I.F.C. Italian Federation of Cardiology

Alpha1-antitrypsin deficiency and cardiovascular disease: questions and issues of a debated relation

Laura Pini[a,b], Jordan Giordani[a], Manuela Ciarfaglia[a], Alessandro Pini[c], Marianna Arici[a] and Claudio Tantucci[a,b]

Alpha1-antitrypsin (AAT) is one of the major inhibitors involved in protease/antiprotease homeostasis, and it is mainly produced by hepatocytes and pulmonary epithelial cells. Its deficiency, called alpha1-antitrypsin deficit (AATD), leads to severe hepatic and respiratory issues. Also, AAT is released into the bloodstream providing systemic anti-inflammatory effects. Apart from acting as an acute-phase anti-inflammatory protein, it can be a biomarker for monitoring disease evolution. A reduced or defective production leads to a loss of anti-inflammatory function, protease−antiprotease imbalance and cellular engorgement due to polymers deposition, with system-wide repercussions. This review aims to evaluate AATD condition in the major vessels of the head and neck, thoracic and abdominal districts. Also, a dedicated focus on autoimmune vascular diseases will be provided.

A critical revision of the main literature findings starting from the 1980s until now has been performed. Studies conducted over the years have provided several contradictory pieces of evidence. Most authors acknowledge the protective and anti-inflammatory AAT role on the vascular endothelium. However, correlations between AATD and major arteries, cerebral and cardiovascular conditions, and autoimmune diseases remain unclear. Most studies recognize the role of AATD in vascular diseases but only as a cofactor inducing cellular and tissue structure impairments. However, this condition alone is not enough to determine new disease onset.

Due to the opposing results reported over the years, there is still a considerable lack of knowledge on the role covered by AATD in vascular diseases. A renewed interest in this research field should be encouraged to grant new solid evidence and validate the putative role of AATD screening and replacement therapy as useful diagnostic and treatment tools.

Introduction

Alpha-1 antitrypsin deficiency (AATD) is described as an autosomal codominant genetic disorder characterized by a reduction in circulating levels of alpha-1 antitrypsin (AAT) protein. This condition causes a loss of systemic balance between protease and antiprotease, and the lack of a fundamental anti-inflammatory acute-phase factor.[1]

Alpha-1 antitrypsin is a protein belonging to the family of serine protease inhibitors and is encoded by the Serpina1 gene, whose locus is located on chromosome 14q32.1. Hepatocytes and bronchial epithelial cells mainly synthesize AAT to grant tissue protection and provide a reliable modulation of the inflammatory response through the signal pathway induced by the binding with scavenging receptor LRP1, also known as AAT-Rec. The identification over the years of more than 100 genetic mutations has allowed several allelic variants to be described. Among these, the Z variant resulting from an aminoacidic substitution GLU342LYS has the most severe clinical consequences, affecting especially its synthesis sites with cirrhosis, emphysema, Chronic Obstructive Pulmonary Disease (COPD) and asthma. The Z variant causes the synthesis of a defective form of AAT with a marked tendency to generate precipitating polymer aggregates leading to cellular engorgement and subsequent tissue damage.[2,3]

In recent decades, research has devoted most of its efforts to finding correlations between AATD and the principal liver and respiratory diseases and in searching for replacement therapies to balance the low serum AAT levels.[4−6] However, we cannot ignore that AAT, when released into the bloodstream, carries out its protective and anti-inflammatory action at a systemic level.[7] Therefore, it can be considered both an anti-inflammatory acute-phase protein and a useful disease evolution biomarker. For all these reasons, the role of AAT and its deficiency impact on the onset and worsening of local and systemic conditions cannot be overlooked. Among these, vascular ones represented a controversial field, rich in studies reporting conflicting results.

On these bases, this review aims to shed light on the relationship between AATD and vascular pathologies and provide the most up-to-date insights on the topic.

Findings
Head and neck district
Cervical arteries dissections

First insights into the relationship between AATD and/or low AAT serum levels have been provided in the 2003 case–control study of Vila et al.[8] analysing 22 patients with spontaneous cervical artery dissection (sCAD). However, in 2004 and 2005, two case–control studies by Grond-Ginsbach et al.[9] and Konrad et al.[10] enriched the knowledge in this field with a genetic segregation analysis conducted on larger samples (74 and 80 patients, respectively) that disproved the former hypothesis.

Nevertheless, it is possible to apprehend a general consensus on the protective and anti-inflammatory role of AAT and how its lowering below physiological values contributes to protease-mediated arterial tissue damage.[9,10] As further evidence, there is a retrospective study by Schievink et al.[11] dated 1994, wherein thickening and disorganization of muscular and connective tissues of the middle tonaca and intimal fibroplasia were reported in samples from individuals with AATD and fibromuscular dysplasia (FMD).

Intracranial aneurysms

The first reports date back to 1995, when a study by Baker et al.[12] compared the elastase:AAT ratio in 19 patients with unruptured intracranial aneurysms and 41 with ruptured aneurysms vs. control. The elastase:AAT ratio was doubled in both the groups compared with controls. However, the higher ratio was primarily related to the increase in elastase levels rather than low AAT levels.[12]

In the following year, a study by Schievink et al.[13] evaluated the prevalence of different AATD phenotypes in 100 patients with intracranial aneurysms. The study documented a higher prevalence of heterozygous and homozygous AATD phenotypes (PiMS, PiMZ and PiZZ) than the general population.[13] This was the first study confirming a relationship between AATD and intracranial aneurysms.

Several years later, in 2004, the same hypothesis was overturned by an extended population study conducted by Yoneyama et al.[14] Genotyping for seven defective AAT allelic variants in 195 Japanese and 189 Korean individuals affected by ruptured intracranial aneurysm vs. control showed no significant differences.[14]

In the end, a 2019 work by Tyagi et al.[15] studied, through RT-PCR and immunohistochemistry techniques, the expression levels of four genes, including the SERPINA gene, by sampling the vascular wall of 35 patients with intracranial aneurysm. These expression levels have been compared with control levels quantified from the extracranial artery wall of the same subjects. The study documented AAT levels 1.46 times higher than the control, showing how high protease activity in aneurismatic vascular walls increases AAT production. Also, the role of AAT as an acute-phase protein able to counter the proteases/antiproteases imbalance and modulate the subsequent inflammatory processes has been underlined. However, from a pathological perspective, AAT alone cannot prevent aneurysm development or size increase, as the augmented protease levels lead to an irreversible process of vessels' extracellular matrix (ECM) remodelling.[15]

Stroke

Available sources for this condition are few and contradictory. A 2006 work by Burghaus et al.,[16] studying 81 white children recovering after a stroke acute phase, documented that AAT concentrations above the 90th age-dependent percentiles were related to a four times increased risk of arterial ischemic stroke (AIS). However, no SERPINA1 alleles genotyping has been conducted in this study. On the basis of these data, AAT could be suggested as a candidate acute-phase biomarker for the AIS onset, but further studies on this topic are needed.

The opposite opinion was provided in 2014 by a comparative work from Moldthan et al.,[17] wherein it was documented how therapy with human AAT in mouse models with an induced ischemic stroke condition improved their outcome and had a protective effect against stroke-associated neurodegenerative processes.

Once again, a 2017 commentary by Meschia[18] on a study provided the same year by Malik et al.[19] focused on AAT as a risk factor for the development of large arteries stroke (LAS). Specifically, they documented a 22% risk increase for LAS development in patients carrying the M1 allelic variant. Following these findings, the author hypothesized that the gene–environment interaction of the M1 variant with cigarette smoke could explain this risk increase. Cigarette smoking is an important risk factor for stroke development and seems to reduce the modulatory AAT activity towards neutrophil elastase.[18,19]

Finally, a recent study of 2020 by Mahta et al.[20] brought some order to this matter. First, the author points out how stroke, by definition, is an extremely heterogeneous clinical condition characterized by different pathogenic mechanisms. Atherosclerotic stroke is the most frequent, and in this picture, AAT plays an important anti-inflammatory and cytoprotective role, capable of slowing down the vascular remodelling processes. Therefore, finding high levels of AAT in individuals affected by stroke could be an acute-phase neuroprotective mechanism to limit acute damage and inflammation of the central nervous system. Another interesting suggestion is the need to identify AAT concentrations suitable for future pharmacological employments to stop vascular remodelling processes and provide valuable preventive therapeutic support.[20]

Pulmonary and cardiovascular system

Aneurysms

Similar to the previously described clinical conditions, there is a very contradictory debate on the role of AAT and AATD in pneumo and cardiovascular diseases. In 2010, a study by Schachner *et al.*[21] showed how AAT serum levels in individuals affected by dissection of the ascending aorta were lower than in healthy individuals, highlighting its protective role against proteolytic damage. Subsequently, in 2012, Vizzardi *et al.*,[22,23] studying a sample of 33 AATD individuals, demonstrated an increased stiffness, reduced distensibility and abnormal strain of the aortic wall, pointing them out as markers of pathological alterations of the elastic tissue. In the same year, a study by Kilickesmez *et al.*[24] related the ascending aorta dilation to AAT and metalloprotease-9 serum levels in individuals with bicuspid aortic valve condition.

Validation of what previously documented was provided by Muhammad *et al.*[25] in 2017 and Fisk *et al.*[26] in 2018, who in an observational study on 2338 individuals and a prospective cross-sectional study on 121 patients (85 with COPD due to smoking, 12 with COPD + AATD and 24 controls equally divided into smokers and nonsmokers), respectively, demonstrated the protective and anti-inflammatory role of AAT as an acute-phase reactant to counter the elastin degradation processes induced by proteases, which in time lead to an increase in aortic stiffness. The documented results made the authors suggest that AAT serum levels quantification could be a useful predictor of aortic dilatation.

The most recent work dates back to June 2021. Dako *et al.*,[27] through a retrospective CT-scan case–control study, analysed the ascending aorta mean diameter of individuals with AATD-related emphysema vs. controls with emphysema alone. A pathological association between AATD and aortic wall distension with a subsequent increased risk for aneurysm development has been documented. At the same time, the author proposed including the measurement of aortic diameter in AATD patients in the diagnostic routine. Conversely, the dosage of AAT levels and eventual genotyping in individuals with aortic wall distension and/or aneurysm has been suggested.[27]

A 2018 article by Guo *et al.*[28] set out to assess the role played by the imbalance between protease and antiprotease in individuals with idiopathic pulmonary hypertension (IPAH), showing that AAT levels did not differ between individuals with IPAH and controls. However, it should be noted that this study did not focus on AATD individuals but only on the balance assessment of the protease–antiprotease axis in IPAH individuals. Although there is no specific evidence in the literature on the relationship between AATD and IPAH, a 2004 work by Aldonyte *et al.*[29] showed that AAT defective forms, during their polymerization phase, are deposited along the pulmonary vascular endothelium, suggesting that cellular AAT polymers, subsequent cellular and tissue damage, and the loss of inflammatory modulation could be determining factors for IPAH development.

Cardiac diseases, atherosclerosis and cardiovascular risk

Several studies tried to characterize the AATD impact on cardiac diseases. In 2003, Engström *et al.*[30] documented a correlation between the increase in inflammation-sensitive acute-phase proteins, including AAT, and myocardial infarction in individuals with no cardiovascular risk factors.

Almost 10 years later, the study of Kanai *et al.*[31] on plasma factors potentially involved in the onset and progression of Kawasaki disease identified peaks of AAT, assuming that they could play an important but not mandatory role in protecting vascular epithelial tissues in individuals with Kawasaki disease-related aneurysmatic disease. Confirming this hypothesis, there is a 2015 study by Feng *et al.*[32] wherein AAT is shown to play a cytoprotective role in the vascular endothelium when affected by hypoxia and subsequent reoxygenation processes, thus suggesting that replacement therapies with AAT may limit the damage resulting from the ischemia and reperfusion phases in tissues damaged by myocardial infraction. An empirical demonstration of this hypothesis comes from several studies developed in the following years. In 2015, Abbate *et al.*[33] showed that in 10 patients with ST-segment elevated myocardial infraction (STEMI), infusion within 12 h of hospital admission of AAT 60 mg/kg intravenously (i.v.) combined with conventional therapeutic protocols turned out to be well tolerated and capable of reducing the inflammatory-processes underlying the cardiac event. In 2016, Toldo *et al.*[34] confirmed Feng's theory by applying recombinant human plasma-derived AAT-Fc in murine models with an induced acute myocardial inflammatory injury, proving its property to reduce the size of the ischemic area and preserve the systolic function independently of the previous neutrophil elastase's effects. More recently, in 2018, Abouzaki *et al.*[35] in a post-hoc analysis of Abbate's work, showed that Prolastin C administered hours after myocardial reperfusion reduces the time to peak and the area under the curve for CK-MP compared with controls, suggesting that it can reduce the duration of the injury related to the ischemia-reperfusion in STEMI patients.

Lastly, in 2016, Turhan Caglar *et al.*[36] studied the serum AAT levels in 50 patients with coronary artery ectasia (CAE) and 46 negative controls, demonstrating an inverse relationship, thus confirming the role of AAT in preserving arterial wall integrity.

The principle of the elastase/antielastase imbalance as one of the mechanisms underlying the destructive processes of vascular connective tissue is reiterated in a 2001

work by Stakisaitis et al.[37] aimed to assess the role of AAT in individuals affected by coronary atherosclerosis. This work showed how AAT levels in individuals with coronary atherosclerosis were higher than in controls. Therefore, it was concluded that congenital conditions such as hyperlipidaemia or carrying defective allelic AAT forms, such as PiZZ, along with acquired conditions such as ageing or cigarette smoking, correlate with an increased progression of coronary atherosclerosis due to a strong protease/antiprotease imbalance.[37]

One year later, Dahl et al.[38] conducted an important case–control study in which 1131 and 2221 patients enrolled from the Copenhagen City Heart Study and the Copenhagen University Hospital affected by ischemic cerebrovascular disease (ICVD) and ischemic heart disease (IHD), respectively, were evaluated in terms of AAT genotyping, blood pressure measurement and cardiovascular risk assessment and then compared with 7963 adult Danish control individuals to demonstrate whether AATD is associated with a reduction in blood pressure, increased risk for ICVD and IHD, and longevity. Data obtained in this study allowed Dahl et al.[38] to state that PiZZ and PiMZ genotypes are related to reduced blood pressure in IHD patients. Also, the PiMZ genotype is associated with a reduced risk for ICVD and IHD.[38]

In 2003, the abovementioned study by Stakisaitis et al.[37] was confirmed by the association analysis performed by Talmud et al.[39] Their study proved how coronary disease progression, documented with the minimum luminal diameter measurement, was associated with AAT defective allelic S and Z forms and low serum AAT levels.[39] Apart from being a protein capable of slowing the progress of coronary atherosclerosis, the study by Towler[40] suggested a new role for AAT as a therapeutic molecule able to reduce the deposition of calcific plaques caused by an increased protease activity.

To conclude, three recent articles produced by Fähndrich et al.,[41] Curjuric et al.[42] and Nakanishi et al.[43] in 2017, 2018 and 2020, respectively, assessed the cardiovascular risk in patients with AATD. Unlike what has been previously documented, Fähndrich et al.[41] found a lower prevalence of cardiovascular comorbidities in a registry of 2645 COPD patients. This contrasts with the findings of previous authors. However, it cannot be excluded that patients involved in the study by Fähndrich et al.[41] had a lower prevalence of cardiovascular comorbidities due to the lifestyle adaptations implemented for their AATD condition and increased clinical follow-up visits over time.[41] Curjuric et al.,[42] in turn, using data from the Swiss population-based SAPALDIA cohort (2614 adult individuals), demonstrated a possible association between AAT deficiency and carotid intima-media thickness (CIMT) and arterial hypertension.[42] Lastly, Nakanishi et al.[43] claimed that PiMZ individuals present a reduced cardiovascular risk.[43] It emerges how

the data of Fähndrich et al.[41] and Nakanishi et al.[43] contradict what has been documented by previous authors. However, the role of AAT as a cytoprotective element for coronary vascular walls is undeniable. For this reason, further clinical and molecular biology studies are mandatory to provide more clarity.

Aortic district
Despite some contradictory findings, a considerable number of studies suggest a relationship between AATD and abdominal vascular disease. However, provided data results are contradictory. The first hypothesis dates back to 1988, with a work by Tilson and Roberts,[44] but in the 1990s, the interest started to rise.

Two studies by Cohen et al.[45] dated 1990 and Schardey et al.[46] dated 1998 agree that deficient allelic AAT forms correlate with a higher incidence of abdominal aortic aneurysm (AAA) development than the general population. On the contrary, numerous studies supported the opposite theory, defining AATD alone as a condition unable to develop abdominal aneurysms.[47–50] The only work that sought to mediate between these two positions was the 1997 study conducted by Ahlgren et al.[51] determining whether there were changes in aortic wall stiffness, assessed by echo-tracking sonography, in 19 men and 17 women with AATD. The study found no significant differences in abdominal aortic wall stiffness compared with control subjects. The only significant evidence was the altered aortic wall distensibility in male subjects as a potential sign of early vascular alteration.[51] This finding leads to the hypothesis that AATD vascular effects may occur at the earliest stages of disease, causing vascular wall abnormalities that contribute to the AAA onset along with other risk factors.

The conflicting and often discouraging results led to a progressive lack of interest in this topic. In the 2000s, two articles by Knapik-Kordecka et al.[52] and Vega de Céniga et al.[53] documented the role of AAT as an independent biomarker of cardiovascular risk during acute inflammation phases, capable of promoting AAA development and growth. At the beginning of the last decade, Pulinx et al.[54] confirmed the presence of increased AAT serum levels in patients with AAA, although they did not find a direct correlation with the increase in aneurysmal diameter. Several years after, Pini et al.[55] brought back the attention with a study involving 138 patients hospitalized for non-traumatic AAA rupture, documenting a higher prevalence of the S deficient AAT allele compared with the general Italian population, pointing to the AATD condition as a candidate risk factor for AAA development.

Other evidence
Regarding the relationship between AATD and other vascular issues, the study conducted in the 2000s by Gaglio et al.[56] demonstrated an increased risk of rupture of splenic artery aneurysms in patients with AATD.

The last field of research that again produced contradictory results is the role of AATD in individuals with FMD of the renal artery. The 2000s study by Bofinger et al.[57] suggested that the AATD leads to the development of more severe forms of renal artery FMD. However, 6 years later, Perdu et al.,[58] studying polymorphisms associated with PiM1, PiZ and PiS allelic variants, documented no correlation with any FMD form.

Inflammatory and autoimmune diseases
AATD could generate issues at a systemic level, as shown in a work of 1996 by Mazodier et al.[59] describing the clinical cases of eight Swedish individuals suffering from AATD and systemic necrotizing vasculitis. Among them, six had systemic vasculitis characterized by microscopic polyangiitis, while the other two were affected by

Wegener's granulomatosis and Schonlein-Henoch's purpura, respectively.[59]

Savige et al.[60] in 1995 and Callea et al.[61] in 1997 documented how low AAT serum levels are associated with more severe and widespread forms of vasculitis, suggesting that AATD leads to a PR3 protease inhibition impairment and an increase in cANCA production. These data raised reflections on the usefulness of AAT as a screening biomarker in individuals with cANCA-positive vasculitis and vice versa.

These findings generated a growing interest in the scientific community. Since the mid-1980 s, an increasing number of dedicated studies can be found. Among these, a 1985 study by Wakefield et al.[62] on a sample of 25 patients attempted to correlate AATD with the onset

Table 1 Literature evidence on the relationship between alpha 1-antitrypsin deficit and/or changes in alpha 1-antitrypsin serum levels and major vascular and autoimmune diseases

	Year	Ref.	Evidence
Cervical artery dissection	2003	Vila et al.[8]	↑ Risk in AATD
	2004	Grond-Ginsbach et al.[9]	No evidence
	2005	Konrad et al.[10]	No evidence
Fibromuscular dysplasia	1994	Schievink et al.[11]	↑ Risk in AATD
Intracranial aneurysms	1995	Baker et al.[12]	Elastase/AAT ratio doubled
	1995	Schievink et al.[13]	↑ Risk in AATD
	2004	Yoneyama et al.[14]	No evidence
	2019	Tyagi et al.[15]	↑ AAT levels
Stroke	2006	Burghaus et al.[16]	Four times higher risk in patients with↑ AAT levels
	2014	Moldthan et al.[17]	Improved outcome with AAT replacement therapy
	2017	Meschia[18]	↑ Risk in M1 variant + cigarette smoking
	2020	Mahta et al.[20]	AAT anti-inflammatory and cytoprotective role
Aortic aneurysms	2010	Schachner et al.[21]	↓ AAT levels in pts with Ascending Aorta Dissection
	2012	Vizzardi et al.[22,23]	↑ Aortic stiffness
	2012	Kilickesmez et al.[24]	Ascending aorta dilation related with AAT and MP9 levels
	2017	Muhammad et al.[25]	AAT as an acute-phase reactant
	2018	Fisk et al.[26]	AAT as an acute-phase reactant
	2021	Dako et al.[27]	↑ Risk in AATD
Idiopathic pulmonary hypertension	2004	Aldonyte et al.[29]	Defective AAT polymers in pulmonary vascular endothelium
	2018	Guo et al.[28]	No evidence
Myocardial infraction	2003	Engström et al.[30]	↑ AAT levels in patients with myocardial infraction
	2015	Feng et al.[32]	Improved outcome with AAT replacement therapy
	2015	Abbate et al.[33]	Improved outcome with AAT replacement therapy
	2016	Toldo et al.[34]	Improved outcome with AAT replacement therapy
	2016	Turhan Caglar et al.[36]	AAT as an arterial wall protector
	2018	Abouzaki et al.[35]	Improved outcome with AAT replacement therapy
Kawasaki disease	2012	Kanai et al.[31]	↑ AAT levels in patients with Kawasaki disease
Coronary artherosclerosis	2001	Stakisaitis et al.[37]	↑ Risk in AATD
	2002	Dahl et al.[38]	PiZZ and PiMZ had ↓ BP in IHD patients
	2003	Talmud et al.[39]	↑ Coronary disease progression and ↓ AAT levels in PiS and PiZ patients
	2015	Towler[40]	AAT reduces calcific plaques deposition
Cardiovascular risk	2017	Fähndrich et al.[41]	↓ prevalence of CV comorbidities in AATD patients
	2018	Curjuric et al.[42]	Association between AATD and CIMT
	2020	Nakanishi et al.[43]	↓ CV risk in PiMZ individuals
Abdominal aortic aneurysms	1997	Ahlgren et al.[51]	Early vascular alteration in AATD male patients
	1998	Cohen et al.[45]	↑ Risk in AATD
	2000	Knapik-Kordecka et al.[52]	AAT levels as marker for AAA
	2000	Vega de Céniga et al.[53]	AAT levels as marker for AAA
	2011	Pulinx et al.[54]	AAT levels as marker for AAA
	2021	Pini et al.[55]	↑ Risk in AATD PiS
Splenic artery aneurysms	2000	Gaglio et al.[56]	↑ Risk in AATD
Renal artery FMD	2000	Bofinger et al.[57]	↑ severe FMD forms in AATD patients
	2006	Perdu et al.[58]	No evidence
Vasculitis	1995	Savige et al.[60]	Worse vasculitis forms in AATD patients and/or ↓ AAT levels
	1996	Mazodier et al.[59]	Systemic necrotizing vasculitis in AATD patients
	1997	Callea et al.[61]	Worse vasculitis forms in AATD patients and/or ↓ AAT levels
Retinal vasculitis	1985	Wakefield et al.[62]	↑ AAT levels in patients with RV
	2001	Audrain et al.[63]	↑ ANCA production in PiZZ patients

and/or progression of retinal vasculitis. Although unsuccessful, the study still documented increased AAT levels during acute retinal vasculitis phases.[62] A later 2001 work by Audrain *et al*.[63] in a population of 191 PiZZ patients vs. PiMM controls reported an increased ANCA, although not directed against the MPO and PR3 antigens. Therefore, the author emphasized the role of AATD only as an additional condition able to contribute to the onset of ANCA-positive vasculitis.

The open perspectives in this field are numerous and highly diversified. There is still much to discover about the role played by the AATD in autoimmune diseases and even more about its impact on small and medium vessels, whose response may differ from what is already known for the large ones.

Discussion

Data from the literature mainly documented vascular alterations in individuals with AATD, especially PiZ ones. However, overall, the results proved to be highly contradictory. A few statistically significant correlations between AATD and vascular diseases have been documented, even rarely with a direct cause–effect association (Table 1 and Fig. 1).

Still, it is undeniable that AAT acutely modulates cellular damage and vascular tissue inflammation caused by the increased expression levels in protease factors, especially neutrophil elastase. The mechanisms underlying the AATD condition, such as the presence of constant subacute tissue inflammation, due to the lowering or loss of AAT as an anti-inflammatory factor, together with the elastase/antielastase imbalance, and the defective AAT polymers intracellular deposition, unavoidably lead to progressive degeneration of the arterial vascular walls, increasing their thickness, reducing elasticity, enhancing the deposition of calcific endothelial plaques and altering the overall cellular intima and media tonaca organization (Fig. 2). For these reasons, we can assume that AATD alone is not a sufficient cause for the new onset of vascular diseases, but it mainly acts as a cofactor.

Fig. 1
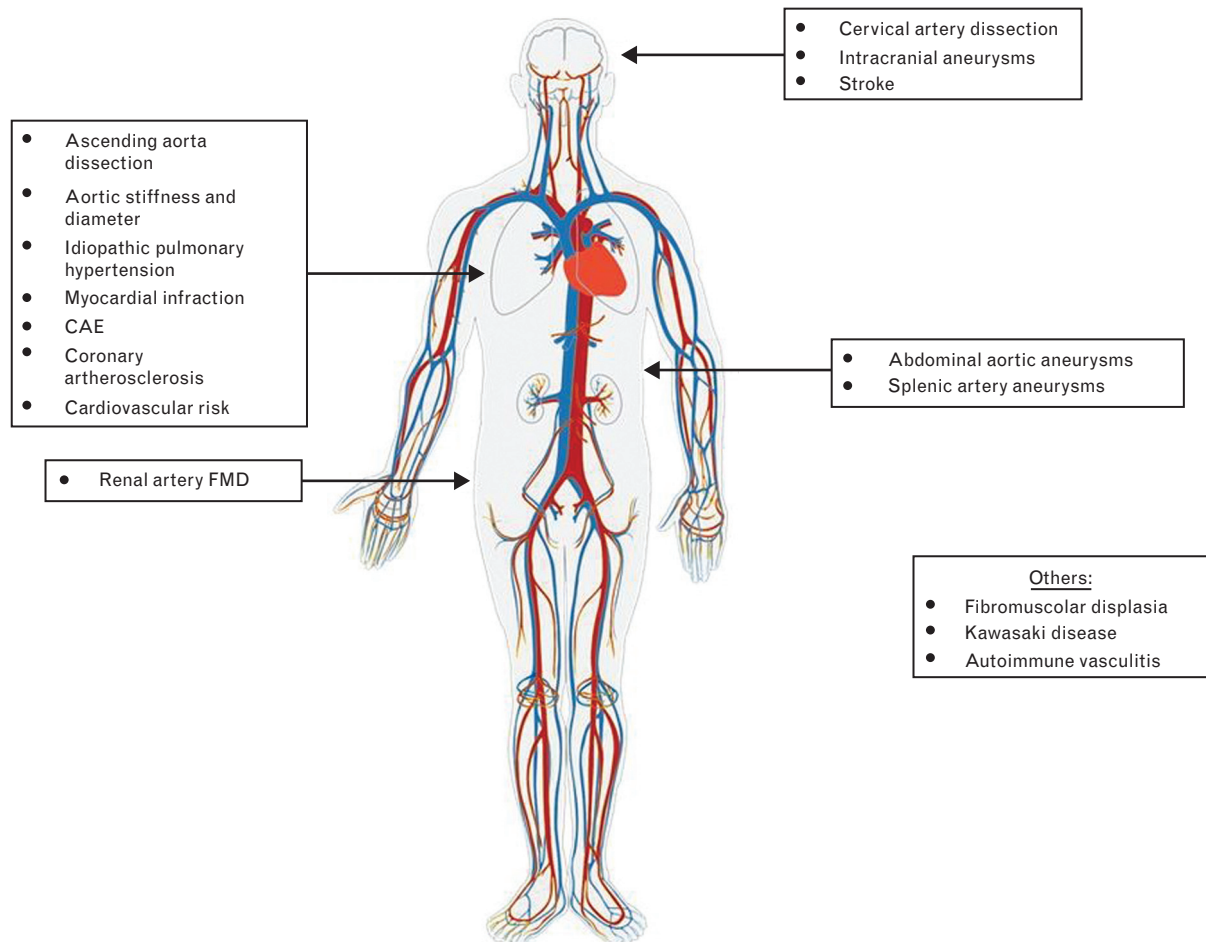
Overview of the main vascular diseases examined.

Fig. 2
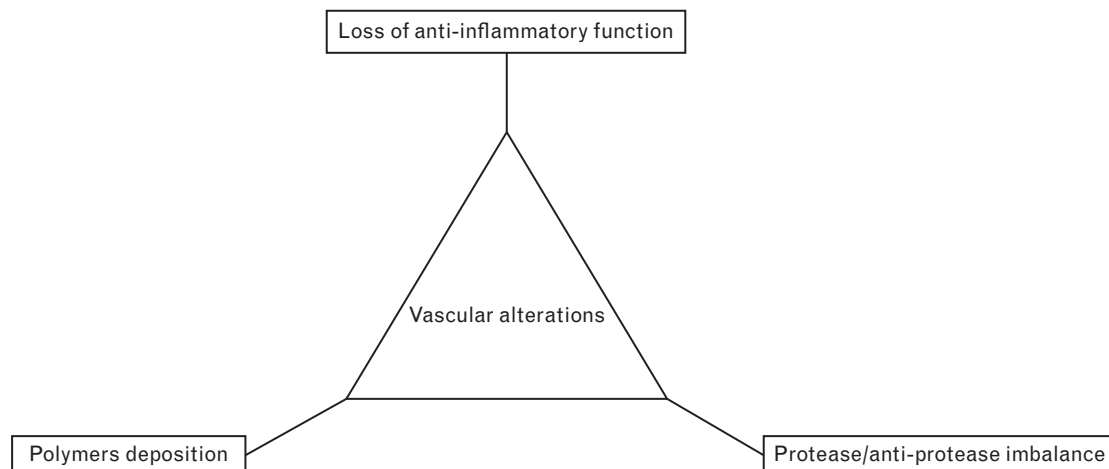
Main mechanisms of tissue damage in individuals with alpha 1-antitrypsin deficit.

Ultimately, we cannot exclude the possibility that primary AATD consequences in the lungs and liver could indirectly impact preexisting vascular conditions. However, in this field, further targeted studies are needed.

This review suggests that AATD could be considered among the several clinical conditions able to contribute to the onset of inflammatory processes and vascular epithelium structural alteration. Another topic is the high heterogeneity of the vascular diseases in which AATD can be implicated. It is impossible to exclude the AATD contribution in tissue or organ alterations from the largest vessels to the lowest branches. In this context, more refined characterizations of the AAT role within molecular dynamics and pathological vascular mechanisms should be encouraged.

Similarly, from a clinical perspective, screening for AATD by serum AAT dosage and genotyping could be an important screening and monitoring tool in patients requiring surgical procedures or long-term follow-up for vascular diseases. On the contrary, screening ultrasound for the most frequent vascular disorders could be considered in patients affected or with a positive familial clinical history of AATD.

Conclusion
Nowadays, the role played by AATD in vascular diseases attracts little interest in the scientific community. The low disease frequency in the general population and conflicting results from various literature data have prevented a clear relationship between AATD and vascular disorders. Therefore, research has been directed mainly at the hepatic and pulmonary area, where the evidences are more defined and promising. In this picture, a

dedicated meta-analysis would be very informative to provide clarity and, therefore, should be encouraged.

Nevertheless, there is still a large lack of knowledge on this topic. This review showed that AATD, combined with other risk factors, enhances the progression of both cardiovascular and autoimmune disorders. Therefore, it would be useful to investigate the molecular mechanisms of vascular AATD-related damage. Moreover, new insights could be provided by promoting prevalence studies in high cardiovascular risk populations or those affected by autoimmune vascular diseases and *vice versa*.

Another issue worthy of investigation, often proposed in various clinical studies over the years, is the putative introduction of AAT serum dosage and genotyping for screening and/or interventional purposes to proactively set replacement therapies aimed at reducing the risk of short- and long-term vascular and surgical complications and slowing their progression.

Conflicts of interest
There are no conflict of interest.

References
1 Kelly E, Greene CM, Carroll TP, McElvaney NG, O'Neill SJ. Alpha-1 antitrypsin deficiency. *Respir Med* 2010; **104**:763–772.
2 Janciauskiene S, Welte T. Well known and less well known functions of alpha-1 antitrypsin: its role in chronic obstructive pulmonary disease and other disease developments. *Ann Am Thorac Soc* 2016; **13 (Suppl 4)**: S280–S288.
3 Pini L, Tiberio L, Arici M, *et al.* Z-alpha 1-antitrypsin polymers and small airways disease: a new paradigm in alfa-1 antitrypsin deficiency-related COPD development? *Monaldi Arch Chest Dis* 2021; **91**:489–493.
4 Pini L, Paoletti G, Heffler E, *et al.*, on behalf of Asthma and Alpha 1-Antitrypsin Research Group. Alpha 1-antitrypsin deficiency and asthma. *Curr Opin Allergy Clin Immunol* 2021; **21**:46–51.
5 Pini L, Tiberio L, Venkatesan N, *et al.* The role of bronchial epithelial cells in the pathogenesis of COPD in Z-alpha 1 antitrypsin deficiency. *Respir Res* 2014; **15**:112.

6 Marengoni A, Nicosia F, Tantucci C, Pini L, Grassi V. Heart and lung in the old age. The association between COPD and cardiovascular diseases: how much and how. *Rass Patol Appar Resp* 2011; **26**:290–297.

7 Janciauskiene SM, Bals R, Koczulla R, Vogelmeier C, Köhnlein T, Welte T. The discovery of α1-antitrypsin and its role in health and disease. *Respir Med* 2011; **105**:1129–1139.

8 Vila N, Millán M, Ferrer X, Riutort N, Escudero D. Levels of alpha 1-antitrypsin in plasma and risk of spontaneous cervical artery dissections: a case-control study. *Stroke* 2003; **34**:E168–E169.

9 Grond-Ginsbach C, Engelter S, Werner I, et al. Alpha-1-antitrypsin deficiency alleles are not associated with cervical artery dissections. *Neurology* 2004; **62**:1190–1192.

10 Konrad C, Langer C, Müller GA, et al. Protease inhibitors in spontaneous cervical artery dissections. *Stroke* 2005; **36**:9–13.

11 Schievink WI, Björnsson J, Parisi JE, Prakash UB. Arterial fibromuscular dysplasia associated with severe alpha 1-antitrypsin deficiency. *Mayo Clin Proc* 1994; **69**:1040–1043.

12 Baker CJ, Fiore A, Connolly ES Jr, Baker KZ, Solomon RA. Serum elastase and alpha-1-antitrypsin levels in patients with ruptured and unruptured cerebral aneurysms. *Neurosurgery* 1995; **37**:56–61; discussion 61–62.

13 Schievink WI, Katzmann JA, Piepgras DG, Schaid DJ. Alpha-1-antitrypsin phenotypes among patients with intracranial aneurysms. *J Neurosurg* 1996; **84**:781–784.

14 Yoneyama T, Kasuya H, Akagawa H, et al. Absence of alpha-1 antitrypsin deficiency alleles (S and Z) in Japanese and Korean patients with aneurysmal subarachnoid hemorrhage. *Stroke* 2004; **35**:e376–e378.

15 Tyagi G, Srinivas D, Nanjaiah ND, et al. Gene expression in intracranial aneurysms-comparison analysis of aneurysmal walls and extracranial arteries with real-time polymerase chain reaction and immunohistochemistry. *World Neurosurg* 2019; **130**:e117–e126.

16 Burghaus B, Langer C, Thedieck S, Nowak-Göttl U. Elevated alpha 1-antitrypsin is a risk factor for arterial ischemic stroke in childhood. *Acta Haematol* 2006; **115**:186–191.

17 Moldthan HL, Hirko AC, Thinschmidt JS, et al. Alpha 1-antitrypsin therapy mitigated ischemic stroke damage in rats. *J Stroke Cerebrovasc Dis* 2014; **23**:e355–e363.

18 Meschia JF. Alpha-1 antitrypsin dysfunction and large artery stroke. *Proc Natl Acad Sci U S A* 2017; **114**:3555–3557.

19 Malik R, Dau T, Gonik M, et al., International Stroke Genetics Consortium. Common coding variant in SERPINA1 increases the risk for large artery stroke. *Proc Natl Acad Sci U S A* 2017; **114**:3613–3618.

20 Mahta A, Yaghi S, Reznik ME, et al. Serum alpha-1 antitrypsin in acute ischemic stroke: a prospective pilot study. *J Clin Neurosci* 2020; **76**:20–24.

21 Schachner T, Golderer G, Sarg B, et al. The amounts of alpha 1 antitrypsin protein are reduced in the vascular wall of the acutely dissected human ascending aorta. *Eur J Cardiothorac Surg* 2010; **37**:684–690.

22 Vizzardi E, Corda L, Pezzali N, et al. Elastic properties of the ascending aorta in patients with α1-antitrypsin deficiency (Z homozygotes). *Heart* 2012; **98**:1354–1358.

23 Vizzardi E, Corda L, Sciatti E, et al. Echocardiographic evaluation in subjects with α1-antitrypsin deficiency. *Eur J Clin Invest* 2015; **45**:949–954.

24 Kilickesmez KO, Abaci O, Kocas C, et al. Dilatation of the ascending aorta and serum alpha 1-antitrypsin level in patients with bicuspid aortic valve. *Heart Vessels* 2012; **27**:391–397.

25 Muhammad IF, Borné Y, Östling G, et al. Acute phase proteins as prospective risk markers for arterial stiffness: the Malmö Diet and Cancer cohort. *PLoS One* 2017; **12**:e0181718.

26 Fisk M, Cheriyan J, Mohan D, et al. Vascular inflammation and aortic stiffness: potential mechanisms of increased vascular risk in chronic obstructive pulmonary disease. *Respir Res* 2018; **19**:100.

27 Dako F, Zhao H, Mulvenna A, Gupta YS, Simpson S, Kueppers F. Relationship between α1-antitrypsin deficiency and ascending aortic distention. *Mayo Clin Proc Innov Qual Outcomes* 2021; **5**:590–595.

28 Guo J, Lodge K, Newnham M, et al. Increased antielastase activity in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Am J Respir Cell Mol Biol* 2018; **59**:652–655.

29 Aldonyte R, Jansson L, Ljungberg O, Larsson S, Janciauskiene S. Polymerized alpha-antitrypsin is present on lung vascular endothelium. New insights into the biological significance of alpha-antitrypsin polymerization. *Histopathology* 2004; **45**:587–592.

30 Engström G, Stavenow L, Hedblad B, et al. Inflammation-sensitive plasma proteins and incidence of myocardial infarction in men with low cardiovascular risk. *Arterioscler Thromb Vasc Biol* 2003; **23**:2247–2251.

31 Kanai T, Shiraishi H, Uehara R, Ito T, Momoi MY. Increased (1-antitrypsin levels in acute-phase Kawasaki disease as shown by SELDI-TOF MS analysis. *Pediatr Cardiol* 2012; **33**:1343–1347.

32 Feng Y, Hu L, Xu Q, et al. Cytoprotective role of alpha-1 antitrypsin in vascular endothelial cell under hypoxia/reoxygenation condition. *J Cardiovasc Pharmacol* 2015; **66**:96–107.

33 Abbate A, Van Tassell BW, Christopher S, et al. Effects of prolastin C (plasma-derived alpha-1 antitrypsin) on the acute inflammatory response in patients with ST-segment elevation myocardial infarction (from the VCU-alpha 1-RT pilot study). *Am J Cardiol* 2015; **115**:8–12.

34 Toldo S, Mauro AG, Marchetti C, et al. Recombinant human alpha-1 antitrypsin-Fc fusion protein reduces mouse myocardial inflammatory injury after ischemia-reperfusion independent of elastase inhibition. *J Cardiovasc Pharmacol* 2016; **68**:27–32.

35 Abouzaki NA, Christopher S, Trankle C, et al. Inhibiting the inflammatory injury after myocardial ischemia reperfusion with plasma-derived alpha-1 antitrypsin: a post hoc analysis of the VCU-α1RT Study. *J Cardiovasc Pharmacol* 2018; **71**:375–379.

36 Turhan Caglar FN, Ksanski V, Polat V, et al. The association between α1-antitrypsin and coronary artery ectasia. *Angiology* 2016; **67**:927–931.

37 Stakisaitis D, Basys V, Benetis R. Does alpha-1-proteinase inhibitor play a protective role in coronary atherosclerosis? *Med Sci Monit* 2001; **7**:701–711.

38 Dahl M, Tybjaerg-Hansen A, Sillesen H, Jensen G, Steffensen R, Nordestgaard BG. Blood pressure, risk of ischemic cerebrovascular and ischemic heart disease, and longevity in alpha (1)-antitrypsin deficiency: the Copenhagen City Heart Study. *Circulation* 2003; **107**:747–752.

39 Talmud PJ, Martin S, Steiner G, et al., Diabetes Atherosclerosis Intervention Study Investigators. Progression of atherosclerosis is associated with variation in the alpha 1-antitrypsin gene. *Arterioscler Thromb Vasc Biol* 2003; **23**:644–649.

40 Towler DA. Arteriosclerotic calcification: a Serpi(n)ginous path to cardiovascular health? *Circ Res* 2015; **117**:744–746.

41 Fähndrich S, Biertz F, Karch A, et al., COSYCONET investigators. Cardiovascular risk in patients with alpha-1-antitrypsin deficiency. *Respir Res* 2017; **18**:171.

42 Curjuric I, Imboden M, Bettschart R, et al. Alpha-1 antitrypsin deficiency: from the lung to the heart? *Atherosclerosis* 2018; **270**:166–172.

43 Nakanishi T, Forgetta V, Handa T, et al. The undiagnosed disease burden associated with alpha-1 antitrypsin deficiency genotypes. *Eur Respir J* 2020; **56**:2001441.

44 Tilson MD, Roberts MP. Molecular diversity in the abdominal aortic aneurysm phenotype. *Arch Surg* 1988; **123**:1202–1206.

45 Cohen JR, Sarfati I, Ratner L, Tilson D. Alpha 1-antitrypsin phenotypes in patients with abdominal aortic aneurysms. *J Surg Res* 1990; **49**:319–321.

46 Schardey HM, Hernandez-Richter T, Klueppelberg U, Tutsch-Bauer E, Lauterjung L. Alleles of the alpha-1-antitrypsin phenotype in patients with aortic aneurysms. *J Cardiovasc Surg (Torino)* 1998; **39**:535–539.

47 Elzouki AN, Eriksson S. Abdominal aortic aneurysms and alpha 1-antitrypsin deficiency. *J Intern Med* 1994; **236**:587–591.

48 St Jean P, Hart B, Webster M, et al. Alpha-1-antitrypsin deficiency in aneurysmal disease. *Hum Hered* 1996; **46**:92–97.

49 Hernandez-Richter T, Schardey HM, Klueppelberg U, Tutsch-Bauer E, Lauterjung L, Schildberg FW. Is heterozygote alpha 1-antitrypsin deficiency a risk factor in the etiology of aortic aneurysm? *Chirurg* 1997; **68**:513–516.

50 Elzouki AN, Rydén Ahlgren A, Länne T, Sonesson B, Eriksson S. Is there a relationship between abdominal aortic aneurysms and alpha 1-antitrypsin deficiency (PiZ)? *Eur J Vasc Endovasc Surg* 1999; **17**:149–154.

51 Ahlgren AR, Piitulainen E, Sonesson B, Länne T. Changes in aortic wall stiffness in men with alpha 1-antitrypsin deficiency. *Eur J Vasc Endovasc Surg* 1997; **14**:252–257.

52 Knapik-Kordecka M, Doskocz R, Adamiec R. Stezenie alpha 1-antytrypsyny a czynniki ryzyka miazdzycy u chorych z tetniakiem aorty brzusznej [Alpha-1 antitrypsin concentration and atherosclerosis risk factors in patients with abdominal aortic aneurysm]. *Pol Merkur Lekarski* 2003; **14**:425–427.

53 Vega de Céniga M, Esteban M, Quintana JM, et al. Search for serum biomarkers associated with abdominal aortic aneurysm growth: a pilot study. *Eur J Vasc Endovasc Surg* 2009; **37**:297–299.

54 Pulinx B, Hellenthal FA, Hamulyák K, van Dieijen-Visser MP, Schurink GW, Wodzig WK. Differential protein expression in serum of abdominal aortic aneurysm patients: a proteomic approach. *Eur J Vasc Endovasc Surg* 2011; **42**:563–570.

55 Pini L, Peroni M, Zanotti C, et al. Investigating the link between alpha-1 antitrypsin deficiency and abdominal aortic aneurysms. *Ann Vasc Surg* 2021; **77**:195–201.

56 Gaglio PJ, Regenstein F, Slakey D, et al. Alpha-1 antitrypsin deficiency and splenic artery aneurysm rupture: an association? *Am J Gastroenterol* 2000; **95**:1531–1534.

57 Bofinger A, Hawley C, Fisher P, Daunt N, Stowasser M, Gordon R. Alpha-1-antitrypsin phenotypes in patients with renal arterial fibromuscular dysplasia. *J Hum Hypertens* 2000; **14**:91–94.

58 Perdu J, Gimenez-Roqueplo AP, Boutouyrie P, *et al.* Alpha 1-antitrypsin gene polymorphisms are not associated with renal arterial fibromuscular dysplasia. *J Hypertens* 2006; **24**:705–710.

59 Mazodier P, Elzouki AN, Segelmark M, Eriksson S. Systemic necrotizing vasculitides in severe alpha 1-antitrypsin deficiency. *QJM* 1996; **89**:599–611.

60 Savige JA, Chang L, Cook L, Burdon J, Daskalakis M, Doery J. Alpha 1-antitrypsin deficiency and antiproteinase 3 antibodies in antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. *Clin Exp Immunol* 1995; **100**:194–197.

61 Callea F, Gregorini G, Sinico A, *et al.* alpha 1-antitrypsin (AAT) deficiency and ANCA-positive systemic vasculitis: genetic and clinical implications. *Eur J Clin Invest* 1997; **27**:696–702.

62 Wakefield D, Easter J, Breit SN, Clark P, Penny R. Alpha 1 antitrypsin serum levels and phenotypes in patients with retinal vasculitis. *Br J Ophthalmol* 1985; **69**:497–499.

63 Audrain MA, Sesboüé R, Baranger TA, *et al.* Analysis of antineutrophil cytoplasmic antibodies (ANCA): frequency and specificity in a sample of 191 homozygous (PiZZ) alpha 1-antitrypsin-deficient subjects. *Nephrol Dial Transplant* 2001; **16**:39–44.