Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2026**; 31(7): 48293
https://doi.org/10.31083/FBL48293

Review

Neutrophil Extracellular Traps in Aortic and Cerebrovascular Diseases: Biomarkers, Immunomodulation, and Device-Related Strategies

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Academic Editor: Graham Pawelec
Submitted: 16 November 2025 Revised: 9 January 2026 Accepted: 21 January 2026 Published: 27 July 2026

Abstract

Neutrophil extracellular traps (NETs) have emerged as important mediators at the interface of innate immunity, thrombosis, and vascular remodeling. Aortic aneurysms and cerebrovascular diseases are now recognized as prototypical NET-driven conditions in which dysregulated immunothrombosis accelerates wall degeneration, promotes thrombus formation, and exacerbates tissue damage. This narrative review synthesizes current evidence on NET biology in the context of abdominal and thoracic aortic aneurysms, acute aortic syndromes, ischemic stroke, and intracerebral hemorrhage. First, we summarize the molecular mechanisms of NET formation, regulation, and clearance, outlining how NETs shape the immunothrombotic niche in aneurysm thrombi and the cerebral vasculature. Following this, experimental and clinical data on circulating and tissue NET markers are examined in relation to disease presence, lesion instability, hematoma expansion, and functional outcome, thereby highlighting their potential as diagnostic and prognostic biomarkers. Thereafter, pharmacological strategies that either inhibit NET formation or enhance NET degradation are discussed. We then examine how multilayered flow modulators, biodegradable scaffolds, and bioinspired stent coatings can modulate NET responses at the blood-device interface. Finally, we explore the emerging roles of multi-omics profiling, molecular imaging, artificial intelligence (AI)-based analyses in integrating NET-related signals into personalized risk prediction, device selection, and treatment monitoring. Collectively, these findings position NETs as central targets for biomarker development, immunomodulatory therapy, and immunobioengineered vascular devices. NET-informed precision management of aortic and cerebrovascular diseases is therefore a key area for further research.

Keywords: neutrophil extracellular traps; aortic aneurysm; stroke; biomarkers; immunomodulation; cardiovascular devices; artificial intelligence

1. Introduction

Aortic aneurysms and cerebrovascular diseases (CBVDs) continue to be significant causes of morbidity and mortality worldwide [1,2]. It is well known that immunothrombotic events such as innate immune activation, coagulation and vascular remodeling are tightly intertwined in these diseases [3]. Neutrophils, among the key cellular drivers, have become a focus of renewed interest with the discovery of neutrophil extracellular traps (NETs), network-like chromatin structures adorned with histones and granular proteins released in response to infectious and sterile stimuli [4,5]. While NETs contribute to host defense, excessive or unregulated NET formation promotes endothelial damage, platelet activation, and tissue damage. Experimental and clinical studies have linked NETs to a wide range of cardiovascular diseases (CVD), including atherosclerosis, coronary and venous thrombosis, myocardial infarction (MI), and especially abdominal aortic aneurysm (AAA) and ischemic stroke (IS) [6,7,8]. This has led to the concept of immunothrombosis, wherein NETs function as both scaffolds and signaling hubs that integrate innate immune responses with intravascular clot formation and organ damage.

The cardiovascular system is particularly vulnerable to NET-mediated damage due to a variety of factors. In the aorta, NETs accumulate in intraluminal thrombi and aneurysm walls, interacting with smooth muscle cells (SMCs), macrophages, and the extracellular matrix to trigger proteolysis and wall weakening [6,9]. High circulating NET markers have been associated with larger aneurysm diameter, more rapid growth, and increased inflammatory activity. In the brain, NET-rich thrombi contribute to resistance to thrombolysis and incomplete reperfusion in IS, while NETs exacerbate blood-brain barrier disruption and perihematomal inflammation in intracerebral hemorrhage (ICH) [7,8,10].

The clinical significance of NETs extends beyond their pathogenic role to include diagnostic and therapeutic implications. Circulating NET markers, such as cell-free DNA (cfDNA), citrullinated histone H3 (H3Cit), and myeloperoxidase-DNA (MPO-DNA) complexes, hold promise as biomarkers for disease detection, progression monitoring, and treatment response assessment [9]. Thera-

peutically, strategies targeting NET formation through inhibition of peptidylarginine deiminase 4 (PAD4) or enhancing NET degradation with DNase have demonstrated efficacy in preclinical models [7,11,12].

The overlap between NET biology and cardiovascular device technology is a rapidly developing research area. Histopathological and experimental studies demonstrate that NETs accumulate on and around endovascular implants, linking blood-device contact with thromboinflammation and impaired endothelialization [13,14]. Next-generation stent platforms, multilayered flow modulators, and bioinspired coatings are therefore being designed not only to restore luminal patency but also to actively suppress NETosis and promote vascular healing [15]. In parallel, multi-omics profiling, molecular imaging, and AI-based analytics are increasingly used to integrate NET-related signals, imaging features, and hemodynamic measurements into personalized risk prediction, device selection, and post-procedural monitoring [15,16].

Studies indicate the roles of neutrophil-derived mediators and NETs in vascular and neurovascular beds, including aneurysm biomarkers, thromboinflammation in venous and arterial diseases, and microglia/macrophage interactions in stroke. In light of these findings, we first summarize the biology and vascular consequences of NET formation, followed by an examination of their role in aortic and CBVDs. We then address device-associated NET modulation, NET-associated biomarkers, and AI-assisted predictive modeling. Finally, we outline pharmacological and bioengineering strategies for targeted NET inhibition and immunomodulation.

Previous NET-focused reviews have generally addressed either cardiovascular disease in general or a single vascular bed. In contrast, this review integrates NET biology across aortic and cerebrovascular circulations using a common immunothrombosis framework, and then extends this synthesis to two translational layers typically addressed separately: (i) practical biomarker interpretation (including assay limitations and level of evidence) and (ii) device-oriented strategies aimed at modulating NET responses at the blood-material interface. Finally, it outlines how multiple omics and artificial intelligence can integrate these signals into risk prediction and treatment monitoring, and explicitly separates established clinical evidence from proof-of-concept modeling.

2. NET Formation and Regulation in the Cardiovascular Context

Neutrophils are the most abundant leukocytes in the circulation and are front-line agents of innate immunity. In addition to phagocytosis and degranulation, they can undergo NETosis, a distinct type of activation characterized by the release of decondensed chromatin decorated with histones, myeloperoxidase (MPO), neutrophil elastase (NE), and other granular proteins [5]. Elevated NET markers have been reported in various cardiovascular conditions, particularly in AAA and IS, where they are associated with disease severity and outcome [6,7,9].

2.1 Molecular Mechanisms of NETosis

NET formation occurs through different pathways classified as suicidal and vital NETosis. The canonical pathway, suicidal NETosis, involves chromatin decondensation mediated by peptidylarginine deiminase-4 (PAD4), which catalyzes histone citrullination, reduces the positive charge of chromatin, and promotes DNA unwinding [17]. This process requires NADPH oxidase-dependent reactive oxygen species (ROS) generation, nuclear membrane disruption, and cytoplasmic mixing of granular proteins with DNA. The resulting NET structure consists of extracellular DNA fibers decorated with histones (H1, H2A, H2B, H3, H4), myeloperoxidase (MPO), neutrophil elastase (NE), cathepsin G, and lactoferrin. Vital NETosis is an alternative pathway that allows neutrophils to release chromatin, maintaining their viability and phagocytic functions [14,18]. This rapid process, occurring within minutes, involves vesicular transport of nuclear or mitochondrial DNA without complete cell lysis. Recent evidence suggests that vital NETosis may predominate in some cardiovascular conditions where sustained neutrophil activity is required [19].

Cardiovascular-specific triggers for NET formation include activated platelets releasing high-mobility group box 1 (HMGB1) and platelet factor 4, oxidized low-density lipoproteins accumulating in atherosclerotic lesions, inflammatory cytokines (IL-8, TNF-α, IL-1β) produced by endothelial and smooth muscle cells, complement components activated during vascular injury, and biomechanical shear stress in regions of impaired flow [10,18,20]. The confluence of these stimuli in the diseased vasculature creates a pro-NETotic microenvironment that perpetuates vascular inflammation.

To understand the therapeutic effects of NET-targeted interventions, it is important to recognize the mechanistic differences between suicidal and vital NETosis (Fig. 1), as these pathways may respond differently to pharmacological modulation.

2.2 NET Components and Vascular Toxicity

The cytotoxic effects of NETs on the cardiovascular system are primarily due to their component proteins. Histones, particularly H3 and H4, exert direct cytotoxicity against endothelial cells by disrupting membrane integrity and inducing apoptosis. Citrullinated histones exhibit higher cytotoxicity compared to native forms, which is associated with increased vascular damage in NET-rich environments [5,14,21]. Myeloperoxidase catalyzes the production of hypochlorous acid and other reactive species that oxidatively modify lipids and proteins, promoting endothelial dysfunction and LDL oxidation [22]. Neutrophil elas-

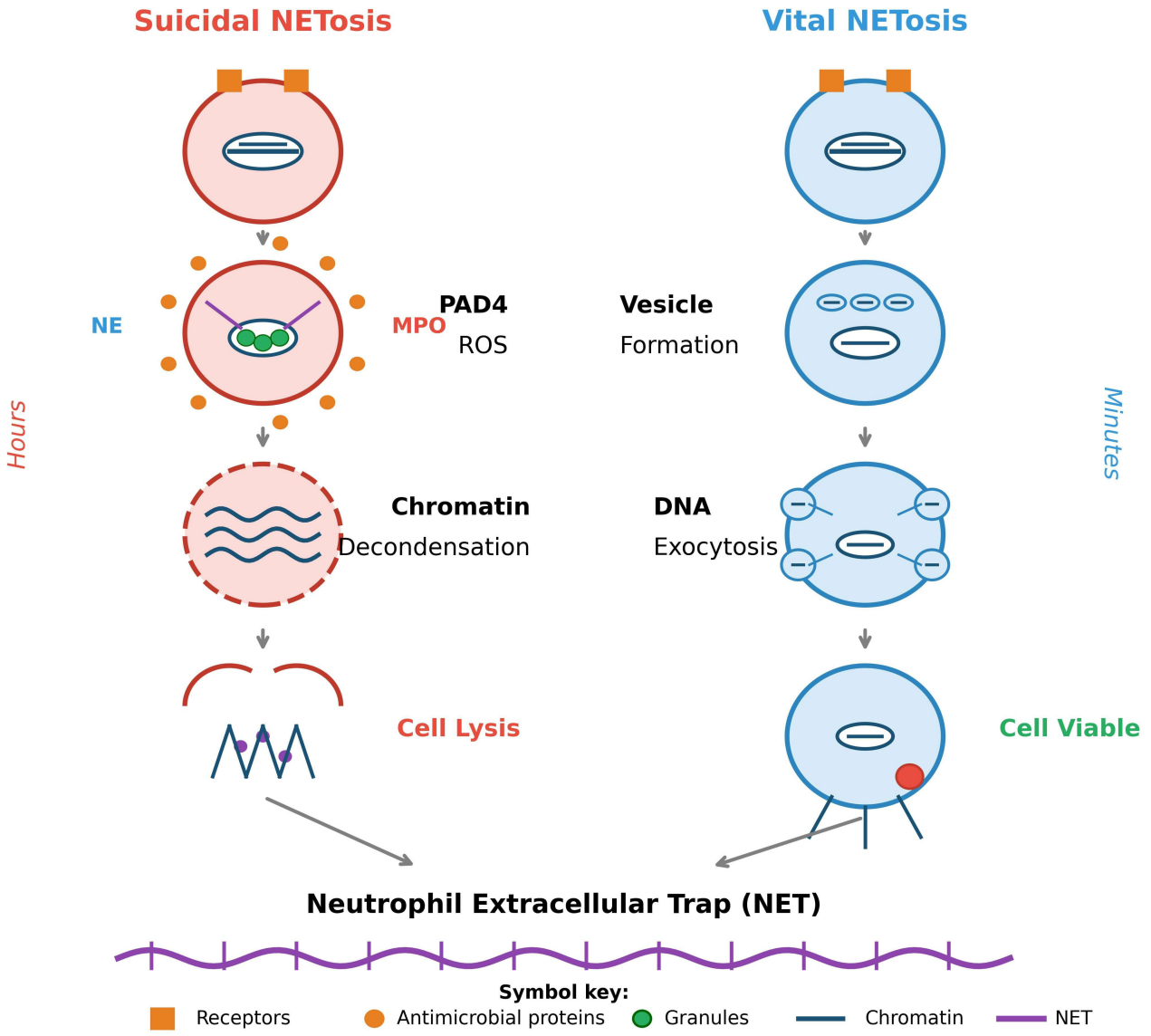

Fig. 1. Neutrophil extracellular trap (NET) formation mechanisms. Suicidal NETosis (left), showing PAD4-dependent chromatin decondensation, ROS formation, and cell lysis occurring within hours, and vital NETosis (right), showing rapid vesicular DNA release while maintaining cell viability within minutes, are schematically shown. Both pathways produce mature NETs consisting of DNA scaffolds decorated with antimicrobial proteins (histones, MPO, NE, cathepsin G, lactoferrin). Abbreviations: MPO, myeloperoxidase; NE, neutrophil elastase; NET, neutrophil extracellular trap; PAD4, peptidylarginine deiminase 4; ROS, reactive oxygen species.

tase directly contributes to aneurysm formation by degrading extracellular matrix components, including elastin and collagen. Additionally, NETs activate matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, thereby promoting proteolytic vascular remodeling. Beyond direct cytotoxicity, NET components activate pattern recognition receptors, including Toll-like receptors (TLR2, TLR4, TLR9) and RAGE (receptor for advanced glycation end products) on endothelial cells, macrophages, and microglia. This perpetuates inflammatory cascades by triggering NF-κB signaling and inflammasome activation [5,19]. Furthermore, NETs activate platelets through histone-mediated pathways, forming platelet-neutrophil aggregates that increase thrombogenicity [23].

2.3 Regulation and Clearance

Physiological control of NETs relies on enzymatic degradation and cellular uptake. DNase I is the main nuclease responsible for the degradation of extracellular DNA structures and, consequently, NET clearance. Experimental and clinical data indicate that impaired DNase activity leads to persistent NET accumulation and promotes autoimmunity and vascular occlusion [24,25]. Simultaneously, macrophages provide a second major clearance pathway

by largely nonphlogistically engulfing NET remnants [26]. More recent studies suggest that soluble mediators released from both M1- and M2-polarized macrophages can directly reduce NET release, and macrophage secretomes contribute to limiting excessive NET formation in inflamed tissues [27].

Immunoregulatory circuits also regulate NETosis. Interactions between regulatory T cells (Tregs) and neutrophils, along with anti-inflammatory cytokines such as IL-10 and TGF-β, can limit neutrophil activation and shape NET responses; however, this interaction appears context-dependent and may contribute to immunosuppression in severe systemic inflammation [28]. Antioxidant systems, including superoxide dismutase and glutathione peroxidase, indirectly reduce NETosis by limiting the availability of ROS necessary for PAD4 activation [29].

In cardiovascular disease, these regulatory mechanisms become quantitatively or qualitatively insufficient. Atherosclerotic plaques exhibit reduced DNase activity and defective efferocytosis, promoting NET persistence within the lesion [30]. In the post-stroke brain, limited penetration of circulating DNases across the blood-brain barrier, combined with microglial dysfunction, leads to prolonged NET survival in peri-ischemic or perihematomal regions [31]. This imbalance between NET formation and clearance is a primary driver of chronic vascular inflammation and immunothrombosis in aortic and cerebrovascular diseases.

2.4 Cellular Interactions

NETs interact with multiple cell types in the vascular microenvironment. Macrophages and monocytes respond to NET-induced DAMPs via TLRs and RAGE, adopt proinflammatory phenotypes, and secrete matrix-degrading enzymes [32]. Microglia in the central nervous system similarly respond to NET components with inflammasome activation and cytokine release [7,8]. Platelets bind to NETs via histones and von Willebrand factor, further enhancing platelet activation and propagating thrombosis [23]. This interaction creates feed-forward loops in which neutrophils, macrophages/microglia, and platelets continuously amplify vascular inflammation and immunothrombotic.

3. NETs in Aortic Diseases

3.1 Pathophysiology of NETs in Abdominal Aortic Aneurysms

AAA is a life-threatening condition characterized by progressive dilation and weakening of the aortic wall. Neutrophil infiltration and NET formation are now recognized as key features of AAA pathology. Abundant NET deposition is detected in the adventitia and intraluminal thrombi of established aneurysms in mouse models based on angiotensin II (AII) infusion or peri-adventitial elastase administration, and treatment strategies that reduce NET burden reduce aneurysm growth and rupture [6]. The mechanisms linking NETs to AAA pathogenesis are multifactorial. First, NET-associated proteases, such as neutrophil elastase and cathepsin G, together with matrix metalloproteinases, directly degrade elastin and collagen, thereby weakening the medial extracellular matrix [5]. Second, NETs propagate inflammation by revealing damage-associated molecular patterns (DAMPs), including extracellular DNA, histones, and HMGB1, which activate macrophages, dendritic cells, and endothelial cells and promote type I interferon and IL-1β signaling [17]. Third, NETs inhibit vascular repair; NET-conditioned media drive vascular smooth muscle cells (SMCs) toward a synthetic, proinflammatory phenotype through pathways such as Hippo-YAP, accompanied by impaired contractile gene expression and increased proliferation and migration [33]. Collectively, these effects provide a mechanistic link between chronic neutrophil activation, medial degeneration, and loss of wall integrity in AAA.

Clinical evidence increasingly supports a pathogenic role for NET-associated material in human AAA. Dihlmann et al. [34] reported that circulating cell-free DNA (cfDNA) levels were significantly higher in patients with AAA than in matched controls, and that cfDNA may amplify vascular inflammation by triggering AIM2 inflammasome activation and downstream IL-1β production *in vitro*. Although cfDNA is not specific to NETs, these findings are consistent with the concept that NET-derived DNA contributes to a proinflammatory environment in the aneurysmal aorta. Complementary experimental and translational studies summarized by Ngo and Gollomp [35] indicate that NET structures and their breakdown products accumulate in inflamed and thrombotic tissues and offer attractive therapeutic targets in sterile cardiovascular disease and infection. Together, these observations support the idea that circulating cfDNA (at least in part NET-derived) may serve both as a biomarker of disease activity and as an active driver of inflammasome-mediated wall degeneration in AAA.

Histological and immunofluorescence analyses of human AAA specimens have shown abundant neutrophils and NET structures within the intraluminal thrombus and adjacent wall, often accompanied by lipoproteins, fragmented elastin, and matrix-degrading enzymes [6,36]. Experimental mouse models support a causal role for NETosis: genetic or pharmacological inhibition of PAD4-dependent NET formation reduces aneurysm incidence, growth, and rupture, accompanied by reduced SMC apoptosis and elastin degradation [33,37]. Recent mechanistic studies have shown that NETs can directly induce a synthetic, proinflammatory SMC phenotype via Hippo-YAP signaling, thus promoting aneurysm formation [33].

Other studies suggest that the gut microbiome is an upstream modulator of NET activity in AAA. In a study combining human and experimental studies, Tian et al. [38] demonstrated that dysbiosis promotes AAA development by increasing NOX2-dependent NET formation and SMC phenotypic change, while restoration of butyrate-

producing bacteria reduces neutrophil infiltration, NETosis, and aneurysm growth. These data suggest that systemic factors, such as microbiota-derived metabolites, may modulate NETogenic stimuli and thus influence aneurysm susceptibility.

Intraluminal thrombus is increasingly recognized as an active immunothrombotic niche where neutrophils, platelets, and red blood cells interact within a NET-rich matrix. This niche sustains proteolytic and oxidative stress at the luminal-wall interface, impairs oxygen diffusion, exacerbating medial hypoxia and cell loss, and provides a reservoir for inflammatory mediators that can be intermittently released into the wall and systemic circulation. By mediating leukocyte recruitment, SMC phenotype, and matrix remodeling, NETs within the thrombus contribute to the transition from stable dilatation to an unstable, rupture-prone aneurysm [6,38].

3.2 NETs in Thoracic Aortic Aneurysm and Dissection: Evidence Overview

Preclinical/translational evidence: Thoracic aortic aneurysms (TAA) and acute aortic dissection (AAD) are multifactorial conditions driven by medial degeneration, genetic predisposition, and hemodynamic stress, with increasing recognition of inflammatory mechanisms [39]. In this context, neutrophil activation and NET-related mediators contribute to vascular damage, chronic matrix remodeling and scar formation [6,9,39].

Clinical evidence: Circulating NET markers in AAD rise sharply in the acute phase. Yang et al. [40] reported that NET-related biomarkers showed diagnostic discrimination and correlated with established markers, supporting their potential role as helpful tools in early assessment and risk stratification.

Interpretation and gaps: While the findings are biologically plausible, the evidence base for TAA and AAD remains smaller and more heterogeneous than that for AAA. Accordingly, NET biomarkers should currently be interpreted as supportive rather than definitive indicators, and further prospective validation using standardized tests is required before they can be applied as routine clinical outcomes.

3.3 NET-Based Biomarkers in Aortic Disease

Developing reliable NET-associated biomarkers for aortic disease is an active area of research. In AAA, several studies have reported increased levels of circulating cfDNA, H3Cit, and MPO-DNA complexes in patients compared to controls, with higher concentrations in larger or more inflamed aneurysms [41]. According to Dihlmann et al. [34], cfDNA was shown to be elevated in AAA and could activate the AIM2 inflammasome and IL-1β release *in vitro*, linking a simple plasma marker to a defined inflammatory pathway. Brandau et al. [36] demonstrated that lipoproteins colocalize with NET structures in AAA tissue, suggesting that NETs may serve as a scaffold for lipid retention and further immune activation. Together, these data support the view that cfDNA and other NET-associated components are markers of aneurysm activity rather than mere bystanders.

In acute AAD, Yang et al. [40] found that circulating cfDNA and H3Cit levels were significantly elevated in the first hours after symptom onset, helping to distinguish AAD from non-dissection chest pain syndromes. NET markers are also associated with systemic inflammation indices and clinical severity, indicating their potential value for early risk assessment and monitoring. It is increasingly recognized that no single NET marker is sufficient for both abdominal and thoracic aortic diseases. Composite panels combining cfDNA, H3Cit, MPO-DNA complexes, and traditional inflammatory markers, ideally supplemented by imaging or thrombus features, are likely to provide more robust information regarding aneurysm growth, rupture risk, or dissection severity [6,34,41]. Our previous study also suggests that integrating neutrophil-derived biomarkers with clinical and imaging variables may improve decision-making beyond purely anatomical thresholds in AAA [42].

To provide an integrated overview of NET-associated biomarkers in aortic and cerebrovascular diseases, the major NET markers in circulation and at the tissue level, detection methods, and clinical associations are summarized in Table 1.

4. NETS in Cerebrovascular Diseases

4.1 Ischemic Stroke

IS, resulting from arterial occlusion, accounts for 85% of stroke cases [43]. Histological analyses show that NET structures are present in both the center and periphery of human stroke thrombi and are often found in association with red blood cells and inflammatory cells [44]. Experimental work by Denorme et al. [8] has demonstrated that genetic or pharmacological inhibition of PAD4-mediated NET formation in mouse middle cerebral artery occlusion reduces infarct size, reduces neuroinflammation, and improves functional outcome. Beyond the occlusive thrombus, NET components accumulate in the downstream microvasculature, where they contribute to “no-backflow” by promoting endothelial activation, leukocyte adhesion, and microvessel occlusion [8]. Clinical studies support the validity of these observations. Increased circulating markers of NETs (such as cfDNA, MPO-DNA complexes, and H3Cit) have been repeatedly reported in patients with acute IS and are associated with stroke severity, infarct volume, and functional outcome [14,45]. Higher NET content in resected thrombi has been associated with resistance to intravenous thrombolysis and poorer angiographic recanalization, while *in vitro* experiments show that DNase enhances tPA-mediated lysis of NET-rich clots [8,44]. Together, these findings identify NETs as central mediators of both thrombus formation and reperfusion injury.

Table 1. NET biomarkers in aortic and cerebrovascular diseases.

Biomarker	Source/Detection	Aortic Diseases	Cerebrovascular Diseases	Clinical Utility	Limitations
cfDNA	Plasma/serum; Fluorometric analysis, qPCR	Elevated in AAA; correlates with size and growth rate	Elevated in IS and ICH; predicts infarct size	Disease detection; progression monitoring	Low NET specificity; requires contextual interpretation with NET-specific markers.
H3Cit	Plasma; ELISA, immunofluorescence	High in AAA walls and ILT; a marker of active NETosis	Elevated in ICH plasma; correlates with stroke severity	NETosis activity; disease severity	Assay heterogeneity; requires validated antibodies and standardized cut-offs.
MPO-DNA complexes	Plasma; Capture ELISA	Correlated with AAA diameter and inflammatory activity	Predicts reperfusion resistance in IS	Thrombotic risk; treatment response	ELISA methods vary; reflect neutrophil activation but are still not entirely specific to NET.
NE-DNA	Serum; ELISA	Elevated in TAA and AAD; predicts complications	Associated with ICH expansion and poor outcomes	Risk stratification; prognosis	Less standardized tests; limited inter-study comparability.
Nucleosomes	Plasma; ELISA	Correlated with aneurysm wall stress	Elevated in acute stroke	Tissue damage markers	Highly non-specific.

Abbreviations: cfDNA, Cell-free DNA; H3Cit, Citrullinated Histone H3; NE, Neutrophil Elastase; AAA, abdominal aortic aneurysm; AAD, acute aortic dissection; ICH, intracerebral hemorrhage; ILT, intraluminal thrombus; IS, ischemic stroke; MPO, myeloperoxidase; TAA, thoracic aortic aneurysm.

4.2 Intracerebral and Subarachnoid Hemorrhage

ICH and subarachnoid hemorrhage (SAH) accounts for approximately 15% of strokes but causes disproportionate morbidity and mortality [43]. In intracerebral hemorrhage (ICH), NETs accumulate within and around the hematoma and in perihematomal brain tissue. Autopsy and experimental studies indicate that NETs are present within the clot and at the hematoma-parenchymal interface, where they exacerbate BBB disruption and edema formation [10,46]. Mechanistically, NETs trigger endothelial and astrocytic damage, upregulate MMP-9 and aquaporin-4 via ERK-dependent pathways, and promote neuronal death. Accordingly, DNase or PAD4 inhibition reduces perihematomal edema and improves neurological recovery in animal models [8,46].

Beyond these observations, there is a tight link between NETs and microglia/macrophage polarization in hemorrhagic stroke. While NET components promote a proinflammatory M1-like phenotype with elevated TNF-α and IL-1β production, pharmacological inhibition of NET formation or enzymatic degradation shifts microglia toward reparative, M2-like profiles with increased IL-10 and TGF-β, resulting in reduced edema and improved functional outcomes [10,47].

SAH provides additional evidence for NET-induced injury. In mouse models, skull-derived neutrophils infiltrate the subarachnoid space, where NETs cause microvascular occlusion and contribute to delayed cerebral ischemia. Genetic or pharmacological NET inhibition alleviates vascular occlusion and neurological deficits [48].

Despite anatomical and hemodynamic differences between the aorta and cerebral vessels, NETs contribute to disease pathogenesis through convergent mechanisms involving thromboinflammation, tissue damage, and adverse remodeling, as summarized in Fig. 2.

4.3 Venous Thromboembolism and the Systemic NET Axis

Although venous thromboembolism (VTE) is not a primary cerebrovascular event, it is closely linked to the same systemic NET axis that drives aortic and cerebral pathology. Experimental and clinical studies indicate that NETs are integral structural components of venous thrombi and promote thrombus formation by providing a scaffold for platelets and red blood cells, while activating intrinsic and extrinsic coagulation pathways [14,49]. NETs play a fundamental role in the pathogenesis of VTE and contribute to all three elements of Virchow's triad: stasis, hypercoagulability, and endothelial damage [23].

In patients with ICH, NET-rich venous thrombi and increased circulating MPO-DNA levels appear to predispose to VTE. Additionally, NET inhibition has been proposed as a potential strategy to reduce thrombotic complications without completely eliminating host defenses [10,35]. These observations support the view that NETs represent a common systemic factor linking arterial, venous, and cerebral thrombotic events.

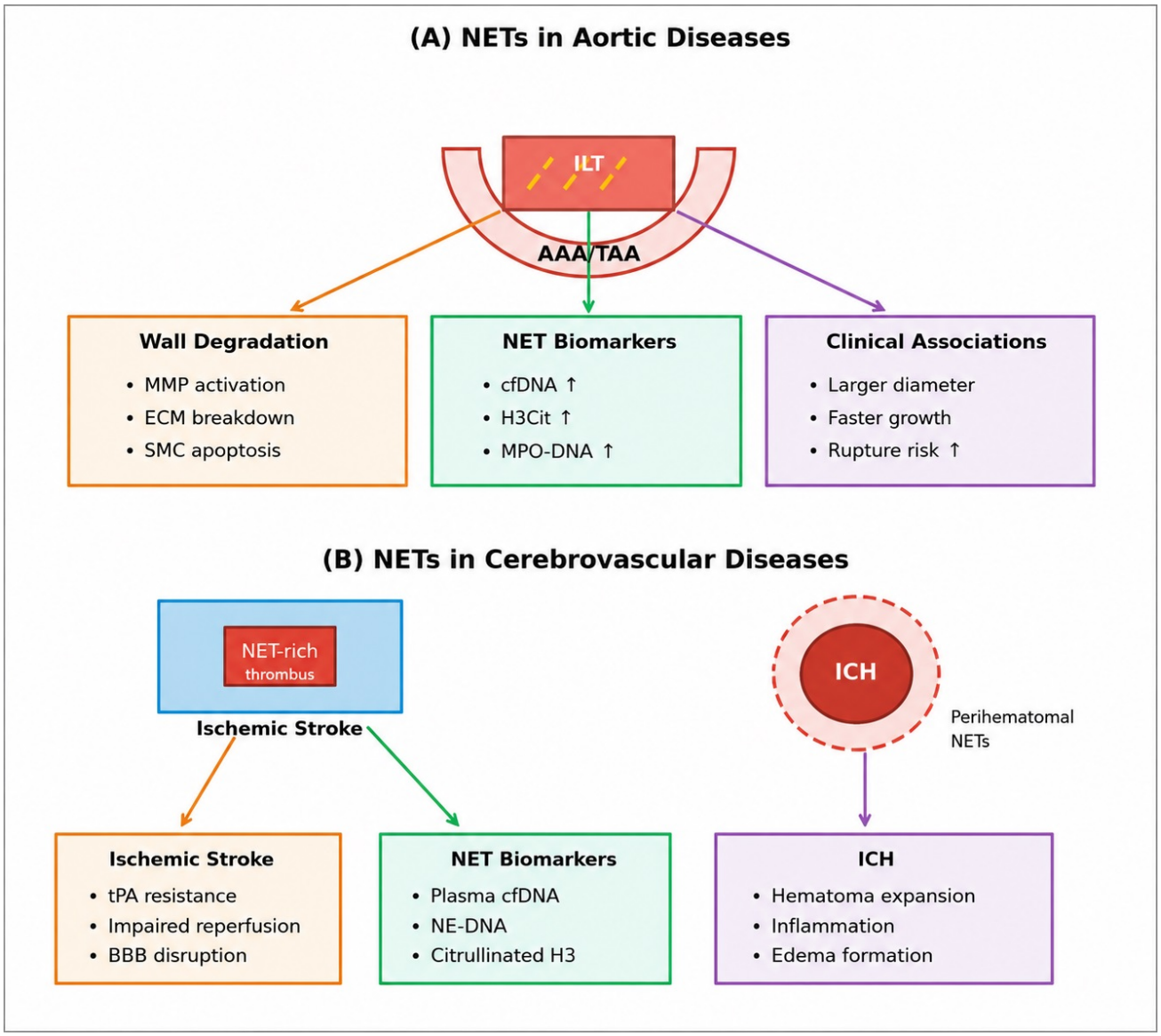

Fig. 2. Role of neutrophil extracellular traps (NETs) in aortic and cerebrovascular diseases. (A) In aortic aneurysms (AAA/TAA), NETs accumulate in intraluminal thrombi and vessel walls, triggering MMP activation, ECM degradation, and SMC apoptosis. NET biomarkers (cfDNA, H3Cit, MPO-DNA) are associated with aneurysm diameter, growth rate, and rupture risk. (B) In cerebrovascular diseases, NETs contribute to tPA-resistant thrombus formation in ischemic stroke and perihematomal blood-brain barrier disruption in intracerebral hemorrhage. Plasma NET markers predict stroke severity and functional outcomes. **Abbreviations**: ↑, increased; AAA, abdominal aortic aneurysm; BBB, blood-brain barrier; cfDNA, cell-free DNA; ECM, extracellular matrix; H3Cit, citrullinated histone H3; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NET, neutrophil extracellular trap; SMC, smooth muscle cell; TAA, thoracic aortic aneurysm; tPA, tissue plasminogen activator.

5. NET-Based Biomarkers in Clinical Decision Making

5.1 Circulating and Local Biomarkers of NET Activity

In inflammatory and cardiovascular conditions, circulating NET markers—including cfDNA, MPO-DNA complexes, and H3Cit—have been associated with adverse outcomes, supporting their potential use as risk markers. Specifically, in aortic and CBVDs, experimental and translational studies show that NET-associated material accumulates in intraluminal thrombi and aneurysm walls, while plasma NET markers are elevated relative to controls and correlate with local inflammatory activity [34,36]. In IS, NET-rich thrombi and high circulating NET markers are associated with larger infarcts and poorer functional outcomes [8,45]. Together, these data suggest that NET biomarkers may capture aspects of immunothrombotic risk not reflected by anatomy alone.

Technically, NET biomarkers can be measured using relatively simple assays. cfDNA is quantified by flu-

orometric or qPCR-based methods, whereas NET-specific components such as MPO–DNA or NE–DNA complexes and H3Cit are assessed using capture or sandwich ELISA. However, recent methodological studies have highlighted shortcomings—including pre-analytical variability, limited assay sensitivity, and the lack of harmonized reference intervals—that currently limit their direct adoption into routine clinical practice [9,50,51]. Therefore, NET biomarkers should currently be viewed as additional variables complementing traditional markers rather than as stand-alone diagnostic tests. For example, combining them with aneurysm diameter and thrombus characteristics, or monitoring the early elevation and subsequent trajectories of NET markers, may improve clinical decision-making in select scenarios. *Ex vivo* histological studies of aneurysm walls and thrombi confirm NET localization within immunothrombotic niches, frequently associated with macrophages, lipids, and degraded elastin [36,52]. These *ex vivo* findings are increasingly supported by imaging modalities such as MRI and PET, where tracers targeting inflammatory activity identify focal vascular segments with high neutrophil and macrophage loads [53,54].

5.2 Artificial Intelligence-Based Predictive Modeling

The current level of maturity of AI applications involving NET biomarkers remains at the proof-of-concept stage, as most are retrospective, single-center, or simulation-based and should be interpreted accordingly rather than as clinically viable decision-support systems. At this stage, AI is best viewed as a tool for exploring multimodal relationships and generating testable hypotheses for prospective, biomarker-guided studies, not as an independent engine for treatment selection.

AI and machine learning (ML) methods are increasingly being used to uncover the complex relationships between NET markers, imaging features, and clinical outcomes. In AAA, ML models integrating clinical variables, aneurysm morphology, and imaging-derived wall stress measurements have shown better prediction of aneurysm growth and endovascular repair failure compared to diameter-based rules [16,55,56]. Liaptsi et al. [45] summarized the growing evidence that NET markers, when combined with established clinical and imaging scores, can improve prognostic models for functional outcome and hemorrhagic transformation in stroke cases. Therefore, it makes sense to extend these concepts to multimodal AI-based cardiovascular decision support, including frameworks that explicitly incorporate biomarkers and device-related features [57,58].

The long-term goal is to integrate NET-related molecular markers, tissue/imaging features, and computational outputs into clinically usable scoring systems for aorta and CBVDs. Conceptual frameworks already exist in other domains, but translation to aorta and CBVD settings is currently limited by small dataset sizes, heterogeneous analysis methods, and the “black box” nature of deep learning. Current regulatory guidelines encourage the development of explainable AI architectures, rigorous external validation, and clear reporting standards for AI models using biomarker data [57,59,60]. AI can integrate multimodal data, including NET biomarkers, imaging features, genomic profiles, and clinical variables, to enable precision medicine approaches in aortic and cerebrovascular diseases (Fig. 3).

When implemented as open, clinician-involved tools, AI-powered decision-making tools for aneurysm disease and device selection can outperform both pure anatomical rules and opaque autonomous algorithms. Current AI applications involving NET-related biomarkers in aortic and cerebrovascular diseases are largely retrospective or modeling-based. Accordingly, the approaches discussed here should be interpreted not as clinically applicable decision support tools, but as proof-of-concept frameworks aimed at generating hypotheses and guiding future prospective validation.

5.3 Implementation and Regulatory Issues

Several hurdles must be overcome for NET-based decision tools to reach guideline level. First, analytical validation is required to standardize measurements across laboratories, including external quality control programs for cfDNA, MPO-DNA, and H3Cit [50,51]. Second, clinical validation in prospective, adequately powered cohorts is required to demonstrate incremental value over existing clinical and imaging scores in AAA, acute aortic syndromes, and stroke. Third, AI-powered models incorporating biomarker data must adhere to emerging frameworks for reliable and explainable medical AI that emphasize transparency, bias assessment, and robust external validation [59,60].

Despite these challenges, the convergence of NET biology, advanced imaging, and artificial intelligence offers a realistic path toward patient-specific vascular care, where decisions about surveillance, timing and type of endovascular repair, and use of additional anti-NET or antithrombotic therapy are guided by quantitative, mechanistically based biomarkers, not just anatomy.

Current and emerging applications of AI for risk prediction, imaging interpretation, and therapeutic decision support related to NET are summarized in Table 2.

6. Therapeutic Strategies and Translational Integration

Targeting NETs offers a variety of complementary therapeutic entry points, ranging from pharmacological agents to device-based and AI-assisted strategies.

6.1 Pharmacological Modulation of NETs

6.1.1 Direct Inhibition of NET Formation

PAD4 is a central enzyme in chromatin citrullination and NET release. In A-II-induced AAA models, genetic

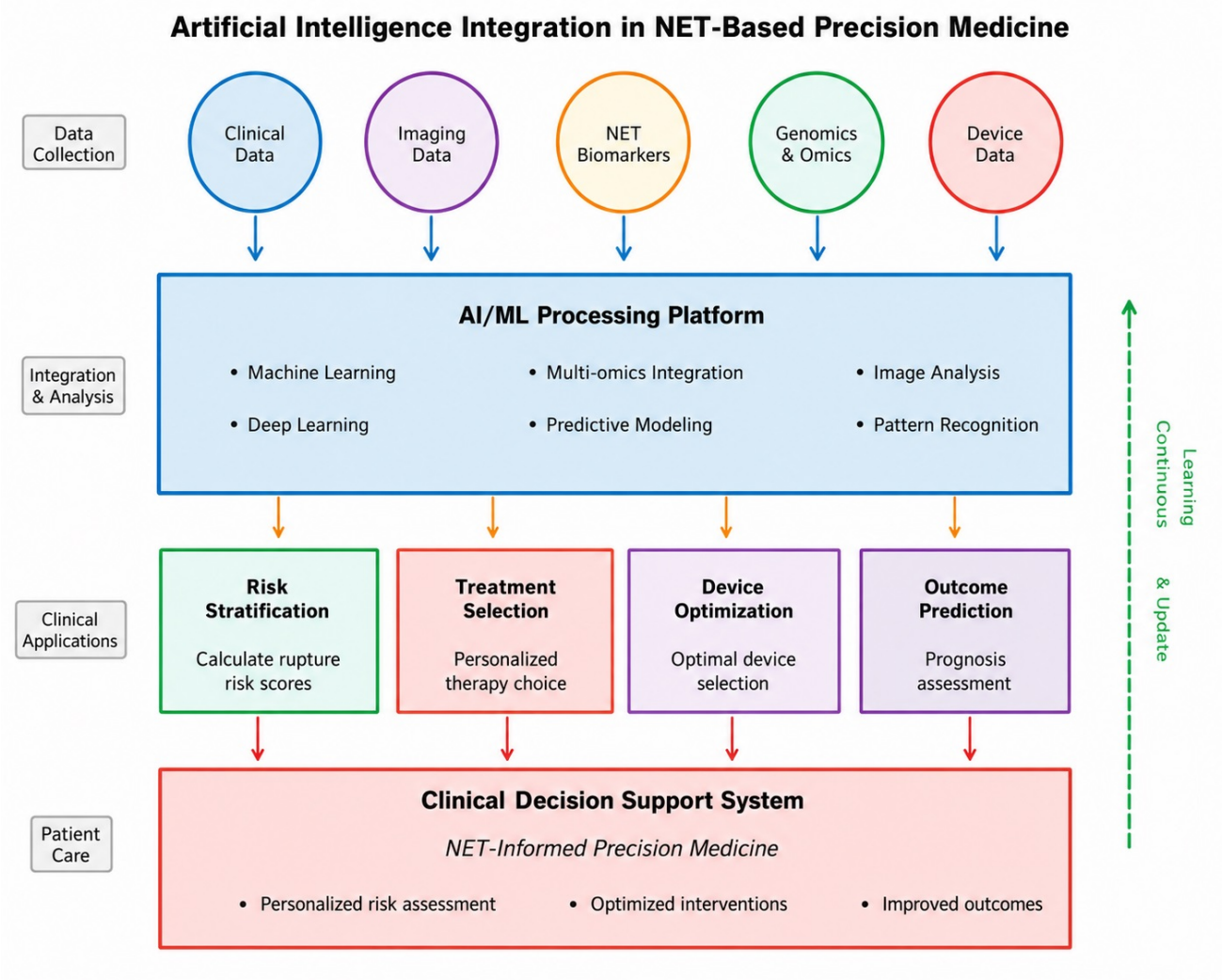

Fig. 3. AI integration in NET-based precision medicine. AI/machine learning platforms integrate multi-source data (clinical, imaging, NET biomarkers, genomics, device data) through machine learning and deep learning to enable risk stratification, personalized treatment selection, device optimization, and outcome prediction. A continuous feedback loop supports model improvement and enhancement of clinical decision-making processes in NET-based cardiovascular care.

Padi4 deletion or pharmacological inhibition with the pan-PAD inhibitor Cl-amidine significantly reduced NET formation, VSMC apoptosis, and aneurysm rupture, identifying PAD4 as a potential therapeutic target in aortic disease [6,37].

In hemorrhagic cerebrovascular models, selective PAD4 inhibition with GSK484 and genetic or pharmacological suppression of PAD4 activity alleviated brain edema, neuronal damage, and microglial inflammation after SAH, supporting PAD4-mediated NETosis as a modifiable driver of secondary brain injury [46,61].

A structured overview of pharmacological, immunomodulatory and device-based strategies targeting NET formation or degradation is presented in Table 3.

6.1.2 Promotion of NET Degradation

DNase I, which enzymatically cleaves extracellular DNA, reduces thrombosis in experimental models of immunothrombosis and venous thrombosis by disrupting NET architecture [23,61]. In IS, adjuvant DNase I improves thrombolysis, reduces infarct size, and does not exacerbate edema or hemorrhagic transformation in several preclinical studies [62,63].

These data have led to early clinical translation. The EXTEND-IA DNase study (NCT05203224) is evaluating intravenous dornase alfa as an adjuvant to standard thrombolysis and thrombectomy in large-vessel IS and uses angiographic reperfusion as the primary endpoint [64]. An additional phase 2 study is testing DNase to attenuate systemic inflammation after IS [65].

Table 2. Artificial intelligence applications in NET-associated cardiovascular diseases.

Application	AI method	Data input	NET related output	Clinical effect
AAA Risk Prediction	Machine learning (RF, SVM)	Demographics, imaging, cfDNA, H3Cit levels	Rupture risk score incorporating NET biomarkers	Advanced risk stratification; surveillance intervals
Stroke Outcome Prediction	Deep learning (CNN)	CT imaging, NET biomarkers, clinical variables	Prediction of hemorrhagic transformation and functional outcome	Treatment decisions; triage optimization
Thrombus Characterization	Neural networks	Histopathology images, immunostaining	NET density measurement; thrombus age	Understanding thrombosis mechanisms
Device Selection	Multi-omics integration	Patient genetics, proteomics, imaging, NET markers	Personalized device recommendations	Optimized intervention planning
Molecular Imaging	Image reconstruction AI	MPO-targeted MPI/PET data	NET localization and quantification in plaques	Non-invasive disease monitoring
Treatment Response	Predictive modeling	Baseline NETs, clinical features, genomics	Prediction of response to PAD4i or DNase therapy	Treatment personalization
Multi-modal Integration	Federated learning	Multicenter NET data, imaging, outcomes	Generalizable NET-based risk models	Scalable precision medicine

Abbreviations: AAA, abdominal aortic aneurysm; cfDNA, cell-free DNA; CNN, convolutional neural network; CT, computed tomography; H3Cit, citrullinated histone H3; MPI, magnetic particle imaging; MPO, myeloperoxidase; PAD4i, peptidylarginine deiminase 4 inhibitor; PET, positron emission tomography; RF, random forest; SVM, support vector machine.

Table 3. Therapeutic strategies targeting NETs in cardiovascular diseases.

Strategy	Agent/Approach	Mechanism	Preclinical Evidence	Clinical Status
Inhibition of NET Formation	PAD4 inhibitors (Cl-amidine, GSK484)	Inhibits histone citrullination and chromatin decondensation	Reduces AAA growth and rupture in mice; improves stroke outcomes	Preclinical; toxicity concerns
	NE inhibitors (Sivelestat)	Inhibits elastase-mediated chromatin release	Reduces NET formation in sepsis models	Approved in Japan for ALI; not tested in cardiovascular disease
NET Degradation	DNase I	Degrades extracellular DNA structures	Reduces thrombosis and improves reperfusion in stroke models	Approved by the FDA for other indications; investigational
	DNase 1L3	Enhanced DNA degradation activity	Prevents NET-induced inflammation in cardiovascular models	Preclinical
Immunomodulation	Anti-HMGB1 antibodies	Neutralizes NET-associated DAMP	Reduces aneurysm progression in animal models	Investigational
Anticoagulant	Heparin	Disrupts NET-platelet interactions and histone binding	Standard anticoagulant with anti-NET properties	Clinical use; not specifically for NETs
Device Coatings	NO-releasing surfaces	Suppresses neutrophil activation and NETosis	Reduces device-associated thrombosis	Experimental; some approved devices
	DNase-releasing scaffolds	Local NET degradation at the device interface	Improves endothelialization in stent models	Preclinical development

Abbreviations: AAA, abdominal aortic aneurysm; ALI, acute lung injury; CVD, cardiovascular disease; DAMP, damage-associated molecular pattern; HMGB1, high mobility group box 1; NE, neutrophil elastase; NO, nitric oxide; PAD4, peptidylarginine deiminase 4.

6.1.3 Upstream Modulators and Repurposed Drugs

NETosis is tightly linked to oxidative burst and protease release. Accordingly, upstream inhibition of NADPH oxidase, NE, or MPO has been proposed. Experimental data suggest that NE contributes to NET-induced endothelial and vascular remodeling, and selective NE inhibitors, such as sivelestat, attenuate NET-associated damage in various inflammatory models; however, their effects on cardiovascular endpoints remain unclear [37,66].

In conjunction, observational and mechanistic studies suggest that commonly used agents—including statins, colchicine, and certain tetracyclines—may indirectly limit

NET formation or downstream proteolysis by reducing oxidative stress and matrix metalloproteinase activity. These effects may contribute to their broader vascular protective properties [6,35].

6.2 Broader Immunomodulatory Strategies

Preclinical evidence suggests that targeting the broader inflammatory milieu that promotes NETosis may be as important as directly inhibiting NET release. IL-1β and IL-6 signaling, complement activation, and the S100A8/A9–TLR4 pathways all promote neutrophil recruitment and NET formation in vascular diseases [6,63]. In aneurysm and stroke models, interventions that modulate macrophage and microglial polarization toward reparative phenotypes (such as mesenchymal stromal cell-derived extracellular vesicles or S100A8/A9 inhibition) reduce NET burden and ameliorate tissue damage [63,67]. Studies in hemorrhagic stroke further highlight the ability of NETs to potentiate proinflammatory microglia/macrophage responses, while suggesting that combined NET inhibition and microglial M2-polarizing strategies may be synergistic.

6.3 Device-Based Modulation of NETs

Beyond systemic therapies, endovascular implants can amplify—or, in some cases, suppress—NET-induced thromboinflammation by intensifying protein adsorption, complement activation, platelet adhesion, and neutrophil recruitment at the blood–material interface. Accordingly, device strategies can be grouped as (i) surface-mediated approaches that reduce neutrophil activation or promote NET degradation, (ii) hemodynamic approaches that normalize local shear patterns and reduce low-flow regions where immunothrombosis propagates.

Notably, most anti-NET device concepts remain at a preclinical stage; as such, this section on Device-Based Modulation of NETs distinguishes established device applications from emerging coatings and biomaterial designs still under development [11,49,68]. More broadly, therapeutic approaches to alleviate NET-mediated pathology span device-based engineering solutions and pharmacological interventions targeting multiple points in NET formation and clearance pathways (Fig. 4).

6.3.1 Thromboinflammation at the Blood-Device Interface

Contact between blood and artificial surfaces triggers a series of events including platelet activation, coagulation, and complement release, which rapidly recruit neutrophils and promotes NET formation. NETs, in turn, act as a scaffold for thrombus stabilization and hold clotting-promoting mediators, linking material-associated thrombosis to inflammation. Consistent with this concept, NET components have been identified in thrombi associated with cardiovascular and cerebrovascular diseases and are increasingly associated with resistance to thrombolysis and adverse outcomes [49,52,69]. These observations support the view that reducing NETosis at the blood-device interface can reduce device-associated thrombotic complications [68,70].

6.3.2 Surface Chemistry and Coatings: Anti-adhesion, Antithrombotic, and NET-targeting Approaches

Material design can shape neutrophil activation and NET release by influencing early protein adsorption and cell adhesion. While heparin and related glycosaminoglycans can bind to cationic histones and reduce thromboinflammation on device surfaces, more broadly, antithrombotic coatings aim to reduce platelet-neutrophil interaction that promotes NETosis [71]. Nitric oxide (NO)-releasing surfaces and other endothelial-mimicking chemistries have also been investigated to limit platelet activation and leukocyte adhesion, thereby indirectly suppressing NET-induced thrombogenesis [71,72].

More directly, DNase-functionalized materials and other bioactive approaches have been proposed to enhance NET degradation on the surface and reduce the persistence of prothrombotic DNA scaffolds; however, these concepts require careful consideration of coating durability, local dosing, and potential impacts on recovery [6,70,73,74]. Overall, while these platforms are not uniformly designed as “anti-NET” devices, their capacity to reduce platelet activation, inflammation, and extracellular DNA persistence may lead to a reduction in NET-mediated thrombosis.

6.3.3 Hemodynamic Modulation and Flow-Mediated NETosis Effects

Hemodynamics significantly shape thromboinflammation. Impaired flow, recirculation, and low wall shear stress zones can promote platelet activation and leukocyte recruitment, creating favorable conditions for immunothrombosis and NET propagation. Multilayer flow modulators and related endovascular structures for complex aneurysm anatomy exemplify strategies that alter local flow patterns and can reduce thromboinflammatory signaling by stabilizing shear and promoting favorable remodeling [67,75,76]. From a NET perspective, these devices can influence the spatial and temporal formation of intraluminal thrombus and the inflammatory microenvironment, potentially reducing persistent neutrophil activation and extracellular DNA scaffolding; however, clinical validation directly focused on NET remains limited [52,68,77]. Therefore, hemodynamic design should be considered not only for its mechanistic performance but also for its downstream impact on thromboinflammation.

6.3.4 Biodegradable, Bioactive, and Biomimetic Platforms

Newer device concepts aim to improve healing while minimizing chronic inflammation. Biodegradable and bioactive stent technologies have been proposed to reduce prolonged foreign body exposure and promote endothe-

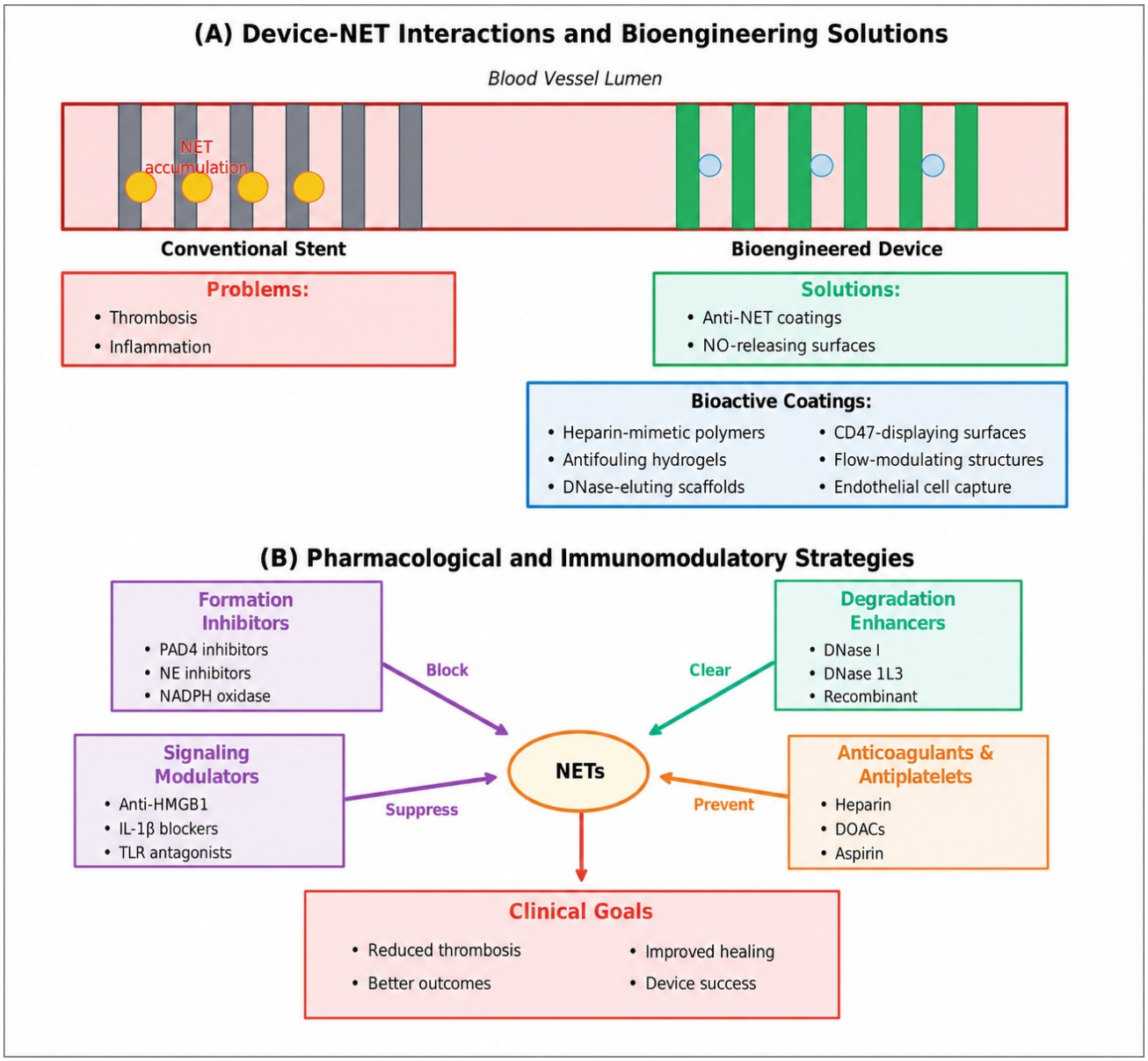

Fig. 4. Device-NET interactions and therapeutic strategies targeting NETs in cardiovascular diseases. (A) While conventional devices promote NET accumulation leading to thrombosis and inflammation, bioengineered devices incorporate anti-NET strategies (NO-releasing surfaces, DNase-releasing scaffolds, heparin-mimicking polymers, anti-fouling hydrogels). (B) Therapeutic approaches target NET formation (PAD4/NE/NADPH oxidase inhibitors), degradation (DNase I/1L3), immunomodulation (anti-HMGB1, IL-1β blockers, TLR antagonists), and thrombosis prevention (anticoagulants/antiplatelets) to reduce complications and improve clinical outcomes. **Abbreviations**: DNase, deoxyribonuclease; HMGB1, high-mobility group box 1; IL, interleukin; NADPH, nicotinamide adenine dinucleotide phosphate; NE, neutrophil elastase; NET, neutrophil extracellular trap; NO, nitric oxide; PAD4, peptidylarginine deiminase 4; TLR, Toll-like receptor.

lialization, potentially reducing sustained leukocyte activation over time [15,72]. In parallel, biomimetic approaches, including exosome-mimicking or cell membrane-inspired coatings, have been explored as strategies to modulate immune recognition and promote healing-promoting signaling at the device interface [16,55,77]. While these concepts are not yet established as NET-targeted therapies, their immunomodulatory potential is significant, as persistent foreign body responses can sustain neutrophil activation, platelet-leukocyte interactions, and thrombosis.

6.3.5 Translation Preparation and Design Priorities

Overall, the evidence supports a consistent rationale for device-mediated NET modulation, although several research gaps remain. First, many anti-NET coating concepts are in the preclinical stage and require standard-

ized evaluation in terms of thrombogenicity, endothelialization, durability, and safety in clinically relevant models [14,78]. Second, NET biomarkers can be useful as exploratory endpoints in device studies, but test variability and disease heterogeneity make inter-study comparisons difficult. Third, since NET biology differs across vascular beds and patient phenotypes, a future direction is immunobioengineering: tailoring surface chemistry and hemodynamics to minimize thromboinflammation while preserving healing [15,77]. These priorities are consistent with emerging efforts to integrate biological readouts with device engineering to reduce NET-related complications [57,58].

6.4 Artificial Intelligence-Enabled Precision Therapy

Given the heterogeneity of NET biology across patients and vascular regions, AI and ML approaches are attractive tools for guiding who should apply NET-targeted therapies, when, and with which devices or drugs. In aneurysmal disease, ML models that integrate clinical variables, aneurysm morphology, and wall stress estimates outperform diameter-based rules for predicting the risk of growth and rupture [16,55,56]. Expanding these frameworks to include circulating NET markers and imaging surrogates of immunothrombosis is a logical next step. In stroke cases, recent reviews highlight that combining NET biomarkers with clinical scales and perfusion imaging can improve prognosis and the selection of additional DNase or PAD4 inhibitor therapy [7,8].

Multimodal AI-driven decision support approaches integrating NET measurements with radiomics, computational fluid dynamics outputs, and device features is feasible and can be implemented as transparent, clinician-involved tools rather than black-box systems [57,58]. Furthermore, regulatory and ethical frameworks for such AI systems are emerging. They emphasize requirements such as explainability, bias reduction, and rigorous external validation; these requirements will be particularly important where algorithms are used to recommend immunomodulatory or device-based interventions [59,60].

In summary, NET-targeted therapies are likely to be multimodal upon application: (i) Direct NET modulation (PAD4 inhibitors, DNase) to reduce scaffold formation or accelerate clearance; (ii) Broader immunomodulation (cytokine, complement, or microglia/macrophage targeting) to reduce upstream drivers and promote repair; (iii) Device-based strategies, including hemodynamic optimization and bioactive coatings, to minimize blood-derived NETosis.

7. Future Directions and Conclusions

7.1 Research Gaps

Several areas of research are likely to reshape how NETs are understood and targeted in aortic and cerebrovascular diseases. Single-cell and spatially resolved technologies are beginning to reveal that neutrophils are not a homogeneous population but consist of subsets with distinct NET-forming capacities, transcriptional programs, and surface receptor profiles [79,80]. Identifying which subsets predominate in abdominal aortic aneurysms, acute aortic syndromes, IS, and intracerebral hemorrhage may open the door to highly selective interventions that preserve host defenses while reducing vascular injury.

In parallel, spatial transcriptomics, multiplex imaging, and advanced microscopy are enabling high-resolution mapping of NETs within aneurysm walls, intraluminal thrombi, and brain parenchyma. These approaches can identify microanatomical niches where NETs interact with macrophages, microglia, smooth muscle cells, and endothelial cells, identifying “hot spots” most suitable for local therapeutic application.

An additional limitation relates to the temporal dimension of NET biology. The kinetics of NET formation, persistence, and clearance during aneurysm development, acute stroke, and post-interventional remodeling have not yet been fully characterized. Longitudinal imaging combined with serial biomarker sampling will be necessary to define therapeutic windows in which NET inhibition is likely to be beneficial and may prevent necessary repair. Furthermore, sex- and age-related differences in neutrophil biology and NET propensity remain underexplored and may have direct implications for personalized treatment strategies [81,82].

7.2 Future Directions

Despite compelling mechanistic evidence, clinical translation of NET-targeted therapies is still in its early stages, pointing to clear directions for future research:

(i) Analytical standardization: Assays for cfDNA, MPO-DNA, citrullinated histones, and related markers vary in terms of pre-analytical use, calibration, and reporting. Consistent protocols and reference ranges are prerequisites for the use of NET biomarkers in multicenter studies or routine decision-making processes.

(ii) Specificity and safety: Many circulating markers are not completely specific for NETs and may be elevated in other forms of cell death or inflammation. Furthermore, global suppression of NET formation carries theoretical risks for infection and wound healing. Strategies focusing on transient inhibition within well-defined clinical windows or local application on device surfaces may offer a more favorable risk-benefit profile.

(iii) Patient selection and endpoints: There is limited data linking NET measurements to definitive clinical outcomes. Further studies are needed to determine which patients benefit most from NET-modulating therapies and which surrogate endpoints, such as changes in NET biomarkers, aneurysm growth rate, thrombus characteristics, or reperfusion quality, best reflect treatment effects.

(iv) Regulatory and ethical frameworks: As AI-powered models begin to integrate NET biomarkers, imaging features, and device characteristics, issues of trans-

parency, bias reduction, and validation become central. Regulatory guidelines for "software as a medical device" and biomarker-based enrichment of clinical trials will significantly impact the pace of adoption [83,84].

Overcoming these limitations will require coordinated efforts across vascular biology, neurology, imaging, biomarker science, data science, and regulatory disciplines.

7.3 Towards Precision Immuno-Bioengineering

Based on current studies, future research will point towards precision immuno-bioengineering, which is the deliberate integration of molecular targeting, device innovation, and intelligent assays. Conceptually, this could include focus on:

(i) Smart endovascular devices that combine optimized hemodynamics with bioactive or exosome-mimicking coatings to minimize NET accumulation and potentially incorporate sensors capable of detecting local inflammatory or thrombotic signals.

(ii) Personalized immunoprofiling that stratifies patients based on NET proneness using combinations of NET biomarkers, multi-omics signatures, and functional neutrophil assays and guides the intensity and duration of NET-directed therapy.

(iii) Cross-vessel integration, where information from aorta, coronary, and neurovascular beds are combined to identify common immunothrombotic nodes, such as PAD4 activity, NET-platelet aggregates, or specific macrophage/microglial states, that can be targeted across organ systems.

(iv) AI-powered prediction and monitoring, a process in which digital twins and computational models simulate how NETs, hemodynamics, and device properties interact in individual patients, informing procedure planning, device selection, and post-procedural monitoring.

In this framework, endovascular intervention is evolving from a purely mechanical action to a feedback-controlled process informed by the immune system, where devices, drugs, and data flows are co-designed.

8. Conclusions

NETs have evolved from an immunological interest to a unifying concept in vascular pathology within a decade. In aortic aneurysms and acute aortic syndromes, NETs trigger extracellular matrix degradation, mural thrombus organization, and maladaptive remodeling of the aortic wall. In ischemic and hemorrhagic stroke, they promote thrombus formation and resistance to fibrinolysis, compromise the blood-brain barrier, and enhance microglial and macrophage-mediated neuroinflammation. In these areas, NET burden consistently correlates with disease severity, procedural complexity, and outcome, positioning NET-associated molecules as promising biomarkers.

The translational landscape summarized in this review encompasses three converging areas: (i) Biomarkers and imaging, where NET-derived signals support anatomical and hemodynamic assessments for risk stratification and treatment monitoring; (ii) Immunomodulatory therapies targeting NET formation, degradation, and interaction with macrophages and microglia; (iii) Device-centric and AI-enabled strategies that utilize bioengineered surfaces, flow modulators, and computational tools to minimize NET-related complications and personalize treatment.

Realizing the full potential of NET-targeted approaches will depend on rigorous test standardization, carefully designed adaptable clinical trials, and regulatory frameworks that embrace explainable AI and biomarker-guided decision support. Equally important will be educating clinicians and patients about the role of NETs in vascular disease and the rationale for new treatments.

If these scientific, technical, and educational elements can be combined, targeting NETs could signal a shift from purely structural correction of aortic and cerebrovascular lesions to immune-informed vascular repair, a paradigm in which predictive, preventive, and personalized interventions are guided by a deep understanding of vascular immunobiology.

Author Contributions

RD and NA designed the study, drafted the manuscript, and supervised and edited it. NA wrote the manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. Both authors read and approved the final version.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

Both authors declare no conflicts of interest. Despite RD is the president of the INVAMED Institute for Medical Innovation. NA is a volunteer consultant for Med-International UK Health Agency Ltd, the judgments in data interpretation and writing were not influenced by this relationship.

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