Artery Research

REVIEW ARTICLE

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Oxidative Stress and Its Biomarkers in Cardiovascular Diseases

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Abstract

Background Cardiovascular diseases (CVDs) are the most common cause of death worldwide. CVDs share heterogeneous pathophysiologic mechanisms, one of which includes increased oxidative stress.

Main Body Surplus levels of reactive oxygen species induce damage to cellular macromolecules such as DNA, proteins, and lipids. Increased reactive oxygen species result in decreased nitric oxide availability, vasoconstriction, and the development of procoagulant and proinflammatory states in blood vessels.

Conclusion Improved knowledge of biomolecular processes triggered by oxidative stress has helped develop tools for assessing oxidative stress markers and applying them in clinical settings. Nevertheless, some research gaps should be filled, specifically by defining the most clinically relevant biomarkers for oxidative stress with high sensitivity and specificity for CVD.

Keywords Biomarkers, Cardiovascular diseases, Endothelial cell dysfunction, Inflammation, Oxidative stress, Reactive oxygen species

1 Background

Cardiovascular diseases (CVDs) remain a top global issue [1] despite numerous initiatives to reduce their prevalence and impact on human health. The most prevalent type of cardiovascular disease (CVD) is coronary heart disease (CHD) [2]. Research evidence indicates that oxidative stress is a significant factor in the development of CVDs [3]. Significant oxidative stress leads to dysfunction and inflammation in blood vessels, primarily affecting endothelial cells (EC). Other blood vessel cells, such as vascular smooth muscle cells (VSMCs) or adventitia cells, are also involved [4]. However, ECs play a critical role in cardiovascular imbalance, e.g., endothelial dysfunction impairs vasoconstriction and vasodilatation, causes EC apoptosis, increases the adhesion of ECs to monocytes, and alters the angiogenic potential of ECs [5]. Consequently, atherosclerotic plaques and lesions form and thus lead to CVD.

Excessive production or accumulation of reactive oxygen species (ROS) contributes to oxidative stress. ROS include the oxygen free radicals superoxide, hydroxyl, and peroxyl radicals) and nonradicals (hydrogen peroxide and hypochlorous acid) [6]. Mitochondria are the primary drivers of intracellular oxidant production in most cell types [7], followed by sources such as nicotinamide adenine dinucleotide phosphate oxidases (NOXs), heme oxygenase 1, xanthine oxidase, and cyclooxygenases [8, 9]. Basal levels of ROS generation are essential for signal transduction pathways, protection against microorganisms, gene expression, and the promotion of cellular survival, apoptosis or death [10, 11]. The body has protective measures against ROS, including enzymatic compounds such as glutathione peroxidase, superoxide dismutase (SOD),

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and catalase, as well as nonenzymatic compounds such as nicotinamide, glutathione and tocopherol [12–15].

Identifying numerous biomarkers for oxidative stress has made it easier to measure the levels of ROS. However, the use of these biomarkers in clinical settings still requires validation because of the considerable variation in oxidative stress levels across different diseases [16]. A biomarker is any substance or process that can be measured in the body or its products and can predict the occurrence of a disease or its outcome [17]. Many markers for oxidative stress can be measured, but their clinical applicability is a concern since there is no consensus on which one is superior to others. For a biomarker to be clinically beneficial, it must meet at least one of the following criteria: (a) demonstrate specificity for a particular disease, (b) have prognostic value, and (c) be correlated with disease activity [16]. This review also highlights the use of currently employed drugs with cardioprotective effects, such as sodium–glucose transport protein 2 (SGLT2), mineralocorticoid receptor antagonists, and glucagon-like peptide-1 (GLP-1) agonists, and their possible effects on oxidative stress.

This study investigated the connection between oxidative stress and endothelial cell dysfunction, particularly the impact of reduced nitric oxide (NO) bioavailability and inflammation caused by ROS. Furthermore, the biomarkers utilized to assess oxidation-specific epitopes (endogenous damage-associated molecular patterns) in CVD as indicators of oxidative stress and currently used drugs with antioxidant effects are reviewed.

Key terms

CVD – refers to atherosclerotic cardiovascular disease due to plaque buildup in artery walls, such as coronary artery disease, including acute coronary syndrome (myocardial infarction) and chronic coronary disease, cerebrovascular disease (stroke, transient ischemic attack, carotid artery stenosis), peripheral artery disease, abdominal and thoracic aortic aneurysm, and intestinal ischemia

Atherosclerosis – condition when cholesterol, fat, blood cells and other substances in blood form plaque on artery wall, leading to artery narrowness

Necrotic core – early stage of atherosclerosis defined by macrophage apoptosis and diminished clearance of apoptotic cells

EC – endothelial cells – cells that are located in tunica intima of blood vessels

Plaque formation – atherosclerotic plaque formation involving low density lipoprotein (LDL) accumulation in tunica intima, oxidation of LDL, recruitment of monocytes-macrophages, uptake of oxidized LDL by macrophages and transformation of macrophages into foam cells

ROS – reactive oxygen species, including free radicals as superoxide, hydroxyl, and peroxyl radicals, and nonradical as hydrogen peroxide and hypochlorous acid

2 The Role of the Endothelium

Oxidative stress is the primary mechanism that provokes endothelial dysfunction characterized by the procoagulant, proinflammatory, and proliferative phenotype of ECs, resulting in atherothrombosis and coexisting inflammation [18, 19]. Additionally, endothelial dysfunction can be directly caused by increased levels of fatty acids in the blood, which induce insulin resistance, activate the renin–angiotensin system, and maintain inflammation [18, 20].

Excess free radicals reduce the bioavailability of endothelium-secreted vasodilators such as nitric oxide (NO) and prostacyclin (PGI_2) [21, 22]. In particular, NO has anti-inflammatory, antithrombotic properties (inhibits platelet aggregation) and protects blood vessels from vasospasm (acts through guanylate cyclase located in the membrane of vascular smooth muscle cells) [23]. However, NO is inactivated during the reaction with superoxide anions, forming peroxynitrite $ONOO^-$. Free radicals also uncouple NO synthase (eNOS), thus decreasing its efficacy and the concentration of its substrates and cofactors (L-arginine and tetrahydrobiopterin BH4, respectively) and increasing the level of the endogenous eNOS inhibitor dimethylarginine (Fig. 1) [19, 24]. Moreover, free radicals monomerize eNOS dimers, significantly reducing the efficiency of NO synthesis. ONOO- nitrates cellular proteins, including those in the electron transport chain, leading to mitochondrial dysfunction and cell apoptosis [19]. The hallmark of mitochondrial dysfunction is disturbed mitochondrial Ca^{2+} ion homeostasis (ROS inhibit mitochondrial Na^+/Ca^{2+} exchangers) and altered membrane potential [25]. The mitochondrion itself also produces ROS, which cause mitochondrial DNA (mtDNA) damage [26] and contribute to endothelial dysfunction [27]. Endogenous and exogenous ROS act through mitogen-activated protein kinases (MAPKs) and increase the concentration of proliferative molecules such as fibroblast growth factor, insulin-like growth factor, platelets, and epidermal growth factor and the expression of their receptors in the vascular smooth muscle layer, which causes smooth muscle cells to migrate toward the endothelium and proliferate [28, 29]. Additionally, a dysfunctional endothelium initiates and maintains coagulation conditions through secreted von Willebrand factor (vWF), which interacts with platelet GPIα receptors, tissue factors, and plasminogen activator inhibitors [19].

3 The Role of Inflammation and Other Cells

During oxidative stress, ROS activate nuclear factor κB (NF-κB), which turns on target genes responsible for producing adhesion molecules (P and E selectins,

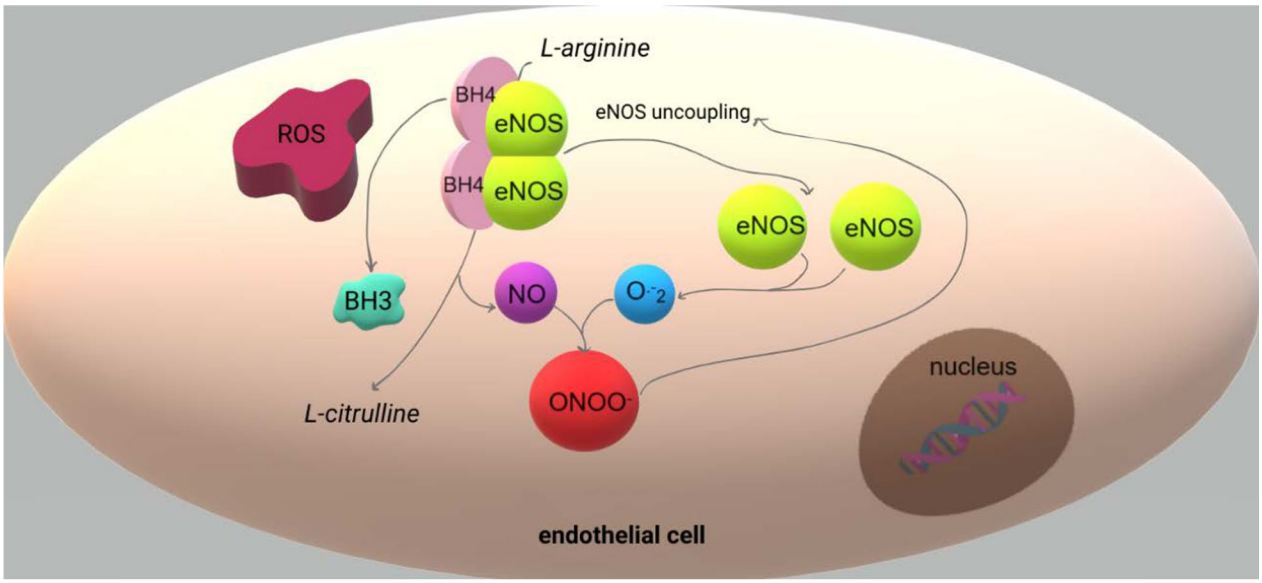

Fig. 1 Oxidative stress induced the uncoupling of eNOS in endothelial cells

ICAM-1, VCAM-1), IL-1, IL-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1). As a consequence, neutrophils and monocytes are activated and migrate to damaged blood vessel tissues (Fig. 2) [30, 31]. Dysfunctional endothelium also secretes extracellular vesicles with microRNA155 (miR155) and miR92a, which induce monocyte polarization toward a proinflammatory M1 phenotype [30]. Additionally, in response to IL-1β, ox-LDL promotes the structural and functional transition of smooth muscle cells to cells with a macrophage phenotype [32, 33]. Activated neutrophils begin to secrete cathepsin G, which acts on platelets such as thrombin (through PAR1 receptors) and tissue factor, triggering the coagulation cascade [34].

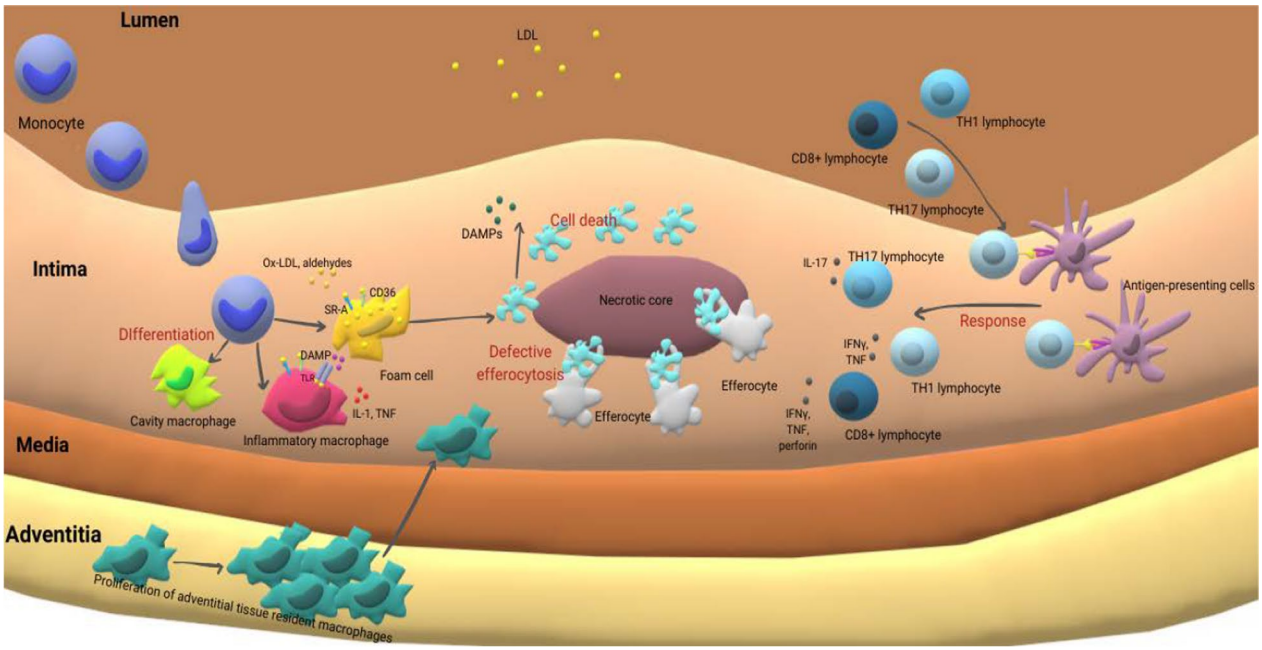

Fig. 2 Mechanisms of atherosclerotic plaque formation. The role of inflammation

Similarly, platelets can also activate neutrophils through their granule components (CXCL4 and HMGB1), stimulating the neutrophil receptors Mac1, PSGL-1, and CD40 [34, 35]. Neutrophils form and secrete neutrophil extracellular traps (NETs) after being stimulated by ox-LDL, cholesterol crystals, activated platelets, and IL-8 [36].

Consequently, NETs stimulate macrophages to produce IL-1β cytokines, further contributing to the migration of neutrophils and T lymphocytes [37]. The latter secrete IL-17 and activate adaptive immunity [36]. When monocytes turn into macrophages, they can absorb lipoproteins via receptors such as CD36, SRA1, and SRA2. This process can cause the transformation of macrophages into foam cells. Furthermore, the expression of the proinflammatory endothelial adhesion molecules netrin-1 and semaphorin-3E restricts macrophage migration from atherosclerotic lesions and blocks the cytokine receptors CCL19 and CCL21, thus inhibiting macrophage chemotaxis [38, 39]. The subsequent retention of macrophage migration and ineffective efferocytosis lead to the formation of a necrotic lipid core with dead foam cells and efferocytes [39]. Mature dendritic cells, triggered by inflammatory cytokines and Toll-like receptor (TLR) agonists, begin to express CD11c+, CD11b+, and CD40 receptors and present antigens to T lymphocyte subtypes (CD8+T lymphocytes through MHC class I molecules and to CD4+through MHC class II molecules) [40–43]. Activated T lymphocytes (helper TH1, TH17 and cytotoxic CD8+T cells) further increase inflammation (secretion of IFNγ, TNF, and IL-17) and stimulate vascular smooth muscle cell proliferation.

4 Oxidative Stress and Cardiovascular Disease

Oxidative stress is one of the most critical components in the pathogenesis of CVD, triggering thromboinflammation [44, 45]. It is caused by the excessive production of free radicals (ROS, nitrogen, and sulfur) or insufficiency of the antioxidant system [19, 46]. ROS include the hydrogen peroxide H_2O_2, superoxide anion O_2^-, and hydroxyl-OH [19]. They are byproducts of mitochondrial metabolism but can also be generated by the action of heme oxygenase 1, xanthine oxidase, and NADPH oxidases (NOXs) [47–49]. The mediators of oxidative stress in CVD include oxidized low-density lipoproteins (ox-LDL), angiotensin II, endothelin I, aldosterone, and glycosylated compounds. They bind to lectin-oxidized LDL receptor-1 (LOX-1) and activate NADPH oxidases (NOXs) [18, 29, 50–53]. Notably, increased blood pressure results in increased expression of LOX-1 and upregulated NOXs (mainly NOX1 and NOX4), leading to decompensated oxidative stress and the development of atherosclerosis in individuals with arterial hypertension [29, 54, 55].

Endothelial dysfunction may lead to the rupture of an atherosclerotic plaque and thus clot formation. The risk of rupture is significantly increased if one of the following conditions are present: a large necrotic core of the plaque, a thin fibrin cap (<65 μm), pronounced inflammation, or vascular remodeling [56]. As a consequence, macrophages express fibrin cap-lysing enzymes (collagenases and gelatinases) and, together with T lymphocytes, secrete IFNγ, which inhibits collagen synthesis and induces VSMC apoptosis [57, 58].

VSMCs activate platelets through C-type lectin-like receptor 2 (CLEC-2), which has a very similar function to the collagen receptor GP VI (which also induces platelet activation) [59] CLEC-2 is a newly identified protein on the surface of platelets [59]. CLEC-2 and podoplanin, endogenous ligands of CLEC-2, are both expressed in advanced atherosclerotic lesions. However, in early atherosclerotic lesions, only CLEC-2-binding sites are colocalized within VMSCs, whereas podoplanin expression is absent [60].

After atherosclerotic plaques rupture, large amounts of collagen, tissue factor, and vWF are released [61, 62]. vWF binds to the GP Ib–IX–V receptor complex of platelets and collagen to GP Ia/IIa and VI receptors, thus activating platelets and changing their shape and granule contents (ADP, serotonin, thromboxane A2), leading to platelet adhesion [63, 64]. The release of tissue factor initiates the coagulation cascade via the extrinsic pathway and fibrin production, causing blood vessel thrombosis and, thus, CVD and possibly death.

5 Biomarkers of Oxidative Stress in Cardiovascular Diseases

There are numerous biomarkers for oxidative stress in CVD. Nevertheless, their clinical applicability is a concern, mostly because no consensus exists on which method is superior. Hence, only biomarkers specific for CVD are discussed below.

5.1 Protein Carbonyls and Advanced Glycation End Products

Protein carbonyls are created in several ways, namely, (a) through the oxidative breakdown of the protein skeleton; (b) through the coupling of aldehydic lipid peroxidation products to lysine, cysteine, and histidine remnants and the production of advanced lipoxidation end products; and (c) through the nonenzymatic glycation of reducing sugars [65–67]. Similarly, advanced glycation end products (AGEs) are formed via reactions between lysine and arginine residues and carbohydrates [16]. AGEs appear throughout normal metabolism but are more highly expressed in oxidative stress and hyperglycemic or hyperlipidemic states [65]. Consequently,

Table 1 Associations between oxidative stress biomarkers and cardiovascular diseases in human studies

Biomarker	Method	Change	Results	Pathology
Protein carbonyls [73, 74]	Reaction of the carbonyl group with 2,4-dinitrophenylhydrazine to form the 2,4-dinitrophenylhydrazone	↑	Cut-off for ACS 2.21 mmoL/mg, AUC 0.84 (specificity 80%, sensitivity 83%)	Unstable angina, non-ST and ST elevation myocardial infarction
Advanced oxidation protein products [75]	Enzyme-linked-immunosorbent assay	↑	Abdominal aortic aneurysms ($r=0.4180$, $p \leq 0.05$), aortoiliac occlusive disease ($r=0.616$, $p \leq 0.05$)	Abdominal aortic aneurysms, aortoiliac occlusive disease
Oxidized low-density lipoproteins (oxidized phospholipids) [90, 91]	Enzyme-linked-immunosorbent assay	↑	Cardiovascular diseases (Effect Size total 0.75 (95% CI: 0.46,1.03)	Cardiovascular diseases
Trans–4–hydroxy–2–nominal [77, 103]	Enzyme-linked immunosorbent assay, co-immunoprecipitation, immunoblot/Western blot	↑	Acute cardiovascular events (myocardial infarction, ischemic stroke), heart failure (HR: 2.23 (95% CI 1.44, 3.44); $p=0.0003$)	Acute cardiovascular events (myocardial infarction, ischemic stroke), heart failure
F_2–isoprostanes [113]	Enzyme-linked immunosorbent assay	↑	Coronary heart disease (OR: (95% CI 2.47 (1.44, 4.26), $p=0.001$), ischemic stroke (medians 0.041 vs. 0.0295, $p=0.012$; AUC = 0.68 (0.55–0.8)	Coronary heart disease, ischemic stroke
Malondialdehyde (114)	Enzyme-linked immunosorbent assay	↑	Chronic heart failure (HR: 1.90 (95% CI 0.99, 3.65), $p=0.05$), history of myocardial infarction (HR: 1.64 (95% CI 1.00, 2.68), $p=0.05$), multivessel disease (HR: 1.78 (95% CI 1.09, 2.91), $p=0.02$)	Chronic heart failure history of myocardial infarction multivessel disease

AGEs interact with macrophages and endothelial cells, induce inflammation in an NF-κB-dependent fashion, and trigger the expression of adhesion molecules and procoagulant tissue factors on the endothelium [68, 69]. AGEs are associated with arteriosclerosis, diabetes mellitus, and other conditions, such as obesity and neurodegenerative diseases [70]. Glycoxidation is another process that results in the generation of AGEs [16, 71, 72]. The essential clinically valuable feature of protein carbonyls is their stability in blood for up to 18 h [16]. Protein carbonyls are identified primarily after the derivatization of 2,4-dinitrophenylhydrazine (DNP) [65, 73]. With respect to CVD (Table 1), Binti et al. compared the mean protein carbonyl levels of patients with acute coronary syndrome, comprising unstable angina, non-ST elevation, and ST-elevation myocardial infarction, with those of the control group. The difference between the groups was notable: 1.63 ± 1.06 nmol/mg in the control group and 3.16 ± 1.29 nmol/mg in the ACS group ($p < 0.0001$) [74]. Gryszczyńska et al. [75] assessed the levels of carbonylated proteins (CP) and advanced oxidation protein products (AOPPs) in patients with abdominal aortic aneurysms (AAAs), aortoiliac occlusive disease (AIOD), and chronic kidney disease (CKD) (predialysis and hemodialysis). The results revealed that the AOPP concentration was highest in the prevalent AAA group, followed by the AIOD group, but lowest in the predialysis and hemodialysis groups. However, CP was greater in the predialysis group than in the AAA or AIOD groups. It is known that increased oxidative stress can lead to CKD, which shares a common pathogenesis mechanism with CVD. This interrelationship has been observed in geriatric patients (aged 60.9 ± 15.2 years) with CKD stages 1–5, where the level of plasma protein carbonyls increases as renal function decreases (as measured by creatinine clearance) ($r = -0.692$, $p < 0.0001$) [76].

5.2 Oxidized Low-Density Lipoprotein

The potential of oxidized low-density lipoproteins (oxLDLs) as biomarkers in CVD has been reviewed in many studies [77–79]. As biomarkers, the most investigated oxLDL component is oxidized phospholipids (oxPLs), and their elevation is thought to play a significant role in oxLDL-induced vascular inflammation and subsequent coronary, carotid and femoral artery diseases [77, 80–82]. OxLDLs, as well as oxPLs, are directly identified by some TLRs (TLR4, TLR6) [83], complement components, and scavenger receptors (CD36) [84–87]. CD36 induces OxLDL uptake and promotes the intracellular formation of cholesterol crystals, further activating the inflammasome via the proinflammatory activity of IL-1 [88].

Furthermore, exogenous oxPLs cause apoptotic cell death, a critical mechanism of atherogenesis [89]. Dijk et al. evaluated six atherosclerotic lesion types of postmortem carotid endarterectomy by immunostaining for the detection of oxPLs, malondialdehyde (MDA) and apoprotein an (apo(a)) epitopes [85]. The results demonstrated that all atherosclerotic lesions, such as necrotic cores, fibrous caps, foamy macrophages, and VSMCs, expressed oxidization-specific epitopes [85]. Furthermore, Tsimikas et al. established a strong positive correlation between oxPLs/apoB and lipoprotein a (LP(a)) ($r = 0.85$, $p < 0.001$), a cardiovascular risk factor [90]. A meta-analysis of three studies [91], in which two assessed oxLDL levels in participants with HIV (human immunodeficiency virus) disease either with or without associated CVD (468 vs. 487, respectively), revealed that increased oxLDL levels were significantly related to CVD.

Notably, the interaction of oxPLs and plasminogen is related to the increased potential to induce fibrinolysis and thus is associated with a lower atherothrombotic risk [92]. Notably, plasma oxLDL has been shown to be steadily increased in patients with CVD, insulin resistance, diabetes and obesity, regardless of the assay used [16, 78].

5.3 Trans-4-hydroxy-2-nominal and malondialdehyde

Aldehydes such as *trans*-4-hydroxy-2-nominal (4-HNE) and malondialdehyde (MDA) are lipid peroxidation products characterized by their rapid reactivity with proteins to form Michael adducts (advanced lipoxidation end products) [16, 93, 94]. 4-HNE is the most plentiful lipid-derived reactive carbonyl species. It is a major toxic product that induces apoptotic cell death [95]. However, the antioxidant system functions normally, and the cell can degrade modified proteins. In that case, glutathione transferases rapidly neutralize these compounds, especially glutathione-S-transferases 4–4, heme oxygenases, aldehyde dehydrogenases and glutamate-cysteine ligases [96–98]. As mentioned above, proteins participating in reactions with aldehydes are residues of apolipoprotein B (apoB) [99], and subsequent alterations in its structure by MDA increase its affinity for the scavenger receptors of macrophages and cause their transformation into foam cells [100]. 4-HNE provokes cellular oxidative stress in addition to inducing the activation of endoplasmic reticulum stress [101]. Both aldehydes and oxidized phospholipids can trigger inflammation by stimulating the expression of inflammation-related genes [85]. This can lead to an increase in the production of *class A* scavenger receptors on macrophages and smooth muscle cells, as well as strong upregulation of the cytokine TGF-β1 and activated NF-κB [88–90]. Notably, 4-HNE, especially MDA and other lipid oxidation end products, are among the most researched and are most commonly used as

oxidative stress markers [77, 93, 102]. Considering CVD, HNE and MDA as markers are preferable to other lipid oxidation products for estimating the risk of acute cardiovascular events, especially myocardial infarction and ischemic stroke [77, 103]. A large study [104] compared the levels of protein-bound HNE products (HNEp) in 61 heart failure (HF) patients with those in 71 healthy individuals. In addition to HNEp, the levels of different types of circulating fatty acids, including n-6 PUFAs, such as linoleic acid, which can conceivably lead to the formation of HNEp, were estimated. In HF, increased HNEp contributed to more severe HF and decreased HDL-C levels. Another work by Taty Zau et al. [105] assessed the effectiveness of a cardiac rehabilitation program in managing systemic oxidative stress in patients with chronic stable coronary disease who underwent coronary artery bypass grafting. A significant and progressive decrease in the oxidative markers of lipid damage, which included MDA and protein carbonyl levels, was observed in this cohort. Additionally, there was an ensuing decrease in superoxide dismutase, catalase, and glutathione peroxidase activities.

5.4 F2-Isoprostanes

F2-isoprostanes, which arise from polyunsaturated fatty acid (PUFA) peroxidation, are prostaglandin-like compounds characterized by platelet–activating and vasoconstrictive properties [102, 106, 107]. Both F_2–isoprostanes (F_2-IsoPs) and reactive γ–ketoaldehydes (isolevuglandins) are formed during the nonenzymatic rearrangement of H_2-isoprostanes [16]. The latter compounds are products of the oxidation of arachidonic acid, which is physiologically esterified in tissue phospholipids [108]. Specifically, F_2-IsoPs are frequently treated as the most credible markers for monitoring oxidative stress in vivo because they are correlated with the extent of CVD, reliable outcome prediction and chemical stability [102, 109, 110]. Several studies have established the level of F_2-IsoPs as one of the many risk factors for coronary heart disease (CHD) [111, 112]. Shishehbor et al. quantified nine distinct lipid peroxidation products in the plasma of patients via mass spectrometry. After this, patients were evaluated by diagnostic.

Coronary angiography revealed a statistically significant correlation between higher lipoxidation product levels and CHD. The results of the study revealed that F_2-IsoPs were significantly greater in those diagnosed with CHD (OR 9,7 in the highest F_2-IsoP quartile and plasma levels 1, fivefold greater in CHD) [112]. A subsequent study revealed 93 patients with CHD patients and 93 healthy controls were confirmed by measuring the levels of F_2-IsoPs along with standard risk markers such as hypercholesterolemia, low HDL, diabetes, body mass index, systolic blood pressure, CRP, and smoking status [111]. A correlation between higher F2-IsoP values and a broader spectrum of risk factors was verified, such as between higher F2-IsoP levels and CHD (OR 27.3 in the highest F2-IsoP tertile) [111]. Many studies have shown that the levels of F_2-IsoPs can be used to indicate CHD severity. Vassalle et al. reported a relationship between elevated plasma levels of F_2-IsoPs and a greater number of diseased vessels (F_2-IsoP plasma levels are 1.5-fold greater with 1-vessel disease and 2.0-fold greater with multiple vessel disease) [115]. In an extensive systematic review [116], higher levels of plasma F2-isoprostanes were measured in ischemic stroke patients than in healthy participants. Furthermore, more elevated urinary 8-iso-PGF2α (a major F2-isoprostane isomer) was observed in patients with chronic lower limb ischemia than in healthy controls. However, F2-isoprostanes were not associated with coronary artery disease.

6 Cardioprotective Drugs with Antioxidant Effects

Current antidiabetic cardiovascular drugs, such as sodium–glucose transport protein 2 inhibitors (SGLT2i), glucagon-like peptide-1 (GLP-1) analogs, and mineralocorticoid receptor antagonists, effectively reduce CVD risk by inhibiting inflammatory and oxidative stress mechanisms [3].

On the basis of numerous clinical trials, the European Society of Cardiology confirmed updated acute and chronic heart failure diagnosis and treatment guidelines, which recommend SGLT2 inhibitors as agents that reduce cardiovascular death, worsening heart failure and hospitalization due to heart failure [117]. The impact of SGTL2i on ameliorating thromboinflammation has been investigated in many basic and clinical studies. Agents such as empagliflozin and ipragliflozin attenuate ROS, VCAM-1 and ICAM-1 in the abdominal aorta of mice [118]. Furthermore, empagliflozin was revealed to decrease mitochondrial production of ROS in the endothelial cells of diabetic and hypertensive elderly patients [119]. Uthman et al. conducted a study to investigate whether empagliflozin and dapagliflozin decrease TNF-α-induced inflammation in human coronary arterial endothelial cells. The results revealed that SGLT2i inhibited ROS generation and thus diminished inflammation in TNF-α-induced coronary arterial endothelial cells [120]. Another study demonstrated that uremic serum from patients with chronic kidney disease harms cardiac microvascular endothelial control of cardiomyocytes and that empagliflozin recovers this intercellular crosstalk by reducing ROS and restoring NO levels in cardiomyocytes, improving their relaxation and contraction [121].

Another antidiabetic agent, GLP-1, is currently being extensively researched. Different clinical trials and

studies have revealed reduced major cardiovascular events in patients treated with GLP-1. In the clinical trial LEADER (Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure), patients treated with liraglutide had a lower risk of cardiovascular death, AMI, or stroke [122]. GLP-1, as well as SGLT2i, has antioxidant effects by decreasing ROS in endothelial cells, reducing the accumulation of macrophages in the vascular wall and the expression of VCAM-1, ICAM-1, and E-selectins and thus preventing atherosclerotic plaque formation [123]. The activation of the mineralocorticoid receptor (MR) in various cell types plays a crucial role in the development of cardiac hypertrophy and dysfunction, ultimately leading to heart failure [124]. For example, Rac1, a Rho family of GTPase members, acts as a cellular modulator that can activate the MR. In mice undergoing transverse aortic constriction, the activation of Rac1 leads to increased accumulation of MR in the nucleus and increased expression of MR target genes, such as the NOX4 gene, resulting in overproduction of ROS [125]. In rodent models of heart failure, MR antagonists have been shown to reduce cardiac hypertrophy and dysfunction [125]. For example, eplerenone has been shown to decrease myocardial fibrosis and apoptosis, whereas spironolactone inhibits cardiac fibroblast proliferation. Compared with eplerenone, finerenone has been demonstrated to significantly reduce left ventricular wall thickness and mass [126]. The Randomized Aldactone Evaluation Study in 1999 reported a significant reduction in mortality in the spironolactone group [127]. For more than 10 years, eplerenone treatment was associated with a reduction in deaths from CVD or hospitalization for heart failure [128]. MR expression is upregulated in the postinfarct state [129]. In rats with myocardial infarction, there is impaired diastolic function and increased collagen content in the LV interstitium and the aorta [130]. MR antagonists were found to reduce the infarct area and abnormal LV remodeling. In addition to improved left ventricular compliance and elastance, treatment with finerenone reduces interstitial fibrosis in mice with MI [131]. A clinical trial called the Role of eplerenone in Acute Myocardial Infarction–Double-Blind, Early Treatment Initiation, Randomized, placebo-controlled, multicenter study (REMINDER) documented a significant reduction in brain natriuretic peptide (BNP)/N-terminal pro-b-type natriuretic peptide (NT-proBNP) levels and the composite primary endpoint in patients receiving eplerenone within 24 h after ST-elevated myocardial infarction (STEMI) [132].

7 Conclusions

Redox imbalance contributes to oxidative stress and triggers the development and acceleration of CVD. Importantly, excess ROS production leads to endothelial dysfunction, which affects cardiovascular homeostasis and orchestrates thromboinflammation. Oxidative stress biomarkers could be utilized for estimating CVD risk or improving the diagnosis of CVD. To date, only some of the researched biomarkers have been used regularly in the clinic as oxidized low-density lipoproteins because of their unstable nature, hardly detectable levels, or methodological challenges. Nevertheless, targeting ROS generation or using cardioprotective drugs with antioxidant effects might aid in restoring endothelial cell function and improving CVD symptoms. Hence, further discoveries on oxidative stress, its biomarkers, and antioxidants will change the routine clinical approach to CVD treatment.

Abbreviations

CVD_s	Cardiovascular diseases
CHD	Chronic heart disease
EC_s	Endothelial cells
ROS	Reactive oxygen species
NOX_s	Nicotinamide adenine dinucleotide phosphate oxidases
SOD	Superoxide dismutase
NET	Neutrophil extracellular trap
NO	Nitric oxide
vWF	von Willebrand factor
DNA	Deoxyribonucleotide acid
AMI	Acute myocardial infarction
HDL	High-density lipoprotein
VTE	Venous thromboembolism
PUFA	Polyunsaturated fatty acid
4-HNE	Trans-4-hydroxy-2-nominal
MDA	: Malondialdehyde
ApoB	Apolipoprotein B
MMPs	Matrix metalloproteinases
ANG II	Angiotensin II
CRP	C-reactive protein
VSMCs	Vascular smooth muscle cells
oxLDL	Oxidized low-density lipoprotein
LOX-1	Lectin oxidized LDL receptor-1
TNF-α	Tumor necrosis factor alpha
PGI_2	Prostacyclin
eNOS	Nitric oxide synthase
BH4	Tetrahydrobiopterin
$MAPK_s$	Mitogen-activated protein kinases
IL-1	Interleukin 1
IL-6	Interleukin-6
VCAM	1-Vascular cell-adhesion molecule-1
ICAM	1-Intracellular cell-adhesion molecule-1
NF-κB	Nuclear factor κB
IL-1β	Interleukin 1β
MHC	Major histocompatibility complex
IFN-γ	Interferon-γ

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Declarations

Conflict of Interest
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Consent for Publication
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