Open Access | Original Research
Journal of Heart Valve Disease, 29(1), 2024 | PP: 16– 29
https://doi.org/10.36923/jhvd.v29i1.210

Predictors And Correlators of Acute Aortic Syndrome: A Critical Review of Current Evidence

Rohan Vyas[1], Jeuela Iris Ravindran[2], Lara Victoria Schmitt[3], Jason Osei-Bonsu[4], Nabil Jaarah[5], Wahaj Munir[6], Mohamad Bashir[7], Mohammed Idhrees[8]

Article History:

Received: 02-05-2024
Accepted: 11-06-2024
Publication: 07-07-2024

Cite this article as:

Vyas, R., Iris Ravindran, J., Victoria Schmitt, L., Osei-Bonsu, J., Jaarah, N., Munir, W., Bashir, M., & Idhrees, M. (2024). Predictors And Correlators Of Acute Aortic Syndrome: A Critical Review Of Current Evidence. *Journal of Heart Valve Disease,* 29(1). 16-29. doi.org/10.36923/jhvd.v29i1.210

Corresponding Author(s):

Rohan Vyas
Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom. Email: rohan-vyas@hotmail.co.uk

Abstract: Background: Acute Aortic Syndrome's (AAS) is a group of acute emergencies that include aortic dissection, intramural haematoma, penetrating atherosclerotic ulcer, and impending or ruptured aortic aneurysms. Various precipitating factors have been associated with the development of AAS, but it is unclear whether these factors are correlators or predictors of the disease. A clear understanding of these elements could improve the diagnosis, prevention, and treatment of AAS, with an accurate appreciation for risk stratification. **Methods:** A thorough literature search was conducted through several electronic databases to collate papers within the literature discussing precipitating factors leading to AAS. These results were discussed and analysed, grouping the individual factors into predictors or correlators of AAS. **Results:** The factors identified as correlators were age, certain chronobiological patterns, polycystic kidney disease and immunology. The factors identified as predictors included genetics, omics, and kidney markers. D-dimer, diabetes mellitus and aortic size were not implicated in the development of AAS, with diabetes mellitus found to be protective against AAS. **Conclusion:** Recognising the precipitating factors that increase the risk of disease empowers clinicians to be more diligent regarding methods of AAS diagnosis and prevention, as well as enables improved treatment techniques to be implemented. These results are key as they can both potentially help reduce the AAS incidence rate and uncover new potential avenues of research that can be explored in the future.

Keywords: Acute aortic syndrome, aortic dissection, intramural haematoma, atherosclerosis, ruptured aortic aneurysm, cardiovascular disease

1. Introduction

Acute aortic syndromes (AAS) encompass a group of conditions affecting the thoracic aorta including aortic dissection (AD), intramural haematoma (IMH), penetrating atherosclerotic ulcer (PAU), which can all lead to rupture (Isselbacher et al., 2022). These present as acute emergencies so affected patients require hospitalisation and urgent treatment. Type A AD has a mortality rate of 1-2% per hour after symptom onset (for the first 48 hours) while Type B has a mortality rate of 10% after 30 days (Tsai et al., 2005). Ruptured aortic aneurysms are a severe acute complication with high mortality figures of approximately 150,000-200,000 deaths worldwide per year (Bossone & Eagle, 2021).

The incidence of AAS has remained relatively static for the last 20 years at approximately 7.67 per 100,000, despite the overall decrease in cardiovascular disease during this time (Dermartino et al., 2018). These statistics demonstrate the need for further research in this area of cardiovascular surgery to alter this stagnation. Current literature suggests, to varying extents, the interlinking of AAS with multiple different factors as potential precipitators for the disease. However, it is not clear whether these factors are predictors of the onset of AAS or whether they correlate with AAS. As such, this paper categorises these factors into two groups. Correlators are studied with the aim of further understanding the pathophysiology of AAS and exploring any association between the correlators and the pathophysiology. Predictors are examined to further understand the pathophysiology of AAS with the intention of identifying ways in which diagnosis, prevention and treatment can be improved.

2. Pathophysiology of Acute Aortic Syndrome

Although the components of AAS are distinct conditions with unique structural impairments, the underlying pathophysiology and associated risk factors are similar. Each component is demonstrated in Table 1.

[1,2,3,4,6] Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom. Email: rohan-vyas@hotmail.co.uk, j.i.ravindran@smd18.qmul.ac.uk, lara.v.schmitt@gmail.com, j.osei-bonsu@smd18.qmul.ac.uk, wahajmunir2000@gmail.com
[5] GKT School of Medical Education, King's College London, London, United Kingdom. Email: Nabil.jaarah@kcl.ac.uk
[7] Vascular & Endovascular Surgery, Health Education & Improvement Wales, United Kingdom. Email: drmobashir@outlook.com
[8] Institute of Cardiac and Aortic Disorders, SRM Institutes for Medical Science (SIMS Hospitals), India. Email: a.m.idhrees@gmail.com

A combination of prolonged elevated luminal pressures causing abnormal shear stress, and release of inflammatory mediators, result in injury to the aortic wall, which is a hallmark pathological feature of AAS, summarised in Figure 1. Guo et al (GUO et al., 2006) discussed the key process of the upregulation of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which contribute to recruiting monocytes (GUO et al., 2006). The resultant activation of macrophages stimulates them to release matrix metalloproteinases (MMPs), which destroy the aortic wall components such as collagen and elastin (Rimmer et al., 2020). Macrophages also release inflammatory mediators such as interleukins and tumour necrosis factor (TNF)-alpha, which causes a loss of vascular smooth muscle cells (VSMCs) in AAS (GUO et al., 2006; Rimmer et al., 2020). The role of transforming growth factor (TGF)-beta in the development of AAS is becoming evident in relation to loss-of-function mutations causing impaired signalling as investigated by Takeda et. al (Takeda et al., 2018) in their study of mechanisms underlying AAS (Isselbacher et al., 2022).

Risk factors for acute aortic syndrome are linked to the pathophysiological pathways that underlie them and can be divided into two broad categories: genetic and acquired (Table 2).

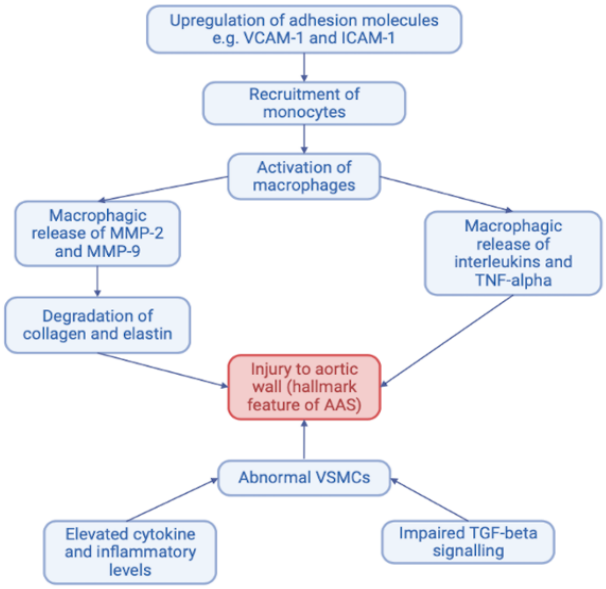


Figure 1: This diagram illustrates the key pathophysiological processes leading to injury of the aortic wall in Acute Aortic Syndrome

Table 1: This table provides an overview of the various conditions that constitute Acute Aortic Syndrome. Each condition is briefly described, highlighting key characteristics and important information relevant to clinical practice.

Acute Aortic Syndrome	Description
Aortic dissection	• Most common form of AAS (85-95%) (Bossone et al., 2018) • Tear in the tunica intima leads to accumulation of blood between the tunica intima and tunica media • Sustained pressures act on the wall cause a separation of layers (Gawinecka et al., 2017; Isselbacher et al., 2022; Tsai et al., 2005) • Stanford classification system describes two types; Type A dissections involve the ascending aorta and Type B only affect the descending aorta (Gawinecka et al., 2017)
Intramural haematoma	• A sealed collection of blood between the tunica intima and medial layers • Most often the lumen is normal or near normal • Formation often a consequence of recent significant aortic pathology (Tsai et al., 2005)
Penetrating atherosclerotic ulcer	• Atherosclerotic plaques cause ulceration and erosion of the aortic wall, resulting in an outpouching • Tunica intima and internal elastic lamina most often affected (Tsai et al., 2005)
Aortic aneurysm	• Characterised by abnormal dilatation of the aorta • Rupture causes an extravascular haemorrhage (Isselbacher et al., 2022; Tsai et al., 2005)

Source: Created by the authors

Table 2: This table categorises the risk factors for Acute Aortic Syndrome into genetic and acquired factors

Genetic Factors	Acquired Risk Factors
• *Marfan syndrome* • *Ehlers-Danlos syndrome* • *Familial thoracic aortic aneurysm disease* • *Bicuspid aortic valve disease* (Bossone et al., 2018)	• *Hypertension* • *Hypercholesterolaemia* • *Smoking* • *Obesity* • *Iatrogenic factors* • *Past medical history and/or family history of aortic disease, atherosclerosis, and ischaemic heart disease* (Bossone et al., 2018).

Source: Created by the authors

3. Management of Acute Aortic Syndrome

A diagnosis of AAS should be considered in all patients presenting with sudden onset tearing chest pain, regardless of radiation to the back. As in acute coronary syndrome, women with AAS are more likely to present atypically, with non-specific symptoms or discomfort as opposed to pain, leading to underdiagnosis and undertreatment (Bossone et al., 2018). The anatomical and pathophysiological changes characteristic of AAS can be visualised clearly using a computed tomography angiography (CTA) scan or magnetic resonance imaging (MRI) (Dudzinski & Isselbacher, 2015). However, CTA is preferred due to higher sensitivity and accessibility (Dudzinski & Isselbacher, 2015). Transthoracic echocardiography (TTE) is effective in visualising the aortic root and the proximal to middle segment of the ascending aorta (Dudzinski & Isselbacher, 2015).

AAS has life-threatening complications and urgent management is always indicated. Intensive medical therapy including beta-blockers is useful in gaining haemodynamic stability by lowering heart rate and blood pressure (Bonaca & O'Gara, 2014). For the majority, surgical management is the mainstay. Urgent open surgery is indicated for Stanford Type-A AD, and it may be considered for Type-A IMH after observation (Bossone et al., 2018; Dudzinski & Isselbacher, 2015). Complicated Stanford Type-B AD and Type B IMH are both treated with thoracic endovascular aortic repair (TEVAR) (Bossone et al., 2018; Dudzinski & Isselbacher, 2015). PAU can be managed with TEVAR or watchful waiting (Bossone et al., 2018; Dudzinski & Isselbacher, 2015). Rapidly expanding or ruptured aortic aneurysms are treated with surgery or TEVAR, depending on their location (Bossone et al., 2018; Dudzinski & Isselbacher, 2015). Complicated presentations include haemodynamically unstable patients, those with signs of rupture or impending rupture, evidence of malperfusion syndrome or uncontrolled hypertension (Moulakakis et al., 2014).

Compromised aortic blood flow can cause significant end-organ damage. Malperfusion syndrome arises due to a combination of dynamic and static arterial obstruction (Crawford et al., 2016). Cerebral malperfusion particularly, caused by limited blood flow in the carotids, is most associated with Type-A AD (Munir et al., 2021). The peripheral malperfusion caused by AAS leads to clinical manifestations such as renal failure and cerebrovascular accidents. Local complications of AAS include aortic regurgitation and cardiac tamponade (Isselbacher et al., 2022).

4. Guidelines: divulging the discrepancies

The implementation of guidelines from the European Society of Cardiology (ESC) and the American Heart Association (AHA) has allowed for standardisation in the care of thoracic aortic pathologies. The discrepancies within the guidance for AAS start with the definition: ESC differs from AHA with the inclusion of contained rupture of aortic aneurysm in their definition (Erbel et al., 2014; Isselbacher et al., 2022).

Both guidelines stress the importance of a risk-scoring system and reference the same system developed by AHA. The diagnostic use of D-dimer is discussed in the two guidelines, with differing outcomes- where ESC sees the need for testing for differential diagnoses and negates AAS for low-risk patients with a negative result, AHA was unable to recommend serum D-dimer for all patients as the biomarker is not considered diagnostic. The differences found within the guidelines could be due to the 8-year difference in publication. Regarding imaging, the use of a TTE as initial imaging is recommended by the ECS, while the AHA recommends the use of CT first and TTE as an alternative. Both, however, recognise the high sensitivity and specificity of TTE and CT, along with MRI.

Both guidelines include a short genetic section based on the presentation of thoracic aortic aneurysm and dissection (TAAD) (Erbel et al., 2014; Isselbacher et al., 2022). Although both mention the inclusion of syndromic mutations (e.g. vascular Ehlers-Danlos, Marfan), AHA further addresses altering the management of female patients with Marfan contemplating pregnancy. Considering nonsyndromic familial TAAD, both guidelines discuss recommendations such as investigations of first-degree relatives. However, ESC is quick to refer to geneticists if familial TAAD is suspected, whereas AHA breaks down their diagnosis through individual steps; imaging of first-degree relatives and referral once a mutant gene is detected as well as sequencing.

The ESC guideline only has a brief genetic section and a lacks of consideration for women with TAAD. Further to this, the guideline is the older of the two and is nine years old in itself. These factors collectively reduce the guideline's value to clinicians and increase the need for a more up-to-date version (Erbel et al., 2014; Isselbacher et al., 2022).

5. Exploring the correlators

5.1. Age

Aortic disease is known to positively correlate with age (Gawinecka et al., 2017). This was demonstrated in a 20-year study conducted by the International Registry of Acute Aortic Dissections (IRAD) showing the mean ages for acute Type-A and B AD were 61.5 and 63.6 years.

Moreover, age seemingly influences management as rates of surgical intervention decrease after the sixth decade. A possible explanation is that mortality following surgical intervention increases with age (Trimarchi, Eagle, et al., 2010).

The effect of age on acute Type-A AD patients was seen by Wang et al. (J.-X. Wang et al., 2022). Older patients were more likely to have co-morbidities preoperatively and experience higher complication rates and mortality postoperatively. Of the 154, 105 (68.2%) were over 50 (p-value=0.016). A 17-month follow-up period showed a similar pattern, finding that 25/38 (68.3%) discharged patients that died were over 50 (J.-X. Wang et al., 2022). Their large sample size (n=1092) increases validity, but retrospective analysis reduces reliability. Another key study is by Devereux et al (Devereux et al., 2012) which concluded that aortic diameter generally increases with age, out of a significantly large population of 1207 patients.

Experimental studies also provide some insight into the effects of advancing age. The study by Groenink et al. (Groenink, 1999) investigated the influence of ageing and aortic stiffness on the structure of the thoracic aorta. They found increasing age was associated with lower pressures required to cause structural changes and greater degrees of irreversible dilation, which may precipitate the effect of AAS (Groenink, 1999). Although effective as the exclusion criteria were aortic disease considering the sole effect of ageing, the sample size was too small (Groenink, 1999).

5.2. Chronobiology: all about timing?

Cardiovascular pathologies such as myocardial infarction, ventricular arrhythmia, and pulmonary embolism (PE) have been linked to seasonal and circadian occurrence.

Manfredini et. al. (Manfredini et al., 2004) produced a comprehensive review regarding the relationship between aortic dissection and abdominal aortic aneurysms (AAA) and their temporal patterns. Studies were found that identified a circadian variation. Exclusively concerning AAA ruptures, multiple studies stated that the risk was significantly increased in the early morning with many describing a peak time starting from 8 am; there was variation regarding when the peak ended but the latest time given was 11 am. Specifically regarding aortic dissections, this same early morning risk was identified but this was based on a single report, thus making the conclusion unreliable. Very little research has been done to examine the presence of a weekly variation, and of those that have been performed, the results were conflicting. In contrast, a seasonal variation has been identified. For both aortic dissections and AAA ruptures, there was a significant increase in risk during the winter months, particularly during the month of January (Manfredini et al., 2004).

The seasonal variability of AAD was further explored in a large international systematic review published in 2015 (Vitale et al., 2015). It yielded similar results, demonstrating a peak incidence of aortic rupture or dissection occurring in December. A potential explanation for these seasonal trends is colder temperatures and decreased daylight, which have been associated with increased blood pressure, platelet activation, and haematocrit which all increase stress within the aortic wall (Stewart et al., 2017).

Therefore, some chronobiological patterns affect AAS incidence. This is applicable through better-allocating resources for winter, along with potentially altering the time of medication administration to decrease aortic wall stress.

5.3. Polycystic Kidney Disease

Polycystic kidney disease (PCKD) is the most common single-gene inherited condition associated with significantly raised mortality, particularly relating to cardiovascular complications including AD.

Silverio et. al. (Silverio et al., 2015) conducted a literature review to examine the relationship between PCKD and AD. Mean age of AD was reduced in the PCKD population ($p < 0.001$) compared to controls, 49(± 12) and 62(± 14) respectively (Silverio et al., 2015). This suggests patients with PCKD are at increased risk of earlier complications, like AD, than those without. However, the retrospective nature introduces information and selection bias. Furthermore, the study fails to include diabetes status in the list of participant characteristics.

Torra et. al (Torra et al., 1996) explored the association between PCKD and AAA with sonographic investigations of the aorta of PCKD patients. They found no significant correlation between aortic diameter and PCKD, and no link between AAA prevalence and PCKD. They concluded that whilst PCKD could be a predisposition for

AAA, it is not a cause. Despite the large sample size (n=288), selection methods, and the single-centre, retrospective nature have implications on the results' validity.

Studies are beginning to shed light on how PCKD differs from the classic presentation of aortic dissection. Additional investigations into PCKD pathogenesis and its potential role in AAS development are needed.

5.4. Immunology

On the microscopic level, factors such as immunological processes and MMPs have been implicated in the pathogenesis of AAS.

The type and role of infiltrates were investigated in 16 patients and compared to 5 controls. They found significant increases in the levels of CD3+ and CD68+ in patients with aneurysms or dissections, compared to controls (He et al., 2006). The study had restrictions, including a small sample size and the exclusive use of end-stage disease tissue samples. Finally, since patients were put on cardiopulmonary bypass, with the aid of hypothermic circulatory arrest, they concluded that the possibility these processes contributed to raised markers cannot be excluded (He et al., 2006).

A more recent study with a larger sample (n=28) by del Porto et al. investigated the immune cells present in the aortic wall in type-A dissections. Macrophages and cytokines (i.e. MCP-1, IL-6, IL-8, and TNF-a) were detected in all cases (Del Porto et al., 2010). This suggests a role for macrophages in AAS, which is complemented by another study by del Porto et al. (n=21), suggesting the release of MMP12 and VEGF (Del Porto et al., 2014). T-lymphocyte count was higher in independent atherosclerotic sites, suggesting their smaller role in AAS pathogenesis (Del Porto et al., 2014).

Anzai et al. triggered acute-AD in mice and investigated subsequent gene expression of IL-6. They found increased expression, predominantly in the adventitia, in mice with dissections (Anzai et al., 2015). They also analysed IL-6 levels in humans with uncomplicated acute Type-B dissections and found consistently raised levels (Anzai, 2018; Anzai et al., 2015). Therefore, an implied correlation exists between IL-6 and AAS, however, the direction of this correlation is unclear.

Recent studies have widened our understanding of the immunological mechanisms involved in AAS. Nappi et al. summarised the potential contribution of Human Cytomegalovirus (HCMV) infection to AAS pathogenesis, mediated by miRNAs that alter immune responses and vascular integrity (Nappi et al, 2023). The use of these biomarkers may allow early detection of AD in the future. A study by Yang et al. explored the role of neutrophil extracellular traps (NETs) in AAS. They found that NETs were abundant in AAD patients and contributed to vascular inflammation and damage. The study highlighted that NET levels correlate with disease severity, highlighting a potential diagnostic target (Yang et al., 2021). Note however that the study is only a single centre with a small sample size which hinders its predictions within the wider population.

Furthermore, a study by Suh et al investigated the role of T-cells in AAA and found that regulatory T-cells (Tregs) were significantly decreased in patients with AAA and significantly decreased aneurysm progression in mice with Treg cells (Suh et al., 2020). This suggests that an imbalance in Treg-mediated immune regulation may contribute to the pathogenesis of AAA. However, the study's use of acute animal models limits its ability to establish causality.

Regarding immunology in IMH or PAU, the literature is limited. Several case-based studies suggested IgG4 in the role of, or mimicking an IMH, thereby serving as a potential correlator (L. Li et al., 2016). These are gaps for further research to identify potential correlations.

5.5. D-Dimer

Multiple studies have shown that D-dimer was raised during acute AD and therefore recommend its diagnostic use (Watanabe et al., 2016).

A systematic review by Watanabe et. al. (Watanabe et al., 2016) included 22 articles with 1140 AAD and 3860 non-AAD subjects, to investigate the accuracy of D-dimer for AAS. Results showed an area under the curve (AUC) of 0.946 (95% CI:0.903-0.994) and a diagnostic OR of 28.5. An AUC of 0.950 (95% CI:0.847-1.000) was observed in 12 studies using a cut-off value of 500 ng/ml, which is the same as for PE (Watanabe et al., 2016). The positive and negative likelihood ratios for the 12 studies using 500 ng/mL as their cut-off value were 2.4 and 0.079 respectively, indicating that d-dimer below 500 ng/mL is useful in ruling out AAS.

This is further supported by Sodeck et. al. (Sodeck et al., 2007) who concluded that D-dimer can be used to rule out AAS and that a D-dimer <0.1 μg/mL will exclude acute AD in 100% of cases.

This indicates that D-dimer can be used to rule out AAS and elevated values increases the risk of AAS. Therefore, clinicians should consider AAS in patients with elevated D-dimer values in the acute setting.

5.6. Diabetes Mellitus… a paradoxical relation?

Despite diabetes mellitus (DM) being a well-known cardiovascular risk factor, various studies have indicated an inverse relationship between DM and AAS (Golledge et al., 2008).

A study by De Rango et al. (De Rango et al., 2012) carried out secondary data analysis from the CAESAR trial. They concluded that progression of small AAA was 60% lower in diabetics compared to non-diabetics. Despite small sample sizes and secondary analysis, various primary studies and trials have had similar findings, concluding that diabetes is associated with reduced aneurysmal growth rates (Nordness et al., 2021).

A variety of studies have looked further into the potential pathophysiological mechanisms contributing to this relationship. Golledge et al. (Golledge et al., 2008) investigated atherosclerotic samples from 20 diabetic patients. They found glycated ECM played a role in reducing the production of MMPs, and levels of IL6, MMP-2 and MMP-9. Note, that these patients were not randomly sampled but selected having readily available data, which affects the results' reliability. However, a similar trend was seen in an experimental animal study analysing the effect of hyperglycaemia on aortic aneurysm progression by Miyami et al. (Miyama et al., 2010). Aneurysmal enlargement was lowest in hyperglycaemic mice. In the cohort on insulin therapy, was associated with aneurysmal enlargement. Further analysis showed reduced levels of MMP-9 and macrophage infiltration. Various literature reviews have shown several different factors that may contribute to the protective nature of DM, including reductions in wall stress, inflammation and neoangiogenesis (Arun et al., 2021). Figure 2 provides a visual summary of the correlators of AAS.

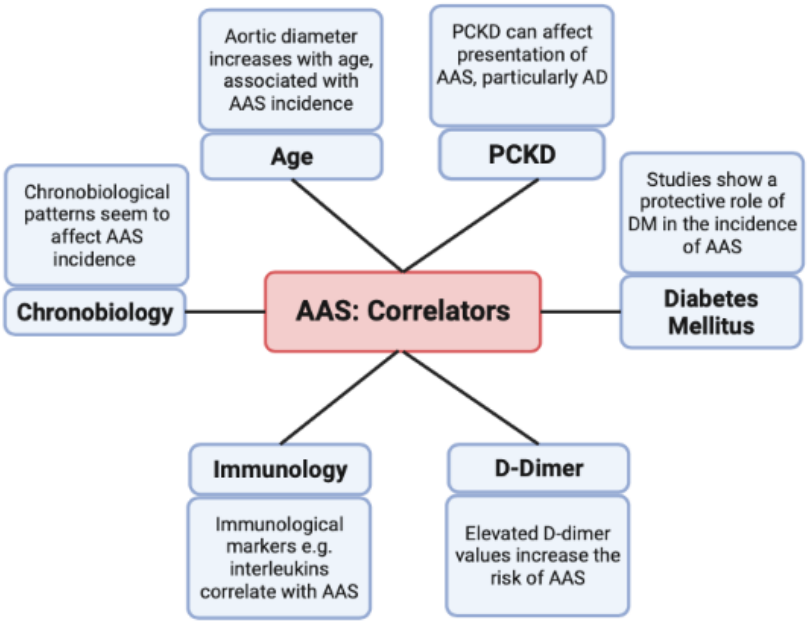


Figure 2: This figure summarises our findings on factors correlated with Acute Aortic Syndrome

6. Exploring the predictors

6.1. Genetics

6.1.1. The true value of genetics

Currently, 37 genes have been linked with TAAD but recent trends show more are being identified each year, and these require validation (Gould et al., 2019). Gene variants predispose patients to syndromic and non-syndromic TAAD, as seen in Table B. Most identified genes encode proteins associated with the VSMC's contractile unit, ECM and TGF-β-signalling pathways. An example is the ROB04 gene discovered by Gould et al. (Gould et al., 2019). Mutations in it led to endothelial barrier dysfunction, which then increased permeability and caused problems including non-syndromic ascending aortic aneurysms (Gould et al., 2019). In the preceding year, the latent transforming growth factor binding proteins family of proteins were also identified as having problematic variants. This family affects the regulation of TGF-β and studies have found that mutations are linked to the development of TAAD through aortic root and ascending aorta enlargement (Guo et al., 2018; Quiñones-Pérez et al., 2018)

As previously discussed, ESC and AHA use genetic screening in some patient groups (Erbel et al., 2014; Isselbacher et al., 2022); however, Carino et. Al. (Carino et al., 2018) suggest screening for all patients presenting with TAAD under 60, as patients with genetic causes typically present at younger. Therefore, with the increasing cost-effectiveness of genetic screening, the literature suggests implementing screening for patients under 60, as this allows for earlier recognition and intervention (Renard et al., 2018).

The inclusion of the latest gene research associated with TAAD and re-evaluating genetic screening eligibility is the next step. Implementing this would prove valuable and is therefore needed in guidelines.

6.1.2. Immunogenetics

We have already discussed a variety of genes and immunological components that are linked to AAS, however, the interaction between them could play a vital role in predicting AAS. A literature review by Yap et al. stated that

genes involved in the TGF-B signalling pathway are involved in the formation of TAAs (Yap et al., 2021). There are some genes such as TGFBR1, SMAD3 and TGF-B2 that are involved in the TGF-B signalling pathway that predispose individuals to TAA (Yap et al., 2021). However, there remains some controversy surrounding its role, with murine studies showing lower levels of TGF-B may increase the rate of TAA formation (Wei et al., 2017). This is due to the role of TGF-B in improving VSMC differentiation (Yap et al., 2021). There is a paucity of research on the link between AAS and immunogenetics. Given the potential significance of this link, this remains a potential avenue for further development to aid the holistic approach of decision-making for management.

6.1.3. Genetic biomarkers

Investigating genetic markers for TAAD in peripheral blood cells (PBC) and blood plasma has been made possible by an improved understanding of its genetics and pathophysiology. Wang et al. (Y. Wang et al., 2007) identified a 41-gene signature, from 61 patients (36 experimental and 25 controls) within the PBC genome that was specific to TAA. TAA and AD share similarities in their genetics, and since TAA can lead to AD, it could be a predictive factor of AD (Ostberg et al., 2020).

The 41-gene classifier identified had an accuracy of 78%, sensitivity of 81%, and specificity of 75%, with further tests using TaqMan real-time PCR to increase the validity on an independent cohort yielding similar results. However, larger studies on more ethnically diverse cohorts are required for wider generalisation. Should blood tests prove capable, they may become an appropriate predictor in a point-of-care setting (Trimarchi, Sangiorgi, et al., 2010).

Özmen et. Al. (Özmen, 2018) investigated nitric oxide synthase (NOS)-3 intron 4b/4a polymorphisms as potential genetic markers for TAAD. They conducted a single-centre study (n=165) (AD: n=38, TAA: n=67, controls: n=60) investigating genetic polymorphisms in PBC. NOS-3 intron 4b polymorphism held a statistically significant difference between the AD and controls, while NOS-3 intron 4b/4a polymorphism was different in TAA compared to the controls (p=0.048), indicating that these may be predictors of TAAD (Özmen, 2018).

Mitochondrial genetics could also be used as a genetic marker for TAA. Statistically significant differences in microRNAs from plasma samples have been seen in TAA patients when compared to controls in a study of 62 patients by Gasiulė et. al (Gasiulė et al., 2019). MicroRNA-sequencing identified 17 differently expressed microRNAs. Two microRNAs, namely miR-122-3p and miR-3-3p had ROC curve analysis yielding an accuracy of 0.84 ($p < 0.001$), supporting their use as a genetic marker.

6.1.4. The impact of the omics

The Omics technologies are a growing sector of medicinal research where, in recent years, promising evidence has accumulated demonstrating their potential use in predicting, diagnosing and managing the disease of AAS (J. Li et al., 2018; Yin (殷晓科) et al., 2019). They comprise a number of divisions such as genomics, proteomics and metabolomics.

6.1.5. Metabolomics

Zhou et al. (Zhou et al., 2019) studied the use of serum metabolomics in identifying biomarkers that predict acute AD and explored differences in metabolomic profile between the two Stanford dissections. Levels of lysophosphatidylcholine, sphinganine, phytosphingosine, and ceramide were lower in both AD groups, compared to controls (P<0.01). This suggests they play a role in the pathogenesis of AD (Zhou et al., 2019). Differences between the two AD groups included lower levels of sphinganine, phytosphingosine, and ceramide (P<0.005). Sphingomyelin was significantly elevated in both AD groups compared to the controls, greatest in the Type-B AD group.

This study provides a promising outlook for screening AD and also differentiating between the types. This is useful since symptomatic AD presentation is variable, and thus can be used in those solely presenting with chest pain (Zhou et al., 2019). Nevertheless, there are notable shortcomings, using healthy controls limits recognising the specificity of the metabolic biomarkers. Confounding variables such as other cardiovascular pathologies, e.g. atherosclerosis, must be considered for these results to be more generalisable due to their role in AD.

Elevated sphingomyelin was found to be associated with TAA and AD in a similar metabolomic profiling study by Doppler et al. (Doppler et al., 2017). It is worth noting that they did not record the smoking status, thereby lowering the validity as smoking is a strong causative factor of AAS (Bossone et al., 2018; Tsai et al., 2005).

Both Zhou et al. and Doppler et al. support the correlation between raised sphingomyelin and AAS, implicating its use as a predictive biomarker in aortic disease. However, testing the sensitivity of this requires larger studies.

A recent study by Zeng et al. explored the serum metabolomics of Stanford type A AD patients providing a detailed profile of associated metabolic pathways and biomarkers (Zeng et al., 2020). By employing global and targeted mass spectrometry-based metabolomics, the researchers identified significant alterations in lipid and polar metabolite levels among AAD patients compared to healthy controls. Notably, increased levels of Trimethylamine N-oxide (TMAO) emerged as a prominent finding in AAD patients ($P < 0.005$), while levels of carnitine, choline, and betaine were notably decreased ($P < 0.05$), suggesting systemic metabolic imbalances that could be pivotal for early diagnosis and risk stratification. Despite its valuable insights, the study's small sample size and study design

limit the generalizability and causative conclusions of the findings. Future research with larger, longitudinal cohorts is needed to validate these biomarkers and fully explore their clinical utility (Zeng et al., 2020)

6.1.6. Proteomics

Cikach et. al., (Cikach et al., 2018) in their recent study of proteomic analysis, explored the involvement of proteoglycans in TAA and AD. The aortic proteoglycanome in individuals with and without thoracic aortic disease was compared; aggrecan and versican were identified as proteoglycans present in both healthy and diseased aortas. However, dense accumulation of both proteoglycans in segments of the ascending aorta affected by aneurysm and dissection was seen. They suggested that elevated levels of aggrecan and versican cause tension and cellular disruption of the aorta, which results in dysregulation of the ECM, and eventually medial degeneration of the aorta, as seen in AAS. This is supported by increased aggrecan and versican deposition in areas of medial degeneration. Notably, these findings were restricted to the medial layer alone, perhaps indicating the need for future research on comparing the proteoglycanome of the layers of aortic tissue. Overall, these findings are strongly suggestive of an association between aggrecan and versican accumulation in AAS and open the prospect of proteomic analysis as a tool for risk prediction in aortic disease.

Recently, multiple studies have utilised proteomic analysis within their studies to investigate the pathogenesis of AAS. A retrospective study by Daskalopoulou et al identified three specific protein biomarkers (chemokine ligand 5, defensin beta 1, intracellular adhesion molecule 1) with a potential role in the prediction, diagnostics and staging of ascending TAA (Daskalopoulou et al., 2023). In addition to this, multiple other studies have found various different protein biomarkers (alpha-2-HS glycoprotein, lumican, etc) implicated in the AAS disease process, showcasing the vast number of biomarkers implicated and the extent to which this research can and needs to develop to increased sensitivity and specificity for AAS diagnostics (Deng et al., 2022; Kazamia et al., 2023). Furthermore, the retrospective nature of these studies and lack of follow-up fail to address the long-term implications of such biomarkers in these patients, indicating a need for larger studies in this area.

6.1.7. Kidney markers

Recent literature highlights kidney markers as new predictors of acute aortic disease. In their study of simple renal cysts (SRCs) and bovine aortic arches (BAAs), Brownstein et. al (Brownstein et al., 2019) explored the relationship between AAS prevalence and patients with existing SRCs and BAAs. Of 35,498 patients, 6,366 had an SRC. Compared with age-matched controls, a significant association was found between SRC and TAD prevalence (OR=2.57) as well as SRC and AAA (OR=2.81). They concluded that SRCs are linked to increased prevalence of AAS, particularly TAD and aneurysmal growth and rupture, hence, these should be considered as markers for aortic disease (Brownstein et al., 2019).

By selecting patients with available CT chest and abdomen scans, a selection bias is imparted which could be in the form of great vessel disease. Despite the large sample size, its retrospective, single-centre nature limits the results' breadth of applicability.

A systematic review and meta-analysis of 11 observational studies by Chewcharat et. al (Chewcharat et al., 2020), investigated the association between SRCs and aortic disease, to identify SRC as a risk factor for aortic disease. From 19,719 patients, the authors suggested MMPs play a large role in the pathogenesis of both SRC and aortic disease, which could underpin the association. Meta-analysis of several observational studies demonstrated higher odds of aortic disease (including, type-A and B, TAD, AAA and TAA) amongst patients with SRC (Chewcharat et al., 2020). Despite a large cohort, the included studies had varying sample sizes from 135 to 12,732. This variance results in one study constituting a large proportion of the meta-analysis, which also affects the review's validity. Finally, the asymmetrical funnel plot highlights the publication bias.

Both studies by Brownstein et. Al and Chewcharat et. al point towards a significant association between SRC and AAS. However, further research exploring the cost-effectiveness of such a screening tool, as well as providing a deeper insight into the underlying pathophysiology is needed.

6.2. Aortic Size

The AHA guidelines demonstrate the importance of aortic size in predicting AAS by suggesting the following parameters for surgical intervention: an ascending aorta measuring 5.5cm or more in diameter or an aortic enlargement of 0.5cm per year (Murphy et al., n.d.). This is based on the general consensus across the literature that larger aneurysms are more likely to rupture. Specifically, regarding those 5cm or more, the risk of these dissecting or rupturing is over 8.9% each year. Comparatively, the risk of dissection and rupture for aortas measuring >5cm is around 4% annually. Regardless of size, the mortality rate following rupture is thought to exceed 90%. Evidently, some form of intervention is necessary at this juncture (Davies et al., 2002).

Nevertheless, there is evidence that suggests aortic size does not hold as much weight as a predictor as historically thought. From the IRAD study, a smaller aortic diameter did not prevent the onset of AAS and surgical intervention in patients with a diameter of 5.5cm or more did not prevent many of the AAS cases in the study (Evangelista et al., 2016). Similarly, a retrospective two-centre cohort study by Heuts et al (Heuts et al., 2020) found 96% of patients that presented with Type-A AD did not meet the 5.5cm threshold prior to admission. Thus,

both these studies oppose the AHA guidelines, suggesting intervention may not need to wait until a size threshold is met (Heuts et al., 2020). Other factors such as family history and genetics must be considered. Nonetheless, even these considerations still make predicting AD difficult and imperfect.

Although current literature shows the importance of recognising that increased aortic size there is also evidence that suggests it cannot be the sole predictor for AAS. A significant number of case series have occurred below the aortic size threshold provided by guidelines, suggesting that other factors are involved, and they must be considered. Figure 3 provides an overall visual summary of predictors of AAS.

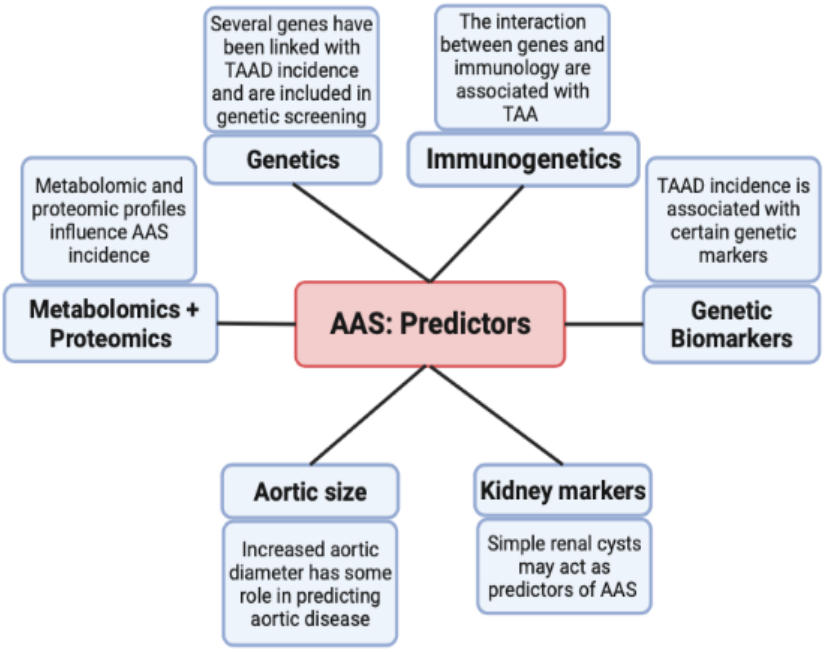


Figure 3: This diagram summarises the key predictors of Acute Aortic Syndrome

7. Conclusion

In conclusion, this paper evaluated whether potential precipitating factors associated with AAS, a type of acute medical emergency, are either correlators or predictors of the group of diseases. It was important to understand why the incidence of AAS has had a prolonged plateau for the last 20 years, as well as look for ways in which diagnosis, prevention and treatment could be improved.

Following the research, factors identified as correlators are age, certain chronobiological patterns, PCKD and immunology, although the association with immunology was limited and requires further research. D-dimer and diabetes mellitus were other potential correlators; however, the literature revealed that neither was implicated in the development of AAS, with the latter being protective warranting deeper investigation into its pathophysiology. Factors identified as potential predictors include genetics, omics and kidney markers. Although aortic size was deemed an important factor, the evidence also suggests that it cannot be considered a predictor on its own.

By incorporating these findings within the clinical setting, the management of AAS could be significantly enhanced. For example, identifying the key genetic markers could promote genetic testing at an early stage to identify individuals with a higher risk. Furthermore, understanding the influence of age and chronobiology can allow the refinement of current screening and diagnostic strategies. These collective measures may mitigate the progression of AAS at an early stage, empowering clinicians to act pre-emptively and ultimately leading to improved patient outcomes and reducing complications in the long term. Biomarkers such as D-dimer could serve as a valuable tool to triage patients with suspected symptoms, streamlining the diagnostic process and avoiding unnecessary imaging. Not only does this impact patient care but it also optimises healthcare resource utilisation. Collaboration among healthcare providers across specialities is essential in translating these insights into actionable plans. By further research with concrete findings, we can ensure that every patient receives personalised care based on their individual risk factors, according to their potential correlators and predictors.

Given the increased risk of disease, the above findings empower clinicians to be more diligent regarding methods of AAS prevention if some of these implicated factors are identified prior to the disease. New forms of diagnosis can be implemented for those with suspected disease, for example performing genetic screening for all prospective patients. Regarding treatments, new techniques can be used to optimise therapies such as altering medication administration times. All these results are key as they can potentially help with the reduction of the AAS incidence rate and uncover new avenues of research that can be explored in the future, which will be vital to our understanding of these potential precipitating factors.

Acknowledgement Statement: The authors would like to thank the reviewers for providing comments in helping this manuscript to completion.

Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT Author contribution statements: All authors contributed to the intellectual property of this manuscript and have been involved in design, structure, data collation, writing, and reviewing of this manuscript.

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

Data Availability Statement: Data is available at request. Please contact the corresponding author for any additional information on data access or usage.

Disclaimer: The views and opinions expressed in this article are those of the author(s) and contributor(s) and do not necessarily reflect JHVD's or editors' official policy or position. All liability for harm done to individuals or property as a result of any ideas, methods, instructions, or products mentioned in the content is expressly disclaimed.

References

Anzai, A. (2018). Inflammatory mechanisms contributing to aortic expansion and rupture after acute aortic dissection. *Journal of Immunological Sciences, 2*(4), 22-26. https://doi.org/10.29245/2578-3009/2018/4.1156

Anzai, A., Shimoda, M., Endo, J., Kohno, T., Katsumata, Y., Matsuhashi, T., Yamamoto, T., Ito, K., Yan, X., Shirakawa, K., Shimizu-Hirota, R., Yamada, Y., Ueha, S., Shinmura, K., Okada, Y., Fukuda, K., & Sano, M. (2015). Adventitial CXCL1/G-CSF expression in response to acute aortic dissection triggers local neutrophil recruitment and activation leading to aortic rupture. *Circulation Research, 116*(4), 612-623. https://doi.org/10.1161/CIRCRESAHA.116.304918 PMid:25563839

Arun, D., Munir, W., Schmitt, L. V., Vyas, R., Ravindran, J. I., Bashir, M., Williams, I. M., Velayudhan, B., & Idhrees, M. (2021). Exploring the correlation and protective role of diabetes mellitus in aortic aneurysm disease. *Frontiers in Cardiovascular Medicine, 8*. https://doi.org/10.3389/fcvm.2021.769343 PMid:34820431

Bonaca, M. P., & O'Gara, P. T. (2014). Diagnosis and management of acute aortic syndromes: Dissection, intramural hematoma, and penetrating aortic ulcer. *Current Cardiology Reports, 16*(10), 536. https://doi.org/10.1007/s11886-014-0536-x PMid:25156302

Bossone, E., & Eagle, K. A. (2021). Epidemiology and management of aortic disease: Aortic aneurysms and acute aortic syndromes. *Nature Reviews Cardiology, 18*(5), 331-348. https://doi.org/10.1038/s41569-020-00472-6 PMid:33353985

Bossone, E., LaBounty, T. M., & Eagle, K. A. (2018). Acute aortic syndromes: Diagnosis and management, an update. *European Heart Journal, 39*(9), 739-749d. https://doi.org/10.1093/eurheartj/ehx319 PMid:29106452

Brownstein, A. J., Bin Mahmood, S. U., Saeyeldin, A., Velasquez Mejia, C., Zafar, M. A., Li, Y., Rizzo, J. A., Dahl, N. K., Erben, Y., Ziganshin, B. A., & Elefteriades, J. A. (2019). Simple renal cysts and bovine aortic arch: Markers for aortic disease. *Open Heart, 6*(1), e000862. https://doi.org/10.1136/openhrt-2018-000862 PMid:30774963

Carino, D., Agostinelli, A., Molardi, A., Benassi, F., Gherli, T., & Nicolini, F. (2018). The role of genetic testing in the prevention of acute aortic dissection. *European Journal of Preventive Cardiology, 25*(1_suppl), 15-23. https://doi.org/10.1177/2047487318756433 PMid:29708033

Chewcharat, A., Hamaya, R., Thongprayoon, C., Cato, L. D., Mao, M. A., & Cheungpasitporn, W. (2020). The association between simple renal cyst and aortic diseases: A systematic review and meta-analysis of observational studies. *Journal of Evidence-Based Medicine, 13*(4), 265-274. https://doi.org/10.1111/jebm.12385 PMid:32452169

Cikach, F. S., Koch, C. D., Mead, T. J., Galatioto, J., Willard, B. B., Emerton, K. B., Eagleton, M. J., Blackstone, E. H., Ramirez, F., Roselli, E. E., & Apte, S. S. (2018). Massive aggrecan and versican accumulation in thoracic aortic aneurysm and dissection. *JCI Insight, 3*(5). https://doi.org/10.1172/jci.insight.97167 PMid:29515038

Crawford, T. C., Beaulieu, R. J., Ehlert, B. A., Ratchford, E. V., & Black, J. H. (2016). Malperfusion syndromes in aortic dissections. *Vascular Medicine, 21*(3), 264-273. https://doi.org/10.1177/1358863X15625371 PMid:26858183

Daskalopoulou, A., Giotaki, S. G., Toli, K., Minia, A., Pliaka, V., Alexopoulos, L. G., Deftereos, G., Iliodromitis, K., Dimitroulis, D., Siasos, G., Verikokos, C., & Iliopoulos, D. (2023). Targeted proteomic analysis of patients with ascending thoracic aortic aneurysm. *Biomedicines, 11*(5), 1273. https://doi.org/10.3390/biomedicines11051273 PMid:37238945

Davies, R. R., Goldstein, L. J., Coady, M. A., Tittle, S. L., Rizzo, J. A., Kopf, G. S., & Elefteriades, J. A. (2002). Yearly rupture or dissection rates for thoracic aortic aneurysms: Simple prediction based on size. *The*

Annals of Thoracic Surgery, 73(1), 17-27; discussion 27-8. https://doi.org/10.1016/s0003-4975(01)03236-2 PMid:11834007

De Rango, P., Cao, P., Cieri, E., Parlani, G., Lenti, M., Simonte, G., & Verzini, F. (2012). Effects of diabetes on small aortic aneurysms under surveillance according to a subgroup analysis from a randomized trial. *Journal of Vascular Surgery, 56*(6), 1555-1563. https://doi.org/10.1016/j.jvs.2012.05.078 PMid:23092644

Del Porto, F., di Gioia, C., Tritapepe, L., Ferri, L., Leopizzi, M., Nofroni, I., De Santis, V., Della Rocca, C., Mitterhofer, A. P., Bruno, G., Taurino, M., & Proietta, M. (2014). The multitasking role of macrophages in Stanford type A acute aortic dissection. *Cardiology, 127*(2), 123-129. https://doi.org/10.1159/000355253 PMid:24334970

Del Porto, F., Proietta, M., Tritapepe, L., Miraldi, F., Koverech, A., Cardelli, P., Tabacco, F., De Santis, V., Vecchione, A., Mitterhofer, A. P., Nofroni, I., Amodeo, R., Trappolini, M., & Aliberti, G. (2010). Inflammation and immune response in acute aortic dissection. *Annals of Medicine, 42*(8), 622-629. https://doi.org/10.3109/07853890.2010.518156 PMid:20860543

Deng, T., Liu, Y., Gael, A., Fu, X., Deng, X., Liu, Y., Wu, Y., Wu, Y., Wang, H., Deng, Y., Lai, J., & Fu, Q. (2022). Study on proteomics-based aortic dissection molecular markers using iTRAQ combined with label free techniques. *Frontiers in Physiology, 13*. https://doi.org/10.3389/fphys.2022.862732 PMid:35910577

Dermartino, R., Indrani, S., Huang, Y., Harmsen, W., Macedo, T., Mandrekar, J., Chamberlain, A., Goodney, P., & Roger, V. (2018). Abstract 14173: Stable incidence of acute aortic syndrome from 1995-2015. *AHA Journals, 136*(1).

Devereux, R. B., de Simone, G., Arnett, D. K., Best, L. G., Boerwinkle, E., Howard, B. V., Kitzman, D., Lee, E. T., Mosley, T. H., Weder, A., & Roman, M. J. (2012). Normal limits in relation to age, body size and gender of two-dimensional echocardiographic aortic root dimensions in persons ≥15 years of age. *The American Journal of Cardiology, 110*(8), 1189-1194. https://doi.org/10.1016/j.amjcard.2012.05.063 PMid:22770936

Doppler, C., Arnhard, K., Dumfarth, J., Heinz, K., Messner, B., Stern, C., Koal, T., Klavins, K., Danzl, K., Pitterl, F., Grimm, M., Oberacher, H., & Bernhard, D. (2017). Metabolomic profiling of ascending thoracic aortic aneurysms and dissections - Implications for pathophysiology and biomarker discovery. *PLOS ONE, 12*(5), e0176727. https://doi.org/10.1371/journal.pone.0176727 PMid:28467501

Dudzinski, D. M., & Isselbacher, E. M. (2015). Diagnosis and management of thoracic aortic disease. *Current Cardiology Reports, 17*(12), 106. https://doi.org/10.1007/s11886-015-0655-z PMid:26468124

Erbel, R., Aboyans, V., Boileau, C., Bossone, E., Bartolomeo, R. Di, Eggebrecht, H., Evangelista, A., Falk, V., Frank, H., Gaemperli, O., Grabenwöger, M., Haverich, A., Iung, B., Manolis, A. J., Meijboom, F., Nienaber, C. A., Roffi, M., Rousseau, H., Sechtem, U., … ESC Committee for Practice Guidelines. (2014). 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). *European Heart Journal, 35*(41), 2873-2926. https://doi.org/10.1093/eurheartj/ehu281 PMid:25173340

Evangelista, A., Maldonado, G., Gruosso, D., Teixido, G., Rodríguez-Palomares, J., & Eagle, K. (2016). Insights from the international registry of acute aortic dissection. *Global Cardiology Science and Practice, 2016*(1). https://doi.org/10.21542/gcsp.2016.8 PMid:29043258

Gasiulė, Stankevičius, Patamsytė, Ražanskas, Žukovas, Kapustina, Žaliaduonytė, Benetis, Lesauskaitė, & Vilkaitis. (2019). Tissue-specific miRNAs regulate the development of thoracic aortic aneurysm: The emerging role of KLF4 network. *Journal of Clinical Medicine, 8*(10), 1609. https://doi.org//10.3390/jcm8101609 PMid:31623405

Gawinecka, J., Schnrath, F., & von Eckardstein, A. (2017). Acute aortic dissection: Pathogenesis, risk factors and diagnosis. *Swiss Medical Weekly*. https://doi.org/10.4414/smw.2017.14489

Golledge, J., Karan, M., Moran, C. S., Muller, J., Clancy, P., Dear, A. E., & Norman, P. E. (2008). Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte-matrix interactions. *European Heart Journal, 29*(5), 665-672. https://doi.org/10.1093/eurheartj/ehm557 PMid:18263873

Gould, R. A., Aziz, H., Woods, C. E., Seman-Senderos, M. A., Sparks, E., Preuss, C., Wünnemann, F., Bedja, D., Moats, C. R., McClymont, S. A., Rose, R., Sobreira, N., Ling, H., MacCarrick, G., Kumar, A. A., Luyckx, I., Cannaerts, E., Verstraeten, A., Björk, H. M., … Dietz, H. C. (2019). ROBO4 variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm. *Nature Genetics, 51*(1), 42-50. https://doi.org/10.1038/s41588-018-0265-y PMid:30455415

Groenink, M. (1999). The influence of aging and aortic stiffness on permanent dilation and breaking stress of the thoracic descending aorta. *Cardiovascular Research, 43*(2), 471-480. https://doi.org/10.1016/S0008-6363(99)00095-4 PMid:10536677

Guo, D., Regalado, E. S., Pinard, A., Chen, J., Lee, K., Rigelsky, C., Zilberberg, L., Hostetler, E. M., Aldred, M., Wallace, S. E., Prakash, S. K., Leal, S. M., Bamshad, M. J., Nickerson, D. A., Natowicz, M., Rifkin, D.

B., & Milewicz, D. M. (2018). LTBP3 pathogenic variants predispose individuals to thoracic aortic aneurysms and dissections. *The American Journal of Human Genetics, 102*(4), 706-712. https://doi.org/10.1016/j.ajhg.2018.03.002 PMid:29625025

Guo, D.-C., Papke, C. L., He, R., & Milewicz, D. M. (2006). Pathogenesis of thoracic and abdominal aortic aneurysms. *Annals of the New York Academy of Sciences, 1085*(1), 339-352. https://doi.org/10.1196/annals.1383.013 PMid:17182954

He, R., Guo, D.-C., Estrera, A. L., Safi, H. J., Huynh, T. T., Yin, Z., Cao, S.-N., Lin, J., Kurian, T., Buja, L. M., Geng, Y.-J., & Milewicz, D. M. (2006). Characterization of the inflammatory and apoptotic cells in the aortas of patients with ascending thoracic aortic aneurysms and dissections. *The Journal of Thoracic and Cardiovascular Surgery, 131*(3), 671-678.e2. https://doi.org/10.1016/j.jtcvs.2005.09.018 PMid:16515922

Heuts, S., Adriaans, B. P., Rylski, B., Mihl, C., Bekkers, S. C. A. M., Olsthoorn, J. R., Natour, E., Bouman, H., Berezowski, M., Kosiorowska, K., Crijns, H. J. G. M., Maessen, J. G., Wildberger, J., Schalla, S., & Sardari Nia, P. (2020). Evaluating the diagnostic accuracy of maximal aortic diameter, length and volume for prediction of aortic dissection. *Heart, 106*(12), 892-897. https://doi.org/10.1136/heartjnl-2019-316251 PMid:32152004

Isselbacher, E. M., Preventza, O., Hamilton Black, J., Augoustides, J. G., Beck, A. W., Bolen, M. A., Braverman, A. C., Bray, B. E., Brown-Zimmerman, M. M., Chen, E. P., Collins, T. J., DeAnda, A., Fanola, C. L., Girardi, L. N., Hicks, C. W., Hui, D. S., Schuyler Jones, W., Kalahasti, V., Kim, K. M., … Woo, Y. J. (2022). 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: A report of the American Heart Association/American College of Cardiology joint committee on clinical practice guidelines. *Circulation, 146*(24). https://doi.org/10.1161/CIR.0000000000001106 PMid:36322642

Kazamia, R., Keravnou, A., Moushi, A., Sokratous, K., Michailidou, K., Yiangou, K., Soteriou, M., Xenophontos, S., Cariolou, M. A., & Bashiardes, E. (2023). Tissue and plasma proteomic profiling indicates AHSG as a potential biomarker for ascending thoracic aortic aneurysms. *BMC Cardiovascular Disorders, 23*(1), 138. https://doi.org/10.1186/s12872-023-03154-6 PMid:36922793

Li, J., Pan, C., Zhang, S., Spin, J. M., Deng, A., Leung, L. L. K., Dalman, R. L., Tsao, P. S., & Snyder, M. (2018). Decoding the genomics of abdominal aortic aneurysm. *Cell, 174*(6), 1361-1372.e10. https://doi.org/10.1016/j.cell.2018.07.021 PMid:30193110

Li, L., Wang, Z., Xu, P., Ruan, Y., Jiang, W., & Wu, Z. (2016). Cardiac mass, aortic intramural hematoma, and IgG4-related disease: A case report. *Annals of Vascular Surgery, 35*, 208.e5-208.e8. https://doi.org/10.1016/j.avsg.2016.02.022 PMid:27263808

Manfredini, R., Boari, B., Gallerani, M., Salmi, R., Bossone, E., Distante, A., Eagle, K. A., & Mehta, R. H. (2004). Chronobiology of rupture and dissection of aortic aneurysms. *Journal of Vascular Surgery, 40*(2), 382-388. https://doi.org/10.1016/j.jvs.2004.04.019 PMid:15297840

Miyama, N., Dua, M. M., Yeung, J. J., Schultz, G. M., Asagami, T., Sho, E., Sho, M., & Dalman, R. L. (2010). Hyperglycemia limits experimental aortic aneurysm progression. *Journal of Vascular Surgery, 52*(4), 975-983. https://doi.org/10.1016/j.jvs.2010.05.086 PMid:20678880

Moulakakis, K. G., Mylonas, S. N., Dalainas, I., Kakisis, J., Kotsis, T., & Liapis, C. D. (2014). Management of complicated and uncomplicated acute type B dissection. A systematic review and meta-analysis. *Annals of Cardiothoracic Surgery, 3*(3), 234-246. https://doi.org/10.3978/j.issn.2225-319X.2014.05.08

Munir, W., Chong, J. H., Harky, A., Bashir, M., & Adams, B. (2021). Type A aortic dissection: Involvement of carotid artery and impact on cerebral malperfusion. *Asian Cardiovascular and Thoracic Annals, 29*(7), 635-642. https://doi.org/10.1177/0218492320984329 PMid:33375820

Murphy, M. C., Castner, C. F., & Kouchoukos, N. T. (n.d.). Acute aortic syndromes: Diagnosis and treatment. *Missouri Medicine, 114*(6), 458-463.

Nappi, F., Alzamil, A., Avtaar Singh, S. S., Spadaccio, C., & Bonnet, N. (2023). Current knowledge on the interaction of human cytomegalovirus infection, encoded miRNAs, and acute aortic syndrome. *Viruses, 15*(10), 2027. https://doi.org/10.3390/v15102027 PMid:37896804

Nordness, M., Baxter, B. T., Matsumura, J., Terrin, M., Webb, N., & Curci, J. (2021). Diabetic patients with small abdominal aortic aneurysms have slower aneurysm growth without differences in inflammatory markers. *Journal of Vascular Surgery, 73*(1), e16-e17. https://doi.org/10.1016/j.jvs.2020.10.037 PMid:31980239

Ostberg, N., Zafar, M., Ziganshin, B., & Elefteriades, J. (2020). The genetics of thoracic aortic aneurysms and dissection: A clinical perspective. *Biomolecules, 10*(2), 182. https://doi.org/10.3390/biom10020182 PMid:31991693

Özmen, R. (2018). Relationship of genetic factors with development of aortic dissection and aneurysm. *The Turkish Journal of Thoracic and Cardiovascular Surgery, 26*(4), 557-564. https://doi.org/10.5606/tgkdc.dergisi.2018.16424 PMid:32082797

Quiñones-Pérez, B., VanNoy, G. E., Towne, M. C., Shen, Y., Singh, M. N., Agrawal, P. B., & Smith, S. E. (2018). Three-generation family with novel contiguous gene deletion on chromosome 2p22 associated with thoracic aortic aneurysm syndrome. *American Journal of Medical Genetics Part A, 176*(3), 560-569. https://doi.org/10.1002/ajmg.a.38590 PMid:29350460

Renard, M., Francis, C., Ghosh, R., Scott, A. F., Witmer, P. D., Adès, L. C., Andelfinger, G. U., Arnaud, P., Boileau, C., Callewaert, B. L., Guo, D., Hanna, N., Lindsay, M. E., Morisaki, H., Morisaki, T., Pachter,

N., Robert, L., Van Laer, L., Dietz, H. C., … De Backer, J. (2018). Clinical validity of genes for heritable thoracic aortic aneurysm and dissection. *Journal of the American College of Cardiology, 72*(6), 605-615. https://doi.org/10.1016/j.jacc.2018.04.089 PMid:30071989

Rimmer, L. J., Moughal, S., & Bashir, M. (2020). Immunological therapeutics in acute aortic syndrome. *Asian Cardiovascular and Thoracic Annals, 28*(8), 512-519. https://doi.org/10.1177/0218492320943350 PMid:32674584

Silverio, A., Prota, C., Di Maio, M., Polito, M. V., Cogliani, F. M., Citro, R., Gigantino, A., Iesu, S., & Piscione, F. (2015). Aortic dissection in patients with autosomal dominant polycystic kidney disease: A series of two cases and a review of the literature. *Nephrology, 20*(4), 229-235. https://doi.org/10.1111/nep.12373 PMid:25476912

Sodeck, G., Domanovits, H., Schillinger, M., Ehrlich, M. P., Endler, G., Herkner, H., & Laggner, A. (2007). D-dimer in ruling out acute aortic dissection: A systematic review and prospective cohort study. *European Heart Journal, 28*(24), 3067-3075. https://doi.org/10.1093/eurheartj/ehm484 PMid:17986466

Stewart, S., Keates, A. K., Redfern, A., & McMurray, J. J. V. (2017). Seasonal variations in cardiovascular disease. *Nature Reviews Cardiology, 14*(11), 654-664. https://doi.org/10.1038/nrcardio.2017.76 PMid:28518176

Suh, M. K., Batra, R., Carson, J. S., Xiong, W., Dale, M. A., Meisinger, T., Killen, C., Mitchell, J., & Baxter, B. T. (2020). Ex vivo expansion of regulatory T cells from abdominal aortic aneurysm patients inhibits aneurysm in humanized murine model. *Journal of Vascular Surgery, 72*(3), 1087-1096.e1. https://doi.org/10.1016/j.jvs.2019.08.285 PMid:31980239

Takeda, N., Hara, H., Fujiwara, T., Kanaya, T., Maemura, S., & Komuro, I. (2018). TGF-β signaling-related genes and thoracic aortic aneurysms and dissections. *International Journal of Molecular Sciences, 19*(7), 2125. https://doi.org/10.3390/ijms19072125 PMid:30037098

Torra, R., Nicolau, C., Badenas, C., Brú, C., Pérez, L., Estivill, X., & Darnell, A. (1996). Abdominal aortic aneurysms and autosomal dominant polycystic kidney disease. *Journal of the American Society of Nephrology : JASN, 7*(11), 2483-2486. https://doi.org/10.1681/ASN.V7112483 PMid:8959643

Trimarchi, S., Eagle, K. A., Nienaber, C. A., Rampoldi, V., Jonker, F. H. W., De Vincentiis, C., Frigiola, A., Menicanti, L., Tsai, T., Froehlich, J., Evangelista, A., Montgomery, D., Bossone, E., Cooper, J. V., Li, J., Deeb, M. G., Meinhardt, G., Sundt, T. M., Isselbacher, E. M., & International Registry of Acute Aortic Dissection Investigators. (2010). Role of age in acute type A aortic dissection outcome: Report from the international registry of acute aortic dissection (IRAD). *The Journal of Thoracic and Cardiovascular Surgery, 140*(4), 784-789. https://doi.org/10.1016/j.jtcvs.2009.11.014 PMid:20176372

Trimarchi, S., Sangiorgi, G., Sang, X., Rampoldi, V., Suzuki, T., Eagle, K. A., & Elefteriades, J. A. (2010). In search of blood tests for thoracic aortic diseases. *The Annals of Thoracic Surgery, 90*(5), 1735-1742. https://doi.org/10.1016/j.athoracsur.2010.04.111 PMid:20971314

Tsai, T. T., Nienaber, C. A., & Eagle, K. A. (2005). Acute aortic syndromes. *Circulation, 112*(24), 3802-3813. https://doi.org/10.1161/CIRCULATIONAHA.105.534198 PMid:16344407

Vitale, J., Manfredini, R., Gallerani, M., Mumoli, N., Eagle, K. A., Ageno, W., & Dentali, F. (2015). Chronobiology of acute aortic rupture or dissection: A systematic review and a meta-analysis of the literature. *Chronobiology International, 32*(3), 385-394. https://doi.org/10.3109/07420528.2014.983604 PMid:25414043

Wang, J.-X., Xue, Y.-X., Zhu, X.-Y., Chong, H.-S., Chen, Z., Zhou, Q., Qu, J.-Z., & Wang, D.-J. (2022). The impact of age in acute type A aortic dissection: A retrospective study. *Journal of Cardiothoracic Surgery, 17*(1), 40. https://doi.org/10.1186/s13019-022-01785-y PMid:35305695

Wang, Y., Barbacioru, C. C., Shiffman, D., Balasubramanian, S., Iakoubova, O., Tranquilli, M., Albornoz, G., Blake, J., Mehmet, N. N., Ngadimo, D., Poulter, K., Chan, F., Samaha, R. R., & Elefteriades, J. A. (2007). Gene expression signature in peripheral blood detects thoracic aortic aneurysm. *PLOS ONE, 2*(10), e1050. https://doi.org/10.1371/journal.pone.0001050 PMid:17940614

Watanabe, H., Horita, N., Shibata, Y., Minegishi, S., Ota, E., & Kaneko, T. (2016). Diagnostic test accuracy of D-dimer for acute aortic syndrome: Systematic review and meta-analysis of 22 studies with 5000 subjects. *Scientific Reports, 6*(1), 26893. https://doi.org/10.1038/srep26893 PMid:27230962

Wei, H., Hu, J. H., Angelov, S. N., Fox, K., Yan, J., Enstrom, R., Smith, A., & Dichek, D. A. (2017). Aortopathy in a mouse model of Marfan syndrome is not mediated by altered transforming growth factor β signaling. *Journal of the American Heart Association, 6*(1). https://doi.org/10.1161/JAHA.116.004968 PMid:28119285

Yang, S., Xiao, Y., Du, Y., Chen, J., Ni, Q., Guo, X., Xue, G., & Xie, X. (2021). Diagnostic and prognostic value of neutrophil extracellular trap levels in patients with acute aortic dissection. *Frontiers in Cardiovascular Medicine, 8*, 683445. https://doi.org/10.3389/fcvm.2021.683445 PMid:35242817

Yap, Z. J., Sharif, M., & Bashir, M. (2021). Is there an immunogenomic difference between thoracic and abdominal aortic aneurysms? *Journal of Cardiac Surgery, 36*(4), 1520-1530. https://doi.org/10.1111/jocs.15440 PMid:33604952

Yin (殷晓科), X., Wanga, S., Fellows, A. L., Barallobre-Barreiro, J., Lu, R., Davaapil, H., Franken, R., Fava, M., Baig, F., Skroblin, P., Xing, Q., Koolbergen, D. R., Groenink, M., Zwinderman, A. H., Balm, R., de Vries, C. J. M., Mulder, B. J. M., Viner, R., Jahangiri, M., … Mayr, M. (2019). Glycoproteomic analysis of the aortic extracellular matrix in Marfan patients. *Arteriosclerosis, Thrombosis, and Vascular Biology, 39*(9), 1859-1873. https://doi.org/10.1161/ATVBAHA.118.312175 PMid:31315432

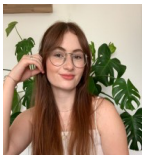
Zeng, Q., Rong, Y., Li, D., Wu, Z., He, Y., Zhang, H., & Huang, L. (2020). Identification of serum biomarker in acute aortic dissection by global and targeted metabolomics. *Annals of Vascular Surgery, 68*, 497-504. https://doi.org/10.1016/j.avsg.2020.06.026 PMid:32599111

Zhou, X., Wang, R., Zhang, T., Liu, F., Zhang, W., Wang, G., Gu, G., Han, Q., Xu, D., Yao, C., Guo, D., Fu, W., Qi, Y., & Wang, L. (2019). Identification of lysophosphatidylcholines and sphingolipids as potential biomarkers for acute aortic dissection via serum metabolomics. *European Journal of Vascular and Endovascular Surgery, 57*(3), 434-441. https://doi.org/10.1016/j.ejvs.2018.07.004 PMid:30087010

About the Author (s)

Rohan Vyas- Rohan is a specialised foundation programme (SFP) trainee at the Royal Free NHS Healthcare Trust. Rohan graduated from Barts and the London School of Medicine and Dentistry and has achieved an MSc (Distinction) in Laparoscopic Surgery and Surgical Skills. Rohan is very interested in cardiology, surgery, medical education, and research. Rohan has published multiple papers and presented at various conferences.

Jeuela Iris Ravindran- Jeuela is a foundation programme trainee at the Queen Elizabeth Hospital. Jeuela graduated from Barts and the London School of Medicine and Dentistry and has also completed an intercalated MSc in Critical Care. Her interests include cardiology, anaesthetics, and paediatrics.

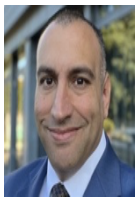


Lara Victoria Schmitt- Lara is a recent medical graduate from Barts and the London School of Medicine and Dentistry and an upcoming foundation trainee. She also completed an intercalated MSc in (Distinction) Clinical Endocrinology. With a background in Germany, and Switzerland and currently living in London, she has a unique understanding of different healthcare systems and approaches to patient care.

Jason Osei-Bonsu- Jason is a recent medical graduate from the Barts and the London School of Medicine and Dentistry. Jason has also completed an MSc in Laparoscopic Surgery and Surgical Skills. Jason has a keen interest in research projects. He is specifically interested in paediatrics, public health, and bloodless medicine.

Nabil Jaarah- Nabil is a junior doctor at Basingstoke and North Hampshire Hospital and a recent medical graduate from King's College London. Nabil also completed an intercalated MSc in Critical Care. Nabil has interests in hospital medicine, intensive care and medical research.

Wahaj Munir-Wahaj is a resident doctor at Imperial College NHS Healthcare Trust. Wahaj graduated in medicine from Barts and the London School of Medicine and Dentistry and has achieved an MSc (Distinction) in Critical Care. Wahaj is interested in cardiovascular medicine, surgery, and academic research. Wahaj has published multiple papers and presented at various conferences.



Professor Mohamad Bashir is based at Velindre University NHS Trust and Health Education and Improvement Wales – Vascular & Endovascular Surgery. He is a Visiting Professor at the University of South Wales and a Professor in Cardiovascular Clinical Research at the Institute of Coronary and Advanced Aortic Diseases at SIMS Hospital in India. He is also a Clinical Professor of Cardiac Surgery at Shahid Rajaei Cardiovascular, Medical, and Research Center in Iran. He is Specialized in the Cardiothoracic Surgery. His Clinical Interests are broadly based around cardiology and cardiac surgery.

Dr Idhrees is an outstanding cardiac surgeon having more than 15 years of clinical practice. He is an alumnus of Madurai Medical College where he completed his general surgery training. His expertise in cardiac surgery includes coronary bypass grafting and heart valve repair. He has an outstanding academic career and has received many awards in the field of medicine. Apart from being an excellent surgeon, he gets involved in research activities.