Oxidative Stress and Human Hypertension: Vascular Mechanisms, Biomarkers, and Novel Therapies

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ABSTRACT

Hypertension is a major cardiovascular risk factor. Of the many processes involved in the pathophysiology of hypertension, vascular damage due to oxidative stress (excess bioavailability of reactive oxygen species [ROS]) is particularly important. Physiologically, ROS regulate vascular function through redox-sensitive signalling pathways. In hypertension, oxidative stress promotes endothelial dysfunction, vascular remodelling, and inflammation, leading to vascular damage. Vascular ROS are derived primarily by nicotinamide adenine dinucleotide phosphate oxidases, which are prime targets for therapeutic development. Although experimental evidence indicates a causative role for oxidative stress in hypertension, human data are less convincing. This might relate, in part, to suboptimal methods to accurately assess the redox state. Herein we review current knowledge on oxidative stress in vascular pathobiology and implications in human hypertension. We also discuss biomarkers to assess the redox state in the clinic, highlight novel strategies to inhibit ROS production, and summarize how lifestyle modifications promote vascular health by reducing oxidative stress.

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Oxidative Stress and ROS: A Brief Overview

The notion of “oxidative stress” was originally defined by Sies in 1985 as an imbalance between pro-oxidants and antioxidants, with consequent increased ROS bioavailability, which leads to tissue damage. Since then it has become clear that oxidative stress plays an important role in the development of hypertension in experimental models. However, the evidence in human hypertension is sparse. Many large antioxidant clinical trials failed to show cardioprotection and reduction in risk of cardiovascular disease. This is potentially due to multiple factors including: (1) complex regulation of ROS and redox signalling in the vascular system; (2) challenges related to direct measurement of ROS in the clinical setting; and (3) suboptimal therapies to reduce oxidative stress. Herein we provide an overview on oxidative stress and vascular injury in hypertension, with a focus specifically on human hypertension. We also discuss methods to assess redox status in the clinical setting and highlight novel ROS-reducing approaches with therapeutic potential.

Figure 1. Scheme demonstrating the relationship between vascular oxidative stress, vascular damage, and development of hypertension. Physiologically, reactive oxygen species play an important role in redox signalling, which controls vascular function and maintains normal vascular tone. In pathological conditions, increased vascular reactive oxygen species bioavailability promotes vascular damage and contributes to blood pressure (BP) increase. Uncontrolled oxidative stress is associated with severe hypertension and target organ damage, including stroke, cardiac failure, renal dysfunction, and aortic aneurysms. Data from Dikalov and Ungvari.

Redox Signalling and Vascular Biology in Hypertension

To appreciate how ROS regulate signalling and vascular function, it is important to know how ROS influence protein activity and cell function. Briefly, proteins that contain cysteine residues are highly sensitive to oxidative modification. These oxidative modifications lead to changes in structure, activity, and function of target proteins. Proteins that are redox-sensitive include ion transporters, receptors, kinases, phosphatases, transcription factors, structural proteins, and matrix metalloproteases, all of which are important in regulating endothelial and VSMC function.

ROS also regulate prostaglandin production and signalling, important in regulating vascular function. In hypertension, oxidative stress induces increased production of prostanoids by constitutive (COX-1) and inducible (COX-2) cyclooxygenases, which lead to increased vasoconstriction and reduced endothelium-dependent vasodilation. H2O2 stimulates production of vasoconstrictor prostanoids thromboxane, prostacyclin and prostaglandin E2, which cause vasoconstriction in hypertension. In addition to stimulating COX activity, COX itself can produce ROS, by oxidizing nicotinamide adenine dinucleotide phosphate (NADPH). Moreover, COX-derived prostanoids function as autocrine stimulators of ROS. Hence, ROS are upstream and downstream of the COX-prostanoid system.

ROS regulate G protein-coupled receptors (GPCRs) in vascular cells, such as angiotensin II receptor subtype 1. In VSMCs, activation of ROS-mediated GPCR signalling influences cell contraction, growth, migration, collagen deposition, and matrix metalloprotease activation, cellular processes important in regulating vascular tone and structure. In addition, GPCR-mediated signalling, through redox processes, stimulates activation of transcription factors and proinflammatory genes, chemokine and cytokine production, and recruitment and activation of inflammatory cells that cause vascular inflammation. Increased oxidative stress shifts the redox balance with consequent decreased NO bioavailability and impaired endothelium-dependent vasorelaxation, leading to increased GPCR-mediated vasoconstriction.

Production and Metabolism of Vascular ROS

In vessels ROS are produced primarily by nonphagocytic NADPH oxidase (Nox), although other enzymatic sources might also contribute, such as xanthine oxidase, mitochondrial electron transport chain, uncoupled endothelial NO
synthase (eNOS), COX, lipoxygenase, and cytochrome P450 oxidases. In human hypertension, Nox and xanthine oxidase appear to be most important in the vasculature.

Vascular Nox

The main function of Nox enzymes is the production of ROS. Nox catalyze the reduction of \( \text{O}_2 \) by NADPH, as electron donor, thereby generating \( \text{O}_2^-/\text{H}_2\text{O}_2 \). Seven Nox isoforms have been identified (Nox 1-5, dual oxidase 1 and 2) of which Nox 1, 2, 4, and 5 are present in arteries. Nox themselves are regulated by binding to various Nox subunits, including p22phox, p47phox (isoform, NADPH oxidase organizer 1), p67phox (isoform, NADPH oxidase activator 1) and p40phox (Table 1). Whereas Nox1, Nox2, and Nox4 require p22phox as a membrane-stabilizing subunit, Nox5 is unique in that it does not require any Nox subunits for its activation. Vascular Nox activity is increased in hypertension and is highly sensitive to prohypertensive factors such as angiotensin II, endothelin-1, and aldosterone. In VSMCs and endothelial cells from small arteries of hypertensive patients, expression of Nox 1, 2, 4, and 5 is upregulated with increased generation of ROS. These processes are associated with oxidative stress and altered redox signalling through mitogen-activated protein kinases and phosphatases leading to endothelial dysfunction and vascular remodelling.

Xanthine oxidase

The main function of xanthine oxidase is the degradation of purines and conversion of hypoxanthine to xanthine and xanthine to uric acid. As a byproduct in the purine

Table 1. Characteristics of Nox isoforms

<table>
<thead>
<tr>
<th>Nox isofrom</th>
<th>NADPH oxidase subunits</th>
<th>Regulators</th>
<th>Tissue expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nox1</td>
<td>p22phox, p47phox/NOXO1, NOXA1</td>
<td>Rac1</td>
<td>Vessels, heart, brain, colon</td>
</tr>
<tr>
<td>Nox2 (gp91phox)</td>
<td>p22phox, p47phox, p67phox</td>
<td>Rac1/Rac2</td>
<td>Immune cells, heart, vessels, lungs, brain</td>
</tr>
<tr>
<td>Nox3</td>
<td>p22phox, p47phox/p67phox or NOXO1/NOXA1</td>
<td>Rac1</td>
<td>Inner ear</td>
</tr>
<tr>
<td>Nox4</td>
<td>p22phox</td>
<td>Poldip2</td>
<td>Heart, vessels, lungs, kidney, liver, prostate</td>
</tr>
<tr>
<td>Nox5</td>
<td>None</td>
<td>Ca++</td>
<td>Vessels, heart, spleen, lymph nodes, testes, ovaries</td>
</tr>
<tr>
<td>Duox1</td>
<td>DUOXA1</td>
<td></td>
<td>Thyroid gland, cerebellum, bronchi, testes, prostate</td>
</tr>
<tr>
<td>Duox2</td>
<td>DUOXA2</td>
<td></td>
<td>Thyroid gland, bronchi, gut, uterus, gallbladder</td>
</tr>
</tbody>
</table>

Duox, dual oxidase; NADPH, nicotinamide adenine dinucleotide phosphate; Nox, NADPH oxidase; NOXA1, p67phox isoform; NOXO1, p47phox isoform. Data from Cifuentes-Pagano et al. Limited role for xanthine oxidase in vascular dysfunction in hypertension. Nox and xanthine oxidase appear to be most important in the vasculature.

**Figure 2.** Scheme demonstrating molecular mechanisms whereby reactive oxygen species (ROS) contribute to vascular dysfunction in hypertension. In the presence of prohypertensive factors, such as activation of the renin angiotensin aldosterone system (RAAS) and sympathetic nervous system (SNS), vascular ROS-generating enzymes are stimulated, in particular nicotinamide adenine dinucleotide phosphate oxidases (Nox), and to a lesser extent, xanthine oxidase and mitochondrial oxidases. In the presence of reduced antioxidants, this leads to increased intracellular ROS levels and oxidative stress, which promotes oxidative modification of signalling proteins and consequent altered vascular signalling. ET-1, endothelin-1; GPCR, G protein-coupled receptor; Gprot, G protein; MAPK, mitogen activated protein kinases; MMP, matrix metalloproteinase; PTP, protein tyrosine phosphatases; TIMP, tissue inhibitors of metalloproteinases.
degradation pathway, xanthine oxidase oxidizes Nicotinamide adenine dinucleotide to form $\text{O}_2^-$ and $\text{H}_2\text{O}_2$. In the endothelium, xanthine oxidase-derived $\text{O}_2^-$ reacts rapidly with NO to form ONOO$^-$, leading to negative feedback of the enzyme. Xanthine oxidase is expressed in vascular cells, and circulates in the plasma binding to endothelial cell extracellular matrix. Activity of the enzyme and serum levels of uric acid are increased in patients with hypertension. Growing evidence supports the role of uric acid as a biomarker of oxidative stress and as a mediator of hypertension.

**Antioxidant enzymes**

Antioxidant enzymes, which reduce ROS bioavailability include superoxide dismutase (SOD), catalase, peroxidases, glutathione, and thioredoxin (Table 2). SOD, of which there are 3 isoforms, are particularly important because they catalyze dismutation of $\text{O}_2^-$ to $\text{H}_2\text{O}_2$ and localize in discrete vascular compartments: cytosol for SOD1, mitochondria for SOD2, and extracellular matrix for SOD3. As such, SOD influences vascular redox signalling in a regulated and compartmentalized manner. In endothelial cells, SOD inhibits oxidative inactivation of NO, thereby reducing ONOO$^-$ formation.

**Nuclear factor-erythroid 2 p45-related factor transcription factor**

Nuclear factor-erythroid 2 p45-related factor (Nrf-2) is an important modulator of intracellular ROS, because it is the master regulator of antioxidant genes and proteins through its control of genes that contain antioxidant response element. Nrf-2 induces transcriptional activation of antioxidant genes containing antioxidant response element, including NADPH dehydrogenase (quinone 1), glutathione peroxidases, heme oxygenase-1, thioredoxin reductase, glutathione-sulfur (S)-transferase, and SOD. Nrf-2 is constitutively controlled by ROS and by repressor protein Kelch-like ECH-associated protein 1 and induces upregulation of antioxidant defense mechanisms in states of cellular stress as a protective response. Nrf-2 activity appears to be downregulated in patients with cardiovascular disease. Treatment of DOCA-salt rats, with an Nrf-2 inductor, epicatechin, resulted in a significant reduction in blood pressure. Cardiovascular and renal protective effects of Nrf-2 activators have also been demonstrated in human studies. For example, early studies in patients with diabetic nephropathy who were treated with the Nrf-2 activator bardoxolone methyl showed significant improvement in renal function.

**Oxidative Stress in Human Hypertension**

Clinical studies in patients with essential hypertension demonstrated that systolic and diastolic blood pressure correlate positively with biomarkers of oxidative stress and negatively with antioxidant levels. Endothelial dysfunction, a hallmark of the vascular phenotype in hypertension, is associated with increased vascular ROS production, oxidative stress, and vascular inflammation. This is evidenced by an inverse association between acetylcholine-dependent vasodilation and plasma levels of e-selectin, p-selectin, monocyte chemotactic protein type 1, metalloproteinases type 1, and thiobarbituric acid (TBA) reactive species (TBARS), and positive associations with serum levels of selenium, vitamin C, erythrocyte glutathione peroxidase, and SOD activities. Direct measurements of ROS production in VSMCs derived from resistance arteries of patients with essential hypertension, demonstrated higher levels of $\text{O}_2^-$ and $\text{H}_2\text{O}_2$ and enhanced angiotensin II-stimulated redox signalling compared with cells from normotensive healthy counterparts. Population-based observational studies have reported an inverse relationship between various plasma antioxidants and blood pressure. Decreased antioxidant activity (SOD, catalase) and reduced levels of ROS scavengers (vitamin E, glutathione) might contribute to oxidative stress in human hypertension. Plasma vitamin C levels are inversely related to blood pressure in normotensive and hypertensive cohorts.

Causes of reduced cellular antioxidants in hypertension are unclear but might relate, in part, to genetic factors. A recent meta-analysis demonstrated an association between polymorphisms in glutathione-S-transferase (intracellular antioxidant enzyme) and risk of essential hypertension. Polymorphisms have also been shown in Nox subunits in hypertensive patients. Individuals with p22phox polymorphisms exhibit altered Nox activity and increased ROS production in human cardiovascular disease. Specifically, the −930(A/G) polymorphism in the p22phox promoter might be a novel genetic marker associated with hypertension.

**Role of Nox and ROS in Vascular Function in Humans: Direct Evidence**

Most studies on the role of ROS in vascular pathobiology and essential hypertension have focused primarily on associative links where indices of oxidative stress and vascular injury are positively related to blood pressure. More direct evidence indicating an important role for ROS in vascular function is derived from studies in patients with chronic granulomatous disease (CGD) who have mutations of Nox subunits and a consequent reduction in ROS generation. In patients with CGD, flow-mediated dilation is increased compared with in control subjects, demonstrating increased endothelium-dependent

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**Table 2. Endogenous antioxidants**

<table>
<thead>
<tr>
<th>Antioxidant enzymes</th>
<th>Superoxide dismutase</th>
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<tbody>
<tr>
<td></td>
<td>Catalase</td>
</tr>
<tr>
<td></td>
<td>Glutathione peroxidase</td>
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<tr>
<td></td>
<td>Glutathione reductase</td>
</tr>
<tr>
<td></td>
<td>Thioredoxin</td>
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<tr>
<td>Antioxidants targeting transition metals</td>
<td>Ceruloplasmin</td>
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<tr>
<td></td>
<td>Transferrin</td>
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<tr>
<td>Reactive oxygen species scavengers</td>
<td>Water-soluble</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
</tr>
<tr>
<td></td>
<td>Urate</td>
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<tr>
<td></td>
<td>Ascorbic acid</td>
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<td></td>
<td>Flavonoids</td>
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<tr>
<td></td>
<td>Thiols</td>
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<tr>
<td></td>
<td>Lipid-soluble</td>
</tr>
<tr>
<td></td>
<td>Vitamin E</td>
</tr>
<tr>
<td></td>
<td>Carotenoids</td>
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</tbody>
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vasodilation and reduced vasoconstriction. In addition, patients with CGD have reduced carotid artery atherosclerosis, assessed using magnetic resonance imaging and computed tomography compared with control subjects. These findings provide direct evidence that Nox and ROS play a role in vascular function and structure in humans.

### Biomarkers of Oxidative Stress in Human Hypertension

ROS are unstable and have a very short half-life. Hence, accurately assessing O₂⁻ and H₂O₂ in the clinic is challenging. As such, methods have been developed to measure stable markers of ROS that reflect oxidative status. Biomarkers of oxidative stress that are currently used to assess redox state in human samples are oxidation products of lipids, DNA, and protein.  

**Lipid peroxidation**

Polyunsaturated fatty acids, including phospholipids, glycolipids, and cholesterol are vulnerable targets of oxidation. Increased ROS levels trigger the process of lipid peroxidation. The most commonly studied markers of lipid peroxidation are malondialdehyde (MDA) and isoprostanes.

MDA. MDA is formed by peroxidation of polyunsaturated fatty acids and can interact with proteins. MDA can be detected with TBA using a colourimetric method based on the reaction between MDA and TBA that gives a pink colour. The products that are measured are called TBARS. The TBARS assay is among the most widely used to evaluate lipid peroxidation in human samples. Plasma TBARS levels are increased in patients with hypertension, atherosclerosis, diabetes, heart failure, stroke, and aging. Cigarette smokers also have increased levels of TBARS, suggesting that the vascular injury effects of smoking are related to oxidative damage induced by lipid peroxidation.

**Isoprostanates**. F2-isoprostanes are stable end products of lipid peroxidation and can be measured in all human tissues and biological fluids, including urine, plasma, and cerebrospinal fluid. Formation of isoprostanes is independent of the COX enzymes that catalyze production of prostaglandins. A metabolite of F2-isoprostanes, 8-iso-prostaglandin F₂α has vasoconstrictor, cell-growth properties and promotes platelet aggregation and as such, is biologically active independently of its biomarker status. Levels of F2-isoprostanes in plasma and urine correlate with ROS levels and oxidative stress in experimental and human studies. In addition, in healthy individuals with risk factors such as obesity, hyperlipidemia, and hyperhomocysteinemia, plasma concentrations of F2-isoprostanes are increased, suggesting that indices of lipid peroxidation might be clinically relevant biomarkers of cardiovascular risk.

**Nonenzymatic total antioxidant capacity**

Total antioxidant capacity is a measure of the combined antioxidant effect of the nonenzymatic defenses in biological fluids and does not take into account the enzymatic antioxidant systems such as superoxide dismutase, catalase, peroxidase, etc. The assay measures low molecular weight antioxidants, water-soluble and lipid-soluble, and includes urate, bilirubin, vitamin C, thiols, flavonoids, carotenoids, and vitamin E. Experimental and clinical studies have shown low levels of total antioxidant capacity in hypertension.

**Oxidative modification of DNA and proteins**

DNA and proteins are highly susceptible to modifications by changes in the redox state. Protein oxidation, which can be reversible or irreversible, leads to changes in the biological function of the target protein. The most common type of irreversible modification is the formation of carbonyl groups. Amino acids prone to carbonylation include proline, arginine, threonine, lysine, histidine, and cysteine. Assessment of the extent of such a general type of oxidation serves as a marker of increased oxidative stress. In contrast, the S-containing amino acids, Cys and Met, are the only amino acids that can undergo modifications that can be reversed by cellular enzymes, and have, therefore, a potential regulatory role in redox signalling. The most common types of oxidative modifications include nitrosylation, S-glutathionylation, peroxidation, and carbonylation.

**Targeting Oxidative Stress as a Therapeutic Strategy in Human Hypertension**

If oxidative stress is indeed involved in the development of hypertension, then reducing oxidative damage by scavenging ROS with antioxidants and/or reducing the production of ROS should ameliorate vascular injury and decrease blood pressure.

**Antioxidants**

The potential of antioxidants in treating conditions associated with oxidative stress is supported by experimental studies, observational findings, small clinical studies, and epidemiological data. However, findings have been inconsistent and clinical trial data from large cardiovascular studies that evaluated various antioxidants, such as vitamins C and E, carotene, and others have been negative. Possible reasons for the disappointing results from antioxidant clinical trials are complex and multifactorial and have been discussed in detail elsewhere. An important point to highlight is that antioxidants scavenge ROS when formed, which might be too late, because irreversible oxidative damage to tissues might have already occurred. There is growing interest in targeting the source of ROS, thereby preventing ROS from being generated rather than scavenging them when they are produced. Potential targets include Nox isoforms and xanthine oxidase.

**Nox inhibitors**

Nox have become a promising therapeutic target for cardiovascular diseases associated with oxidative stress, and thus interest in the development of agents that inhibit Nox. Classical Nox inhibitors, apocynin and diphenylene iodium, are nonspecific and might act as ROS scavengers. Apocynin has intrinsic antioxidant activity and inhibits Rho kinase. Diphenylene iodium acts as a general flavoprotein inhibitor and therefore also inhibits eNOS, xanthine oxidase, and mitochondrial oxidases. Hence, because of the nonspecific...
nature of these agents, they should not be used as selective Nox inhibitors.

Recently, several new isoform-specific Nox inhibitors have been identified from rational drug delivery. These include the small molecule inhibitors GKT137831 and GKT136901 (GenKyotex), which are potent inhibitors of Nox 1, Nox 4 and Nox 5; 2-acetylphenothiazine (ML171; Scripps Research Institute), which inhibits Nox 1; VAS2870 and VAS3947 (Vasorpharm GmbH), which inhibit primarily Nox 2 and to a lesser extent Nox 4; S17834 (Servier), which appears to inhibit Nox 2 and Nox 4; and Fulvene-5, which inhibits Nox 2 and Nox 4. 97–98

A few biological peptidic inhibitors of Nox have been developed by the Pagano group. 99–101 These include NOX2ds-tat (originally termed gp91ds-tat), the first rationally designed biological Nox inhibitor, which prevents p47phox binding to Nox 2, thereby preventing assembly of the active Nox 2 oxidase. NOXA1ds is a Nox 1 inhibitor, which inhibits the binding of NOXA1 to Nox 1 thereby preventing assembly of the active Nox 1 complex. 99–101 Using a similar strategy for selected peptides in the Nox 4 oxidase complex, it was not possible to inhibit Nox 4, suggesting that unlike Nox 1 and Nox 2, Nox 4 exists in a tightly assembled and active conformation that cannot be disrupted by conventional peptidic inhibitors. 102

Of the numerous Nox inhibitors that have been registered in the patent literature, 97–106 only one has progressed through to clinical trials. In particular GKT137831 has entered into a phase II trial in diabetic nephropathy (www.genkyotex.com). Outcomes of this trial should shed light on the role of Nox isoforms as a therapeutic target in oxidative stress-related diseases, such as hypertension. Human studies are still needed to confirm the clinical utility of Nox inhibitors in humans, but these drugs hold some promise in the management of patients with Nox-associated pathologies.

Xanthine oxidase inhibition

Allopurinol is a potent xanthine oxidase inhibitor that is used in hyperuricemic patients to prevent gout. It has also been shown to decrease cardiovascular complications and to reduce blood pressure in hypertensive patients. A systematic review showed that systolic blood pressure decreased by 3.3 mm Hg and diastolic blood pressure decreased by 1.3 mm Hg in patients treated with allopurinol. 103 Clinical studies that examined effects of other xanthine oxidase inhibitors, 104 tetrahydrobiopterin (BH4; sapropterin dihydrochloride [6r-bh4]) and N-acetylcysteine demonstrated improved endothelial function and blood pressure-lowering in patients with hypertension, chronic kidney disease, and pulmonary hypertension. 104–106 Hence, reducing xanthine oxidase-induced ROS generation and uric acid production with xanthine oxidase inhibitors has a small but significant blood pressure-lowering effect.

Other Therapeutic Strategies

BH4

Optimizing eNOS function and reducing ONOO—production might be an attractive approach to treating endothelial dysfunction and hypertension. This can be achieved by cofactors BH4, or substrate L-arginine, or by increasing cyclic guanosine monophosphate availability via phosphodiesterase 5 inhibitors. BH4, a cofactor for NO synthesis is a potentially interesting therapeutic target in the endothelium. In hypertensive patients infused with BH4 intra-arterially, endothelial function was significantly improved as evidenced by increased forearm blood flow. 107 Oral high-dose BH4 produced a significant reduction in blood pressure in patients with essential hypertension. 108 Treatment with resveratrol, which is associated with increased BH4 levels, improved vascular function and dyslipidemia by modulating NO metabolism in hypertensive patients. 69

Nrf-2 activators

Activation of the Nrf-2 pathway, which induces production of antioxidant enzymes, seems to have protective actions in many systems. 109 To date, the best studied Nrf-2 activator in clinical medicine is bardoxolone methyl, which was evaluated for chronic kidney disease in patients with type 2 diabetes. Although earlier studies showed significant renoprotection, the phase III trial, Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: The Occurrence of Renal Events (BEACON), was terminated because of a greater rate of cardiovascular disease in the bardoxolone methyl-treated patients compared with the placebo-treated group. 110,111 Newer bardoxolone methyl derivatives have been developed. 109 There is some evidence that Nrf-2 activators might have antihypertensive actions in experimental models of hypertension and pre-eclampsia. 112,113 However, effects in human hypertension are unknown.

Lifestyle modifications to reduce oxidative stress

Lifestyle modifications such as exercise, weight loss, reduced salt intake, use of the Dietary Approach to Stop Hypertension (DASH) diet, and smoking cessation improve endothelial function, protect against vascular disease, decrease blood pressure, and might lead to reduced cardiovascular complications in patients with hypertension. 114–119 These approaches are associated with decreased levels of biomarkers of oxidative stress (plasma TBARS, isoprostanes) and increased antioxidant capacity. 114,115 Underlying ROS-related mechanisms whereby exercise improves vascular health and blood pressure control include eNOS activation, increased NO production, vascular endothelial growth factor-induced angiogenesis, decreased NO inactivation by ROS, and reduced oxidative stress. 114 Chronic exercise is associated with upregulation of endogenous antioxidants such as SOD, glutathione, thioredoxin, and peroxiredoxin. This occurs through the master regulator of antioxidant genes, Nrf-2, which is activated by exercise. 116

Results from a meta-analysis of >1900 subjects showed that the DASH diet, rich in antioxidants from fruits and vegetables, is associated with significant blood pressure-lowering and a reduction of 13% in the 10-year Framingham risk score for cardiovascular disease. 117,118 Increasing antioxidant capacity through foods and drinks that contain flavonoids has also been shown to improve endothelial
function in some patients with hypertension. Studies in hypertensive patients demonstrated that consumption of dark chocolate, black tea, and red wine increased flow-mediated dilation and improved endothelial function.¹¹⁸

Epidemiological studies have linked low dietary intake of antioxidant vitamins (vitamin C, vitamin E, β-carotene) with cardiovascular disease. Antioxidant vitamins influence endothelial function and vascular contractility. Intra-arterial administration of high doses of vitamin C improved endothelium-dependent vasodilation in the forearm microcirculation of hypertensive patients, by increasing NO bioavailability.¹¹⁷ However, prolonged oral administration of vitamin C had no effect on endothelial function in hypertensive patients and vitamin E supplementation did not improve impaired endothelial function in aged individuals.¹¹⁷

Results of large clinical antioxidant trials have been disappointing in that they failed to demonstrate significant cardiovascular benefits.¹¹⁶ Reasons for this are complex and multifactorial.¹¹⁵,¹¹⁹ First, the underlying hypothesis that oxidative stress is the cause of cardiovascular disease still has to be proven in humans. As discussed herein, it is still very challenging to accurately measure ROS in the clinic, and accordingly establishment of a causal relationship between ROS and essential hypertension is difficult. Second, whereas antioxidants reduce oxidative stress and increase antioxidant capacity in experimental conditions, this might not translate to in vivo conditions in humans. Third, the trial designs might have been suboptimal with respect to duration of treatment, choice of antioxidants used, and doses of antioxidants administered. Cardiovascular disease and hypertension are chronic conditions that develop over time and accordingly long-term antioxidant treatment might be required. Moreover, water-soluble antioxidants such as vitamin C, vs lipid-soluble antioxidants, such as vitamin E, have different pharmacokinetics and tissue distribution and hence concentration of the antioxidants at the tissue level might be variable or suboptimal. Fourth, most trials examined single antioxidants. Considering the complex multifactorial nature of chronic diseases, such as hypertension and cardiovascular disease, combination therapy of multiple antioxidants might be more appropriate. Fifth, it is possible that antioxidant intervention occurred too late, when cardiovascular pathology was already extensive and irreversible. Finally, to date, no large antioxidant clinical trials have actually assessed blood pressure changes as the primary outcome.

Based on the lack of evidence to prove the benefits from use of antioxidants to prevent cardiovascular disease, antioxidant supplementation is not recommended for the prevention or treatment of hypertension. However, most hypertension guidelines suggest that the general population consume a diet with antioxidant-rich fruits and vegetables and whole grains such as in the low sodium DASH diet.¹²⁰

**Conclusions**

Physiologically, ROS play an important role in regulating vascular function through tightly controlled redox-sensitive signalling pathways. Uncontrolled production/degradation of ROS results in oxidative stress, which induces vascular injury with associated increases in systemic blood pressure. Convincing evidence from experimental and animal studies indicate a causative role for oxidative stress and ROS-generating Nox in the pathogenesis of hypertension. However, in humans it is still unclear whether oxidative stress is a prime cause of hypertension, although biomarkers of oxidative stress correlate positively with blood pressure in essential hypertension. Targeting oxidative stress with novel Nox inhibitors and other ROS modulators might be an attractive therapeutic strategy to improve endothelial dysfunction and vascular damage in hypertension. Further clinical research in this field is needed. Amelioration of impaired endothelial function and protection against vascular damage by reducing oxidative stress through exercise, healthy diet, and smoking cessation, but not through antioxidant supplementation, should provide added therapeutic benefit in the management of patients with hypertension. Until more is known about the molecular mechanisms whereby ROS cause vascular damage and hypertension in humans, therapies targeting oxidative stress should focus on promoting vascular health through lifestyle health behaviour modifications, such as exercise, nutrition, and smoking cessation.

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**Disclosures**

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