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FORUM REVIEW ARTICLE

Myeloperoxidase As a Multifaceted Target for Cardiovascular Protection

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Abstract

Significance: Myeloperoxidase (MPO) is a heme peroxidase that is primarily expressed by neutrophils. It has the capacity to generate several reactive species, essential for its inherent antimicrobial activity and innate host defense. Dysregulated MPO release, however, can lead to tissue damage, as seen in several diseases. Increased MPO levels in circulation are therefore widely associated with conditions of increased oxidative stress and inflammation.
Recent Advances: Several studies have shown a strong correlation between MPO and cardiovascular disease (CVD), through which elevated levels of circulating MPO are linked to poor prognosis with increased risk of CVD-related mortality. Accordingly, circulating MPO is considered a ''high-risk'' biomarker for patients with acute coronary syndrome, atherosclerosis, heart failure, hypertension, and stroke, thereby implicating MPO as a multifaceted target for cardiovascular protection. Consistently, recent studies that target MPO in animal models of CVD have demonstrated favorable outcomes with regard to disease progression.
Critical Issues: Although most of these studies have established a critical link between circulating MPO and worsening cardiac outcomes, the mechanisms by which MPO exerts its detrimental effects in CVD remain unclear.
Future Directions: Elucidating the mechanisms by which elevated MPO leads to poor prognosis and, conversely, investigating the beneficial effects of therapeutic MPO inhibition on alleviating disease phenotype will facilitate future MPO-targeted clinical trials for improving CVD-related outcomes. *Antioxid. Redox Signal.* 32, 1135–1149.

Keywords: myeloperoxidase, cardiovascular disease, inflammation, cardioprotection, oxidative stress, biomarker

Introduction

CARDIOVASCULAR DISEASE (CVD) remains the leading cause of death and disability globally, accounting for ~30% mortality, with risk factors, such as smoking, hypertension, diabetes, abdominal obesity, and dyslipidemia, contributing to its clinical outcome. It is a common term used to identify a number of linked pathologies such as coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease and rheumatic and congenital heart diseases, and venous thromboembolism (116). It is also a major economic burden accounting for $555 billion in the United States in 2016, a cost that is projected to reach $1.1 trillion by 2035. Elucidating the underpinning mechanisms of various CVDs

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may provide novel insights into disease progression, as well as pinpoint potential targets for therapeutic intervention.

Myeloperoxidase (MPO) is a member of the superfamily of heme peroxidases, mainly stored in azurophilic granules of leukocytes. It is secreted upon leukocyte activation and plays an important role in innate immunity (85). MPO is primarily found in neutrophils and to a lesser extent in monocytes and macrophages (108). In addition to these inflammatory cell types, MPO expression has also been observed in neurons (41) and endothelial cells (60). During inflammation, MPO is released from leukocytes and catalyzes the formation of several reactive species, including hypochlorous acid (HOCl) and hypothiocyanous acid, which can posttranslationally modify target proteins (1, 66). While this function is essential for its antimicrobial activity and innate immunity, dysregulated MPO release can also lead to tissue damage, as observed in various diseases (4). Increased MPO levels in circulation are therefore widely associated with conditions of increased oxidative stress and inflammation.

Several studies have reported a strong link between MPO and a wide variety of CVDs, through which increased circulating MPO levels are associated with poor prognosis with increased risk of CVD-related mortality (Fig. 1) (80). Accordingly, MPO has been considered to be a biomarker for risk stratification in various CVDs, including acute coronary syndrome (ACS) (9, 13), atherosclerosis, heart failure (HF) (120), hypertension, and stroke (Table 1). In this review, we discuss the recent associations of MPO with various CVDs, as well as provide an overview of the mechanisms by which MPO exerts its detrimental effects and highlight MPO as a potential multifaceted target for cardiovascular protection.

Catalysis Function of MPO

Human MPO is encoded by a single gene located on chromosome 17, whose main translation product is a single protein that undergoes N-linked glycosylation to produce a 92-kDa glycoprotein (79). This pro-MPO then undergoes proteolytic maturation to give rise to the native MPO, a homodimeric protein formed from two monomers that are linked *via* a cysteine bridge. Each monomer itself consists of a heavy chain and a light chain, as well as a functionally identical heme group (Fig. 2) (27). Substrates that are oxidized by MPO bind to a hydrophobic pocket that lies at the entrance to the distal heme cavity.

MPO has limited antimicrobial activity on its own, however, upon interaction with hydrogen peroxide, native MPO is converted to Compound I, which can then enter the ''halogenation cycle'' or the ''peroxidation cycle.'' When entering the halogenation cycle, Compound I can undergo two-electron reductions with halides/pseudohalides such as chloride (Cl^-), bromide (Br^-), iodide (I^-), and thiocyanate (SCN^-) to generate corresponding hypohalous acids (32). When entering the peroxidation cycle, Compound I (*via* the formation of a Compound II intermediate) can undergo two successive one-electron reductions to generate several radicals (20) (Fig. 3). Irrespective of the cycle, all one- and two-electron oxidation reactions catalyzed by MPO must be thermodynamically favorable, in accordance with the redox properties of the reactants (5).

Studies assessing the redox potential of MPO have revealed that the standard reduction potentials of the redox couples (Compound I/native MPO, Compound I/Compound II, and Compound II/native MPO) are critical determinants as to which substrate is oxidized (6, 31). At a pH of 7, the Compound I/Compound II redox couple was found to have the highest standard reduction potential, which would suggest a preference toward the peroxidation cycle. Consistent with these findings, MPO exhibited higher affinity toward peroxidase substrate guaiacol (and not chloride ions) at a pH of 7.4. However, at an acidic pH, the chlorination activity was predominant over the peroxidase activity (125). Within the halogenation cycle itself, there is a preferential substrate oxidation hierarchy, which can be displaced in response to changes in substrate concentration and pH (32, 110). It would therefore seem that apart from the redox and thermodynamic properties of the reactants, other factors such as pH and substrate concentration could favor for a particular cycle.

Despite the ability to catalyze several chemical reactions, the primary action of MPO is the generation of hypochlorous acid (HOCl). HOCl, which is generated *via* Compound I interaction with Cl^-, is a potent antimicrobial oxidant, capable of modifying DNA, lipids, and lipoproteins (68). HOCl can react rapidly with sulfur and nitrogen atoms (nucleophile groups), which are present in thiols and thioethers (cysteine and methionine residues, respectively), as well as amines and amides (90–92). Modification of thiol groups can have opposing effects on cellular components. For instance, oxidation of cysteine residues can lead to inactivation of cellular

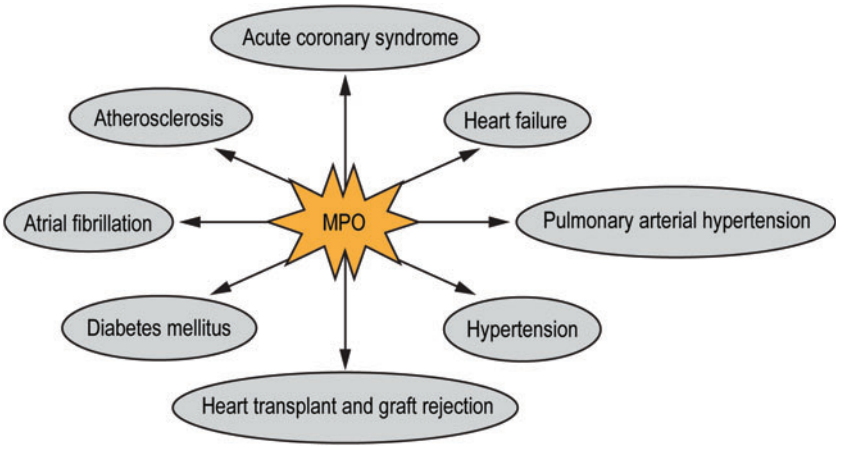

FIG. 1. Schematic representation of cardiovascular diseases in which elevated MPO levels have been detected in circulation. MPO, myeloperoxidase. Color images are available online.

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Table 1. Studies Assessing the Prognostic Value of Myeloperoxidase in Cardiovascular Disease

	Type of disease	*Type of study*	*Number of subjects*	*Major outcomes*	*References*
Heslop *et al.*[47]	ACS	Prospective cohort	885	MPO independently predicted cardiovascular mortality risk in coronary angiography patients. Combination of MPO with C-reactive protein was a stronger predictor of cardiovascular mortality risk	(47)
Rana *et al.*[96]	ACS	Prospective case–control study	2861	Circulating MPO levels (men only) are associated with an increased risk for CHD	(96)
Scirica *et al.*[109]	ACS	Randomized controlled trial	4352	Plasma MPO levels are independently associated with some adverse cardiovascular outcomes in non-ST-segment elevation ACS patients, but do not provide substantial incremental prognostic information when evaluated together with cTnI and NT-proBNP	(109)
Nilsson *et al.*[81]	ACS	Randomized controlled trial	58	Plasma MPO levels did not correlate with measures of infarct size, left ventricular dysfunction, or remodeling	(81)
O'Malley *et al.*[84]	ACS	Randomized controlled trial	4432	Plasma MPO levels are not independently associated with risks of cardiovascular death and heart failure in patients with non-ST-segment elevation ACS	(84)
Mollenhauer *et al.*[73]	ACS	Retrospective cohort	2622	Plasma MPO levels in postischemic patients are independently associated with a history of ventricular arrhythmias, sudden cardiac death, or implantation of an implantable cardioverter defibrillator	(73)
Ferrante *et al.*[26]	Atherosclerosis/ ACS	Prospective cohort	25	Systemic MPO levels are significantly elevated in patients with ACS presenting with eroded culprit plaque compared with patients presenting with ruptured culprit plaque	(26)
Tsimikas *et al.*[122]	Atherosclerosis/ ACS	Prospective case–control study	2160	MPO mass is higher in patients with CAD, but only have a weak potentiation of risk when combined with other oxidative biomarkers	(122)
Barbato *et al.*[10]	Atherosclerosis/ ACS	Randomized controlled trial	1397	Plasma MPO levels are significantly higher in patients who harbor a specific variant in the atrial natriuretic peptide gene that is associated with major adverse cardiovascular events	(10)
Duivenvoorden *et al.*[23]	Atherosclerosis/ ACS	Randomized controlled trial	130	Circulating MPO levels are associated with carotid plaque inflammation and independent of traditional cardiovascular disease risk factors in atherosclerotic plaque	(23)
Sorrentino *et al.*[114]	Diabetes mellitus	Case–control study/ randomized controlled trial	43	HDL-associated MPO activity and protein content, which alter endothelial NO production, are significantly increased in diabetic patients and are reduced after extended-release niacin therapy	(114)
Derosa *et al.*[21]	Diabetes mellitus/ hypertension	Randomized controlled trial	213	MPO identified as a new emerging marker of cardiovascular risk and is reduced in patients with type 2 diabetes mellitus and hypertension after treatment with acetylsalicylic acid	(21)
McLaughlin, *et al.*[69]	Hypertension	Randomized controlled trial	45	Low-molecular-weight heparin induced significant increases in plasma MPO levels in high-risk preeclampsia pregnant women, resulting in improved endothelial function	(69)
Ganz. *et al.*[33]	Stroke	Case–cohort study	2176	Plasma MPO levels are independently associated with the risk of recurrent stroke and improve risk classification when added to a clinical risk algorithm	(33)
Phuah *et al.*[93]	Stroke	Retrospective cohort/ prospective cohort	3033/174	Common genetic variants that result in increased MPO levels increase risk of primary intracerebral hemorrhage and lacunar stroke	(93)
Freedman *et al.*[29]	Obesity/ cardiovascular disease	Prospective cohort	1846	MPO and other specific inflammatory platelet-derived transcripts, including ICAM1, IFNG, IL1R1, IL6, COX2, TNF, TLR2, and TLR4, were significantly associated with higher body mass index	(29)
Olza *et al.*[87]	Obesity/ cardiovascular disease	Prospective case–control study	446	MPO is an early biomarker of inflammation associated with CVD risk in obese children at the prepubertal age	(87)
King *et al.*[56]	Smoking/ cardiovascular disease	Longitudinal cohort	1652	Smoking heaviness is associated with increased MPO	(56)

ACS, acute coronary syndromes; CAD, coronary artery disease; CHD, coronary heart disease; cTnI, cardiac troponin I; CVD, cardiovascular disease; HDL, high-density lipoprotein; MPO, myeloperoxidase; NO, nitric oxide; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

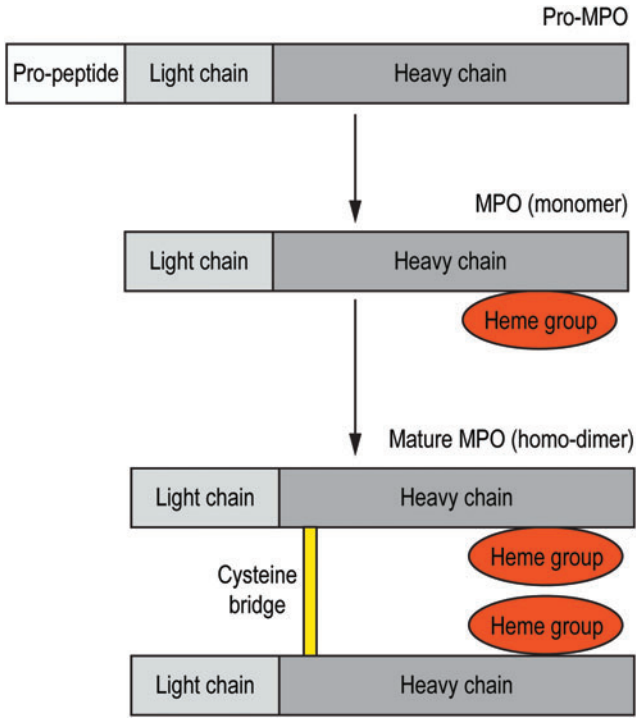

FIG. 2. Schematic illustration of MPO processing. The Pro-MPO undergoes proteolytic cleavage to give rise to the MPO monomer comprising heavy and light chains as well as a heme group. The mature MPO homodimer comprises two monomers that are linked by a cysteine bridge. Adapted and modified from the following study (42). Color images are available online.

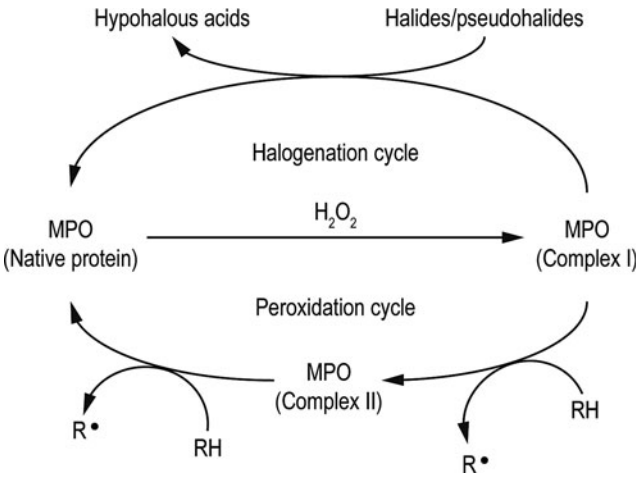

FIG. 3. Schematic illustration of MPO-catalyzed reactions. Upon interaction with hydrogen peroxide, native MPO is converted to Complex I, which can be converted back to the native state by entering either the halogenation cycle (one-step reaction) or the peroxidation cycle (two-step reactions), with the latter giving rise to an intermediary Complex II. The halogenation cycle produces hypohalous acids upon Complex I interaction with halides and pseudohalides, while the peroxidation cycle gives rise to reactive species/radicals ($R^{\bullet}$) upon oxidation of organic peroxidation substrates (RH) such as tyrosine.

enzymes (94) and conversely induce activation of matrix metalloproteinases (MMPs) (30). Similarly, modification of thioethers (oxidation of methionine residues) can lead to enzyme inactivation (45), inhibition of proteinases (124), as well as alterations to signaling cascades (71). Modification of amines and amides by HOCl resulting in the generation of chloramines and chloramides, respectively, could be formed on virtually all organic biological components, which could have serious cellular implications.

Importantly, oxidation of tyrosine residues by HOCl leads to the formation of 3-chlorotyrosine, which is considered a marker for MPO activity, as it is a secondary product that is far more stable than primary MPO-generated species. Similarly, by entering the peroxidation cycle, MPO can give rise to nitrogen dioxide radicals ($^{\bullet}NO_2$) that are capable of nitrating proteins and involved in lipid peroxidation. Much like 3-chlorotyrosine, nitrotyrosine, which is the result of tyrosine oxidation *via* $^{\bullet}NO_2$, is considered a marker of MPO-mediated oxidative stress. 3-Chlorotyrosine and 3-nitrotyrosine have been shown to alter the function of apolipoprotein A-I (apoA-I) by depleting the ATP binding cassette subfamily A member 1 (ABCA1)-dependent cholesterol efflux activity (111, 129). Furthermore, X-ray crystallography studies have revealed that modifications on tyrosine residues could alter protein structure and function by inducing conformational changes and causing steric hindrance (95). Hence, while species generated by MPO are critical for the innate host defense system, their off-target release could lead to compromised cellular/tissue function. For a comprehensive review on the reactive species generated by MPO, we would like to direct the reader to the following excellent reviews (20, 68).

MPO: A Biomarker for Risk Stratification

Acute coronary syndrome

ACS, which refers to a spectrum of clinical presentations (3, 28) ranging from ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (MI), or unstable angina, is usually due to rupture of an unstable atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery (19, 62). In ACS, oxidative stress and inflammation play an important role in the destabilization of coronary plaques (40), and hence, identifying therapeutic targets that contribute to this pathophysiology may have direct clinical implications. Elevated plasma MPO levels have been investigated as a potential biomarker for discriminating chest pain due to ACS from other causes (63), and as a prognostic factor (9).

In an attempt to identify ACS in patients presenting with angina, researchers have investigated the diagnostic efficiency of plasma MPO levels alone or in combination with cardiac troponin I (cTnI) within 6 h of hospital admission. Both MPO and cTnI were found to be significantly lower in non-ACS patients. Interestingly, higher MPO concentrations were observed in troponin-negative ACS patients who became troponin-positive after 6 h, which suggested that combining both MPO and cTnI was more sensitive than assessment of cTnI alone for detecting ACS (107). Elevated MPO levels were also able to distinguish between chest pain due to acute myocardial infarction (AMI) and that due to unstable or stable angina (40). In this study, elevated MPO levels were also associated with subsequent complications such as HF, arrhythmias, and renal

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failure. In another study, MPO levels assessed on admission and 6 h later were able to discriminate between ACS due to angina and other causes (16).

In addition, although elevated plasma MPO levels have been associated with increased incidence of several CVDs, studies investigating the association of intracellular neutrophil or monocyte MPO (mMPO) with CVD are less common. When researchers used flow cytometry, to measure mMPO in 1465 subjects over a median follow-up of 9.6 years, no significant association was observed between mMPO and incident CHD, HF, or all-cause mortality (88). Similarly, a study assessing 123 patients with chronic ischemic heart disease (IHD) actually reported a reduction in neutrophil MPO activity (11). Since inflammation is known to occur in these CVDs, it can be speculated that degranulation and subsequent release of MPO may have already taken place, resulting in the observed intracellular MPO levels.

Researchers have compared the diagnostic accuracy of AMI using high-sensitivity cardiac troponin T (hs-cTnT), MPO, and pregnancy-associated plasma protein A (PAPP-A) in patients at the time of presentation at the emergency department, and found that patients with AMI had higher levels of all three markers, with hs-cTnT demonstrating a better diagnostic performance than MPO and PAPP-A for patients with AMI (53). The time-course of MPO elevation in STEMI treated by primary percutaneous intervention (PPCI) has been shown to display a biphasic pattern, with the highest levels seen at 4 and 24 h after PPCI, with marked decreases at 8 and 12 h, before reaching the lowest level at 168 h. The 24-h MPO level correlated with troponin I, as well as with HF, and hence, in this study, MPO was considered an independent predictor of in-hospital mortality rate (115). In another study of STEMI patients, elevated MPO and C-reactive protein (CRP) levels were shown to be associated with major cardiovascular events, and MPO appeared to be a better predictor than the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels (49, 52). However, not all studies have been positive, with some studies showing no correlation of MPO levels with clinical outcomes following ACS (98, 128).

Atherosclerosis

Atherosclerosis is a chronic arterial disease and a leading cause of vascular disease-related death globally, resulting in major clinical manifestations such as IHD, ischemic stroke, and peripheral arterial disease (46), of which the former remains the leading cause of premature adult mortality (74). Since oxidative stress plays a critical role in the initiation and progression of atherosclerosis, researchers have assessed the role of MPO as a marker of oxidative stress, and whether its circulating levels correlate with the risk of CHD.

In the MONICA/KORA Augsburg study, serum MPO levels were measured in healthy men and women. During the mean follow-up of 10.8 years, in which 333 subjects went on to develop CHD (1727 did not), elevated serum MPO was found to be independently associated with increased risk of incident CHD (50). Given that most patients with recognized atherosclerotic burden are not indicated for revascularization interventions, it is necessary to identify patients at risk for major adverse cardiac events. When assessing plasma MPO concentrations of 1895 patients with known atherosclerotic burden undergoing elective coronary angiography, researchers observed an increased MPO level to be significantly associated with the incidence of major adverse events over a 3-year follow-up. This suggests that MPO could serve as a prognostic marker for adverse events in stable patients with coronary artery disease (CAD) (121). Conversely, in the Dallas Heart Study, where plasma MPO was measured in 3294 subjects, an increased level of MPO was highly associated with aortic, but not coronary atherosclerosis, suggesting MPO to be a potential risk factor in peripheral arterial disease (17). This is consistent with an earlier study involving 156 peripheral artery disease patients, where MPO (but not CRP) was found to predict an increased risk of major cardiac events (14). Similarly, elevated circulating MPO has been reported in patients with atherosclerosis obliterans (ASO), when compared with those who did not have ASO (127).

Since MPO is reported to induce dysfunctional high-density lipoprotein (HDL) (25), a cohort study was performed in a large multiethnic population of 2924 adults free of CVD, to assess whether serum MPO levels indexed to HDL particle concentration (MPO/HDLp) could be correlated with increased CVD risk (54). At a median follow-up of 9.4 years, MPO/HDLp was found to be associated with a 74% increase in incident atherosclerotic CVD (first nonfatal MI, nonfatal stroke, coronary revascularization, or CVD death) and a 9% increase in total incident CVD, suggesting increased MPO/HDLp at baseline to be associated with increased risk of incident CVD events, in a population initially free of CVD.

Additional studies have also been conducted to assess as to whether MPO could also be associated with other risk factors, such as elevated glucose and lipid concentrations. However, when basal levels of MPO were measured in 53 IHD patients over a period of 24 weeks, although MPO was found to be a marker of inflammation in patients with IHD, it could not be associated with other risk factors of atherosclerosis and had no correlation with glucose or lipid values (106). In a similar study that investigated possible associations of serum MPO levels with atherosclerotic plaques in 40 patients without risk factors for atherosclerosis (mainly diabetes, hypertension, obesity, and hyperlipidemia), although researchers found increased MPO levels in patients with atherosclerosis, it could not be used as a predictor of CAD in patients without the risk factors (44).

Heart failure

HF, which arises from cardiac dysfunction, affects multiple organ systems and presents symptoms such as edema, dyspnea, and fatigue. The prevalence of HF is rapidly increasing in aging populations, and hence, understanding its etiology and identifying prognostic markers are essential for effective management strategies. During advanced stages of HF, inflammatory and immune responses have been reported (22) and, as a result, various inflammatory biomarkers may be used to predict the prognosis of patients with acute and chronic HF (CHF).

When 140 patients with chronic systolic HF were examined for correlations between plasma MPO levels and echocardiographic indexes, as well as long-term clinical outcomes, elevated plasma MPO levels, apart from being a predictor of adverse clinical outcomes, were also found to be associated with a higher probability of more advanced HF (120). Similarly, when assessing the combined effect of

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high-sensitivity CRP (hsCRP) and MPO in 136 CHF patients over 34 months, researchers observed a sixfold increase in risk when both markers were elevated (119). Further stratification of patients according to hsCRP, MPO, and NT-proBNP cutoff values provided an increment of risk prediction in adverse events. The study concluded that the combinatorial analysis of hsCRP and MPO measurements provided a complementary prognostic value in these patients. Furthermore, in an attempt to investigate the relationship between MPO and other myocardial damage biomarkers, such as heart-type fatty acid-binding protein (H-FABP) and troponin T (TnT), MPO was significantly associated with serum H-FABP, but not TnT, in 42 CHF patients (34).

In a separate study involving 86 patients with different stages of CHF, in addition to differences in MPO levels being observed between CHF patients and healthy subjects, a positive correlation was established between CHF severity and MPO levels, as MPO was significantly elevated in patients with higher mortality (8). Consistently, when assessing MPO activity in HF, heightened MPO chlorinating activity was found in 81 CHF patients compared with healthy subjects along with a positive correlation with ceruloplasmin, inflammatory, neurohormonal, and nitrosative parameters, suggesting a role of MPO chlorinating activity in HF progression (15). Alternatively, when investigating the probability of MPO levels to predict the risk of developing HF in 3733 healthy elderly subjects over an approximate 7-year follow-up, increased systemic MPO levels were independently associated with the development of HF, especially in subjects without traditional cardiovascular risk factors (118).

Although HF has conventionally been associated with reduced systolic function, HF with preserved systolic function/HF with preserved ejection fraction (HFpEF), which currently accounts for $\sim$50% of all HF cases, is a leading cause of morbidity and mortality (86). Diastolic dysfunction is a key pathophysiological feature of HFpEF that arises from incomplete myocardial relaxation and subsequent impaired rate of ventricular filling, which in turn could result in dyspnea, fatigue, and exercise intolerance (59). As identification of biomarkers for early diagnosis of diastolic dysfunction could lead to improved patient management strategies, researchers assessed the levels of serum MPO in 91 patients diagnosed with diastolic dysfunction. When MPO values were correlated with echocardiography parameters, serum MPO levels were found to be independently or in correlation with the echocardiography parameters associated with diastolic dysfunction (18).

Contrary to these findings, a study using canine models failed to observe a positive correlation with MPO and HF severity (89). Instead, when 69 canines with different stages of HF, due to chronic mitral valvular insufficiency, were compared against 13 healthy controls, a negative correlation between MPO levels and HF severity was observed, as serum MPO levels decreased as the HF increased in severity.

Hypertension

Hypertension is a main contributor to CVD, in both developed and developing countries. Being associated with more than 40% of CVD-related deaths and renal diseases, it is one of the leading causes of mortality globally. Since it is largely asymptomatic, many hypertensive patients are undiagnosed and hence, untreated, resulting in premature deaths due to various complications (77). With the aim of understanding the relationship between the MPO reaction system and oxidative modifications of serum lipoproteins, researchers attempted to compare the peroxidation and chlorination activity of MPO against various oxidative and antioxidative stress-related indices in atherosclerotic patients with hypertension (64). Interestingly, the peroxidation activity, rather than the chlorination activity, correlated with progressive low-density lipoprotein modification in the patient cohort.

Given that obesity is a risk factor for preeclampsia, and that neutrophil infiltration into blood vessels occurs in both obese and preeclamptic women, a study attempted to investigate the effects of MPO under these conditions (112). Interestingly, MPO distribution in blood vessels was found to be different in obese compared with overweight (but not obese) and normal (non-overweight) pregnant women, as immunohistochemical staining showed the most abundant amounts of MPO in the subcutaneous fat of blood vessels of obese pregnant women, followed by overweight and then normal pregnant women. Furthermore, leukocyte infiltration was absent in normal pregnant women, while in obese and preeclamptic pregnant women, leukocytes were found in the lumen, flattened and adhered to the endothelium, and infiltrated into the vessel wall. In general, due to neutrophil infiltration, both obese and preeclamptic women had increased MPO in the systemic vasculature. MPO expression was also increased in the maternal blood vessels of preeclamptic women than normal pregnant or normal nonpregnant women.

In a similar study, when plasma MPO concentrations and activity were measured in 219 healthy pregnant women, and in 130 gestational hypertension and 143 preeclampsia patients, it was found that preeclampsia and gestational hypertension patients not receiving antihypertensive treatment had higher MPO levels and increased MPO activity, respectively (101). Furthermore, higher levels of MPO was in the supernatant obtained from human umbilical vein endothelial cell cultures incubated with plasma from the preeclampsia group compared with healthy pregnant women. The study also demonstrated that elevated MPO levels may contribute to endothelial dysfunction *via* nitric oxide impairment, as inhibition of MPO activity *in vitro* improved nitric oxide bioavailability. Interestingly, antihypertensive drugs seemed to decrease MPO levels in preeclampsia and gestational hypertension patients, but with no impact on MPO activity (101).

Furthermore, in a study aimed at understanding the effects of MPO in hypertensive pregnancy, researchers observed increased cardiac MPO in the left but not right ventricle of hypertensive pregnant rats (131). Increased circulating MPO activities were associated with concomitantly lower number of viable fetuses, litter size, fetal and placenta weights, as well as decreases in nitric oxide in hypertensive rats. Circulating soluble fms-like tyrosine kinase-1 and vascular endothelial growth factor were also increased in the hypertensive pregnant group, which cumulatively suggested preeclampsia to be associated with an inflammatory response.

Stroke is one of the main causes of mortality and morbidity worldwide, with hypertension being an important risk factor. Since stroke survivors have increased risk of recurrent stroke, dementia, and other vascular diseases (132), it is important to identify markers that could predict such events. Consistently, when assessing 13 plasma biomarkers in 2176 participants, of whom 562 had outcome strokes, MPO was independently

associated with the risk of recurrent stroke (33). Alternatively, MPO can also be used as an imaging biomarker to risk-stratify vulnerable stroke patients (12).

Diabetes mellitus

Obesity has become a major public health concern globally, affecting ~1.5 billion people. Given that obesity is a risk factor for various diseases, including type 2 diabetes, the increase in obesity has projected the number of people affected by type 2 diabetes to increase from 366 million in 2011 to 552 million in 2030 (65). An initial study demonstrated MPO to bind to red blood cells (RBC) that resulted in alterations to their biophysical properties. A correlation between plasma MPO concentration and RBC rigidity index in type-2 diabetes mellitus (DM) patients with CHD was also observed, suggesting MPO to alter components of the microcirculation under pathological stress conditions (38). In a study assessing neutrophil activity in type-2 DM patients with and without CHD, researchers found plasma MPO levels to be elevated in those with CHD, suggesting plasma MPO levels to be an additional biomarker of oxidative stress and cardiovascular risk in DM patients (37).

Heart transplant and graft rejection

Rates of graft rejection are high among recipients of heart transplants. As a result, following heart transplantation, endomyocardial biopsy is the standard method to diagnose acute graft rejection, and hence, there is an inherent need to develop a less or noninvasive alternative method of diagnosis. With the aim of achieving this, researchers measured serum MPO and carbonyl proteins (CP) in 28 patients who had undergone heart transplantation and had experienced various grades of rejection (58). Serum MPO and CP levels in posttransplant patients with Grade 2R rejection were significantly elevated at the time of rejection, compared with those measured a month earlier. This highlighted the possibility that serum MPO and CP levels could be used to predict Grade 2R rejection, thereby suggesting the use of these markers to monitor rejection events noninvasively. MPO imaging represents another potential alternative to invasive techniques for diagnosing graft rejection, as mice that underwent heart transplant showed that a specific monocyte subpopulation could accumulate in the allografts and express high levels of MPO (58).

The longevity of heart transplants is heavily dependent on chronic rejection in the form of cardiac allograft vasculopathy (CAV) (70). CAV has high prevalence among heart transplant patients due to both immunological and nonimmunological factors (123). When assessing 47 heart transplant recipients, researchers observed patients with CAV to have a higher oxidative stress index (OSI), MPO levels, and catalase activity, when compared with those who did not have CAV. Upon further stratification of CAV patients to mild and severe, the latter group was associated with higher OSI, and a moderate correlation was observed between the CAV grade and OSI, MPO, and catalase activity (51).

MPO: A Target for Cardiovascular Protection

Atherosclerosis

In one of the first studies aimed at identifying proteins directly targeted by MPO, researchers found apoA-I; the primary protein constituent of HDL to be a selective target for MPO-catalyzed nitration and chlorination (129). Furthermore, these MPO-catalyzed modifications that lead to the oxidation of HDL and apoA-I resulted in the inhibition of ABCA1-dependent cholesterol efflux from macrophages. Interestingly, MPO was found to exert its effects by directly binding to apoA-I, which resulted in the latter's oxidation. In a more recent study, apoA-I nitration and chlorination levels were found to be significantly increased in the serum of diabetic patients, with a concurrent decrease in apoA-I concentration and cholesterol efflux activity (67). Furthermore, *in vitro* studies suggested MPO-catalyzed modifications to impair antiapoptotic properties of HDL. HDL found in atherosclerotic plaques is considered to be cardioprotective (24), an effect that is compromised upon MPO-mediated nitration and chlorination (130).

When the effects of nitrated and chlorinated HDL on vascular smooth muscle cell (VSMC) migration, proliferation, apoptosis, and plaque stability were investigated, researchers found these modifications to inhibit VSMC migration and proliferation, although apoptosis was not affected (130). This was attributed to a reduction in ERK1/2 phosphorylation, which was observed when VSMCs were incubated with oxidized HDL. Consistent with this, the migration defects could be rescued with an MAPK inhibitor, PD98059. Furthermore, in aortic VSMCs that were deficient for scavenger receptor class B, type I (SR-BI), the migration differences observed when VSMCs were treated with either native or oxidized HDL were diminished, suggesting SR-BI to play a role in VSMC migration. Oxidized HDL induced neointima formation and reduced SMCs in atherosclerotic plaque, resulting in an elevated vulnerable index of the plaque, which suggested oxidized HDL to contribute to plaque instability (130).

In another study, researchers investigated the role of MPO to regulate atherosclerotic lesion formation and composition in $LDLR^{-/-}$ mice, a model for atherosclerosis (103). Upon treatment with a selective small-molecule MPO inhibitor, PF-06282999, although there was no effect on the lesion area, a reduced necrotic core was observed in the aortic root. Furthermore, MPO inhibition did not seem to alter leukocyte homing and macrophage content in the plaques. This seemed to suggest that although MPO inhibition had no effect on plaque area nor the homing of inflammatory cells, it could alter the level of inflammation in the lesions, and hence, MPO inhibition could stabilize the plaque and prevent its rupture.

More recently, researchers attempted to target MPO in ruptured atherosclerotic plaques (97). In a tandem stenosis $Apoe^{-/-}$ model of atherosclerotic plaque instability, MPO activity was found to be greater than twofold when plaques were rendered unstable. Genetic deletion of MPO as well as pharmacological treatment with an MPO inhibitor, AZM198, resulted in increased fibrous cap thickness, decreased fibrin and hemosiderin in unstable plaques, suggesting that inhibition of plaque MPO activity could be a potential management strategy for patients with high-risk CAD.

Ischemia/reperfusion injury

Apart from directly inhibiting MPO, researchers have also investigated alternative approaches by which to target MPO activity. Since endothelin (ET) receptor antagonists have been reported to limit myocardial ischemia/reperfusion (I/R)

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injury (43, 105), a study was aimed at assessing the cardioprotective effect of such antagonists, and their ability to inhibit MPO activity during I/R. When pigs were subjected to acute myocardial ischemia followed by reperfusion, infiltration of MPO^+ cells into the ischemic region was observed. However, when a selective ET(A) receptor antagonist LU135252 was administered into the left anterior descending coronary artery during the final 10 min of ischemia and the first 5 min of reperfusion, a marked reduction in final infarct size was achieved in comparison with the vehicle group. Interestingly, MPO activity in the ischemic myocardium was significantly lower in the LU135252-treated group, which suggested a positive correlation between infarct size and MPO activity (36). Hence, by targeting the ET(A) receptor, a cardioprotective effect could be achieved by reducing injury mediated by MPO activity.

In a separate study, the cAMP phosphodiesterase inhibitor, BMY21190, was also found to reduce the infarct zone in a canine model of I/R injury (72), and much like the previous study, MPO activity was significantly lower in the area at risk in the BMY21190-treated group. As phloroglucinol has been reported to have anti-inflammatory and antioxidant properties (55), its effects were investigated in a rat model of I/R injury (61). Post-I/R, in addition to having a large infarct size, control rats comprised increased MPO levels and activity in the plasma and myocardium, which could be alleviated by pretreatment with phloroglucinol.

Diabetes mellitus

In the case of DM, given that vascular dysfunction and inflammation are hallmarks of the disease, and as overexpression of adenosine A3 receptor (A3AR) has been shown to mediate such conditions, researchers attempted to study the role of MPO in adenosine-dependent vasomotor function in a murine model of DM (82). When wild-type and MPO-deficient mice were treated with streptozotocin, an increase in MPO plasma levels was observed in the former group, which led to an enhanced aortic superoxide production. Furthermore, vasoconstriction of aortic segments was increased in diabetic wild-type mice compared with diabetic MPO-deficient mice, which was attributed to MPO-mediated increases in vascular A3AR expression that lead to enhanced vasoconstriction and vascular dysfunction (82).

Atrial fibrillation

In an attempt to assess whether inflammation is the cause of atrial fibrillation, researchers treated mice with angiotensin II to induce leukocyte activation (104). Upon doing so, wild-type mice exhibited higher levels of plasma MPO, abundant levels of 3-chlorotyrosine in the atrial tissue, as well as increased MMP activity and atrial fibrosis. Contrary to this, $MPO^{-/-}$ mice showed a reduction in all endpoints and were also protected against atrial fibrillation, an effect that was lost upon intravenous supplementation of recombinant MPO.

Myocardial infarction

Following MI, the adverse remodeling of the left ventricle and its subsequent dilation are a major cause of congestive HF. In an attempt to determine a link between left ventricle remodeling and inflammation, researchers investigated the effects of MPO in a chronic coronary artery ligation model (7). Interestingly, $MPO^{-/-}$ mice demonstrated decreased leukocyte infiltration and improved left ventricle function, attributed to decreased tissue plasmin activity. Furthermore, MPO and plasminogen activator inhibitor 1 (PAI-1) seemed to have contrasting roles, as $MPO^{-/-}$ mice demonstrated delayed myocardial rupture, whereas PAI-$1^{-/-}$ demonstrated accelerated rupture.

MPO inhibitor molecules have also been reported to alleviate cardiac remodeling and improve function in a mouse MI model (2). When using PF-1355, an oral inhibitor of MPO, 7 days of treatment saw a decrease in the number of inflammatory cells and attenuated left ventricular dilation, while 21 days of treatment saw further improvement in cardiac function and remodeling. Furthermore, early administration of the inhibitor as opposed to later treatment (1 h *vs.* 25 h post-MI) seemed to result in better outcomes.

In an attempt to assess the effects of MPO on postischemic arrhythmogenic ventricular remodeling, researchers found the ventricles of $MPO^{-/-}$ mice to exhibit improved electrical conduction in the peri-infarct zone post-MI, compared with wild-type mice (73). This was attributed to the maintenance of connexin 43, which was broken down in the wild-type mice by an MPO-mediated activation of MMP-7. Furthermore, MPO was capable of transdifferentiating fibroblasts to myofibroblasts, the latter of which was reduced in $MPO^{-/-}$ mice, which coincided with decreased postischemic fibrosis.

In addition to these small animal models of MI, MPO^+ infiltrating cells can also be detected in cardiac tissue obtained from Yorkshire pigs that underwent myocardial injury due to coronary artery ligation (Fig. 4) (76). Future studies on large animal models of CVD could help ascertain the reason for this infiltration, identify mechanisms by which these cells impede cardiac function, as well as assess potential therapeutic outcomes through MPO inhibition strategies.

Pulmonary arterial hypertension

More recently, a study aimed to assess whether MPO is causally liked to pulmonary arterial hypertension (PAH) as two independent clinical cohorts were found to have elevated

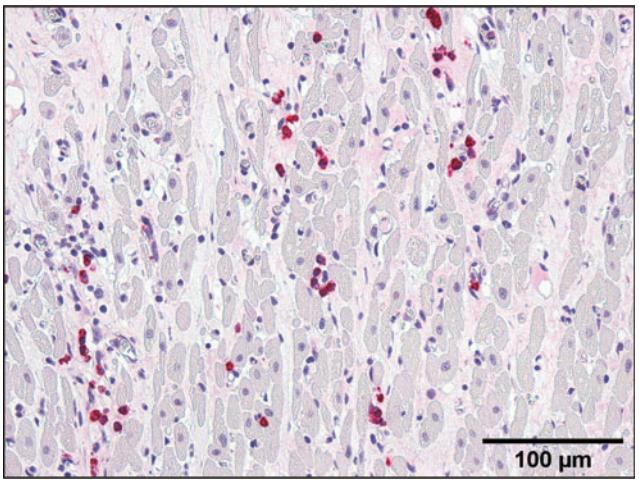

FIG. 4. Immunohistochemistry pictograph showing infiltrating MPO^+ cells (*red*) in porcine myocardium 2 weeks postmyocardial injury. Image captured from cardiac sections used in the following study (76). Color images are available online.

plasma MPO (57). When attempting to decipher the mechanism by which MPO causes PAH, researchers observed that upon hypoxia, the right ventricular pressure was less increased in $MPO^{-/-}$ mice, when compared with wild-type mice. Furthermore, hypoxia induced activation of the Rho-kinase pathway that is reported to be involved in vasoconstriction and structural vascular remodeling (83). Consistently, while this pathway was blunted in $MPO^{-/-}$ mice, infusion of MPO activated this pathway and increased right ventricular pressure, which could be prevented by the Rho-kinase inhibitor, Y-27632. Furthermore, the MPO inhibitor AZM198 attenuated PAH, in a Sugen5416/hypoxia rat model, demonstrating tight interplay between MPO, the Rho-kinase pathway, and vascular function.

Antioxidants and Cardiovascular Protection

Under normal cellular conditions, a balance exists between the generation of reactive species and protection by antioxidants. An imbalance in this process, either due to an increased generation of reactive species or impairment of the antioxidative protective pathways, results in oxidative stress (78). Oxidative stress, although initially confined to reactive oxygen species (ROS), now includes reactive nitrogen species (RNS) as well. ROS are by-products of oxidative metabolism, while RNS are produced by nitric oxide synthase, which is initiated from L-arginine (102). ROS and RNS include (but are not limited to) hydrogen peroxide, superoxide, nitric oxide, and peroxynitrite, all of which could be incorporated into the MPO reaction cycle to generate 3-chlorotyrosine and 3-nitrotyrosine (Fig. 5) (117). Since these reactive species have also been shown to be responsible for the pathophysiology of various CVDs (48, 75), the targeting of oxidative stress *via* the use of antioxidants could be considered an alternative cardioprotective strategy.

Despite positive findings in preclinical and small clinical trials, reports on large clinical trials assessing the protective properties of antioxidants, alone or in combination, have largely been disappointing, with certain antioxidants such as beta-carotene found to increase the risk of death, in subjects who had a previous MI (75, 113). Diverse speculations have been made as to why antioxidant therapies have not been successful, including several generalizations, such as (i) not all reactive species are universally harmful, (ii) excessive amounts of antioxidants could render the cells in a highly reduced harmful state, and that (iii) antioxidants may be metabolized before reaching its target (39).

Interestingly, the endoplasmic reticulum-resident selenoproteins are rapidly emerging as cardioprotective agents, as several studies have linked their dysfunction with susceptibility to oxidative stress and CVD (100). More recently, selenoprotein T was found to exert cardioprotective effects in a rat model of I/R injury (99). Following the use of a peptide encompassing the redox motif of selenoprotein T, researchers observed significant contractile recovery and reduction in infarct size. This protective effect was accompanied by modulation of several favorable signaling pathways, the suppression of proapoptotic factors with concurrent stimulation of antiapoptotic proteins, as well as the reduction of several oxidative and nitrosative stress markers (99). This clearly suggests that the targeting of oxidative stress for cardioprotection does not encompass one pathway, but an intricate network of multiple pathways, and hence, it would be interesting to see if selenoproteins would fare better than their contemporary antioxidants in improving CVD-related outcomes.

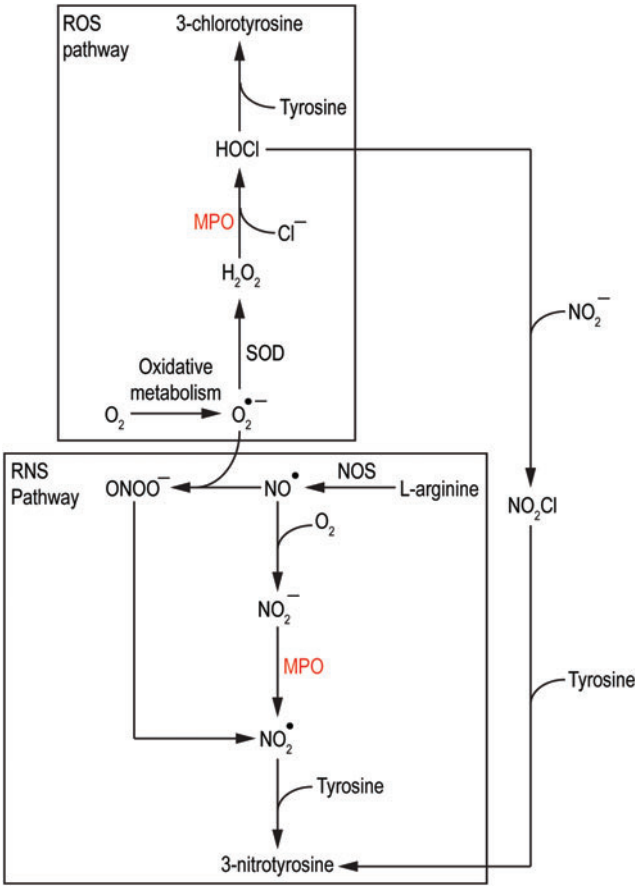

FIG. 5. Schematic illustration as to how reactive species generated from the ROS/RNS pathways act as substrates for MPO-catalyzed reactions, giving rise to 3-chlorotyrosine and 3-nitrotyrosine. In the ROS pathway, superoxide ($^{\bullet}O_2^-$) is produced through oxidative metabolism and converted into hydrogen peroxide (H_2O_2) by SOD. MPO in the presence of hydrogen peroxide and chloride ions (Cl^-) is capable of generating hypochlorous acid (HOCl), which can modify tyrosine residues into 3-chlorotyrosine. In the RNS pathway, NOS catalyzes the production of nitric oxide ($^{\bullet}NO$) from L-arginine. Nitric oxide is converted into nitrite ions (NO_2^-) in the presence of oxygen, followed by conversion into nitrogen dioxide ($^{\bullet}NO_2$), a reaction catalyzed by MPO. Nitrogen dioxide can modify tyrosine residues into 3-nitrotyrosine. Alternatively, nitric oxide, in the presence of superoxide, gives rise to peroxynitrite ($ONOO^-$), which is broken down into nitrogen dioxide. Hypochlorous acid itself can react with nitrite ions to form nitryl chloride (NO_2Cl), which can modify tyrosine residues into 3-nitrotyrosine. NOS, nitric oxide synthase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase. Color images are available online.

Conclusions

Being a prognostic biomarker in a wide variety CVDs, MPO has the potential to be a multifaceted target for

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cardiovascular protection. It is important to note, however, that while several studies support MPO to be a predictor of worsened cardiovascular outcomes, this has not been a universal occurrence, and hence, care should be taken when determining its use as a biomarker for assessing disease severity and heightened risk. This is further confounded by reports which demonstrate that the sample type, the manner in which it was acquired, as well as the storage conditions can affect MPO measurements (126). While these variables can probably be overcome with the development of cost-effective, rapid assays that are resistant to exogenous MPO inhibitors (35), the findings reported from various animal models of CVD, in which inhibition of MPO or its depletion resulted in an alleviated disease phenotype, are highly encouraging. While we wait in anticipation for the results from the clinical trial (NCT03611153) aimed at investigating the effect of MPO inhibition on resting and exercise hemodynamics in patients with HFpEF, further studies aimed at elucidating the mechanisms by which elevated MPO leads to poor prognosis and, conversely, studying the effects of MPO inhibition on alleviating disease phenotype in other CVDs will facilitate future MPO-targeted clinical trials for improving CVD-related outcomes.

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Abbreviations Used

A3AR = adenosine A3 receptor
ABCA1 = ATP binding cassette subfamily A member 1
ACS = acute coronary syndrome
AMI = acute myocardial infarction
apoA-I = apolipoprotein A-I
Apoe = apolipoprotein E
ASO = atherosclerosis obliterans
CAD = coronary artery disease
CAV = cardiac allograft vasculopathy
CHD = coronary heart disease
CHF = chronic heart failure
CP = carbonyl proteins
CRP = C-reactive protein
cTnI = cardiac troponin I
CVD = cardiovascular disease
DM = diabetes mellitus
ET = endothelin
HDL = high-density lipoprotein
HDLp = HDL particle
HF = heart failure
H-FABP = heart-type fatty acid-binding protein
HFpEF = heart failure with preserved ejection fraction
HOCl = hypochlorous acid
hsCRP = high-sensitivity C-reactive protein
hs-cTnT = high-sensitivity cardiac troponin T
I/R = ischemia/reperfusion
IHD = ischemic heart disease
LDLR = low-density lipoprotein receptor
MI = myocardial infarction
MMP = matrix metalloproteinase
mMPO = monocyte MPO
MPO = myeloperoxidase
NT-proBNP = N-terminal prohormone of brain natriuretic peptide
OSI = oxidative stress index
PAH = pulmonary arterial hypertension
PAI-1 = plasminogen activator inhibitor 1
PAPP-A = pregnancy-associated plasma protein A
PPCI = primary percutaneous intervention
RBC = red blood cell
RNS = reactive nitrogen species
ROS = reactive oxygen species
SR-BI = scavenger receptor class B, type I
STEMI = ST-segment elevation myocardial infarction
TnT = troponin T
VSMC = vascular smooth muscle cell

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