Blood coagulation and fibrinolysis in aortic valve stenosis: links with inflammation and calcification

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Summary
Aortic valve stenosis (AS) increasingly afflicts our aging population. However, the pathobiology of the disease is still poorly understood and there is no effective pharmacotherapy for treating those at risk for clinical progression. The progression of AS involves complex inflammatory and fibroproliferative processes that resemble to some extent atherosclerosis. Accumulating evidence indicates that several coagulation proteins and its inhibitors, including tissue factor, tissue factor pathway inhibitor, prothrombin, factor XIII, von Willebrand factor, display increased expression within aortic stenotic valves, predominantly on macrophages and myofibroblasts around calcified areas. Systemic impaired fibrinolysis, along with increased plasma and valvular expression of plasminogen activator inhibitor-1, has also been observed in patients with AS in association with the severity of the disease. There is an extensive cross-talk between inflammation and coagulation in stenotic valve tissue which contributes to the calcification and mineralisation of the aortic valve leaflets. This review summarises the available data on blood coagulation and fibrinolysis in AS with the emphasis on their interactions with inflammation and calcification.

Keywords
Aortic stenosis, blood coagulation, fibrinolysis, fibrin, tissue factor

Pathobiology of aortic valve stenosis
Valvular heart diseases represent an important public health burden worldwide. With decrease in the incidence of rheumatic heart disease, aortic valve stenosis (AS) has now become the most common valvular disease in Western countries. Its prevalence increases with age, affecting about 0.2% in 55- to 64-year-old individuals (1) and 2–3% in subjects older than 65 years (2). Historically, calcific AS had been viewed as a "degenerative" disease of the elderly, except subjects with bicuspid aortic valve occurring in 1% of the general population who are prone to earlier development of AS. Recent studies have demonstrated that development and progression of AS are linked to common cardiovascular risk factors, including arterial hypertension (3), smoking (4), hypercholesterolaemia (5) and diabetes mellitus (6). It is still controversial if there are any genetic risk factors predisposing to AS, as they are in atherosclerosis (7). Not surprisingly, about 50% of AS patients have concomitant coronary artery disease (CAD); however, every second patient with AS is free of clinically overt atherosclerosis (8).

The normal aortic valves are composed of several tissue layers: 1) the ventricularis, on the ventricular side of the leaflet, composed of elastin-rich fibres aligned in a radial direction, 2) the spongiosa, a layer of loose connective tissue at the base of the leaflet, composed of fibroblasts, mesenchymal cells, and a mucopolysaccharide-rich matrix that permits a necessary rearrangement of the collagen and elastin layers throughout the cardiac cycle, 3) the fibrosa, on the aortic side of the leaflet, which is subjected to high shear stress and therefore consists primarily of fibroblasts and collagen fibres arranged circumferentially. An endothelial layer covers the entire external surface of the valve at the blood-contacting surfaces (9, 10) (▶Figure 1A).

In the normal aortic valves the predominant cell type are the spindle-shaped mesenchymal, fibroblast-like cells (characterised by vimentin expression) named valvular interstitial cells (VICs) (11). Single macrophages and T cells occur occasionally in all three layers of the aortic valves (12). Normally, VICs secrete extracellular matrix components (ECM), including collagen, fibronectin and glycosaminoglycans (13), as well as degrading enzymes, in particular several matrix metalloproteinases (14).

During physiological remodelling, myofibroblasts within the aortic valve leaflets are eliminated by apoptosis (15). However, under ongoing stimulation this process is dysregulated, and subsequently myofibroblasts persist producing ECM that leads to pathological fibrosis within the valve (15).

The pathogenesis of AS involves a specific progressive fibrosis and calcification with the gradual reduction of the valve orifice.
The current concept of AS focuses on a role of intravalvular inflammation with a major involvement of accumulating macrophages within the diseased leaflets, which resembles atherosclerotic vascular disease. Enhanced fibrosis and inflammation contribute to aortic valve remodelling and massive calcification, a typical feature of advanced AS (Figure 1B). Despite numerous pathobiological similarities between AS and atherosclerosis (16), including cholesterol accumulation, infiltration of inflammatory cells, neovascularisation, and ECM remodelling, AS is different from CAD in terms of the underlying mechanisms. Growing evidence indicates that the VICs appear to play a key role in specific pathologic alterations in the aortic valve, being responsible for most differences in the pathobiology between AS and atherosclerosis (17). Such cells are not present in atherosclerotic lesions.

Aortic valve (AV) calcification is mediated by VICs differentiation and proliferation into an ossification phenotype induced by an interplay of several mechanisms that includes upregulation of procalcific markers, biomechanical forces, shear stress, inflammatory markers and growth factors. At the beginning of the AV calcification processes, nodules are formed near the margins of the valvular cusps, in the regions of oxidised lipids (18) (sclerosis). As the disease advances, these calcified nodules extend through the cusps, leading to haemodynamic obstruction (stenosis). A subpopulation of the VICs becomes activated upon valve injury and differentiates to express either a myofibroblastic or an osteoblast-like phenotype and are characterised by specific markers, i.e. α-actin for myofibroblasts and alkaline phosphatase, osteopontin (OSP), bone sialoprotein and bone morphogenetic proteins-2 and -4 (BMP-2, -4) for osteoblast-like fibroblasts (19).
The activated myofibroblasts, together with T cells and macrophages, are largely involved in the accelerated fibrosis and calcification in part through their key role in the activation of proinflammatory cytokines, matrix metalloproteinases and calcigeneic proteins (e.g. OSP, osteocalcin, BMP-2,-4, osteochondrogenic transcription factor, chondrocyclic transcription factor Msx2) (20).

Mechanisms that contribute to increased calcification are not clear, but recent data suggest that nonlaminar flow patterns on the aortic side of the valve, reactive oxygen species (ROS), and inflammatory cytokines may be a key initiators of BMP2/4 secretion from the valvular endothelium (21, 22).

BMPs stimulate the calcification of the valve leaflets by activating Smad1/5/8 and Wnt/β-catenin signalling pathways. Smad activation induces the expression of the master osteoblast transcription factor runt-related 2 (Runx2). Runx2 increases the expression of proteins directly associated with calcification and osteoblasts phenotype (23, 24). BMPs also increase the expression of the Msx2 that is important for intra-membranous bone formation.

Wnt/β-catenin signalling pathway is also activated by BMPs to increase the expression of alkaline phosphatase, which facilitates calcification (Figure 1C). In addition, a number of cytokines can activate these signalling pathways, which also leads to increased aortic valve calcification and dysfunction (25).

It is also known that aortic valves calcification is accelerated by chronic kidney disease (26), diabetes mellitus (27), low vitamin D levels (28) and low serum calcium levels (the so-called calcification paradox) (29).

**Blood coagulation in AS**

Recently, several lines of experimental evidence have suggested an active role of the blood coagulation proteins in the regulation of early atherosclerosis and its further progression (30–33). It is thought that the abundance of coagulation factors within early atherosclerotic lesions and local generation of thrombin and consequently fibrin might represent a primary protective mechanism against vascular injury (30). However, the inflammatory environment within the arterial wall, supported by coagulation-mediated actions such as cellular adhesion, migration and angiogenesis, may maintain local thrombin generation and promote platelet- and macrophage-derived coagulation proteins, which are involved in the production of pro-inflammatory cytokines, monocyte recruitment into the atherosclerotic plaque and proliferation of vascular smooth muscle cells, thereby contributing to disease progression (30) (Table 1). Furthermore, fibrinolysis and fibrin degradation products may impair endothelial cell function, leading to increased permeability and endothelial cell migration. The split products of fibrin also enhance chemotaxis of monocytes, and induce interleukin-6 production by monocytes (31).

Available data show that under homeostatic conditions, vascular endothelial cells constitutively express and produce both anti-thrombotic and thrombotic mediators to balance haemostatic effects and prevent thrombus formation. These observations provide the rationale for the hypothesis of significant role of altered haemostatic balance in the early and advanced stages of AS. If so, is there clinical evidence for increased thromboembolic risk in AS, as clearly shown in CAD and other atherosclerotic vascular diseases. Otto et al. demonstrated an increased risk of cardiovascular events, largely thromboembolic by nature, in AS patients (18, 34) and they appear not to be associated solely with concomitant atherosclerosis or comorbidities, especially atrial fibrillation.

Is there evidence for the presence of coagulation proteins within the diseased aortic valves? Indeed, there is growing evidence that various procoagulant and/or fibrinolytic factors exhibit increased expression within the valvular tissue obtained from the AS patients, with or without concomitant clinically evident atherosclerosis. Moreover, increasing evidence points to extensive

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**Figure 1: Continued**

![Figure 1: Continued](https://www.thrombosis-online.com/citations/114.2/2015/Natorska_Undas_Haemostasis_and_aortic_stenosis_219.png)
cross-talk between inflammation and coagulation in AS (35–40). It appears that rather than being one-way process with inflammation leading to enhanced blood coagulation, both systems closely interact, whereby the latter can also substantially modulate inflammatory activity, via among others by activation of specific cell receptors on mononuclear or endothelial cells, which may affect cytokine production (41).

There is evidence that the initiation of pathologic lesions leading to AS is associated with partial denudation of valve surface endothelium (41), which results in impaired anticoagulant and anti-aggregatory effects (42). Monocytes recruited into valves transformed into macrophages synthesise large amounts of TF, the principal initiator of coagulation in vivo (12). As shown within calcified tissues there is an amount of prothrombin (27, 37), thrombin (36), FXIII (38) and fibrin (37), which suggests that other components of the blood coagulation cascade may originate from circulation or being produced in loco by myofibroblasts and/or macrophages like in atherosclerosis, as elegantly shown by Borissoff (43).

Several lines of evidence suggest that aortic stenosis is not simply a mechanical problem limited to the valve leaflets. The disease affects the upstream left ventricle and the downstream systemic vasculature, as well as the valve itself (44). Thus, stenotic valves alter haemodynamic conditions with the subsequent haemostatic abnormalities, which are in part reflected in systemic inflammation, for example elevated fibrinogen (45), a more marked activation of blood coagulation and fibrinolysis (46, 47).

Moreover, patients with AS free of coronary artery disease have decreased endothelial function parameters (48), which leads to cardiovascular events concluding myocardial ischaemia (49). Another possibility might be that diseased endothelium increases risk of thromboembolic events in AS patients; an association between venous thromboembolism and aortic arch calcifications has been shown (50). Furthermore, dilation of the aortic sinuses and ascending aorta frequently accompanies calcific AS and increases thromboembolic risk (51).

This review paper summarises the current evidence for associations between haemostasis and AS with focus on a role of blood coagulation and fibrinolysis in the pathophysiology of this more and more common disease.

### Tissue factor

Tissue factor (TF) is constitutively expressed by among others vascular smooth muscle cells and fibroblasts (52). TF has been identified in atherosclerotic plaques and its role in the progression of cardiovascular disease as well as its thromboembolic complications has been suggested (53).

Expression of TF within the aortic valve leaflets has been reported for the first time in a model of aortic valve sclerosis in New Zealand White rabbits (35). TF antigen has been identified in the lesions at the aortic side of the aortic valve and its amount increased almost three-fold in animals with aortic valve sclerosis compared to controls (35). In rabbits, TF expression was associated with massive macrophage infiltration of the diseased valves (35).

In 2009, TF has been identified within the stenotic aortic valves of patients with moderate-to-severe AS without clinically overt atherosclerosis or CAD (12). The percentage of TF-positive stained area in patients with AS was similar to that observed in the animal model (35) (20 ± 3 % vs 24.6 ± 6.93 %, respectively). In humans like in rabbits, TF was expressed mainly at sites of macrophage infiltrations, suggesting their vital role in the local TF synthesis in AS, and that TF expression is closely linked to valvular inflammation. However, TF was also expressed in areas of the leaflets in which macrophages were sparse or even absent (12). We hypothesized that in such regions TF expression might occur in myofibroblasts.

It has been shown that the severity of AS is positively associated with TF expression within the diseased aortic valves. In AS patients with high transvalvular gradients, there were positive associations between the percentage of TF-positive areas and maximal and mean transvalvular gradients, which might suggest that abnormal haemodynamics of this valvular defect enhances TF expression within the diseased leaflets (12). TF was associated with
not only inflammatory valvular infiltrates but also with calcified areas of the valve in AS patients (12, 36); the highest amount of TF was found in the extensively calcified regions in association with alkaline phosphatase activity (36), a marker for the onset of osteogenic differentiation (54), that is necessary to achieve tissue mineralisation. On the other hand, OSP, a potent inhibitor of the calcification processes (55) colocalised with valvular TF and calcium deposits within calcified human aortic valves (56, 36).

In vitro and in vivo studies showed that TF increases vascular endothelial growth factor (VEGF) production and thereby induces angiogenesis (57). Breyne et al. (36) showed that in stenotic aortic valves neovessel formation was associated with the expression of VEGF, which was significantly higher in the calcified areas. Moreover, valvular TF and VEGF were correlated, suggesting the involvement of TF in the valvular neovascularisation (36).

It has been shown that valvular TF is inhibited by a marked expression of tissue factor pathway inhibitor (TFPI) within the stenotic aortic valves (27, 36) and that valvular TFPI colocalises with both TF- and prothrombin-positive areas at the aortic side of the leaflets (27). In turn, Breyne et al. (36) found over-expression of TFPI in aortic valvular tissue samples of the AS patients. This resulted in a higher TF/TFPI ratio in the calcified regions, which indicates a local excess of TF (36).

Interestingly, Lusczak at al. (58) have shown that there are patients with severe AS, who have detectable plasma TF coagulant activity (0.4–3.4 pmol/l). The AS patients with detectable active TF in their blood had higher maximal and mean transvalvular gradients, compared with those without such activity in plasma (58). Moreover, the AS patients with detectable active TF had higher thrombin generation than in the remainder (58). This intriguing observation suggests that advanced AS like acute coronary syndromes and stable CAD (59) is characterised by a procoagulant state with the presence of tiny amounts of active TF in circulating blood, which might increase the risk of thromboembolic events.

Taken together, available data indicate that TF is probably implicated in calcification and mineralisation within the aortic valve leaflets, thus contributing in the progression and severity of AS (▶Figure 2A).

Prothrombin and thrombin

Thrombin is generated at the site of valvular injury (36). A number of thrombin-mediated actions, which could be involved in AS progression, might include endothelium dysfunction (60), activation of platelets, endothelial cells, macrophages, and vascular smooth muscle cells (61), enhancement of leukocyte migration (62) and angiogenesis (63).

It has been shown that both prothrombin antigen (27) and mRNA (38) were detected in aortic valves from AS patients, which suggests that thrombin could be formed locally. Of note, prothrombin was colocalised with TF and TFPI, however areas positive for prothrombin were also visible in other TF-free regions. Moreover, valvular prothrombin and TF showed a positive correlation (27). There were positive correlations of valvular prothrombin with maximal and mean transvalvular gradients, markers of the severity of AS (27).

Valvular α-thrombin expression has also been reported in human stenotic aortic valves, mostly on the aortic side of the leaflets (36). Thrombin expression was colocalised with TF and OSP expression (36). Moreover, α-thrombin significantly correlated with TF levels and with TF/TFPI ratio in calcified aortic valves (36). Since thrombin expression showed correlation with OSP that is cleaved by thrombin and its thrombin-cleaved N-terminal form is involved in inflammation (55), it has been suggested that thrombin might potentially enhance the inflammatory reactions within stenotic valves (36). Interestingly, Al-Jallad et al. (64) showed that thrombin treatment significantly increases osteoblasts differentiation. Possibly, a similar process can take place in stenotic aortic valves.

In AS patients systemic thrombin generation, as reflected by prothrombin fragment F1+2 levels, has been shown to be associated with areas positive for valvular fibrin (37). Therefore, it is likely that increased shear stress generated by the AS valves predisposes to a prothrombotic state, reflected by heightened thrombin generation and platelet activation (65), which might additionally enhance the disease progression. Based on the available data, thrombin and prothrombin are involved in AS development/progression, although their contribution remains to be established.

Fibrinogen and fibrin

Fibrin as the final product of the blood coagulation has been demonstrated to be a consistent component of atherosclerotic plaques that may promote their growth (66). Fibrin was also observed within the aortic valves of AS patients without clinically overt atherosclerosis or CAD, where it was present in large amounts on the surface and within stenotic valves (37). Two thirds of the area positive for fibrin was identical to that positive for TF, suggesting that conversion of fibrinogen to fibrin may occur within the valve leaflets (37).

Fibrin-positive area within the valve leaflets showed positive correlations with maximum and mean transvalvular gradients in patients with severe AS, free of CAD, which indicates that high pressure gradient in AS patients can induce the prothrombotic state (37).

Given no associations between plasma fibrinogen and the percentage of fibrin-positive areas or the fibrin layer thickness within the valve leaflets in AS patients (37), it can be concluded that accumulation of fibrin within the leaflets is rather the consequence of complex coagulant processes on the surface and within the leaflets, associated with long-standing progressive valve tissue damage.

It has been previously demonstrated that similar plasma fibrinogen levels can be associated with different plasma fibrin clot properties due to modulation of fibrinogen features by several factors, e.g. enhanced inflammation and augmented thrombin production (67–79). It is known that dense fibrin clots composed of thin fibres are relatively resistant to lysis (70–72). However, we
failed to show that formation of more compact plasma fibrin clots assessed ex vivo predisposes to more abundant fibrin accumulation in the AS valves (37).

Interestingly, the thicker fibrin fibres, the thicker fibrin layer on the aortic side of the valves obtained from AS patients (37). It might be suggested that altered plasma fibrin clot formation and structure may contribute to fibrin accumulation detected in AS valves regardless of plasma fibrinogen levels.

Potential mechanisms linking fibrin accumulation with AS involve the contribution of fibrin to the total mass of extracellular matrix, which may increase the lesion growth, promote the local entrapment of circulating monocytes and support the local proliferation and migration of inflammatory cells (Figure 2B).

It can be speculated that blood coagulation and the resultant fibrin formation are involved in the composition of stenotic valvular leaflets in AS patients, and thus they might contribute to the

![Figure 2: Potential mechanisms underlying a role of tissue factor (A) and fibrin (B) in the development and progression of aortic valve stenosis.](image-url)
development and progression of AS, in a similar manner as observed in the atherosclerotic plaque.

**Factor XIII**

In 2012 the expression of factor (F)XIIa, mainly on the aortic side of AS leaflets, similarly to fibrin, was reported in patients with moderate-to-severe AS without clinically overt atherosclerotic vascular disease (38). Relative quantification of mRNA expression showed up-regulation of FXIII-A mRNA in stenotic valves, which positively correlated with FXIII and fibrin expression (38). FXIII was predominantly presented in CD163-positive macrophages (alternatively activated macrophages), suggesting that these cells are a major source of FXIII-A within the leaflets (38). This observation was supported by the fact that FXIII-A mRNA was correlated with valvular macrophages infiltration. It is known that FXIII-A is present in the cytoplasm of the monocytes/ macrophages (73) and its expression may be up-regulated in alternatively activated macrophages (74). Although secretion of FXIII by macrophages has not been proven, it has been demonstrated that FXIII-A might be secreted by macrophages on a nonclassical pathway of extracellular secretion (75). FXIII can also modulate the amount of fibrin within the AS valves in association with the extent of valvular macrophage infiltration (38). It is likely that FXIII-A may be released from damaged alternatively activated macrophages in the proinflammatory milieu and thus enhances fibrin deposition within stenotic valves. Moreover, FXIII-A might regulate extracellular matrix deposition along with transglutaminase 2, which also plays a role in osteoblast differentiation (76) and thus can contribute to valve calcification. Interestingly, increased plasma FXIII activity was also reported in AS patients without clinically overt atherosclerosis and showed association with the disease severity (38). Moreover, elevated plasma FXIII activity in patients with AS was associated with a more abundant presence of valvular fibrin (38). This supports the hypothesis that systemic and local FXIII activity might be involved in the development of advanced stages of AS (38).

**Fibrinolysis**

Plasminogen activators, tissue type plasminogen activator (t-PA), and urokinase-type plasminogen activator (u-PA), convert plasminogen into plasmin (77). The plasmin-generating activity of t-PA and u-PA is controlled by plasminogen activator inhibitor-1 (PAI-1). Among all fibrinolysis components, PAI-1 is of key importance in the pathophysiology of cardiovascular diseases (78).

In 2013 impaired fibrinolysis measured in a global plasma gradient and the deficiency of large vWF multimers was accompanied by increased thrombin generation and platelet activation in various genetic and/or acquired factors are more likely to develop severe forms of AS.

In patients with AS prolonged fibrinolysis was associated with increased fibrin layer within aortic valves and larger calcium deposits resulting in greater thickness of the stenotic valves (79), indicating a relationship between overall efficiency of clot lysis in circulating blood and the composition of the valves in AS patients. Moreover, hypofibrinolysis showed correlations with transvalvular gradients and aortic valve area. Given available data we speculated that subjects with slower plasma fibrin clot lysis are predisposed to faster progression of AS and tend to develop more severe forms of this disease.

Recently Kochtebane et al. (40) have demonstrated that 69% of the human AS valves showed elevated PAI-1 expression. They observed that cultured AS valve cells released u-PA, t-PA, and PAI-1 in the conditioned media after 24 hours of incubation. Moreover, t-PA and PAI-1 were strongly correlated (40).

We also observed that mast cells represent an additional source of PAI-1 within the stenotic aortic valves (80). It is known that in chronic inflammation, profibrinolytic, antithrombotic resting mast cells, that produce active t-PA, change into an antifibrinolytic, prothrombotic phenotype secreting PAI-1 (80). It might be speculated that mast cells could be involved in locally impaired fibrinolysis, fibrin and collagen deposition, and thus AS severity. This hypothesis is in line with the observation that there is a negligible amount of tPA within stenotic aortic valves (40, 79).

Concluding, it appears that the high levels of valvular PAI-1 are associated with valve calcification and inflammation. It remains to be established to what extent local and systemic hypofibrinolytic mechanisms cooperate in AS and whether any intervention in fibrinolysis may affect the progression of this disease.

**von Willebrand factor**

von Willebrand factor (vWF) is essential for platelet-subendothelial adhesion and platelet-to-platelet interactions as well as platelet aggregation at increased shear stress. The largest high-molecular-weight multimers (HMWM) of vWF are most effective in platelet-mediated haemostasis (81).

Several studies demonstrated that bleeding tendency, mostly mucocutaneous and gastrointestinal episodes (Heyde’s syndrome), is observed in up to 20% of patients with severe AS (82). A major mechanism underlying the link between AS and bleeding tendency is commonly perceived as a deficiency in HMWM of vWF, i.e. acquired type 2A von Willebrand disease, due to enhanced proteolysis of vWF multimers (83) generated by high shear stress. Surgical correction of AS has been shown to normalise the distribution of vWF HMWM (82). However, not all bleeding episodes that normalised after aortic valve replacement are associated with decreased amounts of vWF HMWM in circulating blood (84).

In AS patients a marked reduction in the %HMWM and the vWF abnormalities were associated with increased transvalvular gradient and the deficiency of large vWF multimers was accompanied by increased thrombin generation and platelet activation in
moderate-to-severe AS (85). Interestingly, AS patients with low percentage of HMWM had elevated thrombin generation markers and platelet activation markers such as β-thromboglobulin and soluble CD40 ligand (85), which may compensate to some extent the deficiency in HMWM and decrease the risk of bleeding in AS patients.

Recently in loco expression of vWF has been observed within porcine aortic valves (39). Moreover, histamine-stimulated porcine aortic valve endothelial cells released vWF protein and ADAMTS13 (A Disintegrin And Metalloproteinase with Thrombospondin) into culture medium and vWF significantly increased valvular interstitial cell nodule formation and calcification (39), suggesting their contribution in the development/progression of AS.

Conclusions

Based on experimental data from animal models and patient studies, increased expression of several coagulation (in particular TF) and fibrinolysis proteins occurs in stenotic aortic valves (Figure 3), together with increased activation of blood clotting, resulting in the formation of intracardiac thrombi that can lead to valve obstruction, embolic events, and systemic complications.

![Figure 3: Valvular expression of proteins involved in blood coagulation and fibrinolysis in patients with aortic valve stenosis. A) Graph showing the expression of coagulation and fibrinolysis proteins revealed in loco within aortic valve tissue; (*) unpublished data by A. Undas; (†) see reference 49; (‡) see reference 12; (§) see reference 25; (¶) see reference 26; (††) see reference 28; (‡‡) see reference 30; (/) inhibition. B) Representative micrographs of immunoreactive areas of fibrin, tissue factor (TF) (green) co-localised with tissue factor pathway inhibitor (TFPI) (orange), plasminogen activator inhibitor-1 (PAI-1) and factor Xlla. 500 µm; * aortic side of the human valve leaflet. Original magnification ×10.](attachment:figure3.png)
coagulation and impaired fibrinolysis in circulating blood of patients with AS (86). Available data suggest that expression of coagulation proteins within aortic valves is associated with increased local inflammation and mineralisation, significantly contributing to the disease progression. However, a role of local and systemic activation of blood coagulation and fibrinolysis in the initiation and progression of AS is still unclear.

Although there are mechanistic similarities between atherosclerosis and AS, it is not simply atherosclerosis of the valve. Whereas the hallmark of atherosclerosis is the lipid-rich plaque, the hallmark of AS is severe, progressive calcification of the leaflets that stiffens leaflets and leads to haemodynamic obstruction. It seems that the major difference in the pathogenesis between AS and atherosclerosis represents a significant contribution of myofibroblasts in the former disease. Myofibroblasts are absent in atherosclerotic lesions. Since myofibroblasts phenotypically are similar to fibroblasts, which constitutively express TF (52), it is likely that those cells largely contribute to local activation of coagulation cascade. It is also possible that myofibroblasts may alter secretory activity of valvular macrophages.

Moreover, it seems that in AS, in contrast to atherosclerosis, not inflammation but the loss of anti-aggregatory properties of valvular endothelium and impaired nitric oxide (NO) signalling under high shear stress conditions play a key role in the disease development (87).

Miller et al. (22) showed that not only reactive oxygen species (ROS) are increased in calcifying valve leaflets but the primary mechanism of ROS production, uncoupled NO synthase activity, might be tissue-specific and distinct from that seen in vascular atherosclerotic lesions. In AS oxidative stress seems to play an important role in matrix remodelling and myofibroblast transformation toward osteoblastic phenotypes and NO resistance implies a pro-thrombotic milieu for AS patients (88).

Trials based on AS treatment with statins (89), angiotensin II inhibitors (90) and bisphosphonates (91) provided conflicting results. Vitamin K antagonists (VKAs) such as warfarin have been shown to be associated with procalcific effects and AS progression (92, 93). VKA therapy inhibits vitamin K–dependent gamma-carboxylation of glutamine residues of a number of proteins, including matrix GLA protein (MGP), which acts as vitamin K–dependent inhibitor of BMP-2 (94). Since valvular expression of BMP-2 by myofibroblasts and preosteoblasts was shown (95) it is postulated that vitamin-K antagonists may promote valvular calcification via BMP-2-induced differentiation of myofibroblasts toward an osteochondrogenic phenotype (92).

It might be speculated that non-vitamin K oral anticoagulants, dabigatran and factor Xa inhibitors rivaroxaban and apixaban might be useful in patients with early or mild stenosis to prevent its further progression. Recently dabigatran has been shown to reduce the development and increased stability of atherosclerotic lesions and endothelial function in apolipoprotein-E deficient mice (96, 97). It seems that these plaque-stabilising effects might be mediated by reducing the pro-inflammatory cytokines and matrix metalloproteinase production as well as decreasing macrophage infiltration (95). Additionally, beneficial effects of dabigatran on endothelial function with reduced oxidative stress and ROS production were demonstrated (96). The pharmacologic inhibition of factor XII activation could represent a potential therapeutic target of atherosclerosis as suggested by Borissoff (30), thus the use of factor XII might be also useful in AS treatment. Given similarities between AS and atherosclerosis, slower AS development mediated by anticoagulant effects might be hypothesised.

Further studies on coagulation, inflammation and calcification in AS might offer new therapeutic strategies aimed at the treatment and/or limitation of this valvular defect progression.

Conflicts of interest
None declared.

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