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Contemporary, mechanism-anchored biomarkers of endothelial dysfunction and oxidative stress (established and emerging)

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ABSTRACT

Background: Endothelial dysfunction and oxidative stress act together across hypertension, atherosclerosis, coronary disease and heart failure. Loss of nitric oxide (NO) signalling and excess reactive oxygen species (ROS) fuel inflammation, thrombosis and adverse remodelling
Objective: To provide a contemporary, mechanism-anchored review of established and emerging biomarkers of endothelial dysfunction and oxidative stress, explain what each

marker indicates and how it is measured and outline how small multimarker panels can support risk assessment, therapy monitoring and clinical decisions.

Methods: We performed a structured literature search of PubMed/MEDLINE, Embase and the Cochrane Library (Jan 2000–Aug 2025) for human studies in English on endothelial biomarkers (e.g., ADMA, NO/eNOS coupling, OSE, hs-CRP, ICAM-1/VCAM-1/E-selectin) and oxidative-stress biomarkers (e.g., NOX, xanthine oxidase/uric acid, ox-LDL/LOX-1, oxysterols; supportive readouts such as F2-isoprostanes, MPO, 3-nitrotyrosine, 8-OHdG, AOPP). We prioritised clinical trials, prospective cohorts and meta-analyses; mechanistic translational studies were considered when assays or biology were directly relevant. Heterogeneity precluded meta-analysis; therefore, we used a narrative synthesis with cautious language for signals derived from conference abstracts or post-hoc pooled analyses.

Results: Across studies, ADMA, NO/eNOS coupling or FMD, OSE, and hs-CRP/adhesion molecules consistently indicate endothelial activation or impaired vasoprotection. On the oxidative axis, NOX activity, xanthine oxidase/uric acid, ox-LDL/LOX-1, and oxysterols signal lipid oxidation and redox stress within plaques. In practice, compact panels that combine one endothelial, one oxidative and one inflammation marker appear more informative than single tests and may help show target engagement during treatment (e.g., ox-LDL/LOX-1 fall with intensive LDL lowering; urate falls with XO inhibition; FMD and some oxidative footprints improve with lifestyle optimisation).

Conclusions: Biomarkers spanning endothelial function and oxidative injury provide actionable signals for earlier risk identification and therapy monitoring. Using small, feasible panels and standardised measurement can make these tools clinically practical, while future trials should link biomarker change to outcomes.

Keywords: Endothelial dysfunction; oxidative stress; biomarkers; nitric oxide; ADMA; oxidation-specific epitopes; oxidised LDL; LOX-1; NOX; xanthine oxidase; oxysterols; F2-isoprostanes.

Słowa kluczowe: dysfunkcja śródbłonka; stres oksydacyjny; biomarkery; tlenek azotu; ADMA; epitopy utlenieniowe; utlenione LDL; LOX-1; NOX; oksydaza ksantynowa; oksysterole; F2-izoprostany.

INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide. At the heart of these illnesses is the health of the endothelium - a thin layer of cells that lines every blood vessel. Far from being a simple lining, the endothelium is an active organ that helps blood vessels relax or tighten, keeps platelets calm so clots do not form too easily, protects the vessel wall as a selective barrier, and guides immune cells to where they are needed. A key helper is nitric oxide (NO), a short-lived gas made by an enzyme in endothelial cells called endothelial nitric oxide synthase (eNOS). NO tells the muscle in the vessel wall to relax, and it also discourages clots and inflammation [1,2]. In healthy conditions, eNOS makes NO efficiently with the help of nutrients such as L-arginine and cofactors like tetrahydrobiopterin (BH_4). Antioxidant systems in the vessel -superoxide dismutases, catalase, and glutathione enzymes - keep background "cellular rust" under control so NO can do its job [1,2].

Trouble starts when common risk factors - diabetes, high blood pressure, high cholesterol, and smoking are present. The balance shifts toward oxidative stress, meaning there are more reactive oxygen species (ROS) than the body can safely handle. Extra ROS are produced by enzyme systems in the vessel wall, especially NADPH oxidases (NOX2 and NOX4) and xanthine oxidase, by mitochondria, and by "uncoupled" eNOS, which begins to make superoxide instead of NO. Superoxide quickly neutralizes NO and forms more reactive molecules that damage surrounding proteins and lipids, driving a self-reinforcing cycle of injury [1,2,9–12].

Several signals deepen the problem. Levels of asymmetric dimethylarginine (ADMA) can rise when its clearing enzyme (DDAH) is less active; ADMA blocks eNOS and further lowers NO [3,22]. Lipids in the vessel wall become oxidized LDL (ox-LDL) and create oxidation-specific epitopes (OSE). These altered particles attach to receptors such as LOX-1 and switch on inflammatory pathways inside the vessel wall [6–8,15]. The surface of the endothelium then turns "sticky" and "leaky": it shows more adhesion molecules (ICAM-1, VCAM-1, E-selectin) and the body's low-grade inflammation is mirrored by higher high-sensitivity C-reactive protein (hs-CRP) [5,8]. Over time, tiny vessels are lost and the ability of blood vessels to widen when needed - the vasomotor reserve declines. Not surprisingly, tests of endothelial function and measures of oxidative stress often change together and are associated with worse outcomes [4,16,21].

Because this biology is multi-step, no single test tells the whole story. Instead, panels of complementary biomarkers are more informative. ADMA reports inhibition of the NO

pathway, NO/eNOS coupling reflects the vessel's ability to relax, OSE and ox-LDL/LOX-1 capture oxidative injury to lipoproteins, adhesion molecules and hs-CRP indicate vascular inflammation and stable chemical products such as F2-isoprostanes provide a relatively reliable readout of lipid peroxidation in the body [6,7,10,11,23]. This review brings these threads together, explains what each marker tells us and discusses how combining them may improve risk assessment, help guide treatment, and track response.

MATERIALS AND METHODS

Narrative review with a structured search focusing on endothelial dysfunction (ADMA; NO/eNOS coupling/flow-mediated dilation; oxidation-specific epitopes; hs-CRP and soluble ICAM-1/VCAM-1/E-selectin) and oxidative stress (NADPH oxidases; xanthine oxidase/uric acid; oxidised LDL/LOX-1; oxysterols; supportive readouts: F2-isoprostanes, MPO, 3-nitrotyrosine, 8-OHdG, AOPP).

Databases and time window

PubMed/MEDLINE, Embase, Cochrane Library; January 2000 to August 2025; English language; humans.

Search strategy

Boolean combinations of free-text and controlled terms, for example:

("endothelial dysfunction" OR "nitric oxide" OR eNOS OR ADMA OR "flow-mediated dilation" OR "oxidation-specific epitopes" OR OxPL OR "C-reactive protein" OR ICAM OR VCAM OR E-selectin) AND ("oxidative stress" OR NOX OR "NADPH oxidase" OR "xanthine oxidase" OR uric OR "oxidized LDL" OR LOX-1 OR oxysterol OR "F2-isoprostane" OR myeloperoxidase OR nitrotyrosine OR 8-OHdG OR AOPP) AND

("cardiovascular" OR atherosclerosis OR hypertension OR "coronary artery disease" OR "heart failure").

Eligibility criteria

- Inclusion: clinical trials (all phases), prospective/retrospective cohorts, case–control studies, diagnostic accuracy studies, and systematic reviews/meta-analyses; adult humans; studies reporting associations with vascular function, redox status, atherosclerotic burden, or clinical outcomes; translational mechanistic work when it validated assays or clarified biology relevant to clinical interpretation.
- Exclusion: animal/in vitro only; pediatrics-only cohorts (unless mechanistically pivotal); editorials, narrative opinion pieces without data; duplicate publications.

Study selection and data extraction

Two reviewers independently screened titles/abstracts, assessed full texts, and extracted data on population, assay/methods, endpoints, and key findings relevant to mechanism, measurement, and clinical utility. Disagreements were resolved by discussion.

Quality appraisal

We considered study design, blinding, assay validation, pre-analytical handling, and risk of bias. For observational studies we mapped domains akin to the Newcastle-Ottawa approach; for diagnostic/biomarker performance we considered spectrum, reference standard, and precision; for systematic reviews/meta-analyses we noted search transparency and heterogeneity. Overall evidence statements are graded narratively (strong/consistent vs signal/suggestive).

Synthesis

Given heterogeneity of assays, populations and endpoints, we performed a qualitative (narrative) synthesis. Where findings relied on conference abstracts or post-hoc pooled analyses, we deliberately use calibrated terms such as “signal,” “suggestive,” “indicative,” “hypothesis-generating,” rather than “proven.”

BIOMARKERS OF ENDOTHELIAL DYSFUNCTION

ADMA

Asymmetric dimethylarginine (ADMA) is a small molecule that naturally circulates in the blood and blocks the enzyme that makes nitric oxide (eNOS). When ADMA rises, less nitric oxide (NO) is available, vessels relax less, and the lining of the artery behaves “irritably.” Higher ADMA is seen more often with high blood pressure, diabetes, kidney disease, obesity, and smoking, and it tracks with higher cardiovascular risk. It is a simple blood test and a useful window into the NO pathway; lifestyle and risk-factor control tend to move it in the right direction [3,22].

NO bioavailability and eNOS coupling (functional NO)

NO is the endothelium’s protective signal. When NO is scarce or when eNOS becomes “uncoupled” and makes superoxide instead - arteries lose their ability to widen on demand, platelets activate more easily, and inflammation smolders. Clinically we most often “see” this through flow-mediated dilation (FMD) of the brachial artery on ultrasound; some laboratories also look at nitrite/nitrate balance or nitrotyrosine as footprints of NO biology. Lower NO activity (or lower FMD) is common across cardiometabolic risks and carries prognostic value,

while exercise training, weight loss, and good control of blood pressure and lipids can improve it [1,2,4].

Oxidation-specific epitopes (OSE)

When lipids and lipoproteins are oxidized, they show distinctive “danger flags” called oxidation-specific epitopes. These flags accumulate in active plaques and are recognized by the immune system. Blood assays that quantify oxidized phospholipids on apoB or on lipoprotein(a) capture this signal and help refine long-term risk beyond standard factors. Because OSE reflect the biology of the plaque itself, they complement traditional cholesterol tests and tend to fall with sustained LDL-lowering and lifestyle change [6,7,10,11].

Endothelial activation markers (hs-CRP, ICAM-1, VCAM-1, E-selectin)

As the endothelial surface switches from “resting” to “activated,” it becomes stickier for white cells and a little leakier. This state appears in the blood as higher high-sensitivity C-reactive protein (hs-CRP) and higher soluble adhesion molecules (ICAM-1, VCAM-1, E-selectin). The numbers rise with smoking, metabolic syndrome, autoimmune flares, and active atherosclerosis, and they often fall when the drivers are treated. These tests capture the inflammatory tone of the vasculature and pair well with NO-focused measures [5,8].

Table 1. Endothelial dysfunction biomarkers

Biomarker	What it indicates	Typical specimen/test	When it tends to be higher or lower	How clinicians use it
ADMA	Natural blocker of eNOS → less nitric oxide (NO); vessels relax less	Plasma; immunoassay/LC–MS/MS	↑ in hypertension, diabetes, CKD, smoking, obesity	Flags NO-pathway inhibition; can track improvement with risk-factor control
NO bioavailability/eNOS coupling (e.g., FMD; nitrite/nitrate; nitrotyrosine)	How well vessels widen and NO signaling works	**FMD** by ultrasound; blood/urine nitrite–nitrate; nitrotyrosine by immunoassay	↓ FMD or NO surrogates in most cardiometabolic risks	Prognostic for events; improves with exercise, BP/lipid/glucose control
Oxidation-specific epitopes (OSE) (e.g., OxPL-apoB, OxPL-Lp(a))	"Danger flags" on oxidized lipids/lipoproteins within plaques	Serum/plasma; validated immunoassays for oxidized phospholipids	↑ with oxidative injury/active atherosclerosis; fall with sustained LDL lowering	Adds plaque-biology signal beyond LDL-C; helps long-term risk refinement
Endothelial activation markers (**hs-CRP**, **ICAM-1/VCAM-1/E-selectin**)	"Switched-on" endothelium: stickier, leakier, more inflamed	Serum/plasma; standard immunoassays	↑ in smoking, metabolic syndrome, flares, active atherosclerosis	Complements NO-centric tests; integrates vascular inflammation

ADMA - asymmetric dimethylarginine; eNOS - endothelial NO synthase; NO - nitric oxide; FMD - flow-mediated dilation; OSE - oxidation-specific epitopes; OxPL - oxidized phospholipids; hs-CRP - high-sensitivity C-reactive protein.

BIOMARKERS OF OXIDATIVE STRESS

NADPH oxidases (NOX2, NOX4)

NOX enzymes are dedicated “factories” of reactive oxygen species in blood vessels. When their activity is up - common in hypertension, diabetes, and obesity - the oxidative load on the endothelium rises and remodeling of the vessel wall accelerates. In clinical practice we usually gauge NOX activity indirectly (biochemical readouts or expression in research settings), but the concept is clear: more NOX, more oxidative pressure. Therapies that moderate upstream drivers, and experimental NOX-modulating drugs, aim to cool this source at its origin [9–11].

Xanthine oxidase and uric acid

Xanthine oxidase (XO) produces superoxide during purine breakdown; uric acid, its end product, is easy to measure and often serves as a practical signal of XO-related oxidative stress. Higher urate links to hypertension and cardiovascular risk, especially with kidney disease or gout. Hydration, diet and weight optimization, and XO inhibitors such as allopurinol (when clinically indicated) can reduce this enzymatic source of ROS and lower urate levels accordingly [12,13].

Oxidized LDL and LOX-1

When LDL particles are oxidized, they become toxic to the vessel wall. They bind the lectin-like receptor LOX-1 on endothelial and smooth-muscle cells, triggering more ROS, cell stress, and inflammatory signaling that feed plaque growth. Blood levels of oxidized LDL, and in some settings soluble LOX-1, reflect this activity and typically improve with strong LDL-cholesterol lowering (statins/PCSK9), smoking cessation, and heart-healthy diet patterns [8,15].

Oxysterols

Oxysterols are oxidized forms of cholesterol. They accumulate in plaques, injure endothelial cells, and mirror the longer-term oxidative burden on lipids. They are best measured by LC–MS/MS in specialized labs, but conceptually they add a valuable “lipid oxidation” dimension alongside ox-LDL and OSE. Intensive lipid lowering and overall risk-factor control tend to reduce them over time [14].

Table 2. Oxidative-stress biomarkers

Biomarker	What it indicates	Typical specimen/test	When it tends to be higher or lower	How clinicians use it
NADPH oxidases (NOX2/NOX4) (activity/readouts)	Vessel-wall "factories" of ROS; more NOX → higher oxidative pressure	Indirect activity peptides or expression (research); context readouts	↑ in hypertension, diabetes, obesity, vascular remodeling	Anchors mechanism; potential target for future therapies
Xanthine oxidase (XO) and **uric acid**	Enzymatic ROS source during purine breakdown; urate is an easy surrogate	Serum uric acid (routine); XO activity in specialty labs	↑ in hyperuricemia, gout, CKD, metabolic risk	Guides XO-targeted therapy (e.g., allopurinol) when appropriate
Oxidized LDL (ox-LDL) and **LOX-1**	Toxic, oxidized LDL binds LOX-1 → inflammation and plaque growth	Plasma ox-LDL (ELISA); soluble LOX-1 in some labs	↑ with poor lipid control, smoking, active plaques; ↓ with intensive LDL lowering	Monitors lipid-oxidation burden and response to therapy
Oxysterols	Oxidized forms of cholesterol that injure endothelium and mirror long-term lipid oxidation	Serum/plasma by **LC–MS/MS**	↑ with persistent oxidative load/high cholesterol exposure; ↓ with aggressive LDL lowering	Adds a precise "lipid oxidation" dimension alongside ox-LDL/OSE

ROS - reactive oxygen species; CKD - chronic kidney disease; LC-MS/MS - liquid chromatography-tandem mass spectrometry.

CLINICAL TRANSLATION

Biomarkers are most useful when they help us spot risk early, check whether treatment is hitting the right mechanism and decide the next step. Think of them as traffic lights for vascular health.

Early risk detection

If several signals point the same way - lower NO activity (for example, weak FMD or high ADMA), clear signs of lipid oxidation (ox-LDL or OSE), and evidence of vascular inflammation (hs-CRP or higher ICAM-1/VCAM-1) - the person is likely at higher vascular risk, even when routine labs still look “normal” [1,2,4–8,16].

Monitoring treatment (is it hitting the target?)

Marker changes tell you therapy is working. After strong LDL lowering, ox-LDL and LOX-1 usually fall [8,15]. With xanthine-oxidase inhibition, uric acid drops, meaning fewer ROS from that source [12,13]. With exercise, weight loss, and better control of blood pressure and glucose, functional NO typically improves (for example, a better FMD), and oxidative footprints such as F2-isoprostanes tend to decline [4,16,23,24].

A small, useful panel

No single test tells the whole story. A practical starter panel combines one endothelial/NO signal (ADMA or FMD), one oxidative/lipid-injury signal (ox-LDL or, where available, oxysterols or OSE), and one inflammation/activation signal (hs-CRP or an adhesion molecule such as ICAM-1 or VCAM-1). This three-piece set gives a clearer picture than any one marker alone and captures complementary biology [6–8,10,11,23].

Turning results into action

If lipid oxidation dominates, intensify LDL lowering, improve diet quality, and stop smoking [8,15]. If uric acid is high and XO is part of the problem, consider XO-targeted therapy when appropriate [12,13]. If the NO signal is weak, double down on lifestyle (aerobic activity, weight management) and optimize blood pressure, glucose, and comorbidities; functional NO measures often improve with these changes [1,2,4,16].

Use biomarkers to find risk earlier, confirm that therapy hits the mechanism, and track response over time - with a small, diverse, and feasible panel in your setting [6–8,10,11,23].

ANALYTICAL AND IMPLEMENTATION CONSIDERATIONS

Pre-analytical handling, including sample matrix, processing time, storage conditions, and freeze–thaw cycles, materially affects biomarker measurements, especially for lipid

peroxidation adducts and nitrative footprints. Platform choice is equally important. F2-isoprostanes and oxysterols are best quantified by liquid chromatography coupled to tandem mass spectrometry, while immunoassays for OSE require rigorous validation for epitope specificity and interference. Harmonization of methods and participation in external quality assessment are prerequisites for clinical deployment and for achieving cross-study comparability that would permit guideline inclusion [6,14,23].

FUTURE DIRECTIONS

Over the next few years, progress will likely come from small, smarter test panels rather than chasing a single "perfect" biomarker. The idea is to combine one signal of endothelial health (for example, NO/ADMA or a simple vessel-function readout) with one signal of oxidation (such as ox-LDL or OSE) and a broad inflammation marker (like hs-CRP). Used together, these give a clearer, earlier picture of vascular risk than any one test on its own [2,6,21,23]. Just as important, we need studies that link changes in these markers to real-world outcomes - fewer heart attacks and strokes - so that improving a number truly means patients do better [6,8,21]. On the treatment side, the most promising path is targeting the source of the problem (for example, enzymes that generate oxidants like NOX or xanthine oxidase, or pathways that drain NO such as eNOS uncoupling or high ADMA) and using matching markers to prove the target is hit [2,9–12,22]. Finally, simpler standardised testing will help doctors compare results across clinics and use a basic, affordable panel in routine care, reserving advanced assays for specialist centres [14,23].

CONCLUSIONS

Endothelial dysfunction and oxidative stress describe two sides of the same problem: loss of nitric-oxide–mediated vascular protection and excess oxidant burden within the vessel wall. Read together, they offer complementary signals about vascular biology that routine risk factors may miss. In this review we summarised four endothelial markers (ADMA; NO/eNOS coupling or functional NO; oxidation-specific epitopes; hs-CRP and soluble adhesion molecules) and four oxidative markers (NOX activity; xanthine oxidase/uric acid; ox-LDL/LOX-1; oxysterols). Each captures a different step in the cascade - from NO pathway inhibition and endothelial activation to lipid oxidation within plaques and in combination they may provide a clearer picture of vascular risk than any single test.

From a practical standpoint, the most clinic-friendly approach is a small, mechanism-anchored panel: one endothelial/NO signal, one lipid-oxidation signal, and one

inflammation/activation signal. Such a panel may flag higher risk earlier, help clinicians see whether treatment is hitting its target (for example, lower ox-LDL with intensive LDL reduction, falling urate with xanthine-oxidase inhibition, or improved functional NO with lifestyle optimization), and support shared decision-making with patients. These markers should complement - not replace - guideline-directed prevention and therapy.

Translation into routine care will depend on sound measurement. Pre-analytical handling, assay selection (e.g., LC–MS/MS for isoprostanes or oxysterols) and basic harmonization across laboratories can materially influence results. Where availability is limited, a lean panel that pairs a functional endothelial measure (or ADMA) with a lipid-oxidation readout (ox-LDL) and hs-CRP is a feasible starting point, with referral to specialist centers for OSE or oxysterols when added mechanistic depth is needed.

Evidence to date is encouraging but not definitive. Many findings are associative, some derive from pooled or post-hoc analyses, and assays are not yet uniformly standardized. Next steps therefore include prospective validation of compact panels, pragmatic trials that link biomarker change to patient outcomes, and cost-effectiveness work to clarify where testing adds value. It will also be useful to examine subgroups (sex, age, kidney disease, diabetes, heart failure phenotypes) and to integrate biomarkers with imaging, digital phenotypes, and lifestyle data to refine individualized care pathways.

In short, endothelial and oxidative biomarkers may sharpen risk stratification, help guide treatment choices and help monitor response over time when measured well and interpreted in context. With careful standardization and outcome-anchored research, these signals have the potential to move from research tools to everyday clinical aids for cardiovascular prevention and management.

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