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Revisiting pharmacology of oxidative stress and endothelial dysfunction in cardiovascular disease: Evidence for redox-based therapies

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ABSTRACT

According to the latest Global Burden of Disease Study data, non-communicable diseases in general and cardiovascular disease (CVD) in particular are the leading cause of premature death and reduced quality of life. Demographic shifts, unhealthy lifestyles and a higher burden of adverse environmental factors provide an explanation for these findings. The expected growing prevalence of CVD requires enhanced research efforts for identification and characterisation of novel therapeutic targets and strategies. Cardiovascular risk factors including classical (e.g. hypertension, diabetes, hypercholesterolaemia) and non-classical (e.g. environmental stress) factors induce the development of endothelial dysfunction, which is closely associated with oxidant stress and vascular inflammation and results in CVD, particularly in older adults. Most classically successful therapies for CVD display vasoprotective, antioxidant and anti-inflammatory effects, but were originally designed with other therapeutic aims. So far, only a few 'redox drugs' are in clinical use and many antioxidant strategies have not met expectations. With the present review, we summarise the actual knowledge on CVD pathomechanisms, with special emphasis on endothelial dysfunction, adverse redox signalling and oxidative stress, highlighting the preclinical and clinical evidence. In addition, we provide a brief overview of established CVD therapies and their relation to endothelial dysfunction and oxidative stress. Finally, we discuss novel strategies for redox-based CVD therapies trying to explain why, despite a clear link between endothelial dysfunction and adverse redox signalling and oxidative stress, redox- and oxidative stress–based therapies have not yet provided a breakthrough in the treatment of endothelial dysfunction and CVD.

1. Introduction

1.1. Epidemiological evidence for a leading role of cardiovascular disease in global burden of disease and premature deaths – central role of endothelial dysfunction in cardiovascular morbidity

As shown by results of the Global Burden of Disease Study, non-communicable diseases (NCD) such as atherosclerosis are gaining importance for the global burden of disease and premature deaths, outcompeting communicable childhood diseases as the leading drivers for premature death[1] and life years spent with severe illness or disability (DALYs[2]) [1,2]. This shift is most likely due to an aging population with an increased prevalence of NCD and classical risk factors such as hypertension, unhealthy lifestyle (e.g. smoking, inactivity, unhealthy diet, work strain) and environmental factors [3], which outweigh genetic factors by far [4]. The four primary risk factors and diseases for global premature deaths in 2010 were hypertension, ischaemic heart disease, smoking and cerebrovascular disease [2],

Abbreviations: DALYs, disability-adjusted life years; CVD, cardiovascular diseases; NCD, non-communicable diseases; ROS, reactive oxygen species; RONS, reactive oxygen and nitrogen species

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[1] Premature death means dying before the natural age of death (e.g. due to a severe illness or accident).

[2] DALYs means disability adjusted life years and is a measure of life quality. Living with severe illness or disability represents lower life quality and can also be interpreted as 'lost life'.

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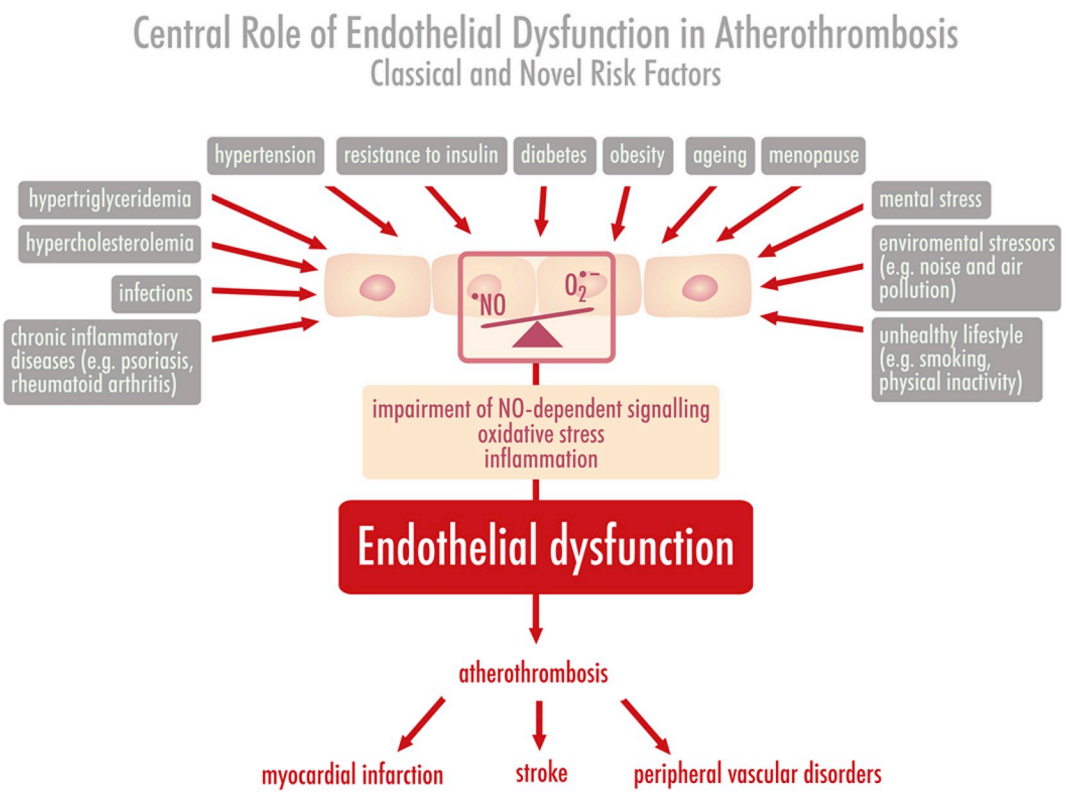

Fig. 1. Cardiovascular risk factors and manifestations of cardiovascular disease. Risk factors collectively impair NO-dependent signalling and induce endothelial dysfunction, with a central role for the loss of homeostatic $^{\bullet}NO/O_2^{\bullet-}$ balance, induction of oxidative stress and low-grade inflammation.

whereas the five primary risk factors in 2015 were hypertension, smoking, high fasting blood glucose, high total cholesterol and ambient air pollution (particulate matter 2.5 μm) [5], all related to cardiovascular complications.

Surprisingly, the Global Burden of Disease Study estimates that all forms of pollution were responsible for as many as 268 million DALYs [6], with air pollution a leading trigger of premature deaths [7,8]. This number is considerable, given that around 422 million people were affected by diabetes [9] in 2014 and 1.6 million global deaths were directly caused by diabetes, with another 2.2 million deaths attributable to high blood glucose – a well-accepted primary risk factor. In fact, diabetes mellitus is an accepted independent risk factor in the development of coronary heart disease with a notable adverse effect on survival; in diabetics, the risk of death from coronary artery disease is two-to four-fold higher [10], according to a meta-analysis reporting a hazard ratio for cardiovascular mortality in screening-detected diabetes of 3.42 (95% confidence interval [CI]: 2.23–5.23) [11]. Additionally, the risk of myocardial infarction (MI) for diabetics diagnosed within 10 years without a preceding MI is equal to the risk level of non-diabetics with a previous MI [10].

All known risk factors of atherosclerosis lead to the development of endothelial dysfunction, which precedes the progression of atherosclerotic plaques and represents an early (subclinical) correlate of atherosclerosis [12,13] (reviewed in [14]). Indeed, as evidenced by multiple experimental and clinical studies, various classical risk factors (e.g. hypercholesterolaemia [12], hypertension [13,15], chronic smoking [16], diabetes mellitus [17]) or non-classical risk factors, such as novel environmental risk factors (e.g. traffic noise exposure [18,19], ambient air pollution [20,21] and mental stress [22,23]) or chronic inflammatory disease (e.g. rheumatoid arthritis [24,25], psoriasis [26]) each induce endothelial dysfunction. Endothelial dysfunction is also correlated with markers of chronic (low-grade) inflammation such as C-reactive protein (CRP) [27] and cardiovascular risk predictors such as adiponectin and brain natriuretic peptide (BNP) [28,29]. Moreover, the presence of several risk factors produces additive (or sometimes even synergistic) effects on endothelial function as well as the associated cardiovascular prognosis [30]. Previous studies have confirmed that hypercholesterolaemia or chronic smoking led to moderate impairment of endothelial function (reduction of the maximal acetylcholine-dependent vasodilation by ~30%), whereas the presence of both risk factors caused severe (additive) endothelial dysfunction (reduction of the maximal acetylcholine-dependent vasodilation by ~60%) [31]. Thus, all risk factors identified so far seem to collectively impair the vasoprotective mechanisms of endothelium, including impairment of nitric oxide (NO)-dependent function promoting oxidative stress, and pro-thrombotic and pro-inflammatory maladaptive mechanisms leading to the development of endothelial dysfunction, atherosclerotic plaques and clinical consequences such as MI, ischaemic stroke and peripheral artery diseases [32–38] (Fig. 1).

Impaired endothelium-dependent vasodilation has prognostic implications, as it predicts adverse cardiovascular events and poor long-term outcomes in patients with risk factors [38–40] or in healthy individuals [33,41]. Accordingly, endothelial dysfunction may be regarded as a barometer of cardiovascular risk [38], representing an integrated index of all atherogenic and atheroprotective factors present in an individual. This may be useful to stratify cardiovascular risk and identify individuals at higher risk [32,35,42–44], having greater predictive value than traditional risk factors [35,41,45] in patients treated optimally according to the medical standards of today [46,47]. Thus, endothelial dysfunction has not only pathophysiological and diagnostic but also important therapeutic significance in atherosclerosis and cardiovascular diseases (CVD).

1.2. Endothelial dysfunction is associated with oxidative stress and vascular inflammation

Endothelial dysfunction is closely interconnected with oxidative stress as well as with vascular inflammation, representing unifying

concepts for the underlying pathophysiology of cardiovascular morbidity and mortality [48,49]. Indeed, low-grade inflammation is a contributor to the hallmark oxidative stress associated with most CVD [50–52], and thus represents a cardiovascular risk factor [53] that can be targeted by pharmacological treatment [54]. Accordingly, psoriasis has been classified as an independent risk factor for CVD [26] and the European League against Rheumatism recommends cardiovascular therapy for patients with psoriasis [55]. Similarly, rheumatoid arthritis is an important contributor to cardiovascular morbidity [56]. Either psoriasis or rheumatoid arthritis–associated inflammation may result in endothelial dysfunction [57,58]. In line with this, the systolic blood pressure of patients with rheumatoid arthritis or psoriasis is reduced by immune-suppressive therapy [59]. Furthermore, inflammation is an important player in various chronic diseases including chronic kidney disease, non-alcoholic fatty liver disease (NAFLD) and neurodegeneration, which are all either triggered by or associated with low-grade inflammation [60–62] and associated with endothelial dysfunction [63–65]. Thus, chronic inflammatory diseases are interrelated with CVD and have a common denominator – inflammation. The accumulated evidence on the major role of inflammation in CVD has led to clinical trials of IL-1 receptor blockers or antagonists (Anakinra, rilonacept, canakinumab [CANTOS trial], gevokizumab) in patients with CVD that are underway or already completed [66], with encouraging results for further studies.

Of note, low-grade inflammation is a hallmark of the aging process (immunosenescence) [49,67] and contributes to a higher prevalence of metabolic and cardiovascular complications in older adults [68], with vascular aging exemplifying the close interrelationship of low-grade inflammation with endothelial dysfunction and oxidant stress.

The concept of “vascular aging” refers today to all age-associated changes in vessels, leading to an increased prevalence of atherosclerotic lesions, vascular injury, impaired angiogenesis, calcification and stiffness [69], and endothelial as well as smooth muscle cells contribute to these phenomena [70]. Importantly, impaired endothelium-dependent relaxation (endothelial dysfunction) in older adults is also linked to impaired vascular regulation [71,72]. Age-dependent endothelial dysfunction is found in all vessels, from macrovessels such as the aorta and coronary arteries to resistance vessels of the microcirculatory system (for review see Ref. [73]), which is mirrored by other disorders related to aging vessels, such as erectile dysfunction, renal dysfunction, Alzheimer's disease and retinopathy [74–77]. Impaired nitric oxide radical ($^{\bullet}$NO) signalling, vascular inflammation and oxidative stress are key players in the pathogenesis of age-dependent endothelial dysfunction [78], as demonstrated by our groups and many others [79] (for review see Ref. [67,80]). In combination, these data all implicate aging as an independent risk factor for CVD, mainly due to oxidative stress–induced endothelial dysfunction and low-grade inflammation [81,82].

Similarly, in a population-based study (n = 631), type 2 diabetes mellitus (T2DM) was cross-sectionally associated with both endothelial dysfunction and low-grade inflammation, explaining approximately 43% of the increase in cardiovascular mortality risk in the diabetic group [83]. Likewise, markers of inflammation (CRP, IL-6 and TNF-α), show a positive correlation with increasing HbA1c values [84], and increased markers of inflammation are associated with a higher risk of T2DM development [85]. Cardiovascular complications in diabetes mellitus are associated with oxidative stress [86,87], as are hypercholesterolaemia and arteriosclerosis [88,89].

Therefore, it seems that there is a close interaction (crosstalk) between inflammatory pathways, oxidative stress and endothelial dysfunction [50]. Better understanding the relationship between these three major hallmarks of vascular pathology and CVD is an important challenge. For example, mitochondrial oxidative stress (mtROS) formation increases with advancing age [67,80] and leads to the activation of immune cells and their phagocytic NADPH oxidase, thereby stimulating cytokine release and the inflammasome [90–95]. Therefore, normalising the chronic inflammatory phenotype and additionally targeting mtROS could represent a promising strategy to increase healthspan [96].

1.3. Endothelial dysfunction in other diseases – endothelial biomedicine

Apart from atherosclerosis, multiple other diseases have been identified in which endothelial dysfunction has a pathophysiological role. Endothelial dysfunction plays a key role in cancer metastasis, as it is present both locally in metastatic organs and in systemic vasculature, and may promote activation of platelets as well as pro-thrombotic and pro-inflammatory mechanisms [97,98]. Endothelial dysfunction also has a pathophysiological role in pulmonary hypertension [99], non-ischaemic heart failure [100], sepsis [101,102], preeclampsia [103], malaria [104], dengue viral infections [105], Chagas disease [106], trauma [107] and many other diseases that cannot be listed and referenced here due to limited space.

Altogether, more than 300,000 published articles relate to endothelium, and endothelial biomedicine – the discipline with the term coined by William C Aird – is expanding progressively [108]. However, despite the increasingly recognised role of endothelium-related mechanisms in cardiovascular and non-cardiovascular disease, the knowledge in endothelial biomedicine that has accumulated over the years has not yet been translated into endothelium-guided diagnostics and endothelium-targeted disease therapies. There are a number of possible reasons for this [109]. However, one of the major limitations to fostering pharmacology of endothelium is the fact that the methods available to diagnose endothelial function in clinical settings are not suited for everyday clinical practice. We briefly summarise this issue in Section 1.4. However, the major aim of this review is to explain why - despite the fact that endothelial dysfunction is mechanistically linked with alterations in redox signalling and oxidative stress - redox and oxidative stress–based therapies have not yet provided a breakthrough in the treatment of endothelial dysfunction and CVD.

1.4. Endothelial function measurements in humans

In clinical conditions, a dysfunctional endothelium is diagnosed based on the impairment of NO-dependent vasodilation initially with the use of angiography [110] or venous occlusion plethysmography [111], nowadays mostly by Doppler ultrasonography in a conduit artery, and by arterial tonometry and finger plethysmography in peripheral circulation [112,113]. Flow-mediated dilation (FMD) by Doppler ultrasonography represents a gold standard approach to assess endothelial function in humans [114], being the method of reference, though it has a number of limitations [115]. Recently, a novel magnetic resonance imaging (MRI)-based approach to assess FMD was proposed for detecting artery dilation, which gave concordant results with standard ultrasound technique in healthy volunteers [116]. MRI also allows the detection of endothelial permeability in patients [117]. Thus, MRI technology, with its versatility and accuracy, provides an excellent tool to gain better insight into the endothelium-dependent mechanisms of health and disease and should be increasingly used in clinical and preclinical studies [118–123]. However, its use for endothelial function testing is still limited.

Recently, an interesting non-invasive approach to measure microvascular endothelial function was introduced – flicker-induced retinal dilatation (dynamic retinal vessel analysis [DVA]), which is considered an NO-dependent response and thus represents a novel approach to study endothelial NO-dependent function in microvasculature [124]. Impairment of retinal vessel dilation in response to flicker light stimulation was a strong independent predictor of all-cause mortality in patients with end-stage kidney disease [125] and was also impaired in prediabetes and diabetes mellitus [126,127], hypertension [128] and stable coronary artery disease (CAD), particularly in patients with impaired left ventricular function [129].

Even though consensus exists that endothelial dysfunction can be

evaluated in macrocirculation and microcirculation, and a number of classical techniques (e.g. FMD, reactive hyperaemia–peripheral arterial tonometry) and novel approaches (e.g. MRI-based measurements of FMD, endothelial permeability, DVA) are available to measure endothelial function in humans, how to use them routinely in clinical settings is yet undetermined. The predictive value of gold-standard FMD is still disputed by some authors. A meta-analysis of 15 cohort studies supported a predictive value of endothelial function measurements using FMD in patients with diagnosed atherosclerosis [130], and a number of studies have highlighted the value of FMD in predicting risk in patients with cardiovascular risks factors [33,38,40,42,43,45,112,115]. Results of the general population–based Gutenberg Health Study (5,000 individuals) revealed a strong correlation between the biomarker of CVD, pro-atrial natriuretic peptide (ANP), and non-invasive measurement of conduit artery and peripheral arterial performance [131]. These reports are contrasted by the failure of endothelial function to predict cardiovascular events in mostly healthy individuals [132] and in those with intermediate cardiovascular risk [133]. According to another large population-based study, non-invasive measurement of vascular function failed to add prognostic value to the European Society of Cardiology risk score [134]. Therefore, measurements of intima–media thickness [132] and stiffness index [135] were recommended for more accurate determination of endothelial and vascular function, especially since intima–media thickness also correlates with redox state and early atherosclerosis [136].

The authors of this present review share the opinion that the above controversies, limitations of some of the techniques used to assess endothelial function in humans, and limited use of endothelial tests in clinical practice are the major obstacles to fostering endothelium-guided diagnostics and endothelium-targeted disease therapies to clinical reality and represent the major determinant of the huge bench-to-bedside gap in endothelial biomedicine [109]. Despite these limitations in the methodologies to reliably assess endothelial function in humans, it is clear that endothelial dysfunction in conduit vessels is mechanistically linked with oxidative stress, as it was demonstrated that vitamin C improved NO-dependent function and the magnitude of this effect had a prognostic value [89]. This underscores oxidant stress as an important hallmark of endothelial dysfunction in humans, as discussed more extensively in Section 2.3.

2. Oxidative stress as a unifying pathomechanism underlying endothelial dysfunction and cardiovascular disease

2.1. Essential background on the oxidative stress and redox signalling concept

All aerobic life requires oxygen. Since oxygen is per se a reactive species, one consequence is that oxygen can be converted to more reactive molecules (e.g. free radicals) that may cause damage to different biological molecules and, in the worst case, cause impairment of cellular function [137]. Most CVD is accompanied by an imbalance between the formation of reactive oxygen and nitrogen species (RONS, including superoxide, hydrogen peroxide and hydroxyl radicals, and $^{\bullet}$NO, as well as products such as peroxynitrite and hypochlorous acid) and detoxification by low molecular weight antioxidants or reactive oxygen species (ROS)-degrading enzymes [88,138], leading to a deviation from the steady state [139]. Some of these species have a role as cellular messengers and contribute to redox signalling via S-nitros(yl)ation, reversible thiol oxidations and ferrous/ferric enzyme equilibria [140–142]. Among these, the best understood is $^{\bullet}$NO, which acts as an important vasodilator and inhibitor of platelet activation [143,144]. The superoxide anion ($O_2^{-\bullet}$) can be formed from different sources such as xanthine oxidase, NADPH oxidases, uncoupled nitric oxide synthases (NOS) and the mitochondrial respiratory chain [145]. Of note, $^{\bullet}$NO can be antagonised by $O_2^{-\bullet}$ radicals leading to the formation of the cytotoxic oxidant peroxynitrite, as shown by Gryglewski et al. [146]. The discovery of superoxide dismutases (mitochondrial MnSOD and cytosolic/extracellular Cu,Zn-SOD) by Fridovich et al. in the 1960s [147] provided molecular proof that superoxide plays a role in organisms and in living cells. Moreover, the existence of enzymes specifically committed to the scavenging of superoxide, the SODs, implied that inappropriately high concentrations of this species may have adverse effects that contribute to pathological processes.

2.2. Molecular proof for the oxidative stress and redox signalling concept in animals

The first reports on the role of oxidative stress in the progression and pathophysiology of CVD were published in the early 1990s by Harrison and Ohara in an experimental model of hypercholesterolaemia [148,149]. The molecular proof suggesting the pathophysiological role of oxidative stress was provided by a large number of preclinical studies using genetic tools (e.g. knockout mice) which clarified the involvement of ROS-producing or -degrading enzymes in the onset and progression of these diseases. In mice with MI, genetic deletion of the NADPH oxidase subunit $p47^{phox}$ almost normalised vascular $^{\bullet}$NO bioavailability, reduced ROS formation, improved heart function and increased survival rate by 20% after MI [150]. Moreover, deletion of the NADPH oxidase subunits $p47^{phox}$ and Nox1 had a protective effect on blood pressure and endothelial function in angiotensin-II (AT–II)–induced hypertension in mice [151,152]. In contrast, overexpression of Nox1 in these transgenic mice caused a further increase in blood pressure [153]. Vice versa, partial deletion of the mitochondrial superoxide dismutase ($MnSOD^{+/-}$) increased age-dependent mitochondrial oxidative stress and endothelial dysfunction [154] and rendered mice more susceptible to nitroglycerin-induced nitrate tolerance and endothelial dysfunction [155]. Likewise, deletion of the glutathione peroxidase-1 resulted in increased atherosclerotic plaque lesion size and vascular oxidative stress in $ApoE^{-/-}$ mice [156].

On the other hand, increasing literature suggests a beneficial role of ROS in the cardiovascular system, with NOX-4 the major enzymatic source for protective ROS [157–161], with the exception of ischaemic stroke, where pharmacological NOX-4 inhibition or deletion of the gene conferred improved prognosis [162–164]. The NOX-4 paradigm also represents an attractive explanation for the failure of most large-scale clinical trials on antioxidants (see ***Section 2.3***), as ROS (mainly H_2O_2) also confer beneficial signalling in essential cellular functions, providing the 'eustress' required for maintaining antioxidant defence. Antioxidant approaches may require fine-tuned, species-specific, space- and time-resolved pharmacological targeting (for review see Ref. [137,165–167]) and, most importantly, complete understanding of their mode of action [168].

The number of studies on the molecular mechanism of oxidative stress in animal disease models using genetically modified mice is too large to be discussed in detail here, but the most important ones, along with the landmark discoveries on ROS playing a role for CVD are listed in Table 1. Regarding the numerous animal experimental studies on pharmacological antioxidant interventions, we would like to refer to relevant previous review articles [49,60,88,169].

2.3. Molecular proof for the oxidative stress and redox signalling concept in humans

The close connection between oxidative stress and cardiovascular prognosis is supported by a number of small-cohort clinical studies (e.g. by differential effects of vitamin C infusion on FMD in patients with high or low burden of ROS formation [89]). Examples include the significantly impaired FMD and reduced circulating glutathione in 52 smokers versus controls [170], a positive correlation between FMD and superoxide dismutase activity and negative correlations between FMD and oxLDL/ADMA levels in 59 patients with chronic kidney disease versus controls [63], and negative correlations between vascular

Table 1
Important (causal) ROS sources or important antioxidant defence enzymes in different animal disease models.

Model and ROS source	Reference
Heparin-binding superoxide dismutase significantly lowered arterial blood pressure in spontaneously hypertensive rats	[330]
Critical role of the NADPH oxidase subunit $p47^{phox}$ for DOCA-salt-induced hypertension	[331]
Critical role of the NADPH oxidase subunit $p47^{phox}$ for AT–II–induced hypertension	[151]
Critical role of the NADPH oxidase isoform Nox1 for AT–II–induced hypertension	[152,153]
Critical role of mitochondrial ROS for AT–II–induced hypertension	[332,333]
Critical role of xanthine oxidase for AT–II–induced hypertension	[334]
Critical role of the NADPH oxidase isoform Nox2 ($gp91^{phox}$) for AT–II–induced hypertension	[335–338]
Critical role of the NADPH oxidase isoform Nox4 for AT–II–induced hypertension	[339,340]
Critical role of heme oxygenase-1 in cardiovascular protection in hypertension, aging and diabetes models	[341,342]
Critical role of the NADPH oxidase subunit $p47^{phox}$ for MI damage	[150]
Critical role of the NADPH oxidase isoform Nox4 for MI damage	[343]
Critical role of the NADPH oxidase isoform Nox2 for MI damage	[344,345]
Critical role of mitochondrial ROS for MI damage	[345–347]
Critical role of xanthine oxidase for MI damage	[150,348–350]
Crosstalk between mitochondrial and NADPH oxidase–derived ROS in nitroglycerin-triggered vascular dysfunction	[351]
Critical role of manganese superoxide dismutase to maintain endothelial function in aged mice and to prevent nitroglycerin-induced oxidative stress	[154,155]
RAGE-induced cytosolic ROS promote mitochondrial superoxide generation in diabetes	[352]
Crosstalk of mitochondria and NADPH oxidases via ROS signalling in white blood cells and its relevance in the aging process, AT–II–induced hypertension – aggravation by MnSOD deficiency and amelioration by cyclophilin D deficiency	[94]
Interaction of mtROS with Nox2 but not Nox1, Nox4 or Nox5 in the AT–II–induced hypertension model via hydrogen peroxide, sSrc, PKCε and mtK_{ATP} channels	[353]
Mitochondrial regulation of NADPH oxidase in hindlimb unweighting rat cerebral arteries	[354]
Genetic endothelial-specific GCH-1 deficiency ($Gch1^{fl/fl}$Tie2cre mice) causes eNOS uncoupling and endothelial dysfunction in arterial resistance arteries	[355,356]
Genetic endothelial- or myelomonocytic-specific AMPK deficiency ($AMPK^{fl/fl}$Tekcre or LysMcre mice) causes endothelial dysfunction, vascular oxidative stress and inflammation in AT-II induced hypertension	[357,358]
Critical role of the NADPH oxidase isoform Nox2 ($gp91^{phox}$) for aircraft noise–induced hypertension, endothelial dysfunction, vascular and cerebral oxidative stress, and inflammation	[359]
Homozygous deletion of SOD2 results in pre- and postnatal death due to dilated cardiomyopathy and neurodegeneration	[360,361]
Age-dependent progressive phenotype of low-grade inflammation, vascular oxidative stress and endothelial dysfunction in glutathione peroxidase-1 (GPx-1) deficient mice	[67,362]

function (reactive hyperaemia index) and malondialdehyde/8-oxo-deoxyguanosine levels in 69 patients with sleep apnoea versus controls [171]. Large clinical trials have also supported the role of oxidative stress in cardiovascular prognosis. For example, the levels of glutathione peroxidase-1 showed a positive correlation with cardiovascular event–free survival in 636 individuals [172], and the oxidative stress serum markers D-ROM (derivatives of reactive oxygen metabolites, indicating ROS levels) and TTL (total thiol levels, representing the redox state) were independently and strongly associated with all-cause and CVD mortality in 10,622 men [173]. More large-scale clinical trials and meta-analyses on the association of oxidative stress markers with CVD or all-cause mortality are shown in Table 2. Different oxidative stress markers such as lipid peroxidation products, 3-nitrotyrosine, oxidative DNA lesions and protein carbonyls were also reviewed in detail regarding their diagnostic value or association with various disease (including CVD and a reliability score), reporting the highest level of evidence for lipid peroxidation products, protein carbonyls, oxidative DNA lesions, GSH/peroxiredoxin redox state, P-VASP and ADMA, followed by 3-nitrotyrosine, 3-chlorotyrosine and MPO [174].

Despite the preclinical and clinical evidence for an important role of oxidative stress in the development and progression of CVD, there are to date only a few examples of clinical studies demonstrating that targeted antioxidant drugs (e.g. xanthine oxidase inhibitors, meta-analysis in 10,684 individuals) [175], α-lipoic acid therapy [176] or tight control of vitamin C plasma levels (e.g. EPIC-Norfolk trial, 19,496 individuals [177]) improve the prognosis of patients with CVD. Antioxidant therapy is also beneficial in diseases with proven oxidative stress conditions such as sickle cell anaemia or thalassaemia, where iron chelators, α-lipoic acid, N-acetyl cysteine, vitamin E or C, or tetrahydrobiopterin therapies are used for prevention of inflammation and oxidative damage of organs including the cardiovascular system [178,179]. However, most large clinical trials and meta-analyses (e.g. HOPE, HOPE-TOO [180]) failed to show any health benefit for the treatment of CVD or for all-cause mortality with non-selective oral antioxidant drugs (reviewed in Ref. [165,181]). The synthetic antioxidant drug NXY-059, despite costly development and clinical testing, also failed to demonstrate any benefit in 3,195 stroke patients [182]. Of note, these findings are contrasted by a large number of small to intermediate-sized clinical interventional trials using either acute vitamin C infusion with significant cardiovascular health benefits or oral treatment of individuals at higher risk with improvement of endothelial dysfunction, a surrogate parameter of early atherosclerosis [14,165]. Some important studies on interventions with classical (oral) antioxidants and dietary interventions, reporting positive and negative outcomes, are shown in Table 3.

2.4. Molecular mechanism of redox regulation of endothelial function and redox signalling concept

According to the concept of 'kindling radicals' or the 'bonfire' hypothesis, the initial formation of superoxide (e.g. from phagocytic NADPH oxidases of infiltrated leukocytes) and subsequent formation of peroxynitrite represent the mechanism of eNOS uncoupling [183]. This kind of ROS-induced ROS formation is also well-known for cross-activation of mitochondrial ROS formation by dysfunctional mitochondria [184] or activation of xanthine oxidase and NADPH oxidases [145,185]. The ROS formation may affect the classical regulatory mechanisms of eNOS activity such as calcium and calmodulin, caveolin, HSP90, palmitoylation and myristoylation that also control the activating phosphorylation by Akt or AMPK at Ser1179 as well as the localisation of eNOS. However, ROS formation more directly affects the non-classical regulation of eNOS activity by so-called 'redox switches', which all may represent pharmacological targets for cardiovascular therapy: the oxidative depletion of tetrahydrobiopterin (BH_4), oxidative disruption of the dimeric eNOS complex by oxidation of the zinc-sulphur-complex, S-glutathionylation of a cysteine in the reductase domain and adverse phosphorylation at Thr495/Tyr657, as well as ROS-triggered increases in levels of the endogenous eNOS inhibitor asymmetric dimethylarginine (ADMA) or direct oxidative break-down of $^{\cdot}NO$ itself (for detailed review see Refs. [14,145,183,186]). The functional correlate of eNOS dysfunction or uncoupling is endothelial dysfunction in coronary and peripheral vessels, which can be measured by

Table 2
Important clinical trials or meta-analysis on the association of oxidative stress markers with cardiovascular disease or all-cause mortality. Also reports on effects of CV drug therapy on oxidative stress markers are listed.

Studies on oxidative stress markers and health effects	Marker and outcome	Included subjects	Reference
Systematic review and meta-analysis on association of 8-hydroxy-2-deoxyguanosine levels with heart failure	8-OHdG ↑ indicates higher risk	140 Ctr, 446 HF patients	[363]
Systematic review and meta-analysis on association of 8-hydroxy-2-deoxyguanosine levels with CVD	8-OHdG ↑ indicates higher risk	1,106 Ctr, 810 CVD patients	[364]
Meta-analysis by CHANCES consortium on association of oxidative stress serum markers with all-cause and CVD mortality	D-ROM ↑ and TTL ↓ indicates higher risk	10,622 (men and women, age 45–85)	[173]
Meta-analysis on association of circulating oxidised LDL with atherosclerotic cardiovascular disease	oxLDL ↑ indicates higher risk	12,143 subjects, 2,365 CV events	[365]
Clinical trial on association of free (F2)-isoprostane with 30-day cardiovascular outcomes in patients with acute coronary syndrome	8-isoPF2α ↑ indicates higher risk	108 CVD patients, 26 events	[366]
Matched case-control study on association of urinary 8-iso-prostaglandin F2alpha with cardiometabolic risk factors in patients with coronary heart disease	8-isoPF2α ↑ indicates higher risk	93 Ctr, 93 CHD patients	[367]
Clinical trial on association of oxidative stress markers with major adverse cardiovascular events in patients with coronary artery disease	D-ROM ↑ and OXY-Adsorbent Test indicates higher risk	97 CAD patients	[368]
Clinical trial on association of 8-isoprostane levels with the presence and extent of coronary stenosis in patients with coronary artery disease	8-isoPF2α ↑ indicates higher risk	241 CAD patients	[369]
Clinical trial on association of 3-nitrotyrosine with the presence of coronary artery disease in patients with prediabetes	3-NT ↑ indicates higher risk	120 prediabetic patients	[370]
Clinical trial on association of serum myeloperoxidase levels with endothelial dysfunction or major adverse cardiovascular events in humans	MPO ↑ indicates higher risk	298 subjects; 3,635 subjects	[371,372]
Clinical trial on association of serum myeloperoxidase levels with CV event risk in patients with acute coronary syndromes or chest pain	MPO ↑ indicates higher risk	1,090 ACS patients; 490 with chest pain	[373,374]
Clinical trial on association of serum 3-chlorotyrosine levels with acute myocardial infarction in patients	3-Cl-Tyr ↑ indicates higher risk	53 Ctr, 77 AMI patients	[375]
Studies on cardiovascular drug therapy and oxidative stress markers	**Marker/intervention, outcome**	**Included subjects**	**Reference**
Clinical trial on effects of simvastatin therapy on F2-isoprostane formation in hypercholesterolemic subjects	Statin decreases 8-isoPF2α in hypercholesterolaemia	43 patients	[376]
Clinical trial on effects of simvastatin on endothelial activation and lipid peroxidation in hypercholesterolaemia	Statin decreases 8-isoPF2α and VCAM-1/E-Sel in hyperchol.	67 hyperchol. patients, 32 normochol.	[377]
Clinical trial on association of nitrotyrosine levels with cardiovascular disease and modulation by atorvastatin therapy	Statin decreases 3-NT in CAD	100 non-CAD patients, 100 CAD patients	[378]
Clinical trial on effects of candesartan on endothelial activation and lipid peroxidation in hypercholesterolaemia	ARB decreases 8-isoPF2α and ICAM-1/MCP-1 in hyperchol.	47 hyperchol. patients	[379]

Abbreviations used are: Ctr (=control); D-ROM (=derivatives of reactive oxygen metabolites, indicating ROS levels) and TTL (=total thiol levels, representing the redox state); 8-OHdG (=8-hydroxy-2-deoxyguanosine); HF (=heart failure); CVD (=cardiovascular disease); 8-isoPF2α (=8-iso-prostaglandin F2α); CHD (=coronary heart disease); CAD (=coronary artery disease); 3-NT (=3-nitrotyrosine); MPO (=myeloperoxidase); ACS (=acute coronary syndrome); 3-Cl-Tyr (=3-chlorotyrosine); AMI (=acute myocardial infarction); VCAM-1 (=vascular cell adhesion molecule-1); E-Sel (=E-selectin); ARB (=AT1-receptor blocker); ICAM-1 (=intercellular adhesion molecule-1); MCP-1 (=monocyte chemoattractant protein-1).

acetylcholine-dependent (plethysmography) or flow-mediated dilation and represents an early predictor of cardiovascular events via its direct connection to the process of atherosclerosis [40,89].

Also down-stream of eNOS, the NO/cGMP signalling pathway contains a number of redox switches. Soluble guanylyl cyclase (sGC) can be inactivated via thiol oxidation, S-nitrosation [187,188] or ROS-triggered loss of the heme group (reviewed in Ref. [14,189]). Likewise, cGMP-degrading phosphodiesterases are activated by ROS [190,191]. In contrast, the cGMP-dependent kinase (PKG) is activated by disulphide bridge protein-dimer formation [192], which could represent a master switch of a terminal target of the NO/cGMP signalling cascade to prevent complete loss of this vasodilation pathway.

2.5. Complex phenotype of endothelial dysfunction

The phenotype of endothelial dysfunction is not limited to the loss of homeostatic $^{\bullet}NO/O_2^{\bullet-}$ balance and induction of oxidative stress (Fig. 1) but involves multiple other pathophysiologically relevant alterations, including dysregulation of numerous other vasodilator and vasoconstrictor mediators, diminished glycocalyx coverage and length, increased endothelial permeability, endothelial (vascular) stiffness, endothelial inflammation, endothelial pro-thrombotic response and impaired fibrinolysis (summarised in Fig. 2 along with potential redox switches in these processes as detailed in Table 4). Other processes related to smooth muscle and vascular dysfunction such as vascular stiffness and calcification are discussed elsewhere in detail [193–195].

An important aspect of the complexity of the phenotype of endothelial function is that at least in the murine model of atherosclerosis relevant to human pathophysiology, multiple endothelial mechanisms are altered simultaneously in early atherosclerosis even before the occurrence of atherosclerotic plaques, as we have demonstrated recently [122]. In fact, impairment of endothelium-dependent vasodilation and NO-dependent function, coinciding with glycocalyx injury, increased endothelial permeability, endothelial stiffness, endothelial inflammation and changes in haemostasis were all detected in the very early stage of endothelial dysfunction prior to the development of atherosclerotic plaques [122]. These results seem to support the concept of 'vicious circle' mechanisms of endothelial dysfunction put recently in the context of impaired endothelial glycocalyx, endothelial mechanotransduction and NO-dependent functions [196]. Numerous studies support that notion. For example, silencing of glypican-1 or SDC-1 inhibited shear stress–induced activation of endothelial NO synthase [197], while replenishment of the glycocalyx improved mechanosensitive NO generation [196]. Increased endothelial cortical stiffness impaired flow-mediated NO production, suggesting that in pathophysiological settings of endothelial dysfunction, NO production is regulated by cortical stiffness, and endothelial nanomechanics appears an important therapeutic target [198] tightly linked with glycocalyx integrity [122]. Glycocalyx injury led to increased endothelial permeability [199] and induced a proinflammatory endothelial response [200], facilitating monocyte adhesion and infiltration, and the development of atherosclerotic plaques [201]. Leukocyte infiltration and

Table 3
Important clinical trials and meta-analyses on the effects of antioxidant therapy on cardiovascular disease or all-cause mortality. Positive and negative outcomes are listed.

Positive studies	Marker/intervention, outcome	Included subjects	Reference
Systematic review and meta-analysis on association of lutein plasma levels with cardiometabolic health (coronary heart disease, stroke, metabolic syndrome) across the life course	Lutein ↑ indicates lower risk	387,569 participants	[380]
Prospective population study (EPIC-Norfolk) on association of plasma ascorbic acid levels with mortality in men and women	Vitamin C ↑ indicates lower risk	19,496 participants	[177]
Meta-analysis on association of xanthine oxidase inhibitor therapy with cardiovascular events and hypertension in patients	XOi therapy no effect on CV death, lower risk for major CV events and hypertension	10,684 patients	[175]
Meta-analysis on association of combined ACEi and XOi therapy with event-free survival of post-AMI patients	XOi and ACEi increases event-free survival in post-AMI patients	3,630 post-AMI patients, 525 treated	[381]
Systematic review and meta-analysis on association of polyphenol-rich interventions with cardiovascular risk factors in haemodialysis	Polyphenols decrease cardiovascular risk markers	520 participants	[382]
A randomised controlled trial and an updated meta-analysis on association of curcuminoid-piperine combination therapy with antioxidant and anti-inflammatory effects of in subjects with metabolic syndrome	Polyphenols increase SOD activity, reduce MDA and CRP	281 participants	[383]
Systematic review and meta-analysis on association of resveratrol supplementation with endothelial function, blood pressures and other parameters among patients with metabolic syndrome and related disorders	Resveratrol increased FMD, no effect on blood pressure; reduced body weight, triglycerides, blood glucose	?	[222,384]
PREDIMED study on association of Mediterranean diet with cardiovascular health status – blood pressure, lipid profiles, lipoprotein particles, inflammation, oxidative stress, carotid atherosclerosis and expression of proatherogenic genes and thrombosis	Mediterranean diet improves CV health and decreases prevalence of metabolic syndrome	7,447 participants, 288 major CVD events	[385]
Negative studies	**Marker/intervention, outcome**	**Included subjects**	**Reference**
Systematic review and meta-analysis on association of mortality in randomised trials with antioxidant supplements for primary and secondary prevention	β-carotene, vitamin E/D ↑ increased risk, vitamin C, Se no effect	232,606 participants	[180]
Randomised controlled trial (HOPE-TOO) on association of long-term vitamin E supplementation with cardiovascular events or cancer	Vitamin E ↑ increased risk for HF, no effect on other CV events and cancer	3,994 participants	[386]
HOPE study on association of long-term vitamin E supplementation with cardiovascular outcomes in people with mild-to-moderate renal insufficiency	Vitamin E ↑ no effect on major CV events and proteinuria	9,541 participants, 993 renal insufficiencies	[387]
Meta-analysis of randomised trials on association of supplementation of antioxidant vitamins for the prevention of cardiovascular disease with all-cause and CV death	Vitamin E ↑ no effect on CV/CBV and other death; β-carotene ↑ increased risk of CV and other death	81,788 (vitamin E) and 138,113 (β-carotene) patients	[388]
HOPE study on association of long-term vitamin E supplementation with cardiovascular and all-cause death in people with cardiovascular disease or diabetes	Vitamin E ↑ no effect on CV and other death, risk for major CV events	9,541 participants	[389]
Clinical studies in progress (on CVD or disease with increased CV risk)	**Number of clinical trials**	**Lead compounds**	**Reference**
NRF-2 activators for rheumatoid arthritis and psoriasis, obstructive sleep apnoea, chronic kidney disease, T2DM, diabetic nephropathy, non-alcoholic fatty liver disease, pulmonary hypertension, intracerebral haemorrhage, acute ischaemic stroke	> 90 phase I–IV trials	Bardoxolone methyl, dimethylfumarate, sulforaphane	[218]
NOX inhibitors for T2DM associated with diabetic nephropathy, stroke; may also be useful for CVD, non-alcoholic fatty liver disease	Few phase II–III trials Preclinical data	GKT136901/137831 (Genkyotex), VAS2870/3947 (Vasopharm)	[327]; [390,391]

Abbreviations used are: XOi (= xanthine oxidase inhibitor); HF (= heart failure); CV (= cardiovascular); CBV (= cerebrovascular) ACEi (= angiotensin converting enzyme inhibitor); AMI (= acute myocardial infarction); SOD (= superoxide dismutase); MDA (= malondialdehyde); CRP (= C-reactive protein); CVD (= cardiovascular disease).

subsequent vascular inflammation further promoted glycocalyx degradation by extrinsic pathways [202]. Inhibition of hyaluronan synthesis, the major component of the glycocalyx, increased leukocyte adhesion, endothelial inflammation and progression of atherosclerosis [203]. Impaired endothelial glycocalyx facilitated platelet adhesion to endothelium [199], whereas, reciprocally, biglycan, a constituent of the glycocalyx of capillaries, inhibited platelet activation and, finally, macrophage-mediated plaque inflammation [204]. Altogether, there exist numerous mechanisms by which glycocalyx injury may contribute to impairment of NO-dependent function, increased endothelial permeability, endothelial stiffness, endothelial inflammation and alterations in haemostasis; these pathological processes may reciprocally promote glycocalyx injury. Angiopoietin-2 has been recently proposed as an important mechanism contributing to glycocalyx integrity, endothelial permeability, endothelial nanomechanics and inflammation with Tie2 activation as a novel therapeutic target [205,206]. However, little is known of how these processes are regulated by specific redox-based mechanisms (some are mentioned in Fig. 2). We can only presume that non-specific interventions targeted to oxidant stress improve glycocalyx integrity, and this could contribute to the improvement of endothelial function.

As summarised in Fig. 2, a number of redox switches and specific mechanisms are described in the numerous components of the multifactorial phenotype of endothelial dysfunction, but the importance of these mechanisms in the pathophysiology of endothelial dysfunction and associated diseases is far from understood. For example, the endothelin-1 mRNA promoter is stabilised by ROS, and vice versa: endothelin-1 can stimulate NADPH oxidase activity and expression levels

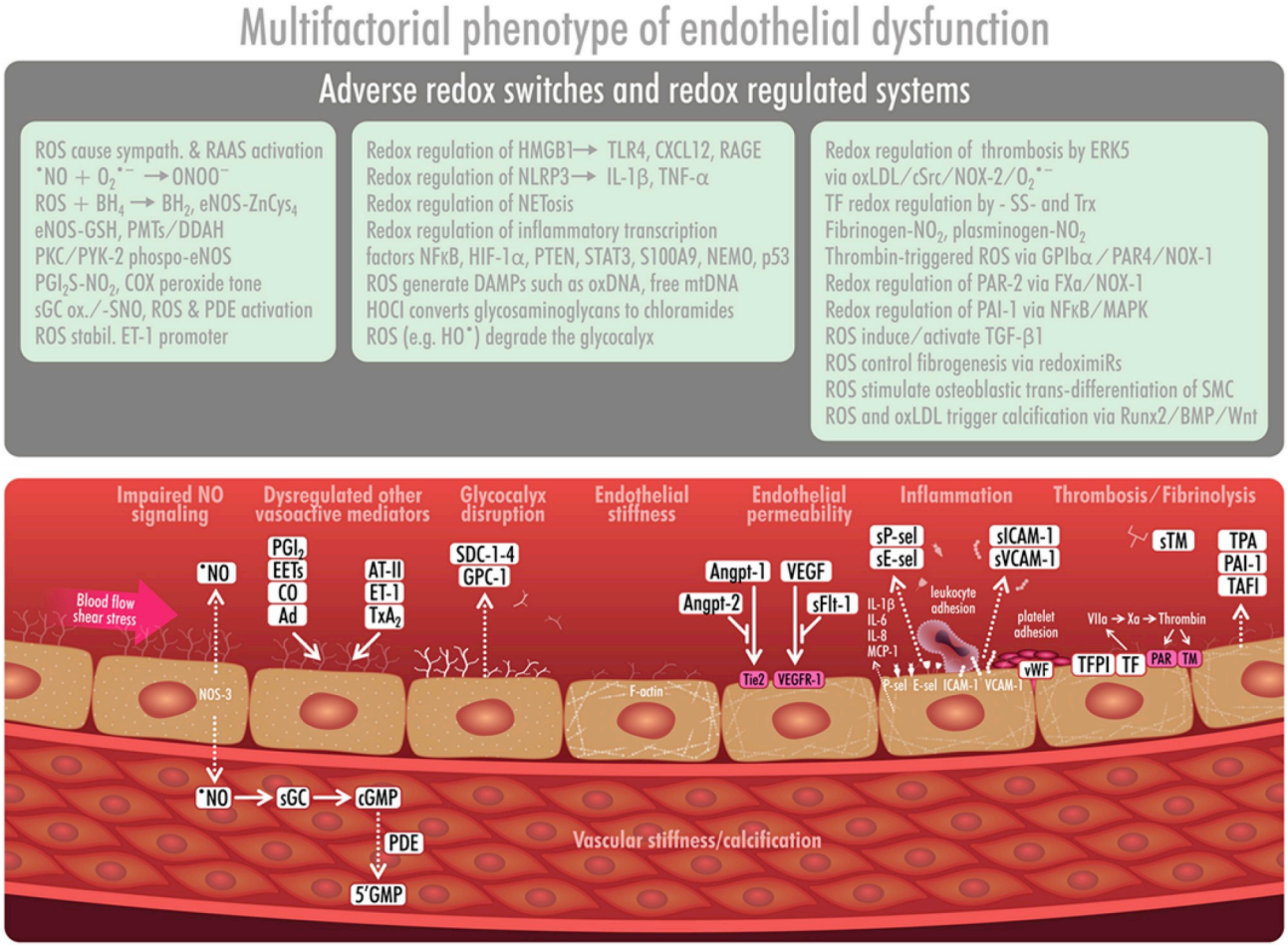

Fig. 2. Endothelial dysfunction – a complex multifactorial phenotype. Processes contributing to endothelial (vascular) dysfunction are not limited to the impaired NO-dependent function but involve also dysregulation of numerous other vasoactive mediators: glycocalyx disruption, endothelial (vascular) stiffness, increased endothelial permeability, endothelial inflammation, and alterations in thrombotic or fibrinolytic mechanisms. Known redox switches in these components are shown above these processes and are listed in detail in Table 4. Modified from Ref. [329].

[189]. Finally, prostaglandin formation is redox-regulated by the 'peroxide tone' needed for the activity of cyclooxygenase-1/2 and inactivation of prostacyclin synthase by tyrosine nitration. As a consequence of these two oxidative processes, a switch of the prostanoid synthesis to thromboxane A_2 inducing a vasoconstrictory and aggregatory phenotype can be observed under oxidative stress conditions [189].

Altogether, given the complex multiparametric nature of endothelial dysfunction, a multitarget therapeutic strategy should be adopted, similar to the recent paradigm shift in the cardioprotection field [207]. Thus, pharmacotherapy of endothelial dysfunction should be therapeutically targeted simultaneously to multiple pathomechanisms of a dysfunctional endothelium as detailed in Fig. 2. Indeed, it is unlikely that the improvement in function of a single endothelial mechanism will be effective in restoring complex multifactorial mechanisms of endothelial dysfunction, unless restoring the one chosen component of dysfunctional endothelial machinery will improve all the others [32,122]. Whether this may be achieved by choosing suitable redox signalling pathways remains to be established.

Surprisingly, drugs with a broader spectrum of pharmacological action on endothelium and vascular walls constitute the forefront of pharmacology of endothelium [32]. Paradoxically, better understanding of the profile of endothelial effects of established cardiovascular drugs effective in the treatment of CVD is mostly achieved after, not prior to, the drug introduction to clinics, and in some cases was unexpected. These discoveries of mechanisms of action of established cardiovascular drugs on endothelium and vascular walls may help to better design efficient redox-based drugs to improve oxidant stress, endothelial dysfunction and vascular inflammation.

3. Pharmacology of the endothelium based on established cardiovascular drugs and experimental/future approaches

3.1. Established cardiovascular drugs

According to a number of reports in the literature, endothelial dysfunction, atherosclerosis and the late cardiovascular complications of these phenomena are associated with chronic activation of the local and/or circulating renin-angiotensin-aldosterone system (RAAS). Suggesting a role of inappropriate ROS production in this setting, diabetic patients show particularly beneficial responses to mineralocorticoid receptor blockade [208], ACE inhibitor [209], AT_1-receptor blockade [210] and renin inhibitor [211] therapy. Statin therapy has also been shown to beneficially affect diabetic cardiovascular complications [212]. This is because ACE inhibitors and statins have antioxidant, anti-inflammatory, anti-thrombotic and vasoprotective properties [32,60] and the effects of ACE inhibitors are also shared to some extent by other RAAS inhibitors.

These established cardiovascular drugs improve cardiovascular prognosis by lowering oxidative stress levels, inflammation and mediators of vascular dysregulation such as lipids and vasoconstrictors (reviewed in Refs. [60,213–215]). An in-depth review of the effects of

Table 4
Adverse redox switches and redox regulated systems involved in the control of vascular tone (as shown in Fig. 2).

Targets and mechanism of redox regulatory pathways	Reference
ROS cause activation of the sympathetic nervous system with release of vasoconstrictors (e.g. catecholamines) in the phenol renal injury and Goldblatt (2K–1C) models of hypertension.	[392–394]
ROS cause activation of the renin-angiotensin-aldosterone system (RAAS) and vice versa in AT-II or aldosterone-driven cardiovascular remodelling and hypertension.	[395–398]
Oxidative breakdown of nitric oxide by superoxide radical anions is well-established and contributes to control of vascular tone as shown by beneficial vasodilatory effects of superoxide dismutase.	[146,399,400]
Oxidative depletion of the eNOS cofactor tetrahydrobiopterin causes uncoupling dysfunction of eNOS with diminished nitric oxide formation. In concert with other redox switches in eNOS (e.g. oxidative disruption of the zinc-sulphur-centre, S-glutathionylation, ADMA synthesis/degradation and adverse redox-driven phosphorylation by PKC and PYK-2), this provides a substantial redox-regulatory network in the vasculature with relevance for hypertension and diabetes.	[145,297,331,401–404]
Oxidative inhibition of prostacyclin synthase by nitration of tyrosine 430, peroxide-driven activation of cyclooxygenase-1/2 and oxidative inhibition of cyclooxygenase-2 by tyrosine nitration provide redox control of prostanoid synthesis and vascular tone with relevance for diabetes, atherosclerosis, diabetes, nitrate tolerance and sepsis.	[14,405–412]
Redox regulation of soluble guanylyl cyclase by thiol oxidation and S-nitros(yl)ation modulates the NO/cGMP signalling cascade. Downstream oxidative activation and upregulation of phosphodiesterases further contribute to this redox-regulatory network.	[14,187,413–417]
The promoter of the potent vasoconstrictor endothelin-1 under oxidative stress conditions leads to its upregulation. Vice versa, endothelin-1 stimulates NADPH oxidase-driven ROS formation, representing another vicious redox circle with relevance for cardiovascular disease.	[220,418–420]
HMGB1 is a central regulator of inflammation and forms complexes with central mediators of inflammation (e.g., TLR4, CXCL12 and RAGE), with subsequent recruitment of inflammatory cells and production of cytokines. It thereby represents a major damage-associated molecular pattern (DAMP). HMGB1 is also a central redox hub in the inflammatory cascade via redox modification of several critical cysteine residues. HMGB1 has important implications for vascular inflammation.	[50,421–423]
Activation of the NLRP3 inflammasome, another central regulator of the inflammatory cascade, controls the innate immune defence and the production of essential pro-inflammatory cytokines (e.g. IL-1β). It can be activated by ROS (e.g. from mitochondria or NADPH oxidase) by complex formation with thioredoxin-interacting protein (TXNIP) on disulphide bridge formation within NLRP3, interaction with thioredoxin/NFkB, activation of NRF2 or free mtDNA.	[50,90–92,424–426]
Direct redox regulation of central transcription factors such as NFkB, HIF-1α, PTEN, STAT3, S100A9, NEMO and p53 are well established and formation/release of damage-associated molecular pattern (DAMPs) such as oxidised DNA or free mtDNA under oxidative stress conditions represent other concepts of redox control of vascular inflammation.	[50,421,427,428]
The glycocalyx forms a network of proteoglycans (e.g. syndecan) and modified sugars (e.g. glycosaminoglycans) covering the endothelial surface with important functions for microvascular homeostasis. It is redox-regulated by oxidative degradation of glycosaminoglycans to chloramides by hypochlorous acid. Other free radicals such as hydroxyl and carbonate anion radicals also contribute to the oxidative degradation of the glycocalyx. The shed glycocalyx fragments have potent immunogenic potential.	[429–431]
Thrombosis is redox-regulated by various mechanisms. Mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase 5 (ERK5), represents a redox sensor that promotes thrombosis by an oxidised low-density lipoprotein (oxLDL), tyrosine kinase (cSrc), NADPH oxidase and ROS-dependent mechanism under hyperlipidaemic conditions.	[432]
Tissue factor activation increases the risk for thrombosis and is redox-activated via disulphide bridge formation in a thioredoxin-dependent manner. The antioxidant enzyme paraoxonase-2 contributes to the control of endothelial tissue factor activity and oxidative stress generally increases the expression of tissue factor.	[433–437]
Nitrated fibrinogen and plasminogen represent thrombotic risk markers. Nitrated plasminogen is less efficiently converted to plasmin, which is important for resolution of thrombus. Vice versa, plasminogen activator inhibitor-1 (PAI-1) is inhibited by oxidation in a NADPH oxidase-dependent manner. PAI-1 expression is regulated via NOX-4-derived ROS and p38 MAPK activation.	[438–443]
Thrombin triggers ROS formation via GPIbα, protease-activated receptor (PAR)-4 and NOX-1 signalling axis. Likewise, activated factor X (FXa) via NOX-1 confers redox regulation of PAR-2.	[444,445]
Vascular cell proliferation can be controlled by cysteine/cystine ratio affecting the activity and level of transforming growth factor (TGF)-β1. Likewise, NOX-4 activation controls TGF-β1 dependent differentiation of cardiac fibroblasts.	[446,447]
Fibrogenesis is controlled by redox-regulated microRNAs (redoximiRs).	[448]
Oxidative stress conditions facilitate the *trans*-differentiation of smooth muscle cells to osteoblasts and thereby the process of vascular calcification. Likewise, oxidised low-density lipoprotein (oxLDL) triggers calcification via Runx2/bone morphogenetic protein (BMP)/Wnt signalling involving NADPH oxidase–derived ROS.	[195,449,450]

established cardiovascular drugs on specific oxidative stress markers in patients with preestablished CVD has been previously published [174]. Surprisingly, these two classes of drugs – ACE inhibitors and statins introduced to clinical medicine to lower arterial blood pressure or blood cholesterol levels, respectively, targeted to inhibit ACE in the blood or HMG-CoA reductase in the liver – exert comprehensive vasoprotective actions, based partially on their primary modes of action but also on complementary endothelial mechanisms, such as improvement of NO/cGMP signalling by beneficial modulation of the redox switches described in Fig. 2 [32]. A mechanistic proof of the antioxidant effects of RAAS inhibitors on NO/cGMP signalling is based on the observation that in patients treated with ramipril or losartan, vitamin C did not improve NO-dependent function [216], in contrast to the seminal study in which the degree of vitamin C–dependent improvement of endothelial function (FMD) was interpreted as the vascular oxidative stress burden with implications for cardiovascular prognosis of CAD patients [89]. The beneficial vasoprotective effects of statins may be also related to the induction of the Nrf2–heme oxygenase-1 system as well as improved function of endothelial progenitor cells [217], and cardiovascular protection by Nrf2 activators has been evaluated in over 90 clinical trials for cardiovascular and other indications (for an overview see Ref. [218]).

The $ET_{A/B}$-receptor blockade confers improved prognosis in patients with pulmonary hypertension [219], which may be explained at least in part by decreased oxidative stress and inflammation, as reported by animal studies [220,221]. Multiple beneficial studies have also been published on the cardioprotective effects of resveratrol, as a prototype nutraceutical drug [222–224]. A summary of important clinical trials supporting antioxidant effects of established cardiovascular drugs in patients with preestablished CVD is also presented in Table 3.

A number of candidates of other drug classes also display highly beneficial vasoprotective effects. Examples include the third-generation β_1-selective β-blocker nebivolol that stimulated endothelial NO formation [225–227], thereby reversing endothelial dysfunction in patients with essential hypertension [228], improved oxidative stress in a rat model of hypertension [229] and prevented multiple complications in experimental MI [230]. Furthermore, the third-generation β-blockers nebivolol and carvedilol display antithrombotic effects not related to their β-blocking activities [231]. Hydralazine was one of the first antihypertensive drugs in clinical use, now mainly used for treatment of

pre-eclampsia [232]. It experienced a revival when a dramatic improvement of heart failure mortality was reported with combination therapy of hydralazine and isosorbide dinitrate (A-HeFT) [233,234], potentially related to its strong antioxidant effects by peroxynitrite scavenging that prevent organic nitrate–induced oxidative stress and nitrate tolerance [235,236]. Pentaerithrityl tetranitrate (PETN) is the only organic nitrate in clinical use devoid of side effects such as oxidative stress, nitrate tolerance and endothelial dysfunction [190,237]. The molecular explanation for the beneficial effects of PETN, not shared by other nitrates, is the induction of heme oxygenase-1 [238,239] and hundreds of other genes in an Nrf2-dependent fashion [240]. The pleiotropic effects of these three drugs and others have been discussed in detail previously [60].

Current evidence suggests that SGLT-2 inhibitors (e.g. empagliflozin) are more effective than both GLP-1 agonists (e.g. liraglutide) and DPP-4 inhibitors (gliptins) in reducing the risk of hospitalisation for heart failure (HHF) in T2DM (87,162 participants) [241], although the latter showed more potency in reducing HHF in T2DM than sulphonylureas (e.g. glibenclamide) and thiazolidinediones (glitazones; 127,555 patients in the meta-analysis) [242]. Both drug classes have cardioprotective effects in models of MI [243–246] and have potent anti-inflammatory properties in humans [247–249] and animal models of atherosclerosis [250–253], as well as antioxidant and antithrombotic effects in animal models of sepsis for GLP-1/DPP-4-based drugs [254–256] and of T1DM/T2DM for empagliflozin [257,258].

Surprisingly, the benefits of dapagliflozin in heart failure have been recently shown to have a similar extent in patients with and without diabetes [259], indicating the novel mechanism of action of SGLT-2 inhibition, including endothelium-targeted mechanisms that were not considered seriously before. In fact, SGLT2 inhibition (canagliflozin/dapagliflozin/empagliflozin) prevented hyperglycaemia-induced endothelial dysfunction and oxidant stress [260], which could involve the activation of AMPK or other mechanisms [261–264]. Furthermore, SGLT2 inhibition preserved and restored the structural integrity of the glycocalyx, which could explain the anti-inflammatory effects of these compounds in the presence of a pro-inflammatory environment [265].

3.2. Targeting eNOS dysfunction and uncoupling by drugs improving vascular redox state and NO (downstream) signalling

Based on the described appreciable redox regulation of the eNOS/NO/sGC/cGMP axis in various CVD, this signalling pathway represents an attractive target for pharmacological therapy [14]. Several of the therapeutic agents that target this signalling pathway represent real success stories, as demonstrated by the following examples. The NO replacement therapy by organic nitrates is a mainstay in cardiovascular therapy of stable angina, congestive heart failure and acute coronary syndromes, despite limitations due to the development of nitrate tolerance and endothelial dysfunction under chronic therapy that are mainly related to the induction of oxidative stress by most organic nitrates [190]. Phosphodiesterase inhibitors prevent the enzymatic degradation of cGMP (and cAMP); prominent examples are sildenafil and cilostazol. They are used for multiple indications comprising erectile dysfunction, pulmonary hypertension and a number of cardiac diseases, and have been reported to prevent endothelial dysfunction, oxidative stress and inflammation (reviewed in Ref. [266]). The fact that cGMP-degrading phosphodiesterases are also activated or upregulated by ROS further increases their benefits under oxidative stress conditions [190,191]. Activators and stimulators of the sGC represent a novel class of repair drugs of an oxidatively damaged sGC enzyme; prominent examples are Cinaciguat™ (BAY 58–2667) and Riociguat™ (BAY 63–2521), which are approved for clinical use in the treatment of different forms of pulmonary hypertension and heart failure [267,268]. They are intended to be used for the therapy of pulmonary hypertension and heart failure but also for other indications such as arterial hypertension, renal fibrosis or failure, liver cirrhosis, erectile dysfunction, atherosclerosis, restenosis, thrombosis and inflammation (reviewed in Ref. [269]). Additionally, direct targeting of eNOS expression and function by so-called eNOS enhancers (e.g. AVE9488 [270] and AVE3085 [271]) and tetrahydrobiopterin replacement therapy (e.g. by folate [272] or sepiapterin [273]) may represent potential therapeutic strategies in the future, as soon as the drugs themselves as well as their administration are optimised (for review see [186]). However, it must be taken into account that a number of interventions are improving NO-dependent endothelial function without strong anti-atherosclerotic effects [118,274–276]. On the other hand, inhibition of multiple mechanisms of endothelial dysfunction by statins or ACE inhibitors results in pronounced anti-atherosclerotic effects, which may be more important for the long-term prognosis of patients [32, 49] (see Section 3.1).

3.3. Actual and future strategies for thiol-targeting redox drugs for cardiovascular therapy

The classical thiol-targeting therapeutic approach is based on administration of reduced thiol drugs such as N-acetylcysteine or α-lipoic acid, leading to higher levels of reduced GSH and cysteine in serum or plasma and tissues, reduced oxidative stress, and improved functional parameters in various disease settings or pharmacological complications (see Table 5). Both thiols have beneficial cardiovascular effects [176,277]. Besides the direct antioxidant effect by scavenging ROS and RNS, these thiols may also interact with proteins and enhance enzymatic activity by redox regulation – in principle, any enzyme with a sulfhydryl group involved in its activity can be targeted by N-acetylcysteine or α-lipoic acid.

In particular, the dithiol α-lipoic acid can easily reverse enzymatic inactivation by S-glutathionylation, sulfenic acid or disulphide bridge formation. This has been demonstrated for the cytoprotective enzyme mitochondrial aldehyde dehydrogenase (ALDH-2), which has two to three cysteines in the active site pocket (depending on the species), and one of these thiol groups is essentially involved in the enzymatic activity [278]. Whereas ALDH-2 confers cytoprotection and prevents cardiac dysfunction [279], representing the major bioactivating pathway for nitroglycerin-dependent vasodilation [280,281], this enzyme is also highly redox-regulated and easily oxidised by peroxynitrite, electrophiles or nitroglycerin-derived ROS/RNS [282–284]. Since oxidation and inactivation of ALDH-2 cause accumulation of toxic aldehydes such as 4-hydroxynonenal [285], this may lead to cardiac dysfunction [286]. Of note, α-lipoic acid is a potent activator of ALDH-2 and thereby improves nitroglycerin vasodilatory and *anti*-ischaemic effects in rat models [283,287] and humans [288]. In addition, α-lipoic acid improves diabetic polyneuropathy [176] by decreasing AGE levels and downstream RAGE signalling [289], and ameliorates endothelial function in patients with diabetes [290].

N-acetylcysteine was used in the past to preserve the vasodilator and antiaggregatory potency of antianginal drugs such as nitroglycerin and isosorbide dinitrate (Table 5 and reviewed in Ref. [291]). Most likely, these beneficial effects are also based on preservation of ALDH-2 activity, suppression of organic nitrate induced oxidative stress or direct activation (or repair) mechanisms of eNOS or sGC, which are both prone to oxidative uncoupling and inactivation. Besides decreasing oxidative stress and preserving vascular function in a number of animal models of oxidative stress, it may show benefits on cardiac surgery complications and reduce DNA damage in children with β-thalassaemia (Table 5).

Novel strategies for thiol-based drugs may be based on H_2S-releasing drugs, which may form a complex redox-regulatory network with potent vasodilator properties [292,293]. The enzymatic targets of H_2S have been reviewed in detail, comprising angiogenesis, vasorelaxation, atheroprotection and permeability (Fig. 3) [294], which may show the future direction for development of more site-specific drugs. Multiple targets for H_2S-releasing drugs have been identified and

Table 5
Important animal experimental studies, clinical trials and meta-analyses on the effects of thiol-based antioxidant therapy on cardiovascular disease or all-cause mortality.

Animal (cell culture) experimental studies	Marker/intervention, outcome	Included studies	Reference
Systematic review on the protective effect of N-acetyl cysteine against diabetes-associated cardiovascular complications in animals and cultured cells	NAC improves diabetes-associated complications (ROS, MI)	49 independent animal and cell culture studies	[451]
Animal study on N-acetylcysteine, vitamins and other natural antioxidants prevention of $CBrCl_3$-induced oxidative tissue damage in vivo in a rat model	NAC in combination with lipophilic antioxidants confers best protection	–	[452]
Animal study on N-acetylcysteine prevention of vascular dysfunction and endothelial epigenetic programming in intrauterine growth–restricted guinea pigs	NAC prevents complications in intrauterine growth restriction	–	[453]
Study on effects of N-acetylcysteine in combination with nitroglycerin on aggregation of isolated platelets	NAC/GTN improves IC50 for aggregation 50-fold over single drugs	–	[454]
Animal study on effects of reduced lipoic acid on redox regulation of mitochondrial aldehyde dehydrogenase (ALDH-2) activity and nitroglycerin tolerance	α-lipoic acid confers activation of cytoprotective ALDH-2 and prevents nitrate tolerance	–	[283]
Clinical trials and meta-analyses	**Marker/intervention, outcome**	**Included subjects**	**Reference**
Meta-analysis (ALADIN I, ALADIN III, SYDNEY, NATHAN II) on association of alpha-lipoic acid supplementation with symptomatic polyneuropathy in diabetic patients	α-lipoic acid therapy improves polyneuropathy	1,258 patients	[176]
Systematic review and meta-analysis on association of antioxidant supplementations with atrial fibrillation after cardiac surgery	NAC (and vitamin C or PUFA) improves atrial fibrillation	4,278 patients with cardiac surgery	[455]
Systematic review and meta-analysis on effects of high/low-dose N-acetylcysteine on chronic obstructive pulmonary disease	NAC at high dose decreased COPD-associated complications	11 studies	[456]
Meta-analysis on association of N-acetylcysteine with prognosis of sepsis and systemic inflammatory response in adults	NAC had no effect on outcome	2,768 patients	[457]
Clinical trial on effects of alpha-lipoic acid and ascorbic acid on endothelium-dependent, nitric oxide–mediated vasodilation in diabetic patients	α-lipoic acid therapy improves endothelial function in diabetes	11 Ctr, 39 patients	[290]
Randomised clinical trial on N-acetylcysteine reduction of oxidative stress and DNA damage in children with β-thalassaemia	NAC reduced oxidative stress index and DNA damage (comet assay)	28 Ctr, 75 patients	[458]
Clinical trial on N-acetylcysteine improvement of coronary and peripheral vascular function in patients undergoing cardiac catheterisation	NAC potentiates ACh-mediated coronary vasodilation	16 patients	[459]
Clinical trial on effects of N-acetylcysteine in combination with nitroglycerin and streptokinase on evolving acute myocardial infarction in patients undergoing cardiac catheterisation	NAC decreases MDA and increases GSH; improves perfusion and left ventricular function by trend	27 patients	[460]
Double-blind, randomised, crossover study on N-acetylcysteine prevention of isosorbide dinitrate induced nitrate tolerance and loss of *anti*-ischaemic potency in patients with angina pectoris or heart failure	NAC prevents ISDN-induced ROS-associated nitrate tolerance	10 patients; 14 patients	[461,462]
Clinical trial on effects of N-acetylcysteine on nitroglycerin-induced nitrate tolerance, loss of venodilation and potentiation of vasodilation in patients with coronary artery disease or angina pectoris	NAC prevents GTN-induced ROS-associated nitrate tolerance	20 patients; 10 patients; 16 patients; 18 patients	[463–466]
Double-blind, randomised clinical trial on effects of N-acetylcysteine in combination with nitroglycerin on acute myocardial infarction and blood pressure in patients with severe unstable angina pectoris	NAC/GTN confers best protection against AMI but causes hypotension	46 patients	[467]

Abbreviations used are: NAC (=N-acetyl cysteine); MI (=myocardial infarction); PUFAs (=polyunsaturated fatty acids); COPD (=chronic obstructive pulmonary disease); ACh (=acetylcholine); MDA (=malondialdehyde); GSH (=glutathione); ISDN (=isosorbide dinitrate); GTN (=nitroglycerin); AMI (=acute myocardial infarction).

summarised for pre- and postconditioning and remote conditioning in MI, reperfusion injury and cardioprotection, such as mitochondrial permeability and activation (mPTP, K_{ATP}, PKC), eNOS/cGMP signalling, the ERK/GSK3β pathway and JAK2/STAT-3/iNOS signalling [295]. The interest in H_2S-releasing drugs for therapeutic exploitation is also reflected by the large number of patents filed for this drug class [296].

S-glutathionylation at cysteine residues Cys689 and Cys908 represents an important redox switch in eNOS leading to uncoupling of the electron flow within the enzyme and superoxide formation [297,298]. This redox-regulatory mechanism gained even more biological relevance with results indicating that eNOS S-glutathionylation can be biologically reversed by glutaredoxin-1 (Grx-1) [299]. In general, glutaredoxins confer important redox signalling (pro- or antioxidant depending on the cell type and disease conditions) [300] and may be implicated in antiatherosclerotic protection of the cardiovascular system [301]. GSH and Grx1 provide an alternative mechanism to thioredoxin and thioredoxin reductase for peroxiredoxin-2 (Prx2) recycling, and Prx2 represents a major defence mechanism against hydrogen peroxide–mediated oxidative stress [302]. Grx-1 deficiency causes fatty liver and dyslipidaemia by S-glutathionylation and inhibition of sirtuin-1 (Sirt-1), suggesting that upregulation of hepatic Grx-1 may be a beneficial strategy for NAFLD [303]. Grx-2 has also been shown to play an essential role in the development of the vascular system by preventing S-glutathionylation of sirtuin-1 and thereby preserving the activity of this NAD^+-dependent protein deacetylase and epigenetic regulator [304], suggesting that specific targeting of the different isoforms may be important. Grx-2 deficiency causes increased superoxide and hydrogen peroxide release from cardiac and liver mitochondria [305]. Many more potential targets of pharmacological modulation of protein S-glutathionylation in CVD and other diseases, including ryanodine receptors, ion channels and pumps such as SERCA and various potassium channels, kinases such as Ras/MEKK/c-Jun/Akt/PKC, apoptosis pathway constituents such as p53/caspase, and central regulators of inflammation such as NFkB are considered [306,307]. The S-glutathionylation of the Na^+–K^+ pump in the cardiovascular system seems to represent another redox key mechanism that controls cardiovascular health [308]. Thiol-dependent regulatory mechanisms (e.g. thioredoxin [Trx]/Grx-based) have also been discussed in detail for redox control of vascular homeostasis [309], protein degradation [310], ischaemic preconditioning [311] and myocardial remodelling [312]. Therefore, pharmacological targeting of Trx, Grx, peroxiredoxin (Prx) and protein disulphide isomerase (PDI) enzymes represents an attractive redox-based therapeutic approach. Besides the preclinical

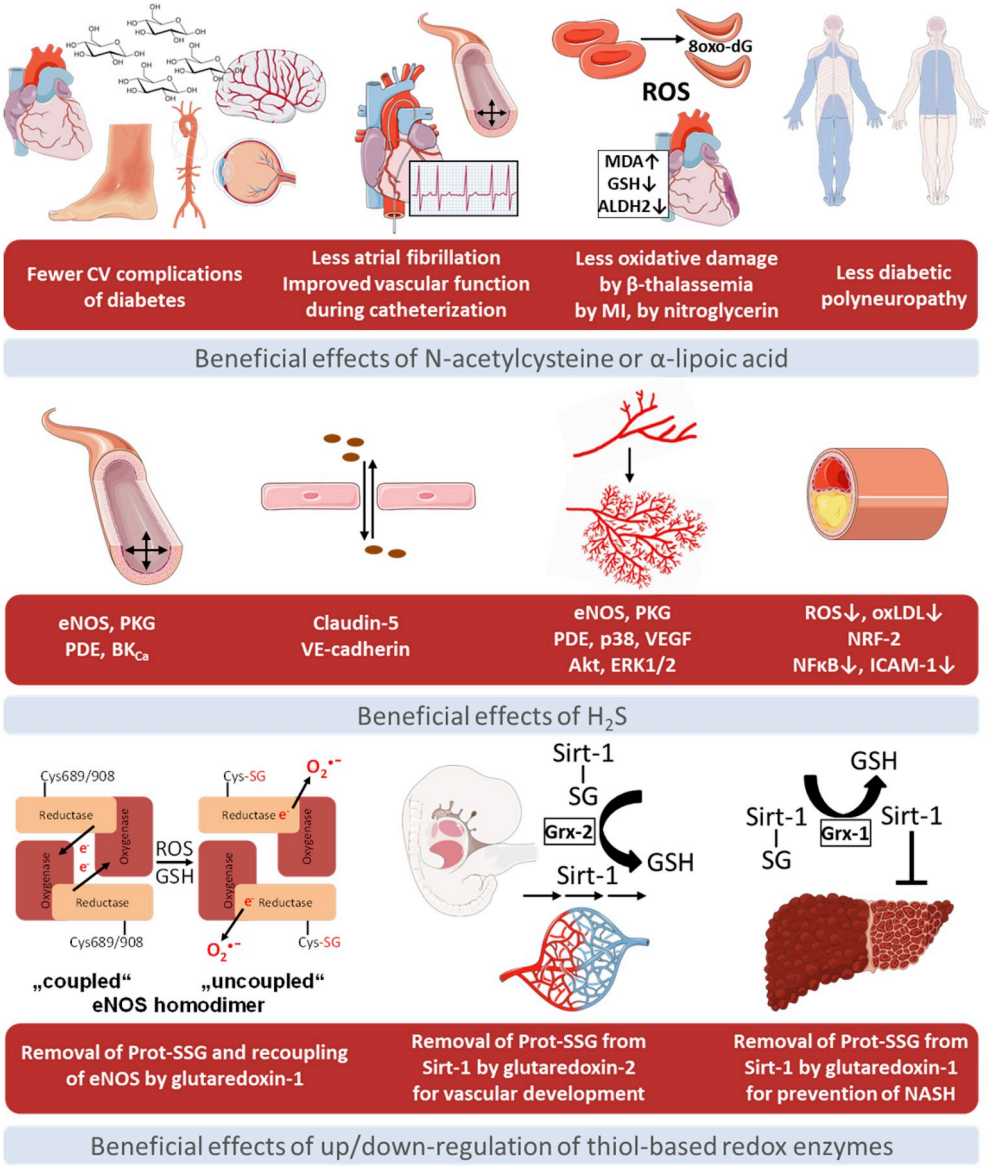

Fig. 3. Thiol-based drugs and future redox therapeutic strategies. Beneficial clinical and preclinical effects of N-acetylcysteine and α-lipoic acid (upper panel). Beneficial preclinical effects of H_2S-releasing drugs (middle panel). Beneficial preclinical effects of glutaredoxin enzymes (lower panel). Contains images from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License.

evidence presented here, it is also encouraged by the fact that thiol oxidation represents a cellular response to oxidative stress [313], while thiol reduction and disulphide bond exchange by PDI are involved in integrin receptor activation [314].

However, it remains to be established whether eNOS S-glutathionylation represents a drug-targetable pathomechanism, since, paradoxically, research has found Grx-1 knockout mice were protected from AT-II induced vascular oxidative stress and dysfunction, potentially related to impaired NADPH oxidase activation by beneficial S-glutathionylation signalling [315]. Since the NADPH oxidase activation process relies on a complex thiol–disulphide mechanism, catalysed by PDI [316], overexpression or pharmacological activation of Grx-1 may be detrimental under certain conditions. Additional concerns for pharmacological activation of Grx-1 are based on the observation that glutathione adducts induced by ischaemia and deletion of Grx-1 stabilise HIF-1α and improve limb revascularisation [317]. Whether the antiangiogenic effect of Grx-1 activation or overexpression may be pharmacologically exploited for anti-tumour therapy remains to be established. Finally, upregulation of Grx-1 activates microglia and promotes neurodegeneration, all of which contribute to the progression of Parkinson's disease [318].

Thioredoxin (Trx), glutaredoxin (Grx) and peroxiredoxin (Prx) have been implicated in a large number of CVD, including ischaemic heart disease, cardiac hypertrophy, diabetes, obesity, atherosclerosis and hypertension (reviewed in Ref. [319]). Accordingly, these enzymes were proposed as biomarkers as well as for gene therapy in CVD [307,319,320]. The half-life for recombinant human Trx-1 in the plasma of rodents or monkeys is one to 8 h but can be prolonged by polyethyleneglycol modification [321]. Most data are available for Trx-1 gene delivery in CVD therapy, which has been broadly studied at the preclinical level, but beneficial effects of gene delivery or tissue-specific overexpression of Trx-2, Grx-1, Grx-2, Prx-3 and Trx reductase have also been reported in different CVD models (reviewed in Ref. [319]). Grx protein expression is most likely regulated via antioxidant response element (ARE) or electrophile response element (EpRE) in the encoding gene, explaining induction of Grx by electrophilic or pro-oxidant compounds: oxidants in general (e.g. H_2O_2), UV_B radiation and chemical ROS generators such as adriamycin [306], the radical scavenger

tert-butylated hydroxyanisole (BHA) [322], epidermal growth factor, TGFβ, cyclic AMP, and retinoic acid [323] or 17β-estradiol [323]. Whether these Grx inducers can be exploited therapeutically for reversal of S-glutathionylation in specific CVD remains to be established. Finally, protein disulphide isomerases represent protein-folding chaperones and central regulators of cellular functions, and their pharmacological targeting may represent another thiol-based strategy for the treatment of cancer and neurodegenerative diseases (reviewed in Ref. [324,325]).

3.4. Actual and future strategies for ROS scavengers and source-targeting redox drugs for cardiovascular therapy

Direct ROS scavengers are mainly based on natural compounds such as vitamins C, E and D as well as thiol-based drugs. Metal complexes have also been tested in recent years as SOD mimetics, with some specific developments made, such as ebselen as a GPx mimetic, NXY-059 and some other spin traps (for review see Ref. [165]). However, so far none of these drugs are used for broad clinical applications, and only some are used for niche therapies (e.g. anticancer chemo- or radiation therapy). Some more recent candidates that are at least in clinical phase II or III trials are mitochondria-targeted antioxidants such as the direct ROS scavenger mitoQ [165,326,327] and NRF-2 activators with the lead compounds bardoxolone methyl, dimethylfumarate and sulforaphane [218]. Strong evidence for the protective NRF-2 concept is also based on a systematic review and meta-analysis of the antioxidant (by MDA) and anti-inflammatory (by TNF-α) effects of resveratrol on multiple organ injury induced by sepsis in animal models (11 combined studies) [328], since resveratrol is known to act, besides sirtuin-1 signalling, by activation of the Nrf2-heme oxygenase-1 axis [218]. The most promising candidates of the group of ROS source inhibitors are NADPH oxidase inhibitors with the lead compounds GKT136901/137831 (Genkyotex) and VAS2870/3947 (Vasopharm) [327] and xanthine oxidase inhibitors such as allopurinol and febuxostat [327] (Table 3). Other ROS source inhibitors are monoamine oxidase inhibitors (most advanced clinical proof-of-concept trials for depression and neurodegenerative disease), NOS inhibitors (most advanced clinical proof-of-concept trials for traumatic brain injury, whereas those for septic shock failed) and inhibitors of the ROS toxifier myeloperoxidase (several drug candidates are currently in development; for review see Ref. [327]).

3.5. Future strategies for redox drugs for cardiovascular therapy – A personal perspective

Although impairment of $^{\bullet}$NO-dependent endothelial function represents a central diagnostic approach to measure endothelial dysfunction and has prognostic value, therapeutic strategies targeted to restore the function of endothelial $^{\bullet}$NO have failed. $^{\bullet}$NO donors, L-arginine and BH_4-based approaches do not seem to afford long-term cardiovascular benefits for CVD, but as known for organic nitrates, sodium nitroprusside and other $^{\bullet}$NO donors can be used for acute management of hypertensive crisis or acute treatment of angina symptoms. Only strategies targeted to downstream mechanisms of $^{\bullet}$NO signalling, including sGC activators and stimulators, or phosphodiesterase inhibitors, are promising. Thus, attempts to achieve antioxidant effects by $^{\bullet}$NO replacement therapy have not endured over time, and endogenous $^{\bullet}$NO activation by eNOS enhancers, L-arginine and BH_4 has led to controversial reports or become deadlocked at the drug development stage. Furthermore, only $^{\bullet}$NO donors that have an intrinsic antioxidant potential such as PETN, inducing HO-1, do not induce oxidant stress on their own and have proven beneficial in many clinical indications. Many of the specifically targeted redox-based strategies have so far not met their expectations, such as NOX inhibitors. On the other hand, non-specific approaches with H_2S donors or N-acetylcysteine have demonstrated vast potential as they target many mechanisms and most likely many targets. Similarly, some of the established cardiovascular drugs are effective in improvement of endothelial function and restoring multiple detrimental and pathophysiology-relevant mechanisms, including oxidative stress, vascular inflammation and prothrombotic mechanisms. Collectively, the data support that drugs displaying a broader spectrum of pharmacological action on the endothelium or following a multitarget strategy represent the best therapeutic approach to treat endothelial dysfunction and accordingly CVD. This conclusion seems not surprising, given the complex multifactorial nature of the diseased endothelium with many pathways and various pathophysiologically relevant functional changes that by far exceed the loss of homeostatic $^{\bullet}NO/O_2^{\bullet-}$ balance, although the latter plays a central but not unique role in the pathophysiology of endothelial dysfunction. Thus, our future therapeutic strategies should be not limited to restoring $^{\bullet}NO/O_2^{\bullet-}$ balance but to restoring the whole complexity of the phenotype of endothelial function maintaining cardiovascular homeostasis.

Thus, the current challenge is to better understand the relative importance of various mechanisms of endothelial dysfunction, apart from $^{\bullet}NO/O_2^{\bullet-}$ balance, as well as their reciprocal interactions in various diseases linked to endothelial dysfunction, to propose the most effective therapeutic approaches. So far, unsurprisingly considering the multifactorial nature of endothelial dysfunction and CVD, the most effective vasoprotective redox drugs are rather unspecific thiol-based antioxidants (Table 5). Improvement of redox balance is also shared by established cardiovascular drugs. However, their comprehensive mechanisms of action on the endothelium and vascular walls were discovered mostly after, not prior to, their introduction to clinical practice, as was the case with RAAS inhibitors, statins, SGLT-2 inhibitors and third-generation β-blockers, for example. Against expectation, established cardiovascular drugs seem to be still at the forefront of the pharmacology of endothelial dysfunction, and we can still learn from their clinical successes how to design novel endothelial-targeted treatments.

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Declaration of competing interest

The authors declare that they have no conflicts of interest with the contents of this article.

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References

[1] S.S. Lim, T. Vos, A.D. Flaxman, G. Danaei, K. Shibuya, H. Adair-Rohani, M. Amann, H.R. Anderson, K.G. Andrews, M. Aryee, C. Atkinson, L.J. Bacchus, A.N. Bahalim, K. Balakrishnan, J. Balmes, S. Barker-Collo, A. Baxter, M.L. Bell, J.D. Blore, F. Blyth, C. Bonner, G. Borges, R. Bourne, M. Boussinesq, M. Brauer, P. Brooks, N.G. Bruce, B. Brunekreef, C. Bryan-Hancock, C. Bucello, R. Buchbinder, F. Bull, R.T. Burnett, T.E. Byers, B. Calabria, J. Carapetis, E. Carnahan, Z. Chafe, F. Charlson, H. Chen, J.S. Chen, A.T. Cheng, J.C. Child, A. Cohen, K.E. Colson, B.C. Cowie, S. Darby, S. Darling, A. Davis, L. Degenhardt, F. Dentener, D.C. Des

Jarlais, K. Devries, M. Dherani, E.L. Ding, E.R. Dorsey, T. Driscoll, K. Edmond, S.E. Ali, R.E. Engell, P.J. Erwin, S. Fahimi, G. Falder, F. Farzadfar, A. Ferrari, M.M. Finucane, S. Flaxman, F.G. Fowkes, G. Freedman, M.K. Freeman, E. Gakidou, S. Ghosh, E. Giovannucci, G. Gmel, K. Graham, R. Grainger, B. Grant, D. Gunnell, H.R. Gutierrez, W. Hall, H.W. Hoek, A. Hogan, H.D. Hosgood 3rd, D. Hoy, H. Hu, B.J. Hubbell, S.J. Hutchings, S.E. Ibeanusi, G.L. Jacklyn, R. Jasrasaria, J.B. Jonas, H. Kan, J.A. Kanis, N. Kassebaum, N. Kawakami, Y.H. Khang, S. Khatibzadeh, J.P. Khoo, C. Kok, F. Laden, R. Lalloo, Q. Lan, T. Lathlean, J.L. Leasher, J. Leigh, Y. Li, J.K. Lin, S.E. Lipshultz, S. London, R. Lozano, Y. Lu, J. Mak, R. Malekzadeh, L. Mallinger, W. Marcenes, L. March, R. Marks, R. Martin, P. McGale, J. McGrath, S. Mehta, G.A. Mensah, T.R. Merriman, R. Micha, C. Michaud, V. Mishra, K. Mohd Hanafiah, A.A. Mokdad, L. Morawska, D. Mozaffarian, T. Murphy, M. Naghavi, B. Neal, P.K. Nelson, J.M. Nolla, R. Norman, C. Olives, S.B. Omer, J. Orchard, R. Osborne, B. Ostro, A. Page, K.D. Pandey, C.D. Parry, E. Passmore, J. Patra, N. Pearce, P.M. Pelizzari, M. Petzold, M.R. Phillips, D. Pope, C.A. Pope 3rd, J. Powles, M. Rao, H. Razavi, E.A. Rehfuess, J.T. Rehm, B. Ritz, F.P. Rivara, T. Roberts, C. Robinson, J.A. Rodriguez-Portales, I. Romieu, R. Room, L.C. Rosenfeld, A. Roy, L. Rushton, J.A. Salomon, U. Sampson, L. Sanchez-Riera, E. Sanman, A. Sapkota, S. Seedat, P. Shi, K. Shield, R. Shivakoti, G.M. Singh, D.A. Sleet, E. Smith, K.R. Smith, N.J. Stapelberg, K. Steenland, H. Stockl, L.J. Stovner, K. Straif, L. Straney, G.D. Thurston, J.H. Tran, R. Van Dingenen, A. van Donkelaar, J.L. Veerman, L. Vijayakumar, R. Weintraub, M.M. Weissman, R.A. White, H. Whiteford, S.T. Wiersma, J.D. Wilkinson, H.C. Williams, W. Williams, N. Wilson, A.D. Woolf, P. Yip, J.M. Zielinski, A.D. Lopez, C.J. Murray, M. Ezzati, M.A. AlMazroa, Z.A. Memish, A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet 380 (2012) 2224–2260.

[2] C.J. Murray, M. Ezzati, A.D. Flaxman, S. Lim, R. Lozano, C. Michaud, M. Naghavi, J.A. Salomon, K. Shibuya, T. Vos, D. Wikler, A.D. Lopez, GBD 2010: design, definitions, and metrics, Lancet 380 (2012) 2063–2066.

[3] A. Daiber, J. Lelieveld, S. Steven, M. Oelze, S. Kroller-Schon, M. Sorensen, T. Munzel, The "exposome" concept - how environmental risk factors influence cardiovascular health, Acta Biochim. Pol. 66 (2019) 269–283.

[4] K. Sainani, Taking on the exposome - bringing bioinformatics tools to the environmental side of the health equation, Biomed. Comput. Rev. Fall 2016 (2016) 14–21.

[5] A.J. Cohen, M. Brauer, R. Burnett, H.R. Anderson, J. Frostad, K. Estep, K. Balakrishnan, B. Brunekreef, L. Dandona, R. Dandona, V. Feigin, G. Freedman, B. Hubbell, A. Jobling, H. Kan, L. Knibbs, Y. Liu, R. Martin, L. Morawska, C.A. Pope 3rd, H. Shin, K. Straif, G. Shaddick, M. Thomas, R. van Dingenen, A. van Donkelaar, T. Vos, C.J.L. Murray, M.H. Forouzanfar, Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015, Lancet 389 (2017) 1907–1918.

[6] G.B.D. DALYs, H. Collaborators, Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 388 (2016) 1603–1658.

[7] J. Lelieveld, K. Klingmuller, A. Pozzer, U. Poschl, M. Fnais, A. Daiber, T. Munzel, Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions, Eur. Heart J. 40 (2019) 1590–1596.

[8] D.E. Newby, P.M. Mannucci, G.S. Tell, A.A. Baccarelli, R.D. Brook, K. Donaldson, F. Forastiere, M. Franchini, O.H. Franco, I. Graham, G. Hoek, B. Hoffmann, M.F. Hoylaerts, N. Kunzli, N. Mills, J. Pekkanen, A. Peters, M.F. Piepoli, S. Rajagopalan, R.F. Storey, E.A.f.C.P. Esc Working Group on Thrombosis, Rehabilitation, E.S.C.H.F. Association, Expert position paper on air pollution and cardiovascular disease, Eur. Heart J. 36 (2015) 83–93b.

[9] WHO Report Diabetes, (2016) https://apps.who.int/iris/bitstream/handle/10665/204871/9789241565257_eng.pdf?sequence=1.

[10] E. Standl, O. Schnell, A new look at the heart in diabetes mellitus: from ailing to failing, Diabetologia 43 (2000) 1455–1469.

[11] T. Nakagami, Q. Qiao, J. Tuomilehto, B. Balkau, N. Tajima, G. Hu, K. Borch-Johnsen, Screen-detected diabetes, hypertension and hypercholesterolemia as predictors of cardiovascular mortality in five populations of Asian origin: the DECODA study, Eur. J. Cardiovasc. Prev. Rehabil. 13 (2006) 555–561.

[12] J.A. Vita, C.B. Treasure, E.G. Nabel, J.M. McLenachan, R.D. Fish, A.C. Yeung, V.I. Vekshtein, A.P. Selwyn, P. Ganz, Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease, Circulation 81 (1990) 491–497.

[13] J.A. Panza, A.A. Quyyumi, J.E. Brush Jr., S.E. Epstein, Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension, N. Engl. J. Med. 323 (1990) 22–27.

[14] A. Daiber, S. Steven, A. Weber, V.V. Shuvaev, V.R. Muzykantov, I. Laher, H. Li, S. Lamas, T. Munzel, Targeting vascular (endothelial) dysfunction, Br. J. Pharmacol. 174 (2017) 1591–1619.

[15] F. Perticone, R. Ceravolo, A. Pujia, G. Ventura, S. Iacopino, A. Scozzafava, A. Ferraro, M. Chello, P. Mastroroberto, P. Verdecchia, G. Schillaci, Prognostic significance of endothelial dysfunction in hypertensive patients, Circulation 104 (2001) 191–196.

[16] D.S. Celermajer, K.E. Sorensen, D. Georgakopoulos, C. Bull, O. Thomas, J. Robinson, J.E. Deanfield, Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults, Circulation 88 (1993) 2149–2155.

[17] A. Calver, J. Collier, P. Vallance, Inhibition and stimulation of nitric oxide synthesis in the human forearm arterial bed of patients with insulin-dependent diabetes, J. Clin. Invest. 90 (1992) 2548–2554.

[18] F.P. Schmidt, M. Basner, G. Kroger, S. Weck, B. Schnorbus, A. Muttray, M. Sariyar, H. Binder, T. Gori, A. Warnholtz, T. Munzel, Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults, Eur. Heart J. 34 (2013) 3508–3514a.

[19] F. Schmidt, K. Kolle, K. Kreuder, B. Schnorbus, P. Wild, M. Hechtner, H. Binder, T. Gori, T. Munzel, Nighttime aircraft noise impairs endothelial function and increases blood pressure in patients with or at high risk for coronary artery disease, Clin. Res. Cardiol. 104 (2015) 23–30.

[20] N.L. Mills, H. Tornqvist, S.D. Robinson, M. Gonzalez, K. Darnley, W. MacNee, N.A. Boon, K. Donaldson, A. Blomberg, T. Sandstrom, D.E. Newby, Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis, Circulation 112 (2005) 3930–3936.

[21] R.D. Brook, B. Urch, J.T. Dvonch, R.L. Bard, M. Speck, G. Keeler, M. Morishita, F.J. Marsik, A.S. Kamal, N. Kaciroti, J. Harkema, P. Corey, F. Silverman, D.R. Gold, G. Wellenius, M.A. Mittleman, S. Rajagopalan, J.R. Brook, Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans, Hypertension 54 (2009) 659–667.

[22] L. Ghiadoni, A.E. Donald, M. Cropley, M.J. Mullen, G. Oakley, M. Taylor, G. O'Connor, J. Betteridge, N. Klein, A. Steptoe, J.E. Deanfield, Mental stress induces transient endothelial dysfunction in humans, Circulation 102 (2000) 2473–2478.

[23] A.J. Broadley, A. Korszun, E. Abdelaal, V. Moskvina, C.J. Jones, G.B. Nash, C. Ray, J. Deanfield, M.P. Frenneaux, Inhibition of cortisol production with metyrapone prevents mental stress-induced endothelial dysfunction and baroreflex impairment, J. Am. Coll. Cardiol. 46 (2005) 344–350.

[24] R. Bergholm, M. Leirisalo-Repo, S. Vehkavaara, S. Makimattila, M.R. Taskinen, H. Yki-Jarvinen, Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis, Arterioscler. Thromb. Vasc. Biol. 22 (2002) 1637–1641.

[25] S. Hansel, G. Lassig, F. Pistrosch, J. Passauer, Endothelial dysfunction in young patients with long-term rheumatoid arthritis and low disease activity, Atherosclerosis 170 (2003) 177–180.

[26] N.N. Mehta, R.S. Azfar, D.B. Shin, A.L. Neimann, A.B. Troxel, J.M. Gelfand, Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database, Eur. Heart J. 31 (2010) 1000–1006.

[27] M.A. Gonzalez, A.P. Selwyn, Endothelial function, inflammation, and prognosis in cardiovascular disease, Am. J. Med. 115 (Suppl 8A) (2003) 99S–106S.

[28] M. Pauriah, F. Khan, T.K. Lim, D.H. Elder, V. Godfrey, G. Kennedy, J.J. Belch, N.A. Booth, A.D. Struthers, C.C. Lang, B-type natriuretic peptide is an independent predictor of endothelial function in man, Clin. Sci. (Lond.) 123 (2012) 307–312.

[29] H. Okui, S. Hamasaki, S. Ishida, T. Kataoka, K. Orihara, T. Fukudome, M. Ogawa, N. Oketani, K. Saihara, T. Shinsato, T. Shirasawa, E. Mizoguchi, T. Kubozono, H. Ichiki, Y. Ninomiya, T. Matsushita, M. Nakasaki, C. Tei, Adiponectin is a better predictor of endothelial function of the coronary artery than HOMA-R, body mass index, immunoreactive insulin, or triglycerides, Int. J. Cardiol. 126 (2008) 53–61.

[30] T. Munzel, C. Sinning, F. Post, A. Warnholtz, E. Schulz, Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction, Ann. Med. 40 (2008) 180–196.

[31] T. Heitzer, S. Ylä-Herttuala, J. Luoma, S. Kurz, T. Munzel, H. Just, M. Olschewski, H. Drexler, Cigarette smoking potentiates endothelial dysfunction of forearm resistance vessels in patients with hypercholesterolemia: role of oxidized LDL, Circulation 93 (1996) 1346–1353.

[32] S. Chlopicki, R.J. Gryglewski, Angiotensin converting enzyme (ACE) and HydroxyMethylGlutaryl-CoA (HMG-CoA) reductase inhibitors in the forefront of pharmacology of endothelium, Pharmacol. Rep. 57 (Suppl) (2005) 86–96.

[33] D.G. Della Rocca, C.J. Pepine, Endothelium as a predictor of adverse outcomes, Clin. Cardiol. 33 (2010) 730–732.

[34] M.A. Gimbrone Jr., M.I. Cybulsky, N. Kume, T. Collins, N. Resnick, Vascular endothelium. An integrator of pathophysiological stimuli in atherogenesis, Ann. N. Y. Acad. Sci. 748 (1995) 122–131 discussion 131-122.

[35] Y. Matsuzawa, A. Lerman, Endothelial dysfunction and coronary artery disease: assessment, prognosis, and treatment, Coron. Artery Dis. 25 (2014) 713–724.

[36] A.A. Quyyumi, Endothelial function in health and disease: new insights into the genesis of cardiovascular disease, Am. J. Med. 105 (1998) 32S–39S.

[37] P. Rajendran, T. Rengarajan, J. Thangavel, Y. Nishigaki, D. Sakthisekaran, G. Sethi, I. Nishigaki, The vascular endothelium and human diseases, Int. J. Biol. Sci. 9 (2013) 1057–1069.

[38] J.A. Vita, J.F. Keaney Jr., Endothelial function: a barometer for cardiovascular risk? Circulation 106 (2002) 640–642.

[39] J.P. Halcox, W.H. Schenke, G. Zalos, R. Mincemoyer, A. Prasad, M.A. Waclawiw, K.R. Nour, A.A. Quyyumi, Prognostic value of coronary vascular endothelial dysfunction, Circulation 106 (2002) 653–658.

[40] V. Schachinger, M.B. Britten, A.M. Zeiher, Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease, Circulation 101 (2000) 1899–1906.

[41] M. Shechter, A. Shechter, N. Koren-Morag, M.S. Feinberg, L. Hiersch, Usefulness of brachial artery flow-mediated dilation to predict long-term cardiovascular events in subjects without heart disease, Am. J. Cardiol. 113 (2014) 162–167.

[42] Y. Matsuzawa, R.R. Guddeti, T.G. Kwon, L.O. Lerman, A. Lerman, Secondary prevention strategy of cardiovascular disease using endothelial function testing, Circ. J. 79 (2015) 685–694.

[43] Y. Matsuzawa, T.G. Kwon, R.J. Lennon, L.O. Lerman, A. Lerman, Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis, J. Am. Heart Assoc. 4 (2015).

[44] Y. Xu, R.C. Arora, B.M. Hiebert, B. Lerner, A. Szwajcer, K. McDonald, C. Rigatto, P. Komenda, M.M. Sood, N. Tangri, Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis, Eur. Heart J. Cardiovasc. Imag. 15 (2014) 736–746.
[45] M. Reriani, J.D. Sara, A.J. Flammer, R. Gulati, J. Li, C. Rihal, R. Lennon, L.O. Lerman, A. Lerman, Coronary endothelial function testing provides superior discrimination compared with standard clinical risk scoring in prediction of cardiovascular events, Coron. Artery Dis. 27 (2016) 213–220.
[46] Y. Kitta, J.E. Obata, T. Nakamura, M. Hirano, Y. Kodama, D. Fujioka, Y. Saito, K. Kawabata, K. Sano, T. Kobayashi, T. Yano, K. Nakamura, K. Kugiyama, Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease, J. Am. Coll. Cardiol. 53 (2009) 323–330.
[47] M.G. Modena, L. Bonetti, F. Coppi, F. Bursi, R. Rossi, Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women, J. Am. Coll. Cardiol. 40 (2002) 505–510.
[48] T. Munzel, A. Daiber, Environmental stressors and their impact on health and disease with focus on oxidative stress, Antioxidants Redox Signal. 28 (2018) 735–740.
[49] S. Steven, K. Frenis, M. Oelze, S. Kalinovic, M. Kuntic, M.T. Bayo Jimenez, K. Vujacic-Mirski, J. Helmstadter, S. Kroller-Schon, T. Munzel, A. Daiber, Vascular inflammation and oxidative stress: major triggers for cardiovascular disease, Oxid. Med. Cell Longev. 2019 (2019) 7092151.
[50] P. Wenzel, S. Kossmann, T. Munzel, A. Daiber, Redox regulation of cardiovascular inflammation - immunomodulatory function of mitochondrial and Nox-derived reactive oxygen and nitrogen species, Free Radic. Biol. Med. 109 (2017) 48–60.
[51] S. Karbach, P. Wenzel, A. Waisman, T. Munzel, A. Daiber, eNOS uncoupling in cardiovascular diseases–the role of oxidative stress and inflammation, Curr. Pharmaceut. Des. 20 (2014) 3579–3594.
[52] D.G. Harrison, T.J. Guzik, H.E. Lob, M.S. Madhur, P.J. Marvar, S.R. Thabet, A. Vinh, C.M. Weyand, Inflammation, immunity, and hypertension, Hypertension 57 (2011) 132–140.
[53] S. Kaptoge, S.R. Seshasai, P. Gao, D.F. Freitag, A.S. Butterworth, A. Borglykke, E. Di Angelantonio, V. Gudnason, A. Rumley, G.D. Lowe, T. Jorgensen, J. Danesh, Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis, Eur. Heart J. 35 (2014) 578–589.
[54] P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, R.J. Glynn, C.T. Group, Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (2017) 1119–1131.
[55] M.J. Peters, D.P. Symmons, D. McCarey, B.A. Dijkmans, P. Nicola, T.K. Kvien, I.B. McInnes, H. Haentzschel, M.A. Gonzalez-Gay, S. Provan, A. Semb, P. Sidiropoulos, G. Kitas, Y.M. Smulders, M. Soubrier, Z. Szekanecz, N. Sattar, M.T. Nurmohamed, EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis, Ann. Rheum. Dis. 69 (2010) 325–331.
[56] M.A. Gonzalez-Gay, C. Gonzalez-Juanatey, M.J. Lopez-Diaz, A. Pineiro, C. Garcia-Porrua, J.A. Miranda-Filloy, W.E. Ollier, J. Martin, J. Llorca, HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis, Arthritis Rheum. 57 (2007) 125–132.
[57] A. Sodergren, K. Karp, K. Boman, C. Eriksson, E. Lundstrom, T. Smedby, L. Soderlund, S. Rantapaa-Dahlqvist, S. Wallberg-Jonsson, Atherosclerosis in early rheumatoid arthritis: very early endothelial activation and rapid progression of intima media thickness, Arthritis Res. Ther. 12 (2010) R158.
[58] D.D. Balci, A. Balci, S. Karazincir, E. Ucar, U. Iyigun, F. Yalcin, E. Seyfeli, T. Inandi, E. Egilmez, Increased carotid artery intima-media thickness and impaired endothelial function in psoriasis, J. Eur. Acad. Dermatol. Venereol. : JEADV 23 (2009) 1–6.
[59] J. Herrera, A. Ferrebuz, E.G. MacGregor, B. Rodriguez-Iturbe, Mycophenolate mofetil treatment improves hypertension in patients with psoriasis and rheumatoid arthritis, J. Am. Soc. Nephrol. : JASN (J. Am. Soc. Nephrol.) 17 (2006) S218–S225.
[60] S. Steven, T. Munzel, A. Daiber, Exploiting the pleiotropic antioxidant effects of established drugs in cardiovascular disease, Int. J. Mol. Sci. 16 (2015) 18185–18223.
[61] A. Daiber, S. Steven, A. Weber, V.V. Shuvaev, V.R. Muzykantov, I. Laher, H. Li, S. Lamas, T. Munzel, Targeting vascular (endothelial) dysfunction, Br. J. Pharmacol. (2016).
[62] A. Daiber, F. Di Lisa, M. Oelze, S. Kroller-Schon, S. Steven, E. Schulz, T. Munzel, Crosstalk of mitochondria with NADPH oxidase via reactive oxygen and nitrogen species signalling and its role for vascular function, Br. J. Pharmacol. (2015).
[63] M.I. Yilmaz, M. Saglam, K. Caglar, E. Cakir, A. Sonmez, T. Ozgurtas, A. Aydin, T. Eyileten, O. Ozcan, C. Acikel, M. Tasar, G. Genctoy, K. Erbil, A. Vural, C. Zoccali, The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine, Am. J. Kidney Dis. 47 (2006) 42–50.
[64] C. Iadecola, The pathobiology of vascular dementia, Neuron 80 (2013) 844–866.
[65] E. Maslak, A. Gregorius, S. Chlopicki, Liver sinusoidal endothelial cells (LSECs) function and NAFLD; NO-based therapy targeted to the liver, Pharmacol. Rep. 67 (2015) 689–694.
[66] B.W. Van Tassell, S. Toldo, E. Mezzaroma, A. Abbate, Targeting interleukin-1 in heart disease, Circulation 128 (2013) 1910–1923.
[67] Y. Mikhed, A. Daiber, S. Steven, Mitochondrial oxidative stress, mitochondrial DNA damage and their role in age-related vascular dysfunction, Int. J. Mol. Sci. 16 (2015) 15918–15953.
[68] V. Guarner, M.E. Rubio-Ruiz, Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease, Interdiscipl. Top Gerontol. 40 (2015) 99–106.
[69] M.D. Herrera, C. Mingorance, R. Rodriguez-Rodriguez, M. Alvarez de Sotomayor, Endothelial dysfunction and aging: an update, Ageing Res. Rev. 9 (2010) 142–152.
[70] R.T. Ras, M.T. Streppel, R. Draijer, P.L. Zock, Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis, Int. J. Cardiol. 168 (2013) 344–351.
[71] D.R. Seals, K.L. Jablonski, A.J. Donato, Aging and vascular endothelial function in humans, Clin. Sci. (Lond.) 120 (2011) 357–375.
[72] H. Tanaka, F.A. Dinenno, D.R. Seals, Age-related increase in femoral intima-media thickness in healthy humans, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 2172.
[73] E. Crimi, L.J. Ignarro, C. Napoli, Microcirculation and oxidative stress, Free Radic. Res. 41 (2007) 1364–1375.
[74] A.L. Burnett, The role of nitric oxide in erectile dysfunction: implications for medical therapy, J. Clin. Hypertens. 8 (2006) 53–62.
[75] A. Csiszar, J. Toth, J. Peti-Peterdi, Z. Ungvari, The aging kidney: role of endothelial oxidative stress and inflammation, Acta Physiol. Hung. 94 (2007) 107–115.
[76] J.M. Price, A. Hellermann, G. Hellermann, E.T. Sutton, Aging enhances vascular dysfunction induced by the Alzheimer's peptide beta-amyloid, Neurol. Res. 26 (2004) 305–311.
[77] H.R. Coleman, C.C. Chan, F.L. Ferris 3rd, E.Y. Chew, Age-related macular degeneration, Lancet 372 (2008) 1835–1845.
[78] M. El Assar, J. Angulo, L. Rodriguez-Manas, Oxidative stress and vascular inflammation in aging, Free Radic. Biol. Med. 65 (2013) 380–401.
[79] J. Majerczak, M. Grandys, M. Frolow, Z. Szkutnik, A. Zakrzewska, R. Nizankowski, K. Duda, S. Chlopicki, J.A. Zoladz, Age-dependent impairment in endothelial function and arterial stiffness in former high class male athletes is No different to that in men with No history of physical training, J. Am. Heart Assoc. 8 (2019) e012670.
[80] A. Daiber, J. Kienhoefer, R. Zee, V. Ullrich, B. Van der Loo, M. Bachschmid, The role of mitochondrial reactive oxygen species formation for age-induced vascular dysfunction, in: S.C. Bondy, K. Maiese (Eds.), Aging and Age-Related Disorders: Springer (Humana Press), 2010, pp. 237–257.
[81] M. Gerhard, M.A. Roddy, S.J. Creager, M.A. Creager, Aging progressively impairs endothelium-dependent vasodilation in forearm resistance vessels of humans, Hypertension 27 (1996) 849–853.
[82] P. Jousilahti, E. Vartiainen, J. Tuomilehto, P. Puska, Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland, Circulation 99 (1999) 1165–1172.
[83] J. de Jager, J.M. Dekker, A. Kooy, P.J. Kostense, G. Nijpels, R.J. Heine, L.M. Bouter, C.D. Stehouwer, Endothelial dysfunction and low-grade inflammation explain much of the excess cardiovascular mortality in individuals with type 2 diabetes: the Hoorn Study, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 1086–1093.
[84] Y. Wang, J. Wang, Z. Deng, J. Jin, H. Jiang, J. Meng, H. Xu, J. Zhao, G. Sun, H. Qian, Chronic osteomyelitis increases the incidence of type 2 diabetes in humans and mice, Int. J. Biol. Sci. 13 (2017) 1192–1202.
[85] X. Wang, W. Bao, J. Liu, Y.Y. Ouyang, D. Wang, S. Rong, X. Xiao, Z.L. Shan, Y. Zhang, P. Yao, L.G. Liu, Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis, Diabetes Care 36 (2013) 166–175.
[86] J.F. Keaney Jr., J. Loscalzo, Diabetes, oxidative stress, and platelet activation, Circulation 99 (1999) 189–191.
[87] B. Lipinski, Pathophysiology of oxidative stress in diabetes mellitus, J. Diabet. Complicat. 15 (2001) 203–210.
[88] K.K. Griendling, G.A. FitzGerald, Oxidative stress and cardiovascular injury: Part II: animal and human studies, Circulation 108 (2003) 2034–2040.
[89] T. Heitzer, T. Schlinzig, K. Krohn, T. Meinertz, T. Munzel, Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease, Circulation 104 (2001) 2673–2678.
[90] A.C. Bulua, A. Simon, R. Maddipati, M. Pelletier, H. Park, K.Y. Kim, M.N. Sack, D.L. Kastner, R.M. Siegel, Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS), J. Exp. Med. 208 (2011) 519–533.
[91] A.P. West, I.E. Brodsky, C. Rahner, D.K. Woo, H. Erdjument-Bromage, P. Tempst, M.C. Walsh, Y. Choi, G.S. Shadel, S. Ghosh, TLR signalling augments macrophage bactericidal activity through mitochondrial ROS, Nature 472 (2011) 476–480.
[92] R. Zhou, A.S. Yazdi, P. Menu, J. Tschopp, A role for mitochondria in NLRP3 inflammasome activation, Nature 469 (2011) 221–225.
[93] R. Zhou, A. Tardivel, B. Thorens, I. Choi, J. Tschopp, Thioredoxin-interacting protein links oxidative stress to inflammasome activation, Nat. Immunol. 11 (2010) 136–140.
[94] S. Kroller-Schon, S. Steven, S. Kossmann, A. Scholz, S. Daub, M. Oelze, N. Xia, M. Hausding, Y. Mikhed, E. Zinssius, M. Mader, P. Stamm, N. Treiber, K. Scharffetter-Kochanek, H. Li, E. Schulz, P. Wenzel, T. Munzel, A. Daiber, Molecular mechanisms of the crosstalk between mitochondria and NADPH oxidase through reactive oxygen species-studies in white blood cells and in animal models, Antioxidants Redox Signal. 20 (2014) 247–266.
[95] R.R. Nazarewicz, S.I. Dikalov, Mitochondrial ROS in the prohypertensive immune response, Am. J. Physiol. Regul. Integr. Comp. Physiol. 305 (2013) R98–R100.
[96] T.K. Howcroft, J. Campisi, G.B. Louis, M.T. Smith, B. Wise, T. Wyss-Coray, A.D. Augustine, J.E. McElhaney, R. Kohanski, F. Sierra, The role of inflammation in age-related disease, Aging (N Y) 5 (2013) 84–93.
[97] A. Blazejczyk, D. Papiernik, K. Porshneva, J. Sadowska, J. Wietrzyk, Endothelium

and cancer metastasis: perspectives for antimetastatic therapy, Pharmacol. Rep. 67 (2015) 711–718.
[98] M. Morganti, A. Carpi, A. Nicolini, I. Gorini, B. Glaviano, M. Fini, G. Giavaresi, C. Mittermayer, R. Giardino, Atherosclerosis and cancer: common pathways on the vascular endothelium, Biomed. Pharmacother. 56 (2002) 317–324.
[99] M. Guazzi, M. Gomberg-Maitland, R. Naeije, Impact of pharmacologic interventions–treating endothelial dysfunction and group 2 pulmonary hypertension, Prog. Cardiovasc. Dis. 57 (2015) 473–479.
[100] D. Neglia, C. Michelassi, M.G. Trivieri, G. Sambuceti, A. Giorgetti, L. Pratali, M. Gallopin, P. Salvadori, O. Sorace, C. Carpeggiani, R. Poddighe, A. L'Abbate, O. Parodi, Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction, Circulation 105 (2002) 186–193.
[101] L. Becker, K. Prado, M. Foppa, N. Martinelli, C. Aguiar, T. Furian, N. Clausell, L.E. Rohde, Endothelial dysfunction assessed by brachial artery ultrasound in severe sepsis and septic shock, J. Crit. Care 27 (2012) 316 e319–314.
[102] W.C. Aird, Endothelium as a therapeutic target in sepsis, Curr. Drug Targets 8 (2007) 501–507.
[103] D.S. Boeldt, I.M. Bird, Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia, J. Endocrinol. 232 (2017) R27–R44.
[104] M.R. Gillrie, M. Ho, Dynamic interactions of Plasmodium spp. with vascular endothelium, Tissue Barriers 5 (2017) e1268667.
[105] G.N. Malavige, G.S. Ogg, Pathogenesis of vascular leak in dengue virus infection, Immunology 151 (2017) 261–269.
[106] J.P. Borges, F.S.N.S. Mendes, G.O. Lopes, A.S. Sousa, M.F.F. Mediano, E. Tibirica, Is endothelial microvascular function equally impaired among patients with chronic Chagas and ischemic cardiomyopathy? Int. J. Cardiol. 265 (2018) 35–37.
[107] M. Tuma, S. Canestrini, Z. Alwahab, J. Marshall, Trauma and endothelial glycocalyx: the microcirculation helmet? Shock 46 (2016) 352–357.
[108] W.C. Aird, W.C. Aird (Ed.), Endothelial Biomedicine, Cambridge University Press, 2007.
[109] S. Chlopicki, Perspectives in pharmacology of endothelium: from bench to bedside, Pharmacol. Rep. 67 (2015) vi–ix.
[110] P.L. Ludmer, A.P. Selwyn, T.L. Shook, R.R. Wayne, G.H. Mudge, R.W. Alexander, P. Ganz, Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries, N. Engl. J. Med. 315 (1986) 1046–1051.
[111] I.B. Wilkinson, D.J. Webb, Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications, Br. J. Clin. Pharmacol. 52 (2001) 631–646.
[112] A.J. Flammer, T. Anderson, D.S. Celermajer, M.A. Creager, J. Deanfield, P. Ganz, N.M. Hamburg, T.F. Luscher, M. Shechter, S. Taddei, J.A. Vita, A. Lerman, The assessment of endothelial function: from research into clinical practice, Circulation 126 (2012) 753–767.
[113] M. Frolow, A. Drozdz, A. Kowalewska, R. Nizankowski, S. Chlopicki, Comprehensive assessment of vascular health in patients; towards endothelium-guided therapy, Pharmacol. Rep. 67 (2015) 786–792.
[114] O.T. Raitakari, D.S. Celermajer, Flow-mediated dilatation, Br. J. Clin. Pharmacol. 50 (2000) 397–404.
[115] D.H.J. Thijssen, R.M. Bruno, A.C.C.M. van Mil, S.M. Holder, F. Faita, A. Greyling, P.L. Zock, S. Taddei, J.E. Deanfield, T. Luscher, D.J. Green, L. Ghiadoni, Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans, Eur. Heart J. 40 (2019) 2534–2547.
[116] C.P. Leeson, M. Robinson, J.M. Francis, M.D. Robson, K.M. Channon, S. Neubauer, F. Wiesmann, Cardiovascular magnetic resonance imaging for non-invasive assessment of vascular function: validation against ultrasound, J. Cardiovasc. Magn. Reson. 8 (2006) 381–387.
[117] L.C. Engel, U. Landmesser, A. Goehler, K. Gigengack, T.H. Wurster, C. Manes, G. Girke, M. Jaguszewski, C. Skurk, D.M. Leistner, A. Lauten, A. Schuster, M. Noutsias, B. Hamm, R.M. Botnar, B. Bigalke, M.R. Makowski, Noninvasive imaging of endothelial damage in patients with different HbA1c levels: a proof-of-concept study, Diabetes 68 (2019) 387–394.
[118] A. Bar, K. Kus, A. Manterys, B. Proniewski, M. Sternak, K. Przyborowski, M. Moorlag, B. Sitek, B. Marczyk, A. Jasztal, T. Skorka, M. Franczyk-Zarow, R. Kostogrys, S. Chlopicki, Vitamin K2-MK-7 improves nitric oxide-dependent endothelial function in ApoE/LDLR(-/-) mice, Vascul. Pharmacol. (2019) 106581.
[119] A. Bar, M. Olkowicz, U. Tyrankiewicz, E. Kus, K. Jasinski, R.T. Smolenski, T. Skorka, S. Chlopicki, Functional and biochemical endothelial profiling in vivo in a murine model of endothelial dysfunction; comparison of effects of 1-methylnicotinamide and angiotensin-converting enzyme inhibitor, Front. Pharmacol. 8 (2017) 183.
[120] A. Bar, T. Skorka, K. Jasinski, S. Chlopicki, MRI-based assessment of endothelial function in mice in vivo, Pharmacol. Rep. 67 (2015) 765–770.
[121] A. Bar, T. Skorka, K. Jasinski, M. Sternak, Z. Bartel, U. Tyrankiewicz, S. Chlopicki, Retrospectively gated MRI for in vivo assessment of endothelium-dependent vasodilatation and endothelial permeability in murine models of endothelial dysfunction, NMR Biomed. 29 (2016) 1088–1097.
[122] A. Bar, M. Targosz-Korecka, J. Suraj, B. Proniewski, A. Jasztal, B. Marczyk, M. Sternak, M. Przybylo, A. Kurpinska, M. Walczak, R.B. Kostogrys, M. Szymonski, S. Chlopicki, Degradation of glycocalyx and multiple manifestations of endothelial dysfunction coincide in the early phase of endothelial dysfunction before atherosclerotic plaque development in apolipoprotein E/Low-Density lipoprotein receptor-deficient mice, J. Am. Heart Assoc. 8 (2019) e011171.
[123] A. Phinikaridou, M.E. Andia, A. Protti, A. Indermuehle, A. Shah, A. Smith, A. Warley, R.M. Botnar, Noninvasive magnetic resonance imaging evaluation of endothelial permeability in murine atherosclerosis using an albumin-binding contrast agent, Circulation 126 (2012) 707–719.
[124] M.E. Hall, A. Hamid, A.A. Oshunbade, The eyes, Circ. Res. 124 (2019) 1692–1694.
[125] R. Gunthner, H. Hanssen, C. Hauser, S. Angermann, G. Lorenz, S. Kemmner, J. Matschkal, M.C. Braunisch, C. Kuechle, L. Renders, P. Moog, S. Wassertheurer, M. Baumann, H.P. Hammes, C.C. Mayer, B. Haller, S. Stryeck, T. Madl, J. Carbajo-Lozoya, U. Heemann, K. Kotliar, C. Schmaderer, Impaired retinal vessel dilation predicts mortality in end-stage renal disease, Circ. Res. (2019).
[126] R. Heitmar, G.Y.H. Lip, R.E. Ryder, A.D. Blann, Retinal vessel diameters and reactivity in diabetes mellitus and/or cardiovascular disease, Cardiovasc. Diabetol. 16 (2017) 56.
[127] B.M. Sorensen, A.J. Houben, T.T. Berendschot, J.S. Schouten, A.A. Kroon, C.J. van der Kallen, R.M. Henry, A. Koster, S.J. Sep, P.C. Dagnelie, N.C. Schaper, M.T. Schram, C.D. Stehouwer, Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: the maastricht study, Circulation 134 (2016) 1339–1352.
[128] M. Ritt, J.M. Harazny, C. Ott, U. Raff, P. Bauernschubert, M. Lehmann, G. Michelson, R.E. Schmieder, Impaired increase of retinal capillary blood flow to flicker light exposure in arterial hypertension, Hypertension 60 (2012) 871–876.
[129] J. Barthelmes, M.P. Nagele, S. Cantatore, E. Novruzov, V. Ludovici, E.A. von, M. Frank, F. Ruschitzka, I. Sudano, A.J. Flammer, Retinal microvascular dysfunction in patients with coronary artery disease with and without heart failure: a continuum? Eur. J. Heart Fail. 21 (2019) 988–997.
[130] M.M. Garcia, P.R. Lima, L.C. Correia, Prognostic value of endothelial function in patients with atherosclerosis: systematic review, Arq. Bras. Cardiol. 99 (2012) 857–865.
[131] R.B. Schnabel, P.S. Wild, A. Schulz, T. Zeller, C.R. Sinning, S. Wilde, J. Kunde, E. Lubos, K.J. Lackner, A. Warnholtz, T. Gori, S. Blankenberg, T. Munzel, I. Gutenberg Health Study, Multiple endothelial biomarkers and noninvasive vascular function in the general population: the Gutenberg Health Study, Hypertension 60 (2012) 288–295.
[132] A. Suessenbacher, J. Dorler, J. Wunder, F. Hohenwarter, H.F. Alber, O. Pachinger, M. Frick, Comparison of brachial artery wall thickness versus endothelial function to predict late cardiovascular events in patients undergoing elective coronary angiography, Am. J. Cardiol. 111 (2013) 671–675.
[133] W.P. Roos, B. Kaina, DNA damage-induced cell death: from specific DNA lesions to the DNA damage response and apoptosis, Canc. Lett. 332 (2013) 237–248.
[134] R.B. Schnabel, A. Schulz, P.S. Wild, C.R. Sinning, S. Wilde, M. Eleftheriadis, S. Herkenhoff, T. Zeller, E. Lubos, K.J. Lackner, A. Warnholtz, T. Gori, S. Blankenberg, T. Munzel, Noninvasive vascular function measurement in the community: cross-sectional relations and comparison of methods, Circ. Cardiovasc. Imag. 4 (2011) 371–380.
[135] G.F. Mitchell, Arterial stiffness: insights from Framingham and Iceland, Curr. Opin. Nephrol. Hypertens. 24 (2015) 1–7.
[136] S. Ashfaq, J.L. Abramson, D.P. Jones, S.D. Rhodes, W.S. Weintraub, W.C. Hooper, V. Vaccarino, D.G. Harrison, A.A. Quyyumi, The relationship between plasma levels of oxidized and reduced thiols and early atherosclerosis in healthy adults, J. Am. Coll. Cardiol. 47 (2006) 1005–1011.
[137] J. Egea, I. Fabregat, Y.M. Frapart, P. Ghezzi, A. Gorlach, T. Kietzmann, K. Kubaichuk, U.G. Knaus, M.G. Lopez, G. Olaso-Gonzalez, A. Petry, R. Schulz, J. Vina, P. Winyard, K. Abbas, O.S. Ademowo, C.B. Afonso, I. Andreadou, H. Antelmann, F. Antunes, M. Aslan, M.M. Bachschmid, R.M. Barbosa, V. Belousov, C. Berndt, D. Bernlohr, E. Bertran, A. Bindoli, S.P. Bottari, P.M. Brito, G. Carrara, A.I. Casas, A. Chatzi, N. Chondrogianni, M. Conrad, M.S. Cooke, J.G. Costa, A. Cuadrado, P. My-Chan Dang, B. De Smet, B. Debelec-Butuner, I.H.K. Dias, J.D. Dunn, A.J. Edson, M. El Assar, J. El-Benna, P. Ferdinandy, A.S. Fernandes, K.E. Fladmark, U. Forstermann, R. Giniatullin, Z. Giricz, A. Gorbe, H. Griffiths, V. Hampl, A. Hanf, J. Herget, P. Hernansanz-Agustin, M. Hillion, J. Huang, S. Ilikay, P. Jansen-Durr, V. Jaquet, J.A. Joles, B. Kalyanaraman, D. Kaminskyy, M. Karbaschi, M. Kleanthous, L.O. Klotz, B. Korac, K.S. Korkmaz, R. Koziel, D. Kracun, K.H. Krause, V. Kren, T. Krieg, J. Laranjinha, A. Lazou, H. Li, A. Martinez-Ruiz, R. Matsui, G.J. McBean, S.P. Meredith, J. Messens, V. Miguel, Y. Mikhed, I. Milisav, L. Milkovic, A. Miranda-Vizuete, M. Mojovic, M. Monsalve, P.A. Mouthuy, J. Mulvey, T. Munzel, V. Muzykantov, I.T.N. Nguyen, M. Oelze, N.G. Oliveira, C.M. Palmeira, N. Papaevgeniou, A. Pavicevic, B. Pedre, F. Peyrot, M. Phylactides, G.G. Pircalabioru, A.R. Pitt, H.E. Poulsen, I. Prieto, M.P. Rigobello, N. Robledinos-Anton, L. Rodriguez-Manas, A.P. Rolo, F. Rousset, T. Ruskovska, N. Saraiva, S. Sasson, K. Schroder, K. Semen, T. Seredenina, A. Shakirzyanova, G.L. Smith, T. Soldati, B.C. Sousa, C.M. Spickett, A. Stancic, M.J. Stasia, H. Steinbrenner, V. Stepanic, S. Steven, K. Tokatlidis, E. Tuncay, B. Turan, F. Ursini, J. Vacek, O. Vajnerova, K. Valentova, F. Van Breusegem, L. Varisli, E.A. Veal, A.S. Yalcin, O. Yelisyeyeva, N. Zarkovic, M. Zatloukalova, J. Zielonka, R.M. Touyz, A. Papapetropoulos, T. Grune, S. Lamas, H. Schmidt, F. Di Lisa, A. Daiber, European contribution to the study of ROS: a summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS), Redox Biol. 13 (2017) 94–162.
[138] K.K. Griendling, G.A. FitzGerald, Oxidative stress and cardiovascular injury: Part I: basic mechanisms and in vivo monitoring of ROS, Circulation 108 (2003) 1912–1916.
[139] H. Sies, Oxidative stress: a concept in redox biology and medicine, Redox Biol. 4 (2015) 180–183.
[140] S.G. Rhee, Redox signaling: hydrogen peroxide as intracellular messenger, Exp. Mol. Med. 31 (1999) 53–59.
[141] J.S. Stamler, Redox signaling: nitrosylation and related target interactions of nitric oxide, Cell 78 (1994) 931–936.
[142] V. Ullrich, R. Kissner, Redox signaling: bioinorganic chemistry at its best, J. Inorg. Biochem. 100 (2006) 2079–2086.
[143] M.W. Radomski, R.M. Palmer, S. Moncada, An L-arginine/nitric oxide pathway present in human platelets regulates aggregation, Proc. Natl. Acad. Sci. U. S. A. 87

(1990) 5193–5197.
[144] R.F. Furchgott, J.V. Zawadzki, The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine, Nature 288 (1980) 373–376.
[145] E. Schulz, P. Wenzel, T. Munzel, A. Daiber, Mitochondrial redox signaling: interaction of mitochondrial reactive oxygen species with other sources of oxidative stress, Antioxidants Redox Signal. 20 (2014) 308–324.
[146] R.J. Gryglewski, R.M. Palmer, S. Moncada, Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor, Nature 320 (1986) 454–456.
[147] J.M. McCord, B.B. Keele Jr., I. Fridovich, An enzyme-based theory of obligate anaerobiosis: the physiological function of superoxide dismutase, Proc. Natl. Acad. Sci. U. S. A. 68 (1971) 1024–1027.
[148] Y. Ohara, T.E. Peterson, D.G. Harrison, Hypercholesterolemia increases endothelial superoxide anion production, J. Clin. Invest. 91 (1993) 2546–2551.
[149] D.G. Harrison, Y. Ohara, Physiologic consequences of increased vascular oxidant stresses in hypercholesterolemia and atherosclerosis: implications for impaired vasomotion, Am. J. Cardiol. 75 (1995) 75B–81B.
[150] C. Doerries, K. Grote, D. Hilfiker-Kleiner, M. Luchtefeld, A. Schaefer, S.M. Holland, S. Sorrentino, C. Manes, B. Schieffer, H. Drexler, U. Landmesser, Critical role of the NAD(P)H oxidase subunit p47phox for left ventricular remodeling/dysfunction and survival after myocardial infarction, Circ. Res. 100 (2007) 894–903.
[151] U. Landmesser, H. Cai, S. Dikalov, L. McCann, J. Hwang, H. Jo, S.M. Holland, D.G. Harrison, Role of p47(phox) in vascular oxidative stress and hypertension caused by angiotensin II, Hypertension 40 (2002) 511–515.
[152] K. Matsuno, H. Yamada, K. Iwata, D. Jin, M. Katsuyama, M. Matsuki, S. Takai, K. Yamanishi, M. Miyazaki, H. Matsubara, C. Yabe-Nishimura, Nox1 is involved in angiotensin II-mediated hypertension: a study in Nox1-deficient mice, Circulation 112 (2005) 2677–2685.
[153] A. Dikalova, R. Clempus, B. Lassegue, G. Cheng, J. McCoy, S. Dikalov, A. San Martin, A. Lyle, D.S. Weber, D. Weiss, W.R. Taylor, H.H. Schmidt, G.K. Owens, J.D. Lambeth, K.K. Griendling, Nox1 overexpression potentiates angiotensin II-induced hypertension and vascular smooth muscle hypertrophy in transgenic mice, Circulation 112 (2005) 2668–2676.
[154] P. Wenzel, S. Schuhmacher, J. Kienhofer, J. Muller, M. Hortmann, M. Oelze, E. Schulz, N. Treiber, T. Kawamoto, K. Scharffetter-Kochanek, T. Munzel, A. Burkle, M.M. Bachschmid, A. Daiber, Manganese superoxide dismutase and aldehyde dehydrogenase deficiency increase mitochondrial oxidative stress and aggravate age-dependent vascular dysfunction, Cardiovasc. Res. 80 (2008) 280–289.
[155] A. Daiber, M. Oelze, S. Sulyok, M. Coldewey, E. Schulz, N. Treiber, U. Hink, A. Mulsch, K. Scharffetter-Kochanek, T. Munzel, Heterozygous deficiency of manganese superoxide dismutase in mice (Mn-SOD+/-): a novel approach to assess the role of oxidative stress for the development of nitrate tolerance, Mol. Pharmacol. 68 (2005) 579–588.
[156] M. Torzewski, V. Ochsenhirt, A.L. Kleschyov, M. Oelze, A. Daiber, H. Li, H. Rossmann, S. Tsimikas, K. Reifenberg, F. Cheng, H.A. Lehr, S. Blankenberg, U. Forstermann, T. Munzel, K.J. Lackner, Deficiency of glutathione peroxidase-1 accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice, Arterioscler. Thromb. Vasc. Biol. 27 (2007) 850–857.
[157] R. Ray, C.E. Murdoch, M. Wang, C.X. Santos, M. Zhang, S. Alom-Ruiz, N. Anilkumar, A. Ouattara, A.C. Cave, S.J. Walker, D.J. Grieve, R.L. Charles, P. Eaton, A.C. Brewer, A.M. Shah, Endothelial Nox4 NADPH oxidase enhances vasodilatation and reduces blood pressure in vivo, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 1368–1376.
[158] C. Schurmann, F. Rezende, C. Kruse, Y. Yasar, O. Lowe, C. Fork, B. van de Sluis, R. Bremer, N. Weissmann, A.M. Shah, H. Jo, R.P. Brandes, K. Schroder, The NADPH oxidase Nox4 has anti-atherosclerotic functions, Eur. Heart J. 36 (2015) 3447–3456.
[159] K. Schroder, M. Zhang, S. Benkhoff, A. Mieth, R. Pliquett, J. Kosowski, C. Kruse, P. Luedike, U.R. Michaelis, N. Weissmann, S. Dimmeler, A.M. Shah, R.P. Brandes, Nox4 is a protective reactive oxygen species generating vascular NADPH oxidase, Circ. Res. 110 (2012) 1217–1225.
[160] F.J. Sanchez-Gomez, E. Calvo, R. Breton-Romero, M. Fierro-Fernandez, N. Anilkumar, A.M. Shah, K. Schroder, R.P. Brandes, J. Vazquez, S. Lamas, NOX4-dependent Hydrogen peroxide promotes shear stress-induced SHP2 sulfenylation and eNOS activation, Free Radic. Biol. Med. 89 (2015) 419–430.
[161] S.P. Gray, E. Di Marco, K. Kennedy, P. Chew, J. Okabe, A. El-Osta, A.C. Calkin, E.A. Biessen, R.M. Touyz, M.E. Cooper, H.H. Schmidt, K.A. Jandeleit-Dahm, Reactive oxygen species can provide atheroprotection via NOX4-dependent inhibition of inflammation and vascular remodeling, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 295–307.
[162] K.A. Radermacher, K. Wingler, F. Langhauser, S. Altenhofer, P. Kleikers, J.J. Hermans, M. Hrabe de Angelis, C. Kleinschnitz, H.H. Schmidt, Neuroprotection after stroke by targeting NOX4 as a source of oxidative stress, Antioxidants Redox Signal. 18 (2013) 1418–1427.
[163] A.I. Casas, E. Geuss, P.W.M. Kleikers, S. Mencl, A.M. Herrmann, I. Buendia, J. Egea, S.G. Meuth, M.G. Lopez, C. Kleinschnitz, H. Schmidt, NOX4-dependent neuronal autotoxicity and BBB breakdown explain the superior sensitivity of the brain to ischemic damage, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 12315–12320.
[164] P.W. Kleikers, V.T. Dao, E. Gob, C. Hooijmans, J. Debets, H. van Essen, C. Kleinschnitz, H.H. Schmidt, SFRR-E Young Investigator AwardeeNOXing out stroke: identification of NOX4 and 5as targets in blood-brain-barrier stabilisation and neuroprotection, Free Radic. Biol. Med. 75 (Suppl 1) (2014) S16.
[165] H.H. Schmidt, R. Stocker, C. Vollbracht, G. Paulsen, D. Riley, A. Daiber, A. Cuadrado, Antioxidants in translational medicine, Antioxidants Redox Signal. 23 (2015) 1130–1143.
[166] H. Sies, C. Berndt, D.P. Jones, Oxidative stress, Annu. Rev. Biochem. 86 (2017) 715–748.
[167] A.L. Levonen, B.G. Hill, E. Kansanen, J. Zhang, V.M. Darley-Usmar, Redox regulation of antioxidants, autophagy, and the response to stress: implications for electrophile therapeutics, Free Radic. Biol. Med. 71 (2014) 196–207.
[168] H.J. Forman, K.J. Davies, F. Ursini, How do nutritional antioxidants really work: nucleophilic tone and para-hormesis versus free radical scavenging in vivo, Free Radic. Biol. Med. 66 (2014) 24–35.
[169] H. Li, S. Horke, U. Forstermann, Oxidative stress in vascular disease and its pharmacological prevention, Trends Pharmacol. Sci. 34 (2013) 313–319.
[170] A. Fratta Pasini, A. Albiero, C. Stranieri, M. Cominacini, A. Pasini, C. Mozzini, P. Vallerio, L. Cominacini, U. Garbin, Serum oxidative stress-induced repression of Nrf2 and GSH depletion: a mechanism potentially involved in endothelial dysfunction of young smokers, PloS One 7 (2012) e30291.
[171] B. Jurado-Gamez, M.C. Fernandez-Marin, J.L. Gomez-Chaparro, L. Munoz-Cabrera, J. Lopez-Barea, F. Perez-Jimenez, J. Lopez-Miranda, Relationship of oxidative stress and endothelial dysfunction in sleep apnoea, Eur. Respir. J. 37 (2011) 873–879.
[172] S. Blankenberg, H.J. Rupprecht, C. Bickel, M. Torzewski, G. Hafner, L. Tiret, M. Smieja, F. Cambien, J. Meyer, K.J. Lackner, Glutathione peroxidase 1 activity and cardiovascular events in patients with coronary artery disease, N. Engl. J. Med. 349 (2003) 1605–1613.
[173] B. Schottker, H. Brenner, E.H. Jansen, J. Gardiner, A. Peasey, R. Kubinova, A. Pajak, R. Topor-Madry, A. Tamosiunas, K.U. Saum, B. Holleczek, H. Pikhart, M. Bobak, Evidence for the free radical/oxidative stress theory of ageing from the CHANCES consortium: a meta-analysis of individual participant data, BMC Med. 13 (2015) 300.
[174] J. Frijhoff, P.G. Winyard, N. Zarkovic, S.S. Davies, R. Stocker, D. Cheng, A.R. Knight, E.L. Taylor, J. Oettrich, T. Ruskovska, A.C. Gasparovic, A. Cuadrado, D. Weber, H.E. Poulsen, T. Grune, H.H. Schmidt, P. Ghezzi, Clinical relevance of biomarkers of oxidative stress, Antioxidants Redox Signal. 23 (2015) 1144–1170.
[175] M. Bredemeier, L.M. Lopes, M.A. Eisenreich, S. Hickmann, G.K. Bongiorno, R. d'Avila, A.L.B. Morsch, F. da Silva Stein, G.G.D. Campos, Xanthine oxidase inhibitors for prevention of cardiovascular events: a systematic review and meta-analysis of randomized controlled trials, BMC Cardiovasc. Disord. 18 (2018) 24.
[176] D. Ziegler, H. Nowak, P. Kempler, P. Vargha, P.A. Low, Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis, Diabet. Med. 21 (2004) 114–121.
[177] K.T. Khaw, S. Bingham, A. Welch, R. Luben, N. Wareham, S. Oakes, N. Day, Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. European Prospective Investigation into Cancer and Nutrition, Lancet 357 (2001) 657–663.
[178] D.G.H. Silva, E. Belini Junior, E.A. de Almeida, C.R. Bonini-Domingos, Oxidative stress in sickle cell disease: an overview of erythrocyte redox metabolism and current antioxidant therapeutic strategies, Free Radic. Biol. Med. 65 (2013) 1101–1109.
[179] S. Voskou, M. Aslan, P. Fanis, M. Phylactides, M. Kleanthous, Oxidative stress in beta-thalassaemia and sickle cell disease, Redox Biol. 6 (2015) 226–239.
[180] G. Bjelakovic, D. Nikolova, L.L. Gluud, R.G. Simonetti, C. Gluud, Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis, Jama 297 (2007) 842–857.
[181] T. Munzel, T. Gori, R.M. Bruno, S. Taddei, Is oxidative stress a therapeutic target in cardiovascular disease? Eur. Heart J. 31 (2010) 2741–2748.
[182] A. Shuaib, K.R. Lees, P. Lyden, J. Grotta, A. Davalos, S.M. Davis, H.C. Diener, T. Ashwood, W.W. Wasiewski, U. Emeribe, S.I.T. Investigators, NXY-059 for the treatment of acute ischemic stroke, N. Engl. J. Med. 357 (2007) 562–571.
[183] A. Daiber, M. Oelze, S. Daub, S. Steven, A. Schuff, S. Kroller-Schon, M. Hausding, P. Wenzel, E. Schulz, T. Gori, T. Munzel, Vascular redox signaling, redox switches in endothelial nitric oxide synthase and endothelial dysfunction, in: I. Laher (Ed.), Systems Biology of Free Radicals and Antioxidants, Springer-Verlag, Berlin Heidelberg, 2014, pp. 1177–1211.
[184] D.B. Zorov, M. Juhaszova, S.J. Sollott, Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release, Physiol. Rev. 94 (2014) 909–950.
[185] A. Daiber, Redox signaling (cross-talk) from and to mitochondria involves mitochondrial pores and reactive oxygen species, Biochim. Biophys. Acta 1797 (2010) 897–906.
[186] A. Daiber, N. Xia, S. Steven, M. Oelze, A. Hanf, S. Kroller-Schon, T. Munzel, H. Li, New therapeutic implications of endothelial nitric oxide synthase (eNOS) function/dysfunction in cardiovascular disease, Int. J. Mol. Sci. 20 (2019) 187.
[187] P.A. Crassous, S. Couloubaly, C. Huang, Z. Zhou, P. Baskaran, D.D. Kim, A. Papapetropoulos, X. Fioramonti, W.N. Duran, A. Beuve, Soluble guanylyl cyclase is a target of angiotensin II-induced nitrosative stress in a hypertensive rat model, Am. J. Physiol. Heart Circ. Physiol. 303 (2012) H597–H604.
[188] B.A. Maron, Y.Y. Zhang, D.E. Handy, A. Beuve, S.S. Tang, J. Loscalzo, J.A. Leopold, Aldosterone increases oxidant stress to impair guanylyl cyclase activity by cysteinyl thiol oxidation in vascular smooth muscle cells, J. Biol. Chem. 284 (2009) 7665–7672.
[189] A. Daiber, F. Di Lisa, M. Oelze, S. Kroller-Schon, S. Steven, E. Schulz, T. Munzel, Crosstalk of mitochondria with NADPH oxidase via reactive oxygen and nitrogen species signalling and its role for vascular function, Br. J. Pharmacol. 174 (2017) 1670–1689.
[190] T. Munzel, A. Daiber, T. Gori, Nitrate therapy: new aspects concerning molecular action and tolerance, Circulation 123 (2011) 2132–2144.
[191] T. Munzel, A. Daiber, V. Ullrich, A. Mulsch, Vascular consequences of endothelial nitric oxide synthase uncoupling for the activity and expression of the soluble guanylyl cyclase and the cGMP-dependent protein kinase, Arterioscler. Thromb.

Vasc. Biol. 25 (2005) 1551–1557.
[192] J.R. Burgoyne, O. Rudyk, H.J. Cho, O. Prysyazhna, N. Hathaway, A. Weeks, R. Evans, T. Ng, K. Schroder, R.P. Brandes, A.M. Shah, P. Eaton, Deficient angiogenesis in redox-dead Cys17Ser PKARIalpha knock-in mice, Nat. Commun. 6 (2015) 7920.
[193] K.C. Das, V. Kundumani-Sridharan, J. Subramani, Role of thioredoxin in age-related hypertension, Curr. Hypertens. Rep. 20 (2018) 6.
[194] C.H. Byon, J.M. Heath, Y. Chen, Redox signaling in cardiovascular pathophysiology: a focus on hydrogen peroxide and vascular smooth muscle cells, Redox Biol. 9 (2016) 244–253.
[195] J.S. Shao, Z.A. Aly, C.F. Lai, S.L. Cheng, J. Cai, E. Huang, A. Behrmann, D.A. Towler, Vascular Bmp Msx2 Wnt signaling and oxidative stress in arterial calcification, Ann. N. Y. Acad. Sci. 1117 (2007) 40–50.
[196] X. Zhang, D. Sun, J.W. Song, J. Zullo, M. Lipphardt, L. Coneh-Gould, M.S. Goligorsky, Endothelial cell dysfunction and glycocalyx - a vicious circle, Matrix Biol. 71–72 (2018) 421–431.
[197] E.E. Ebong, S.V. Lopez-Quintero, V. Rizzo, D.C. Spray, J.M. Tarbell, Shear-induced endothelial NOS activation and remodeling via heparan sulfate, glypican-1, and syndecan-1, Integr. Biol. (Camb.) 6 (2014) 338–347.
[198] J. Fels, K. Kusche-Vihrog, Endothelial nanomechanics in the context of endothelial (Dys)function and inflammation, Antioxidants Redox Signal. 30 (2019) 945–959.
[199] F.E. Curry, R.H. Adamson, Endothelial glycocalyx: permeability barrier and mechanosensor, Ann. Biomed. Eng. 40 (2012) 828–839.
[200] P.L. Voyvodic, D. Min, R. Liu, E. Williams, V. Chitalia, A.K. Dunn, A.B. Baker, Loss of syndecan-1 induces a pro-inflammatory phenotype in endothelial cells with a dysregulated response to atheroprotective flow, J. Biol. Chem. 289 (2014) 9547–9559.
[201] M.I. Noble, A.J. Drake-Holland, H. Vink, Hypothesis: arterial glycocalyx dysfunction is the first step in the atherothrombotic process, QJM 101 (2008) 513–518.
[202] S. Dogne, B. Flamion, N. Caron, Endothelial glycocalyx as a shield against diabetic vascular complications: involvement of hyaluronan and hyaluronidases, Arterioscler. Thromb. Vasc. Biol. 38 (2018) 1427–1439.
[203] N. Nagy, T. Freudenberger, A. Melchior-Becker, K. Rock, B.M. Ter, H. Jastrow, M. Kinzig, S. Lucke, T. Suvorava, G. Kojda, A.A. Weber, F. Sorgel, B. Levkau, S. Ergun, J.W. Fischer, Inhibition of hyaluronan synthesis accelerates murine atherosclerosis: novel insights into the role of hyaluronan synthesis, Circulation 122 (2010) 2313–2322.
[204] M. Grandoch, C. Kohlmorgen, A. Melchior-Becker, K. Feldmann, S. Homann, J. Muller, L.S. Kiene, J. Zeng-Brouwers, F. Schmitz, N. Nagy, A. Polzin, N.S. Gowert, M. Elvers, P. Skroblin, X. Yin, M. Mayr, L. Schaefer, L.R. Tannock, J.W. Fischer, Loss of biglycan enhances thrombin generation in apolipoprotein E-deficient mice: implications for inflammation and atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 36 (2016) e41–e50.
[205] C.C. Drost, A. Rovas, K. Kusche-Vihrog, S.P. Van, H. Kim, V.C. Hoang, J.T. Maynes, D.O. Wennmann, H. Pavenstadt, W. Linke, A. Lukasz, B. Hesse, P. Kumpers, Tie2 Activation Promotes Protection and Reconstitution of the Endothelial Glycocalyx in Human Sepsis, Thromb. Haemost, 2019.
[206] A. Lukasz, C. Hillgruber, H. Oberleithner, K. Kusche-Vihrog, H. Pavenstadt, A. Rovas, B. Hesse, T. Goerge, P. Kumpers, Endothelial glycocalyx breakdown is mediated by angiopoietin-2, Cardiovasc. Res. 113 (2017) 671–680.
[207] S.M. Davidson, P. Ferdinandy, I. Andreadou, H.E. Botker, G. Heusch, B. Ibanez, M. Ovize, R. Schulz, D.M. Yellon, D.J. Hausenloy, D. Garcia-Dorado, Multitarget strategies to reduce myocardial ischemia/reperfusion injury: JACC review topic of the week, J. Am. Coll. Cardiol. 73 (2019) 89–99.
[208] B. Pitt, C.T. Stier Jr., S. Rajagopalan, Mineralocorticoid receptor blockade: new insights into the mechanism of action in patients with cardiovascular disease, J. Renin-Angiotensin-Aldosterone Syst. JRAAS 4 (2003) 164–168.
[209] P.S. Mehler, J.R. Coll, R. Estacio, A. Esler, R.W. Schrier, W.R. Hiatt, Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes, Circulation 107 (2003) 753–756.
[210] U. Kintscher, P. Bramlage, W.D. Paar, M. Thoenes, T. Unger, Irbesartan for the treatment of hypertension in patients with the metabolic syndrome: a sub analysis of the Treat to Target post authorization survey. Prospective observational, two armed study in 14,200 patients, Cardiovasc. Diabetol. 6 (12) (2007).
[211] H.H. Parving, B.M. Brenner, J.J. McMurray, D. de Zeeuw, S.M. Haffner, S.D. Solomon, N. Chaturvedi, M. Ghadanfar, N. Weissbach, Z. Xiang, J. Armbrecht, M.A. Pfeffer, Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design, Nephrol. Dial. Transplant. 24 (2009) 1663–1671.
[212] K.K. Koh, S. Lim, H. Choi, Y. Lee, S.H. Han, K. Lee, P.C. Oh, I. Sakuma, E.K. Shin, M.J. Quon, Combination pravastatin and valsartan treatment has additive beneficial effects to simultaneously improve both metabolic and cardiovascular phenotypes beyond that of monotherapy with either drug in patients with primary hypercholesterolemia, Diabetes 62 (2013) 3547–3552.
[213] T. Munzel, T. Gori, J.F. Keaney Jr., C. Maack, A. Daiber, Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications, Eur. Heart J. 36 (2015) 2555–2564.
[214] T.N. Patel, M.H. Shishehbor, D.L. Bhatt, A review of high-dose statin therapy: targeting cholesterol and inflammation in atherosclerosis, Eur. Heart J. 28 (2007) 664–672.
[215] T.L. Goodfriend, M.E. Elliott, K.J. Catt, Angiotensin receptors and their antagonists, N. Engl. J. Med. 334 (1996) 1649–1654.
[216] B. Hornig, U. Landmesser, C. Kohler, D. Ahlersmann, S. Spiekermann, A. Christoph, H. Tatge, H. Drexler, Comparative effect of ace inhibition and angiotensin II type 1 receptor antagonism on bioavailability of nitric oxide in patients with coronary artery disease: role of superoxide dismutase, Circulation 103 (2001) 799–805.
[217] B. Hibbert, T. Simard, F.D. Ramirez, A. Pourdjabbar, J.E. Raizman, R. Maze, K.R. Wilson, S. Hawken, E.R. O'Brien, The effect of statins on circulating endothelial progenitor cells in humans: a systematic review, J. Cardiovasc. Pharmacol. 62 (2013) 491–496.
[218] A. Cuadrado, G. Manda, A. Hassan, M.J. Alcaraz, C. Barbas, A. Daiber, P. Ghezzi, R. Leon, M.G. Lopez, B. Oliva, M. Pajares, A.I. Rojo, N. Robledinos-Anton, A.M. Valverde, E. Guney, H. Schmidt, Transcription factor NRF2 as a therapeutic target for chronic diseases: a systems medicine approach, Pharmacol. Rev. 70 (2018) 348–383.
[219] T. Pulido, I. Adzerikho, R.N. Channick, M. Delcroix, N. Galie, H.A. Ghofrani, P. Jansa, Z.C. Jing, F.O. Le Brun, S. Mehta, C.M. Mittelholzer, L. Perchenet, B.K. Sastry, O. Sitbon, R. Souza, A. Torbicki, X. Zeng, L.J. Rubin, G. Simonneau, S. Investigators, Macitentan and morbidity and mortality in pulmonary arterial hypertension, N. Engl. J. Med. 369 (2013) 809–818.
[220] M. Oelze, M. Knorr, S. Kroller-Schon, S. Kossmann, A. Gottschlich, R. Rummler, A. Schuff, S. Daub, C. Doppler, H. Kleinert, T. Gori, A. Daiber, T. Munzel, Chronic therapy with isosorbide-5-mononitrate causes endothelial dysfunction, oxidative stress, and a marked increase in vascular endothelin-1 expression, Eur. Heart J. 34 (2013) 3206–3216.
[221] S. Steven, M. Oelze, M. Brandt, E. Ullmann, S. Kroller-Schon, T. Heeren, L.P. Tran, S. Daub, M. Dib, D. Stalleicken, P. Wenzel, T. Munzel, A. Daiber, Pentaerythritol tetranitrate in vivo treatment improves oxidative stress and vascular dysfunction by suppression of endothelin-1 signaling in monocrotaline-induced pulmonary hypertension, Oxid. Med. Cell Longev. 2017 (2017) 4353462.
[222] M. Akbari, O.R. Tamtaji, K.B. Lankarani, R. Tabrizi, E. Dadgostar, F. Kolahdooz, M. Jamilian, H. Mirzaei, Z. Asemi, The effects of resveratrol supplementation on endothelial function and blood pressures among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials, High Blood Pres. Cardiovasc. Prev. 26 (2019) 305–319.
[223] A.F.G. Cicero, F. Fogacci, M. Banach, Botanicals and phytochemicals active on cognitive decline: the clinical evidence, Pharmacol. Res. 130 (2018) 204–212.
[224] N. Xia, A. Daiber, U. Forstermann, H. Li, Antioxidant effects of resveratrol in the cardiovascular system, Br. J. Pharmacol. 174 (2017) 1633–1646.
[225] M.A. Broeders, P.A. Doevendans, B.C. Bekkers, R. Bronsaer, E. van Gorsel, J.W. Heemskerk, M.G. Egbrink, E. van Breda, R.S. Reneman, van Der Zee, R. Nebivolol, A third-generation beta-blocker that augments vascular nitric oxide release: endothelial beta(2)-adrenergic receptor-mediated nitric oxide production, Circulation 102 (2000) 677–684.
[226] S. Chlopicki, V.I. Kozlovski, R.J. Gryglewski, No-dependent vasodilation induced by nebivolol in coronary circulation is not mediated by beta-adrenoceptors or by 5 HT1A-receptors, J. Physiol. Pharmacol. 53 (2002) 615–624.
[227] P. Szajerski, J. Zielonka, A. Sikora, J. Adamus, A. Marcinek, J. Gebicki, V.I. Kozlovski, L. Drelicharz, S. Chlopicki, Radical scavenging and NO-releasing properties of selected beta-adrenoreceptor antagonists, Free Radic. Res. 40 (2006) 741–752.
[228] N. Tzemos, P.O. Lim, T.M. MacDonald, Nebivolol reverses endothelial dysfunction in essential hypertension: a randomized, double-blind, crossover study, Circulation 104 (2001) 511–514.
[229] M. Oelze, A. Daiber, R.P. Brandes, M. Hortmann, P. Wenzel, U. Hink, E. Schulz, H. Mollnau, A. von Sandersleben, A.L. Kleschyov, A. Mulsch, H. Li, U. Forstermann, T. Munzel, Nebivolol inhibits superoxide formation by NADPH oxidase and endothelial dysfunction in angiotensin II-treated rats, Hypertension 48 (2006) 677–684.
[230] S.A. Sorrentino, C. Doerries, C. Manes, T. Speer, C. Dessy, I. Lobysheva, W. Mohmand, R. Akbar, F. Bahlmann, C. Besler, A. Schaefer, D. Hilfiker-Kleiner, T.F. Luscher, J.L. Balligand, H. Drexler, U. Landmesser, Nebivolol exerts beneficial effects on endothelial function, early endothelial progenitor cells, myocardial neovascularization, and left ventricular dysfunction early after myocardial infarction beyond conventional beta1-blockade, J. Am. Coll. Cardiol. 57 (2011) 601–611.
[231] V.I. Kozlovski, M. Lomnicka, M. Bartus, M. Sternak, S. Chlopicki, Anti-thrombotic effects of nebivolol and carvedilol: involvement of beta2 receptors and COX-2/PGI2 pathways, Pharmacol. Rep. 67 (2015) 1041–1047.
[232] L.A. Magee, E. Abalos, P. von Dadelszen, B. Sibai, T. Easterling, S. Walkinshaw, C.S. Group, How to manage hypertension in pregnancy effectively, Br. J. Clin. Pharmacol. 72 (2011) 394–401.
[233] A.L. Taylor, J. Lindenfeld, S. Ziesche, M.N. Walsh, J.E. Mitchell, K. Adams, S.W. Tam, E. Ofili, M.L. Sabolinski, M. Worcel, J.N. Cohn, Outcomes by gender in the african-American heart failure trial, J. Am. Coll. Cardiol. 48 (2006) 2263–2267.
[234] A.L. Taylor, S. Ziesche, C. Yancy, P. Carson, R. D'Agostino Jr., K. Ferdinand, M. Taylor, K. Adams, M. Sabolinski, M. Worcel, J.N. Cohn, Combination of isosorbide dinitrate and hydralazine in blacks with heart failure, N. Engl. J. Med. 351 (2004) 2049–2057.
[235] A. Daiber, A. Mulsch, U. Hink, H. Mollnau, A. Warnholtz, M. Oelze, T. Munzel, The oxidative stress concept of nitrate tolerance and the antioxidant properties of hydralazine, Am. J. Cardiol. 96 (2005) 25i–36i.
[236] A. Daiber, M. Oelze, M. Coldewey, K. Kaiser, C. Huth, S. Schildknecht, M. Bachschmid, Y. Nazirisadeh, V. Ullrich, A. Mulsch, T. Munzel, N. Tsilimingas, Hydralazine is a powerful inhibitor of peroxynitrite formation as a possible explanation for its beneficial effects on prognosis in patients with congestive heart failure, Biochem. Biophys. Res. Commun. 338 (2005) 1865–1874.
[237] T. Munzel, T. Meinertz, U. Tebbe, H.T. Schneider, D. Stalleicken, M. Wargenau, T. Gori, I. Klingmann, C.S. Investigators, Efficacy of the long-acting nitro

vasodilator pentaerithrityl tetranitrate in patients with chronic stable angina pectoris receiving anti-anginal background therapy with beta-blockers: a 12-week, randomized, double-blind, placebo-controlled trial, Eur. Heart J. 35 (2014) 895–903.
[238] S. Oberle, A. Abate, N. Grosser, H.J. Vreman, P.A. Dennery, H.T. Schneider, D. Stalleicken, H. Schroder, Heme oxygenase-1 induction may explain the antioxidant profile of pentaerythrityl trinitrate, Biochem. Biophys. Res. Commun. 290 (2002) 1539–1544.
[239] P. Wenzel, M. Oelze, M. Coldewey, M. Hortmann, A. Seeling, U. Hink, H. Mollnau, D. Stalleicken, H. Weiner, J. Lehmann, H. Li, U. Forstermann, T. Munzel, A. Daiber, Heme oxygenase-1: a novel key player in the development of tolerance in response to organic nitrates, Arterioscler. Thromb. Vasc. Biol. 27 (2007) 1729–1735.
[240] S. Schuhmacher, M. Oelze, F. Bollmann, H. Kleinert, C. Otto, T. Heeren, S. Steven, M. Hausding, M. Knorr, A. Pautz, K. Reifenberg, E. Schulz, T. Gori, P. Wenzel, T. Munzel, A. Daiber, Vascular dysfunction in experimental diabetes is improved by pentaerithrityl tetranitrate but not isosorbide-5-mononitrate therapy, Diabetes 60 (2011) 2608–2616.
[241] C.K. Kramer, C. Ye, S. Campbell, R. Retnakaran, Comparison of new glucose-lowering drugs on risk of heart failure in type 2 diabetes: a network meta-analysis, JACC Heart Fail 6 (2018) 823–830.
[242] G.P. Fadini, A. Avogaro, L. Degli Esposti, P. Russo, S. Saragoni, S. Buda, G. Rosano, S. Pecorelli, L. Pani, D.B.N. OsMed Health, Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database, Eur. Heart J. 36 (2015) 2454–2462.
[243] L. Timmers, J.P. Henriques, D.P. de Kleijn, J.H. Devries, H. Kemperman, P. Steendijk, C.W. Verlaan, M. Kerver, J.J. Piek, P.A. Doevendans, G. Pasterkamp, I.E. Hoefer, Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury, J. Am. Coll. Cardiol. 53 (2009) 501–510.
[244] B. Hocher, Y. Sharkovska, M. Mark, T. Klein, T. Pfab, The novel DPP-4 inhibitors linagliptin and BI 14361 reduce infarct size after myocardial ischemia/reperfusion in rats, Int. J. Cardiol. 167 (2013) 87–93.
[245] I. Andreadou, P. Efentakis, E. Balafas, G. Togliatto, C.H. Davos, A. Varela, C.A. Dimitriou, P.E. Nikolaou, E. Maratou, V. Lambadiari, I. Ikonomidis, N. Kostomitsopoulos, M.F. Brizzi, G. Dimitriadis, E.K. Iliodromitis, Empagliflozin limits myocardial infarction in vivo and cell death in vitro: role of STAT3, mitochondria, and redox aspects, Front. Physiol. 8 (2017) 1077.
[246] H. Oshima, T. Miki, A. Kuno, M. Mizuno, T. Sato, M. Tanno, T. Yano, K. Nakata, Y. Kimura, K. Abe, W. Ohwada, T. Miura, Empagliflozin, an SGLT2 inhibitor, reduced the mortality rate after acute myocardial infarction with modification of cardiac metabolomes and anti-oxidants in diabetic rats, J. Pharmacol. Exp. Therapeut. (2018).
[247] F. Bonnet, A.J. Scheen, Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease, Diabetes Metab. 44 (2018) 457–464.
[248] S.L. Atkin, N. Katsiki, M. Banach, D.P. Mikhailidis, M. Pirro, A. Sahebkar, Effect of dipeptidyl peptidase-4 inhibitors on circulating tumor necrosis factor-alpha concentrations: a systematic review and meta-analysis of controlled trials, J. Diabet. Complicat. 31 (2017) 1458–1464.
[249] Y.S. Lee, H.S. Jun, Anti-inflammatory effects of GLP-1-based therapies beyond glucose control, Mediat. Inflamm. 2016 (2016) 3094642.
[250] J. Matsubara, S. Sugiyama, K. Sugamura, T. Nakamura, Y. Fujiwara, E. Akiyama, H. Kurokawa, T. Nozaki, K. Ohba, M. Konishi, H. Maeda, Y. Izumiya, K. Kaikita, H. Sumida, H. Jinnouchi, K. Matsui, S. Kim-Mitsuyama, M. Takeya, H. Ogawa, A dipeptidyl peptidase-4 inhibitor, des-fluoro-sitagliptin, improves endothelial function and reduces atherosclerotic lesion formation in apolipoprotein E-deficient mice, J. Am. Coll. Cardiol. 59 (2012) 265–276.
[251] Z. Shah, T. Kampfrath, J.A. Deiuliis, J. Zhong, C. Pineda, Z. Ying, X. Xu, B. Lu, S. Moffatt-Bruce, R. Durairaj, Q. Sun, G. Mihai, A. Maiseyeu, S. Rajagopalan, Long-term dipeptidyl-peptidase 4 inhibition reduces atherosclerosis and inflammation via effects on monocyte recruitment and chemotaxis, Circulation 124 (2011) 2338–2349.
[252] Y. Nakatsu, H. Kokubo, B. Bumdelger, M. Yoshizumi, T. Yamamotoya, Y. Matsunaga, K. Ueda, Y. Inoue, M.K. Inoue, M. Fujishiro, A. Kushiyama, H. Ono, H. Sakoda, T. Asano, The SGLT2 inhibitor luseogliflozin rapidly normalizes aortic mRNA levels of inflammation-related but not lipid-metabolism-related genes and suppresses atherosclerosis in diabetic ApoE KO mice, Int. J. Mol. Sci. 18 (2017).
[253] J.H. Han, T.J. Oh, G. Lee, H.J. Maeng, D.H. Lee, K.M. Kim, S.H. Choi, H.C. Jang, H.S. Lee, K.S. Park, Y.B. Kim, S. Lim, The beneficial effects of empagliflozin, an SGLT2 inhibitor, on atherosclerosis in ApoE (-/-) mice fed a western diet, Diabetologia 60 (2017) 364–376.
[254] S. Kroller-Schon, M. Knorr, M. Hausding, M. Oelze, A. Schuff, R. Schell, S. Sudowe, A. Scholz, S. Daub, S. Karbach, S. Kossmann, T. Gori, P. Wenzel, E. Schulz, S. Grabbe, T. Klein, T. Munzel, A. Daiber, Glucose-independent improvement of vascular dysfunction in experimental sepsis by dipeptidyl-peptidase 4 inhibition, Cardiovasc. Res. 96 (2012) 140–149.
[255] S. Steven, M. Hausding, S. Kroller-Schon, M. Mader, Y. Mikhed, P. Stamm, E. Zinssius, A. Pfeffer, P. Welschof, S. Agdauletova, S. Sudowe, H. Li, M. Oelze, E. Schulz, T. Klein, T. Munzel, A. Daiber, Gliptin and GLP-1 analog treatment improves survival and vascular inflammation/dysfunction in animals with lipopolysaccharide-induced endotoxemia, Basic Res. Cardiol. 110 (6) (2015).
[256] S. Steven, K. Jurk, M. Kopp, S. Kroller-Schon, Y. Mikhed, K. Schwierczek, S. Roohani, F. Kashani, M. Oelze, T. Klein, S. Tokalov, S. Danckwardt, S. Strand, P. Wenzel, T. Munzel, A. Daiber, Glucagon-like peptide-1 receptor signalling reduces microvascular thrombosis, nitro-oxidative stress and platelet activation in endotoxaemic mice, Br. J. Pharmacol. 174 (2017) 1620–1632.
[257] M. Oelze, S. Kroller-Schon, P. Welschof, T. Jansen, M. Hausding, Y. Mikhed, P. Stamm, M. Mader, E. Zinssius, S. Agdauletova, A. Gottschlich, S. Steven, E. Schulz, S.P. Bottari, E. Mayoux, T. Munzel, A. Daiber, The sodium-glucose co-transporter 2 inhibitor empagliflozin improves diabetes-induced vascular dysfunction in the streptozotocin diabetes rat model by interfering with oxidative stress and glucotoxicity, PloS One 9 (2014) e112394.
[258] S. Steven, M. Oelze, A. Hanf, S. Kroller-Schon, F. Kashani, S. Roohani, P. Welschof, M. Kopp, U. Godtel-Armbrust, N. Xia, H. Li, E. Schulz, K.J. Lackner, L. Wojnowski, S.P. Bottari, P. Wenzel, E. Mayoux, T. Munzel, A. Daiber, The SGLT2 inhibitor empagliflozin improves the primary diabetic complications in ZDF rats, Redox Biol. 13 (2017) 370–385.
[259] M. Packer, Lessons learned from the DAPA-HF trial concerning the mechanisms of benefit of SGLT2 inhibitors on heart failure events in the context of other large-scale trials nearing completion, Cardiovasc. Diabetol. 18 (2019) 129.
[260] M. El-Daly, V.K. Pulakazhi Venu, M. Saifeddine, K. Mihara, S. Kang, P.W.M. Fedak, L.A. Alston, S.A. Hirota, H. Ding, C.R. Triggle, M.D. Hollenberg, Hyperglycaemic impairment of PAR2-mediated vasodilation: prevention by inhibition of aortic endothelial sodium-glucose-co-Transporter-2 and minimizing oxidative stress, Vasc. Pharmacol. 109 (2018) 56–71.
[261] L. Uthman, A. Baartscheer, C.A. Schumacher, J.W.T. Fiolet, M.C. Kuschma, M.W. Hollmann, R. Coronel, N.C. Weber, C.J. Zuurbier, Direct cardiac actions of sodium glucose cotransporter 2 inhibitors target pathogenic mechanisms underlying heart failure in diabetic patients, Front. Physiol. 9 (2018) 1575.
[262] S.A. Hawley, R.J. Ford, B.K. Smith, G.J. Gowans, S.J. Mancini, R.D. Pitt, E.A. Day, I.P. Salt, G.R. Steinberg, D.G. Hardie, The Na+/Glucose cotransporter inhibitor canagliflozin activates AMPK by inhibiting mitochondrial function and increasing cellular AMP levels, Diabetes 65 (2016) 2784–2794.
[263] S.J. Mancini, D. Boyd, O.J. Katwan, A. Strembitska, T.A. Almabrouk, S. Kennedy, T.M. Palmer, I.P. Salt, Canagliflozin inhibits interleukin-1beta-stimulated cytokine and chemokine secretion in vascular endothelial cells by AMP-activated protein kinase-dependent and -independent mechanisms, Sci. Rep. 8 (2018) 5276.
[264] S. Khemais-Benkhiat, E. Belcastro, N. Idris-Khodja, S.H. Park, L. Amoura, M. Abbas, C. Auger, L. Kessler, E. Mayoux, F. Toti, V.B. Schini-Kerth, Angiotensin II-induced redox-sensitive SGLT1 and 2 expression promotes high glucose-induced endothelial cell senescence, J. Cell Mol. Med. (2019).
[265] S. Cooper, H. Teoh, M.A. Campeau, S. Verma, R.L. Leask, Empagliflozin restores the integrity of the endothelial glycocalyx in vitro, Mol. Cell. Biochem. 459 (2019) 121–130.
[266] V. Boswell-Smith, D. Spina, C.P. Page, Phosphodiesterase inhibitors, Br. J. Pharmacol. 147 (Suppl 1) (2006) S252–S257.
[267] V. Mitrovic, A.F. Hernandez, M. Meyer, M. Gheorghiade, Role of guanylate cyclase modulators in decompensated heart failure, Heart Fail. Rev. 14 (2009) 309–319.
[268] L.M. Mielniczuk, J.R. Swiston, S. Riociguat Mehta, A novel therapeutic option for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, Can. J. Cardiol. 30 (2014) 1233–1240.
[269] O.V. Evgenov, P. Pacher, P.M. Schmidt, G. Hasko, H.H. Schmidt, J.P. Stasch, NO-independent stimulators and activators of soluble guanylate cyclase: discovery and therapeutic potential, Nat. Rev. Drug Discov. 5 (2006) 755–768.
[270] D. Fraccarollo, J.D. Widder, P. Galuppo, T. Thum, D. Tsikas, M. Hoffmann, H. Ruetten, G. Ertl, J. Bauersachs, Improvement in left ventricular remodeling by the endothelial nitric oxide synthase enhancer AVE9488 after experimental myocardial infarction, Circulation 118 (2008) 818–827.
[271] Q. Yang, H.M. Xue, W.T. Wong, X.Y. Tian, Y. Huang, S.K. Tsui, P.K. Ng, P. Wohlfart, H. Li, N. Xia, S. Tobias, M.J. Underwood, G.W. He, AVE3085, an enhancer of endothelial nitric oxide synthase, restores endothelial function and reduces blood pressure in spontaneously hypertensive rats, Br. J. Pharmacol. 163 (2011) 1078–1085.
[272] C. Antoniades, C. Shirodaria, N. Warrick, S. Cai, J. de Bono, J. Lee, P. Leeson, S. Neubauer, C. Ratnatunga, R. Pillai, H. Refsum, K.M. Channon, 5-methyltetrahydrofolate rapidly improves endothelial function and decreases superoxide production in human vessels: effects on vascular tetrahydrobiopterin availability and endothelial nitric oxide synthase coupling, Circulation 114 (2006) 1193–1201.
[273] M. Tsutsui, S. Milstien, Z.S. Katusic, Effect of tetrahydrobiopterin on endothelial function in canine middle cerebral arteries, Circ. Res. 79 (1996) 336–342.
[274] T. Munzel, A. Daiber, Role of endothelial and macrophage tetrahydrobiopterin in development and progression of atherosclerosis: BH4 puzzle solved? Cardiovasc. Res. 114 (2018) 1310–1312.
[275] H. Li, U. Forstermann, Prevention of atherosclerosis by interference with the vascular nitric oxide system, Curr. Pharmaceut. Des. 15 (2009) 3133–3145.
[276] J.D. Miller, Y. Chu, L.E. Castaneda, K.M. Serrano, R.M. Brooks, D.D. Heistad, Vascular function during prolonged progression and regression of atherosclerosis in mice, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 459–465.
[277] S.D. Wollin, P.J. Jones, Alpha-lipoic acid and cardiovascular disease, J. Nutr. 133 (2003) 3327–3330.
[278] H.N. Larson, H. Weiner, T.D. Hurley, Disruption of the coenzyme binding site and dimer interface revealed in the crystal structure of mitochondrial aldehyde dehydrogenase "Asian" variant, J. Biol. Chem. 280 (2005) 30550–30556.
[279] T. Munzel, A. Daiber, The potential of aldehyde dehydrogenase 2 as a therapeutic target in cardiovascular disease, Expert Opin. Ther. Targets 22 (2018) 217–231.
[280] Z. Chen, J. Zhang, J.S. Stamler, Identification of the enzymatic mechanism of nitroglycerin bioactivation, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 8306–8311.
[281] Z. Chen, M.W. Foster, J. Zhang, L. Mao, H.A. Rockman, T. Kawamoto, K. Kitagawa,

K.I. Nakayama, D.T. Hess, J.S. Stamler, An essential role for mitochondrial aldehyde dehydrogenase in nitroglycerin bioactivation, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 12159–12164.
[282] A. Daiber, M. Oelze, M. Coldewey, M. Bachschmid, P. Wenzel, K. Sydow, M. Wendt, A.L. Kleschyov, D. Stalleicken, V. Ullrich, A. Mulsch, T. Munzel, Oxidative stress and mitochondrial aldehyde dehydrogenase activity: a comparison of pentaerythritol tetranitrate with other organic nitrates, Mol. Pharmacol. 66 (2004) 1372–1382.
[283] P. Wenzel, U. Hink, M. Oelze, S. Schuppan, K. Schaeuble, S. Schildknecht, K.K. Ho, H. Weiner, M. Bachschmid, T. Munzel, A. Daiber, Role of reduced lipoic acid in the redox regulation of mitochondrial aldehyde dehydrogenase (ALDH-2) activity. Implications for mitochondrial oxidative stress and nitrate tolerance, J. Biol. Chem. 282 (2007) 792–799.
[284] M. Oelze, M. Knorr, R. Schell, J. Kamuf, A. Pautz, J. Art, P. Wenzel, T. Munzel, H. Kleinert, A. Daiber, Regulation of human mitochondrial aldehyde dehydrogenase (ALDH-2) activity by electrophiles in vitro, J. Biol. Chem. 286 (2011) 8893–8900.
[285] K.M. Gomes, L.R. Bechara, V.M. Lima, M.A. Ribeiro, J.C. Campos, P.M. Dourado, A.J. Kowaltowski, D. Mochly-Rosen, J.C. Ferreira, Aldehydic load and aldehyde dehydrogenase 2 profile during the progression of post-myocardial infarction cardiomyopathy: benefits of Alda-1, Int. J. Cardiol. 179 (2015) 129–138.
[286] J. Wang, H. Wang, P. Hao, L. Xue, S. Wei, Y. Zhang, Y. Chen, Inhibition of aldehyde dehydrogenase 2 by oxidative stress is associated with cardiac dysfunction in diabetic rats, Mol. Med. 17 (2011) 172–179.
[287] A. Daiber, P. Wenzel, M. Oelze, S. Schuhmacher, T. Jansen, T. Munzel, Mitochondrial aldehyde dehydrogenase (ALDH-2)–maker of and marker for nitrate tolerance in response to nitroglycerin treatment, Chem. Biol. Interact. 178 (2009) 40–47.
[288] P. Wenzel, E. Schulz, T. Gori, M.A. Ostad, F. Mathner, S. Schildknecht, S. Gobel, M. Oelze, D. Stalleicken, A. Warnholtz, T. Munzel, A. Daiber, Monitoring white blood cell mitochondrial aldehyde dehydrogenase activity: implications for nitrate therapy in humans, J. Pharmacol. Exp. Therapeut. 330 (2009) 63–71.
[289] A. Bierhaus, S. Chevion, M. Chevion, M. Hofmann, P. Quehenberger, T. Illmer, T. Luther, E. Berentshtein, H. Tritschler, M. Muller, P. Wahl, R. Ziegler, P.P. Nawroth, Advanced glycation end product-induced activation of NF-kappaB is suppressed by alpha-lipoic acid in cultured endothelial cells, Diabetes 46 (1997) 1481–1490.
[290] T. Heitzer, B. Finckh, S. Albers, K. Krohn, A. Kohlschutter, T. Meinertz, Beneficial effects of alpha-lipoic acid and ascorbic acid on endothelium-dependent, nitric oxide-mediated vasodilation in diabetic patients: relation to parameters of oxidative stress, Free Radic. Biol. Med. 31 (2001) 53–61.
[291] A. Daiber, T. Munzel, Organic nitrate therapy, nitrate tolerance, and nitrate-induced endothelial dysfunction: emphasis on redox biology and oxidative stress, Antioxidants Redox Signal. 23 (2015) 899–942.
[292] D.J. Polhemus, D.J. Lefer, Emergence of hydrogen sulfide as an endogenous gaseous signaling molecule in cardiovascular disease, Circ. Res. 114 (2014) 730–737.
[293] J.T. Hancock, M. Whiteman, Hydrogen Sulfide Signaling: Interactions with Nitric Oxide and Reactive Oxygen Species, Ann N Y Acad Sci, 2015.
[294] N.L. Kanagy, C. Szabo, A. Papapetropoulos, Vascular biology of hydrogen sulfide, Am. J. Physiol. Cell Physiol. 312 (2017) C537–C549.
[295] I. Andreadou, E.K. Iliodromitis, T. Rassaf, R. Schulz, A. Papapetropoulos, P. Ferdinandy, The role of gasotransmitters NO, H2S and CO in myocardial ischaemia/reperfusion injury and cardioprotection by preconditioning, postconditioning and remote conditioning, Br. J. Pharmacol. 172 (2015) 1587–1606.
[296] R. Verma, Y. Akhtar, S. Singh, A review of patents on therapeutic potential and delivery of hydroge n sulfide, Recent Pat. Drug Deliv. Formulation 11 (2017) 114–123.
[297] C.A. Chen, T.Y. Wang, S. Varadharaj, L.A. Reyes, C. Hemann, M.A. Talukder, Y.R. Chen, L.J. Druhan, J.L. Zweier, S-glutathionylation uncouples eNOS and regulates its cellular and vascular function, Nature 468 (2010) 1115–1118.
[298] J.L. Zweier, C.A. Chen, L.J. Druhan, S-glutathionylation reshapes our understanding of endothelial nitric oxide synthase uncoupling and nitric oxide/reactive oxygen species-mediated signaling, Antioxidants Redox Signal. 14 (2011) 1769–1775.
[299] C.A. Chen, F. De Pascali, A. Basye, C. Hemann, J.L. Zweier, Redox modulation of endothelial nitric oxide synthase by glutaredoxin-1 through reversible oxidative post-translational modification, Biochemistry 52 (2013) 6712–6723.
[300] A. Holmgren, Antioxidant function of thioredoxin and glutaredoxin systems, Antioxidants Redox Signal. 2 (2000) 811–820.
[301] M. Okuda, N. Inoue, H. Azumi, T. Seno, Y. Sumi, K. Hirata, S. Kawashima, Y. Hayashi, H. Itoh, J. Yodoi, M. Yokoyama, Expression of glutaredoxin in human coronary arteries: its potential role in antioxidant protection against atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 21 (2001) 1483–1487.
[302] A.V. Peskin, P.E. Pace, J.B. Behring, L.N. Paton, M. Soethoudt, M.M. Bachschmid, C.C. Winterbourn, Glutathionylation of the active site cysteines of peroxiredoxin 2 and recycling by glutaredoxin, J. Biol. Chem. 291 (2016) 3053–3062.
[303] D. Shao, J. Han, X. Hou, J. Fry, J.B. Behring, F. Seta, M.T. Long, H.K. Roy, R.A. Cohen, R. Matsui, M.M. Bachschmid, Glutaredoxin-1 deficiency causes fatty liver and dyslipidemia by inhibiting sirtuin-1, Antioxidants Redox Signal. 27 (2017) 313–327.
[304] L. Brautigam, L.D. Jensen, G. Poschmann, S. Nystrom, S. Bannenberg, K. Dreij, K. Lepka, T. Prozorovski, S.J. Montano, O. Aktas, P. Uhlen, K. Stuhler, Y. Cao, A. Holmgren, C. Berndt, Glutaredoxin regulates vascular development by reversible glutathionylation of sirtuin 1, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 20057–20062.
[305] J. Chalker, D. Gardiner, N. Kuksal, R.J. Mailloux, Characterization of the impact of glutaredoxin-2 (GRX2) deficiency on superoxide/hydrogen peroxide release from cardiac and liver mitochondria, Redox Biol. 15 (2018) 216–227.
[306] J.J. Mieyal, M.M. Gallogly, S. Qanungo, E.A. Sabens, M.D. Shelton, Molecular mechanisms and clinical implications of reversible protein S-glutathionylation, Antioxidants Redox Signal. 10 (2008) 1941–1988.
[307] C. Berndt, C.H. Lillig, A. Holmgren, Thiol-based mechanisms of the thioredoxin and glutaredoxin systems: implications for diseases in the cardiovascular system, Am. J. Physiol. Heart Circ. Physiol. 292 (2007) H1227–H1236.
[308] G.A. Figtree, G. Keyvan Karimi, C.C. Liu, H.H. Rasmussen, Oxidative regulation of the Na(+)-K(+) pump in the cardiovascular system, Free Radic. Biol. Med. 53 (2012) 2263–2268.
[309] H. Yamawaki, J. Haendeler, B.C. Berk, Thioredoxin: a key regulator of cardiovascular homeostasis, Circ. Res. 93 (2003) 1029–1033.
[310] T.D. Lockwood, Redox control of protein degradation, Antioxidants Redox Signal. 2 (2000) 851–878.
[311] D.K. Das, Thioredoxin regulation of ischemic preconditioning, Antioxidants Redox Signal. 6 (2004) 405–412.
[312] G.M. Kuster, D.A. Siwik, D.R. Pimentel, W.S. Colucci, Role of reversible, thioredoxin-sensitive oxidative protein modifications in cardiac myocytes, Antioxidants Redox Signal. 8 (2006) 2153–2159.
[313] J. Ying, N. Clavreul, M. Sethuraman, T. Adachi, R.A. Cohen, Thiol oxidation in signaling and response to stress: detection and quantification of physiological and pathophysiological thiol modifications, Free Radic. Biol. Med. 43 (2007) 1099–1108.
[314] N. Rosenberg, R. Mor-Cohen, V.H. Sheptovitsky, O. Romanenco, O. Hess, J. Lahav, Integrin-mediated cell adhesion requires extracellular disulfide exchange regulated by protein disulfide isomerase, Exp. Cell Res. 381 (2019) 77–85.
[315] M.M. Bachschmid, S. Xu, K.A. Maitland-Toolan, Y.S. Ho, R.A. Cohen, R. Matsui, Attenuated cardiovascular hypertrophy and oxidant generation in response to angiotensin II infusion in glutaredoxin-1 knockout mice, Free Radic. Biol. Med. 49 (2010) 1221–1229.
[316] F.R. Laurindo, D.C. Fernandes, A.M. Amanso, L.R. Lopes, C.X. Santos, Novel role of protein disulfide isomerase in the regulation of NADPH oxidase activity: pathophysiological implications in vascular diseases, Antioxidants Redox Signal. 10 (2008) 1101–1113.
[317] Y. Watanabe, C.E. Murdoch, S. Sano, Y. Ido, M.M. Bachschmid, R.A. Cohen, R. Matsui, Glutathione adducts induced by ischemia and deletion of glutaredoxin-1 stabilize HIF-1alpha and improve limb revascularization, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 6011–6016.
[318] O. Gorelenkova Miller, J.B. Behring, S.L. Siedlak, S. Jiang, R. Matsui, M.M. Bachschmid, X. Zhu, J.J. Mieyal, Upregulation of glutaredoxin-1 activates microglia and promotes neurodegeneration: implications for Parkinson's disease, Antioxidants Redox Signal. 25 (2016) 967–982.
[319] M.K. Ahsan, I. Lekli, D. Ray, J. Yodoi, D.K. Das, Redox regulation of cell survival by the thioredoxin superfamily: an implication of redox gene therapy in the heart, Antioxidants Redox Signal. 11 (2009) 2741–2758.
[320] D. Popov, Protein S-glutathionylation: from current basics to targeted modifications, Arch. Physiol. Biochem. 120 (2014) 123–130.
[321] H. Nakamura, Extracellular functions of thioredoxin, Novartis Found. Symp. 291 (2008) 184–192 discussion 192-185, 221-184.
[322] P. Di Simplicio, H. Jensson, B. Mannervik, Effects of inducers of drug metabolism on basic hepatic forms of mouse glutathione transferase, Biochem. J. 263 (1989) 679–685.
[323] J.B. Park, M. Levine, The human glutaredoxin gene: determination of its organization, transcription start point, and promoter analysis, Gene 197 (1997) 189–193.
[324] T.J. Bechtel, E. Weerapana, From structure to redox: the diverse functional roles of disulfides and implications in disease, Proteomics 17 (2017).
[325] J. Yoshioka, Thioredoxin superfamily and its effects on cardiac physiology and pathology, Comp. Physiol. 5 (2015) 513–530.
[326] R.A. Smith, R.C. Hartley, M.P. Murphy, Mitochondria-targeted small molecule therapeutics and probes, Antioxidants Redox Signal. 15 (2011) 3021–3038.
[327] V.T. Dao, A.I. Casas, G.J. Maghzal, T. Seredenina, N. Kaludercic, N. Robledinos-Anton, F. Di Lisa, R. Stocker, P. Ghezzi, V. Jaquet, A. Cuadrado, H.H. Schmidt, Pharmacology and clinical drug candidates in redox medicine, Antioxidants Redox Signal. 23 (2015) 1113–1129.
[328] J. Zhou, D. Yang, K. Liu, L. Hou, W. Zhang, Systematic review and meta-analysis of the protective effect of resveratrol on multiple organ injury induced by sepsis in animal models, Biomed. Rep. 10 (2019) 55–62.
[329] M. Walczak, J. Suraj, K. Kus, A. Kij, A. Zakrzewska, S. Chlopicki, Towards a comprehensive endothelial biomarkers profiling and endothelium-guided pharmacotherapy, Pharmacol. Rep. 67 (2015) 771–777.
[330] K. Nakazono, N. Watanabe, K. Matsuno, J. Sasaki, T. Sato, M. Inoue, Does superoxide underlie the pathogenesis of hypertension? Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 10045–10048.
[331] U. Landmesser, S. Dikalov, S.R. Price, L. McCann, T. Fukai, S.M. Holland, W.E. Mitch, D.G. Harrison, Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension, J. Clin. Invest. 111 (2003) 1201–1209.
[332] A.E. Dikalova, A.T. Bikineyeva, K. Budzyn, R.R. Nazarewicz, L. McCann, W. Lewis, D.G. Harrison, S.I. Dikalov, Therapeutic targeting of mitochondrial superoxide in hypertension, Circ. Res. 107 (2010) 106–116.
[333] A.K. Doughan, D.G. Harrison, S.I. Dikalov, Molecular mechanisms of angiotensin II-mediated mitochondrial dysfunction: linking mitochondrial oxidative damage and vascular endothelial dysfunction, Circ. Res. 102 (2008) 488–496.
[334] U. Landmesser, S. Spiekermann, C. Preuss, S. Sorrentino, D. Fischer, C. Manes,

M. Mueller, H. Drexler, Angiotensin II induces endothelial xanthine oxidase activation: role for endothelial dysfunction in patients with coronary disease, Arterioscler. Thromb. Vasc. Biol. 27 (2007) 943–948.
[335] C.E. Murdoch, S.P. Alom-Ruiz, M. Wang, M. Zhang, S. Walker, B. Yu, A. Brewer, A.M. Shah, Role of endothelial Nox2 NADPH oxidase in angiotensin II-induced hypertension and vasomotor dysfunction, Basic Res. Cardiol. 106 (2011) 527–538.
[336] J.K. Bendall, R. Rinze, D. Adlam, A.L. Tatham, J. de Bono, N. Wilson, E. Volpi, K.M. Channon, Endothelial Nox2 overexpression potentiates vascular oxidative stress and hemodynamic response to angiotensin II: studies in endothelial-targeted Nox2 transgenic mice, Circ. Res. 100 (2007) 1016–1025.
[337] S. Chrissobolis, B. Banfi, C.G. Sobey, F.M. Faraci, Role of Nox isoforms in angiotensin II-induced oxidative stress and endothelial dysfunction in brain, J. Appl. Physiol. 113 (2012) 184–191.
[338] H.D. Wang, S. Xu, D.G. Johns, Y. Du, M.T. Quinn, A.J. Cayatte, R.A. Cohen, Role of NADPH oxidase in the vascular hypertrophic and oxidative stress response to angiotensin II in mice, Circ. Res. 88 (2001) 947–953.
[339] D.Y. Lee, F. Wauquier, A.A. Eid, L.J. Roman, G. Ghosh-Choudhury, K. Khazim, K. Block, Y. Gorin, Nox4 NADPH oxidase mediates peroxynitrite-dependent uncoupling of endothelial nitric-oxide synthase and fibronectin expression in response to angiotensin II: role of mitochondrial reactive oxygen species, J. Biol. Chem. 288 (2013) 28668–28686.
[340] K. Wingler, S. Wunsch, R. Kreutz, L. Rothermund, M. Paul, H.H. Schmidt, Upregulation of the vascular NAD(P)H-oxidase isoforms Nox1 and Nox4 by the renin-angiotensin system in vitro and in vivo, Free Radic. Biol. Med. 31 (2001) 1456–1464.
[341] S. Schuhmacher, P. Wenzel, E. Schulz, M. Oelze, C. Mang, J. Kamuf, T. Gori, T. Jansen, M. Knorr, S. Karbach, M. Hortmann, F. Mathner, A. Bhatnagar, U. Forstermann, H. Li, T. Munzel, A. Daiber, Pentaerythritol tetranitrate improves angiotensin II-induced vascular dysfunction via induction of heme oxygenase-1, Hypertension 55 (2010) 897–904.
[342] P. Wenzel, H. Rossmann, C. Muller, S. Kossmann, M. Oelze, A. Schulz, N. Arnold, C. Simsek, J. Lagrange, R. Klemz, T. Schonfelder, M. Brandt, S.H. Karbach, M. Knorr, S. Finger, C. Neukirch, F. Hauser, M.E. Beutel, S. Kroller-Schon, E. Schulz, R.B. Schnabel, K. Lackner, P.S. Wild, T. Zeller, A. Daiber, S. Blankenberg, T. Munzel, Heme oxygenase-1 suppresses a pro-inflammatory phenotype in monocytes and determines endothelial function and arterial hypertension in mice and humans, Eur. Heart J. 36 (2015) 3437–3446.
[343] D.W. Infanger, X. Cao, S.D. Butler, M.A. Burmeister, Y. Zhou, J.A. Stupinski, R.V. Sharma, R.L. Davisson, Silencing nox4 in the paraventricular nucleus improves myocardial infarction-induced cardiac dysfunction by attenuating sympathoexcitation and periinfarct apoptosis, Circ. Res. 106 (2010) 1763–1774.
[344] Y.H. Looi, D.J. Grieve, A. Siva, S.J. Walker, N. Anilkumar, A.C. Cave, M. Marber, M.J. Monaghan, A.M. Shah, Involvement of Nox2 NADPH oxidase in adverse cardiac remodeling after myocardial infarction, Hypertension 51 (2008) 319–325.
[345] I. Somasuntharam, A.V. Boopathy, R.S. Khan, M.D. Martinez, M.E. Brown, N. Murthy, M.E. Davis, Delivery of Nox2-NADPH oxidase siRNA with polyketal nanoparticles for improving cardiac function following myocardial infarction, Biomaterials 34 (2013) 7790–7798.
[346] C. Piot, P. Croisille, P. Staat, H. Thibault, G. Rioufol, N. Mewton, R. Elbelghiti, T.T. Cung, E. Bonnefoy, D. Angoulvant, C. Macia, F. Raczka, C. Sportouch, G. Gahide, G. Finet, X. Andre-Fouet, D. Revel, G. Kirkorian, J.P. Monassier, G. Derumeaux, M. Ovize, Effect of cyclosporine on reperfusion injury in acute myocardial infarction, N. Engl. J. Med. 359 (2008) 473–481.
[347] R.A. Kloner, S.L. Hale, W. Dai, R.C. Gorman, T. Shuto, K.J. Koomalsingh, J.H. Gorman 3rd, R.C. Sloan, C.R. Frasier, C.A. Watson, P.A. Bostian, A.P. Kypson, D.A. Brown, Reduction of ischemia/reperfusion injury with bendavia, a mitochondria-targeting cytoprotective Peptide, J. Am. Heart Assoc. 1 (2012) e001644.
[348] S. Akizuki, S. Yoshida, D.E. Chambers, L.J. Eddy, L.F. Parmley, D.M. Yellon, J.M. Downey, Infarct size limitation by the xanthine oxidase inhibitor, allopurinol, in closed-chest dogs with small infarcts, Cardiovasc. Res. 19 (1985) 686–692.
[349] S.W. Werns, M.J. Shea, S.E. Mitsos, R.C. Dysko, J.C. Fantone, M.A. Schork, G.D. Abrams, B. Pitt, B.R. Lucchesi, Reduction of the size of infarction by allopurinol in the ischemic-reperfused canine heart, Circulation 73 (1986) 518–524.
[350] N. Engberding, S. Spiekermann, A. Schaefer, A. Heineke, A. Wiencke, M. Muller, M. Fuchs, D. Hilfiker-Kleiner, B. Hornig, H. Drexler, U. Landmesser, Allopurinol attenuates left ventricular remodeling and dysfunction after experimental myocardial infarction: a new action for an old drug? Circulation 110 (2004) 2175–2179.
[351] P. Wenzel, H. Mollnau, M. Oelze, E. Schulz, J.M. Wickramanayake, J. Muller, S. Schuhmacher, M. Hortmann, S. Baldus, T. Gori, R.P. Brandes, T. Munzel, A. Daiber, First evidence for a crosstalk between mitochondrial and NADPH oxidase-derived reactive oxygen species in nitroglycerin-triggered vascular dysfunction, Antioxidants Redox Signal. 10 (2008) 1435–1447.
[352] M.T. Coughlan, D.R. Thorburn, S.A. Penfold, A. Laskowski, B.E. Harcourt, K.C. Sourris, A.L. Tan, K. Fukami, V. Thallas-Bonke, P.P. Nawroth, M. Brownlee, A. Bierhaus, M.E. Cooper, J.M. Forbes, RAGE-induced cytosolic ROS promote mitochondrial superoxide generation in diabetes, J. Am. Soc. Nephrol. 20 (2009) 742–752.
[353] S.I. Dikalov, R.R. Nazarewicz, A. Bikineyeva, L. Hilenski, B. Lassegue, K.K. Griendling, D.G. Harrison, A.E. Dikalova, Nox2-Induced production of mitochondrial superoxide in angiotensin II-mediated endothelial oxidative stress and hypertension, Antioxidants Redox Signal. 20 (2014) 281–294.
[354] R. Zhang, H.H. Ran, L. Peng, F. Xu, J.F. Sun, L.N. Zhang, Y.Y. Fan, L. Peng, G. Cui, Mitochondrial regulation of NADPH oxidase in hindlimb unweighting rat cerebral arteries, PloS One 9 (2014) e95916.
[355] T. Munzel, A. Daiber, Does endothelial tetrahydrobiopterin control the endothelial NO synthase coupling state in arterial resistance arteries? Br. J. Pharmacol. 174 (2017) 2422–2424.
[356] S. Chuaiphichai, M.J. Crabtree, E. McNeill, A.B. Hale, L. Trelfa, K.M. Channon, G. Douglas, A key role for tetrahydrobiopterin-dependent endothelial NOS regulation in resistance arteries: studies in endothelial cell tetrahydrobiopterin-deficient mice, Br. J. Pharmacol. 174 (2017) 657–671.
[357] S. Kroller-Schon, T. Jansen, T.L.P. Tran, M. Kvandova, S. Kalinovic, M. Oelze, J.F. Keaney Jr., M. Foretz, B. Viollet, A. Daiber, S. Kossmann, J. Lagrange, K. Frenis, P. Wenzel, T. Munzel, E. Schulz, Endothelial alpha1AMPK modulates angiotensin II-mediated vascular inflammation and dysfunction, Basic Res. Cardiol. 114 (8) (2019).
[358] T. Jansen, S. Kroller-Schon, T. Schonfelder, M. Foretz, B. Viollet, A. Daiber, M. Oelze, M. Brandt, S. Steven, M. Kvandova, S. Kalinovic, J. Lagrange, J.F. Keaney Jr., T. Munzel, P. Wenzel, E. Schulz, alpha1AMPK deletion in myelomonocytic cells induces a pro-inflammatory phenotype and enhances angiotensin II-induced vascular dysfunction, Cardiovasc. Res. 114 (2018) 1883–1893.
[359] S. Kroller-Schon, A. Daiber, S. Steven, M. Oelze, K. Frenis, S. Kalinovic, A. Heimann, F.P. Schmidt, A. Pinto, M. Kvandova, K. Vujacic-Mirski, K. Filippou, M. Dudek, M. Bosmann, M. Klein, T. Bopp, O. Hahad, P.S. Wild, K. Frauenknecht, A. Methner, E.R. Schmidt, S. Rapp, H. Mollnau, T. Munzel, Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation, Eur. Heart J. 39 (2018) 3528–3539.
[360] R.M. Lebovitz, H. Zhang, H. Vogel, J. Cartwright Jr., L. Dionne, N. Lu, S. Huang, M.M. Matzuk, Neurodegeneration, myocardial injury, and perinatal death in mitochondrial superoxide dismutase-deficient mice, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 9782–9787.
[361] Y. Li, T.T. Huang, E.J. Carlson, S. Melov, P.C. Ursell, J.L. Olson, L.J. Noble, M.P. Yoshimura, C. Berger, P.H. Chan, et al., Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase, Nat. Genet. 11 (1995) 376–381.
[362] M. Oelze, S. Kroller-Schon, S. Steven, E. Lubos, C. Doppler, M. Hausding, S. Tobias, C. Brochhausen, H. Li, M. Torzewski, P. Wenzel, M. Bachschmid, K.J. Lackner, E. Schulz, T. Munzel, A. Daiber, Glutathione peroxidase-1 deficiency potentiates dysregulatory modifications of endothelial nitric oxide synthase and vascular dysfunction in aging, Hypertension 63 (2014) 390–396.
[363] A. Di Minno, L. Turnu, B. Porro, I. Squellerio, V. Cavalca, E. Tremoli, M.N. Di Minno, 8-Hydroxy-2-deoxyguanosine levels and heart failure: a systematic review and meta-analysis of the literature, Nutr. Metabol. Cardiovasc. Dis. 27 (2017) 201–208.
[364] A. Di Minno, L. Turnu, B. Porro, I. Squellerio, V. Cavalca, E. Tremoli, M.N. Di Minno, 8-Hydroxy-2-Deoxyguanosine levels and cardiovascular disease: a systematic review and meta-analysis of the literature, Antioxidants Redox Signal. 24 (2016) 548–555.
[365] S. Gao, D. Zhao, M. Wang, F. Zhao, X. Han, Y. Qi, J. Liu, Association between circulating oxidized LDL and atherosclerotic cardiovascular disease: a meta-analysis of observational studies, Can. J. Cardiol. 33 (2017) 1624–1632.
[366] R.M. LeLeiko, C.S. Vaccari, S. Sola, N. Merchant, S.H. Nagamia, M. Thoenes, B.V. Khan, Usefulness of elevations in serum choline and free F2)-isoprostane to predict 30-day cardiovascular outcomes in patients with acute coronary syndrome, Am. J. Cardiol. 104 (2009) 638–643.
[367] E. Schwedhelm, A. Bartling, H. Lenzen, D. Tsikas, R. Maas, J. Brummer, F.M. Gutzki, J. Berger, J.C. Frolich, R.H. Boger, Urinary 8-iso-prostaglandin F2alpha as a risk marker in patients with coronary heart disease: a matched case-control study, Circulation 109 (2004) 843–848.
[368] C. Vassalle, S. Bianchi, D. Battaglia, P. Landi, F. Bianchi, C. Carpeggiani, Elevated levels of oxidative stress as a prognostic predictor of major adverse cardiovascular events in patients with coronary artery disease, J. Atherosclerosis Thromb. 19 (2012) 712–717.
[369] B. Wang, J. Pan, L. Wang, H. Zhu, R. Yu, Y. Zou, Associations of plasma 8-iso-prostane levels with the presence and extent of coronary stenosis in patients with coronary artery disease, Atherosclerosis 184 (2006) 425–430.
[370] C.S. Chu, K.T. Lee, K.H. Cheng, M.Y. Lee, H.F. Kuo, T.H. Lin, H.M. Su, W.C. Voon, S.H. Sheu, W.T. Lai, Postchallenge responses of nitrotyrosine and TNF-alpha during 75-g oral glucose tolerance test are associated with the presence of coronary artery diseases in patients with prediabetes, Cardiovasc. Diabetol. 11 (2012) 21.
[371] J.A. Vita, M.L. Brennan, N. Gokce, S.A. Mann, M. Goormastic, M.H. Shishehbor, M.S. Penn, J.F. Keaney Jr., S.L. Hazen, Serum myeloperoxidase levels independently predict endothelial dysfunction in humans, Circulation 110 (2004) 1134–1139.
[372] W.H. Tang, N. Iqbal, Y. Wu, S.L. Hazen, Usefulness of cardiac biomarker score for risk stratification in stable patients undergoing elective cardiac evaluation across glycemic status, Am. J. Cardiol. 111 (2013) 465–470.
[373] S. Baldus, C. Heeschen, T. Meinertz, A.M. Zeiher, J.P. Eiserich, T. Munzel, M.L. Simoons, C.W. Hamm, C. Investigators, Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes, Circulation 108 (2003) 1440–1445.
[374] S.J. Nicholls, W.H. Tang, D. Brennan, M.L. Brennan, S. Mann, S.E. Nissen, S.L. Hazen, Risk prediction with serial myeloperoxidase monitoring in patients with acute chest pain, Clin. Chem. 57 (2011) 1762–1770.
[375] M.L. Cheng, C.M. Chen, P.W. Gu, H.Y. Ho, D.T. Chiu, Elevated levels of myeloperoxidase, white blood cell count and 3-chlorotyrosine in Taiwanese patients with acute myocardial infarction, Clin. Biochem. 41 (2008) 554–560.
[376] R. De Caterina, F. Cipollone, F.P. Filardo, M. Zimarino, W. Bernini, G. Lazzerini, T. Bucciarelli, A. Falco, P. Marchesani, R. Muraro, A. Mezzetti, G. Ciabattoni, Low-

density lipoprotein level reduction by the 3-hydroxy-3-methylglutaryl coenzyme-A inhibitor simvastatin is accompanied by a related reduction of F2-isoprostane formation in hypercholesterolemic subjects: no further effect of vitamin E, Circulation 106 (2002) 2543–2549.
[377] G. Desideri, G. Croce, M. Tucci, G. Passacquale, S. Broccoletti, L. Valeri, A. Santucci, C. Ferri, Effects of bezafibrate and simvastatin on endothelial activation and lipid peroxidation in hypercholesterolemia: evidence of different vascular protection by different lipid-lowering treatments, J. Clin. Endocrinol. Metab. 88 (2003) 5341–5347.
[378] M.H. Shishehbor, R.J. Aviles, M.L. Brennan, X. Fu, M. Goormastic, G.L. Pearce, N. Gokce, J.F. Keaney Jr., M.S. Penn, D.L. Sprecher, J.A. Vita, S.L. Hazen, Association of nitrotyrosine levels with cardiovascular disease and modulation by statin therapy, J. Am. Med. Assoc. 289 (2003) 1675–1680.
[379] S. Wassmann, S. Hilgers, U. Laufs, M. Bohm, G. Nickenig, Angiotensin II type 1 receptor antagonism improves hypercholesterolemia-associated endothelial dysfunction, Arterioscler. Thromb. Vasc. Biol. 22 (2002) 1208–1212.
[380] E.T. Leermakers, S.K. Darweesh, C.P. Baena, E.M. Moreira, D. Melo van Lent, M.J. Tielemans, T. Muka, A. Vitezova, R. Chowdhury, W.M. Bramer, J.C. Kiefte-de Jong, J.F. Felix, O.H. Franco, The effects of lutein on cardiometabolic health across the life course: a systematic review and meta-analysis, Am. J. Clin. Nutr. 103 (2016) 481–494.
[381] C. Borghi, S. Omboni, G. Reggiardo, S. Bacchelli, D.D. Esposti, E. Ambrosioni, S.W. Project, Effects of the concomitant administration of xanthine oxidase inhibitors with zofenopril or other ACE-inhibitors in post-myocardial infarction patients: a meta-analysis of individual data of four randomized, double-blind, prospective studies, BMC Cardiovasc. Disord. 18 (2018) 112.
[382] W. Marx, J. Kelly, S. Marshall, S. Nakos, K. Campbell, C. Itsiopoulos, The effect of polyphenol-rich interventions on cardiovascular risk factors in haemodialysis: a systematic review and meta-analysis, Nutrients 9 (2017).
[383] Y. Panahi, M.S. Hosseini, N. Khalili, E. Naimi, M. Majeed, A. Sahebkar, Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis, Clin. Nutr. 34 (2015) 1101–1108.
[384] S. Asgary, R. Karimi, S. Momtaz, R. Naseri, M.H. Farzaei, Effect of resveratrol on metabolic syndrome components: a systematic review and meta-analysis, Rev. Endocr. Metab. Disord. 20 (2019) 173–186.
[385] E. Ros, M.A. Martinez-Gonzalez, R. Estruch, J. Salas-Salvado, M. Fito, J.A. Martinez, D. Corella, Mediterranean diet and cardiovascular health: teachings of the PREDIMED study, Adv. Nutr. 5 (2014) 330S–336S.
[386] E. Lonn, J. Bosch, S. Yusuf, P. Sheridan, J. Pogue, J.M. Arnold, C. Ross, A. Arnold, P. Sleight, J. Probstfield, G.R. Dagenais, Hope, H.-T.T. Investigators, Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial, J. Am. Med. Assoc. 293 (2005) 1338–1347.
[387] J.F. Mann, E.M. Lonn, Q. Yi, H.C. Gerstein, B.J. Hoogwerf, J. Pogue, J. Bosch, G.R. Dagenais, S. Yusuf, Effects of vitamin E on cardiovascular outcomes in people with mild-to-moderate renal insufficiency: results of the HOPE study, Kidney Int. 65 (2004) 1375–1380.
[388] D.P. Vivekananthan, M.S. Penn, S.K. Sapp, A. Hsu, E.J. Topol, Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials, Lancet 361 (2003) 2017–2023.
[389] S. Yusuf, G. Dagenais, J. Pogue, J. Bosch, P. Sleight, Vitamin E supplementation and cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators, N. Engl. J. Med. 342 (2000) 154–160.
[390] V. Jaquet, L. Scapozza, R.A. Clark, K.H. Krause, J.D. Lambeth, Small-molecule NOX inhibitors: ROS-generating NADPH oxidases as therapeutic targets, Antioxidants Redox Signal. 11 (2009) 2535–2552.
[391] G. Teixeira, C. Szyndralewiez, S. Molango, S. Carnesecchi, F. Heitz, P. Wiesel, J.M. Wood, Therapeutic potential of NADPH oxidase 1/4 inhibitors, Br. J. Pharmacol. 174 (2017) 1647–1669.
[392] S. Ye, H. Zhong, S. Yanamadala, V.M. Campese, Oxidative stress mediates the stimulation of sympathetic nerve activity in the phenol renal injury model of hypertension, Hypertension 48 (2006) 309–315.
[393] R.R. Campos, E.B. Oliveira-Sales, E.E. Nishi, J.F. Paton, C.T. Bergamaschi, Mechanisms of renal sympathetic activation in renovascular hypertension, Exp. Physiol. 100 (2015) 496–501.
[394] E.B. Oliveira-Sales, E.E. Nishi, B.A. Carillo, M.A. Boim, M.S. Dolnikoff, C.T. Bergamaschi, R.R. Campos, Oxidative stress in the sympathetic premotor neurons contributes to sympathetic activation in renovascular hypertension, Am. J. Hypertens. 22 (2009) 484–492.
[395] S.B. Rajamohan, G. Raghuraman, N.R. Prabhakar, G.K. Kumar, NADPH oxidase-derived H(2)O(2) contributes to angiotensin II-induced aldosterone synthesis in human and rat adrenal cortical cells, Antioxidants Redox Signal. 17 (2012) 445–459.
[396] S. Keidar, M. Kaplan, E. Pavlotzky, R. Coleman, T. Hayek, S. Hamoud, M. Aviram, Aldosterone administration to mice stimulates macrophage NADPH oxidase and increases atherosclerosis development: a possible role for angiotensin-converting enzyme and the receptors for angiotensin II and aldosterone, Circulation 109 (2004) 2213–2220.
[397] A. Emmerson, S.C. Trevelin, H. Mongue-Din, P.D. Becker, C. Ortiz, L.A. Smyth, Q. Peng, R. Elgueta, G. Sawyer, A. Ivetic, R.I. Lechler, G. Lombardi, A.M. Shah, Nox2 in regulatory T cells promotes angiotensin II-induced cardiovascular remodeling, J. Clin. Invest. 128 (2018) 3088–3101.
[398] P. Wenzel, M. Knorr, S. Kossmann, J. Stratmann, M. Hausding, S. Schuhmacher, S.H. Karbach, M. Schwenk, N. Yogev, E. Schulz, M. Oelze, S. Grabbe, H. Jonuleit, C. Becker, A. Daiber, A. Waisman, T. Munzel, Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction, Circulation 124 (2011) 1370–1381.
[399] J.S. Beckman, W.H. Koppenol, Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly, Am. J. Physiol. 271 (1996) C1424–C1437.
[400] T. Munzel, T. Heitzer, D.G. Harrison, The physiology and pathophysiology of the nitric oxide/superoxide system, Herz 22 (1997) 158–172.
[401] A.E. Loot, J.G. Schreiber, B. Fisslthaler, I. Fleming, Angiotensin II impairs endothelial function via tyrosine phosphorylation of the endothelial nitric oxide synthase, J. Exp. Med. 206 (2009) 2889–2896.
[402] M.I. Lin, D. Fulton, R. Babbitt, I. Fleming, R. Busse, K.A. Pritchard Jr., W.C. Sessa, Phosphorylation of threonine 497 in endothelial nitric-oxide synthase coordinates the coupling of L-arginine metabolism to efficient nitric oxide production, J. Biol. Chem. 278 (2003) 44719–44726.
[403] N.J. Alp, S. Mussa, J. Khoo, S. Cai, T. Guzik, A. Jefferson, N. Goh, K.A. Rockett, K.M. Channon, Tetrahydrobiopterin-dependent preservation of nitric oxide-mediated endothelial function in diabetes by targeted transgenic GTP-cyclohydrolase I overexpression, J. Clin. Invest. 112 (2003) 725–735.
[404] M.H. Zou, C. Shi, R.A. Cohen, Oxidation of the zinc-thiolate complex and uncoupling of endothelial nitric oxide synthase by peroxynitrite, J. Clin. Invest. 109 (2002) 817–826.
[405] U. Hink, M. Oelze, P. Kolb, M. Bachschmid, M.H. Zou, A. Daiber, H. Mollnau, M. August, S. Baldus, N. Tsilimingas, U. Walter, V. Ullrich, T. Munzel, Role for peroxynitrite in the inhibition of prostacyclin synthase in nitrate tolerance, J. Am. Coll. Cardiol. 42 (2003) 1826–1834.
[406] P. Schmidt, N. Youhnovski, A. Daiber, A. Balan, M. Arsic, M. Bachschmid, M. Przybylski, V. Ullrich, Specific nitration at tyrosine 430 revealed by high resolution mass spectrometry as basis for redox regulation of bovine prostacyclin synthase, J. Biol. Chem. 278 (2003) 12813–12819.
[407] M. Bachschmid, S. Thurau, M.H. Zou, V. Ullrich, Endothelial cell activation by endotoxin involves superoxide/NO-mediated nitration of prostacyclin synthase and thromboxane receptor stimulation, Faseb. J. 17 (2003) 914–916.
[408] S. Schildknecht, M. Bachschmid, V. Ullrich, Peroxynitrite provides the peroxide tone for PGHS-2-dependent prostacyclin synthesis in vascular smooth muscle cells, Faseb. J. 19 (2005) 1169–1171.
[409] S. Schildknecht, C. Karreman, A. Daiber, C. Zhao, J. Hamacher, D. Perlman, B. Jung, B. van der Loo, Peter O'Connor, M. Leist, V. Ullrich, M. Bachschmid, Autocatalytic Nitration of Prostaglandin Endoperoxide Synthase-2 by Nitrite Inhibits Prostanoid Formation in Rat Alveolar Macrophages, Antioxid Redox Signal, 2012.
[410] M. Zou, C. Martin, V. Ullrich, Tyrosine nitration as a mechanism of selective inactivation of prostacyclin synthase by peroxynitrite, Biol. Chem. 378 (1997) 707–713.
[411] M.H. Zou, M. Bachschmid, Hypoxia-reoxygenation triggers coronary vasospasm in isolated bovine coronary arteries via tyrosine nitration of prostacyclin synthase, J. Exp. Med. 190 (1999) 135–139.
[412] M.H. Zou, C. Shi, R.A. Cohen, High glucose via peroxynitrite causes tyrosine nitration and inactivation of prostacyclin synthase that is associated with thromboxane/prostaglandin H(2) receptor-mediated apoptosis and adhesion molecule expression in cultured human aortic endothelial cells, Diabetes 51 (2002) 198–203.
[413] B. Brune, K.U. Schmidt, V. Ullrich, Activation of soluble guanylate cyclase by carbon monoxide and inhibition by superoxide anion, Eur. J. Biochem. 192 (1990) 683–688.
[414] M. Weber, N. Lauer, A. Mulsch, G. Kojda, The effect of peroxynitrite on the catalytic activity of soluble guanylyl cyclase, Free Radic. Biol. Med. 31 (2001) 1360–1367.
[415] J.A. Riego, K.A. Broniowska, N.J. Kettenhofen, N. Hogg, Activation and inhibition of soluble guanylyl cyclase by S-nitrosocysteine: involvement of amino acid transport system L, Free Radic. Biol. Med. 47 (2009) 269–274.
[416] A. Beuve, Thiol-based redox modulation of soluble guanylyl cyclase, the nitric oxide receptor, Antioxidants Redox Signal. 26 (2017) 137–149.
[417] T.S. Radhakrishnan, H.S. Savithri, N.A. Rao, T.A. Venkitasubramanian, Temperature and thiol-induced desensitization of a Ca2+-sensitive cyclic-3',5'-nucleotide phosphodiesterase from sheep lung, Biochem. Int. 17 (1988) 927–933.
[418] J. Kahler, S. Mendel, J. Weckmuller, H.D. Orzechowski, C. Mittmann, R. Koster, M. Paul, T. Meinertz, T. Munzel, Oxidative stress increases synthesis of big endothelin-1 by activation of the endothelin-1 promoter, J. Mol. Cell. Cardiol. 32 (2000) 1429–1437.
[419] L. Li, G.D. Fink, S.W. Watts, C.A. Northcott, J.J. Galligan, P.J. Pagano, A.F. Chen, Endothelin-1 increases vascular superoxide via endothelin(A)-NADPH oxidase pathway in low-renin hypertension, Circulation 107 (2003) 1053–1058.
[420] L. Li, S.W. Watts, A.K. Banes, J.J. Galligan, G.D. Fink, A.F. Chen, NADPH oxidase-derived superoxide augments endothelin-1-induced venoconstriction in mineralocorticoid hypertension, Hypertension 42 (2003) 316–321.
[421] Y. Lei, K. Wang, L. Deng, Y. Chen, E.C. Nice, C. Huang, Redox regulation of inflammation: old elements, a new story, Med. Res. Rev. 35 (2015) 306–340.
[422] C. Janko, M. Filipovic, L.E. Munoz, C. Schorn, G. Schett, I. Ivanovic-Burmazovic, M. Herrmann, Redox modulation of HMGB1-related signaling, Antioxidants Redox Signal. 20 (2014) 1075–1085.
[423] E. Venereau, M. Casalgrandi, M. Schiraldi, D.J. Antoine, A. Cattaneo, F. De Marchis, J. Liu, A. Antonelli, A. Preti, L. Raeli, S.S. Shams, H. Yang, L. Varani, U. Andersson, K.J. Tracey, A. Bachi, M. Uguccioni, M.E. Bianchi, Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release, J. Exp. Med. 209 (2012) 1519–1528.
[424] J.M. Abais, M. Xia, Y. Zhang, K.M. Boini, P.L. Li, Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? Antioxidants Redox Signal. 22 (2015) 1111–1129.

[425] C. Janko, M. Filipovic, L.E. Munoz, C. Schorn, G. Schett, I. Ivanovic-Burmazovic, M. Herrmann, Redox Modulation of HMGB1-Related Signaling, Antioxid Redox Signal, 2013.
[426] A. Abderrazak, T. Syrovets, D. Couchie, K. El Hadri, B. Friguet, T. Simmet, M. Rouis, NLRP3 inflammasome: from a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases, Redox Biol. 4 (2015) 296–307.
[427] Y. Mikhed, A. Gorlach, U.G. Knaus, A. Daiber, Redox regulation of genome stability by effects on gene expression, epigenetic pathways and DNA damage/repair, Redox Biol. 5 (2015) 275–289.
[428] B. Brune, N. Dehne, N. Grossmann, M. Jung, D. Namgaladze, T. Schmid, A. von Knethen, A. Weigert, Redox control of inflammation in macrophages, Antioxidants Redox Signal. 19 (2013) 595–637.
[429] R.F. van Golen, M.J. Reiniers, N. Vrisekoop, C.J. Zuurbier, P.B. Olthof, J. van Rheenen, T.M. van Gulik, B.J. Parsons, M. Heger, The mechanisms and physiological relevance of glycocalyx degradation in hepatic ischemia/reperfusion injury, Antioxidants Redox Signal. 21 (2014) 1098–1118.
[430] E.C. Kennett, M.J. Davies, Glycosaminoglycans are fragmented by hydroxyl, carbonate, and nitrogen dioxide radicals in a site-selective manner: implications for peroxynitrite-mediated damage at sites of inflammation, Free Radic. Biol. Med. 47 (2009) 389–400.
[431] R.F. van Golen, T.M. van Gulik, M. Heger, Mechanistic overview of reactive species-induced degradation of the endothelial glycocalyx during hepatic ischemia/reperfusion injury, Free Radic. Biol. Med. 52 (2012) 1382–1402.
[432] M. Yang, B.C. Cooley, W. Li, Y. Chen, J. Vasquez-Vivar, N.O. Scoggins, S.J. Cameron, C.N. Morrell, R.L. Silverstein, Platelet CD36 promotes thrombosis by activating redox sensor ERK5 in hyperlipidemic conditions, Blood 129 (2017) 2917–2927.
[433] P. Wang, Y. Wu, X. Li, X. Ma, L. Zhong, Thioredoxin and thioredoxin reductase control tissue factor activity by thiol redox-dependent mechanism, J. Biol. Chem. 288 (2013) 3346–3358.
[434] J. Ebert, P. Wilgenbus, J.F. Teiber, K. Jurk, K. Schwierczek, M. Dohrmann, N. Xia, H. Li, L. Spiecker, W. Ruf, S. Horke, Paraoxonase-2 regulates coagulation activation through endothelial tissue factor, Blood 131 (2018) 2161–2172.
[435] A. Gorlach, R.P. Brandes, S. Bassus, N. Kronemann, C.M. Kirchmaier, R. Busse, V.B. Schini-Kerth, Oxidative stress and expression of p22phox are involved in the up-regulation of tissue factor in vascular smooth muscle cells in response to activated platelets, Faseb. J. 14 (2000) 1518–1528.
[436] H.H. Versteeg, W. Ruf, Tissue factor coagulant function is enhanced by protein-disulfide isomerase independent of oxidoreductase activity, J. Biol. Chem. 282 (2007) 25416–25424.
[437] J. Ahamed, H.H. Versteeg, M. Kerver, V.M. Chen, B.M. Mueller, P.J. Hogg, W. Ruf, Disulfide isomerization switches tissue factor from coagulation to cell signaling, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 13932–13937.
[438] U. Agarwal, X. Zhou, K. Weber, A.R. Dadabayev, M.S. Penn, Critical role for white blood cell NAD(P)H oxidase-mediated plasminogen activator inhibitor-1 oxidation and ventricular rupture following acute myocardial infarction, J. Mol. Cell. Cardiol. 50 (2011) 426–432.
[439] P. Nowak, J. Kolodziejczyk, B. Wachowicz, Peroxynitrite and fibrinolytic system: the effect of peroxynitrite on plasmin activity, Mol. Cell. Biochem. 267 (2004) 141–146.
[440] S.P. Heffron, I. Parastatidis, M. Cuchel, M.L. Wolfe, M.G. Tadesse, E.R. Mohler 3rd, H. Ischiropoulos, D.J. Rader, M.P. Reilly, Inflammation induces fibrinogen nitration in experimental human endotoxemia, Free Radic. Biol. Med. 47 (2009) 1140–1146.
[441] M. Martinez, A. Cuker, A. Mills, R. Lightfoot, Y. Fan, W.H. Tang, S.L. Hazen, H. Ischiropoulos, Nitrated fibrinogen is a biomarker of oxidative stress in venous thromboembolism, Free Radic. Biol. Med. 53 (2012) 230–236.
[442] C. Vadseth, J.M. Souza, L. Thomson, A. Seagraves, C. Nagaswami, T. Scheiner, J. Torbet, G. Vilaire, J.S. Bennett, J.C. Murciano, V. Muzykantov, M.S. Penn, S.L. Hazen, J.W. Weisel, H. Ischiropoulos, Pro-thrombotic state induced by post-translational modification of fibrinogen by reactive nitrogen species, J. Biol. Chem. 279 (2004) 8820–8826.
[443] A. Jaulmes, P. Sansilvestri-Morel, G. Rolland-Valognes, F. Bernhardt, R. Gaertner, B.P. Lockhart, A. Cordi, M. Wierzbicki, A. Rupin, T.J. Verbeuren, Nox4 mediates the expression of plasminogen activator inhibitor-1 via p38 MAPK pathway in cultured human endothelial cells, Thromb. Res. 124 (2009) 439–446.
[444] N. Carrim, J.F. Arthur, J.R. Hamilton, E.E. Gardiner, R.K. Andrews, N. Moran, M.C. Berndt, P. Metharom, Thrombin-induced reactive oxygen species generation in platelets: a novel role for protease-activated receptor 4 and GPIbalpha, Redox Biol. 6 (2015) 640–647.
[445] K. Jobi, B.H. Rauch, S. Dangwal, K. Freidel, A. Doller, W. Eberhardt, J.W. Fischer, K. Schror, A.C. Rosenkranz, Redox regulation of human protease-activated receptor-2 by activated factor X, Free Radic. Biol. Med. 51 (2011) 1758–1764.
[446] S.K. Das, A.C. White, B.L. Fanburg, Modulation of transforming growth factor-beta 1 antiproliferative effects on endothelial cells by cysteine, cystine, and N-acetylcysteine, J. Clin. Invest. 90 (1992) 1649–1656.
[447] I. Cucoranu, R. Clempus, A. Dikalova, P.J. Phelan, S. Ariyan, S. Dikalov, D. Sorescu, NAD(P)H oxidase 4 mediates transforming growth factor-beta1-induced differentiation of cardiac fibroblasts into myofibroblasts, Circ. Res. 97 (2005) 900–907.
[448] M. Fierro-Fernandez, V. Miguel, S. Lamas, Role of redoximiRs in fibrogenesis, Redox Biol. 7 (2016) 58–67.
[449] H. You, H. Yang, Q. Zhu, M. Li, J. Xue, Y. Gu, S. Lin, F. Ding, Advanced oxidation protein products induce vascular calcification by promoting osteoblastic trans-differentiation of smooth muscle cells via oxidative stress and ERK pathway, Ren. Fail. 31 (2009) 313–319.
[450] F. Parhami, A.D. Morrow, J. Balucan, N. Leitinger, A.D. Watson, Y. Tintut, J.A. Berliner, L.L. Demer, Lipid oxidation products have opposite effects on calcifying vascular cell and bone cell differentiation. A possible explanation for the paradox of arterial calcification in osteoporotic patients, Arterioscler. Thromb. Vasc. Biol. 17 (1997) 680–687.
[451] P.V. Dludla, S.C. Dias, N. Obonye, R. Johnson, J. Louw, B.B. Nkambule, A systematic review on the protective effect of N-acetyl cysteine against diabetes-associated cardiovascular complications, Am. J. Cardiovasc. Drugs 18 (2018) 283–298.
[452] H. Chen, A.L. Tappel, Protection of vitamin E, selenium, trolox C, ascorbic acid palmitate, acetylcysteine, coenzyme Q0, coenzyme Q10, beta-carotene, canthaxanthin, and (+)-catechin against oxidative damage to rat blood and tissues in vivo, Free Radic. Biol. Med. 18 (1995) 949–953.
[453] E.A. Herrera, F. Cifuentes-Zuniga, E. Figueroa, C. Villanueva, C. Hernandez, R. Alegria, V. Arroyo-Jousse, E. Penaloza, M. Farias, R. Uauy, P. Casanello, B.J. Krause, N-Acetylcysteine, a glutathione precursor, reverts vascular dysfunction and endothelial epigenetic programming in intrauterine growth restricted Guinea pigs, J. Physiol. 595 (2017) 1077–1092.
[454] J. Loscalzo, N-Acetylcysteine potentiates inhibition of platelet aggregation by nitroglycerin, J. Clin. Invest. 76 (1985) 703–708.
[455] S. Ali-Hassan-Sayegh, S.J. Mirhosseini, M. Rezaeisadrabadi, H.R. Dehghan, F. Sedaghat-Hamedani, E. Kayvanpour, A.F. Popov, O.J. Liakopoulos, Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: an updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials, Interact. Cardiovasc. Thorac. Surg. 18 (2014) 646–654.
[456] Y. Shen, W. Cai, S. Lei, Z. Zhang, Effect of high/low dose N-acetylcysteine on chronic obstructive pulmonary disease: a systematic review and meta-analysis, COPD 11 (2014) 351–358.
[457] T. Szakmany, B. Hauser, P. Radermacher, N-acetylcysteine for Sepsis and Systemic Inflammatory Response in Adults, *Cochrane Database Syst Rev*:CD006616, 2012.
[458] Z.C. Ozdemir, A. Koc, A. Aycicek, A. Kocyigit, N-Acetylcysteine supplementation reduces oxidative stress and DNA damage in children with beta-thalassemia, Hemoglobin 38 (2014) 359–364.
[459] N.P. Andrews, A. Prasad, A.A. Quyyumi, N-acetylcysteine improves coronary and peripheral vascular function, J. Am. Coll. Cardiol. 37 (2001) 117–123.
[460] M.A. Arstall, J. Yang, I. Stafford, W.H. Betts, J.D. Horowitz, N-acetylcysteine in combination with nitroglycerin and streptokinase for the treatment of evolving acute myocardial infarction. Safety and biochemical effects, Circulation 92 (1995) 2855–2862.
[461] S. Boesgaard, J. Aldershvile, H.E. Poulsen, Preventive administration of intravenous N-acetylcysteine and development of tolerance to isosorbide dinitrate in patients with angina pectoris, Circulation 85 (1992) 143–149.
[462] A. Mehra, A. Shotan, E. Ostrzega, W. Hsueh, J. Vasquez-Johnson, U. Elkayam, Potentiation of isosorbide dinitrate effects with N-acetylcysteine in patients with chronic heart failure, Circulation 89 (1994) 2595–2600.
[463] S. Ghio, S. de Servi, R. Perotti, E. Eleuteri, C. Montemartini, G. Specchia, Different susceptibility to the development of nitroglycerin tolerance in the arterial and venous circulation in humans. Effects of N-acetylcysteine administration, Circulation 86 (1992) 798–802.
[464] J.D. Horowitz, E.M. Antman, B.H. Lorell, W.H. Barry, T.W. Smith, Potentiation of the cardiovascular effects of nitroglycerin by N-acetylcysteine, Circulation 68 (1983) 1247–1253.
[465] L. Pizzulli, A. Hagendorff, M. Zirbes, W. Jung, B. Luderitz, N-acetylcysteine attenuates nitroglycerin tolerance in patients with angina pectoris and normal left ventricular function, Am. J. Cardiol. 79 (1997) 28–33.
[466] M.D. Winniford, P.L. Kennedy, P.J. Wells, L.D. Hillis, Potentiation of nitroglycerin-induced coronary dilatation by N-acetylcysteine, Circulation 73 (1986) 138–142.
[467] J.D. Horowitz, C.A. Henry, M.L. Syrjanen, W.J. Louis, R.D. Fish, T.W. Smith, E.M. Antman, Combined use of nitroglycerin and N-acetylcysteine in the management of unstable angina pectoris, Circulation 77 (1988) 787–794.