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Article/Review

The PRMT–ADMA–DDAH Axis in Cardiovascular Disease: Linking Protein Arginine Methylation to Endothelial Dysfunction and Vascular Remodeling

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Abstract:
Endothelial dysfunction is a central pathophysiological process underlying the initiation and progression of cardiovascular disease and is characterized by impaired nitric oxide (NO) bioavailability, increased oxidative stress, inflammation, vasoconstriction, and prothrombotic vascular signaling. Among the endogenous regulators of the NO pathway, asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, has emerged as an important molecular link between metabolic stress and vascular dysfunction. However, circulating ADMA represents only one component of a broader regulatory network involving protein arginine methyltransferases (PRMTs), dimethylarginine dimethylaminohydrolases (DDAHs), and alternative methylarginine-metabolizing pathways. This review examines the molecular architecture of the PRMT–ADMA–DDAH–eNOS/NO axis and its contribution to atherosclerosis, coronary artery disease, hypertension, heart failure, cardiometabolic disorders, chronic kidney disease, and metabolic dysfunction-associated steatotic liver disease. Finally, we discuss the therapeutic potential and limitations of targeting PRMT activity, ADMA metabolism, DDAH1, AGXT2, and NO bioavailability. Understanding this regulatory network may provide a mechanistic framework for identifying endothelial phenotypes of residual cardiovascular risk and developing more individualized strategies for cardiovascular prevention and treatment.

Keyword: PRMT1, ADMA, DDAH1, DDAH2, AGXT2, endothelial dysfunction, nitric oxide, eNOS, oxidative stress, cardiovascular disease, cardiometabolic risk.

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Introduction

Cardiovascular diseases (CVDs) remain a major cause of morbidity and mortality worldwide and arise from a complex interplay between traditional risk factors, metabolic abnormalities, chronic inflammation, oxidative stress, and vascular dysfunction [1]. Despite substantial advances in lipid-lowering, antihypertensive, antithrombotic, and glucose-lowering therapies, a considerable proportion of cardiovascular events occurs despite apparently adequate control of conventional risk factors [2]. This residual cardiovascular risk has stimulated increasing interest in molecular pathways that integrate metabolic and inflammatory disturbances with vascular injury [3]. Among these mechanisms, endothelial dysfunction represents a particularly important link between systemic cardiometabolic stress and the initiation, progression, and clinical expression of cardiovascular disease [4].

The vascular endothelium is a highly active regulatory organ that controls vascular tone, platelet activity, leukocyte adhesion, vascular permeability, smooth-muscle-cell behavior, angiogenesis, and inflammatory signaling [5]. A central mediator of these protective endothelial functions is nitric oxide (NO), predominantly generated in vascular endothelial cells by endothelial nitric oxide synthase (eNOS; NOS3) [6]. Under physiological conditions, eNOS-derived NO promotes vasodilation,

inhibits platelet aggregation and leukocyte–endothelial interactions, and restrains vascular smooth-muscle-cell proliferation [7].

Conversely, impaired NO synthesis or bioavailability shifts the vascular phenotype toward vasoconstriction, oxidative stress, inflammation, thrombogenicity, and pathological remodeling [8]. Experimental disruption of pathways regulating endogenous NOS inhibitors produces reduced NO signaling, increased vascular resistance, and impaired vascular homeostasis, supporting a causal rather than purely associative relationship between disturbed NO regulation and vascular dysfunction [9].

Among endogenous regulators of the L-arginine–NO pathway, asymmetric dimethylarginine (ADMA) has attracted particular attention. ADMA is an endogenous competitive inhibitor of nitric oxide synthases and can reduce NO production by interfering with L-arginine-dependent NOS activity [10]. Importantly, ADMA should not be regarded merely as a circulating biomarker of endothelial dysfunction. Its concentration reflects a dynamic balance among protein arginine methylation, proteolytic release of methylated arginine residues, cellular transport, enzymatic degradation, and renal elimination [11]. Experimental alteration of ADMA metabolism directly influences vascular NO bioavailability and endothelial function [12]. For example, disruption of methylarginine metabolism leads to ADMA accumulation and abnormalities of vascular homeostasis, whereas enhanced expression of dimethylarginine dimethylaminohydrolase (DDAH) lowers endogenous NOS inhibitors and increases NO production [13].

The biochemical origin of ADMA places protein arginine methyltransferases (PRMTs) upstream of this regulatory pathway. PRMTs transfer methyl groups from S-adenosyl-L-methionine to guanidino nitrogen atoms of arginine residues within proteins. Type I PRMTs generate asymmetric dimethylated arginine residues, which subsequently yield free ADMA following proteolysis. PRMT1 is the predominant [14] Type I PRMT in mammalian cells and has therefore traditionally been considered an important upstream determinant of ADMA generation [15]. Emerging human evidence supports a relationship between PRMT1 regulation, circulating ADMA, and vascular phenotype. In patients with type 2 diabetes mellitus, the PRMT1-related rs892151 variant was associated with altered PRMT1 expression, higher circulating ADMA concentrations, and impaired vascular function, providing clinical evidence that genetic variation in an upstream methylation enzyme may influence the ADMA–NO pathway [16].

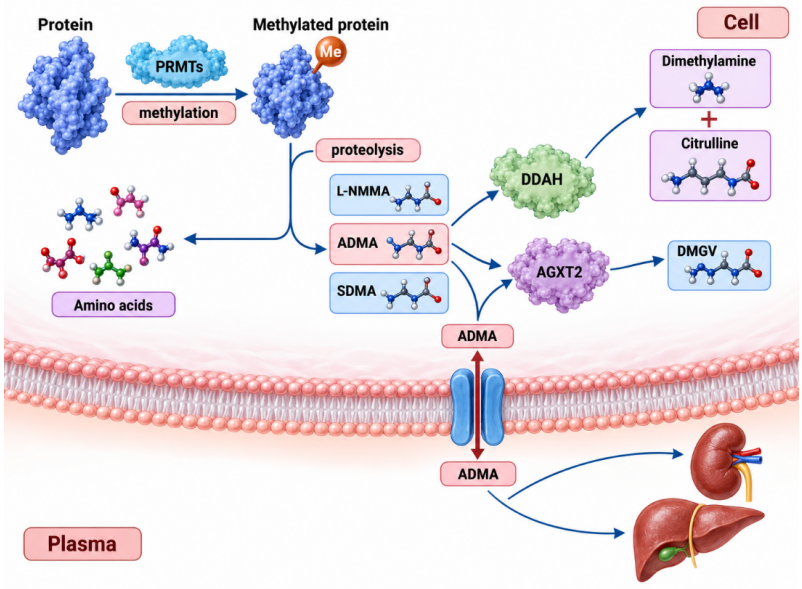


Figure 1. Schematic of the biosynthesis, metabolism, and excretion pathways of ADMA. (There is no copyright issue). Protein arginine methylation by PRMTs generates methylated proteins that, upon proteolysis, release free ADMA, SDMA, and L-NMMA. Intracellular ADMA and L-NMMA are largely degraded by DDAH (to citrulline and dimethylamine) or, for ADMA, partly by AGAT2 (to DMGV). Residual ADMA is exported into plasma, where it inhibits nitric oxide synthase, before being cleared by the kidney and liver.

However, recent findings indicate that the biological role of PRMT1 in the endothelium is considerably more complex than a linear model in which increased PRMT activity simply produces more ADMA and thereby suppresses NO [17]. Endothelial-specific PRMT1 ablation has been shown to induce barrier disruption, inflammation, apoptosis, and endothelial senescence, accompanied by hyperactivation of nuclear factor-κB signaling. In experimental endothelial cells, inhibition of PRMT1 aggravated tumor necrosis factor-α-induced dysfunction, whereas PRMT1 overexpression attenuated endothelial injury. These observations suggest that PRMT1 participates in direct methylation-dependent control of intracellular signaling pathways independently of its contribution to free ADMA generation. Thus, both excessive and insufficient PRMT1 activity may be biologically unfavorable depending on cellular context, substrate availability, tissue type, and inflammatory state. This emerging PRMT1 paradox challenges an oversimplified interpretation of PRMT1 as exclusively detrimental and has important implications for potential therapeutic strategies targeting protein arginine methylation [18].

The downstream regulation of ADMA is similarly complex. Dimethylarginine dimethylaminohydrolase 1 (DDAH1) is a major enzyme responsible for degradation of ADMA and N-G-monomethyl-L-arginine and plays a critical role in maintaining endogenous methylarginine homeostasis [19]. Genetic deletion of DDAH1 results in marked impairment of ADMA metabolism, increased endogenous NOS inhibition, reduced NO bioavailability, and increased blood pressure, demonstrating the physiological importance of DDAH1 in vascular regulation. Although DDAH2 has also been implicated in cardiovascular NO regulation, the extent to which it directly contributes to systemic ADMA degradation remains less clearly defined [20]. Nevertheless, human genetic evidence suggests that DDAH2-related variation may influence cardiovascular phenotype: the functional rs9267551 polymorphism was associated with a lower risk of myocardial infarction in two independent cohorts of patients with type 2 diabetes, potentially through altered ADMA accumulation and NO availability. These findings underline the need to distinguish the biological roles of the two DDAH isoforms rather than considering them functionally interchangeable [21].

By shifting the focus from ADMA as an isolated biomarker toward an integrated regulatory network, this review seeks to define a mechanistic framework connecting protein arginine methylation with endothelial dysfunction, vascular remodeling, and cardiovascular disease [22].

The PRMT1 Paradox: Beyond ADMA Generation

Protein arginine methyltransferase 1 (PRMT1) occupies a unique position at the intersection of protein post-translational modification, methylarginine metabolism, and vascular homeostasis. As the predominant Type I protein arginine methyltransferase, PRMT1 catalyzes the transfer of methyl groups from S-adenosyl-L-methionine to guanidino nitrogen atoms of arginine residues within target proteins, generating monomethylarginine and asymmetric dimethylarginine residues [24]. Free asymmetric dimethylarginine (ADMA) is subsequently released during proteolytic turnover of these methylated proteins. Thus, PRMT1 does not directly synthesize circulating free ADMA; rather, it determines the intracellular pool of asymmetrically methylated protein substrates from which ADMA can ultimately be liberated [25].

This distinction is mechanistically important because the relationship between PRMT1 expression and biologically active free ADMA is neither immediate nor necessarily linear. Free ADMA concentrations are determined by the balance among PRMT-dependent protein methylation, proteolytic turnover, intracellular transport, DDAH-mediated degradation, AGXT2-dependent metabolism, and renal elimination. Nevertheless, several experimental models of vascular and metabolic stress demonstrate that increased PRMT1 expression occurring in parallel with reduced DDAH activity can favor ADMA accumulation and impaired nitric oxide (NO) signaling [26].

High glucose, oxidative stress, lysophosphatidylcholine, activation of the renin–angiotensin system, and other vascular stressors have been shown to influence the PRMT–DDAH–ADMA pathway, providing a plausible mechanism linking cardiometabolic injury to endothelial NO deficiency [27].

Human genetic data provide additional support for this upstream role of PRMT1. In patients with type 2 diabetes mellitus, the PRMT1-related rs892151 variant was associated with higher PRMT1 mRNA expression and increased circulating ADMA. Carriers of the GA/AA genotype also demonstrated greater brachial–ankle pulse-wave velocity, whereas circulating ADMA was inversely associated with the reactive hyperemia index, linking genetically determined PRMT1 regulation to

ADMA accumulation, endothelial dysfunction, and arterial stiffness. These observations provide clinically relevant evidence that variation in the PRMT1–ADMA pathway may influence vascular phenotype in humans [28].

Although this pathway is biologically relevant, it represents only one dimension of PRMT1 function. PRMT1 methylates a broad spectrum of histone and non-histone proteins and thereby regulates transcription, signal transduction, protein–protein interactions, RNA processing, cellular stress responses, proliferation, differentiation, and survival. Consequently, changes in PRMT1 activity may alter endothelial phenotype independently of changes in circulating ADMA [29].

This distinction is particularly important when interpreting genetic deletion or pharmacological inhibition studies. If PRMT1 acted exclusively through ADMA generation, loss of PRMT1 would be expected to uniformly improve endothelial function by reducing the precursor pool for ADMA formation. Recent experimental evidence demonstrates that this prediction is incorrect. Endothelial PRMT1 appears to have essential homeostatic functions that cannot be explained by the ADMA–NOS pathway alone [30].

Endothelial PRMT1 deficiency: evidence for a protective homeostatic role

A major contribution to this concept came from a 2025 study examining endothelial-specific PRMT1 ablation [31]. Loss of PRMT1 in endothelial cells produced endothelial barrier abnormalities, increased inflammatory signaling, apoptosis, and cellular senescence. Mechanistically, PRMT1 deficiency was associated with enhanced NF-κB pathway activation. PRMT1 inhibition also aggravated tumor necrosis factor-α-induced endothelial dysfunction in cultured endothelial cells, whereas restoration or overexpression of PRMT1 attenuated several features of endothelial injury. These findings establish that basal PRMT1 activity can exert a protective role in maintaining endothelial homeostasis under inflammatory stress [32].

The physiological importance of PRMT1 is not restricted to endothelial cells. In vascular smooth muscle cells (VSMCs), inducible deletion of PRMT1 in adult mice produced profound impairment of the contractile phenotype and promoted aortic pathology, including aortic dissection. These observations indicate that adequate PRMT1-dependent methylation is required for maintenance of vascular-wall integrity and smooth-muscle-cell function [30,31]. Together, these findings challenge the concept that reduction of PRMT1 activity should necessarily be vasculoprotective. Instead, PRMT1 appears to operate within an optimal functional range: excessive or pathologically redirected activity may contribute to methylarginine accumulation and vascular injury, whereas insufficient PRMT1 activity may impair essential methylation-dependent mechanisms required for endothelial and vascular homeostasis [33].

PRMT1, inflammation, senescence, and cellular stress signaling

The ADMA-independent actions of PRMT1 are particularly relevant to vascular inflammation. Protein arginine methylation can regulate transcription factors and signaling molecules involved in inflammatory activation and cellular stress responses. Recent evidence suggests that PRMT1 restrains inappropriate activation of NF-κB-dependent signaling in endothelial cells, thereby limiting inflammatory activation and premature senescence. Loss of this regulatory influence may shift endothelial cells toward a pro-inflammatory, senescent, and barrier-disrupted phenotype [34].

This mechanism provides an important conceptual link between protein methylation and endothelial aging. Endothelial senescence is characterized by impaired regenerative capacity, altered NO signaling, increased oxidative stress, and a senescence-associated secretory phenotype capable of sustaining vascular inflammation. Therefore, PRMT1-dependent regulation of senescence may influence cardiovascular biology through mechanisms that are only partially reflected by circulating ADMA measurements [35].

The biological consequences of PRMT1 modulation may also depend on its substrates. PRMT1-mediated methylation can modify protein stability, subcellular localization, protein–protein interactions, and transcriptional activity. Consequently, an identical change in total PRMT1 abundance could produce different functional outcomes depending on which substrates are available in a given cell type and disease state. This substrate dependence provides one explanation for apparently conflicting observations across endothelial cells, VSMCs, cardiomyocytes, and other cardiovascular tissues [36].

Oxidative stress introduces an additional layer of complexity. Cardiometabolic disorders are frequently associated with increased PRMT1 expression and ADMA accumulation; however, PRMT1

Table 1. Representative evidence supporting the PRMT–ADMA–DDAH axis in endothelial dysfunction and cardiovascular remodeling.

Study	Experimental/clinical setting	Component of the axis	Relevance to cardiovascular disease
Ito et al., 1999	Endothelial-cell and vascular studies	DDAH → ADMA → NO	Established DDAH dysregulation as an upstream mechanism of endothelial dysfunction, rather than considering ADMA elevation solely as an epiphenomenon.
Böger et al., 2000	Human endothelial cells exposed to native/oxidized LDL	PRMT → ADMA	Provides a mechanistic bridge between atherogenic dyslipidemia, protein arginine methylation, ADMA accumulation, and endothelial dysfunction.
Dayoub et al., 2003	DDAH1-transgenic mice and cultured endothelial cells	DDAH1 → ↓ADMA → ↑NO	Strong genetic evidence that DDAH1 controls the ADMA–NO pathway and systemic vascular tone.
Jacobi et al., 2005	DDAH-overexpressing experimental models	DDAH → ADMA → angiogenesis	Links the pathway to endothelial repair, angiogenesis and vascular regeneration, beyond regulation of vasomotor tone.
Tanaka et al., 2005	Experimental graft coronary artery disease	DDAH → ADMA → vascular remodeling	Indicates that manipulation of the pathway can influence neointimal/vascular remodeling and coronary vasculopathy.
Pyun et al., 2021	Conditional PRMT1 deletion in adult VSMCs	PRMT1-dependent protein methylation	Shows that PRMT1 influences vascular integrity through ADMA-independent protein-methylation mechanisms, broadening the biological meaning of the PRMT–ADMA–DDAH axis.
Kopaliani et al., 2021	Angiotensin-II–induced hypertension/remodeling	DDAH1 → ADMA → cardiovascular remodeling	Supports DDAH1 as a potential protective regulator of hypertensive vascular and cardiac remodeling.
Ragavan et al., 2023	Multicenter biochemical/enzymatic investigation	DDAH1 versus DDAH2	Modernizes the classical model: DDAH1 should be regarded as the principal ADMA-metabolizing DDAH isoform, whereas DDAH2 may exert cardiovascular effects through other mechanisms.
Nair et al., 2024	Contemporary mechanistic review	DDAH1/DDAH2 biology	Supports a revised conceptual model in which the classical PRMT–ADMA–DDAH1–eNOS pathway coexists with ADMA-independent actions of PRMTs and DDAH2.

catalytic activity itself is redox sensitive [23,34]. Experimental work examining the redox control of PRMT1 demonstrated that reducing conditions increase PRMT1 activity, whereas oxidation can directly suppress catalytic activity, despite conditions in which PRMT1 protein expression may be increased [37].

Accordingly, increased PRMT1 expression should not automatically be interpreted as increased PRMT1 enzymatic activity. In an oxidatively stressed vascular environment, transcriptional upregulation of PRMT1 may coexist with changes in enzyme oxidation, substrate availability, DDAH inhibition, altered proteolysis, and impaired ADMA clearance [38]. The observed increase in circulating ADMA may therefore arise from several coordinated abnormalities rather than from PRMT1 overactivity alone.

This distinction is especially relevant in diabetes, dyslipidemia, hypertension, chronic kidney disease, and other disorders characterized by oxidative stress. In such conditions, increased ADMA may represent a composite biochemical signature of altered protein methylation, reduced DDAH-dependent degradation, altered methylarginine transport, and renal dysfunction rather than a direct surrogate marker of PRMT1 activity [39].

Therapeutic implications of the PRMT1 paradox

Recognition of this paradox has important therapeutic implications. Global or sustained PRMT1 inhibition may reduce selected pathogenic methylation events and could theoretically decrease the generation of ADMA-containing protein residues. However, indiscriminate inhibition may simultaneously disrupt methylation-dependent pathways required for endothelial integrity, anti-inflammatory signaling, vascular smooth-muscle-cell differentiation, and cellular survival. The

observation that endothelial or vascular smooth-muscle PRMT1 deficiency itself produces vascular pathology argues against assuming that systemic PRMT1 suppression will necessarily improve cardiovascular outcomes.

Accordingly, future therapeutic strategies may need to move beyond nonspecific PRMT1 inhibition toward context-dependent modulation of PRMT1 signaling. Potential approaches could include targeting specific PRMT1–substrate interactions, selectively modifying pathological PRMT1 activity within particular vascular cell types, restoring DDAH-mediated ADMA degradation without disrupting physiological protein methylation, or identifying molecular phenotypes in which PRMT1-dependent ADMA generation is demonstrably dominant.

The distinction between PRMT1 abundance, catalytic activity, substrate-specific methylation, and downstream ADMA concentration will also be essential for future translational studies. Measuring circulating ADMA alone cannot determine whether a patient's phenotype is driven by enhanced PRMT1-dependent methylation, impaired DDAH function, altered AGXT2 metabolism, renal clearance, or a combination of these mechanisms [40].

Current Knowledge Gaps and Future Directions

Despite substantial progress in understanding the biology of asymmetric dimethylarginine (ADMA), several fundamental questions regarding the PRMT–ADMA–DDAH–eNOS/NO axis remain unresolved. A major limitation of the current literature is that individual components of this pathway have often been investigated separately. PRMT activity, circulating ADMA, DDAH expression, nitric oxide (NO) bioavailability, endothelial function, and cardiovascular phenotype are rarely characterized simultaneously within the same experimental or clinical population. Consequently, although strong mechanistic links exist between these components, the extent to which disruption of the complete pathway drives cardiovascular disease in humans remains incompletely defined [41].

One of the most important conceptual gaps is the frequent use of circulating ADMA as a surrogate for the activity of the entire PRMT–DDAH pathway. This assumption is unlikely to be sufficient. Plasma ADMA represents the net result of several processes, including PRMT-dependent formation of methylated proteins, proteolytic release of free ADMA, cellular transport, DDAH1-dependent degradation, alternative metabolism, and renal elimination [41]. Experimental deletion of DDAH1 causes marked accumulation of ADMA and impaired NO signaling, illustrating how strongly degradation can influence ADMA independently of its upstream generation.

Human genetic observations further demonstrate that circulating ADMA reflects contributions from several regulatory genes rather than a single upstream mechanism. Variability within DDAH1, DDAH2, AGXT2, and PRMT1 has been investigated in relation to circulating ADMA, supporting a polygenic architecture of methylarginine homeostasis. Future studies should therefore move from isolated ADMA measurement toward a pathway-level phenotype incorporating PRMT expression or activity, methylated protein signatures, ADMA and related methylarginines, DDAH1 activity, AGXT2-related metabolism, L-arginine availability, and downstream indices of NO signaling [42].

Such an approach may help distinguish patients with apparently similar ADMA concentrations but fundamentally different underlying mechanisms-for example, increased methylarginine generation versus impaired degradation or renal clearance.

A second major gap concerns the relationship between circulating biomarkers and tissue-specific pathway activity. PRMT1, DDAH1, DDAH2, AGXT2, and NOS isoforms display distinct tissue and cellular distributions. Therefore, systemic ADMA concentrations may not accurately reflect intracellular methylarginine concentrations within coronary endothelial cells, cardiomyocytes, vascular smooth-muscle cells, renal tissue, or hepatocytes [43].

Future research should therefore determine whether cardiovascular risk is more closely related to circulating ADMA, intracellular ADMA, tissue-specific DDAH activity, or specific PRMT1-dependent methylation signatures. Single-cell transcriptomics, spatial transcriptomics, proteomics, and methyl-proteomics may be particularly valuable for defining cell-specific alterations of this pathway within human atherosclerotic plaques, coronary vessels, myocardium, liver, and kidney.

Discussion

The PRMT–ADMA–DDAH axis represents an important molecular interface between protein arginine methylation, nitric oxide (NO) signaling, endothelial homeostasis, and structural vascular

remodeling. Evidence accumulated over the past two decades indicates that disturbances at several levels of this pathway can converge on reduced endothelial NO bioavailability, oxidative stress, inflammation, altered vascular smooth muscle cell (VSMC) behavior, and ultimately progression of cardiovascular disease. Importantly, the pathway should not be viewed simply as a linear biochemical sequence. Rather, PRMT-dependent protein methylation, generation of free asymmetric dimethylarginine (ADMA), DDAH1-mediated ADMA degradation, and ADMA-independent actions of PRMTs and DDAH proteins appear to constitute an interconnected regulatory network influencing vascular phenotype. PRMTs catalyze methyl-group transfer from S-adenosyl-L-methionine to arginine residues within proteins. Type I PRMTs generate asymmetrically dimethylated arginine residues, from which free ADMA is subsequently released during protein turnover and proteolysis. Thus, PRMT activity controls the upstream substrate pool for ADMA generation rather than directly synthesizing circulating free ADMA. This distinction is important when interpreting circulating ADMA concentrations, which represent the net result of protein methylation, proteolytic release, intracellular metabolism, cellular transport, and renal elimination.

Cardiovascular risk factors may influence this upstream process. Böger et al. demonstrated that native and oxidized LDL increased methyltransferase activity and ADMA release in human endothelial cells, providing an early mechanistic connection between atherogenic lipoproteins, protein arginine methylation, and impaired NO biology. These observations suggest that the PRMT–ADMA pathway may function as a molecular sensor through which metabolic and oxidative disturbances are translated into endothelial dysfunction. The role of PRMTs in vascular disease, however, extends beyond ADMA formation. PRMT-dependent methylation regulates protein–protein interactions, transcription, RNA processing, chromatin biology, and intracellular signaling. This broader role is illustrated by experimental deletion of PRMT1 in adult VSMCs, which resulted in loss of the normal contractile phenotype, elastic-fiber degeneration, aortic dilation, and dissection. Consequently, PRMT1 can affect vascular structural integrity independently of circulating ADMA. These findings expand the conventional PRMT–ADMA paradigm and indicate that abnormal protein arginine methylation may directly contribute to vascular remodeling.

Among methylarginines, ADMA has attracted particular cardiovascular interest because it acts as an endogenous inhibitor of nitric oxide synthase. Increased ADMA availability can reduce L-arginine utilization by endothelial nitric oxide synthase (eNOS), impair NO generation, and favor endothelial dysfunction. Reduced NO bioavailability has multiple downstream consequences, including impaired vasodilation, increased leukocyte and platelet adhesion, enhanced vascular inflammation, increased VSMC proliferation and migration, and loss of the normal antithrombotic properties of the endothelium.

This mechanism provides a plausible explanation for the association between elevated ADMA concentrations and cardiovascular risk. In patients with established coronary artery disease, higher ADMA levels have been associated with subsequent cardiovascular events and mortality, supporting its potential prognostic significance. Elevated ADMA has also been associated with adverse outcomes after percutaneous coronary intervention and in other high-risk cardiovascular populations.

These clinical associations are biologically meaningful because experimental evidence supports a functional role for ADMA rather than its being merely an inert disease marker. The resulting reduction in NO can alter vascular tone and promote a proatherogenic endothelial phenotype. Thus, ADMA may be considered simultaneously a biomarker of impaired endothelial metabolism and a mediator capable of amplifying vascular dysfunction.

Nevertheless, circulating ADMA should not be interpreted in isolation. Plasma concentrations reflect several processes, including PRMT activity, protein turnover, DDAH1 activity, renal function, cellular uptake and export, oxidative stress, and metabolic status. These determinants may partly explain variability in ADMA concentrations across clinical populations and the differences in proposed diagnostic thresholds among individual studies. The DDAH pathway is central to maintaining intracellular methylarginine homeostasis. Earlier models often assigned ADMA-metabolizing activity to both DDAH1 and DDAH2. More recent genetic and biochemical evidence, however, requires refinement of this concept. DDAH1 knockout experiments provided particularly strong evidence for the importance of DDAH1 in vivo. Hu et al. showed that loss of DDAH1 substantially increased circulating and tissue ADMA concentrations, impaired NO signaling, and increased arterial blood

pressure, while DDAH2 expression did not compensate adequately for loss of DDAH1 activity. These observations identify DDAH1 as a critical determinant of endogenous ADMA clearance and support a causal relationship between impaired ADMA metabolism and abnormal vascular function.

A major clarification was provided by a multicenter biochemical study published in 2023, which demonstrated that DDAH2 does not metabolize ADMA under the experimental conditions tested. This finding challenges the conventional representation of DDAH1 and DDAH2 as equivalent ADMA-degrading enzymes. Accordingly, the classical pathway is more accurately represented as PRMT $\rightarrow$ methylated proteins $\rightarrow$ ADMA $\rightarrow$ DDAH1, whereas DDAH2 should be considered separately until its ADMA-independent cardiovascular functions are more completely characterized. This distinction has therapeutic relevance. Strategies designed to reduce excessive ADMA through enhanced enzymatic degradation should primarily focus on DDAH1 rather than assuming interchangeable actions of the two DDAH isoforms.

Oxidative stress appears to be both a cause and a consequence of dysregulation of the PRMT–ADMA–DDAH system. Cardiometabolic conditions characterized by oxidative stress-including dyslipidemia, diabetes, obesity, hypertension, renal dysfunction, and atherosclerosis-can alter enzymes involved in methylarginine metabolism. At the same time, increased ADMA and diminished NO availability favor endothelial oxidative imbalance.

Such a feed-forward mechanism is especially relevant in chronic cardiovascular disease, where multiple metabolic and inflammatory abnormalities coexist. It may also explain why ADMA frequently correlates with conventional and metabolic cardiovascular risk factors rather than representing an isolated biochemical abnormality.

A major conceptual advance is the recognition that the consequences of PRMT–ADMA–DDAH dysregulation extend beyond transient impairment of endothelium-dependent vasodilation. Chronic reduction in NO bioavailability changes vascular cell behavior and may contribute to structural remodeling.

NO normally restrains VSMC proliferation and migration, platelet activation, leukocyte adhesion, and extracellular-matrix remodeling. Persistent reduction in NO signaling therefore creates conditions favoring intimal hyperplasia, arterial stiffening, maladaptive vascular remodeling, and progression of atherosclerotic disease. Experimental manipulation of DDAH/ADMA signaling has additionally linked this pathway to endothelial repair, angiogenesis, neointimal formation, and responses to vascular injury.

At the upstream level, PRMT1-dependent regulation of the VSMC phenotype provides another mechanism through which protein arginine methylation may influence arterial structure. The severe aortic phenotype observed following inducible VSMC PRMT1 deletion emphasizes that vascular effects of PRMT signaling cannot be explained solely by changes in circulating ADMA. The emerging model therefore integrates at least two mechanisms: ADMA-dependent suppression of endothelial NO signaling and ADMA-independent regulation of vascular cell function through protein methylation.

The pathway has several potential clinical applications. First, ADMA may contribute to cardiovascular risk stratification as a biochemical indicator of impaired NO homeostasis. Prospective observations in coronary artery disease demonstrate associations between circulating ADMA and future cardiovascular events, although its incremental predictive value over established clinical risk scores and routinely available biomarkers requires further definition.

Second, the pathway offers several potential therapeutic targets, including PRMT-dependent methylation, ADMA transport, DDAH1 activity, and downstream restoration of eNOS/NO signaling. Among these, enhancement or preservation of DDAH1 function is particularly attractive mechanistically because DDAH1 occupies a key regulatory position in ADMA clearance. However, direct therapeutic manipulation requires caution. PRMTs regulate numerous essential proteins and transcriptional processes, while NO signaling has tissue- and context-dependent effects. Nonselective modification of either system could therefore have unintended consequences.

Third, measurement methodology remains an important limitation to clinical translation. Differences in analytical platforms, biological matrices, renal function, comorbidities, medication exposure, and population characteristics may influence reported ADMA concentrations and proposed cut-off values. Standardized analytical techniques and prospective validation are therefore required before ADMA can be routinely incorporated into cardiovascular decision-making.

Several important questions remain unresolved. The relative contribution of increased PRMT-mediated methylation versus impaired DDAH1 degradation to ADMA elevation in individual cardiovascular diseases has not been fully established. Tissue-specific regulation is also likely to be important because circulating ADMA may not precisely reflect intracellular methylarginine concentrations within endothelial cells, cardiomyocytes, or VSMCs.

Future research should therefore move beyond isolated measurement of circulating ADMA toward integrated characterization of the complete pathway. Simultaneous assessment of PRMT expression or activity, protein methylation patterns, ADMA concentrations, DDAH1 expression and activity, oxidative stress, and endothelial function may provide a more biologically informative phenotype. Longitudinal studies are also required to determine whether dynamic changes in pathway activity parallel disease progression or therapeutic response.

Another priority is differentiation between ADMA-dependent and ADMA-independent effects of PRMTs and DDAH proteins. The demonstration that DDAH2 lacks detectable ADMA-metabolizing activity and that PRMT1 directly controls VSMC phenotype illustrates why the traditional linear representation of the pathway requires revision. Advanced proteomics and methyl-proteomics may help identify specific arginine-methylated proteins responsible for vascular phenotypes and could reveal more selective therapeutic targets than global PRMT inhibition.

Finally, adequately powered prospective studies are needed to establish whether interventions that modify PRMT–ADMA–DDAH1 signaling translate into meaningful reductions in cardiovascular events.

Conclusion

The PRMT–ADMA–DDAH axis provides a mechanistic framework connecting protein arginine methylation with endothelial dysfunction and vascular remodeling. Type I PRMT-mediated asymmetric arginine methylation creates the precursor pool from which ADMA is released during protein turnover. Accumulation of ADMA, particularly when DDAH1-mediated degradation is impaired, suppresses eNOS-dependent NO signaling and favors vasoconstriction, oxidative stress, inflammation, endothelial dysfunction, and maladaptive vascular remodeling. Genetic evidence demonstrating increased ADMA and vascular dysfunction after DDAH1 deletion strongly supports the biological importance of this pathway.

Clinically, elevated ADMA provides a biologically plausible indicator of disturbed endothelial homeostasis and has been associated with adverse cardiovascular outcomes, including in patients with coronary artery disease. However, standardization of ADMA measurement, clarification of disease- and tissue-specific regulation, and prospective demonstration of incremental clinical utility remain necessary before routine implementation.

Future studies integrating methyl-proteomics, PRMT activity, ADMA metabolism, DDAH1 function, endothelial phenotyping, and cardiovascular outcomes may identify more precise molecular signatures and therapeutic targets. Such an integrated approach could shift the field from considering ADMA predominantly as a circulating biomarker toward understanding the entire arginine-methylation pathway as a modifiable regulator of vascular disease.

Authors' contribution

Conceptualization, N.M. and M.M.; methodology, N.M. and M.M.; software, M.M.; validation, M.M.; formal analysis, M.M.; investigation, M.M.; resources, N.M. and M.M.; data curation, N.M. and M.M.; writing - original draft preparation, N.M. and M.M.; writing-review and editing, N.M. and M.M.; visualization, M.M.; supervision, N.M.; project administration, N.M.; funding acquisition, N.M. All authors have read and agreed to the published version of the manuscript.

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Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Tashkent State Medical University (protocol code №11166).

Consent for publication.

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

We encourage all authors of articles published in the journal to share their research data. In this section, please specify where the data supporting the reported results can be found, including links to publicly archived datasets analyzed or generated during the study. If no new data were created or if data is unavailable due to privacy or ethical restrictions, a statement is still required.

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Conflict of interest

The authors declare no conflicts of interest.

Abbreviations

ADMA	Asymmetric dimethylarginine
CAD	Coronary artery disease
CVD	Cardiovascular disease
DDAH	Dimethylarginine dimethylaminohydrolase
DDAH1	Dimethylarginine dimethylaminohydrolase 1
DDAH2	Dimethylarginine dimethylaminohydrolase 2
eNOS	Endothelial nitric oxide synthase
LDL	Low-density lipoprotein
NO	Nitric oxide
NOS	Nitric oxide synthase
PRMT	Protein arginine methyltransferase
PRMT1	Protein arginine methyltransferase 1
ROS	Reactive oxygen species

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