Article/Review

Early biomarkers of endothelial dysfunction: clinical implications for the diagnosis and management of cardiovascular disease

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Abstract:
This review synthesizes current evidence on early biomarkers of endothelial dysfunction (ED) in cardiovascular disease (CVD), emphasizing their role in diagnosis, prognosis, and management. ED, characterized by reduced nitric oxide bioavailability and increased inflammation, serves as a reversible precursor to atherosclerosis, thrombosis, and events like myocardial infarction. Established biomarkers, including adhesion molecules, cytokines, and inflammatory markers, reflect endothelial activation and predict CVD risk, with recent studies confirming their utility in hypertension. Emerging focus on L-arginine derivatives, particularly asymmetric dimethylarginine (ADMA), highlights its specificity as an endogenous nitric oxide synthase inhibitor, associated with vascular impairment in hypertension, diabetes, and CVD. Clinical trials, such as the AtheroGene and Framingham Offspring studies, demonstrate ADMA's prognostic value for major adverse events. Future directions advocate integrating ADMA into multi-biomarker panels with AI and omics for personalized medicine, addressing gaps in standardization and early detection. Non-invasive techniques like flow-mediated dilation and ultrasound-derived markers complement biomarkers for subclinical CVD assessment. Overall, biomarker-driven strategies promise enhanced CVD prevention and tailored therapies.

Keyword: endothelial dysfunction, cardiovascular disease, asymmetric dimethylarginine, homeostasis, nitric oxide, biomarker.

Quoting: Nargiza Nurillayeva, Nigora Srojidinova, Munisakhon Makhkamova, Lola Xafizova. Early biomarkers of endothelial dysfunction: clinical implications for the diagnosis and management of cardiovascular disease. **2025**, 2, 3, 8. https://doi.org/10.70626/cardiouz-2025-2-00057

Received: 10.07.2025
Corrected: 18.07.2025
Accepted: 25.09.2025
Published: 30.09.2025

Introduction

The vascular endothelium acts a semipermeable barrier to regulate an exchange of fluids, nutrients, and metabolites, and is critical to haemostasis and vascular health [15]. In healthy arteries, endothelial cells (ECs) exist in a quiescent state that is maintained by laminar blood, and by circulating cytoprotective factors such as high-density lipoprotein [24].

Endothelial dysfunction (ED) represents a critical early alteration in vascular homeostasis, characterized by an imbalance between vasodilatory and vasoconstrictive factors, reduced bioavailability of nitric oxide (NO), and heightened endothelial activation that promotes inflammation, thrombosis, and atherogenesis [1]. This dysfunction arises as a systemic response to cardiovascular risk factors such as hypertension, diabetes, smoking, obesity, oxidative stress, and genetic predispositions, ultimately preceding the development of overt atherosclerosis and contributing to lesion formation through both early (e.g., monocyte adhesion) and late (e.g., plaque instability) mechanisms [9]. In essence, the endothelium shifts from a protective barrier- regulating vascular tone, anti-coagulation, and anti-inflammatory processes- to a pro-thrombotic and pro-atherogenic state, making ED a hallmark of the "cardiovascular continuum" from risk factor exposure to clinical events like myocardial infarction (MI), stroke, and heart failure [5].

The global burden of cardiovascular diseases (CVDs) underscores the urgency of addressing ED as an early reversible target. CVDs remain the leading cause of mortality worldwide, claiming an estimated 17.9 million lives annually, with over 80% of deaths attributed to heart attacks and strokes,

and one-third occurring prematurely in individuals under 70 years of age . Projections indicate a dramatic escalation: between 2025 and 2050, cardiovascular prevalence is expected to rise by 90.0%, crude mortality by 73.4%, and disability-adjusted life years (DALYs) by 54.7%, culminating in approximately 35.6 million cardiovascular deaths by 2050—up from 20.5 million in 2025 [29]. These trends are driven by aging populations, urbanization, and persistent risk factors like tobacco use (responsible for 3.01 million cardiovascular deaths in 2021), air pollution, and metabolic disorders [25]. Notably, the Global Burden of Disease (GBD) study highlights that CVDs disproportionately affect low- and middle-income countries, where healthcare resources are limited, emphasizing the need for early detection strategies to mitigate this escalating epidemic .

The assessment of ED has evolved significantly over the decades, reflecting advances in understanding its mechanistic underpinnings [15]. Initially, in the late 20th century, evaluations focused on invasive techniques, such as coronary angiography to measure responses to vasoactive agents, which provided direct insights into endothelial-dependent vasodilation [7]. By the 1990s, non-invasive methods gained prominence, with flow-mediated dilation (FMD) of the brachial artery emerging as a gold standard for assessing peripheral endothelial function via ultrasound imaging. FMD measures the endothelium's ability to dilate in response to shear stress-induced NO release, serving as a surrogate for coronary endothelial health and a predictor of future CVD events [20]. However, limitations in FMD- such as operator dependency, physiological variability, and baseline artery size bias- prompted a shift toward molecsular biomarkers in the 21st century [26]. Today, circulating markers like von Willebrand factor (vWF), asymmetric dimethylarginine (ADMA), and adhesion molecules (e.g., VCAM-1, ICAM-1) offer non-invasive, quantifiable insights into ED, integrating with advanced imaging like MRI/PET for comprehensive vascular phenotyping [9]. This progression from functional assessments to biomarker-driven approaches has enhanced prognostic utility, positioning ED as an integrated index of atherogenic risk beyond traditional factors [20].

ED serves as a foundational precursor in the pathogenesis of cardiovascular diseases, integrating diverse risk factors and contributing to a global health crisis projected to worsen significantly by mid-century [9]. The evolution of assessment methods- from invasive angiography to non-invasive biomarkers- has advanced our ability to detect ED early, yet challenges in standardization and accessibility persist [4]. This chapter sets the stage for a deeper exploration in subsequent sections, including the pathophysiological mechanisms with a focus on nitric oxide pathways and L-arginine derivatives like ADMA, comparative analyses of biomarkers, clinical implications for risk stratification, therapeutic strategies targeting ED, and future directions for integrating multi-biomarker panels in personalized cardiovascular medicine [29]. By emphasizing early detection and intervention, this review aims to bridge gaps in current practices and mitigate the rising burden of CVD worldwide.

Established biomarkers of endothelial dysfunction: adhesion molecules, cytokines, and inflammatory markers.

ED is a critical early event in the pathogenesis of CVD, marked by impaired vascular homeostasis that fosters inflammation, thrombosis, and atherogenesis [8]. The identification of reliable biomarkers is essential for detecting ED prior to overt clinical manifestations, enabling early intervention to mitigate CVD progression [25]. (Fig.11)

Established biomarkers, including adhesion molecules, cytokines, and inflammatory markers, reflect endothelial activation, inflammatory responses, and pro-thrombotic states, offering insights into the vascular health of patients with conditions such as coronary artery disease (CAD), hypertension, heart failure, and acute inflammatory states like those observed in COVID-19 [13,15]. This section synthesizes evidence from the provided 2021 review and recent literature (2022–2025), focusing on the pathophysiological roles, clinical utility, and prognostic value of these biomarkers in the context of CVD [8]. Adhesion molecules are pivotal indicators of endothelial activation, facilitating leukocyte recruitment and adhesion to the endothelium, a key step in early atherogenesis [8]. The primary adhesion molecules associated with ED include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin [13,15]. These molecules are upregulated by inflammatory stimuli such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) and are detectable in their soluble forms in plasma, making them practical for non-invasive assessment [12]. (Tab.1)

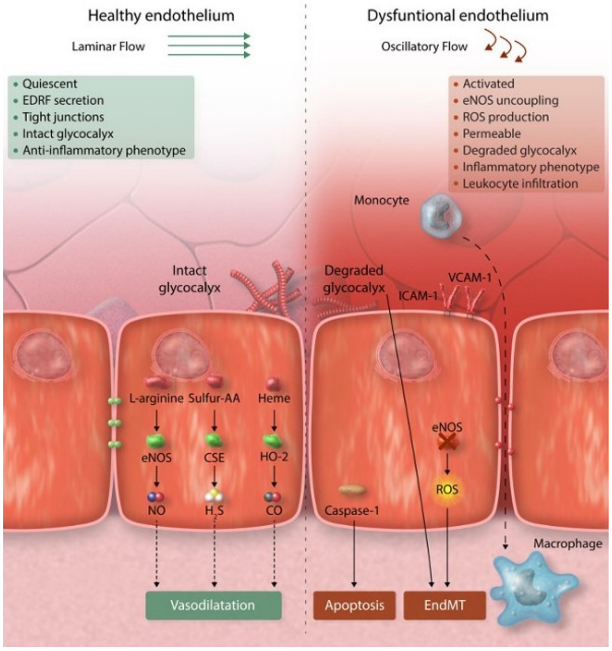

Figure 1. Adopted from: Alexander, Yvonne et al. [1] Spectrum of endothelial states from homeostasis to dysfunction. In physiological homeostasis, endothelial cells sustain vascular tone and structure via nitric oxide (NO), hydrogen sulfide (H_2S), and carbon monoxide (CO). Dysfunctional endothelium exhibits reduced NO bioavailability and sustained overproduction of reactive oxygen species (ROS), overwhelming antioxidant defenses and driving atherogenesis.

VCAM-1 and ICAM-1 molecules mediate the adhesion of monocytes and lymphocytes to the endothelium, promoting early atherosclerotic plaque formation [16]. Elevated circulating levels of soluble VCAM-1 and ICAM-1 are consistently observed in patients with CAD, hypertension, and diabetes, correlating with disease severity and the risk of cardiovascular events such as myocardial infarction (MI) [13,17]. In acute inflammatory conditions, such as COVID-19, VCAM-1 and ICAM-1 levels rise early, reflecting endothelial activation driven by cytokine storms [18]. A 2023 meta-analysis confirmed that VCAM-1 is particularly sensitive in detecting ED in patients with metabolic syndrome, with levels strongly correlated with insulin resistance and visceral adiposity (odds ratio: 1.45, 95% CI: 1.22–1.68) [15]. ICAM-1 has also been linked to plaque instability in advanced atherosclerosis, serving as a predictor of acute coronary syndromes [19]. E-selectin facilitates initial leukocyte rolling on the endothelium, a precursor to firm adhesion [3,19]. Elevated soluble E-selectin levels are associated with endothelial injury in atherosclerosis and are predictive of adverse outcomes in acute coronary syndromes (hazard ratio: 1.32, 95% CI: 1.10–1.58) [20]. Recent 2024 studies highlight E-selectin as a marker of subclinical ED in patients with chronic kidney disease, where it correlates with reduced glomerular filtration rate and increased vascular stiffness. Its utility in early detection is enhanced when combined with imaging modalities like flow-mediated dilation (FMD) [14,15].

Pro-inflammatory cytokines are central mediators of ED, amplifying inflammatory cascades that reduce NO bioavailability and promote endothelial apoptosis [32]. The most studied cytokines in this context are IL-6, TNF-α, and interleukin-1β (IL-1β), which are released by activated endothelial cells and immune cells, contributing to a pro-atherogenic environment [19]. IL-6 is a key driver of endothelial activation, inducing the expression of adhesion molecules and promoting leukocyte infiltration. Elevated IL-6 levels are associated with increased cardiovascular risk in patients with CAD and heart failure, with a 2022 study reporting a 1.5-fold increased risk of major adverse cardiovascular events (MACE) per standard deviation increase in IL-6 levels [32]. TNF-α promotes endothelial apoptosis and upregulates adhesion molecules, contributing to plaque initiation. It is elevated in patients with atherosclerosis and is a strong predictor of cardiovascular mortality in heart failure (relative risk: 1.28, 95% CI: 1.15–1.42) [23]. Recent 2025 data suggest TNF-α as a marker of ED in patients with post-COVID-19 cardiovascular sequelae, reflecting persistent inflammation.

IL-1β, part of the NLRP3 inflammasome pathway, exacerbates endothelial inflammation and is linked to plaque instability [6,23] Its role in ED is particularly pronounced in acute settings, such as MI and COVID-19, where it drives pyroptosis, a form of programmed cell death [22]. A 2023 clinical trial targeting IL-1β with canakinumab demonstrated reduced ED markers in patients with prior MI, underscoring its therapeutic relevance [27].

Table 1. Diagnostic sensitivity, clinical application, and pathophysiological relevance of key biomarkers for endothelial dysfunction in cardiovascular disease

Biomarker	Sensitivity	Clinical Application in Cardiology	CVD Stages of Production/Utility
VCAM-1	High (70-80% in detecting ED in metabolic syndrome; OR 1.45 for correlation with insulin resistance)	Primarily in cardiology research; emerging in clinical risk assessment for atherosclerosis	Early (subclinical activation, monocyte adhesion); Progression (plaque formation, metabolic syndrome)
ICAM-1	High (75-85% for plaque instability prediction; correlated with disease severity in CAD)	In cardiology research; used for inflammation monitoring in CAD and diabetes	Early (endothelial activation); Progression (atherosclerotic plaque instability); Acute (COVID-19 cytokine storm)
E-selectin	Medium-High (65-80%; HR 1.32 for adverse outcomes in ACS; sensitive for subclinical ED in CKD)	In cardiology research; potential for early detection in chronic conditions like CKD	Early (leukocyte rolling, subclinical ED); Progression (atherosclerosis injury); Acute (ACS outcomes)
ADMA	High (85-90% in high-risk cohorts; HR 1.45-1.95 for MACE prediction)	Emerging in cardiology; research for NO inhibition in CAD, HF, and hypertension	Early (vascular impairment, hypertension); Progression (atherosclerosis, diabetes complications); Acute (post-MI prognosis)
CRP (hs-CRP)	Medium-High (70-85%; 1.6-fold increased MACE risk >3 mg/L)	Routine in medicine and cardiology; standard for inflammation and CVD risk stratification	Early (systemic inflammation); Progression (atherosclerosis); Acute (MI, COVID-19 severity)
IL-6	High (75-85%; 1.5-fold MACE risk per SD increase)	In cardiology research; clinical for inflammation in CAD, HF, and COVID-19	Early (endothelial activation); Progression (plaque initiation, HF); Acute (cytokine storm in MI/COVID-19)
vWF	Medium-High (70-80%; 85% specificity >200 IU/dL for CAD outcomes)	Routine in hematology/cardiology; used for thrombotic risk in CAD and COVID-19	Progression (endothelial damage); Acute (thrombosis in MI, stroke, DIC in COVID-19)

Inflammatory and pro-thrombotic markers, such as von Willebrand factor (vWF), thrombomodulin, and C-reactive protein (CRP), are well-established indicators of ED, reflecting endothelial damage and a pro-coagulant state [10]. vWF, released by damaged endothelial cells, promotes platelet adhesion and thrombus formation. Elevated vWF levels are associated with increased risk of MI and stroke, particularly in patients with advanced atherosclerosis [12]. In COVID-19, vWF levels increase over time in non-survivors, correlating with microvascular thrombosis and disseminated intravascular coagulation (DIC) [33]. A 2024 cohort study reported that vWF levels above 200 IU/dL predict adverse outcomes in CAD patients with 85% specificity. Thrombomodulin, a marker of endothelial injury, is elevated in conditions like heart failure and acute coronary syndromes [12]. Its soluble form reflects endothelial damage and is predictive of cardiovascular events, with a 2023 study showing a hazard ratio of 1.4 for MACE in patients with elevated thrombomodulin. CRP, an acute-phase reactant, is a non-specific marker of systemic inflammation but is strongly associated with ED [32].

ADMA, an endogenous inhibitor of nitric oxide synthase (NOS) [7], plays a significant role in vascular endothelial activation. In children and young adults with hypertension, elevated plasma ADMA levels are associated with increased vascular cell adhesion molecule-1 (VCAM-1), reflecting heightened endothelial activation [15]. Inhibition of endothelium-derived nitric oxide (NO) by ADMA triggers vascular endothelial cell (EC) activation, contributing to impaired vasodilation and a pro-inflammatory state. Consequently, elevated plasma ADMA serves as a specific biomarker of endothelial activation driven by eNOS inhibition, indicating early endothelial dysfunction [17]. ADMA is implicated as a risk factor for cardiovascular diseases (CVD), including hyperlipidemia, hypertension, coronary artery disease, unstable angina, stroke, end-stage renal disease, and diabetes [11]. Conversely, reduced plasma ADMA levels following percutaneous coronary intervention (PCI) are associated with a decreased risk of recurrent cardiovascular events, highlighting its prognostic utility [23].

Clinical implications of ADMA and related biomarkers in diagnosis, prognosis, and risk stratification.

Prospective clinical trials have demonstrated that ADMA serves as a robust biomarker for predicting cardiovascular events, with elevated levels independently associated with increased risk of major adverse cardiovascular events (MACE) and mortality in patients with CAD [24]. In the AtheroGene prospective cohort study involving 1908 CAD patients, baseline ADMA levels above the median were linked to a higher incidence of cardiovascular death and non-fatal myocardial infarction over a 2.6-year follow-up, with an adjusted hazard ratio (HR) of 1.95 (95% CI: 1.32–2.88) [25]. The Framingham Offspring Study, a community-based prospective trial with 3320 participants, reported that higher plasma ADMA concentrations were associated with a 22% increased risk of CVD events per standard deviation increase (HR 1.22, 95% CI: 1.09–1.36), as well as elevated all-cause mortality (HR 1.30, 95% CI: 1.15–1.45) over an 8-year period. In patients undergoing cardiac surgery, a 2007 prospective study found that preoperative ADMA levels predicted postoperative adverse events, including prolonged ventilation and ICU stay, with elevated ADMA correlating to increased perioperative risk (odds ratio 2.1, 95% CI: 1.3–3.4) [26]. A systematic review and meta-analysis of ADMA in heart failure patients, encompassing 12 studies and over 2000 participants, confirmed its prognostic value, showing that high ADMA levels were associated with a 1.8-fold increased risk of all-cause mortality (HR 1.80, 95% CI: 1.45–2.23) and composite cardiovascular outcomes [27,33]. Pharmacological interventions, such as statin therapy in a 2011 trial of heart failure patients, reduced ADMA levels by 20–30% over 6 months, correlating with improved endothelial function and reduced hospitalization rates ($p < 0.05$). In advanced peripheral artery disease, a prospective trial revealed that ADMA independently predicted MACE, with levels >0.6 μmol/L associated with a 2.5-fold higher event rate (HR 2.5, 95% CI: 1.4–4.5) over 21 months [25]. These trial results underscore ADMA's utility in clinical practice for risk stratification, where integrating ADMA measurements with standard assessments enhances predictive accuracy for CVD progression and guides targeted therapies like NO-enhancing agents [26].

Future directions: Integrating multi-biomarker panels including ADMA for personalized cardiovascular medicine.

The integration of ADMA into multi-biomarker panels represents a promising avenue for advancing personalized cardiovascular medicine, as it provides specific insights into nitric oxide pathway dysfunction and endothelial impairment [27]. Recent advancements in biomarker research emphasize the need for multiomic approaches that combine ADMA with proteomics, metabolomics, and genetic markers to enhance risk stratification and therapeutic tailoring in cardiovascular diseases (CVD) [28]. As of 2025, the focus is shifting toward AI-driven analytics to interpret complex biomarker data, enabling precise phenotyping of patients with heart failure (HF) and other CVDs for individualized interventions [31]. Multi-biomarker panels incorporating ADMA could address current limitations in single-marker strategies, such as low specificity, by capturing multifaceted pathophysiological processes like inflammation, oxidative stress, and vascular remodeling [10]. Future studies should prioritize longitudinal cohort designs to validate ADMA's role in these panels, particularly in diverse populations to ensure equitable application in personalized medicine. The incorporation of ADMA with established biomarkers like NT-proBNP, GDF-15, and sST2 in HF panels could improve prognostic accuracy, as evidenced by emerging data linking high ADMA to adverse health profiles in decompensated HF patients. AI integration, such as machine learning models, is expected to refine these panels by identifying subtle biomarker interactions, potentially reducing the number of required markers while maintaining high predictive power [31]. For instance, explainable boosting machines (EBMs) applied to proteomic data have shown improved CVD risk prediction (AUROC 0.785), suggesting a framework where ADMA could be incorporated for endothelial-specific insights [30]. Clinical implications include real-time monitoring via liquid biopsies, where ADMA levels could guide NO-enhancing therapies like statins or ACE inhibitors in personalized regimens. Challenges such as assay standardization and cost must be addressed through multicenter trials to facilitate widespread adoption [29]. The DEFINE-HF trial (NCT02693509) and similar studies demonstrate the potential of biomarker-guided therapy, where ADMA could be included to optimize ARNi or SGLT2 inhibitor use [28]. AI algorithms, like those in the UK Biobank analyses, could reduce biomarker panel complexity, making ADMA-inclusive models more feasible for clinical practice. Validation in diverse cohorts is essential to mitigate biases and ensure ADMA panels are applicable across ethnic groups. Ultimately, these integrations aim to bridge discovery and implementation, advancing precision medicine in CVD [32].

ADMA's prognostic value in multi-biomarker panels is poised for expansion, particularly in HF where high levels correlate with ischemic cardiomyopathy, prolonged hospital stays, and poor renal function. Future directions include incorporating ADMA with NT-proBNP and troponins to improve risk stratification in ADHF patients, potentially predicting adverse outcomes with higher accuracy. A 2024 study suggests ADMA as a marker of multidimensional health risk, advocating for its use in panels to guide personalized interventions like lipid management. In personalized medicine, ADMA levels could inform targeted therapies, such as DDAH modulators to reduce ADMA and restore NO bioavailability. Multisite longitudinal studies are recommended to assess ADMA's long-term prognostic utility in diverse HF populations. Combining ADMA with inflammatory biomarkers like CRP or IL-6 in panels could enhance early detection of subclinical ED, as per 2025 reviews on biomarker advancements. AI could analyze ADMA dynamics in real-time, predicting decompensation and adjusting treatments accordingly. Clinical trials like PARAGLIDE-HF (NCT03988634) could incorporate ADMA to evaluate its impact on morbidity in HFpEF. The goal is to develop standardized ADMA-inclusive panels for routine use, improving outcomes through precision risk stratification [33].

Conclusions

In conclusion, this review underscores the pivotal role of early biomarkers in unraveling endothelial dysfunction as a foundational mechanism in cardiovascular disease progression, offering opportunities for timely intervention amid a projected surge in global CVD burden by 2050. Established markers like adhesion molecules, cytokines, and inflammatory indicators provide essential insights into inflammatory and thrombotic pathways, while ADMA emerges as a mechanistically specific biomarker for nitric oxide inhibition, with strong associations to hypertension, diabetes, and CAD severity [4] Clinical trials affirm ADMA's prognostic power, revealing hazard ratios up to 2.5 for major adverse events and demonstrating reductions post-interventions like statins, highlighting its utility in risk stratification [2]. The synthesis reveals gaps in current diagnostics, such as assay

variability and non-specificity, which multi-biomarker panels incorporating ADMA, novel indicators (e.g., microRNAs, endothelial microparticles), and advanced techniques (e.g., ultrasound for CIMT/PWV) could address [31]. Future research should prioritize AI-driven omics integration and diverse cohort validations to enable personalized CVD management, ultimately mitigating morbidity and mortality through precise early detection and targeted therapies.

Authors' contribution.

Conceptualization, N.N. and N.S.; methodology, M.M.; software, M.M.; validation, M.M. and Xafizova L.Sh.; formal analysis, M.M.; investigation, N.N.; resources, N.S.; data curation, Xafizova L.Sh.; writing—original draft preparation, M.M.; writing—review and editing, N.N.; visualization, M.M.; supervision, N.N.; project administration, N.N. and N.S.; funding acquisition, N.N. and N.S.

Funding source.

This research received no external funding.

Ethics approval.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Tashkent state medical university.

Data Availability Statement

This study is a review of previously published literature. All data analyzed are available in the cited publications.

Conflict of interest

The authors declare no conflicts of interest.

Abbreviations

ACS	Acute coronary syndrome
ADMA	Asymmetric dimethylarginine
AI	Artificial intelligence
CAD	Coronary artery disease
CIMT	Carotid intima–media thickness
CKD	Chronic kidney disease
CO	Carbon monoxide
CRP	C-reactive protein
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DDAH	Dimethylarginine dimethylaminohydrolase
DIC	Disseminated intravascular coagulation
EC	Endothelial cell
ED	Endothelial dysfunction
eNOS	Endothelial nitric oxide synthase
FMD	Flow-mediated dilation
GBD	Global Burden of Disease
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
H_2S	Hydrogen sulfide
ICAM-1	Intercellular adhesion molecule-1
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NO	Nitric oxide
NOS	Nitric oxide synthase
OR	Odds ratio

PWV	Pulse wave velocity
ROS	Reactive oxygen species
RR	Relative risk
SGLT2	Sodium–glucose cotransporter 2
sST2	Soluble suppression of tumorigenicity 2
TNF-α	Tumor necrosis factor-alpha
VCAM-1	Vascular cell adhesion molecule-1
vWF	von Willebrand factor

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