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Review

The Four-Hit Framework of Aortic Aneurysm Progression: From Wall Injury to Imaging and Targeted Intervention

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ABSTRACT: Aortic aneurysm (AA) is a life-threatening vascular disease characterized by progressive aortic dilatation, wall degeneration, and risk of rupture. Although diameter-based imaging remains central to clinical decision-making, it does not fully reflect the biological processes underlying aneurysm initiation, expansion, and rupture. Recent advances in omics, vascular biology, functional imaging, and nanomedicine provide new opportunities to reinterpret AA pathogenesis. In this review, we propose the Four-Hit Hypothesis as an integrative framework for understanding AA progression. The four hits include disruption of the aortic barrier environment, immune-inflammatory invasion, maladaptive proliferative repair, and aging-associated structural destruction. We discuss their roles across disease stages, the differences between abdominal and thoracic aortic aneurysms, and their implications for biomarkers, imaging, and therapeutic development. This review aims to organize current evidence on AA biology and highlight potential directions for future studies in risk assessment, imaging, and targeted intervention.

Keywords: Aortic aneurysm; Vascular inflammation; Functional imaging

1. Introduction

Aortic aneurysm (AA) is a life-threatening vascular disorder characterized by segmental and progressive dilatation of the aorta, degenerative remodeling of the aortic wall, and an increased risk of rupture. Clinically, AA is commonly classified into thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA), which differ in anatomical location, epidemiology, risk adrs, genetic contribution, and dominant pathological features. The increasing global burden of AA, together with the high mortality of

rupture and the substantial cost of surgical or endovascular repair, highlights the need for improved approaches to disease assessment and intervention [1]. Current clinical management relies largely on diameter-based surveillance, but aortic diameter does not fully reflect the biological activity within the aneurysm wall, including inflammation, metabolic dysregulation, extracellular matrix remodeling, impaired repair, and cellular senescence [2]. At present, no pharmacological therapy has been established in routine clinical practice to effectively halt AA progression [3].

Over the past two decades, studies using animal models, human aneurysm tissues, genetic analyses, multi-omics approaches, single-cell sequencing, and vascular biology methods have identified multiple mechanisms involved in AA pathogenesis, including endothelial dysfunction, smooth muscle cell phenotypic switching, immune-cell infiltration, oxidative stress, proteolytic matrix degradation, maladaptive repair, and aging-associated vascular degeneration [4–10]. However, these processes are often discussed as separate pathological events, and their relative importance may differ between AAA and TAA, between genetic and non-genetic aneurysms, and across disease stages. In this review, we propose the Four-Hit Hypothesis as an integrative framework for understanding AA progression. The framework includes four broad biological domains: disruption of the aortic barrier environment, immune-inflammatory invasion, maladaptive proliferative repair, and aging-associated structural destruction. Rather than representing a new standalone mechanism or a universal linear pathway, the Four-Hit Hypothesis is used here as an organizing framework to summarize current evidence and discuss implications for biomarkers, imaging, and therapeutic development.

2. Clinical and Biological Heterogeneity of Aortic Aneurysm

An aortic aneurysm should be viewed as a spectrum of biologically distinct disorders rather than a single, uniform disease entity. Although thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA) share the final phenotype of progressive aortic dilatation and wall weakening, they differ markedly in developmental origin, anatomical environment, cellular composition, genetic architecture, inflammatory burden, and clinical behavior [11]. In TAA, particularly heritable forms such as Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, and familial nonsyndromic TAA, disease initiation often stems from intrinsic medial vulnerability, including defects in extracellular matrix integrity, transforming growth factor-β signaling, smooth muscle cell contractile function, and mechanotransduction. However, recent studies indicate that TAA is not simply a passive consequence of structural weakness. Zhang et al. showed that aortic stress activates an adaptive smooth muscle cell program that preserves aortic strength and protects against aneurysm and dissection in mice [6]. Huang et al. demonstrated that CX3CR1-positive macrophages can promote aneurysm progression in a Marfan syndrome model [12]. These findings suggest that TAA progression reflects a dynamic balance among inherited wall vulnerability, stress-responsive smooth muscle cell adaptation, immune cell activity, and maladaptive repair (Table 1).

Table 1. Representative evidence illustrating mechanistic heterogeneity across aortic aneurysm subtypes.

Four-Hit Component	Representative Evidence	Aneurysm Context	Heterogeneity Highlighted
Hits 1/3: Barrier disruption/maladaptive proliferative repair	Stress-responsive adaptive SMC program (Zhang et al.)	TAA model	Medial vulnerability and wall-stress response
Hit 2: Immune-inflammatory invasion.	CX3CR1 + macrophage-driven progression (Huang et al.)	Marfan-associated TAA	Immune modification of a genetic aneurysm
Hit 2: Immune-inflammatory invasion.	IFN-inducible monocyte/macrophage states (Le et al.)	AAA single-cell analysis	Immune-cell state heterogeneity
Hit 2: Immune-inflammatory invasion.	Microbiome-NET axis (Tian et al.)	Experimental AAA	Systemic inflammatory input
Hit 4: Aging-associated structural destruction.	miR-1204-MYLK aging axis (Liu et al.)	AAD model	Aging-driven disease amplification

Hit 4: Aging-associated structural destruction.	Age-associated aortic proteomic remodeling (Tyrrell et al.)	Human aorta/TAA	Age-related molecular remodeling
Cross-cutting heterogeneity	Shared genetic susceptibility with cardiometabolic traits (Zheng et al.)	AAA genetic analysis	Genetic-metabolic convergence

By contrast, degenerative AAA is more closely linked to aging, smoking, cardiometabolic risk factors, intraluminal thrombus, chronic inflammation, and proteolytic extracellular matrix destruction. Sex-related hormonal factors may further contribute to aneurysm heterogeneity. Androgen signaling exerts context-dependent effects on endothelial function, inflammation, vascular smooth muscle cell homeostasis, and extracellular matrix remodeling, with its vascular consequences varying with hormone levels, cellular context, and disease state [13]. This disease is increasingly recognized as an active thrombo-inflammatory and immune-remodeling process rather than a simple mechanical enlargement of the infrarenal aorta. Single-cell and mechanistic studies have strengthened this concept: Le et al. identified interferon-inducible monocytes/macrophages as candidate cellular drivers of AAA progression and rupture risk [14]; Tian et al. linked gut microbiome dysbiosis to neutrophil extracellular trap formation and aneurysm development [15]; and Wang et al. showed that macrophage ILF3 promotes AAA by inducing an inflammatory imbalance [16]. At the same time, the boundary between genetic and acquired disease is not absolute. Zheng et al. reported shared genetic susceptibility between AAA and cardiometabolic traits related to lipid metabolism and inflammation [17], while Liu et al. and Tyrrell et al. highlighted aging-associated molecular and proteomic remodeling as active modifiers of aneurysm biology [4,18]. Together, these findings support a model in which aneurysm subtype, etiology, disease stage, and dominant biological activity determine the relative contribution of barrier disruption, immune-inflammatory invasion, maladaptive repair, and aging-associated structural destruction (Figure 1).

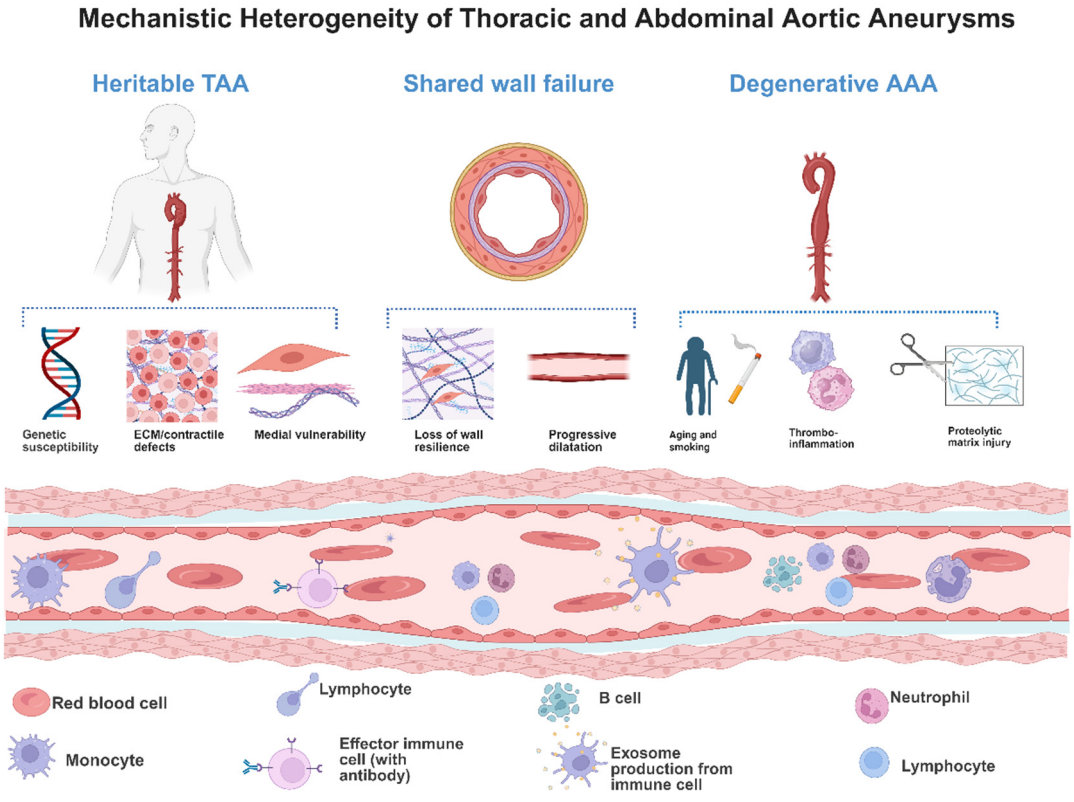

Figure 1. Mechanistic heterogeneity of thoracic and abdominal aortic aneurysms. Distinct mechanisms underlying TAA and AAA converge on a shared phenotype of aortic wall weakening and progressive dilatation. AAA, abdominal aortic aneurysm; ECM, extracellular matrix; TAA, thoracic aortic aneurysm.

Thus, the Four-Hit Hypothesis is best understood not as a universal linear pathway or a new standalone mechanism, but as a comparative framework or tool for synthesizing established and emerging evidence and organizing heterogeneous mechanisms across aneurysm subtypes.

3. The Four-Hit Hypothesis of Aortic Aneurysm Progression

Aortic aneurysm progression can be framed as a breakdown of coordinated aortic wall maintenance. The normal aortic wall depends on endothelial integrity, vascular smooth muscle cell homeostasis, extracellular matrix organization, mechanosensitive signaling, and controlled immune surveillance to preserve tensile strength under continuous pulsatile stress. Disruption of these systems has been implicated at multiple biological levels: endothelial tight-junction dysfunction has been linked to thoracic aortic aneurysm and dissection [19], improved endothelial barrier function has been shown to decelerate early abdominal aortic aneurysm progression [20], altered smooth muscle mechanosensation can promote aneurysm formation [21], and epigenetic control of vascular smooth muscle cell homeostasis has been shown to protect against abdominal aortic aneurysm formation [22]. Building on these observations, the Four-Hit Hypothesis organizes aneurysm progression into four partially overlapping biological domains: disruption of the aortic barrier environment, immune-inflammatory invasion, maladaptive proliferative repair, and aging-associated structural destruction. This framework provides a structured way to discuss how loss of wall integrity, inflammatory amplification, incomplete repair, and progressive tissue degeneration may jointly shape aneurysm evolution.

3.1. Hit 1: Disruption of the Aortic Barrier Environment

The first hit can be conceptualized as a failure of the aortic wall to preserve compartmental integrity and buffer mechanical stress. The aorta is not simply a passive conduit; it is a multilayered biological barrier in which endothelial junctions regulate luminal permeability, medial smooth muscle cells and elastic lamellae absorb pulsatile load, extracellular matrix networks maintain tensile strength, and the adventitia participates in immune surveillance and repair. When this barrier environment is disturbed, circulating inflammatory mediators, metabolic stress, thrombotic signals, and oxidative injury can more readily access or reshape the vessel wall, lowering the threshold for downstream inflammation and structural degeneration. Recent studies support this barrier-centered view at the luminal interface: Yang et al. showed that endothelial tight junction disruption contributes to thoracic aortic aneurysm and dissection [19], whereas another study by Yang et al. demonstrated that improving endothelial barrier function through ALDH2-LIN28B-ELK3 signaling slows early progression of abdominal aortic aneurysm. Luo et al. further linked endothelial dysfunction to aneurysm and dissection through an HDAC1-ZEB2-NuRD complex that regulates protein S-sulfhydration [23], and Stammer et al. reported VE-cadherin shedding in patients with aortic aneurysm and dissection [24]. These findings suggest that endothelial instability may contribute to the creation of a permissive interface for inflammatory entry and wall injury.

Barrier disruption also involves the medial compartment's failure to sense and appropriately absorb mechanical stress. Qian et al. showed that microskeletal stiffness promotes aneurysm formation by sustaining pathological vascular smooth muscle cell mechanosensation through Piezo1 [21], while Zhao et al. reported that BAF60c protects against abdominal aortic aneurysm formation through epigenetic control of vascular smooth muscle cell homeostasis. These studies extend the concept of "barrier" beyond the endothelial monolayer to encompass medial stress buffering and maintenance of smooth muscle cell state. In heritable TAA, this first hit may be dominated by intrinsic medial vulnerability and abnormal mechanotransduction; in degenerative AAA, it may be more closely linked to endothelial dysfunction, metabolic injury, thrombotic signaling, adventitial inflammation, and proteolytic matrix damage. Thus,

disruption of the aortic barrier environment creates the permissive biological ground on which immune-inflammatory invasion and maladaptive repair can subsequently develop.

3.2. Hit 2: Immune-Inflammatory Invasion

Following disruption of the aortic barrier environment, inflammation becomes a mechanism of biological amplification rather than a nonspecific bystander response. The injured aneurysmal wall provides multiple entry points and niches for immune activation, including endothelial dysfunction, medial injury, adventitial remodeling, intraluminal thrombus, and perivascular tissue. Within these compartments, macrophages, neutrophils, lymphocytes, mast cells, platelets, fibroblasts, and smooth muscle cells can form multicellular inflammatory circuits that sustain cytokine signaling, protease activity, oxidative stress, and regulated cell death. Recent studies have moved the field beyond the idea of diffuse inflammatory infiltration toward a more resolved view of cell-cell communication and immune niches. This reciprocal immune-vascular interaction is not unique to aneurysm disease. In pulmonary arterial hypertension, crosstalk among immune cells, endothelial cells, smooth muscle cells, and fibroblasts similarly sustains endothelial dysfunction, proliferative remodeling, and fibrosis. Although the vascular territories differ, these observations reinforce the concept that inflammation is maintained through bidirectional cellular communication rather than isolated immune-cell infiltration [25]. Wu et al. showed that NINJ1 facilitates abdominal aortic aneurysm formation by enhancing macrophage infiltration through the TLR4-ANXA2 axis [26]. Thayaparan et al. linked endothelial dysfunction to macrophage-dependent abdominal aortic aneurysm formation in an atherosclerotic plaque context [27]. Wagenhäuser et al. further demonstrated that platelet crosstalk with macrophages and fibroblasts aggravates inflammation, aortic wall stiffening, and osteopontin release in abdominal aortic aneurysm [28]. In parallel, neutrophil-related injury illustrates how innate immune activation can be converted into structural damage: Chen et al. reported that mesenchymal stem cell-derived extracellular vesicles protect against abdominal aortic aneurysm formation by inhibiting NET-induced ferroptosis [29], Qi et al. showed that NET-induced ferroptosis promotes aneurysm formation through SLC25A11-mediated mitochondrial glutathione depletion [30], and Xiong et al. demonstrated that PI3Kγ promotes NET formation through noncanonical pyroptosis in abdominal aortic aneurysm [31].

The inflammatory profile of the second hit is unlikely to be uniform across aneurysm subtypes. In a degenerative abdominal aortic aneurysm, immune-inflammatory invasion is often a dominant feature, supported by macrophage and neutrophil infiltration, intraluminal thrombus-associated inflammation, NET formation, oxidative stress, and proteolytic matrix remodeling. In contrast, in many forms of heritable thoracic aortic aneurysm, inflammation may act more as a disease modifier than as the initiating event, superimposed on intrinsic medial vulnerability, smooth muscle cell dysfunction, and extracellular matrix defects. Moreover, immune activation is not uniformly destructive. Depending on timing and cellular state, macrophage polarization, regulatory T cells, and reparative stromal responses may either restrain inflammation or contribute to maladaptive remodeling. Single-cell immune profiling has begun to capture this complexity, with Yuan et al. deconstructing immune-cell distributions in experimental abdominal aortic aneurysm [32]. Thus, the second hit should be interpreted as a context-dependent immune remodeling program rather than a simple accumulation of inflammatory cells. Its pathological consequence is to amplify matrix degradation, vascular cell dysfunction, and the transition toward maladaptive repair.

3.3. Hit 3: Maladaptive Proliferative Repair

The third hit captures a central paradox in aneurysm biology: the same reparative programs that may preserve wall integrity can, when dysregulated, accelerate wall failure. After barrier disruption and immune-mediated injury, the aortic wall activates smooth muscle cell plasticity, extracellular matrix remodeling, fibroblast and stromal-cell expansion, endothelial-to-mesenchymal transition, and growth

factor signaling in an attempt to restore mechanical competence. These responses are not intrinsically harmful; in early or localized injury, they may reinforce the wall and compensate for matrix loss. However, when repair is prolonged, spatially disorganized, or uncoupled from the original injury, it can produce fibrosis, stiffness, cellular exhaustion, matrix disarray, and progressive loss of tensile strength. Recent studies support this shift from adaptive to maladaptive repair. Song et al. showed that SLC44A2 regulates vascular smooth muscle cell phenotypic switching and aortic aneurysm formation [33], whereas Zhang et al. reported that HINT1 aggravates aneurysm by targeting the ITGA6/FAK axis in vascular smooth muscle cells [34]. Guo et al. further linked LXRα to abdominal aortic aneurysm formation through UHRF1-mediated epigenetic modification of miR-26b-3p [35]. These findings place smooth muscle cell state transitions at the center of the repair response, where plasticity may be either compensatory or pathogenic depending on timing, context, and persistence of injury.

The form of maladaptive repair differs across aneurysm subtypes. In heritable thoracic aortic aneurysm, repair failure is often superimposed on intrinsic medial weakness, abnormal smooth muscle cell contractility, extracellular matrix instability, and altered mechanobiological signaling; in this setting, insufficient or misdirected repair may be unable to restore medial strength. In a degenerative abdominal aortic aneurysm, repair occurs within a more inflammatory and proteolytic environment shaped by thrombus-associated injury, adventitial activation, macrophage and neutrophil signaling, and matrix degradation. Non-smooth muscle cell compartments also contribute to this process: Pan et al. identified SM22α-lineage perivascular stromal cells as contributors to abdominal aortic aneurysm [36], and Millar et al. linked endothelial-to-mesenchymal transition to interleukin-1 pathway activity during aneurysm formation [37]. From a translational perspective, Wei et al. showed that extravascular administration of IGF1R agonists protects against aneurysm formation in rodent and porcine models [38], suggesting that repair-associated growth factor pathways may be therapeutically modifiable. Thus, the third hit is context-dependent in at least four respects: the aneurysm subtype in which repair occurs, the injury milieu that shapes the reparative response, the timing and persistence of repair activation, and the cellular source and matrix quality of the newly formed tissue. A response that is stabilizing in one setting may become pathogenic in another when chronic inflammation, thrombus-derived proteases, or persistent growth factor signaling drive disorganized fibrosis and wall stiffening. Therefore, maladaptive proliferative repair should be understood not simply as “excess repair” or “failed repair”, but as a remodeling state in which compensatory programs become insufficient, misdirected, or biologically costly.

3.4. Hit 4: Aging-Associated Structural Destruction

The fourth hit represents the point at which aneurysm biology shifts from potentially compensated remodeling to progressive structural failure. Aging should not be interpreted simply as a demographic risk factor; it changes the biological reserve of the aortic wall. With aging, vascular smooth muscle cells and stromal compartments become more vulnerable to senescence, mitochondrial dysfunction, oxidative stress, proteostatic failure, and regulated cell death. These processes reduce the capacity of the wall to restore matrix organization, resolve inflammation, and maintain mechanical resilience after repeated injury. Recent work has begun to connect these aging-related programs with aneurysm vulnerability. Sun et al. showed that pro-ferroptotic signaling promotes arterial aging through vascular smooth muscle cell senescence [39], whereas Zhang et al. reported that ganglioside GM3 protects against abdominal aortic aneurysm by suppressing ferroptosis [40]. Wang et al. further demonstrated that targeting the smooth muscle cell Keap1-Nrf2-GSDMD-pyroptosis axis prevents abdominal aortic aneurysm formation [41]. These studies suggest that late-stage wall destruction is not merely the passive result of matrix wear, but may reflect active coupling among senescence, oxidative injury, ferroptosis, pyroptosis, and failed repair.

The consequences of aging are likely to differ between aneurysm subtypes. In a degenerative abdominal aortic aneurysm, aging interacts with smoking, intraluminal thrombus, chronic inflammation,

and metabolic injury, creating a milieu in which oxidative stress, immune activation, and proteolytic matrix degradation reinforce one another [42]. Evidence from peripheral artery disease further suggests that smoking-related vascular injury may be biologically embedded through accelerated epigenetic aging. Sheng et al. found that a DNA methylation-derived measure of aging partially mediated the association between early-life smoking and lower ankle-brachial index and increased peripheral artery disease risk. Although obtained in a different vascular disorder, these findings provide a mechanistic precedent for linking environmental exposure, epigenetic aging, and persistent vascular vulnerability [43]. In thoracic aortic aneurysm, aging may lower the threshold at which medial degeneration, abnormal mechanotransduction, extracellular matrix instability, or stress-response pathways become clinically expressed [44–46]. In both settings, however, aging reduces the compensatory reserve needed to buffer the earlier hits: barrier disruption becomes more difficult to repair, immune-inflammatory signals are less effectively resolved, and proliferative repair is more likely to become exhausted, fibrotic, or misdirected. Consistent with this model, GSDME-dependent pyroptosis has been linked to abdominal aortic aneurysm through promotion of vascular senescence [47], and smooth muscle cell oxidative-inflammatory signaling through STING has been shown to exacerbate aortic aneurysm and dissection [48] (Figure 2).

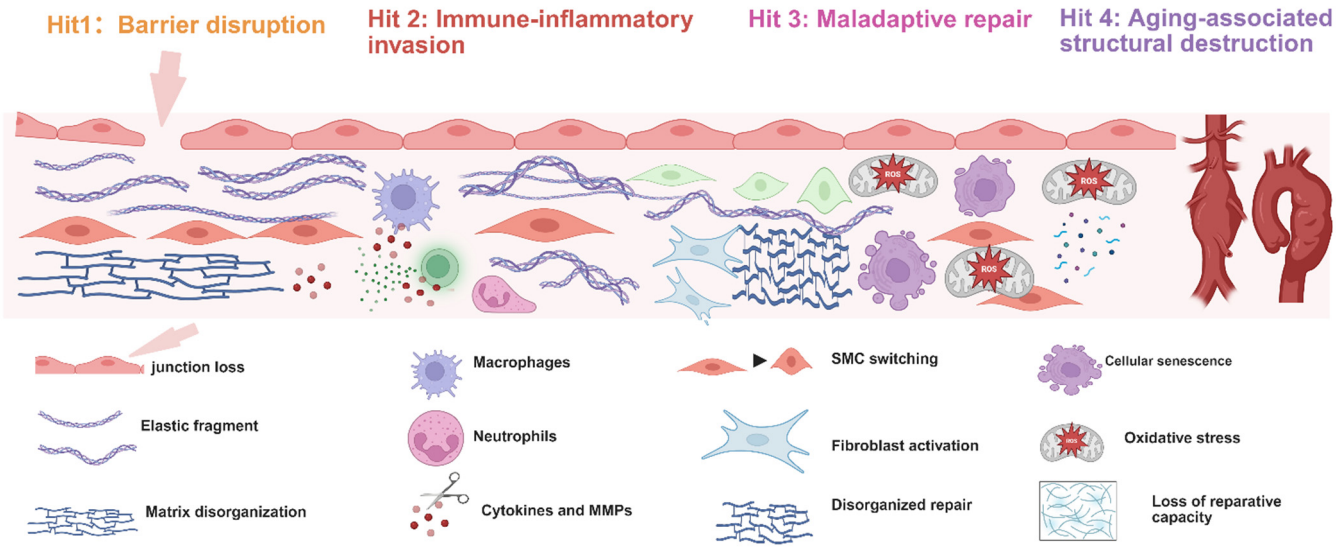

Figure 2. The Four-Hit Framework of Aortic Aneurysm Progression. Four interacting pathological processes promote aortic dilatation, wall degeneration, and rupture. The four domains overlap and interact dynamically and should not be interpreted as a fixed temporal sequence.

Thus, aging-associated structural destruction should be understood as a disease-amplifying state in which the aneurysmal wall progressively loses resilience, making rapid expansion and rupture more likely outcomes.

4. Biomarkers and Imaging Readouts of the Four-Hit Framework

Maximum aortic diameter remains the dominant criterion for aneurysm surveillance and intervention, yet it represents an anatomical consequence rather than a direct measure of disease activity. This distinction is important within the Four-Hit framework because barrier dysfunction, immune-inflammatory activation, maladaptive repair, and aging-associated structural destruction may emerge before overt enlargement and may continue despite apparently stable diameter. Increasing evidence indicates that aneurysm progression is influenced by biological and biomechanical features beyond size alone. Intraluminal thrombus has been associated with rapid abdominal aortic aneurysm growth [49], and proteolytic activity has been linked to aneurysm wall morphology and thrombus volume [50]. Biomechanical analyses further suggest that

rupture-related parameters can evolve independently of vessel geometry during aneurysm growth [51], while finite element analysis has shown that predicted rupture risk may correlate with aortic wall histology in individual patients [52]. These findings support the view that diameter-based imaging is often downstream of the biological processes that determine wall instability. Accordingly, biomarkers and imaging readouts should be considered complementary tools for identifying active aneurysm biology, refining patient phenotypes, and supporting mechanism-based clinical trial design, rather than replacements for established anatomical thresholds (Table 2).

Table 2. Translational landscape of aortic aneurysm assessment tools.

Assessment Domain	Representative Readouts	Biological Information	Potential Application	Evidence Stage	Key Limitation
Circulating inflammation	CRP, IL-6, chemokines	Systemic and vascular inflammation	Activity assessment and longitudinal monitoring	Clinical investigation	Limited aortic specificity
Matrix turnover	MMP-2, MMP-9, elastin- and collagen-derived fragments	Extracellular matrix degradation	Detection of active wall remodeling	Clinical investigation	Assay and cohort heterogeneity
Thrombus activity	D-dimer, fibrin degradation products	Thrombus formation and fibrinolysis	Assessment of thrombus-associated AAA activity	Clinical investigation	Confounding by systemic thrombosis
Molecular signatures	miRNAs, extracellular vesicles, proteomic profiles	Cell communication and molecular remodeling	Patient stratification and biomarker panels	Exploratory	Limited external validation
Ultrasound and CTA	Diameter, growth, volume, morphology, and intraluminal thrombus	Structural disease burden	Surveillance and procedural planning	Clinical standard	Limited biological information
MRI and 4D-flow MRI	Wall characteristics, flow patterns, and hemodynamics	Tissue remodeling and altered flow	Functional phenotyping	Emerging clinical	Cost and technical complexity
PET imaging	Tracer uptake in the aneurysm wall or thrombus	Inflammation, metabolism, or matrix activity	Identification of biologically active regions	Clinical investigation	Variable tracer specificity
Molecular imaging	Targeted probes for proteases, inflammation, or thrombus	Specific molecular activity *in vivo*	Early detection and treatment monitoring	Predominantly preclinical	Translation and safety barriers

Circulating biomarkers provide a minimally invasive approach to interrogating aneurysm biology, but their clinical utility remains limited by insufficient disease specificity and biological overlap with systemic inflammation, thrombosis, atherosclerosis, renal dysfunction, and aging. Matrix remodeling and thrombus-associated markers remain among the most extensively investigated candidates. Circulating matrix metalloproteinase-9 has been associated with the presence of abdominal aortic aneurysm in a meta-analysis [53], whereas plasma fibrinogen and D-dimer have been linked to aneurysm presence, consistent with activation of coagulation and fibrinolysis, and intraluminal thrombus biology [54]. D-dimer has also been reported as a predictor of abdominal aortic aneurysm progression [55] and as a diagnostic biomarker in patients with peripheral artery disease [56]. More recent studies have moved toward multidimensional biomarker discovery. Circulating cardiovascular biomarkers have been associated with aneurysm volume [57], blood-based biomarker discovery has been explored for abdominal aortic aneurysm detection [58], and targeted proteomics and metabolomics have been applied to biomarker discovery in abdominal aortic aneurysm and post-EVAR sac volume assessment [59]. These data suggest that single biomarkers are unlikely to capture the complexity of aneurysm progression. Within the Four-Hit framework, biomarker

signals should instead be interpreted as overlapping biological signatures, in which proteolysis, thrombus activity, inflammation, repair remodeling, and tissue degeneration converge.

Imaging provides a spatial and anatomical context that circulating biomarkers cannot offer. Ultrasound, computed tomography angiography, and magnetic resonance angiography remain indispensable for measuring diameter, defining anatomy, detecting thrombus, and planning open or endovascular repair. However, functional imaging may provide additional insight into active biological processes within the aneurysm wall and thrombo-inflammatory microenvironment. In abdominal aortic aneurysm, ^{18}F-sodium fluoride positron emission tomography identifies focal microcalcification activity and was associated with aneurysm progression and clinical events in the SoFIA3 study [60]. ^{18}F-fluorodeoxyglucose PET has been used to assess vascular inflammation; increased uptake has been associated with inflammatory features, wall instability, and acute symptoms in some studies [61], although systematic evaluation has highlighted heterogeneity in its relationship with aneurysm growth and rupture [62]. This inconsistency may reflect differences in patient selection, imaging protocols, background atherosclerosis, partial-volume correction, and the dynamic nature of inflammatory activity. Advanced magnetic resonance approaches offer a complementary perspective. Four-dimensional flow MRI can quantify abnormal flow patterns, flow stasis, wall shear stress, and thrombus-related hemodynamic changes in abdominal aortic aneurysm [63,64]. These methods may help connect local mechanics with barrier injury, thrombus-wall interaction, and regional remodeling, but require further standardization and prospective validation before routine clinical implementation.

Molecular and nanoparticle-based imaging approaches extend biological readouts beyond morphology and hemodynamics, particularly in preclinical and early translational studies. PET imaging of vessel-wall matrix metalloproteinase activity has demonstrated the feasibility of visualizing proteolytic remodeling within abdominal aortic aneurysm tissue [65]. Experimental imaging strategies have also targeted macrophage-rich inflammation, including computed tomography imaging of macrophage phagocytic activity in abdominal aortic aneurysm [66], and CXCR4-targeted magnetic particle imaging has been explored to detect inflammatory cell accumulation and assess aneurysm activity [67]. Conceptually, these approaches align with the Four-Hit framework: endothelial or thrombus-associated probes may report barrier disruption, macrophage- or neutrophil-targeted probes may reflect immune-inflammatory invasion, MMP- or collagen-turnover probes may indicate maladaptive repair and matrix remodeling, and future probes directed at senescence or regulated cell death may help capture late structural destruction. Nevertheless, most molecular probes and nanoparticle platforms remain investigational.

Their near-term translational value is more likely to lie in mechanistic studies, biological phenotyping, and the enrichment of clinical trials with patients who have active inflammatory, proteolytic, thrombotic, or repair-associated disease. A realistic goal is therefore not to replace anatomical imaging, but to integrate anatomical, biochemical, molecular, and biomechanical information into a more informative model of aneurysm risk (Figure 3).

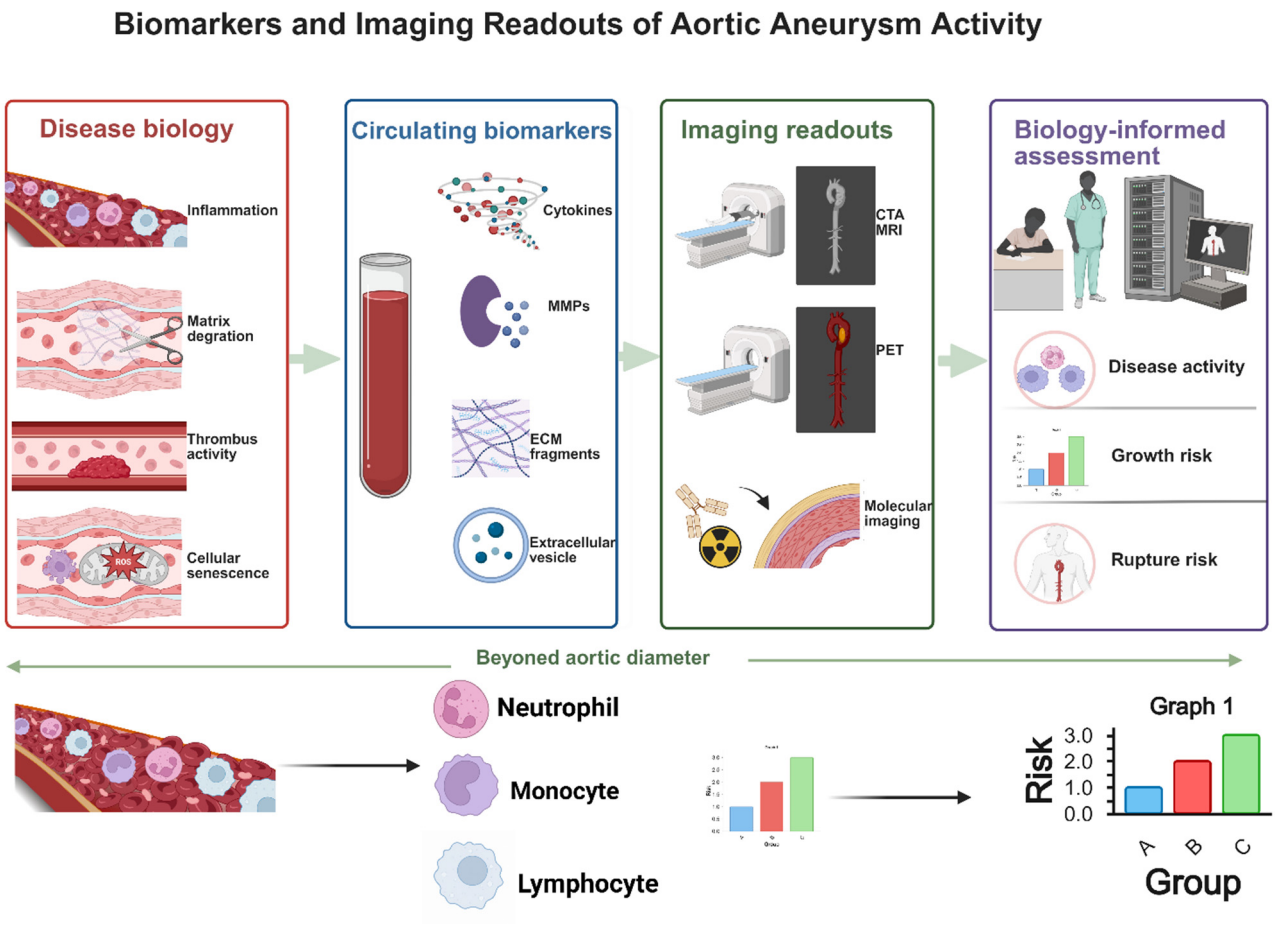

Figure 3. Biomarkers and Imaging Readouts of Aortic Aneurysm Activity. Circulating biomarkers and imaging modalities capture complementary aspects of aneurysm biology and may support biology-informed assessment of disease activity, growth, and rupture risk. Most circulating biomarkers and molecular imaging approaches remain investigational and are not established replacements for diameter-based surveillance.

5. Therapeutic Implications and Future Directions

The expanding mechanistic landscape of aortic aneurysm has yet to translate into an effective disease-modifying therapy. No pharmacological intervention has been conclusively shown to prevent expansion of abdominal aortic aneurysm (AAA) or to avert the need for surgical or endovascular repair, and aggregate clinical trial evidence remains largely neutral [68]. The failure of apparently rational therapies may reflect not only insufficient target engagement but also the biological heterogeneity of enrolled populations and the use of anatomical growth as a late therapeutic endpoint. Doxycycline exemplifies this disconnect: despite its matrix metalloproteinase–inhibitory activity, it did not reduce the growth of small infrarenal AAAs in a randomized trial [69]. By contrast, observational evidence has linked metformin use to slower AAA growth, although residual confounding precludes designating it as an aneurysm-specific therapy [69–71]. Therapeutic principles are also unlikely to be interchangeable across aneurysm subtypes. In Marfan syndrome, losartan may modestly attenuate aortic root dilatation, but its incremental benefit over β-blockade and its efficacy across genetic backgrounds remain uncertain [72,73]. These findings argue against a uniform pharmacological strategy for degenerative AAA and genetically mediated thoracic aortic aneurysm.

Preclinical evidence nevertheless identifies several therapeutically tractable processes, including endothelial dysfunction, immune-cell activation, neutrophil extracellular trap formation, smooth muscle cell instability, proteolytic matrix remodeling, senescence, and regulated cell death. Their relevance, however, is likely to depend on timing and pathological context. Inhibition of neutrophil extracellular traps

attenuated experimental AAA progression in a thrombus-dependent manner, indicating that local disease architecture can modify therapeutic efficacy [74]. Pharmacological inhibition of gasdermin D also suppressed angiotensin II–induced aneurysm formation, implicating pyroptotic signaling as a potential target [75], whereas restoration of GPX4 activity limited smooth muscle cell ferroptosis and aneurysmal remodeling [76]. These observations should not be interpreted as support for indiscriminate suppression of inflammation or cellular plasticity. Immune responses and smooth muscle cell state transitions may be either destructive or protective depending on disease stage, cellular context, and the capacity for compensatory repair. The Four-Hit framework may therefore be most useful for distinguishing interventions that preserve wall homeostasis from those that restrain inflammatory amplification, redirect maladaptive remodeling, or limit irreversible structural loss, without imposing a fixed therapeutic sequence.

Targeted delivery systems may help address this biological complexity by increasing drug exposure within inflamed or proteolytically active aneurysm tissue while limiting systemic toxicity. Reactive oxygen species–responsive nanoparticles have demonstrated targeted antioxidant and anti-inflammatory effects in experimental AAA [77], and nanoparticle-mediated delivery of pitavastatin to monocytes and macrophages inhibited aneurysm formation in mice [78]. More recent platforms have combined inflammatory suppression with extracellular matrix stabilization or enabled targeted small-interfering RNA delivery [79,80]. Nevertheless, these technologies remain preclinical, and their translation will require rigorous assessment of biodistribution, clearance, immunogenicity, manufacturing consistency, long-term toxicity, and efficacy in large-animal models. Future trials should align therapeutic selection with aneurysm subtype, dominant biological activity, and disease stage, supported where appropriate by biomarkers and functional imaging. The principal translational value of the Four-Hit framework is therefore not the proposal of a universal treatment algorithm, but the organization of therapeutic hypotheses and the development of biologically enriched clinical trials (Figure 4).

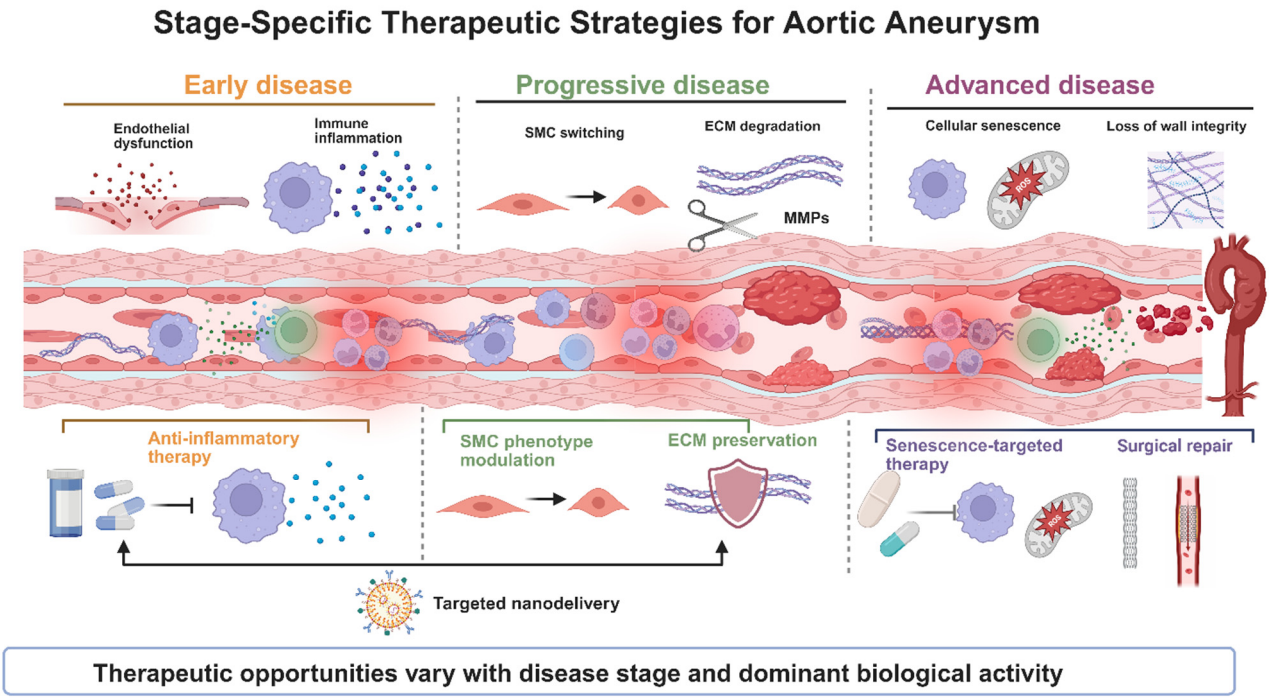

Figure 4. Stage-Specific Therapeutic Strategies for Aortic Aneurysm. Potential interventions targeting inflammation, vascular wall remodeling, matrix degradation, and cellular senescence are shown across conceptual disease phases. These phases do not represent a validated clinical staging system. Most pharmacological and targeted-delivery strategies remain investigational, whereas open or endovascular repair remains the established treatment for anatomically advanced disease. (The graphical elements and symbols used in Figure 4 are consistent with those defined and annotated in Figures 1–3.)

6. Conclusions

Aortic aneurysm is a heterogeneous group of disorders in which genetic susceptibility, vascular wall injury, immune-inflammatory activation, maladaptive repair, and aging-related degeneration converge to promote progressive dilatation and rupture. The Four-Hit Hypothesis integrates these processes into four partially overlapping biological domains: disruption of the aortic barrier environment, immune-inflammatory invasion, maladaptive proliferative repair, and aging-associated structural destruction. This framework is not intended to define a universal linear pathway or propose a new standalone mechanism, but to organize established and emerging evidence across aneurysm subtypes and disease stages. Its potential value lies in connecting mechanistic heterogeneity with complementary biomarkers, functional imaging, and biologically informed therapeutic development. Future studies should validate these relationships in longitudinal human cohorts, distinguish clinically actionable signals from preclinical observations, and determine whether biological stratification can improve risk assessment and clinical trial design beyond anatomical measurements alone.

Author Contributions

Conceptualization, H.W. and G.Z.; Investigation, M.Y., H.Z., K.F., J.H., S.Z. and Y.W.; Writing—Original Draft Preparation, M.Y. and H.Z.; Writing—Review & Editing, H.W. and G.Z.; Visualization, M.Y., H.Z. and K.F.; Supervision, H.W. and G.Z. All authors have read and agreed to the published version of the manuscript.

Ethics Statement

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Informed Consent Statement

Not applicable.

Data Availability Statement

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Declaration of Competing Interest

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

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