# Inflammatory regulatory mechanisms and targeted therapy of antineutrophil cytoplasmic antibodies in atherosclerosis (Review)

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**Abstract.** Atherosclerosis is the core pathological basis of cardiocerebrovascular diseases, and inflammatory response runs through the course of its occurrence, progression, and adverse events. Antineutrophil cytoplasmic antibodies (ANCAs) are autoantibodies targeting the lysosomal components in the cytoplasm of neutrophils and monocytes, and their association with atherosclerosis and pathogenic effects have become a research hotspot in cardiovascular medicine. The present review systematically examined the core molecular mechanisms of ANCA-mediated atherosclerosis, focusing on analyzing the pro-atherogenic effects of ANCAs through the regulation of monocyte dysfunction, induction of the formation of neutrophil extracellular traps, and activation of the synergistic complement-platelet pathway, and clarified the subtype-specific pathogenic pathways mediated by myeloperoxidase-ANCAs and proteinase 3-ANCAs. The present review also summarized the clinical evidence linking ANCA positivity to the risk of atherosclerosis, plaque characteristics, and clinical outcomes and explores the precise intervention strategies for targeting ANCA-related pathways in atherosclerosis. Finally, it highlighted the limitations of current research and future directions to provide a theoretical reference and novel insights for the risk stratification of populations at high risk of atherosclerosis and the precise management of residual inflammatory risk.

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## 1. Introduction

Atherosclerosis, characterized by the formation of lipid-rich fibrous plaques within the arterial intima, is the underlying pathological basis of cardiovascular and cerebrovascular diseases and is accompanied by inflammation throughout its development, from disease initiation and plaque progression to adverse clinical events (1,2). Previous studies have thoroughly characterized the core pathological cascade, including endothelial dysfunction, oxidative modification of low-density lipoprotein (LDL), monocyte recruitment, foam cell formation, and vascular smooth muscle cell-mediated intimal remodeling (3-9).

Antineutrophil cytoplasmic antibodies (ANCAs), predominantly of the IgG isotype, are autoantibodies directed against lysosomal granule components of neutrophils and monocytes. Proteinase 3 (PR3)-ANCAs and myeloperoxidase (MPO)-ANCAs are the two main pathogenic subtypes closely

linked to small-vessel vasculitis. ANCAs promote vascular injury by inducing excessive neutrophil activation, triggering the release of inflammatory mediators and lytic enzymes, and stimulating neutrophil extracellular trap (NET) formation, thereby establishing a self-amplifying inflammatory cascade (10).

Although the full mechanistic link between ANCAs and atherosclerosis remains unclear, convergent clinical and preclinical data have validated a significant association between the two (11-13). In patients with ANCA-associated vasculitis (AAV), chronic ANCA-mediated immune activation has been shown to drive mononuclear phagocyte system hyperactivity, endothelial damage, and platelet dysfunction, collectively accelerating atherogenesis and increasing cardiovascular risk (14-18). Compared with the general population, patients with AAV exhibit a higher burden of subclinical atherosclerosis and an increased incidence of adverse cardiovascular events, which cannot be fully explained by traditional cardiovascular risk factors (19-22).

The present review systematically examined the inflammatory regulatory mechanisms of ANCAs in atherosclerosis and summarized the clinical evidence of their association with cardiovascular risk, as well as targeted therapeutic strategies, to provide a theoretical reference for cardiovascular risk screening and precision interventions in high-risk populations (Fig. 1).

The novelty of this review is threefold. First, it considers ANCA as a central pathogenic effector and systematically dissects the inflammatory regulatory network underlying ANCA-mediated atherosclerosis, with a detailed comparison of the distinct pathogenic pathways associated with MPO-ANCA and PR3-ANCA. Second, it integrates clinical evidence on plaque phenotypic characteristics and dynamic biomarker monitoring, thereby strengthening the translational clinical value of the review. Third, it provides a comprehensive overview of mechanism-targeted therapeutic strategies and proposes a subtype-oriented investigational framework, offering a research roadmap for precision intervention in ANCA-positive atherosclerosis.

## 2. Core inflammatory regulatory mechanisms of ANCA-mediated atherosclerosis

This section first systematically summarizes the main effector cells, key regulatory pathways, and proatherosclerotic effects of ANCA-mediated atherosclerosis (Table I) to provide an overall framework for the subsequent detailed elaboration of molecular mechanisms.

*Central role of monocyte dysfunction in ANCA-promoted atherosclerosis*. Monocytes are the core effector cells through which ANCAs regulate atherosclerosis onset and progression. Bioinformatics analysis has also confirmed that monocytes are the most abundant activated inflammatory cell population in ANCA-related inflammatory responses (23), and their dysfunction drives the development and progression of atherosclerotic plaques by regulating multiple core links, including vascular inflammation and lipid deposition. According to the differential expression of the CD14 pattern recognition receptor and CD16 Fcγ receptor on the cell surface, human peripheral blood monocytes can be divided into three subsets: Classical monocytes [(CM), $CD14^{++}CD16^{-}$], intermediate monocytes [(IM), $CD14^{++}CD16^{+}$], and nonclassical monocytes [(NCM), $CD14^{+}CD16^{++}$]. Among them, CM highly expresses markers related to phagocytosis, inflammation, and cell movement, IM is mainly involved in cytokine secretion and antigen presentation, and NCM is characterized by vascular patrolling and nucleic acid and virus recognition (24-26). ANCAs can induce characteristic remodeling of monocyte subsets by inhibiting the signaling pathway mediated by the transcription factor nuclear receptor subfamily 4 group A member 1 (NR4A1), hindering the conversion of CM to NCM, and ultimately resulting in an immune imbalance state with an increased proportion of CM, but a decreased proportion of NCM (27). In patients with active AAV, the median proportion of CM in the peripheral blood was shown to be significantly elevated to 91.0% (vs. 82.7% in healthy controls, P=0.0013), whereas NCM were markedly decreased to 5.8% (vs. 14.1% in healthy controls, P=0.0005), with IM at 3.5% (vs. 6.9% in healthy controls, P=0.061) (28), providing direct clinical evidence for ANCA-mediated monocyte subset disturbance.

The nuclear receptor subfamily 4 group A (NR4A) family is widely expressed in vascular smooth muscle cells and macrophages in atherosclerotic plaques, where it negatively regulates macrophage-mediated inflammatory response (29,30). Animal studies have shown that whole-body deletion of NR4A3 can significantly reduce the atherosclerotic plaque burden in apolipoprotein E-deficient mice (31), whereas NR4A1 deficiency can significantly increase the expression of inflammatory cytokines and hypoxia-inducible factor 1α in atherosclerotic lesions of *Ldlr*$^{-/-}$ mice (32). These findings suggest that ANCAs block the conversion of monocyte subsets by inhibiting the NR4A1 pathway, one of the core mechanisms by which it drives vascular inflammation and atherosclerosis progression. Targeted restoration of NR4A1 activity has also become a potential direction for the management of ANCA-positive atherosclerosis. In addition to inducing monocyte subtype imbalance, ANCAs can directly activate the inflammatory activation program of monocytes, promote the secretion of various proinflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6, and amplify the local vascular inflammatory microenvironment (33-36). Under the action of ANCAs, neutrophils can recruit monocytes into the vascular wall tissue through chemotaxis, further inducing the release of proinflammatory mediators, reactive oxygen species (ROS), and lytic enzymes and aggravating the inflammatory cascade and vascular endothelial injury (37). Even in the remission phase, the sustained activation of monocytes mediated by ANCAs can maintain a subclinical chronic inflammatory state, which becomes an important trigger for atherosclerosis onset and progression (14,38).

Abnormal monocyte recruitment into the arterial intima is the key event in the initiation and maintenance of the inflammatory cycle underlying atherosclerosis. ANCAs can enhance the chemotaxis and transendothelial migration ability of monocytes by upregulating the expression of chemokine receptors, such as C-C chemokine receptor type 2 (CCR2) and C-C chemokine receptor type 5 (CCR5), on the surface of monocytes, promoting their infiltration into the arterial intima and then participating in plaque development and

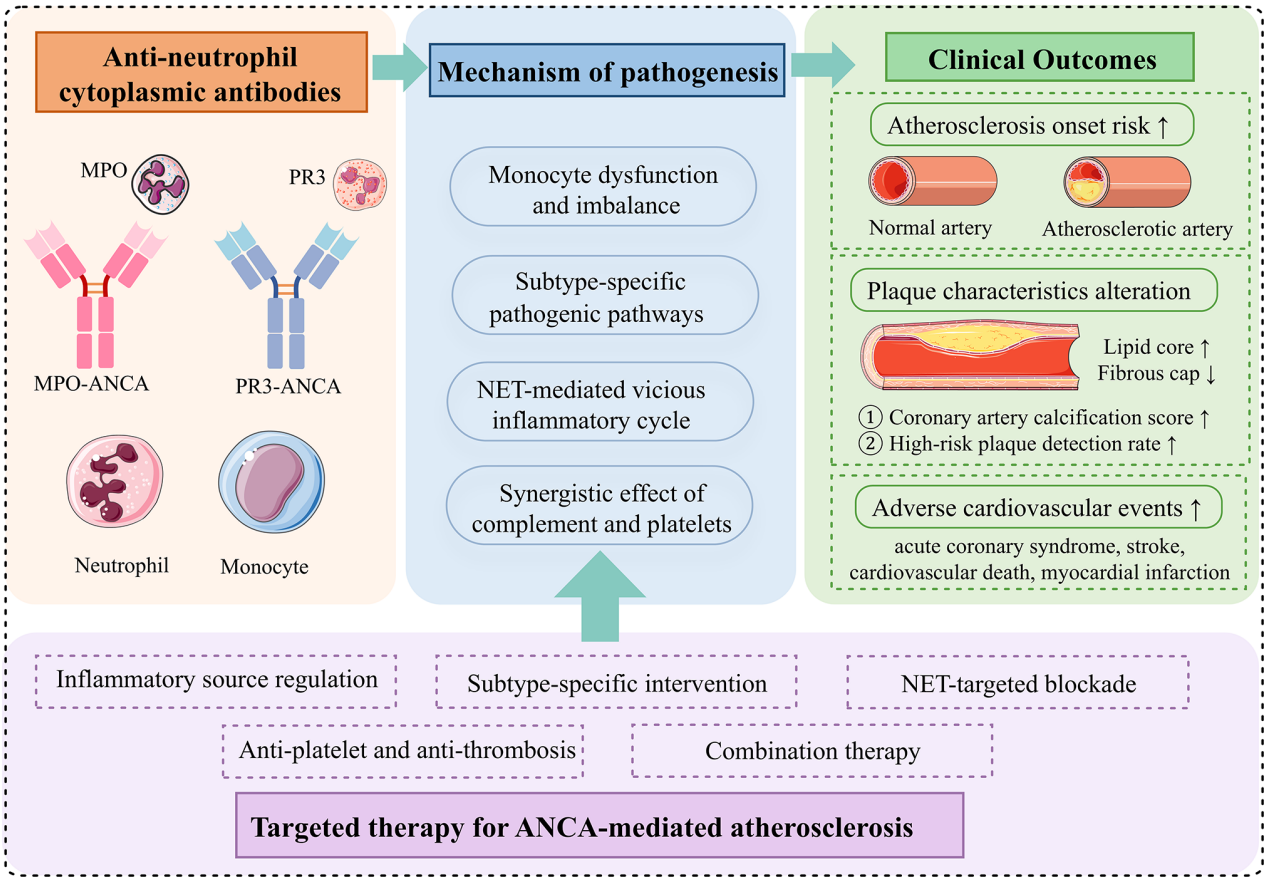



Figure 1. Inflammatory mechanisms, clinical consequences, and therapeutic strategies in ANCA-mediated atherosclerosis. This image illustrates ANCA-driven pathogenic mechanisms, clinical outcomes, and targeted interventions in atherosclerosis. ANCA (MPO-ANCA and PR3-ANCA) trigger monocyte dysfunction, NET-mediated inflammatory cycles, and complement-platelet synergistic activation. These pathways promote accelerated atherosclerosis, characterized by an increased lipid core, a reduced fibrous cap, elevated coronary calcification, and high-risk plaques, ultimately leading to acute coronary syndrome, stroke, or cardiovascular death. The lower panel highlights intervention strategies: Inflammatory source regulation, antiplatelet/antithrombotic therapies, subtype-specific approaches (MPO-ANCA vs. PR3-ANCA), and combination regimens, aiming for precision treatment of ANCA-associated atherosclerotic risk. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; NET; neutrophil extracellular trap.

progression (39). A systematic review and meta-analysis revealed that gene knockout or pharmacological blockade of the CCR2/CCR5 signaling pathway can significantly reduce macrophage infiltration in plaques and lower plaque burden, among which CCR2 plays a more critical and stable role in regulating monocyte recruitment (40). Phenotypic analysis of monocytes from patients with AAV showed that monocytes from patients with PR3-ANCA-positive disease expressed higher levels of CCR2 and CCR5, resulting in significantly enhanced chemotactic and migratory abilities. By contrast, monocytes from patients with MPO-ANCA-positive disease were enriched with genes associated with inflammation, coagulation, and interferon signaling. The two chemokine receptors could jointly drive vascular inflammation and accelerated progression of atherosclerosis through different pathways (28), suggesting that CCR2/CCR5 is an important molecular link between ANCA-mediated autoimmune inflammation and cardiovascular complications of atherosclerosis. ANCAs can also directly participate in the pathogenesis of atherosclerosis by regulating the lipid metabolism of monocytes. ANCAs can significantly enhance the lipid uptake capacity of monocytes, accelerate foam cell formation after the differentiation of monocytes into macrophages, and promote the expansion of the plaque lipid core, an effect independent of traditional cardiovascular risk factors (41,42). Monocyte phenotypic analysis revealed significant upregulation of the expression of lipid metabolism-related genes in monocytes of patients with active AAV, among which lipid metabolism disorder was more prevalent in patients positive for MPO-ANCAs, a finding consistent with their higher risk of cardiovascular events (28). In addition, ANCA-mediated abnormal recruitment of monocytes can lead to impaired efferocytosis of macrophages and disorderly clearance of apoptotic cells, further promoting the release of proinflammatory factors and migration of LDL-cholesterol into the arterial intima, aggravating plaque progression (14,42).

*Subtype-specific pathogenic pathways of atherosclerosis mediated by MPO-ANCAs and PR3-ANCAs.* MPO-ANCAs and PR3-ANCAs promote atherosclerosis progression through distinct subtype-specific pathogenic pathways, resulting in heterogeneous clinical cardiovascular manifestations. The two ANCA subtypes were systematically compared with respect to their pathogenic mechanisms, plaque characteristics, and clinical phenotypes.

MPO-ANCAs participate in atherosclerosis development and progression mainly through an oxidative stress-driven pathway, with MPO as its core effector molecule. MPO can

Table I. ANCA-mediated atherosclerosis: Integrated framework of effector cells, molecular mechanisms, and subtype-specific pathogenic pathways.

| Effector cell | Key regulatory pathway | Pro-atherosclerotic effects | MPO-ANCA specificity | PR3-ANCA specificity | (Refs.) |
|---|---|---|---|---|---|
| Monocytes | i) NR4A1 signaling inhibition-mediated subset remodeling; ii) CCR2/CCR5 chemokine receptor axis; iii) pro-inflammatory cytokine secretion (IL-1β, TNF-α, and IL-6) | i) Induces immune imbalance with elevated CM (91.0%) and decreased NCM (5.8%); ii) enhances chemotaxis and recruitment to arterial intima; iii) promotes macrophage differentiation and foam cell formation; and iv) amplifies local vascular inflammatory microenvironment | ↑ Lipid metabolism-related genes; ↑ sustained inflammation in remission | ↑ CCR2/CCR5 expression; ↑ chemotaxis and transendothelial migration | (14,23-28,33-38) |
| Neutrophils | i) NADPH oxidase-ROS-PAD4 axis-mediated NETosis; ii) FcγR-mediated cell overactivation; and iii) MPO/PR3 antigen exposure and release | i) Releases NETs to form vicious inflammatory cycle and promote autoantibody production; ii) secretes ROS and lytic enzymes to damage vascular endothelium; iii) provides autoantigens to sustain autoimmune response; and iv) induces platelet activation and thrombosis | MPO-containing NETs; ↑ oxidative stress | PR3-containing NETs; ↑ autoantigen presentation | (10,56-67) |
| Platelets | i) Thrombin-PAR pathway; and ii) P-selectin/PSGL-1-mediated PMC formation | i) Forms PMCs to induce monocyte pro-inflammatory/procoagulant phenotypic switch; ii) acts as a physical scaffold to promote plateletadhesion and aggregation; iii) releases pro-inflammatory factors to amplify vascular inflammation; and iv) activates the alternative complement pathway to form an inflammatory amplification loop | ↑ Chronic platelet activation; ↑ VTE risk | ↑ Acute platelet activation; ↑ ACS events | (52,72,74-76) |
| Vascular endothelial cells | i) NF-κB pathway-mediated inflammatory activation; and ii) complement C5a/C5aR axis activation | i) Impairs endothelial barrier integrity and induces apoptosis; ii) upregulates adhesion molecule expression to promote inflammatory cell recruitment; and iii) triggers initiation of the atherosclerotic inflammatory cycle | ↑ Chronic endothelial injury via MPO-mediated oxidative stress | ↑ Acute endothelial injury via tTNF-α mediated NF-κB activation | (49,69-73) |

ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; NR4A1, nuclear receptor subfamily 4 group A member 1; CCR2, C-C chemokine receptor type 2; CCR5, C-C chemokine receptor type 5; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; CM, classical monocytes; NCM, non-classical monocytes; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; PAD4, peptidylarginine deiminase 4; FcγR, fragment crystallizable γ receptor; NETs, neutrophil extracellular traps; PMCs, platelet-monocyte complexes; PAR, protease-activated receptor; P-selectin, platelet selectin; PSGL-1, P-selectin glycoprotein ligand-1; VTE, venous thromboembolism; ACS, acute coronary syndrome; NF-κB, nuclear factor-κB; C5a, complement component 5a; C5aR, complement component 5a receptor.

catalyze the production of hypochlorous acid (HOCl), a strong oxidizing substance, which directly induces the oxidative modification of LDL to form oxidized LDL (ox-LDL), disrupt the structural integrity and barrier function of vascular endothelial cells, and creates conditions for inflammatory cell infiltration (43). HOCl can generate 3-chlorotyrosine, a specific MPO marker, by chlorinating lysine and tyrosine residues of apolipoprotein B-100, with significantly elevated expression in atherosclerotic lesions and positively correlated with ox-LDL levels (44,45). Mass spectrometry and immunohistochemical studies have confirmed that HOCl-mediated protein oxidation products are abundantly enriched in the aortic intima of human atherosclerotic lesions and in LDL recovered from human atherosclerotic plaques (46,47). HOCl-modified LDL can also aggregate and transform into a form with high uptake by macrophages, accelerating foam cell formation (48). In addition to mediating endothelial injury, ox-LDL can directly weaken the stability of atherosclerotic plaques and increase the risk of plaque rupture and acute cardiovascular events (43,46). Furthermore, MPO can catalyze the production of hypothiocyanous acid, which oxidizes tryptophan residues of apolipoprotein A-I, leading to high-density lipoprotein dysfunction and weakening its antiatherosclerotic effect. MPO can also aggravate vascular endothelial dysfunction by consuming nitric oxide and inhibiting nitric oxide synthase activity, further amplifying oxidative stress damage (47).

PR3-ANCAs contribute to atherosclerosis primarily by amplifying the inflammatory cascade in the vascular wall through the nuclear factor-κB (NF-κB) signaling pathway. Rather than directly activating the NF-κB pathway, PR3-ANCAs initiate a signaling cascade through intercellular communication. Following the activation of primed neutrophils, soluble mediators such as TNF-α, are released and activate the NF-κB in the form of p50/p65 heterodimer in glomerular endothelial cells in the absence of direct cell contact. This activation upregulates the expression of proinflammatory factors, such as IL-8, and enhances the adhesion of neutrophils, monocytes, and endothelial cells to promote the infiltration of inflammatory cells into the vascular wall (49). Mechanistically, TNF-α released from ANCA-activated neutrophils binds to TNF receptor 1 on endothelial cells, recruiting the adaptor proteins TNFRSF1A associated via death domain (TRADD) and TNF receptor-associated factor 2 (TRAF2) and activating the kinase transforming growth factor-β-activated kinase 1 (TAK1), which subsequently phosphorylates the IκB kinase (IKK)β subunit of the IKK complex; this leads to inhibitor of κBα (IκBα) phosphorylation and proteasomal degradation, allowing nuclear translocation of the p50/p65 NF-κB heterodimer and transcription of proinflammatory target genes such as *IL-8* (49). Conversely, abnormal activation of the NF-κB pathway can synergistically promote B-cell proliferation, plasma cell differentiation, and PR3 autoantibody production, and the generated autoantibodies can further activate the NF-κB pathway in neutrophils and endothelial cells, forming a vicious cycle of inflammation amplification (50). In addition, NF-κB activation in monocytes can regulate the expression of B-cell activating factor and a proliferation-inducing ligand, maintain the activation of autoreactive B cells and continuous production of ANCAs, and indirectly enhance monocyte-endothelial cell adhesion and vascular inflammatory infiltration (51). Targeting key molecules of the NF-κB pathway can block signal transduction at multiple targets, providing a potential intervention direction for populations at high risk of atherosclerosis with positive PR3-ANCAs.

MPO-ANCAs and PR3-ANCAs lead to significant subtype heterogeneity in atherosclerosis-related cardiovascular risk through differentiated pathogenic pathways. MPO-ANCAs are associated with persistent inflammation and platelet activation. They can activate neutrophils to release inflammatory mediators and promote platelet activation and formation of neutrophil-platelet complexes. These complexes continuously adhere to the vascular endothelium, aggravating chronic endothelial injury and promoting the progression of chronic stable atherosclerosis and directly increasing the risk of thrombosis (52). A clinical cohort study confirmed that the incidence of major adverse cardiovascular events in patients with MPO-ANCA-positive disease was significantly higher than those with PR3-ANCA-positive disease, and MPO-ANCAs remained a potential risk factor for adverse cardiovascular outcomes after adjustment for traditional cardiovascular risk factors (53).

By contrast, PR3-ANCAs are mainly associated with acute inflammatory episodes and enhanced monocyte chemotaxis. They can upregulate the expression of chemokine receptors, Toll-like receptor (TLR)2/4, and integrins on the surface of monocytes and enhance their chemotactic and transendothelial migration ability and recruitment to the vascular wall to trigger acute inflammatory outbreaks. PR3-ANCA-mediated acute inflammatory endothelial injury and plaque instability were revealed to be important aspects of acute cardiovascular events, such as acute coronary syndrome (54). *In vitro* experiments have shown that PR3-ANCAs can significantly promote the release of proinflammatory factors such as IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and TNF-α from peripheral blood mononuclear cells, whereas MPO-ANCAs can exert an inhibitory effect on the TLR4 signaling pathway and cytokine secretion of monocytes, with significant differences in their cellular regulatory effects (14,36). The above subtype-specific pathological characteristics and clinical risk differences provide a basis for risk stratification, precise screening, and individualized intervention of populations at high risk of atherosclerosis.

Although the aforementioned findings focused on MPO-ANCAs and PR3-ANCAs as distinct serotypes, a subset of patients exhibit dual positivity for both antibodies (DP-ANCAs). A comprehensive analysis of 103 DP-ANCA cases identified four distinct phenotypic profiles (55): i) Idiopathic AAV (~30%); ii) drug-induced AAV (~25%), mainly related to propylthiouracil or cocaine/levamisole; iii) autoimmune diseases with low vasculitis risk (~20%); and iv) immune-disrupting comorbidities such as infections or malignancies without AAV (~25%). In idiopathic DP-ANCAs, MPO-AAV appears to represent the 'dominant' phenotype. Compared with the single-positive group, the DP-ANCA group exhibits considerably more kidney dysfunction than the PR3-ANCA group and greater upper airway involvement than the MPO-ANCA group. The poorest remission rate among patients with AAV was observed in the DP-ANCA group (55). Mechanistically, the simultaneous presence of

both autoantibody specificities may reflect broader immune dysregulation with overlapping activation of oxidative stress pathways (MPO-mediated) and NF-κB-driven inflammatory cascades (PR3-mediated), potentially amplifying endothelial injury. However, to the best of our knowledge, no studies have examined cardiovascular risk and plaque characteristics specifically in patients with DP-ANCA-positive disease.

*Role of the NET-mediated vicious inflammatory cycle in atherosclerosis progression*. Abnormal NET formation is a key pathological link in the ANCA-mediated progression of atherosclerosis, and ANCAs can drive NETosis in neutrophils by activating the NADPH oxidase (NOX)-ROS-peptidylarginine deiminase 4 (PAD4) axis. After priming with TNF-α, IL-8, or complement C5a, ANCA target antigens, particularly PR3, are translocated from intracellular granules to the neutrophil surface. Mechanistically, C5a binding to its high-affinity G protein-coupled receptor C5aR (CD88) on neutrophils activates p38 mitogen-activated protein kinase (p38MAPK), extracellular signal-regulated kinase (ERK), and phosphoinositide 3-kinase (PI3K) signaling pathways. Pharmacological inhibition of these kinases was shown to significantly reduce C5a-induced surface expression of PR3, as demonstrated by flow cytometry (56), indicating that these pathways are critically involved in PR3 membrane exposure. Notably, the same study showed that C5a does not significantly increase membrane-bound MPO, suggesting that PR3 and MPO follow distinct mobilization routes (56). Thus, the kinase-inhibitor experiments specifically support the role of p38MAPK, ERK and PI3K in PR3 surface translocation, rather than a generalized mechanism governing the release of all azurophilic granule contents. Complement C5a can synergistically enhance the activation efficiency of neutrophils with ANCA downstream signals, and in the active phase of the disease, high-affinity MPO-ANCAs can further improve the activation sensitivity of neutrophils (10,56). ANCAs initiate dual-signal activation by binding to target antigens on the membrane surface via the fragment antigen-binding (Fab) segment and cross-linking fragment crystallizable γ receptor (FcγR)IIa/FcγRIIIb via the Fc segment, activating the spleen tyrosine kinase (Syk)-PI3K-protein kinase B (Akt) and Raf kinase (Raf)-mitogen-activated protein kinase kinase (MEK)-ERK pathways and promoting the assembly of NOX2 subunits into an active complex, laying a molecular foundation for the initiation of NETosis (57). Activated NOX catalyzes ROS production, which forms HOCl through a cascade reaction to amplify the oxidative stress effect. As the core messenger driving NETosis, ROS directly damage the nuclear membrane and plasma membrane of neutrophils and activates PAD4 and promotes its nuclear translocation, catalyzing the citrullination of histones H3 and H4 to trigger chromatin decondensation (58). In addition, neutrophil elastase released from azurophilic granules enters the nucleus to degrade the nuclear structure and synergizes with PAD4 to hasten nuclear envelope rupture, ultimately prompting neutrophils to undergo NETosis and release NETs containing proinflammatory components such as MPO, PR3, and neutrophil elastase (57,58).

NETs participate in the pathogenesis of atherosclerosis by promoting endothelial dysfunction, platelet aggregation, and inflammatory response (59). Ox-LDL can activate NOX2 in neutrophils through a signaling pathway similar to that of ANCAs to drive abnormal NETosis, whereas ROS released by NETs can further oxidize LDL to generate ox-LDL, which reversely induces more NETosis. Moreover, NETs can cross-link with plaque components to promote foam cell aggregation, accelerating the formation and destabilization of atherosclerotic plaques (58).

NETs participate in ANCA-mediated atherosclerosis progression through multiple pathological mechanisms, forming a cascade-amplified vicious inflammatory cycle. Specifically, the surface of NETs is enriched with ANCA target antigens such as PR3 and MPO, which can be uptaken and presented by dendritic cells as an 'autoantigen library', thereby activating T/B cell-mediated autoimmune responses and inducing continuous ANCA production. The generated ANCAs can further activate neutrophils to release more NETs, forming a positive feedback loop of 'ANCA-NETs-ANCA' (58). Animal experiments have confirmed that the injection of NET-loaded dendritic cells into mice can directly induce ANCA production and related vascular pathological changes, whereas deoxyribonuclease I (DNase I)-induced degradation of NETs can block this process. Conversely, histones released by NETs can directly destroy the integrity of the vascular endothelial cell membrane and induce apoptosis and necrosis of endothelial cells. Proteases such as neutrophil elastase and PR3 can degrade the endothelial basement membrane and extracellular matrix, and MPO can further aggravate endothelial injury and dysfunction by triggering oxidative stress and activating the alternative complement pathway, with endothelial injury as the initiating link of atherosclerosis (60,61). In addition, the DNA skeleton of NETs can serve as a physical scaffold to promote the adhesion and aggregation of platelets and red blood cells, and histone contents can directly activate the coagulation cascade to promote thrombosis. Furthermore, activated platelets can further stimulate neutrophils to release NETs through molecules such as P-selectin and high mobility group box 1, forming an amplification loop of thrombosis and inflammation and increasing the risk of acute cardiovascular events after atherosclerotic plaque rupture (60,62,63).

Impaired NET clearance is an important amplification mechanism for ANCA-mediated vascular inflammation and atherosclerosis progression. In patients with AAV, clinical studies have confirmed significant reduction in the serum DNase I activity in these patients, resulting in continuous NET accumulation that cannot be effectively degraded, thereby aggravating vascular inflammation and pathogenesis of atherosclerosis through multiple pathways (64).

Specifically, continuous accumulation of NETs can sustain activation of the autoimmune response through PR3 and MPO enriched on their surfaces and promote ANCA production. In drug-induced AAV, propylthiouracil can induce the formation of DNase I-resistant NETs and modify the structure of MPO. These NETs can directly promote MPO-ANCA production *in vivo*, further confirming the driving effect of NET accumulation on ANCA autoimmune response (65). Moreover, accumulated NETs can continuously damage the vascular endothelium by releasing histones, proteases, and MPO, and can act as a scaffold for activating the alternative complement pathway, further amplifying endothelial injury and inflammatory cell infiltration (65,66). In addition,

persistent NETs can continuously promote platelet adhesion and aggregation through their DNA scaffold, while their externalized tissue factor can activate the coagulation cascade, thereby exacerbating local vascular inflammation and thrombosis and accelerating atherosclerosis progression and destabilization (67).

*Synergistic pathogenic effect of the complement system and platelets*. Abnormal activation of the complement system is a key bridge for the inflammatory cascade in ANCA-mediated atherosclerosis. The complex formed by ANCAs and neutrophils specifically activates the alternative complement pathway and sequentially forms C3 convertase (C3bBb) and C5 convertase (C3bBbC3b), with the involvement of factor B, factor D, and properdin, thereby cleaving C5 to produce the core inflammatory mediator C5a (68-70). Activated neutrophils can also release key complement components, such as properdin and factor B, further strengthening the complement activation signal and forming an inflammation amplification loop (71,72). C5a exerts multiple proinflammatory effects by binding to C5aR on the surface of neutrophils and monocytes. It cannot only chemotactically recruit inflammatory cells to the site of vascular injury but also upregulate the expression of ANCA target antigens, such as MPO and PR3, on the surface of neutrophils, promote ROS production, protease release, and NET formation (10,64). In addition, it induces monocytes to secrete proinflammatory factors, such as IL-6 and IL-17, aggravating vascular endothelial injury and local inflammatory infiltration and directly participating in atherosclerosis development and progression. Clinical studies have confirmed that the serum C5a level in patients with AAV is positively correlated with disease activity, and the C5a-mediated inflammation amplification effect is an important driving factor for vascular injury (73). The C5a receptor antagonist avacopan can effectively block this inflammatory loop, providing an important direction for the precise intervention in patients with ANCA-positive atherosclerosis (70,73).

Platelet-monocyte complexes (PMCs) are the core hub for the cross-regulation of ANCA-mediated inflammatory response and thrombosis, and their abnormal formation can synergistically accelerate atherosclerosis progression and significantly increase thrombotic risk (74,75). ANCAs induce platelet activation mainly by activating neutrophils to release NETs (section, '*Role of the NET-mediated vicious inflammatory cycle in atherosclerosis progression*' for detailed mechanisms of NET formation and their effects on endothelial injury and coagulation activation), which in turn triggers platelet activation through the thrombin-protease-activated receptor signaling pathway and upregulates the expression of activation markers such as P-selectin on its surface (71,72). Clinical tests have shown that the levels of CD62P-positive platelets and PMCs in the peripheral blood of patients with active AAV are significantly higher than those in patients with disease remission and healthy individuals, and are positively correlated with disease activity (71,76). Activated platelets form stable PMCs through the specific binding of surface P-selectin to P-selectin glycoprotein ligand-1 on the surface of monocytes (75). This process not only upregulates the expression of adhesion molecules, such as CD11b/CD18, thereby enhancing the adhesion and transendothelial migration ability of monocytes, but also induces monocytes to differentiate into proinflammatory and procoagulant phenotypes through platelet-derived granular contents, such as CXCL4 and TNF-α. These activated monocytes secrete numerous proinflammatory factors and activate the alternative complement pathway, amplifying local inflammatory response and inducing a vicious inflammatory cycle (75). PMCs can drive atherosclerosis progression from multiple links. After migrating to the vascular intima, phenotypically transformed monocytes readily differentiate into pro-atherogenic macrophages, with significantly enhanced lipid uptake capacity and accelerated foam cell formation. In addition, they secrete matrix metalloproteinases to degrade the extracellular matrix, resulting in fibrous cap thinning and decreased plaque stability (72). The tissue factor highly expressed on the surface of PMCs can directly activate the coagulation cascade, and PMCs can act as a physical scaffold to promote platelet adhesion and aggregation, which doubly aggravates the local coagulation activation state of blood vessels (72). Clinical cohort studies have confirmed that the risk of arterial and venous thrombosis in patients with AAV is 2 to 3 times higher than that in healthy people, and the PMC level in the peripheral blood is positively correlated with thrombosis (74). This finding suggests that targeted blocking of PMC formation or phenotypic transformation of monocytes mediated by them is a potential novel direction to reduce the risk of atherosclerotic cardiovascular complications in patients with ANCA-positive disease (Fig. 2).

## 3. Clinical correlation evidence between ANCAs and atherosclerosis

Epidemiological and cohort studies have confirmed the close correlation between ANCA positivity and the onset, progression, and adverse prognosis of atherosclerosis. To facilitate rigorous interpretation of the clinical evidence, the included studies have been graded according to an adapted clinical epidemiology evidence hierarchy: Levels I, systematic reviews/meta-analyses of prospective cohorts; II, large prospective cohort studies; III, retrospective cohort or case-control studies; IV, cross-sectional studies or small case series; and V, case reports/expert opinions. Cross-sectional studies (Level IV) can identify associations but cannot establish temporal relationships or causality, whereas retrospective studies (Level III) are at risk of selection bias, confounding, and incomplete data. The evidence for the association between ANCA positivity and cardiovascular outcomes is derived predominantly from Level II-IV studies, with no randomized controlled trials available to date. The key clinical evidence supporting this correlation is systematically graded in Table II.

*Epidemiological association between ANCA positivity and the risk of atherosclerosis*. The persistent inflammatory effect of ANCAs can progressively impair vascular endothelial function and accelerate atherosclerotic plaque formation and destabilization. A proteomic analysis of presymptomatic individuals with AAV, which isolated MPO-ANCAs and PR3-ANCAs, revealed that individuals with MPO-ANCA-positive disease among the pre-AAV population had significantly elevated levels of proinflammatory factors, such as colony-stimulating factor 1, TNF superfamily member 14, and MCP-1 (77). These

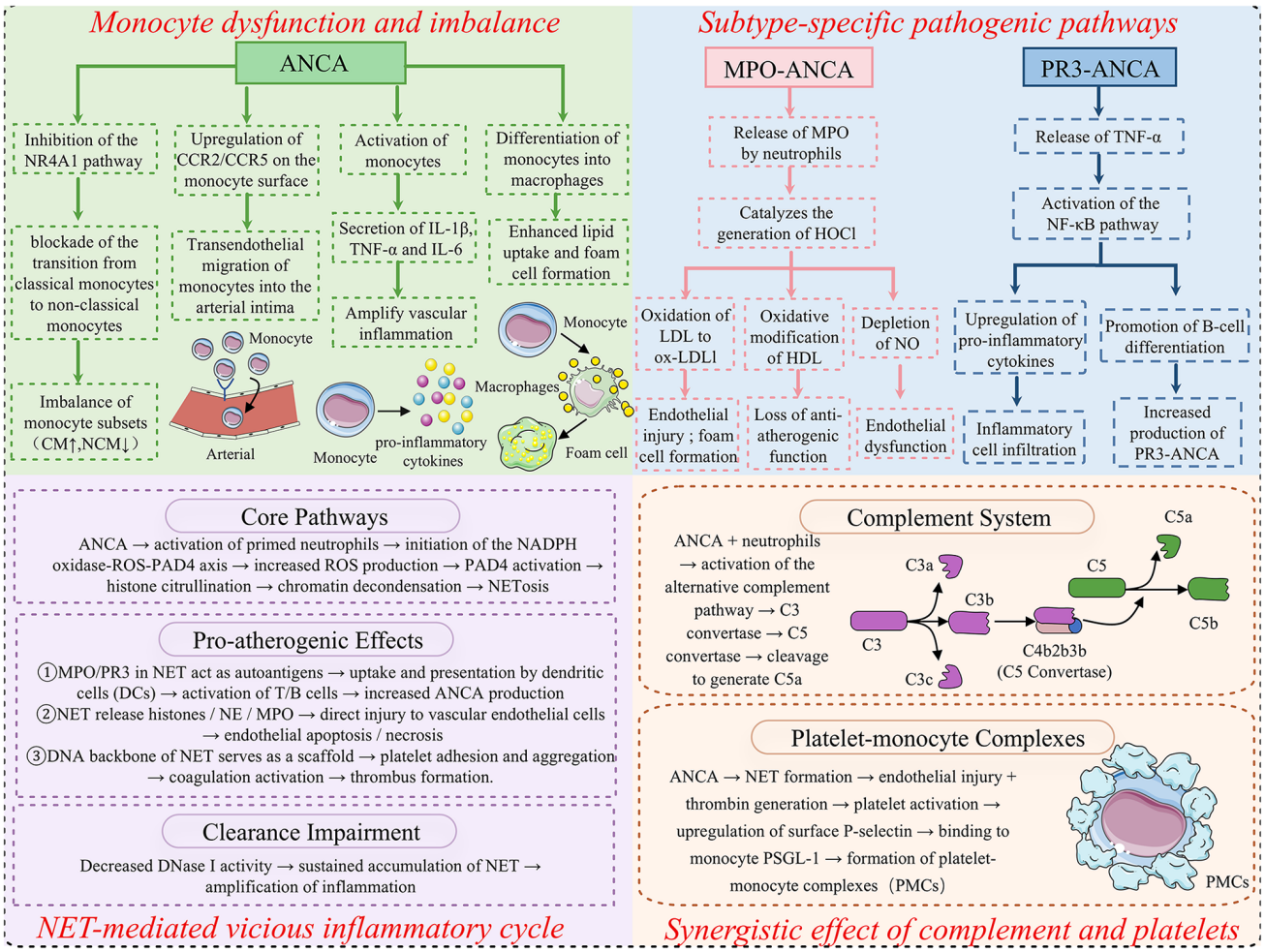



Figure 2. Integrated schematic of ANCA-mediated atherosclerotic pathogenic mechanisms. This image illustrates four interconnected mechanisms: Monocyte dysfunction and subset imbalance; subtype-specific MPO-ANCA/PR3-ANCA pathways; NET-mediated vicious cycle; and complement-platelet synergy. Collectively, these pathways drive atherosclerosis initiation, plaque progression, instability, and adverse cardiovascular events. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; NET; neutrophil extracellular trap.

factors can further enhance monocyte recruitment and activation, thereby exacerbating vascular inflammation and the progression of atherosclerosis.

ANCA positivity can provide early risk warning for cardiovascular events before the onset of clinical symptoms of related diseases. A Swedish case-control study revealed that PR3-ANCAs and MPO-ANCAs can be detected years before the onset of AAV symptoms, with a median lead time of 2.0 (0.9-3.5) years for MPO-ANCAs and up to 2.7 (0.3-7.7) years for PR3-ANCAs, which can be detected as early as 9.7 years before symptom onset (78). A nationwide nested case-control study conducted in Denmark further confirmed that ANCA-related cardiovascular risk has been initiated before the diagnosis of AAV: The risk of major adverse cardiovascular events (including myocardial infarction and stroke) was significantly increased 12 months before diagnosis and peaked 1 month before diagnosis (79). This 'pre-diagnostic high-risk window' indicates that ANCA-related inflammation is initiated at the early stage of vascular injury rather than being a secondary consequence after disease progression, providing key evidence for ANCAs as predictors of cardiovascular risk in non-AAV populations.

In addition, a study on patients with Takayasu arteritis (a non-AAV condition) revealed that 6.6% of the patients with MPO-ANCA-positive disease had a significantly increased risk of advanced coronary artery occlusive disease (80). This finding suggests that the risk predictive value of ANCAs is not limited to the AAV population but can be extended to a broader range of non-AAV autoimmune-related groups, indicating that ANCA positivity may be an independent biomarker of cardiovascular risk rather than a disease-specific accompanying phenomenon of AAV.

The effect of ANCAs on cardiovascular risk is independent of traditional risk factors. After adjusting for confounding factors, including age, sex, chronic kidney disease, hypertension, and diabetes, the Danish study still found a significantly high risk of cardiovascular events in the ANCA-positive population (79). This finding reconfirms that ANCAs are not a 'surrogate marker' of traditional risk factors but an independent risk driver with a sustained risk effect. Even in the absence of overt autoimmune disease, ANCAs can chronically increase the risk of coronary heart disease and stroke through persistent activation of inflammatory pathways and impairment of the vascular endothelium.

Table II. Clinical evidence of the association between ANCA positivity and atherosclerosis onset and prognosis.

| Study type | Study population | Core findings | Evidence level | (Refs.) |
|---|---|---|---|---|
| Nationwide nested case-control | Danish nationwide population with incident AAV | MACE risk significantly increased 12 months before AAV diagnosis, peaking at 1 month before diagnosis; ANCA positivity remained an independent risk factor for cardiovascular events after adjusting for traditional risk factors | III | (79) |
| Case-control | Swedish pre-symptomatic AAV population | PR3-ANCA and MPO-ANCA detectable years before AAV symptom onset; median lead time 2.0 years (MPO-ANCA) and up to 2.7 years (PR3-ANCA) | III | (78) |
| Cross-sectional proteomic analysis | Pre-symptomatic individuals with AAV | MPO-ANCA$^+$ pre-AAV individuals had elevated pro-inflammatory factors (CSF-1, TNFSF14, MCP-1) promoting monocyte recruitment and atherosclerosis progression | IV | (77) |
| Cross-sectional | Takayasu arteritis patients (non-AAV) | 6.6% MPO-ANCA$^+$; significantly increased risk of advanced coronary artery occlusive disease | IV | (80) |
| Cross-sectional | AAV patients with coronary artery calcification assessment | 73% MPO-ANCA+; 39% had CAC score ≥100; median CAC score significantly higher in MPO-ANCA$^+$ vs. PR3-ANCA$^+$ patients | IV | (81) |
| Retrospective cohort | Patients with AAV | MACE incidence significantly higher in MPO-ANCA-positive vs. PR3-ANCA-positive group; PR3-ANCA-positive events dominated by acute MI, synchronized with peak of acute inflammation | III | (53) |

Evidence levels are adapted from the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence for prognostic studies. Level II, large prospective cohort studies; Level III, retrospective cohort studies, nested case-control studies, and case-control studies; Level IV, cross-sectional studies, cross-sectional omic analyses, and small case series. This grading is based predominantly on study design and reflects the relative strength of causal inference; it does not constitute an individual risk-of-bias assessment for each study, and methodological quality may vary within each evidence level. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; MACE, major adverse cardiovascular events; ANCA, antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; CSF-1, colony-stimulating factor 1; TNFSF14, tumor necrosis factor superfamily member 14; MCP-1, monocyte chemoattractant protein-1; CAC, coronary artery calcification; MI, myocardial infarction.

*Effects of ANCA positivity on atherosclerotic plaque characteristics and lesion progression*. Calcification score, as a key quantitative indicator for evaluating the severity of atherosclerosis, is significantly and positively correlated with ANCA positivity. A study on the burden of coronary artery calcification in patients with AAV showed that 73% of the patients had MPO-ANCA-positive disease, and 39% of the cohort had a coronary artery calcification score ≥100, indicating a significant atherosclerotic plaque burden (81). Furthermore, the median coronary artery calcification score of the MPO-ANCA-positive group was significantly higher than that of the PR3-ANCA-positive group, as was the age-, sex-, and race-standardized percentile of the coronary artery calcification score (81). During the follow-up of patients with AAV, the risk of major adverse cardiovascular events showed an increasing trend in those with a coronary artery calcification score ≥100 (81).

The detection rate of high-risk plaques (including low-density plaques and napkin-ring sign) in the ANCA-positive group, especially those positive for MPO-ANCAs, was shown to be significantly higher than that in the PR3-ANCA-positive group (81). A long-term follow-up study (with a mean follow-up of 7.5 years) revealed that the incidence of major adverse cardiovascular events (including myocardial infarction, stroke, and all-cause mortality) in the MPO-ANCA-positive group was significantly higher than that in the PR3-ANCA-positive group (53). Imaging studies based on coronary computed tomography (CT) angiography have confirmed that high-risk features such as low-density plaques and napkin-ring sign are significantly associated with the risk of acute coronary events (82). However, current CT-based plaque attenuation measurement cannot fully capture the differences in MPO-mediated plaque instability. For example, some plaques with elevated MPO activity do not show typical high-risk features on CT, suggesting the more complex risk characteristics of high-risk plaques associated with ANCAs (83).

*Specific association between ANCA subtypes and atherosclerotic clinical phenotypes as well as cardiovascular events*. Distinct subtype specificity exists among different ANCA subtypes in mediating atherosclerosis-related cardiovascular injury: MPO-ANCAs are more associated with chronic and stable atherosclerosis, whereas PR3-ANCAs are more likely to be linked to acute cardiovascular events such as

acute coronary syndrome, with significant differences between in inflammatory patterns, lesion characteristics, and event types. These characteristics are consistent with the pathogenic mechanisms of MPO-ANCAs and PR3-ANCAs (22,81).

A previous clinical study showed that the MPO-ANCA-positive group had a significantly higher coronary artery calcification score and heavier calcification burden than the PR3-ANCA-positive group (81). The lesions of the MPO-ANCA-positive group were characterized by a progressive increase in plaque burden, and cardiovascular events were mainly manifested as stable ischemic symptoms, with an overall slow progression course that was highly consistent with the onset and development of chronic atherosclerosis (81). In addition, MPO-ANCA-mediated chronic inflammation can also promote chronic sclerotic lesions in sites such as the aortic valve, further supporting its association with systemic chronic stable atherosclerosis (84).

Large-sample follow-up studies have indicated that cardiovascular events in the PR3-ANCA-positive group are dominated by acute myocardial infarction (28), which mostly occurs in the early stage of disease activity and is highly synchronized with the peak of acute inflammation (53). It has been shown that compared with MPO-ANCAs, PR3-ANCAs are more likely to trigger acute plaque rupture and thrombosis, with clinical manifestations more consistent with the pathogenic characteristics of acute coronary syndrome (22). These subtype-specific clinical differences can provide an important basis for clinical risk stratification and serve as early warning of cardiovascular events.

*Clinical evidence linking C5a-platelet-monocyte pathways to atherosclerotic phenotypes and cardiovascular events*. The separate mechanistic components of the hypothetical C5a-platelet-monocyte-NET axis described in '*Synergistic pathogenic effect of the complement system and platelets*' are each supported by discrete clinical observations in patients with AAV. Plasma C5a concentrations were found to be significantly higher in patients with active AAV than in those in remission, and MPO-positive microparticle-bound C5a levels were reported to be positively associated with Birmingham Vasculitis Activity Score (BVAS) (73,85). Elevated C5a levels have been associated with increased carotid intima-media thickness (cIMT) in other autoimmune conditions, and patients with AAV are known to have increased cIMT compared with healthy controls (69,86,87), suggesting that complement activation may contribute to early vascular remodeling. In parallel, circulating PMC proportions have been found to be elevated during active AAV vs. disease remission (75,85). From a clinical-outcome perspective, patients with AAV demonstrate a substantially elevated risk of venous thromboembolism, and platelet activation together with PMC formation have been implicated in this hypercoagulable state (88-90). Collectively, these independent mechanistic and clinical findings generate a testable hypothesis that an integrated C5a-PMC-NET axis may contribute to subclinical atherosclerosis burden and thrombotic event risk in AAV, although this complete causal cascade has not yet been formally established in human studies. Furthermore, given the established role of NETs in promoting atherosclerosis and plaque destabilization (58), it is biologically plausible that C5a-driven NETosis contributes to the development of high-risk plaque features, such as low-attenuation plaques and positive remodeling, in patients with systemic vasculitis. However, direct evidence from coronary CT angiography studies examining these specific plaque phenotypes in AAV cohorts is currently lacking.

*Dynamic monitoring value of ANCAs combined with NET-related biomarkers*. Beyond static serological status, serial monitoring of ANCA titer dynamics, combined with NET-related biomarkers, provides incremental value for atherosclerotic risk stratification and disease follow-up (91,92). Persistent elevation or progressive increase in ANCA titer reflects sustained neutrophil activation and chronic vascular inflammation, which has been associated with progression of subclinical atherosclerosis as measured by cIMT in patients with systemic inflammatory conditions (86,93). In AAV, rising or persistently positive ANCA titers precede disease flares and are linked to ongoing endothelial injury, a key initiating driver of early atherogenesis (73,78).

When combined with circulating citrullinated histone H3 (CitH3), a core marker of NET formation, and serum DNase I activity, the composite biomarker panel can better reflect NET clearance imbalance and inflammatory amplification *in vivo* (94,95). Elevated circulating CitH3 has been linked to increased necrotic core size and thinner fibrous caps in human atherosclerotic plaques, as well as a higher risk of acute coronary syndromes, supporting its role as a surrogate marker of plaque instability (96-98). Reduced serum DNase I activity, which impairs NET degradation and promotes sustained NET accumulation, has been documented in active AAV and associated with disease activity and vascular damage (99,100).

Based on these findings, it is proposed that elevated CitH3 and decreased DNase I activity, together with rising ANCA titers, may indicate enhanced intraplaque NET deposition and increased plaque instability, and could serve as an early warning signature for high-risk plaques and acute cardiovascular events (41,101). Such a combined detection strategy may help to dynamically evaluate residual inflammatory risk of atherosclerosis and guide the timing and intensity of anti-inflammatory intervention. It is acknowledged that this integrated monitoring framework remains hypothesis-generating at present; dedicated prospective cohort studies are required to confirm whether the ANCA-CitH3-DNase I composite panel adds incremental prognostic value beyond traditional risk factors for atherosclerotic cardiovascular events.

## 4. Therapeutic strategies for atherosclerosis targeting ANCA-related pathways

Based on the aforementioned pathogenic mechanisms, multiple targeted therapeutic strategies for ANCA-mediated atherosclerosis have been explored in preclinical and clinical studies. The detailed information on these strategies, including core targets, representative agents, mechanisms of action, and research stage, is comprehensively listed in Table III and Fig. 3.

*Targeted regulation of the source of ANCA-mediated inflammatory response*. Precision targeted intervention is an important direction for the clinical treatment and risk

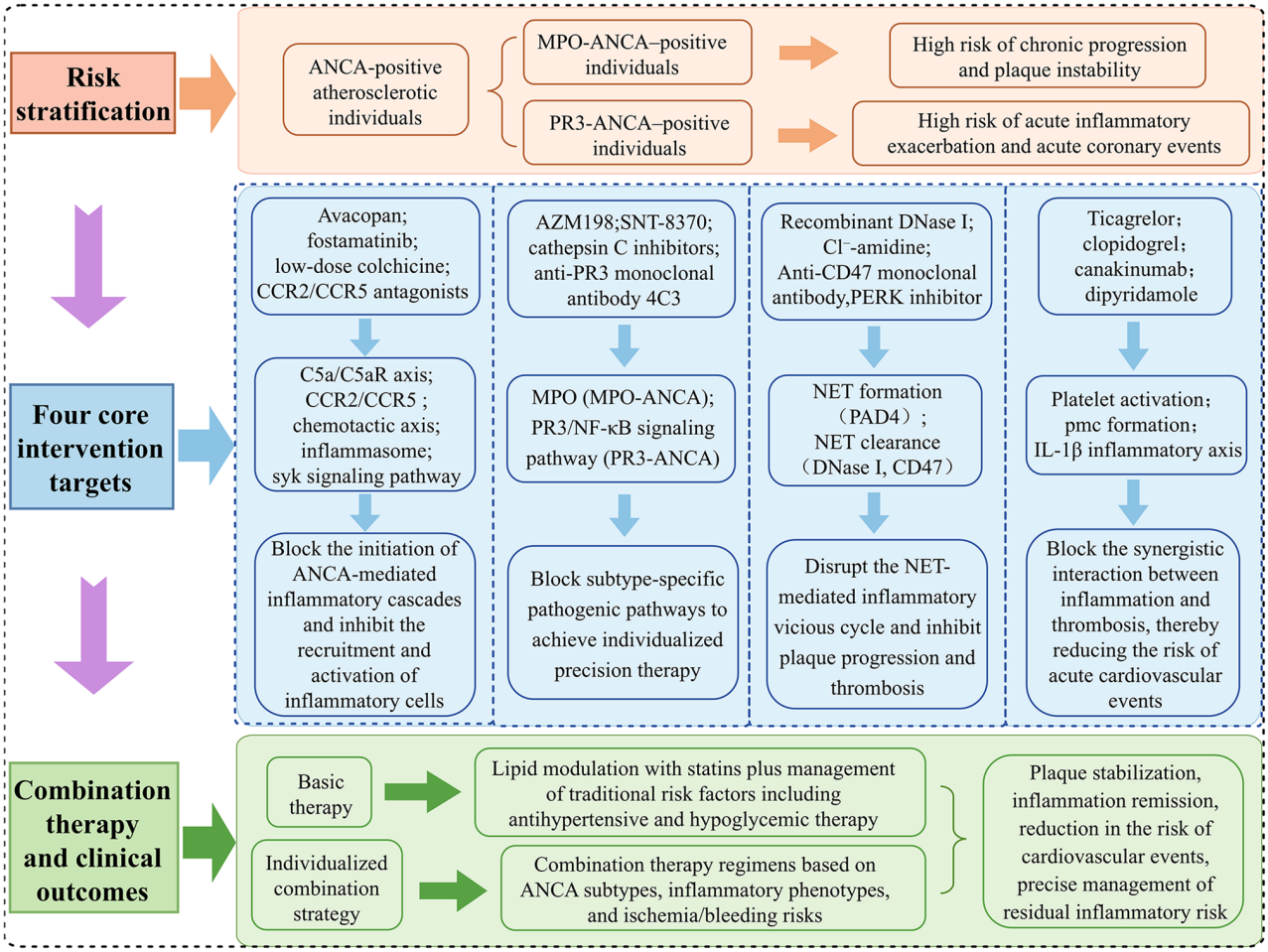



Figure 3. Precision therapeutic framework targeting ANCA-mediated atherosclerosis. This pyramid outlines a stepwise treatment strategy: ANCA subtype-based risk stratification (MPO-ANCA vs. PR3-ANCA) guide selection among four intervention modules, inflammatory source regulation, subtype-specific targeting, NET blockade, and inflammation-thrombosis synergy interruption, integrated with statin therapy and individualized combination regimens, ultimately achieving plaque stabilization, inflammation resolution, and reduced cardiovascular events.

management of patients with atherosclerosis, aiming at the core pathological links of ANCA-mediated disease, including inflammatory cascade, endothelial injury, and thrombosis. The regulation of inflammatory sources is the core strategy to block the proatherosclerotic effect of ANCAs, which mainly includes two categories: ANCA activation pathway inhibitors and inflammatory cell function regulators. Syk is a key signaling molecule in neutrophil activation mediated by ANCA-IgG, and its direct and selective inhibitor fostamatinib can inhibit ANCA-mediated inflammatory cell activation by interfering with Syk-dependent Fc receptor signal transduction (102-104). These effects are supported by mechanistic studies using patient-derived cells and preclinical animal models of AAV (102-104); no clinical trials of fostamatinib in AAV or ANCA-associated atherosclerosis have been completed to date.

By contrast, sodium tanshinone IIA sulfonate has been shown to suppress SYK phosphorylation and modulate the SYK-NLR family pyrin domain-containing 3 (NLRP3) inflammasome-matrix metalloproteinase (MMP)2/9 pathway, thereby exerting anti-inflammatory, antioxidative, and vasodilatory effects and protecting vascular diastolic function from hyperlipidemia-induced injury (105). However, direct binding of sodium tanshinone IIA sulfonate to SYK or direct inhibition of SYK enzymatic activity was not demonstrated in this aforementioned study, and the observed suppression of SYK phosphorylation may occur through indirect mechanisms. Avacopan, an oral small-molecule complement C5a receptor antagonist, has been shown to selectively block C5a receptor-mediated chemotaxis and neutrophil activation and inhibit the inflammatory amplification loop of complement-ANCA synergistic activation (106). The Phase III ADVOCATE trial demonstrated that avacopan effectively modulates ANCA-related inflammation while reducing glucocorticoid exposure in patients with AAV (107,108). Given the key role of C5a in ANCA-mediated vascular inflammation and atherosclerosis, avacopan has emerged as a potential therapeutic strategy for ANCA-positive atherosclerosis. However, no clinical trials have evaluated its effects on atherosclerotic cardiovascular outcomes. Therefore, evidence supporting its potential antiatherosclerotic effect remains indirect and is primarily extrapolated from its efficacy in AAV and mechanistic studies (107-109).

For the regulation of inflammatory cell recruitment and activation, low-dose colchicine, the first anti-inflammatory drug approved by the US Food and Drug Administration for the secondary prevention of cardiovascular events in patients with established atherosclerotic disease, can reduce the level

Table III. Therapeutic strategies targeting ANCA-related pathways for atherosclerosis: Key agents and clinical development status.

| Therapeutic target | Drug category | Representative agents | Mechanism of action | Overall clinical development status (with trial identifiers) | Evidence level for ANCA-atherosclerosis | (Refs.) |
|---|---|---|---|---|---|---|
| ANCA activation upstream signaling | Syk inhibitor | Fostamatinib | Blocks Syk-dependent Fc receptor signal transduction; inhibits ANCA-mediated inflammatory cell activation | Preclinical in AAV animal models; Phase II completed in IgA nephropathy (NCT02112838); no clinical trials in AAV | Mechanistic (patient-derived cells) + preclinical (AAV animal models); not evaluated in ANCA-atherosclerosis | (102-104) |
| ANCA activation upstream signaling | Multi-target agent | Sodium tanshinone IIA sulfonate | Modulates SYK-NLRP3 inflammasome-MMP2/9 pathway as one of multiple downstream targets; exerts anti-inflammatory, antioxidative, and vasodilatory effects; direct SYK binding or inhibition has not been demonstrated | Preclinical (animal models of atherosclerosis) | Preclinical (general atherosclerosis models); not evaluated in ANCA-atherosclerosis | (105) |
| Complement-ANCA synergistic activation loop | C5a receptor antagonist | Avacopan | Selectively blocks C5aR-mediated neutrophil chemotaxis and activation; inhibits inflammatory amplification loop; reduces glucocorticoid exposure | Approved for AAV by FDA and EMA (ADVOCATE Phase III trial, NCT02994927); no dedicated CVD trials in ANCA-atherosclerosis | Approved for AAV; mechanistic rationale for atherosclerosis; hypothetical for ANCA-atherosclerosis without dedicated CVD trials | (106-109) |
| Inflammatory cell recruitment | CCR2/CCR5 antagonist | CCR2 mAb, CCR5 inhibitors | Blocks monocyte chemotactic recruitment to arterial intima; reduces macrophage infiltration and plaque burden | Preclinical only (animal models of atherosclerosis) | Preclinical (general atherosclerosis animal models); not evaluated in ANCA-atherosclerosis | (40, 114) |
| Inflammatory cascade amplification | Inflammasome inhibitor | Low-dose colchicine | Inhibits inflammasome activation; reduces circulating CCL2 levels; lowers recurrent cardiovascular event risk | Approved by FDA for secondary prevention of cardiovascular events in established atherosclerotic cardiovascular disease (COLCOT: NCT02551692, post-myocardial infarction; LoDoCo2: NCT02916446, chronic coronary disease) | Approved for general ASCVD secondary prevention; not specifically evaluated in ANCA-atherosclerosis | (111-113) |

Table III. Continued.

| Therapeutic target | Drug category | Representative agents | Mechanism of action | Overall clinical development status (with trial identifiers) | Evidence level for ANCA-atherosclerosis | (Refs.) |
|---|---|---|---|---|---|---|
| MPO-ANCA mediated oxidative stress | MPO inhibitor | AZM198, SNT-8370, ABAH | Inhibits MPO catalytic activity; reduces HOCl production and ox-LDL formation; prevents unstable plaque formation; stabilizes atherosclerotic lesions | Preclinical only (animal models of atherosclerosis) | Preclinical (general atherosclerosis animal models); not evaluated in ANCA-atherosclerosis | (118-120) |
| PR3-ANCA mediated inflammatory activation | Cathepsin C inhibitor | GSK2793660 | Downregulates PR3 antigen expression and membrane exposure on neutrophils; suppresses PR3-ANCA-mediated neutrophil activation | Phase I in healthy volunteers (NCT02058407); no clinical trials in AAV or atherosclerosis | Preclinical (*in vitro* and *ex vivo* AAV models); hypothetical for ANCA-atherosclerosis | (121-125) |
| PR3-ANCA mediated inflammatory activation | Anti-PR3 monoclonal antibody | 4C3 mAb | Competitively blocks pathogenic PR3-ANCA binding to neutrophils; inhibits neutrophil autoimmune activation | Preclinical only (*in vitro*) | Preclinical (*in vitro*); hypothetical for ANCA-atherosclerosis | (122-125, 127, 128) |

ANCA, anti-neutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; Syk, spleen tyrosine kinase; IgA, immunoglobulin A; SYK, spleen tyrosine kinase; NLRP3, NLR family pyrin domain containing 3; MMP2/9, matrix metalloproteinases 2 and 9; C5a, complement component 5a; C5aR, complement component 5a receptor; FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; CVD, cardiovascular disease; CCR2, C-C chemokine receptor 2; CCR5, C-C chemokine receptor 5; mAb, monoclonal antibody; CCL2, C-C motif chemokine ligand 2; ASCVD, atherosclerotic cardiovascular disease; COLCOT, Colchicine Cardiovascular Outcomes Trial; LoDoCo2, Low-Dose Colchicine 2 trial; MPO, myeloperoxidase; ABAH, 4-aminobenzoic acid hydrazide; HOCl, hypochlorous acid; ox-LDL, oxidized low-density lipoprotein; PR3, proteinase 3.

of C-C motif chemokine ligand 2 in coronary circulation by inhibiting inflammasome activation. Two large-scale clinical trials, COLCOT and LoDoCo2, demonstrated that colchicine significantly reduces the risk of recurrent cardiovascular events in patients with coronary artery disease (110-113). However, these trials were conducted in general atherosclerotic populations, and the efficacy of colchicine in patients with ANCA-positive atherosclerosis has not been prospectively evaluated. CCR2/CCR5 antagonists can block the chemotactic recruitment of monocytes into the arterial intima; a preclinical meta-analysis of animal models has demonstrated that these agents exert arterial protective effects in atherosclerosis, and combination with traditional lipid-lowering drugs may help manage residual inflammatory risk (40,114). In addition, novel strategies such as macrophage-targeted nanotherapy and 4-phenylbutyric acid-reprogrammed monocytes can target and regulate the inflammatory microenvironment in plaques and reduce plaque burden, providing novel research directions for treatment (115,116).

*Precision targeted intervention based on ANCA subtype differences*. From a translational research perspective, the distinct pathogenic mechanisms of MPO-ANCAs and PR3-ANCAs in atherosclerosis provide a mechanistic rationale for subtype-oriented investigational strategies, framed here as a hypothetical framework for future research. For the MPO-ANCA-mediated oxidative stress and lipid modification pathway, MPO inhibitors suppress HOCl production and ox-LDL formation by inhibiting the catalytic activity of MPO, thereby mitigating endothelial injury and plaque instability (117). Multiple candidate agents, including ABAH, INV-315, and AZM198, have shown promising activity in preclinical studies. In animal models, the selective MPO inhibitor AZM198 effectively prevented unstable plaque formation and promoted stability of vulnerable atherosclerotic lesions without impairing circulating immune cell function or causing detectable adverse reactions (118-120). The dual inhibitor SNT-8370, targeting both vascular adhesion protein-1 and MPO, has demonstrated greater anti-inflammatory and vascular protective effects than monotherapy in models of acute inflammation and myocardial ischemia-reperfusion injury (121), supporting its preclinical potential for MPO-ANCA-associated atherosclerosis. For the PR3-ANCA-mediated inflammatory cascade, cathepsin C (CatC) inhibitors have been shown to downregulate PR3 antigen expression and membrane exposure on the neutrophil surface (122,123), suppress PR3-ANCA-mediated neutrophil activation, and attenuate microvascular endothelial injury (124-126). Furthermore, the non-pathogenic anti-PR3 monoclonal antibody 4C3 was found to competitively inhibit the binding of pathogenic PR3-ANCAs to neutrophils and effectively block PR3-ANCA-mediated neutrophil autoimmune activation (122-125,127,128). Similarly, CCR2/CCR5 antagonists have shown atheroprotective effects in preclinical meta-analyses of animal models (40,114), but their efficacy specifically in ANCA-positive atherosclerosis remains to be established in human studies.

Collectively, while these subtype-specific approaches are mechanistically attractive, all remain at preclinical or early developmental stages. None are currently approved or established for the treatment of ANCA-associated atherosclerosis, and their clinical utility awaits rigorous evaluation in dedicated clinical trials. Notably, current clinical management of patients with AAV and elevated cardiovascular risk must follow established, evidence-based AAV treatment guidelines and standard cardiovascular risk reduction guidelines, irrespective of ANCA serotype (MPO vs. PR3) (129,130). The subtype-targeted investigational approaches outlined above are presented solely as a hypothetical framework for future research and are not intended to guide routine clinical practice at this time.

*Targeted blockade strategies for NET-mediated pathological circuits*. Intervention strategies targeting NETs (whose pathogenic mechanisms are detailed in '*Role of the NET-mediated vicious inflammatory cycle in atherosclerosis progression*') mainly fall into two directions: NET clearance and inhibition of NET formation. In terms of NET clearance, recombinant DNase I can specifically degrade the nucleic acid backbone of NETs, reducing autoantigen exposure and persistent vascular wall damage. Animal experiments have confirmed that exogenous supplementation with DNase I significantly reduces the NET content within atherosclerotic plaques, decreases necrotic core area, increases collagen content, and improves plaque remodeling (131-133), while also accelerating thrombolysis and reducing the risk of thrombotic events (134). CD47 monoclonal antibody can block signals on the NET surface, enhance macrophage phagocytic clearance of NETs, and reduce their persistent accumulation in the vasculature (135). PERK inhibitors have been shown to alleviate endoplasmic reticulum stress-mediated impairment of macrophage DNase secretion, enhance endogenous NET clearance, and significantly improve plaque stability and reduce pro-inflammatory cytokine expression in mouse models of atherosclerosis (136). Regarding inhibition of NET formation, PAD4 inhibitors were found to suppress the NETosis process by blocking histone citrullination. Myeloid PAD4-deficient $Apoe^{-/-}$ mice exhibited significantly reduced atherosclerotic burden and markedly attenuated aortic inflammation (137). Among these, Cl-amidine and other inhibitors have been demonstrated to effectively reduce NET formation and alleviate vascular inflammation in vasculitis models (138,139). In addition, NADPH oxidase inhibitors, ROS scavengers, alpha-1 antitrypsin, etc., can inhibit aberrant NET formation through different pathways, providing multi-target intervention options for the treatment of ANCA-associated atherosclerosis (136,140).

*Multi-pathway synergistic intervention and combination therapy regimens*. Given the intersecting pathological mechanisms of ANCA-mediated inflammation, lipid metabolism abnormalities, and thrombosis, coordinated multi-pathway intervention represents a key strategy for the clinical management of ANCA-positive atherosclerosis patients. In terms of antiplatelet therapy, the risk of arteriovenous thrombotic events is significantly elevated in ANCA-positive patients (141,142). Antiplatelet regimens centered on P2Y12 receptor antagonists can effectively inhibit ANCA-induced platelet activation and platelet-monocyte complex (PMC) formation, thereby blocking the synergistic amplification between inflammation and thrombosis. Among these, clopidogrel and prasugrel are

prodrugs that irreversibly inhibit ADP-induced platelet aggregation after metabolic activation (143,144). Notably, prasugrel differs from clopidogrel in its metabolic activation pathway. Esterases hydrolyze prasugrel as the first step of its activation pathway, whereas the same enzymes shunt the majority (~85%) of clopidogrel into an inactive dead-end metabolite. Furthermore, prasugrel requires only one CYP-dependent oxidative step to generate its active metabolite, whereas clopidogrel requires two separate CYP-dependent oxidative steps, primarily involving CYP2C19 (143). This more efficient activation pathway, which lacks a significant inactive shunt, results in more rapid, consistent, and higher systemic exposure to the active metabolite with prasugrel, leading to faster onset and more predictable platelet inhibition compared with clopidogrel (143,144). This rapid and stable efficacy profile is similar to that of ticagrelor, which does not require metabolic activation and directly and reversibly inhibits the P2Y12 receptor. Ticagrelor, as a reversible P2Y12 receptor antagonist, exerts rapid antiplatelet effects without requiring metabolic activation, while also conferring anti-inflammatory and cardioprotective benefits, making it a preferred option for patients at high ischemic risk (145,146). Dipyridamole, on the other hand, elevates intracellular cAMP levels and promotes $PGI_2$ release, thereby exerting antiplatelet and vascular endothelial protective effects (147,148). Clinically, individualized antiplatelet regimens can be tailored based on the balance between ischemic and bleeding risks in each patient.

In terms of combined anti-inflammatory and lipid-lowering therapy, the combination of statins with agents targeting inflammatory pathways is a core strategy for managing residual cardiovascular risk in atherosclerosis. The CANTOS trial demonstrated that canakinumab, a monoclonal antibody targeting IL-1β, significantly reduces the risk of major adverse cardiovascular events in patients with high inflammatory status without affecting lipid levels, directly validating the clinical value of targeted anti-inflammatory therapy in atherosclerosis (149). A 2025 network meta-analysis showed that adding low-dose colchicine to statin therapy was superior to intensive lipid-lowering regimens such as ezetimibe or PCSK9 inhibitors in reducing the risk of major adverse cardiovascular events, stroke, and coronary revascularization (150). Mechanistic studies have confirmed that IL-1β inhibitors can enhance plaque stability by promoting extracellular matrix deposition and thickening the fibrous cap, making them particularly suitable for patients with high inflammatory states such as AAV. However, IL-1β blockade exhibits stage-dependent effects; monotherapy during the plaque regression phase may increase plaque vulnerability, and is accompanied by an elevated risk of infections. Therefore, strict patient selection and individualized combination regimens are required in clinical practice (151,152).

Despite the therapeutic promise of ANCA-targeted strategies, their clinical translation faces substantial safety and practical challenges. C5a receptor antagonists, exemplified by avacopan, have demonstrated a favorable overall safety profile in clinical trials, with fewer infections and adverse events than glucocorticoid-based regimens (153,154). However, post-marketing pharmacovigilance has identified hepatobiliary disorders as a significant concern, with drug-induced liver injury occurring in ~40% of patients in some cohorts and vanishing bile duct syndrome reported in rare but fatal cases (155-157). Elderly patients, those with low body weight, and concomitant use of rituximab or proton-pump inhibitors appear to be at increased risk (155-158). Real-world data also suggest age- and sex-dependent differences in adverse event patterns, with hepatobiliary events more frequent among geriatric and female patients (134). MPO inhibitors remain largely in preclinical or early-phase clinical development; while agents such as mitiperstat (AZD4831) are generally well tolerated in healthy volunteers, their efficacy and long-term safety in atherosclerotic populations have not been established (159). NET-targeted therapies, including PAD4 inhibitors and DNase-based approaches, face additional biological risks: PAD4 inhibition extends beyond suppressing NETosis to affect citrullination of non-histone substrates, with consequences for antigen presentation, cytokine function, and adaptive immunity (160). Therapeutic targeting of NETs may increase microbial load in infections, impair peripheral tolerance in autoimmunity, and reduce adaptive immunity in cancer (161). Beyond safety concerns, practical barriers further limit clinical adoption: Most candidates remain in preclinical stages; the high cost of biologic agents and small-molecule inhibitors poses significant economic burdens; and the lack of validated biomarkers to identify patients most likely to benefit hampers personalized application. These obstacles underscore the need for continued pharmacovigilance, biomarker development, and cost-effectiveness evaluations to facilitate the safe and equitable translation of these novel therapies into clinical practice.

## 5. Research challenges and future perspectives

Current research on ANCA-related mechanisms and atherosclerosis faces several key limitations that constrain mechanistic understanding and clinical translation.

First, there is substantial heterogeneity across clinical studies, and study design alone does not determine overall study quality. The evidence hierarchy applied in this review (adapted from the Oxford Centre for Evidence-Based Medicine 2011 prognostic framework) (162) classifies studies by design to reflect relative evidentiary strength for causal inference, but it is not a substitute for formal risk-of-bias assessment. Individual studies within the same design grade can vary widely in methodological quality, risk of selection bias, confounding control, and outcome ascertainment. ANCA detection methods remain incompletely standardized, and enrolled populations differ markedly in baseline characteristics, including underlying autoimmune disease activity, medication history, and comorbidities, which limits direct comparisons and complicates the integration of findings. Moreover, causal inference is hampered by the inherent constraints of observational designs, including pervasive confounding and competing risks. While chronic atherosclerotic inflammation alone is insufficient to induce pathogenic ANCA production (41,163), persistent low-grade systemic inflammation and neutrophil activation in advanced atherosclerosis may facilitate NET release and exposure of MPO/PR3 autoantigens, potentially giving rise to low-titer non-pathogenic ANCA positivity and thereby biasing cross-sectional association estimates (164,165). This reverse causality hypothesis remains biologically plausible but has not been directly validated in population-based studies.

Beyond reverse causality, several additional factors may confound the relationship between ANCA status and atherosclerotic lesions. First, disease activity, although not consistently associated with cardiovascular events in prospective cohorts as measured by BVAS, may still influence cardiovascular risk through related mechanisms, such as chronic inflammation and cumulative steroid exposure (166); notably, AAV itself is associated with a 65% higher risk of cardiovascular events relative to the general population (167). Second, treatment exposure warrants consideration: Long-term glucocorticoid therapy exacerbates metabolic and hemodynamic profiles (such as hyperglycemia, hypertension, and adverse lipid patterns) and is associated with dose-dependent increases in cardiovascular events, potentially confounding the attribution of lesion progression solely to vasculitis-driven inflammation (41,89). Indeed, a substantial proportion of patients with AAV develop hypertension, diabetes mellitus, and hypercholesterolaemia, whether as consequences of immunosuppressive therapy or as manifestations of the underlying disease (141). Third, kidney involvement is independently associated with cardiovascular events (hazard ratio 3.02) (168), and it functions as both a mediator and a confounder in the association between ANCA and cardiovascular risk. As a mediator, renal dysfunction is a direct end-organ consequence of ANCA-mediated small-vessel injury, lying on the causal pathway between vasculitis activity and adverse cardiovascular outcomes. As a confounder, renal impairment independently increases cardiovascular risk through mechanisms including volume overload, uremic toxin accumulation, anemia, and mineral bone disorders; it also is associated with more severe vasculitis and greater cumulative glucocorticoid exposure, which may distort estimates of the independent cardiovascular effect of ANCA itself. Fourth, competing risks must be acknowledged: Premature non-cardiovascular death, particularly from infections, malignancies, and end-stage renal disease, can substantially distort cardiovascular event estimates in AAV cohorts (169,170). Major causes of death in AAV include cardiovascular disease, infections, and neoplasms; treatment-related immunosuppression further heightens susceptibility to serious infections, which may lead to non-cardiovascular death and thus compete with cardiovascular outcomes (171). Failure to account for such competing risks may result in overestimation of event rates in conventional Kaplan-Meier analyses; accordingly, future studies should employ appropriate methods, such as Fine-Gray competing-risk regression, to obtain more accurate cumulative incidence estimates.

Although most cohort studies have adjusted for at least some of these covariates, residual confounding persists, limiting precise interpretation of the contribution of ANCAs to atherosclerotic risk. Consequently, large-scale prospective cohorts with rigorous confounder adjustment, alongside targeted interventional trials, are needed to establish a causal relationship.

Second, mechanistic studies are constrained by model limitations. Existing *in vitro* models are challenging to use to simulate the complex cell-cell interactions and pathological microenvironment of the vascular wall *in vivo*, and no specific animal models can accurately simulate ANCA-mediated inflammation driving atherosclerosis. Conventional AAV animal models, particularly the passive anti-MPO antibody transfer model, induce acute necrotizing glomerulonephritis and pulmonary capillaritis within days but cannot capture the chronic, progressive course of human atherosclerosis, which develops over decades (172,173). These short-term models cannot capture the slow atherogenic process, and atherosclerosis-relevant endpoints (plaque burden, fibrous cap thickness, and necrotic core size) are not assessable in such short-term experiments. Notably, depending on the source of antibodies used in each experiment, passively transferred exogenous ANCAs may exhibit potential model-dependent limitations when compared with endogenous pathogenic human ANCAs, including possible divergences in affinity maturation, epitope recognition profiles, and Fc-region glycosylation features (173). Of note, direct head-to-head experimental studies simultaneously validating these three molecular discrepancies between patient-derived endogenous ANCAs and immunization-derived exogenous antibodies are currently lacking. Individual existing reports provide fragmented evidence: Bruner *et al* (174) characterized human immunodominant MPO-ANCA epitopes, whereas Yoshida *et al* (175) demonstrated that antibody affinity of human MPO-ANCAs is associated with NET-associated renal vasculitis activity; however, neither work constitutes a complete cross-species comparative analysis. The lack of a reliable PR3-ANCA model, owing to species-specific differences in PR3 expression and the involvement of the neutrophil-specific CD177 receptor in PR3 surface presentation, further limits generalizability (12,176). Existing *in vitro* systems, typically using isolated neutrophils or monocytes co-cultured with endothelial monolayers under static conditions, cannot reproduce the complex three-dimensional vascular microenvironment, dynamic cell interactions, or hemodynamic shear stress that profoundly influences leukocyte adhesion and transmigration (177,178). These model limitations collectively limit our ability to examine the chronic effects of ANCAs on atherogenesis, evaluate long-term drug efficacy, and translate preclinical findings to clinical applications.

Third, the clinical and mechanistic significance of DP-ANCAs represents a major knowledge gap. Although recent studies have characterized the phenotypic and prognostic features of patients with DP-ANCAs, virtually no data exist regarding their cardiovascular risk profile, atherosclerotic plaque characteristics, or response to targeted anti-inflammatory or antiplatelet therapies. Whether patients with DP-ANCA experience additive or synergistic cardiovascular risk, combining the chronic oxidative stress burden of MPO-ANCA with the acute inflammatory flare propensity of PR3-ANCAs remains unknown. Furthermore, the temporal stability of dual positivity is poorly understood; some cases may convert to single positivity or negativity over time, raising questions about whether DP-ANCA represents a distinct disease entity, a transitional state, or an assay-related phenomenon. Future investigations should assess cardiovascular outcomes in DP-ANCA cohorts and investigate the molecular mechanisms by which concurrent MPO and PR3 autoimmunity modulates vascular inflammation.

Future research should focus on four priority areas. First, molecular mechanistic research should encompass the epigenetic regulatory network of ANCA-mediated monocyte phenotypic transformation and clarify the cross-nodes

and specific effects of downstream signaling pathways of MPO-ANCAs and PR3-ANCAs to provide a theoretical basis for precision targeting. Second, clinical translational research should include randomized controlled trials based on subtype stratification in ANCA-positive atherosclerosis populations, clarify the differential efficacy of targeted anti-inflammatory and lipid-lowering combination regimens, and establish evidence-based intervention pathways. Third, risk prediction biomarkers must be optimized using composite biomarker panels combining ANCA titers with NET-related markers (such as CitH3, cell-free DNA, and DNase I activity) to improve the accuracy of predicting atherosclerosis onset and progression. Fourth, precision medicine practice should be further advanced by developing individualized treatment strategies based on ANCA subtypes, inflammatory phenotypes, and treatment response characteristics and exploring targeted alternative regimens for patients with glucocorticoid insensitivity to achieve safer and more effective individualized management.

## 6. Conclusion

In summary, ANCAs can act as a key effector molecule in the inflammatory regulatory network of atherosclerosis by mediating excessive monocyte activation, NET formation, and an abnormal synergistic effect of the complement system and platelets, with clear subtype-specific pathogenic characteristics between MPO-ANCAs and PR3-ANCAs. Clinically, ANCAs not only serve as novel biomarkers for risk screening and stratification of populations at high risk of atherosclerosis but also mediate key inflammatory pathways that represent promising therapeutic targets, such as statins combined with targeted anti-inflammatory therapy targeting the IL-1β/NLRP3 axis, laying a theoretical foundation for the precise management of residual inflammatory risk in atherosclerosis.

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## Availability of data and materials

Not applicable.

## Authors' contributions

QC and LA conceived and designed the review. JC and QC wrote the manuscript. JD and LS contributed to the revision and language polishing of the manuscript. XL and WC helped search and organize the literature. All authors contributed to the article and approved the submitted version. All authors read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

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Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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