



# ABOUT NOXA, VASCULAR RISK FACTORS, ENDOTHELIAL DYSFUNCTION, AND CONSECUTIVE VASCULOPATHY BUT A LITTLE DIFFERENTLY: HOLISTIC APPROACH OF THE PROBLEM (PRELIMINARY COMMUNICATION)

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## ABSTRACT

The endothelial system assures unhindered functioning and stability of the internal milieu maintaining vascular health and protecting against vascular injury, noxa, by producing, synthesising and excreting various substances: vasodilators and vasoconstrictors, growth factors and their inhibitors, pro-inflammatory and anti-inflammatory agents, pro-thrombotic and fibrinolytic factors, and by keeping them in a strict equilibrium: endothelial dysfunction is the change of these properties, what is inappropriate with regard to the preservation of organ function ("endothelial dysfunction" has been used to define diverse syndromes characterized by changes in distinct endothelial functions, related to a cellular phenotypic switch from a quiescent to an activated state and this multifaceted disorder actually encompasses a spectrum of disturbances in vasomotor responses, antithrombotic properties, vascular permeability, leukocyte recruitment [inflammation!] and endothelial cell proliferation [remodelling]).

In the genesis and later development of chronic vascular injury/vasculopathy (e.g. atherosclerosis) endothelial dysfunction (ED) has a crucial key role. The so called risk factors lead to vascular injury through the same mechanism of actions, by inducing oxidative stress (OS → ED!): Harm (noxa, i.e. risk factors [RFs]) → oxidative stress [OS] → endothelial activation [EA], endothelial dysfunction [ED], respectively → vascular injury, vascular disease). Under physiological conditions free radicals are generated during mitochondrial oxidative metabolism: The walls of the mitochondria are leaky to oxygen radicals produced during metabolism. 1% of oxygen used in respiration actually leaks from the mitochondria in the form of superoxide, but in older subjects, and/or in pathological states, in case of risk factor's existence (i.e., repeated and/or prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic foreign impacts/disturbing influences/noxious effects!), respectively the proportion is greater: it exposes the cellular constituents to internally generated oxidative attack. As a part of the host defense response, any kind of noxa including the risk factors endangering steadiness of homeostasis start/trigger off an defensive chain founded on increased ROS formation (permanently existing/repeating noxa→persistent/lasting increased ROS formation→oxidative stress→endothelial activation, endothelial dysfunction, respectively → [chronic] vascular injury). The difference between normal host defense and detrimental cellular activation may well be a consequence of the nature, extent, duration, and combination of the proinflammatory stimuli: a profound but transient reduction of endothelium-dependent dilatation may be adaptive and not necessarily pro-vasculopathogenic, but could become so if other adverse environmental conditions are also present, or if the foreign/unaccustomed stimuli become stable/permanent/lasting, respectively.

Wall of blood vessels may be triggered by several repeated and/or prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic influences-impacts-stimuli (noxa), against which protracted response, the so-called host defense response may develop, and in consequence of this, vascular damage pathological consecutive changes ending in vascular injury, ultimately, may develop.

Recovery of endothelial function occurs in response to strategies known to reduce cardiovascular events: this adds support to the concept that restoration of endothelial function can restabilize the chronic vascular disease process. (I) Non-medicinal influencing of vascular endothelial dysfunction (ED), the lifestyle modifications, respectively, is of indispensable importance. Lifestyle risk factors modifications, including (1) smoking, (2) dietary habits (prescribing flavonoids, omega-3 long-chain polyunsaturated fatty acids (LCPUFAs), management of dietary GI), (3) modification of physical inactivity, (4) adiposity, (5) prescribing caloric restriction (CR), (6) elimination/discontinuance of the stressful lifestyle, strongly influence the established vascular risk factors, and also affect novel pathways of risk such as inflammation/oxidative stress, endothelial function, thrombosis/coagulation, and modest alterations of these lifestyle risk factors are achievable and have substantial effects on (cardio)vascular risk. (II) Medical treatment/influencing of vascular endothelial dysfunction (1) the RAAS-inhibiting angiotensin converting enzyme inhibitors and (2) angiotensin receptor blockers [AT1 receptor blocker telmisartan included]; (3) direct renin inhibitors; (4) statins; (5) acetylsalicylic acid; (6) trimetazidin; (7) third generation beta blockers; (8) PPARgamma agonist; (9) folate; (10) vitamin D; (11) "causal" AOVs; (12) melatonin; (13) AGE crosslink breakers alagebrium; (14) ET receptor antagonist, bosentan; (15) coenzyme Q10; (16) the "causal" antioxidant, (17) N-acetyl-cysteine, (18) treprostinil, (19) selectin inhibitors, (20) melatonin (21) resveratrol, (22) L-arginine, (23) 5-HT(1A) receptor agonists 8-OH DPAT, (24) TNF-α blockers have beneficial in ED also exert a favourable effect on all vessels of the human organism/body; (III) We should strive to completely eliminate the risk factors of the CV disease which induce OS and consequential ED, in addition.- In the end, let me point out that although pharmacocetical interventions to delay vascular injury/events show promise, the main interventions that could be recommended now to human on the basis of evidence is the therapeutic lifestyle interventions[!].)

**Keywords:** Endothelial dysfunction, oxidative stress, risk factors, primary and secondary prevention

## INTRODUCTION

Several weighty evidences are at our disposal establishing the key role of endothelial activation (EA), endothelial dysfunction (ED), respectively, in the development and progression of (chronic) vascular diseases (ChVDs). Vascular endothelial dysfunction precedes the development of vascular injury, therefore, preservation or recovery of endothelial function is important to inhibit the development of vasculopathy and thereby prevent the occurrence of cardiovascular events.

The starting step of ChVD begins in the endothelium (Et), in this, organ" which products/secretes several dozens of endocrine/paracrine/apocrine substances, hormone-like compounds, and takes care scrupulously of the integrity, stability, permanence/homeostasis of internal milieu. The

endothelial system (ES) assures unhindered functioning and stability of the internal milieu<sup>1,2</sup>.

The vascular endothelium/the ES plays a pivotal role in maintaining vascular health and protecting against harms, endogen and/or exogen (arising inside and/or outside the organism) noxa [in author's opinion, the so-called risk factors [RFs]] endangering/imperiling steadiness and inviolability/invulnerability of homeostasis) by producing, synthesising and excreting various substances: vasodilators and vasoconstrictors, growth factors and their inhibitors, pro-inflammatory and anti-inflammatory agents, pro-thrombotic and fibrinolytic factors, and by keeping them in a strict equilibrium.

The intimal layer of blood vessels, i.e., the Et may be affected by several repeated and/or prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic foreign

impacts/disturbing influences/noxious effects/so-called vascular risk factors (endangering the steadiness of homeostasis against which protracted responses, the so called host defense response develops) → increased ROS formation → oxidative stress → endothelial activation, endothelial dysfunction, respectively (in order to eliminate/avert/clear disturbing noxa) may develop: in consequence of this, → chronic vascular injury (functional and then structural alteration of the vessel), pathological change [remodelling] may originate<sup>3,4</sup>.

The endothelial dysfunction is of general nature, and human vascular system is an uniform entity, all (central and peripheral) parts of it are consubstantial physiologically and pathophysiologically as well as regarding its ability to react (i.e. also from a therapeutic aspect)<sup>5</sup>.

ED emerged as an important intermediate factor in organ disease with the decreasing/disturbed endothelial function of the vasculature is progressively exposed to a burden of pathogenetic conditions responsible for severe functional changes in the endothelium, such as reactive oxygen species [ROS], assymetrical dimethylarginine [ADMA], homocysteine or glycosylated end products) should more appropriately be considered as endothelial activation (EA), which may eventually contribute to vascular disease.

Endothelial dysfunction" [ED] has been used to define diverse syndromes characterized by changes in distinct endothelial functions, related to a cellular phenotypic switch from a quiescent to an activated state and this multifaceted disorder actually encompasses a spectrum of disturbances in vasomotor responses, antithrombogenic properties, vascular permeability.

Endothelial activation (EA) represents a switch from a quiescent

phenotype toward phenotype one that involves the host defense response: any kind of noxa endangering steadiness of homeostasis [=risk factors, in my view] → increased ROS formation → oxidative stress → endothelial activation, endothelial dysfunction, respectively → vascular injury). Indeed, most vascular risk factors activate molecular machinery in the endothelium (namely, all these risk factors initially damage the endothelial cells with reduced NO activity<sup>6</sup>) that results in expression of cytokine, chemokines, and adhesion molecules designed to target inflammation to specific tissues to eliminate/avert/clear disturbing noxa: endothelial function is an integrative marker of the net effects of damage from traditional and emerging risk factors on the arterial wall and its intrinsic capacity for repair, and this endothelial-dependent vascular biology is critical, not only in the initiation and progression of chronic inflammatory vascular disease (atherosclerosis), but also in the transition from a stable to an unstable disease state with attendant risks. Initiation and progression of vascular, cardiovascular disease, and its later activation to increase the risk of morbid vascular events, depends on profound dynamic changes in vascular biology. Global or regional hemodynamic disturbances may also be responsible for endothelial hypoxia and activate the endothelial cells, and endothelial activation and subsequent adhesion of leukocytes to the endothelium creates hemodynamic resistances which reduce regional blood flow, and all this underlines the importance of endothelial activation in the genesis of local inflammation at early stages of inflammatory tissue/organ diseases<sup>6,7</sup>.

Endothelium-derived NO plays a key role to maintain the vascular wall in a quiescent state by inhibition of

inflammation, cellular proliferation, and thrombosis: laminar shear stress [=appropriate physical activity!] is probably the major factor that maintains this quiescent, NO-dominated, endothelial phenotype.

Under physiological conditions in the human body free radicals are generated during mitochondrial oxidative metabolism: Humans are carbon-based life forms who burn carbon-based molecules to stay alive, and in the process, free radicals are produced by intention in a process designed to stay within mitochondria. The walls of the mitochondria are curiously leaky to oxygen radicals produced during metabolism. Large amounts of superoxide leak from the mitochondrial walls, such that 1% of oxygen used in respiration actually leaks from the mitochondria in the form of superoxide, but in older subjects, and/or in pathological states, in case of risk factor's existence (i. e., repeated and/or prolonged mechanical, physical, chemical, microbiological, immunologic, and genetic foreign impacts/disturbing influences/noxious effects!), respectively the proportion is greater: it thus potentially exposes the cellular constituents to internally generated oxidative attack. As a part of the host defense response, any kind of noxa including the well-known and the not yet known risk factors endangering steadiness of homeostasis start/trigger off an defensive chain founded on increased ROS formation (permanently existing/repeating noxa→persistent/lasting increased ROS formation→oxidative stress→endothelial activation, endothelial dysfunction, respectively → [chronic] vascular injury). The difference between normal host defense and detrimental cellular activation may well be a consequence of the nature, extent, duration, and combination of the proinflammatory stimuli: a profound but transient reduction of endothelium-dependent dilatation may be adaptive and not necessarily pro-vasculopathogenic, but could become so if other adverse environmental conditions are also present, or if the foreign/unaccustomed stimuli become stable/permanent/lasting, respectively<sup>8,6</sup>.

The eNOS, which normally helps maintain the quiescent state of the endothelium, can switch to generate ROS in appropriate circumstances as part of endothelial activation (EA). This is termed eNOS uncoupling, and results in superoxide formation if the key cofactor tetrahydrobiopterin is not present, or generation of hydrogen peroxide if the substrate L-arginine is deficient. Thus, the ability of eNOS to regulate both the quiescent and activated endothelial phenotype puts this enzyme at the center of endothelial homeostasis. The difference between normal host defense and detrimental cellular activation may well be a consequence of the nature, extent, duration, and combination of the proinflammatory stimuli: a profound but transient reduction of endothelium-dependent dilatation may be adaptive and not necessarily pro-vasculopathogenic, but could become so if other adverse environmental conditions are also present, or if the foreign/unaccustomed stimuli become stable/permanent/lasting, respectively<sup>9</sup>.

Aging per se, in the absence of other risk factors is associated with oxidative/nitrosative stress and inflammatory changes in the phenotype of blood vessels, and primary abnormalities in perfusion worsen with age, secondarily causing dysfunction of the cells, predisposing to organic cell injury and damage: these changes together with individual's (environmental) risk factors set the stage for the development of chronic vascular disease.

The elderly organism is exposed to a continuous oxidative attack as in the mitochondria of its cells free oxygen-containing radicals and other oxidants, primarily superoxide anions (O<sub>2</sub><sup>-</sup>) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) are generated in an increased amount during the imperfectly proceeding terminal oxidation.

The overproduction of reactive oxygen- and nitrogen-containing radicals and other oxidants, one of the most potent oxidants, which is produced in the reaction of superoxide anions and nitrogen monoxide, enters the cells where it aggressively attacks the most different cellular structures. It starts the chain reaction of lipid peroxidation and elicits DNA damage, chain breaks: DNA chain breaks activate the poly (ADP-ribose) polymerase (PARP) enzyme in the cellular nucleus: it creates energetic crisis in the endothelial cells what reduces NO synthesis occurring upon the effect of endothelium-dependent vasorelaxant agents in the endothelial cells<sup>10</sup>.

The human vascular system is uniform, representing an entity, all of its parts (central and peripheral vessels) are consubstantial<sup>2</sup>: Not regarding familial accumulation, it cannot be predicted, either, if an individual with coexisting risk factors will suffer myocardial infarction or stroke in the future, if he/she develops AMD or, what is very common, more organ systems will be affected by chronic vascular disease at the same time: one can conclude to the general, systemic nature of endothelial dysfunction, the consubstantiality of vascular system.

As human vascular system is uniform, and consubstantial representing an entity, all of its parts (central and peripheral vessels) are consubstantial, it is almost impossible (or at least it seems to be forced, artificial) the vascular events to be discussed clinically separated as sharply discerned entities. Some examples of this<sup>6,11</sup>:

(1) In patients with vascular type erectile dysfunction (vascular injury of the internal iliac arteries and/or the smaller vessels supplying the penis), flow-mediated dilatation (FMD) in the brachial artery is decreased to a significant extent, as well as the incidence of vascular diseases including coronary artery disease and peripheral arterial disease and stroke is increased in patients with erectile dysfunction.

(2) In endothelial dysfunction of the coronaries – also without an occlusive CAD – there is a significantly increased chance of developing cerebrovascular even.

(3) In patients with type 2 diabetes mellitus age-related macular degeneration (ED of chorioid arteries injury) has proven to be an independent risk factor of cardiovascular mortality.

(4) Plaques in the carotid bifurcation were associated with a 4.7 times increased prevalence odds of macular degeneration; those with plaques in the common carotid artery showed an increased prevalence odds of 2.5; lower extremity arterial disease (ankle-arm index less than 0.90 on at least one side) was associated with a 2.5 times increased prevalence odds of AMD, respectively.

(5) Age-related macular degeneration (AMD) developed in 22% of patients with coronary artery disease (CAD) who require coronary intervention or underwent it: this percentage of incidence is strongly significantly higher than the percentage occurring in the general population.

(6) The presence of AMD also signals an increased risk of CVD, independent of the effect of age and shared risk factors; where those with late AMD had triple the risk of incident coronary heart disease (CHD): prevalence of early

AMD is significantly higher in patients with MI than in a random sample of the population.

(7) Presence of AMD, especially neovascular AMD, is prospectively associated with a higher risk of incident myocardial infarction (MI), and this finding suggests the possibility of shared common antecedents between MI and AMD.

(8) Several prospective studies have demonstrated that (both early and advanced AMD-related) retinal changes are important independent risk factors for the incidence of myocardial infarction.

(9) Disorders of the retinal microvascular system are good predictors of severe cardiovascular and cerebral events. Narrower retinal arterioles (retinal arteriolar narrowing is a marker of systemic microvascular damage) are associated with lower hyperemic myocardial blood flow and perfusion reserve (perfusion reserve reflects microvascular processes in the organ) in asymptomatic adults with no coronary calcification, which is primary mediated by traditional cardiovascular risk factors<sup>1,18</sup>: this finding suggest that retinal arteriolar narrowing may serve as a marker of coronary microvascular disease.

(10) The microvascular pathogenic process in different circulatory beds is affected by common risk factors, and these data are supported, by the studies showing a relationship between coronary flow reserve and microvascular structure in subcutaneous fat tissue: vascular structure in subcutaneous small arteries predicts cardiovascular events.

(11) Women who have experienced pre-eclampsia are more likely to develop cardiovascular disease in later life. In the maternal syndrome of pre-eclampsia arises from a generalised maternal inflammatory systemic response incorporating a substantive component of endothelial cell dysfunction: flow-mediated dilatation (FMD) in the brachial artery is decreased to a significant extent. Pregnant women with pre-eclampsia often demonstrate decreased blood flow in the uterine artery, and poor utero-placental blood flow (placental underperfusion associates with placental oxidative stress!) sets up a chain of events which culminates in the development of pre-eclampsia in a woman susceptible of the disease. ED, unlike pre-eclampsia does not resolve post-partum, and persistence of this defect may underpin the increased risk of (cardio)vascular disease in later life: a history of pre-eclampsia increases the risk of future hypertension, ischaemic heart disease, stroke, vascular death, and venous thromboembolism.

(12) The significantly lower FMD in patients with glaucomatocyclitic crisis (GCC) implies (peripheral) vascular endothelial dysfunction (several studies have shown impaired vascular endothelial function in glaucoma, also). The impairment of endothelial function of the brachial artery in patients with GCC observed indicated a systemic rather than a local vascular effect. Improvement of endothelial dysfunction may inhibit flare-ups of GCC.

(13) Persons with early AMD (ED of the choroidal arteries!) had double the risk of incident stroke over 10 years: the increased risk of both cerebral infarction and intracerebral hemorrhage refers to common pathophysiological processes between AMD and stroke subtypes.

From the fact that in the conditions listed in points 1-13, the vascular events presented themselves also at areas of supply (internal iliac artery, arteries of the penis, coronaries, uterine artery, subcutaneous vessels, cerebral vessel, choroidal



vessels) far from the brachial artery that showed ED, one can conclude to the general, systemic nature of endothelial dysfunction, the consubstantiality of vascular system<sup>11</sup>.

The cause of this cognition of essential importance may be partly, in the author's opinion, the following: Until recently, it was believed that the bioactivity of the NO is limited to close temporal and spatial proximity of the endothelium and that NO is mere autocrine/paracrine effector, i.e., that it can only travel short distances in the bloodstream: however, recent studies suggest that free NO is in equilibrium with a pool of various NO-containing compounds in blood (i.e. plasma nitroso compounds - RXNOs) that have bioactivity that in every respect, resembles that of authentic NO. These nitroso compounds (RXNOs) are transported and delivered along the complete vascular tree to dilate distal arteries and the microvasculature. ED in patients with CV RFs is associated with decreased levels of circulating RXNOs, plasma RXNOs (plasma nitroso compounds referred to as the circulating NO pool) may be a surrogate index of ED!<sup>12</sup>.

For the almost regularly returning, repeated phenomenon, I recommend the use of the term chain of systemic vascular events, emphasising the physiological, pathophysiological and therapeutic unity, consubstantiality of the human vascular system also by this way. That is why it seems to be more reasonable, more correct to disregard the terms by organ (system) (stroke prevention, AMD prevention, MI prevention) and simply to say vascular (system) prevention<sup>13</sup>. If we thoroughly analyse the conditions which are considered as cardiovascular risk factors of VD (Table I)<sup>6,13</sup> ("classical" risk factors: and „more recent" risk factors), it attracts notice that all of these risk factors which seem essentially different lead to (chronic) vascular injury based, after all, on the same mechanism of action: by inducing oxidative stress and consequential endothelial dysfunction. The classical cardiovascular risk factors (CRFs) act directly on the endothelium through an increase in the production of reactive oxygen species, promoting an endothelial activation mediated by the expression of adhesion and proinflammatory molecules, which lead to endothelial dysfunction, the onset of (cardio)vascular disease, and the progression of the vascular injury/vasculopathy. Thus endothelial dysfunction itself is a consequential phenomenon, and it is a clinically-pathophysiologically important connecting link between harm (noxa) and vascular injury.-

As a part of the host defense response, any kind of noxa including the well-known and the not yet known risk factors endangering steadiness of homeostasis start/trigger off an defensive chain founded on increased ROS formation (permanently existing/repeating noxa→persistent/lasting increased ROS formation→oxidative stress→endothelial activation, endothelial dysfunction, respectively): indeed, most cardiovascular risk factors activate molecular machinery in the endothelium that results in expression of chemokines, cytokines, and adhesion molecules designed to interact with leukocytes and platelets and target inflammation to specific tissues to eliminate/clear/avert noxa<sup>6,14</sup>.

Strategies to reverse endothelial function<sup>6, 15</sup> have been examined in a wide range of patients with vascular disease. Benefit has been shown with a number of pharmacological interventions, which include drugs that lower lipids and blood pressure, as well as with novel therapies based on new understanding of endothelial biology. Recovery of endothelial function occurs in response to strategies known to reduce cardiovascular events. This adds support to the

concept that restoration of endothelial function can restabilize the chronic vascular disease process.

Several classes of drugs have been shown to have direct actions on the endothelium that are independent of their effects on cardiovascular risk factors. Author would like to stress the importance of the greatly leveraged gains that can be anticipated from early intervention.

(1) Non-medicinal influencing of endothelial dysfunction (ED), the lifestyle modifications of patient, respectively, is of indispensable importance, indeed, our health also depends on our lifestyle choice. It is very important to identify modifiable risk factors (lifestyle risk factors) that may reduce disease occurrence or prevent progression to advanced stages. Lifestyle risk factors modifications, including smoking, dietary habits, physical inactivity, adiposity, caloric restriction (CR) elimination/discontinuance of the stressful lifestyle, strongly influence the established vascular risk factors and also affect novel pathways of risk such as inflammation/oxidative stress, endothelial function, thrombosis/coagulation, and modest alterations of these lifestyle risk factors are achievable and have substantial effects on (cardio)vascular risk.

#### (1) Smoking cessation<sup>16</sup>,

Smoking cessation is of vital importance, smoking has been linked to increased oxidative stress, platelet aggregation, higher fibrinogen level, and reduced plasma high-density lipoprotein and diminished antioxidant levels<sup>109, 60</sup>, increases inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol. Cigarette smoke exposure increases oxidative stress as a potential mechanism for initiating vascular dysfunction, and upregulates pro-angiogenic vascular endothelial growth factor (VEGF).

#### (2) Caloric restriction (CR)<sup>17</sup>

CR is a dietary regimen confers vasoprotection. The mechanisms underlying the beneficial vascular effects of CR are undoubtedly multifaceted and may include improvement of systemic risk factors for vascular diseases, such as decreases in serum cholesterol, triglycerides, fasting glucose and fasting insulin levels, and reduction of systolic and diastolic blood pressure as well as direct antiaging effects exerted on the vasculature per se. The molecular mechanism by which CR promotes a beneficial endothelial phenotype includes upregulation and activation of eNOS.

#### (3) Elimination/discontinuance of the stressful lifestyle

Reduction in flow-mediated vasodilation was seen during mental stress. A stressful lifestyle, is also a well-known risk factor for the development and progression of vascular injury.

#### (4) Regular physical activity

Regular physical activity promotes mitochondrial health, induces mitochondrial biogenesis, and upregulates mitochondrial antioxidant systems, which also may contribute to its vasoprotective properties (physical activity → increased shear-stress by physical exercise → improvement of ED!). Physical activity increases vascular expression of eNOS, and increased NO synthesis secondary to amplified shear stress induces extracellular superoxide dismutase (SOD) expression. Physical activity raises high-density lipoprotein cholesterol, lowers low-density lipoprotein cholesterol and triglycerides, lowers blood pressure, improves fasting and postprandial glucose-insulin homeostasis, induces and maintains weight loss, improves physiological well-being, and likely lowers inflammation. Regular exercise reduces CRP, IL-6, and TNF-α levels and

also increases anti-inflammatory substances such as IL-4 and IL-10).<sup>18</sup>

#### (5) Prescribing a diet

Diet which assures the intake of an appropriate dose of the most important polyunsaturated fatty acid (PUFA), and contains flavonoids (polyphenols), natural antioxidants in abundance, is rich in vegetables and fruits.

a) Flavonoids<sup>19</sup> (large family of polyphenols ubiquitously expressed in plants) possess several anti-inflammatory activities due to their ability to scavenge reactive oxygen and nitrogen species (ROS and RNS), to inhibit the pro-inflammatory activity of ROS-generating enzymes including cyclooxygenase (COX), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS).

b) Omega-3 long-chain polyunsaturated fatty acids (LCPUFAs)<sup>20, 6</sup> may act in a protective role against ischemia-, oxygen-, inflammatory-, and age-associated pathology of the vasculature. Eicosapentaenoic acid- (EPA-) rich diet results in significant suppression of inflammatory molecules (intercellular adhesion molecule [ICAM]-1, monocyte chemotactic protein [MCP]-1, interleukin [IL]-6), and vascular endothelial growth factor (VEGF), and EPA prevents inflammation and oxidative impairment by inhibiting inflammatory and oxidative stress response. PUFAs intervention decreases the neovascular activity via PPAR-dependent reduction of inflammatory mediators and attenuation of EC activation.

#### c) Glycemic index (GI)<sup>21</sup>

Management of dietary GI appears to be an effective intervention for the prevention of metabolic diseases. Epidemiological evidence indicates positive associations between GI and risk for diabetes, vascular disease: a low GI diet may be beneficial in reducing vascular disease risk. The risks for major age-related debilities including coronary heart disease, diabetes are diminished in people who consume lower glycemic index (GI) diets.

#### (d) Dietary sodium restriction<sup>22</sup>

Low sodium intake markedly enhanced NO-mediated endothelial-dependent dilatation (EDD) (by greater forearm blood flow  $|\Delta FBF|$ (ACh) with endothelial NO synthase inhibition, restores BH(4) bioactivity, and increases circulating superoxide dismutase activity.

#### (II) Medical treatment of vascular dysfunction

The beneficial effect of a favourable influence on ED, its successful medicinal therapy established fact in (cardio)vascular (CV) diseases (VD), and the treatment of ED is an inherent part of the therapy of "underlying disease": both primary and secondary prevention of ChVD could be realised by this way.

The concept of lifetime risk management can be modeled to demonstrate the great potential for event-free life prolongation in individual subjects that can result from even modest reductions in risk factors introduced at an early stage of the ChVD.- Oxidative stress (OS) and endothelial dysfunction (ED) due to the risk factors of chronic inflammatory vascular disease (ChVD) and their consequences can be significantly mitigated or prevented by ACE inhibitors and/or ARBs and statins, and by ASA, trimetazidine, third generation beta blockers as well as PPARgamma agonist (or rather by the concomitant, combined administration of all these medicines).

Medical treatment/medicinal influencing of vascular endothelial dysfunction should be aimed not only at increasing levels of NO but also at reducing those of vascular

superoxid and peroxinitrit: substances that simply deliver NO will worsen rather than improve endothelial dysfunction via further peroxinitrite formation. In the setting of endothelial dysfunction and high oxidative stress the ideal compound should stimulate NO production and simultaneously reduce oxidative stress within vascular tissues.

(1) ACE inhibition attenuates the superoxide-generating effects of angiotensin II, impaired the breakdown of bradykinin, and increased the production of endothelium-derived nitric oxide (EDNO). Angiotensin converting enzyme inhibitors (ACEIs) facilitates nitrogen monoxide (NO) production causing vasodilatation: EDNO besides inhibits aggregation of platelets, inhibits adhesion of monocytes and leukocytes to the endothelium, inhibits smooth muscle cell proliferation and inhibits oxidation of LDL also, reduces vascular inflammation, and counteracts endothelial cell senescence via facilitating NO production, and plays a key role to maintain the vascular wall, healthy in a quiescent NO-dominated, endothelial phenotype<sup>23</sup>.

(2) AR-blockers/AT1-receptor antagonists (ARBs) act against the unfavourable, harmful vascular effects of angiotensin II exerted on the AT1 receptors, and significantly inhibit them. AT1-receptor antagonists (ARBs) increase/enhance the expression of AT2 receptors, and that so indirectly stimulated AT2 receptors, prevent/stall all unfavourable effects of angiotensin II to be realised on the AT1 receptors ("receptor switching phenomenon").

Tissue RAS is activated in the pathogenesis of neoangiogenesis (NAG), leading to angiotensin type-1-receptor(AT1-R)-mediated expression of inflammation-related molecules including vascular endothelial growth factor (VEGF), intercellular adhesion molecule (ICAM)-1, and monocyte chemotactic protein(MCP)-1. The blockade of AT1 receptors (executed by an ARB product) leads to significant suppression of NAG.

The AT1 receptor blocker telmisartan, by putting peroxisome proliferator-activated receptor-gamma (PPARGgamma) effects into operation, inhibits the development of NAG, and clinically beneficially influences, improves choroidal neovascularisation (CNV)<sup>24</sup>.

Most probably, concomitant therapeutic administration of ACEI and ARB may be the most expedient<sup>25</sup>: one of the agents ensures the benefits of elevated bradykinin level, while the other drug inhibits the unfavourable effects of angiotensin II exerted on the AT1 receptor.

#### (3) Direct renin inhibitors<sup>26</sup>

Recently the armamentarium of clinical medicine has included an orally acting direct renin inhibitor aliskiren (a RAS blocker). We can reasonably presume that the inhibition of renin will be a better strategy than the currently existing ACEI and ARB medicines: as the direct renin inhibitor aliskiren blocks the deleterious microvascular effects of renin and prorenin occurring upon their binding to the (pro)renin receptors, this may mean a considerable therapeutic advantage in comparison to ACE-inhibitors and AR-blockers, and it may actually mediate more robust vascular protection than either ACEI or ARB.

#### (4) Statins (HMGCoA)<sup>27</sup>

Of the anti-lipaeamic products, the up-to-date hydroxymethylglutaryl-coenzyme A (HMGCoA) reductase inhibitor statins (simvastatin, lovastatin, atorvastatin, resuvastatin, fluvastatin, etc.) improve endothelial function (EF) and substantially reduce ED. This is independent of the cholesterol-lowering effect of these drugs. They increase the

bioavailability/usability of NO and increase flow-mediated dilatation (FMD) that depends on the endothelium. They increase and enhance the activity of endothelial nitric oxide synthetase (eNOS) also indirectly by reducing the serum level of CRP. They also inhibit vascular inflammation by suppressing the expression and activity of adhesion molecules and chemokines, they promote the process of restoring endothelial injuries and actively participate in it by increasing the number and improving the function of endothelial progenitor cells (EPCs), significantly mitigate inflammation as they stimulate the expression of peroxisome proliferator-activated receptor-gamma (PPARgamma). Statins reduces endothelial cell apoptosis by confining inflammation, by increasing the bioavailability of nitric oxide, and through their anti-oxidative effects.

#### (5) Acetylsalicylic acid (ASA)

Acetylsalicylic acid (ASA) (aspirin) acts not only by inhibiting platelet aggregation, but just by restoring the balance of endothelium regarding its vasodilating, antiadhesive, antithrombotic, and anti-inflammatory functions: the significant effects of aspirin which have a pleiotropic activity include inhibition of angiotensin II, and ASA exerts that through its potent antioxidant (i.e. anti-ED) properties by inhibiting vascular superoxide production. Aspirin is associated with decreased rates of CNV among AMD patients.<sup>28</sup>

#### (6) Trimetazidine (TMZ) (1-[2,3,4-trimethoxybenzyl] piperazine, dihydrochloride)

TMZ attains its beneficial effect by partial inhibition of fatty acid oxidation and substantial mitigation/reduction of damage due to free radicals including endothelial dysfunction. Trimetazidine substantially mitigates oxidative stress, has a beneficial effect on lipid peroxidation and changes due to ischemic injury.<sup>29</sup>

#### (7) Third generation beta blockers<sup>30</sup>

The third generation beta blockers: carvedilol, nebivolol<sup>191</sup> exert its vascular protective effects exactly via mitochondrial antioxidant activity. Nebivolol inhibits the gene expression of adhesion molecules (P and E selectins and VCAM-1) of vascular wall, endothelium and smooth muscle cells, as well as it reduces the number of macrophages migrating into the intimal layer and neointima formation, and increases the NO production, inhibits the free oxygen radicals. Nebivolol a vasodilating beta blocker with antioxidant activity improves OS and endothelial function.

#### (8) PPARgamma agonists<sup>31</sup>

The PPARgamma agonists reduce the expression of NADPH oxidase and vascular oxidative stress, they suppress inflammatory processes. They directly inhibit the activation of vascular endothelial growth factor (VEGF), PPARγ agonists increase endothelial NO release without altering endothelial NO synthase expression, they also stimulate both activity and expression of Cu/Zn-SOD: these findings illuminate additional molecular mechanisms by which PPARγ agonists may directly alter vascular endothelial function, to advantage.

#### (9) Folate<sup>32</sup>

Folate improves endothelial dysfunction by reducing the serum levels of homocysteine: elevated levels of homocysteine (Hcy) promote endothelial dysfunction by their toxic effects on the endothelium, probably mediated by an increase in oxidative stress and inhibition of NO production. Daily supplementation with folic acid (2,5 mg/d), pyridoxine

(50 mg/d), and cyanocobalamin (1 mg/d) may reduce the risk of vasculopathy.

#### (10) Vitamin D status<sup>33</sup>

Vitamin D - because of its anti-inflammatory, immune modulating properties - may suppress the cascade of destructive inflammation. The increase of circulating 25(OH) (vitamin D) results in a significant decrease of the systemic inflammation biomarkers, hsCRP, serum amyloid antigen (SAA), TNF-α and IL-6 (anti-inflammatory effects of cholecalciferol!), vitamin D has been shown to have anti-angiogenic properties.

#### (11) Antioxidant vitamins (AOVs)

The „symptomatic” AOVs (12) (vitamin C, E) used for preventing, conventionally, OS<sup>152</sup> did not really live up to the hopes placed in them: the activity of AOVs against OS is limited only to scavenging the already formed oxidative products. That is why they are called “symptomatic” and not “causal” antioxidants (AO) protecting the integrity of cellular mitochondria.

#### (12) The “causal” AOVs products<sup>34</sup>

The clinical development of “causal” AOVs products with “mitochondrial” activity (SOD and catalase mimetics, t-propionyl carnitine, LY3335311, PJ3 and FP15 metalloporphyrin as well as the PAP-inhibitor INO-1001) are in progress. The inhibition of the reaction pathway peroxynitrite → DNA damage → PARP by rapid catalytic breakdown of peroxynitrite with the help of the FP15 metalloporphyrin compound, showing great promise, or by the inhibition of PARP with the drug INO-1001 may open a new possibility in the treatment of OS induced vascular dysfunction in several pathologic conditions.

Nevertheless, we have excellent therapeutic possibilities also until then: statins, ACEIs ARBs, ASA (aspirin), trimetazidine, third generation beta blockers, PPARgamma agonists.

#### (13) Melatonin<sup>35</sup>

Melatonin is a strong antioxidant and can induce the expression of various antioxidant enzymes by activation of melatonin receptors. Long-term melatonin treatment may prevent the age-dependent mitochondrial oxidative stress due to its direct free radical scavenger activity. Melatonin inhibits leukocyte-endothelial interaction, the first step of the inflammatory process.

#### (14) Resveratrol (RSV) (3,5,4'-trihydroxystilbene)<sup>36</sup>

RSV (3,5,4'-trihydroxystilbene) a diet-derived polyphenol (polyphenolic phytoalexin), was reported to mimic many respect of caloric restriction (CR) and to exert vasoprotective effects, attenuating OS, improving endothelial function, inhibiting vascular inflammation, and decreasing the rate of endothelial apoptosis.

A component of red wine, independent of ethanol, possibly a polyphenol such as resveratrol, may confer vasculoprotection (improvement in microvessel function[!]).

#### (14) L-arginine<sup>37</sup>

L-arginine supplementation is a reasonable method to increase endothelium NO production and lower free radicals formation: dietary supplementation (7g/day) of arginine reverses endothelial dysfunction associated with major vascular risk factors and ameliorates many common vascular disorders

#### (15) Coenzyme Q10 (CoQ10)<sup>38</sup>

CoQ10 supplementation is associated with significant improvement in endothelial function (120 mg/day) via reversal of mitochondrial dysfunction. CoQ10 is a potent



antioxidant: presence of adequate tissue concentrations of CoQ may be important in limiting oxidative and nitrosative damage.

#### (23) N-acetyl-cysteine (NAC)<sup>39</sup>

A potent antioxidant N-acetyl-cysteine (NAC) inhibits indicators of oxidative stress and the activation of NF-κB, and, consequently, suppresses macrophage and neutrophil infiltration: NAC is a potent antioxidant that is known to be a precursor of glutathione (GSH), and NAC acted directly as free radical scavengers and is independent of its ability to enhance GSH synthesis.

#### (24) Selectin inhibitors

Therapies based on selectin inhibitors has beneficial effects on the reduction of endothelial dysfunction to alleviate inflammation, hemodynamic disturbances, hypoxia increasing NO bioavailability. This strategy targets distinct aspects of endothelial pathophysiology, thereby reducing specific consequences of concerning organ endothelial functional alterations.

#### (25) Doxycycline<sup>40</sup>

Doxycycline ameliorates hypertension-induced endothelial dysfunction by inhibiting oxidative stress generation and improving NO bioavailability, in addition to its inhibitory effects on MMP activity.

(III) Furthermore, obviously, we have to strive for the possibly complete elimination, aversion of all risk factors of VD.

In the end, let me point out that although pharmacocoeutical interventions to delay vascular injury/events show promise, the main interventions that could be recommended now to human on the basis of evidence is the therapeutic lifestyle interventions.

### Abbreviations

ACE I = angiotensin converting enzyme inhibitor; AMD = age-related macular degeneration; Ang-II = angiotensin II; AO = antioxidant; AOVs = antioxidant vitamins; ARB = angiotensin II receptor blocker; ASA = acetylsalicylic acid; AS = atherosclerosis; AT1R = AT1 receptor of angiotensin II; CAD = coronary artery disease; CHD = coronary heart disease; CNV = choroidal neovascularisation; ChVD = chronic ascular diseases CR = caloric restriction; CRP = C-reactive protein; CV = cardiovascular; CVD = cardiovascular disease; DHA = docosahexaenoic acid; E = endothelium, endothelial system; EA = endothelial activation; ED = endothelial dysfunction; EF = endothelial function; EPCs = endothelial progenitor cells; ES = endothelial system; Et = endothel, endothelium; ET-1 = endothelin 1; eNOS = endothelial nitric oxide synthetase; FMD = flow-mediated dilatation; GCC = glaucomatocyclitic crisis; GI = glycaemic index; H2O2 = hydrogen peroxide; HDL-C = high density lipoprotein cholesterol; HMGCoA = hydroxy-methylglutaryl-coenzyme A; hsCRP = high sensitivity C-reactive protein; ICAM = intracellular adhesion molecule; IL-6 = interleukin 6; INO-1001 = poly(ADP-ribose) polymerase inhibitor; LDL-C = low density lipoprotein cholesterol; Lp(a) = lipoprotein (a); LCPUFAs = long-chain polyunsaturated fatty acids; MCP-1 = monocyte chemotactic protein-1; MI = myocardial infarction; NAG = neoangiogenesis; NO = nitrogen monoxid; Nrf2 = nuclear fa0ctor-E(2)-related factor-2; NF-kappaB = nuclear factor kappa B; O2- = superoxide anions; OS = oxidative stress; ox = oxidized; PARP = poly (ADP-ribose) polymerase; pp = postprandial; PPAR = peroxisome proliferator-activated receptor; PAP-I = purple acid

phosphatase inhibitor; PUFA = polyunsaturated fatty acid; RAAS = renin-angiotensin-aldosterone system; RF = risk factor; ROS = Reactive oxygen species RXNOs plasma nitroso compounds; SOD = superoxide dismutase; TNF-α = tumor necrosis factor-alpha; vWF = von Willebrand factor; += overlap between CV and AMD risk factors.

Table 1: Cardiovascular and AMD risk factors
Cardiovascular RFs
"Classical" risk factors:
– smoking
– hypertension, – higher systolic, diastolic and mean arterial BPs, resp.
– increased LDL-C
– aging
– diabetes mellitus
– early AS in the family
– overweight
– physical inactivity
– atherogenic nutrition
– cholesterol-enriched diet
– high fat intake in diet
– concomitant cardiovascular
– lower extremity arterial disease
"More recent" risk factors:
high fibrinogen level
– high ox-LDL-C level
– high LDL level
– low HDL level
– elevated serum apo Lp(a)
– high serum ICAM level
– elevated serum homocysteine
– high aPL = antiphospholipid antibody levels
– pp hyperglycaemia
– low serum zink level
– pp hypertriglyceridaemia
– diabetic dysmetabolism
– metabolic syndrome
– insulin resistance
– left ventricular hypertrophy
– chronic renal disease, – pathological serum cystatin C level, resp.
– bronchial asthma
– chronic obstructive pulmonary disease (COPD)
– cardiac valve calcification
– migraine (ophthalmic)
– high serum uric acid level
– elevated hsCRP
– higher resting heart rate
– great amplitude of blood pressure
– increased vascular wall rigidity/systemic arterial stiffness
– osteoporosis
– obstructive sleep apnoea
– increased serum triglyceride level at decreased LDL-C
– high IL-6
– elevated vWF
– elevated ADMA
– accumulation of AGE
– high SSAO
– chronic infections/inflammatory conditions
– immune diseases
–systemic complement activation
– oestrogen deficiency
– alcohol abuse


[Modified, after Fischer: JPSI 1(6), Nov – Dec 2012, 15-35.]<sup>6</sup>

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