical features at presentation				
Systolic blood pressure (mm Hg)	145 ± 42 (389/398)	134 ± 38 (253/258)	168 ± 39 (136/140)	<0.001
Systolic blood pressure ≤ 90 mm Hg	68/389 (17,5%)	58/253 (22,9%)	10/136 (7,3%)	<0.001
Systolic blood pressure > 160 mm Hg	125/389 (32,1%)	58/253 (22,9%)	67/136 (49,3%)	<0.001
Back pain	194 (48,7%)	96 (37,2%)	98 (70,0%)	<0.001
Chest pain	261 (65,6%)	187 (72,5%)	74 (52,8%)	<0.001
Migratory pain	51 (12,8%)	31 (12,0%)	20 (14,3%)	0.624
Abdominal pain	110 (27,6%)	55 (21,3%)	55 (39,3%)	<0.001

Pain plus syncope	34 (8,5%)	30 (11,6%)	4 (2,8%)	0,005
Pain plus shock	44 (11,1%)	41 (15,9%)	3 (2,1%)	<0.001
Pain plus cerebrovascular accident	12 (3,0%)	11 (4,3%)	1 (0,8%)	0,095
Pain plus paraplegia	10 (2,5%)	9 (3,5%)	1 (0,8%)	0,176
Peripheral pulse deficits	91 (22,8%)	63 (24,4%)	28 (20,0%)	0.380
Dyspnea	58 (14,6%)	34 (13,2%)	24 (17,1%)	0.357
Autonomic symptoms	155 (38,9%)	118 (45,7%)	37 (26,4%)	<0.001
Shock within 12 of admission	57 (14,3%)	51 (19,8%)	6 (4,2%)	<0.001
ACS-like ECG + chest pain	72 (18,1%)	58 (22,5%)	14 (10,0%)	0.003
Disease complications				
Cardiac tamponade	38 (9,5%)	38 (14,7%)	0 (0%)	<0.001
Pleural effusion	99 (24,9%)	56 (21,7%)	43 (30,7%)	0.062
Pericardial effusion	123 (30,9%)	109 (42,2%)	14 (10,0%)	<0,001
Periaortic effusion	63 (15,8%)	34 (13,2%)	29 (20,7%)	0,068
Moderate/severe aortic regurgitation	106 (26,6%)	96 (43,4%)	10 (7,1%)	<0.001
Coronary ostia involvement	22 (5,5%)	22 (8,5%)	0 (0%)	<0.001
Presence of intramural hematoma	117 (29,4%)	64 (24,8%)	53 (37,8%)	0.009
Presence of plaque rupture/ulceration	25 (6,3%)	10 (3,9%)	15 (10,7%)	0.014

Table 1.B Instrumental examinations, treatment and outcome in overall study population and according to Stanford type.

VARIABLE	OVERALL (n=398)	Type A (n=258)	Type B (n=140)	P value
Instrumental examinations				
Computed tomography	372 (93,5%)	234 (90,7%)	138 (98,6%)	0.005
Transesophageal echocardiography	87 (21,8%)	66 (25,6%)	21 (15,0%)	0.021
Transthoracic echocardiography	222 (55,8%)	137 (53,1%)	85 (60,7%)	0.176
Chest radiograph	237 (59,5%)	138 (53,5%)	99 (70,7%)	0.001
Abdominal ultrasound	78 (19,6%)	39 (15,1%)	39 (27,8%)	0.003
Magnetic resonance imaging	20 (5,0%)	4 (1,6%)	16 (11,4%)	<0.001
Angiography	42 (10,6%)	24 (9,3%)	18 (12,8%)	0.352
ACS-like electrocardiogram	102 (25,6%)	75 (29,1%)	27 (19,3%)	0.044
Troponin positivity	70/248 (28,2%)	50/167 (29,9%)	20/81 (24,7%)	0.477
Treatment				
Surgery/Endovascular	287 (72,1%)	221 (85,6%)	66 (47,1%)	<0.001
Only medical treatment	111 (27,9%)	37 (14,3%)	74 (52,8%)	
Outcome				
In-h death	87 (21,8%)	68 (26,3%)	19 (13,6%)	0,005
In-h death of patients surgically treated	55 (13,8%)	45/221 (20,4%)	10/66 (15,2%)	0,444
In-h death of patients treated with medical therapy	32 (8,0%)	23/37 (62,1%)	9/74 (12,2%)	0,001

ACS indicates acute coronary syndromes; in-h, in-hospital.

Table 2. Baseline characteristics and outcomes of Acute Aortic Dissection patients with Troponin positive vs. negative values according to different assays.

	Overall n= 248			**Standard cTn** n = 171			**HS-cTn** n = 77		
	cTn - n = 178 (72%)	**cTn +** n = 70 (28%)	**p**	**Standard cTn -** n = 143 (84%)	**Standard cTn +** n = 28 (16%)	**p**	**HS-cTn -** n = 35 (46%)	**HS-cTn +** n = 42 (54%)	**p**
Age	67 ± 12	69 ± 14	0,16	66 ± 14	68 ± 12	0,23	65 ± 12	69 ± 13	0,14
Male gender	126 (71%)	40 (57%)	0,05	104 (73%)	15 (54%)	0,07	22 (63%)	25 (60%)	0,94
Stanford A	117 (66%)	50 (71%)	0,47	94 (66%)	20 (71%)	0,71	23 (66%)	30 (70%)	0,77
ACS-like ECG findings	39 (21,9%)	29 (41,4%)	0,003	34 (24%)	13 (46%)	0,02	5 (7%)	16 (38%)	0,03
In-hospital mortality	35 (19,7%)	20 (28,6%)	0,17	31 (22%)	12 (43%)	0,03	4 (11%)	8 (19%)	0,54

Abbreviations: cTn: cardiac troponin; HS : high sensitivity; ACS: acute coronary syndrome; IQR : interquartile range

Table 3.A Baseline characteristics of patients according to troponin test results.

VARIABLE	OVERALL (n=248)	Abnormal Troponin T values (n=70)	Normal Troponin T values (n=178)	P value
Patients' characteristics				
Age (yrs), mean ± SD	68 ± 13	69 ± 14	67 ± 12	0.261
Stanford A	167 (67,3%)	50 (71,4%)	117 (65,7%)	0.477
Men	166 (66,9%)	40 (57,1%)	126 (70,8%)	0.057
Hypertension (history)	191 (77,0%)	51 (72,5%)	140 (78,6%)	0.419
Anti-hypertensive therapy	166 (66,9%)	41 (58,6%)	125 (70,2%)	0.108
Marfan syndrome	3 (1,2%)	1 (1,4%)	2 (1,1%)	0.654
Bicuspid aortic valve	7 (2,8%)	2 (2,9%)	5 (2,8%)	0.685
Aortic coarctation	1 (0,4%)	0 (0%)	1 (0,6%)	0.628
Known thoracic aortic aneurysm	17 (6,8%)	3 (4,3%)	14 (7,9%)	0.468
Known abdominal aortic aneurysm	15 (6,0%)	3 (4,3%)	12 (6,7%)	0.664
Previous ascending aorta and/or valve surgery	5 (2,0%)	3 (4,3%)	2 (1,1%)	0.274
Previous stroke	15 (6,0%)	4 (5,7%)	11 (6,2%)	0.875
Coronary artery disease (history)	19 (7,7%)	7 (10,0%)	12 (6,7%)	0.546
Clinical features at presentation				
Systolic blood pressure (mm Hg)	146 ± 42 (245/248)	142 ± 41 (70/71)	148 ± 42 (175/178)	0.309
Systolic blood pressure ≤ 90	43/245 (17,6%)	17/70(24,3%)	26/175 (14,8%)	0.983

mm Hg				
Systolic blood pressure > 160 mm Hg	82/245 (33,6%)	23/70 (32,8%)	59/175 (33,7%)	0.915
Back pain	116 (46,8%)	32 (45,7%)	84 (47,2%)	0.945
Chest pain	186 (75,0%)	59 (84,3%)	127 (71,3%)	0.051
Migratory pain	32 (12,9%)	8 (11,4%)	24 (13,5%)	0.823
Abdominal pain	72 (29,0%)	15 (21,4%)	57 (32,0%)	0.134
Pain plus syncope	27 (10,9%)	11 (15,7%)	16 (9,0%)	0.192
Pain plus shock	28 (11,3%)	11 (15,7%)	17 (9,6%)	0.247
Pain plus paraplegia	4 (1,6%)	2 (2,9%)	2 (1,1%)	0.678
Pain plus aortic regurgitation	66 (26,6%)	15 (21,4%)	51 (28,6%)	0.318
Pain plus pulse deficit	48 (19,3%)	15 (21,4%)	33 (18,5%)	0.734
Pain plus cerebrovascular accident	9 (3,6%)	3 (4,3%)	6 (3,4%)	0.976
Pain in other sites	46 (18,5%)	12 (17,1%)	34 (19,1%)	0.861
No pain	16 (6,5%)	7 (10,0%)	9 (5,1%)	0.255
Peripheral pulse deficits	54 (21,8%)	17 (24,3%)	37 (20,8%)	0.667
Dyspnea	48 (19,3%)	13 (18,6%)	22 (12,3%)	0.288
Syncope	37 (14,9%)	15 (21,4%)	22 (12,3%)	0.108
Autonomic symptoms	105 (42,3%)	27 (38,6%)	78 (43,8%)	0.542
Paraplegia	6 (2,4%)	2 (2,9%)	4 (2,2%)	0.859
Shock within 12 of admission	37 (14,9%)	15 (21,4%)	22 (12,3%)	0.108
Lower limbs pain alone	5 (2,0%)	1 (1,4%)	4 (2,2%)	0.929
Neurological symptoms alone	10 (4,0%)	3 (4,3%)	7 (3,9%)	0.817
Cardiac tamponade	30 (12,1%)	8 (11,4%)	22 (12,3%)	0.989

Pleural effusion	62 (25,0%)	21 (30,0%)	41 (23,0%)	0.328
Pericardial effusion	88 (35,5%)	26 (37,1%)	62 (34,8%)	0.845
Periaortic effusion	41 (16,5%)	9 (12,8%)	32 (18,0%)	0.431
Moderate/severe aortic regurgitation	70 (28,2%)	18 (25,7%)	52 (29,2%)	0.693
Coronary ostia involvment	13 (5,2%)	5 (7,1%)	8 (4,5%)	0.599
Presence of intramural hematoma	76 (30,6%)	24 (34,3%)	52 (29,2%)	0.531
Presence of plaque rupture/ulceration	18 (7,3%)	5 (7,1%)	13 (7,3%)	0.820

Table 3.B Instrumental examinations, treatment and outcome according to troponin test results.

VARIABLE	OVERALL (n=248)	Abnormal Troponin T values (n=70)	Normal Troponin T values (n=178)	P value
Instrumental examinations				
Computed tomography	232 (93,5%)	64 (91,4%)	168 (94,4%)	0.572
Transesophageal echocardiography	55 (22,2%)	10 (14,3%)	45 (25,3%)	0.088
Transthoracic echocardiography	144 (58,1%)	35 (50,0%)	109 (61,2%)	0.141
Chest radiograph	154 (62,1%)	41 (58,6%)	113 (63,5%)	0.567
Abdominal ultrasound	42 (16,9%)	9 (12,8%)	33 (18,5%)	0.376
Magnetic resonance imaging	10 (4,0%)	5 (7,1%)	5 (2,8%)	0.229
Angiography	25 (10,1%)	7 (10,0%)	18 (10,1%)	0.835
ACS-like electrocardiogram	68 (27,4%)	29 (41,4%)	39 (21,9%)	0.003
Treatment				
Surgical/endovascular treatment	173 (69,7%)	48 (68,6%)	125 (70,2%)	0.919
Only medical treatment	75 (30,2%)	22 (31,4%)	53 (29,8%)	0.919
Outcome				
In-hospital death	55 (22,2%)	20 (28,6%)	35 (19,7%)	0.177
In-h death in patients surgically treated	31/173 (17,9%)	9/48 (18,7%)	22/125 (17,6%)	0.964
In-h death in patients treated with medical therapy	24/75 (32,0%)	11/22 (50,0%)	13/53 (24,5%)	0.060

Delays (median, Q1-Q3)				
Pre-hospital delay, min	90 (50-190)	95 (49-227)	87 (50-183)	0.21
In-hospital delay, min	190 (101-406)	210 (103-829)	177 (100-342)	0.042
Global delay, min	347 (195-895)	439 (197-1500)	313 (195-725)	0.035

Table 4. Univariate and multivariate analysis for late in-hospital diagnosis (cutoff > 75 th percentile).

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Dyspnea	2.65 (1.48 - 4.74)	.001	2.43 (1.29-4.59)	.006
Pleural effusion	2.01 (1.28 - 3.43)	.003	2.02 (1.16-3.50)	.01
Troponin positivity (vs. neg Tn +Tn unavailable)	1.87 (1.07-3.26)	.026	1.92 (1.05-3.52)	.03
Pericardial effusion	1.72 (1.07-2.77)	.02		
Transfer from primary hospital	1.55 (0.89-2.72)	.12		
Syncope	1.46 (0.77-2.79)	.24		
Aortic regurgitation	1.27 (0.81 -2.01)	.29		
Hypertension (history of)	1.20 (0.69-2.08)	.50		
ACS-like ECG	1.15 (0.69-1.93)	.57		
Age (for each 1 year increase)	0.99 (0.98 - 1.01)	.74		
Cardiac tamponade	0.91 (0.42-2.03)	.82		
Male gender	0.75 (0.46-1.20)	.24		
Pulse deficit	0.51 (0.28-0.95)	.03		
SBP < 90 mmHg	0.51 (0.25-1.01)	.06	0.31 (0.14-0.68)	.003
Back pain	0.48 (0.31-0.77)	.002	0.51 (0.31-0.86)	.01

Tn indicates Troponin; ACS, acute coronary syndromes; and SBP, systolic blood pressure.

Table 5. Univariate and multivariate analysis for composite endpoint (in-hospital delay, coronary angiography, antithrombotic therapy).

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Dyspnea	2.17 (1.23-3.84)	0.008	2.30 (1.21-4.37)	0.01
Syncope	1.68 (0.91-3.11)	0.09	2.13 (1.07-4.48)	0.03
ACS-like ECG	1.87 (1.16-3.01)	0.01	2.12 (1.26-3.59)	0.005
Pleural effusion	2.04 (1.27-3.28)	0.003	1.8 (1.06-3.06)	0.029
Pericardial effusion	1.6 (1.01-2.51)	0.044		
Troponin positivity (vs. neg Tn +Tn unavailable)	1.64 (0.95-2.8)	0.073		
Aortic regurgitation	1.48 (0.96 -2.29)	0.07		
Transfer from primary hospital	1.17 (0.67-2.03)	0.58		
Hypertension (history of)	1.12(0.67-1.87)	0.67		
Age (for each 1 year increase)	0.99 (0.98 - 1.01)	0.66		
Cardiac tamponade	0.83 (0.39-1.77)	0.63		
Male gender	0.86 (0.55-1.35)	0.50		
Back pain	0.57 (0.37-0.88)	0.01	0.61 (0.37-0.99)	0.047
Pulse deficit	0.57 (0.32-0.99)	0.05	0.50 (0.27-0.93)	0.029
SBP < 90 mmHg	0.61 (0.33-1.13)	0.12	0.34 (0.16-0.72)	0.004

Tn indicates Troponin; ACS, acute coronary syndromes; and SBP, systolic blood pressure.

Table 6. Univariate and multivariate analysis for in-hospital mortality.

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Pleural effusion	3.16 (1.66-5.99)	0.001	2.28 (1.17-4.57)	0.02
Dyspnea	2.31 (1.29-7.2)	0.001	2.92 (1.30-6.54)	0.009
Shock	2.17 (1.02-4.63)	0.043	2.21(0.99-4.96)	0.056
Stanford type A	1.56 (1.03 - 4.34)	0.140	2.05 (0.96 - 4.38)	0.063
ACS-like ECG	1.93 (1.01-3.59)	0.047		
Cardiac tamponade	1.92 (0.84- 4.39)	0.121		
Troponin positivity	1.63 (0.86-3.10)	0.131		
Diagnostic delay > 75 th percentile	1.31 (0.67-256)	0.43		
SBP < 90 mmHg	1.27 (0.59-2.74)	0.53		
Syncope	1.15 (0.50-2.59)	0.74		
Age (for each 1 year increase)	1.06 (1.03-1.09	0.001	1.05 (1.02-1.09)	0.001
Male gender	0.67 (0.36-1.25)	0.22		

Tn indicates Troponin; ACS, acute coronary syndromes; and SBP, systolic blood pressure.

Table 7. Univariate and multivariate analysis for in-hospital mortality of surgically treated Stanford type A patients.

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
ACS-like ECG	2.24 (1.11-4.49)	0.02	2.26 (1.10-4.60)	0,025
Pleural effusion	2.14 (1.03-4.59)	0,049	1.89 (0.80-4.24)	0,123
Shock	2.24 (1.04-4.81)	0,038		
Cardiac tamponade	1.82 (0.71-4.31)	0.168		
Troponin positivity	1.02 (0.39-2.70)	0.131		
Age (for each 1 year increase)	1.03 (1.01-1.07)	0,012	1.04 (1.01-1.07)	0,015
Surgical delay (for each minute increase)	0.99 (0.99-1.01)	0,74		
Male gender	0.93 (0.41-1.82)	0,846		

ACS indicates acute coronary syndromes.

Supplementary Table 1 A. Risk factors and clinical characteristics in overall study population according to Troponin T results availability.

VARIABLE	OVERALL (n=398)	Troponin T available (n=248)	Troponin T unavailable (n=150)	P value
Patients' characteristics				
Age (yrs), mean ± SD	66,7 ± 13	68 ± 13	65 ± 14	0,031
Stanford A	258 (64,8%)	167 (67,3%)	91 (60,7%)	0,214
Men	266 (66,8%)	166 (66,9%)	100 (66,7%)	0,956
Hypertension (history)	304 (76,4%)	191 (77%)	113 (75,3%)	0,794
Anti-hypertensive therapy	263 (66,1%)	166 (66,9%)	97 (64,7%)	0,723
Marfan syndrome	7 (2,1%)	3 (1,2%)	4 (2,7%)	0,498
Bicuspid aortic valve	9 (2,3%)	7 (2,8%)	2 (1,3%)	0,535
Aortic coarctation	1 (0,3%)	1 (0,4%)	0 (0%)	0,799
Known thoracic aortic aneurysm	20 (5%)	17 (6,8%)	3 (2%)	0,056
Re-dissection	6 (1,5%)	1 (0,4%)	5 (3,3%)	0,057
Previous stroke	22 (5,5%)	15 (6%)	7 (4,7%)	0,72
Coronary artery disease (history)	28 (7%)	19 (7,7%)	9 (6%)	0,67
Clinical features at presentation				
Systolic blood pressure (mm Hg)	145 ± 42 (389/398)	146 ± 42 (244/248)	145 ± 41 (145/150)	0,816
Systolic blood pressure ≤ 90 mm Hg	68/389 (17,5%)	43/244 (17,6%)	25/145 (17,2%)	0,915
Systolic blood pressure > 160 mm Hg	125/389 (32,1%)	82/244 (33,6%)	43/145 (29,7%)	0,487

Back pain	194 (48,7%)	116 (46,8%)	78 (52%)	0,364
Chest pain	261 (65,6%)	186 (75%)	75 (50%)	<0,001
Migratory pain	51 (12,8%)	32 (12,9%)	19 (12,7%)	0,931
Abdominal pain	110 (27,6%)	72 (29%)	38 (25,3%)	0,494
Pain plus syncope	34 (8,5%)	27 (10,9%)	7 (4,7%)	0,049
Pain plus shock	44 (11,1%)	28 (11,3%)	16 (10,7%)	0,978
Pain plus cerebrovascular accident	12 (3%)	9 (3,6%)	3 (2%)	0,536
Pain plus paraplegia	10 (2,5%)	4 (1,6%)	6 (4%)	0,253
Peripheral pulse deficits	91 (22,8%)	54 (21,8%)	37 (24,7%)	0,587
Dyspnea	58 (14,6%)	36 (14,5%)	22 (14,7%)	0,916
Autonomic symptoms	155 (38,9%)	105 (42,3%)	50 (33,3%)	0,093
Shock within 12 of admission	57 (14,3%)	37 (14,9%)	20 (13,3%)	0,772
ACS-like ECG + chest pain	72 (18,1%)	51 (20,6%)	21 (14%)	0,13
Disease complications				
Cardiac tamponade	38 (9,5%)	30 (12,1%)	8 (5,3%)	0,04
Pleural effusion	99 (24,9%)	62 (25%)	37 (24,7%)	0,964
Pericardial effusion	123 (30,9%)	88 (35,5%)	35 (23,3%)	0,015
Periaortic effusion	63 (15,8%)	41 (16,5%)	22 (14,7%)	0,725
Moderate/severe aortic regurgitation	106 (26,6%)	70 (28,2%)	36 (24%)	0,42
Coronary ostia involvment	22 (5,5%)	13 (5,2%)	9 (6%)	0,925
Presence of intramural hematoma	117 (29,4%)	76 (30,6%)	41 (27,3%)	0,556
Presence of plaque rupture/ulceration	25 (6,3%)	18 (7,3%)	7 (4,7%)	0,413

Supplementary Table 1B. Instrumental examinations, treatment and outcome in overall study population and according to Troponin T availability.

VARIABLE	OVERALL (n=398)	Troponin T available (n=248)	Troponin T unavailable (n=150)	P value
Instrumental examinations				
Computed tomography	372 (93,5%)	232 (93,5%)	140 (93,3%)	0,9
Transesophageal echocardiography	87 (21,8%)	55 (22,2%)	32 (21,3%)	0,942
Transthoracic echocardiography	222 (55,8%)	144 (58,1%)	78 (52%)	0,282
Chest radiograph	237 (59,5%)	154 (62,1%)	83 (55,3%)	0,22
Abdominal ultrasound	78 (19,6%)	42 (16,9%)	36 (24%)	0,112
Magnetic resonance imaging	20 (5%)	10 (4%)	10 (6,7%)	0,353
Angiography	42 (10,6%)	25 (10,1%)	17 (11,3%)	0,821
ACS-like electrocardiogram	102 (25,6%)	68 (27,4%)	34 (22,7%)	0,35
Treatment				
Surgery/Endovascular	287 (72,1%)	173 (69,7%)	114 (76%)	0,219
Only medical treatment	111 (27,9%)	75 (30,2%)	36 (24%)	0,219
Outcome				
In-hospital death	87 (21,8%)	55 (22,2%)	32 (21,3%)	0,942
In-h death of patients surgically treated	55/287 (19,2%)	31/173 (17,9%)	24/114 (21,1%)	0,612
In-h death of patients treated with medical therapy	32/111 (8%)	24/75(32,1%)	8/36 (22,2%)	0,400

Supplementary Table 2.A Baseline clinical characteristics according to Stanford type in patients with available troponin values.

VARIABLE	OVERALL (n=248)	Type A (n=167)	Type B (n=81)	P value
Patients' characteristics				
Age (yrs), mean ± SD	68 ± 13	68 ± 13	67 ± 13	0,57
Men	166 (66,9%)	105 (62,9%)	61 (75,3%)	0,071
Hypertension (history)	191 (77%)	127 (76%)	64 (79%)	0,719
Anti-hypertensive therapy	166 (66,9%)	117 (70,1%)	49 (60,5%)	0,175
Marfan syndrome	3 (1,2%)	1 (0,6%)	2 (2,5%)	0,519
Bicuspid aortic valve	7 (2,8%)	5 (3%)	2 (2,5%)	0,861
Aortic coarctation	1 (0,4%)	0 (0%)	1 (1,2%)	0,711
Known thoracic aortic aneurysm	17 (6,8%)	11 (6,6%)	6 (7,4%)	0,978
Re-dissection	1 (0,4%)	1 (0,6%)	0 (0%)	0,711
Previous stroke	15 (6%)	10 (6%)	5 (6,2%)	0,821
Coronary artery disease (history)	19 (7,7%)	13 (7,8%)	6 (7,4%)	0,881
Clinical features at presentation				
Systolic blood pressure (mm Hg)	146 ± 42 (244/248)	134 ± 38 (163/167)	170 ± 40 (81/81)	<0,001
Systolic blood pressure ≤ 90 mm Hg	43/244 (17,6%)	36/163 (22,1%)	7/81 (8,6%)	0,016
Systolic blood pressure > 160 mm Hg	82/244 (33,6%)	37/163 (22,7%)	45/81 (55,6%)	<0,001
Back pain	116 (46,8%)	59 (35,3%)	57 (70,4%)	<0,001
Chest pain	186 (75%)	128 (76,6%)	58 (71,6%)	0,482
Migratory pain	32 (12,9%)	23 (13,8%)	9 (11,1%)	0,701

Abdominal pain	72 (29%)	34 (20,4%)	38 (46,9%)	<0,001
Pain plus syncope	27 (10,9%)	23 (13,8%)	4 (4,9%)	0,06
Pain plus shock	28 (11,3%)	26 (15,6%)	2 (2,5%)	0,004
Pain plus cerebrovascular accident	9 (3,6%)	8 (4,8%)	1 (1,2%)	0,297
Pain plus paraplegia	4 (1,6%)	3 (1,8%)	1 (1,2%)	0,835
Peripheral pulse deficits	54 (21,8%)	34 (20,4%)	20 (24,7%)	0,541
Dyspnea	36 (14,5%)	22 (13,2%)	14 (17,3%)	0,503
Autonomic symptoms	105 (42,3%)	80 (47,9%)	25 (30,9%)	0,016
Shock within 12 of admission	37 (14,9%)	34 (20,4%)	3 (3,7%)	0,001
ACS-like ECG + chest pain	51 (20,6%)	43 (25,7%)	8 (9,9%)	0,006
Disease complications				
Cardiac tamponade	30 (12,1%)	30 (18%)	0 (0%)	<0,001
Pleural effusion	62 (25%)	41 (24,6%)	21 (25,9%)	0,938
Pericardial effusion	88 (35,5%)	79 (47,3%)	9 (11,1%)	<0,001
Periaortic effusion	41 (16,5%)	24 (14,4%)	17 (21%)	0,257
Moderate/severe aortic regurgitation	70 (28,2%)	58 (34,7%)	12 (14,8%)	0,002
Coronary ostia involvement	13 (5,2%)	13 (7,8%)	0 (0%)	0,023
Presence of intramural hematoma	76 (30,6%)	46 (27,5%)	30 (37%)	0,17
Presence of plaque rupture/ulceration	18 (7,3%)	5 (3%)	13 (16%)	<0,001

Supplementary Table 2.B Instrumental examinations, treatment and outcome according to Stanford type in patients with available troponin values.

VARIABLE	OVERALL (n=248)	Type A (n=167)	Type B (n=81)	P value
Instrumental examinations				
Computed tomography	232 (93,5%)	153 (91,6%)	79 (97,5%)	0,133
Transesophageal echocardiography	55 (22,2%)	44 (26,8%)	11 (13,6%)	0,035
Transthoracic echocardiography	144 (58,1%)	99 (59,3%)	45 (55,6%)	0,674
Chest radiograph	154 (62,1%)	96 (57,5%)	58 (71,6%)	0,044
Abdominal ultrasound	42 (16,9%)	24 (14,4%)	18 (22,2%)	0,172
Magnetic resonance imaging	10 (4%)	4 (2,4%)	6 (7,4%)	0,124
Angiography	25 (10,1%)	13 (7,8%)	12 (14,8%)	0,134
ACS-like electrocardiogram	68 (27,4%)	52 (31,1%)	16 (19,8%)	0,083
Troponin positivity	70 (28,2%)	50 (29,9%)	20 (24,7%)	0,470
Treatment				
Surgery/Endovascular	173 (69,7%)	138 (82,6%)	35 (43,2%)	<0,001
Only medical treatment	75 (30,2%)	29 (17,4%)	46 (56,8%)	
Outcome				
In-hospital death	55 (22,2%)	42 (25,1%)	13 (16%)	0,146
In-h death of patients surgically treated	31/173 (17,9%)	25/138 (18,1%)	6/35 (17,1%)	0,91
In-h death of patients treated with medical therapy	24/75 (32%)	17/29 (58,6%)	7/46 (15,2%)	<0,001
Delays (median, Q1-Q3)				
Pre-hospital delay, min	90 (50-190)	75 (45-180)	120 (60-233)	0,08
In-hospital delay, min	190 (101-406)	180 (113-536)	170 (95-277)	0,57

Global delay, min	347 (195-895)	255 (158-716)	290 (155-510)	0,12
Surgical delay, min	NA	180 (162-306)	NA	NA

Supplementary Table 3. Clinical profile and diagnostic delays according to ECG/TnT findings.

	ACS-like ECG +/ Tn+ n = 29	**ACS-like ECG - / Tn+ n = 41**	**ACS-like ECG +/ Tn- n = 39**	**ACS-like ECG - / Tn- n = 139**	**P**
Characteristics					
Age, mean (SD), y	69 ± 15	69 ± 13	67 ± 12	67 ± 12	.24
Male gender, No. (%)	17 (58%)	23 (56%)	27 (69%)	99 (71%)	.305
Type of dissection					.377
Stanford type A	23 (79%)	27 (66%)	29 (74%)	88 (63%)	
Stanford type B	6 (21%)	14 (34%)	10 (26%)	51 (37%)	
Hypertension , No. (%)	19 (66%)	32 (78%)	32 (82%)	96 (69%)	.365
History of CAD	2 (7%)	5 (12%)	2 (5%)	8 (6%)	.706
Symptoms					
Chest pain	21 (72%)	25 (61%)	30 (77%)	97 (70%)	.637
Back pain	14 (48%)	18 (44%)	15 (38%)	69 (50%)	.871
Syncope	8 (28%)	7 (17%)	5 (13%)	17(12%)	.256
Dyspnea	9 (31%)	4 (8%)	4 (10%)	19 (14%)	.06
Autonomic symptoms	13 (45%)	14 (34%)	15 (38%)	63 (45%)	.513
Signs					
SBP < 90 mm Hg	9 (31%)	8 (20%)	8 (21%)	18 (13%)	.142
SBP >160 mm Hg	9 (31%)	14 (34%)	15 (38%)	44 (32 %)	.615
Pulse deficit	8 (28%)	9 (22%)	10 (26%)	27(19%)	.973
Pleural effusion	8 (28%)	13 (32%)	13 (33%)	28 (20%)	.754
Cardiac tamponade	1 (3%)	7 (17%)	6 (15%)	16 (11%)	.445
Moderate/severe aortic regurgitation	14 (48%)	4 (10%)	15 (38%)	28(20%)	.001
Coronary osthia involvement	4 (14%)	1 (2%)	4 (10%)	4 (3%)	.05
Shock	9 (31%)	6 (15%)	6 (15%)	16 (11%)	.08
Surgery	20 (69%)	28 (68%)	27 (69%)	98 (70%)	.99
In-hospital mortality	10 (34%)	10 (24%)	11 (28%)	24 (17%)	.190
Delays (median, Q1-Q3)					
Pre-hospital delay, min	100 (47-297)	90 (50-175)	80 (47-184)	88 (50-180)	.65
In-hospital delay, min	300 (260-1500)	180 (100-580)	180 (122-285)	170 (93-341)	.01
Global delay, min	810 (260-1500)	330 (191-1091)	280 (198-707)	330 (195-746)	.002

Supplementary Table 4. Instrumental findings, antithrombotic medications, and interventions of positive troponin patients with AAS presenting as "true" ST-elevation myocardial infarction.

Patients	**Stanford type A**	**ECG leads (ST-segment elevation)**	**Shock**	**Coronary angiography**	**PCI**	**Antiplatelets drugs**	**Anticoagulant**
1	Yes	D2,D3,aVF and V1-V2 (right ventricle)	Yes	No	No	Yes (aspirin)	No
2	Yes	V2-V5	Yes	No	No	Yes (aspirin)	Yes (heparin)
3	Yes	D2,D3,aVF	No	Yes	Yes	Yes (aspirin, clopidogrel, abciximab)	Yes (heparin)
4	No	D2,D3,aVF	No	No	No	No	No
5	No	D2,D3,aVF (prior MI)	No	No	No	Yes (aspirin)	No
6	Yes	D2,D3,aVF	No	No	No	No	No
7	Yes	D2,D3,aVF and V1-V2 (right ventricle)	Yes	Yes	No	Yes (aspirin, clopidogrel)	Yes (heparin)
8	Yes	D2,D3,aVF	No	No	No	No	No
9	Yes	V3-V6	No	Yes	No	Yes (aspirin)	Yes (heparin)
Total	**77%** (7/9)	**77% inferior leads**	**33%** (3/9)	**33%** (3/9)	**11%** **(**1/9)	**66%** (6/9)	**44%** (4/9)

		(7/9)					

Supplementary Table 5A. Baseline clinical characteristics in patients alive or dead at hospital discharge.

VARIABLE	**OVERALL (n=398)**	**Alive at hospital discharge (n=310)**	**Dead at hospital discharge (n=88)**	**P Value**
Type A	258 (64,8%)	190 (61,3%)	68 (77,3%)	0,008
Type B	140 (35,2%)	120 (38,7%)	20 (22,7%)	
Patients' characteristics				
Age (yrs), mean ± SD	66,7 ± 13,3	65,2 ± 13,4	71,6 ± 5,5	<0,001
Men	266 (66,8%)	214 (69%)	52 (59,1%)	0,105
Hypertension (history)	304 (76,4%)	237 (76,5%)	67 (76,1%)	0,936
Anti-hypertensive therapy	263 (66,1%)	205 (66,1%)	58 (65,9%)	0,929
Marfan syndrome	7 (2,1%)	6 (1,9%)	1 (1,1%)	0,965
Bicuspid aortic valve	9 (2,3%)	8 (2,6%)	1 (1,1%)	0,691
Aortic coarctation	1 (0,3%)	1 (0,3%)	0 (0%)	0,501
Known thoracic aortic aneurysm	20 (5,0%)	13 (4,2%)	7 (8%)	0,263
Re-dissection	6 (1,5%)	5 (1,6%)	1 (1,1%)	0,864
Clinical features at presentation				
Systolic blood pressure (mm Hg)	145 ± 42 (389/398)	147 ± 21 (303/310)	140 ± 7 (86/88)	0,003
Systolic blood pressure ≤ 90 mm Hg	68/389 (17,5%)	46/303 (15,2%)	22/86 (25,6%)	0,037
Systolic blood pressure > 160 mm Hg	125/389 (32,1%)	99/303 (32,8%)	26/86 (29,9%)	0,767

Back pain	194 (48,7%)	157 (50,6%)	37 (42%)	0,192
Chest pain	261 (65,6%)	205 (66,1%)	56 (63,6%)	0,759
Migratory pain	51 (12,8%)	39 (12,6%)	12 (13,6%)	0,936
Abdominal pain	110 (27,6%)	84 (27,1%)	26 (29,5%)	0,750
Pain plus syncope	34 (8,5%)	23 (7,4%)	11 (12,5%)	0,197
Pain plus shock	44 (11,1%)	24 (7,7%)	20 (22,7%)	<0,001
Pain plus cerebrovascular accident	12 (3,0%)	9 (2,9%)	3 (3,4%)	0,914
Pain plus paraplegia	10 (2,5%)	6 (1,9%)	4 (4,5%)	0,320
Peripheral pulse deficits	91 (22,8%)	66 (21,3%)	25 (28,4%)	0,208
Dyspnea	58 (14,6%)	37 (11,9%)	21 (23,9%)	<0,001
Autonomic symptoms	155 (38,9%)	113 (36,5%)	42 (47,7%)	0,073
Shock within 12 of admission	57 (14,3%)	34 (11%)	23 (26,1%)	<0,001
ACS-like ECG + chest pain	72 (18,1%)	48 (15,5%)	24 (27,3%)	0,017
Disease complications				
Cardiac tamponade	38 (9,5%)	24 (7,7%)	14 (15,9%)	0,036
Pleural effusion	99 (24,9%)	66 (21,3%)	33 (37,5%)	0,003
Pericardial effusion	123 (30,9%)	87 (28,1%)	36 (40,9%)	0,030
Periaortic effusion	63 (15,8%)	45 (14,5%)	18 (20,5%)	0,237
Moderate/severe aortic regurgitation	106 (26,6%)	68 (21,9%)	38 (43,2%)	<0,001
Coronary ostia involvement	22 (5,5%)	10 (3,2%)	12 (13,6%)	<0,001
Presence of intramural	117 (29,4%)	96 (31%)	21 (23,9%)	0,247

hematoma				
Presence of plaque rupture/ulceration	25 (6,3%)	14 (4,5%)	11 (12,5%)	0,013

Supplementary Table 5B. Instrumental examinations and treatment in patients alive or dead at hospital discharge.

VARIABLE	**OVERALL (n=398)**	**Alive at hospital discharge (n=310)**	**Dead at hospital discharge (n=88)**	**P value**
Instrumental examinations				
Computed tomography	372 (93,5%)	293 (94,5%)	79 (89,8%)	0,179
Transesophageal echocardiography	87 (21,8%)	60 (19,4%)	27 (30,7%)	0,034
Transthoracic echocardiography	222 (55,8%)	174 (56,1%)	48 (54,5%)	0,887
Chest radiograph	237 (59,5%)	185 (59,7%)	52 (59,1%)	0,981
Abdominal ultrasound	78 (19,6%)	68 (21,9%)	10 (11,4%)	0,040
Magnetic resonance imaging	20 (5,0%)	16 (5,2%)	4 (4,5%)	0,966
Angiography	42 (10,6%)	32 (10,3%)	10 (11,4%)	0,933
ACS-like electrocardiogram	102 (25,6%)	69 (22,3%)	33 (37,5%)	0,006
Troponin positivity	70/248 (28,2%)	50/192 (26%)	20/56 (35,7%)	0,213
Treatment				
Surgery/Endovascular	287 (72,1%)	232 (74,8%)	55 (62,5%)	0,032
Only medical treatment	111 (27,9%)	78 (25,2%)	33 (37,5%)	

Figure 1. Impact of Troponin elevation and ACS-like ECG abnormalities on in-hospital diagnostic time and inappropriate treatments.

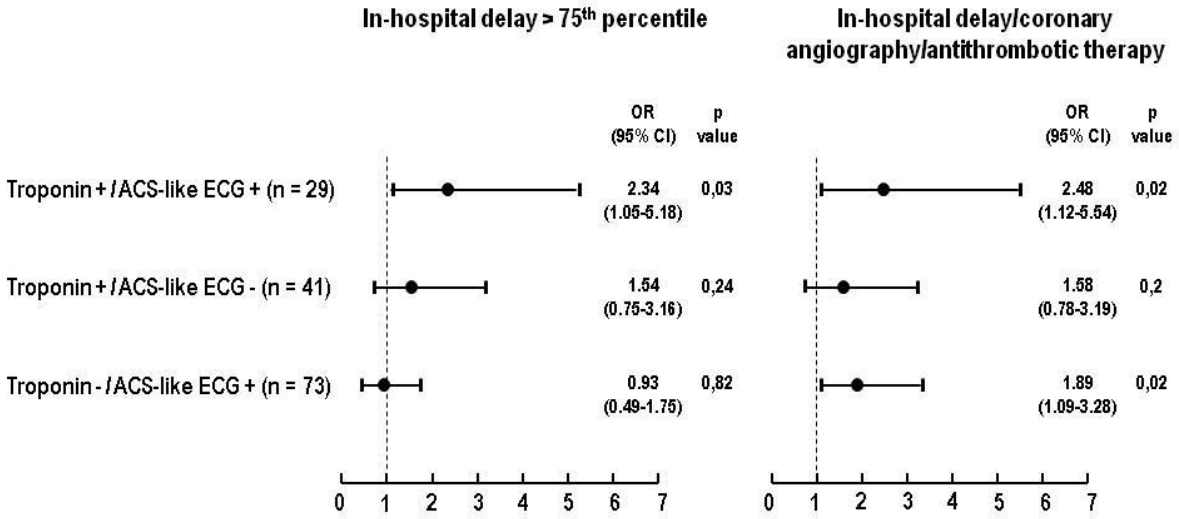
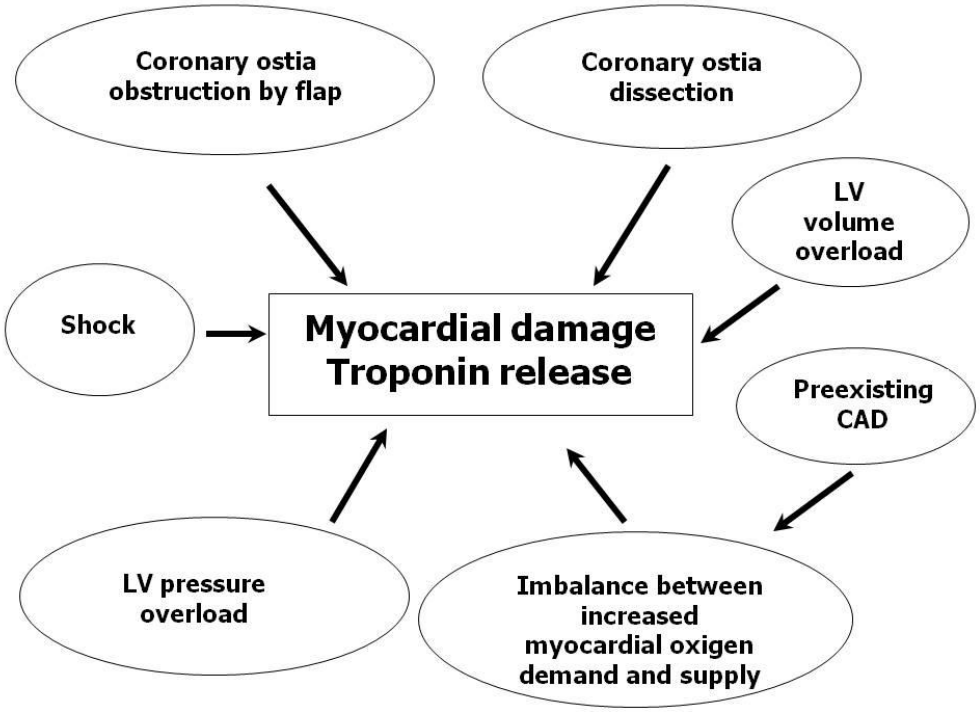


Figure 2. Pathophysiological mechanisms underlying troponin positivity in acute aortic syndromes.



PART II

ACUTE HEART FAILURE IN PATIENTS WITH ACUTE AORTIC SYNDROME: PATHOPHYSIOLOGY AND CLINICAL-PROGNOSTIC IMPLICATIONS.

Background

Acute heart failure (AHF) is rightly regarded as not a single disease but a syndrome that can be caused by different mechanisms and different diseases. Although it is known that aortic dissection is one of the possible causes of AHF (29,30), the literature is mainly represented by case reports (31-36). The only systematic approach to this issue dates back to 10 years ago (30). A research letter of 2005 summarizes findings from IRAD registry but only partially specifies the mechanisms leading to AHF. Since then, diagnostic tools and surgical techniques have developed enough to warrant a revision of this serious complication of AAS in the current "era"

Aims

The objectives of this study were to assess the frequency of acute heart failure (AHF) in AAS, to characterize the clinical and instrumental profile of these patients, to explore pathophysiological mechanisms underlying this condition and to evaluate the impact on treatment and in-hospital mortality.

Methods

Setting, patients, and data collection

AESA (Archivio Elettronico Sindromi Aortiche acute) registry includes data from all consecutive patients referred to our Institution between 2000 and 2013 who received a final diagnosis of spontaneous Acute Aortic Syndrome. The S.Orsola - Malpighi University Hospital is the referral centre for AAS treatment in a metropolitan hospital network that covers Bologna and its hinterland (catchment area approximately 1.000.000 people).

The database contains information on patient demographics, history, clinical presentations, physical findings, laboratory findings, imaging study results, details of medical and surgical treatment, and patient outcomes, including mortality. Baseline characteristics included "classic" risk factors for AAS and cardiovascular/ non-cardiovascular comorbidities. Pain features and presentation symptoms were reported in detail. Two experienced cardiologists blindly reviewed all the electrocardiograms. Laboratory findings included information on cardiac troponin test, when performed according to the standard protocol used in chest pain unit (until 2010 the standard test was used, then replaced by high sensitivity assay). Imaging was interpreted by specialized radiologists and echocardiographers and entered into the data form. Helical computed tomography, transesophageal/transthoracic echocardiography, magnetic resonance imaging, and/or angiography were obtained and reviewed.

Details of the relevant diagnostic time intervals were prospectively collected: 1) symptoms onset to presentation at any hospital; 2) hospital presentation to final AAS diagnosis; 3) global diagnostic delay (symptoms onset to final AAS diagnosis at any hospital).

Surgical delay (for Stanford type A) was defined by the time gap between symptom onset and operating room.

Patients with symptoms onset >14 days at hospital presentation were not included in the registry. AAS (aortic dissection, penetrating ulcer and intramural hematoma) were defined according to the Stanford classification.

In all cases (presenting at either a hub or a spoke centre) the diagnosis was confirmed by a multidisciplinary team that included a cardiologist, heart surgeon and cardiovascular radiologist.

The study was approved by the local ethics committee and all patients provided written informed consent.

Definitions and mechanisms

Patients with AHF were identified by the presence of dyspnea as presentation symptom or radiological signs of pulmonary congestion or cardiogenic shock, including patients with cardiac tamponade. Shock was defined as sustained hypotension (systolic blood pressure <90 mm Hg for >30 minutes) accompanied by clinical signs of peripheral/cerebral hypoperfusion (24). We used standard definition for cardiac tamponade (25).

Clinical and instrumental data of each patients with AHF were systematically reviewed in order to identify the mechanisms leading to AHF. A distinction between "main" and "contributing" mechanism was made by two cardiologists on a case-by-case basis by using the following hierarchy: cardiac tamponade, severe aortic regurgitation, myocardial ischemia, ischemia, hypertensive crisis.

Electrocardiogram (ECG) was considered to be acute coronary syndrome (ACS)-like in the presence of ≥ 1 of the following characteristics: 1) ST-segment elevation in two contiguous leads with the cut-point ≥ 0.1 mV in all leads other than leads V2-V3, where the cut- point is ≥ 0.2 mV; 2) horizontal or down-sloping ST-segment depression ≥ 0.05 mV in two contiguous leads; 3) T-wave inversion ≥ 0.1 mV in two contiguous leads.

The diagnosis of troponin positivity using standard cTnT testing was made in the presence of at least one value of cTnT > 30 ng/L (10% CV cut-off). When HS-cTnT was used, the diagnosis of troponin positivity was made in the presence of at least one value of HS-cTnT > 14 ng/L (URL).

Myocardial ischemia was defined by the presence of ACS-like ECG findings and/or troponin positivity.

Aortic regurgitation was considered a possible mechanism of AHF only when severe or moderate-to-severe at transthoracic/transesophageal echocardiography. Mechanisms leading to aortic regurgitation in type A AAS were classified according to previous study by Movsowitz et Al. (37).

Hypertensive crisis was defined according to current ESC guidelines on arterial hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg) (38).

Pleural effusion was diagnosed by chest x-ray or CT scan. Pericardial effusion was diagnosed by transthoracic/transesophageal echocardiogram, cardiac tomogram, or magnetic resonance imaging. Periaortic hematoma was diagnosed by transthoracic/ transesophageal echocardiogram, CT, or magnetic resonance imaging (26).

Statistical analysis

Categorical data were expressed as proportions and continuous variables reported as mean□SD or medians and interquartile range (IQR), as appropriate. The Chi-square test for categorical variables was used to compare groups. The two-tailed Student *t* test was used to compare normally distributed continuous variables. Comparison of non-normally distributed variables were conducted using the Mann-Whitney U test.

We explored the association between diagnostic delay and clinical-instrumental profile of the patient. In order to identify unusually long diagnostic times we used 75th percentile of in-hospital delay as cut-off in keeping with previous analyses (15).

Logistic regression analysis was performed to identify predictors of in-hospital delay and of in-hospital mortality. Non correlated variables with $p<0.2$ at the univariate analyses were included in the multivariate analysis. Model discrimination was assessed with the c-statistic, and model calibration was assessed with the Hosmer-Lemeshow statistic.

A p value < 0.05 in the two-tailed tests was considered significant. All analyses were performed with the STATA/SE 12.1 software for Windows (StataCorp LP, College Station, Texas, USA).

Results

Frequency and profile of patients presenting with AHF

During the study period a total of 398 patients received a final diagnosis of spontaneous AAS and were entered into the AESA Registry.

Epidemiological, clinical, instrumental and outcome findings of the patients presenting with / without AHF are shown in Tables 1A and 1B. The overall frequency of AHF among patients with AAS was 28% (113/398); presentation with AHF was more common in patients with Stanford type A AAS (84/258, 32%) vs. Stanford type B (29/140, 20%), (p = 0.01). Regarding clinical history, prior coronary artery disease (CAD) was the only feature more often observed among patients presenting with AHF. These patients were more likely to present significant aortic regurgitation, pleural effusion and ACS-like ECG findings. On the other hand, patients without AHF had a higher systolic blood pressure and more frequently reported back or abdominal pain.

Pathophysiological Mechanism

A characterization of probable mechamism(s) underlying AHF was possible only in 89 of 113 patients. In Type A patients aortic insufficiency was the single most frequent mechanism (alone or in combination) followed by cardiac tamponade, whereas myocardial ischemia and hypertensive crisis were the leading causes of AHF in Type B (Table 2). Among the 38 patients with aortic insufficiency, a spectrum of causes of regurgitation was identified including : pre-existing aortic valve disease (bicuspid aortic valve or degenerative leaflet thickening); incomplete leaflet closure due to dilatation of the sino-tubular junction, aortic leaflet prolapse/disruption, and prolapse ("intussusception") of the dissection flap through aortic valve orifice producing a "funnel effect".

Diagnostic delays

Median global diagnostic delay (time to diagnosis) was 307 (Q1-Q3, 180 - 900) minutes. Median pre-hospital (time to presentation) and in-hospital delays were 90 (Q1-Q3, 50 - 210) minutes and 190 (Q1-Q3, 101-406) minutes respectively (Table 1B). The median time from symptom onset to presentation was shorter among patients with AHF whereas no difference was noted for both in-hospital and global diagnostic times (Table 1B, Figure 1) . Importantly, presentation with AHF wads associated to increased surgical delay among type A AAS patients (Figure 2).

Table 3 shows results of univariate/multivariate analysis of predictors of in-hospital diagnostic delay. Excess risk was related to pleural effusion whereas back pain and pulse deficit resulted to be protective from late in-hospital diagnosis. Of note AHF as clinical presentation of AAS did not influence in-hospital diagnostic time (OR 1.43 95% CI 0.88-2.32, p = 0,152).

In-hospital outcome

Overall mortality of patients presenting with AHF were two-fold compared those presenting without (table 4), mainly due to an excess risk in type A pts. Independent predictors of in-hospital mortality in the whole population and in Type A AAS undergoing surgery are reported in table 5 and 7 respectively. AHF was indeed an independent risk factor in conjunction with age, Stanford type A, pleural effusion, ACS-like ECG findings, pulse deficit. Surgery or endovascular treatment resulted to be protective.

DISCUSSION

The main result of our analysis is that AHF occurs in more than one fourth of patients with AAS of both type A and type B, is associated with increased surgical delay and in-hospital mortality.

The study population of our single centre series is comparable to that of the largest available AAS registry, the IRAD registry, in particular with regard to age (mean value 66.7 yrs), male prevalence (67%), relative frequency of Stanford type A, frequency and distribution of signs and symptoms at presentation (27). A history of hypertension was the most frequent risk factor (76%), while Marfan syndrome and bicuspid aortic valve were found only in 2.1% and 2.3% of patients respectively.

Presentation with AHF occurred in 28% of our population, ranging from 20% among type B patients to 32% of those with type A AAS. The prevalence reported in IRAD is consistently lower (6%), but differences in the definition of AHF can explain this discrepancy. While in the study by Januzzi et al (30) the diagnosis of CHF was based on the impressions of the managing physicians as noted in the IRAD case report form, we included all the patients with dyspnea at presentation or pulmonary congestion at x-Ray or cardiogenic shock in order to assume as more as possible the unbiased perspective of a

physician evaluating an acutely ill patient facing the entire spectrum of diseases underlying AHF. Interestingly, in our study both categories of AHF proposed by ESC guidelines (29) are represented: 56 of 113 patients presented with pulmonary congestion/oedema without shock; 57 of 113 patients presented with hypotension, hypoperfusion or shock. So the physician should consider the possibility of AAS (when the clinical context is appropriate), in front of both presentations of AHF.

Our registry, although not specifically aimed to investigate the mechanistic aspects, offers several insights into the possible mechanisms underlying AHF during AAS due to the prospective collection of many clinical and instrumental variables in all the patients, including standard ECG, Troponin values, TTE and TEE.

It should be noted, first, that the frequency of the possible mechanisms is different between type A and type B (Table 2). In type A AAS, aortic regurgitation and cardiac tamponade are the main causes of AHF. During AAS cardiac tamponade may cause sudden death but it can also occur over a relatively long time leading to progressive heart failure and subsequent shock at presentation.

Aortic regurgitation may be due to a variety of mechanisms which were explored by TE echocardiography: 1) incomplete leaflet closure that occurs when the sino-tubular junction dilates relative to the aortic annulus resulting in leaflet tethering and a persistent diastolic orifice, 2) aortic leaflet prolapse that occurs when the dissection extends into the aortic root and disrupts normal leaflet attachment to the aortic wall, thereby resulting in abnormal leaflet coaptation and eccentric regurgitation; 3) prolapse of the dissection flap through aortic valve orifice 4) pre-existing aortic valve disease (bicuspid aortic valve or degenerative leaflet thickening).

Myocardial ischemia, which leads to left ventricular systolic or diastolic dysfunction, may be related to a clear anatomic obstruction of at least one coronary artery due to coronary

dissection or to diastolic apposition of the flap to the ostium. In the remaining cases the mechanism, albeit undefined, is probably multifactorial including acute pressure overload in patients with or without pre-existing coronary.

Although most patients with AHF in our series had type A AAS, this study show that as many as 25% of patients with AHF had a distal dissection; when AHF is a presenting symptom of type B AAS, this may be due to myocardial ischemia or hypertensive crisis.

Indeed, 1 out of 3 patients with AHF showed ACS-like ECG abnormalities and/or troponin T positivity, irrespective to Stanford subtype.

The clinical profile of patients with AHF is similar to that of patients without AHF regarding age and risk factors (Table 1A). On the other hand, AHF patients are more likely to have type A AAS, low blood pressure and less likely to present with back-pain; more frequently, however, the pain is associated with syncope and a pleural effusion is detectable at chest X-ray.

Although some of these findings (such as dyspnea and pleural effusion) could theoretically lead to long in-hospital delay (15), median time to diagnosis was not significantly different between patients presenting with/without AHF, and AHF was not identified as an independent predictor of late in-hospital diagnosis at multivariable analysis (Table 3). These results are consistent with previous findings from IRAD registry (30).

It is possible that the overall perception of increased severity of AHF patient by the physician determined a faster diagnostic work up, and that this fact balanced out an initial delay of the hypothesis of AAS; thus, the two effects tended to offset each other.

Patients with AHF tended to have a shorter median time from symptom onset to presentation indeed, probably because of the more severe clinical picture that induces an early access to the emergency department. Conversely, median time to surgical treatment (when performed) was longer among patients presenting with AHF (Figure 2). Notably, in our study as in the

IRAD patients with type A AAS and concomitant AHF underwent surgery later than those without AHF. Although the exact explanation of this finding is not clear, it could be argued that this delay was due to the increased complexity of the management of such patients and to the temptation to stabilize them before taking to the operating room. Presentation with AHF is an incremental risk factor for in-hospital mortality of type A AAS patients (both operated and not operated) probably due to a more advanced preoperative multi-organ damage.

LIMITATIONS

Our prospective registry refers to a single hub center operating in a rather densely populated urban area with a long lasting hub & spoke organization. So the findings regarding hospital arrival times cannot be generalized to more challenging geographic settings. Inevitably, this registry included only patients who reached a final diagnosis of AAS and could not consider (or include) the patients that never received a diagnosis of AAS, or had a post-mortem diagnosis.

Our definition of AHF may have overestimated its prevalence in AAS patients. We included indeed all the patients with dyspnea at presentation or pulmonary congestion at x-Ray or cardiogenic shock in order to assume as more as possible the unbiased perspective of a physician evaluating an acutely ill patient facing the entire spectrum of diseases underlying AHF. Therefore this difference should be taken into account when comparing our study with other reports.

Table 1A Baseline clinical characteristics in overall study population and according to AHF on presentation.

VARIABLE	OVERALL (n=398)	AHF (n=113)	No AHF (n=285)	P value
Patients' characteristics				
Age (yrs), mean ± SD	66,7 ± 13,3	69,7 ± 13,4	70,4 ± 13,9	0,647
Men	266 (66,8%)	69 (61,1%)	197 (69,1%)	0,155
Hypertension (history)	304 (76,4%)	86 (76,1%)	218 (76,5%)	0,961
Anti-hypertensive therapy	263 (66,1%)	76 (67,3%)	187 (65,6%)	0,846
Marfan syndrome	7 (2,1%)	1 (0,9%)	6 (2,1%)	0,68
Bicuspid aortic valve	9 (2,3%)	3 (2,7%)	6 (2,1%)	0,967
Aortic coarctation	1 (0,3%)	0 (0%)	1 (0,4%)	0,631
Known thoracic aortic aneurysm	20 (5,0%)	5 (4,4%)	15 (5,3%)	0,928
Re-dissection	6 (1,5%)	1 (0,9%)	5 (1,8%)	0,853
Previous stroke	22 (5,5%)	5 (4,4%)	17 (6%)	0,717
Coronary artery disease (history)	28 (7,0%)	14 (12,4%)	14 (4,9%)	0,016
Clinical features at presentation				
Systolic blood pressure (mm Hg)	145 ± 42 (389/398)	125 ± 21 (111/113)	154 ± 39 (278/285)	<0,001
Systolic blood pressure ≤ 90 mm Hg	68/389 (17,5%)	47/111 (42,3%)	21/278 (7,6%)	<0,001
Systolic blood pressure > 160 mm Hg	125/389 (32,1%)	22/111 (19,8%)	103/278 (37,1%)	0,002
Back pain	194 (48,7%)	39 (34,5%)	155 (54,4%)	<0,001
Chest pain	261 (65,6%)	79 (69,9%)	182 (63,9%)	0,304
Migratory pain	51 (12,8%)	10 (8,8%)	41 (14,4%)	0,186
Abdominal pain	110 (27,6%)	24 (21,2%)	86 (30,2%)	0,094
Pain plus syncope	34 (8,5%)	19 (16,8%)	15 (5,3%)	<0,001
Pain plus shock	44 (11,1%)	44 (38,9%)	0 (0%)	<0,001
Pain plus cerebrovascular accident	12 (3,0%)	4 (3,5%)	8 (2,8%)	0,952
Pain plus paraplegia	10 (2,5%)	2 (1,8%)	8 (2,8%)	0,81
Peripheral pulse deficits	91 (22,8%)	27 (23,9%)	64 (22,5%)	0,861
Dyspnea	58 (14,6%)	58 (51,3%)	0 (0%)	NA
Autonomic symptoms	155 (38,9%)	58 (51,3%)	97 (34%)	0,002
Shock within 12 of admission	57 (14,3%)	57 (50,4%)	0 (0%)	NA
Stanford Type A	258 (64,8%)	84 (74%)	174 (61,1%)	

Stanford Type B	140 (35,2%)	29 (25%)	111 (38,9%)	0.017
Disease complications				
Cardiac tamponade	38 (9,5%)	30 (26,5%)	8 (2,8%)	NA
Pleural effusion	99 (24,9%)	42 (37,2%)	57 (20%)	<0,001
Pericardial effusion	123 (30,9%)	54 (47,8%)	69 (24,2%)	<0,001
Periaortic effusion	63 (15,8%)	23 (20,4%)	40 (14%)	0,160
Moderate/severe aortic regurgitation	106 (26,6%)	38 (33,6%)	59 (20,7%)	0,05
Coronary ostia involvement	22 (5,5%)	13 (11,5%)	9 (3,2%)	0,002
Presence of intramural hematoma	117 (29,4%)	30 (26,5%)	87 (30,5%)	0,507
Presence of plaque rupture/ulceration	25 (6,3%)	13 (11,5%)	12 (4,2%)	0,013

Table 1.B Instrumental examinations, treatment and outcome in overall study population and according to AHF at presentation.

VARIABLE	OVERALL (n=398)	AHF at presentation (n=113)	NO-AHF at presentation (n=285)	P value
Instrumental examinations				
Computed tomography	372 (93,5%)	99 (87,6%)	273 (95,8%)	0,006
Transesophageal echocardiography	87 (21,8%)	29 (25,7%)	58 (20,4%)	0,307
Transthoracic echocardiography	222 (55,8%)	63 (55,8%)	159 (55,8%)	0,916
Chest radiograph	237 (59,5%)	78 (69%)	159 (55,8%)	0,021
Abdominal ultrasound	78 (19,6%)	21 (18,6%)	57 (20%)	0,856
Magnetic resonance imaging	20 (5,0%)	7 (6,2%)	13 (4,6%)	0,676
Angiography	42 (10,6%)	11 (9,7%)	31 (10,9%)	0,878
ACS-like electrocardiogram	102 (25,6%)	38 (33,6%)	64 (22,5%)	0,03
Troponin positivity	70/248 (28,2%)	25/69 (36,2%)	45/179 (25,1%)	0,114
Treatment				
Surgery/Endovascular	287 (72,1%)	85 (75,2%)	202 (70,9%)	0,455
Only medical treatment	111 (27,9%)	28 (24,8%)	83 (29,1%)	
Outcome				
In-hospital death	87 (21,8%)	39 (34,5%)	48 (16,8%)	<0,001
In-h death of patients surgically treated	55 (13,8%)	27 (23,9%)	28 (9,8%)	<0,001
In-h death of patients treated with medical therapy	32 (8,0%)	12 (10,6%)	20 (7%)	0,324
Delays (median, Q1-Q3)				
Pre-hospital delay*, min	90 (50-210)	73 (41-180)	90 (60-210)	0.05
In-hospital delay, min	166 (90-353)	209 (92-510)	160 (86-322)	NS
Global delay †, min	307 (180-900)	333 (180-1112)	300 (193-840)	0.86

*Time from symptom onset to presentation

† Time from symptom onset to diagnosis

Table 2 Mechanism of AHF in AAS

	Main mechanism			Contributing mechanism		
	OVERALL N=113	**TYPE A N=84**	**TYPE B N=29**	**OVERALL N=113**	**TYPE A N=84**	**TYPE B N=29**
Cardiac Tamponade	30/113 (26%)	30/84 (36%)	0/29 (0%)	0/113 (0%)	0/84 (0%)	0/29 (0%)
Aortic Regurgitation	29/113 (25%)	29/84 (35%)	0/29 (0%)	9/113 (8%)	9/84 (11%)	0/29 (0%)
Myocardial Ischemia	19/113 (17%)	12/84 (14%)	7/29 (24%)	29/113 (26%)	29/84 (35%)	0/29 (0%)
Hypertensive Crisis	11/113 (10%)	1/84 (1%)	10/29 (34%)	10/113 (9%)	4/84 (5%)	6/29 (20%)
Unknown	24/113 (21%)	12/84 (14%)	12/29 (41%)			

Table 3: Univariate and multivariate analysis for late in-hospital diagnosis (cutoff > 75th percentile, 406 min).

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Pleural effusion	2,1 (1,28-3,44)	0,003	2,17 (1,31-3,6)	0,003
Pericardial effusion	1,67 (1,04-2,68)	0,033		
Acute heart failure	1,43 (0,88-2,32)	0,152		
Male gender	0,75 (0,47-1,21)	0,236		
Pulse deficit	0,50 (0,27-0,92)	0,027	0,56 (0,30-1,05)	0,003
Back pain	0,48 (0,31-0,77)	0,002	0,51 (0,32-0,81)	0,005

Table 4 In-hospital mortality rates in patients with/without AHF

Variable	AHF	No AHF	P value
Overall AAS	39/113 (34.5%)	48/285 (16,8%)	< 0,001
Type A-AAS	34/84 (40,1%)	34/174 (19,5%)	< 0,001
Type B-AAS	5/29 (17%)	14/111 (12%)	0,731

Table 5 Univariate and multivariate analysis for in-hospital mortality of **AAS patients**

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Stanford type A	2,28 (1,30-3,98)	0,004	3,22 (1,65-6,22)	0,001
Acute heart failure	2,60 (1,58-4,27)	<0,001	1,97 (1,14-3,36)	0,014
Pleural effusion	2,27 (1,36-3,78)	0,002	1,80 (1,03-3,20)	0,043
ACS-like ECG	2,14 (1,29-3,56)	0,003	1,81 (1,03-3,11)	0,037
Pericardial effusion	1,82 (1,11-2,98)	0,018		
Troponin positivity	1,63 (0,86-3,09)	0,131		
Pulse deficit	1,5 (0,87-2,56)	0,142	1,70 (0,91-3,01)	0,08
Age (for each 1 year increase)	1,04 (1,02-1,06)	<0,001	1,03 (1,02-1,05)	0,007
Surgery/EVAR	0,44 (0,22-0,68)	0.001	0,41 (0,21-0,77)	0,006
Male gender	0,63 (0,39-1,03)	0,067		

Table 6 Univariate and multivariate analysis for in-hospital mortality of **Type A-AAS** patients

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Acute heart failure	2,80 (1,58-4,97)	<0,001	2,40 (1,30-4,51)	0,006
Pleural effusion	2,98 (1,59-5,57)	0,001	1,98 (1,01-3,97)	0,050
ACS-like ECG	2,21 (1,21-3,82)	0,011	1,90 (0,99-3,06)	0,056
Pericardial effusion	1,53 (0,87-2,60)	0,13		
Periaortic effusion	1,92 (0,88-4,22)	0,100		
Age (for each 1 year increase)	1,04 (1,02-1,07)	<0,001	1,02 (1,00-1,05)	0,008
Surgery	0,16 (0,07-0,32)	<0,001	0,21 (0,09-0,49)	<0.001
Male gender	0,61 (0,34-1,08)	0,091		

Table 7 Univariate and multivariate analysis for in-hospital mortality in **Type A surgically treated patients**.

Variable	**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Acute heart failure	2,95 (1,51-5,8)	0,002	2,91 (1,4-6,06)	0,004
Periaortic effusion	2,83 (1,23-6,55)	0,014	2,71 (1,08-6,77)	0,033
ACS-like ECG	2,19 (1,11-4,34)	0,024	2,49 (1,17-5,29)	0,018
Pleural effusion	2,15 (1,01-4,56)	0,049		
Abdominal pain	1,7 (0,81-3,57)	0,164		
Age (for each 1 year increase)	1,04 (1,01-1,07)	0,012	1,04 (1,01-1,07)	0,018
Transfer to “hub” center	0,45 (0,17-1,23)	0,120		

FIGURE 1 Time to presentation (median values, hours) and time to diagnosis (median values, hours) in the overall study population according to the presence of AHF.

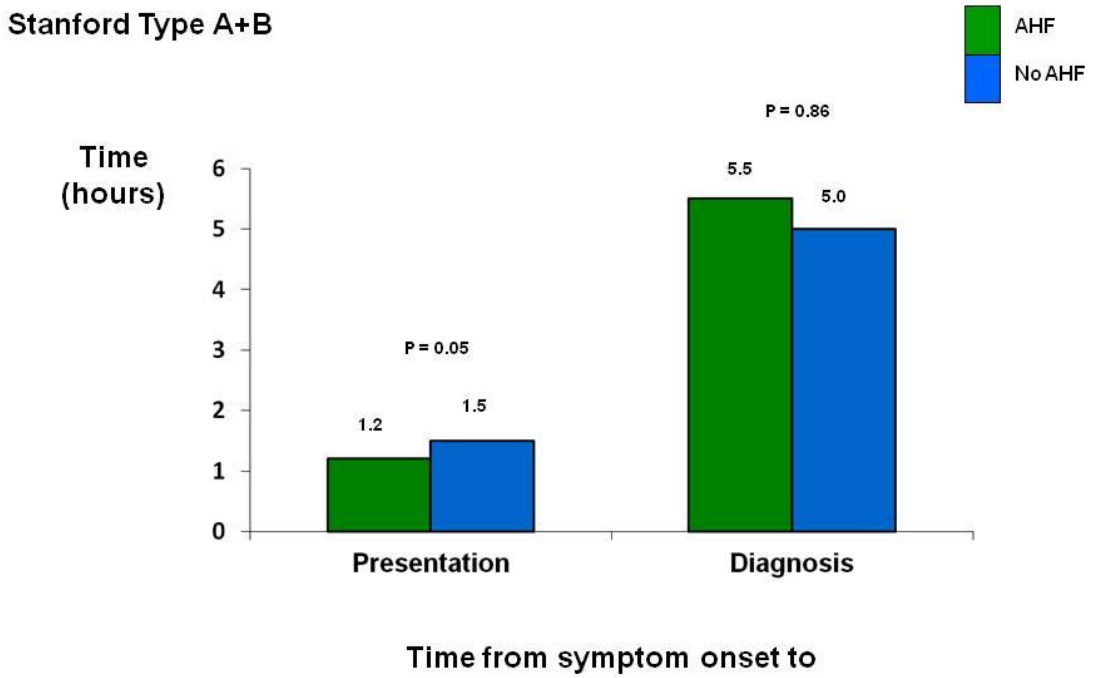
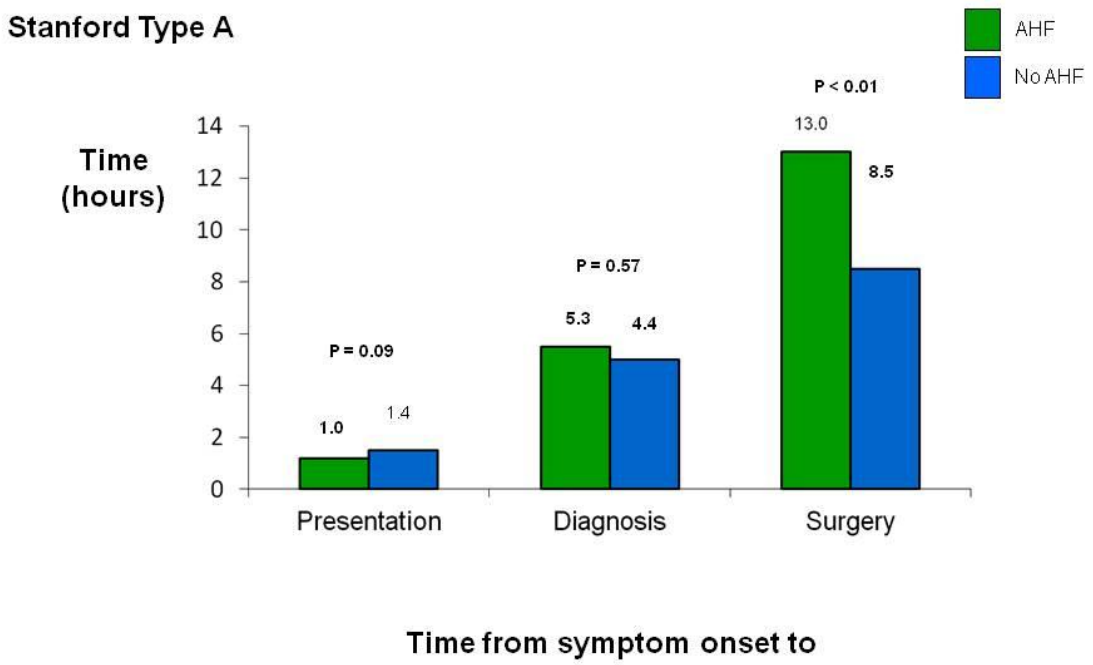


FIGURE 2 Time to presentation (median values, hours), time to diagnosis (median values, hours), and time to surgery (median values, hours) in Stanford type A AAS according to the presence of AHF.



CONCLUSIONS

Troponin positivity is a frequent finding in AAS patients, particularly when a high sensitivity assay is employed. The mechanism of troponin release is plausibly multifactorial, including coronary dissection, interference between flap and coronary ostia, acute LV pressure overload, acute LV volume overload, and shock in patients with or without pre-existing coronary disease. Abnormal troponin values are strongly associated with ACS-like ECG findings and with in-hospital diagnostic delay and misdiagnosis, although apparently they do not directly influence in-hospital mortality.

The second main result of our analysis is that AHF occurs in more than one fourth of patients with AAS of both type A and type B, is associated with increased surgical delay and in-hospital mortality. AHF was due to a variety of pathophysiological mechanisms including cardiac tamponade, aortic regurgitation, myocardial ischemia, hypertensive crisis.

The awareness of frequency and potential mechanisms of troponin positivity and AHF in AAS is essential to guide physicians in this complex and challenging disease.

REFERENCES

1. Erbel R, Aboyans V, Boileau C, Bossone E, Di Bartolomeo R, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for PracticeGuidelines.
   2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014 Nov 1;35(41):2873-926.
2. Howard DP, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM. Populationbased study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. Circulation 2013; 127:2031–2037.
3. Olsson C, Thelin S, Stahle E, Ekbom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomesreported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. Circulation 2006;114:2611–2618.
4. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, Evangelista A, Fattori R, Suzuky T, Oh JK. The International registry of acute aortic dissection: new insights into an old disease. JAMA 2000; 283: 897-903.
5. Erbel R, Oelert H, MeyerJ, Puth M, Mohr-Katoly S,Hausmann D, DanielW, Maffei S, Caruso A, Covino FE. Effect of medical and surgical therapy on aortic dissection evaluated by transesophageal echocardiography. Implications for prognosis and therapy. The European Cooperative Study Group on Echocardiography. Circulation 1993;87:1604–1615.

6. Gilon D, Mehta RH, Oh JK, Januzzi JL Jr., Bossone E, Cooper JV, Smith DE, Fang J, Nienaber CA, Eagle KA, Isselbacher EM. Characteristics and in-hospital outcomes of patients with cardiac tamponade complicating typeAacute aortic dissection. Am J Cardiol 2009;103:1029–103
7. Bossone E, Corteville DC, Harris KM, Suzuki T, Fattori R, Hutchison S, Ehrlich MP, Pyeritz RE, Steg PG, Greason K, Evangelista A, Kline-Rogers E, Montgomery DG, Isselbacher EM, Nienaber CA, Eagle KA. Stroke and outcomes in patients with acute type A aortic dissection. Circulation 2013;128:S175–S179.
8. Di Eusanio M, Trimarchi S, Patel HJ, Hutchison S, Suzuki T, Peterson MD, Di Bartolomeo R, Folesani G, Pyeritz RE, Braverman AC, Montgomery DG, Isselbacher EM, Nienaber CA, Eagle KA, Fattori R. Clinical presentation, management, and short-term outcome of patients with type A acute dissection complicated by mesenteric malperfusion: observations from the International Registry of Acute Aortic Dissection. J Thorac Cardiovasc Surg 2013;145:p385–390
9. Rogers AM, Hermann LK, Booher AM, Nienaber CA, Williams DM, Kazerooni EA, Froehlich JB, O'Gara PT, Montgomery DG, Cooper JV, Harris KM, Hutchison S, Evangelista A, Isselbacher EM, Eagle KA. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the international registry of acute aortic dissection. Circulation 2011;123:2213–2218.
10. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr., Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the

American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010;121:e266–e369.

11. Van Arsdell GSMD, David TEMD, Butany JMD. Autopsies in acute type A aortic dissection: surgical implications. Circulation 1998;98: 299II–302II.
12. Ranasinghe AM, Bonser RS. Biomarkers in acute aortic dissection and other aortic syndromes. J Am Coll Cardiol. 2010 Nov 2;56(19):1535-41.
13. Raghupathy A, Nienaber CA, Harris KM, et al. Geographic differences in clinical presentation, treatment, and outcomes in type A acute aortic dissection (from the International Registry of Acute Aortic Dissection). Am J Cardiol 2008;102:1562– 6.
14. Davies RR, Coe MP, Mandapati D, et al. Thoracic Surgery Directors Association Award. What is the optimal management of latepresenting survivors of acute type A aortic dissection? Ann Thorac Surg 2007;83:1593– 601, discussion 1601–2.
15. Rapezzi C, Longhi S, Graziosi M, Biagini E, Terzi F, Cooke RT, Quarta Cm Sangiorgi D, Ciliberti P, Di Pasquale G, Branzi A. Risk factors for diagnostic delay in acute aortic dissection. Am J Cardiol 2008; 102: 1399-1406.
16. Corsini A*, Vagnarelli F*, Bugani G, Bacchi Reggiani ML, Semprini F, Nanni S, Cinti L, Norscini G, Vannini A, Beltrandi E, Cavazza M, Branzi A, Rapezzi C, Melandri G. (*co-first authors) Impact of high-sensitivity Troponin T on hospital admission, resources utilization, and outcomes. Eur Heart J Acute Cardiovasc Care. 2014 Aug 14. pii: 2048872614547687.
17. Nienaber CA, Powell JT. Management of acute aortic syndromes. Eur Heart J 2012; 33: 26-35.

18. Bonnefoy E, Godon P, Kirkorian G, Chabaud S, Touboul P. Significance of serum troponin I elevation in patients with acute aortic dissection of the ascending aorta. Acta Cardiol 2005; 60: 165-170.

19. Hansen MS, Nogareda GJ, Hutchison SJ. Frequency of and inappropriate treatment of misdiagnosis of acute aortic dissection. Am J Cardiol 2007; 99: 852-856.

20. Biagini E, Lofiego C, Ferlito M, Fattori R, Rocchi G, Graziosi M, Lovato L, Di Diodoro L, Cooke RT, Petracci E, Bacchi Reggiani ML, Zannoli R, Branzi A, Rapezzi C. Frequency, determinants, and clinical relevance of acute coronary syndrome-like electrocardiographic findings in patients with acute aortic syndrome. Am J Cardiol 2007; 100: 1013-1019.

21. Harris KM, Strauss CE, Eagle KA, Hirsch AT, Isselbacher EM, Tsai TT, Shiran H, Fattori R, Evangelista A, Cooper JV, Montgomery DG, Froehlich JB, Nienaber CA. Correlates of Delayed Recognition and Treatment of Acute Type A Aortic Dissection: The International registry of acute aortic dissection. Circulation 2011; 124: 1911-1918.

22. Daily PO, Trueblood HW, Stinson EB, Wuerflein RD, Shumway ND. Management of acute aortic dissection. Am Thorac Surg 1970; 10: 237–247.

23. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD: the writing group on behalf of the joint ESC/ACCF/AHA/WHF Task Force for the universal definition of myocardial infarction. Third universal definition of myocardial infarction. Eur Heart J 2012; 33: 2551-2567.

24. Hollenberg SM, Kavinski CJ, Parillo JE. Cardiogenic shock. Ann Intern Med 1999; 131: 47-59.

25. Spodick DH. Acute cardiac tamponade. N Eng J Med 2003; 349: 684-690.

26. Evangelista A, Mukherjee D, Mehta RH, O'Gara PT, Fattori R, Cooper JV, Smith DE, Oh JK, Hutchinson S, Sechtem U. Internation Registry of Aortic dissection Investigator. Acute intramural hematoma of the aorta: a mistery in evolution. Circulation 2005; 111: 1063-1070

27. Tsai TT, Trimarchi S, Nienaber CA. Acute Aortic Dissection: perspectives from the international registry of Acute Aortic Dissection (IRAD). Eur J Vasc Endovasc Surg 2009; 37: 149-159.

28. Suzuki T, Distante A, Zizza A, Trimarchi S, Villani M, Salerno Uriarte JA, De Luca Tupputi Schinosa L, Renzulli A, Sabino F, Nowak R, Birkhahan R, Hollander JE, Counselman F, Bossone E, Eagle K, on behalf of the International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) Investigators. Preliminary experience with the smooth muscle troponin-like protein, calponin, as a novel biomarker for diagnosing acute aortic dissection. Eur Heart J 2008; 29: 1439-1445.

29. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY,Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F,Zeiher A; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Eur J Heart Fail. 2012;14(8):803-69.

30. Jannuzzi JL, Eagle KA, Cooper JV, et Al. Acute aortic dissection presenting with congestive heart failure: results from the International registry of acute aortic dissection. J Am Coll Cardiol 2005; 46: 733-35.

31. Agrawal S, Longfield S, George G. Congestive cardiac failure and aortic dissection in a young man with Marfan's syndrome. J Accid Emerg Med 1994;11:259–60.

32. Niitsuma Y, Takahara Y, Sudo Y, Nakano H. Acute type A aortic dissection associated with an aortic annular abscess. Ann Thorac Surg 2001;72:2136 –7.

33. Oliveira JS, Bestetti RB, Marin-Neto JA, Costa RS, Carneiro JJ. Ruptured aortic dissection into the left atrium: a rare cause of congestive heart failure. Am Heart J 1991;121:936–8.

34. Patsouras D, Argyri O, Siminilakis S, Michalis L, Sideris D. Aortic dissection with aorto-left atrial fistula formation soon after aortic valve replacement: a lethal complication diagnosed by transthoracic and transesophageal echocardiography. J Am Soc Echocardiogr 2002;15: 1409–11

35. Shimazaki Y, Uesho K, Takeda F, Nakashima K, Inui K. Concomitant David's operation and total arch replacement for acute type A aortic dissection. Jpn J Thorac Cardiovasc Surg 2003;51:609 –11.

36. Van Camp G, Liebens I, Silance PG, Cham B, Vandenbossche JL. Ruptured aortic dissection into the left atrium which presented as congestive heart failure and was diagnosed by transoesophageal echocardiography. Br Heart J 1994;72:400 –2.

37. Movsowitz HD, Levine RA, Hilgenberg AD, Isselbacher EM. Transesophageal echocardiographic description of the mechanisms of aortic regurgitation in acute type A aortic dissection: implications for aortic valve repair. J Am Coll Cardiol. 2000;36(3):884-90.

38. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T,Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J,Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P,Zamorano JL, Achenbach S, Baumgartner H. 2013 ESH/ESC Guidelines for the management of arterial hypertension Eur Heart J 2013; 34: 2159–2219.