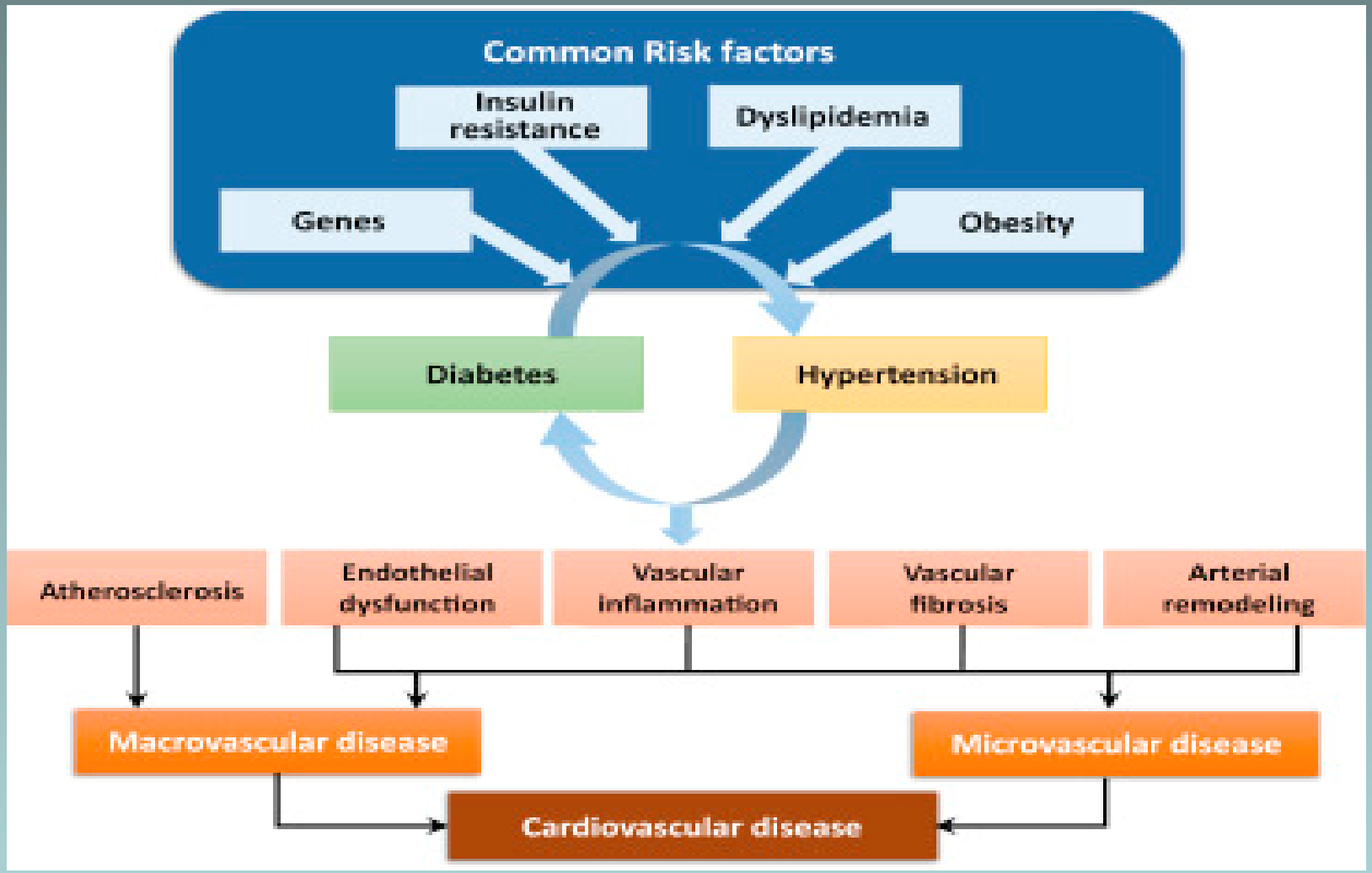
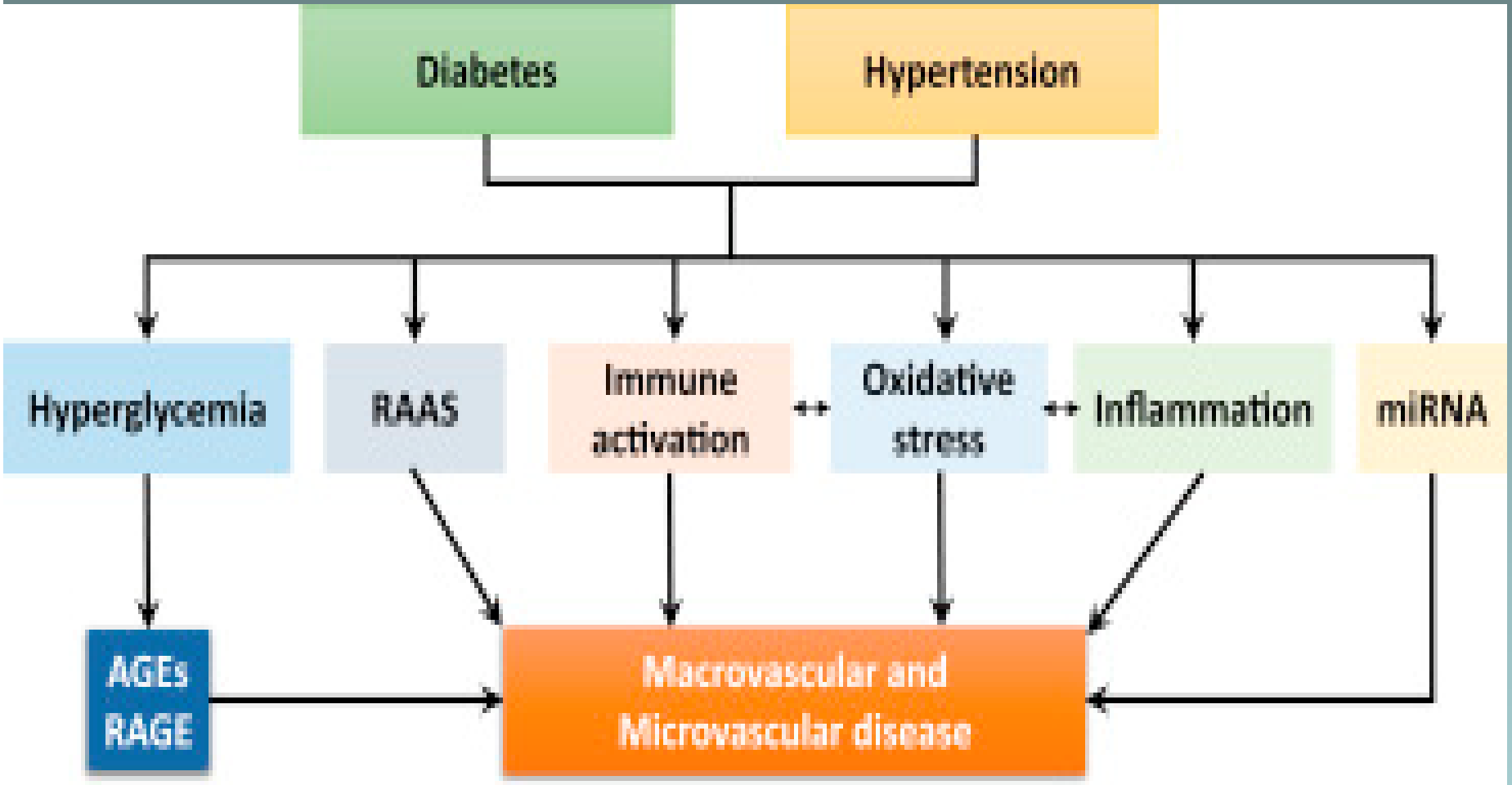
INSULIN RESISTANCE/ DIABETES/ CV DYSFUNCTION

Prof.Dr.Nuray ARI, 2018



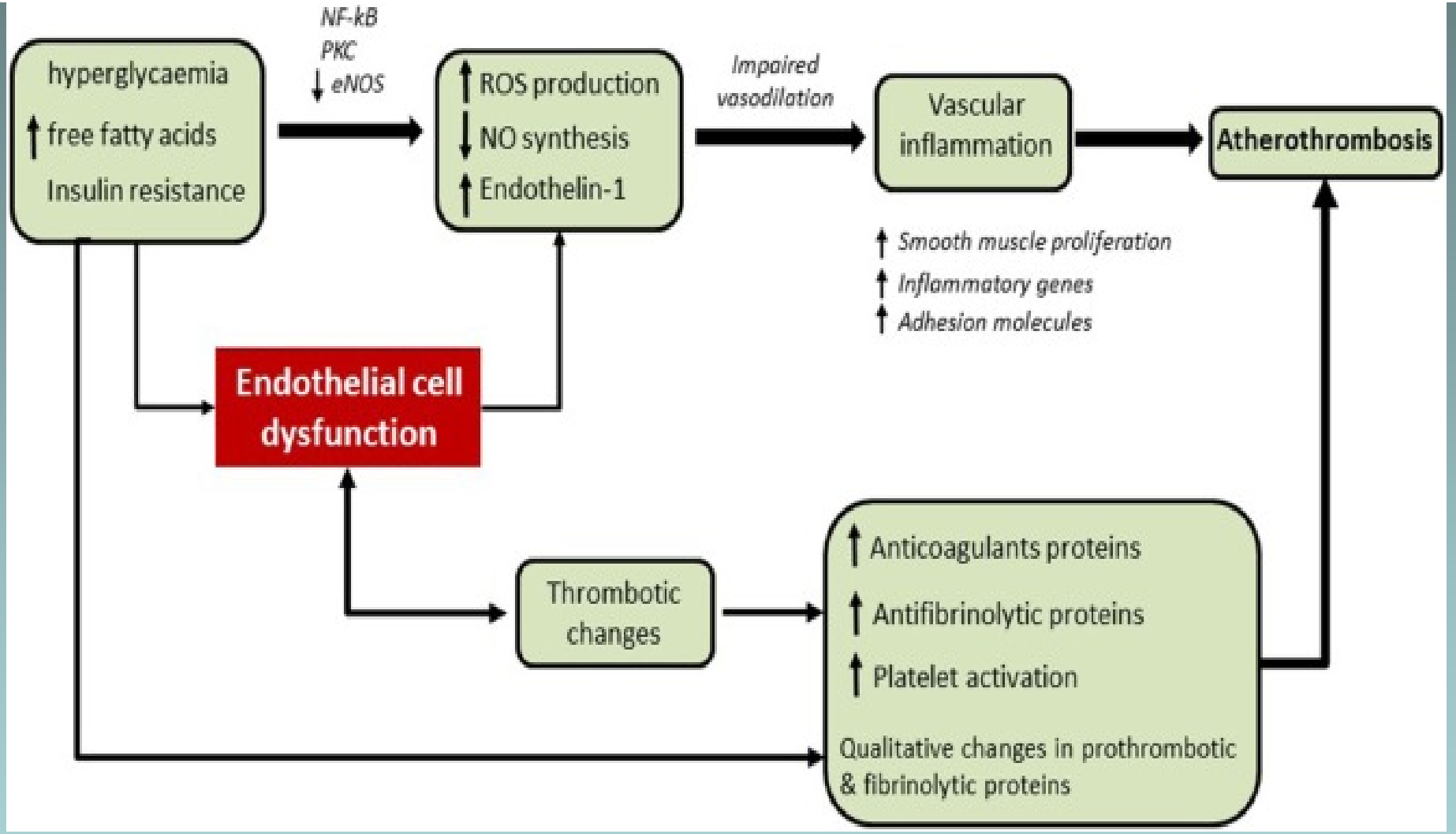
Vascular processes whereby diabetes and hypertension predispose to cardiovascular disease.

Can J Cardiol. 2017 Dec 11. pii: S0828-282X(17)31214-X. doi: 10.1016/j.cjca.2017.12.005. [Epub ahead of print] ***Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms.*** *Petrie JR*



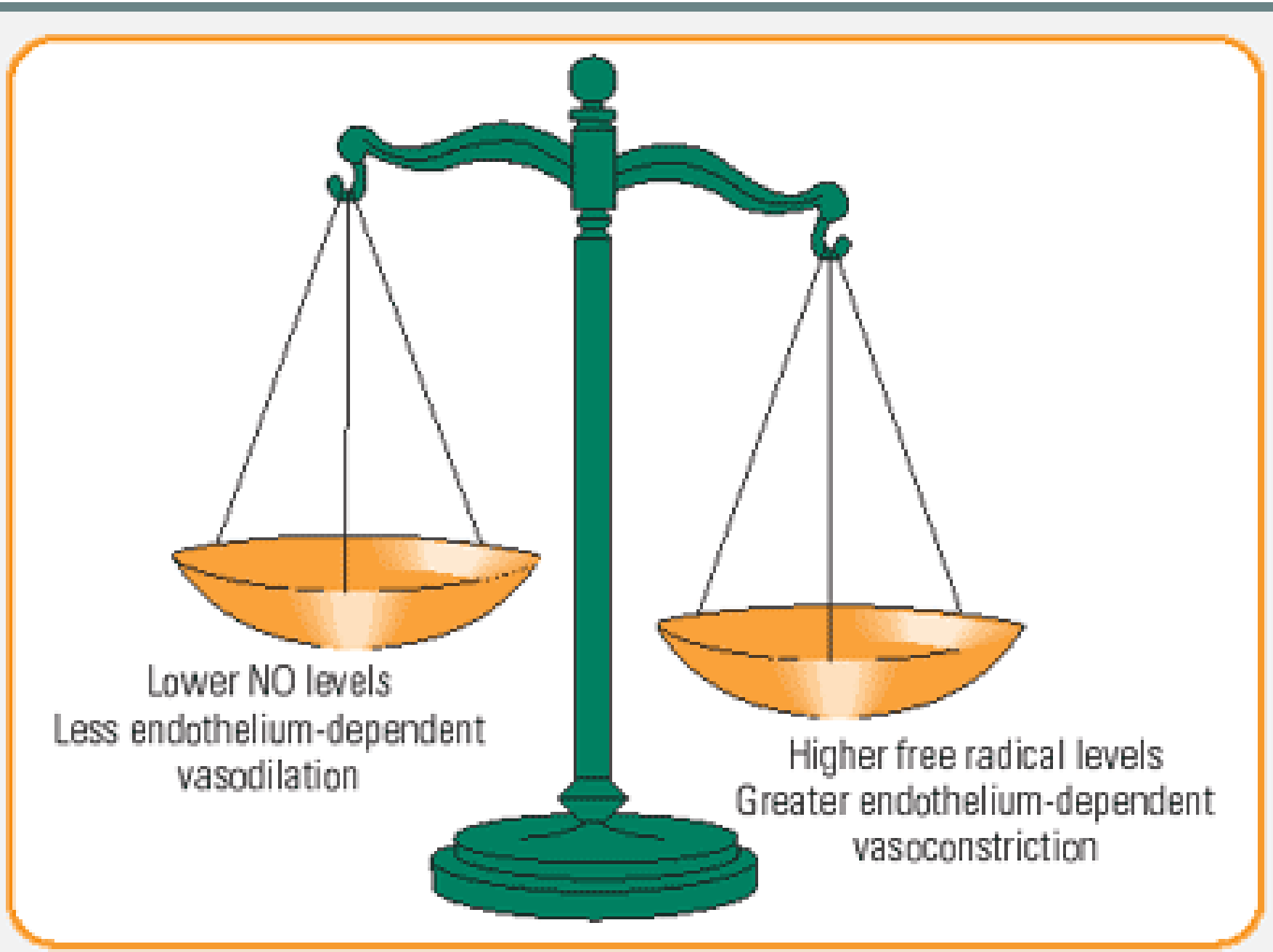
Putative mechanisms whereby diabetes and hypertension cause vascular disease. Immune cell activation and inflammation are mediated through oxidative stress.

Can J Cardiol. 2017 Dec 11. pii: S0828-282X(17)31214-X. doi: 10.1016/j.cjca.2017.12.005. [Epub ahead of print] **Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms.** Petrie JR



The accelerated vascular pathology and enhanced thrombotic environment in diabetes. Endothelial dysfunction plays a key role in all stages of the atherosclerotic process

Front Cardiovasc Med. 2018 Jan 19;5:1. doi: 10.3389/fcvm.2018.00001. eCollection 2018. **Thrombosis and Vascular Inflammation in Diabetes: Mechanisms and Potential Therapeutic Targets.** Pechlivani N, Ajjan RA.


Lower NO levels
Less endothelium-dependent
vasodilation
Higher free radical levels
Greater endothelium-dependent
vasoconstriction

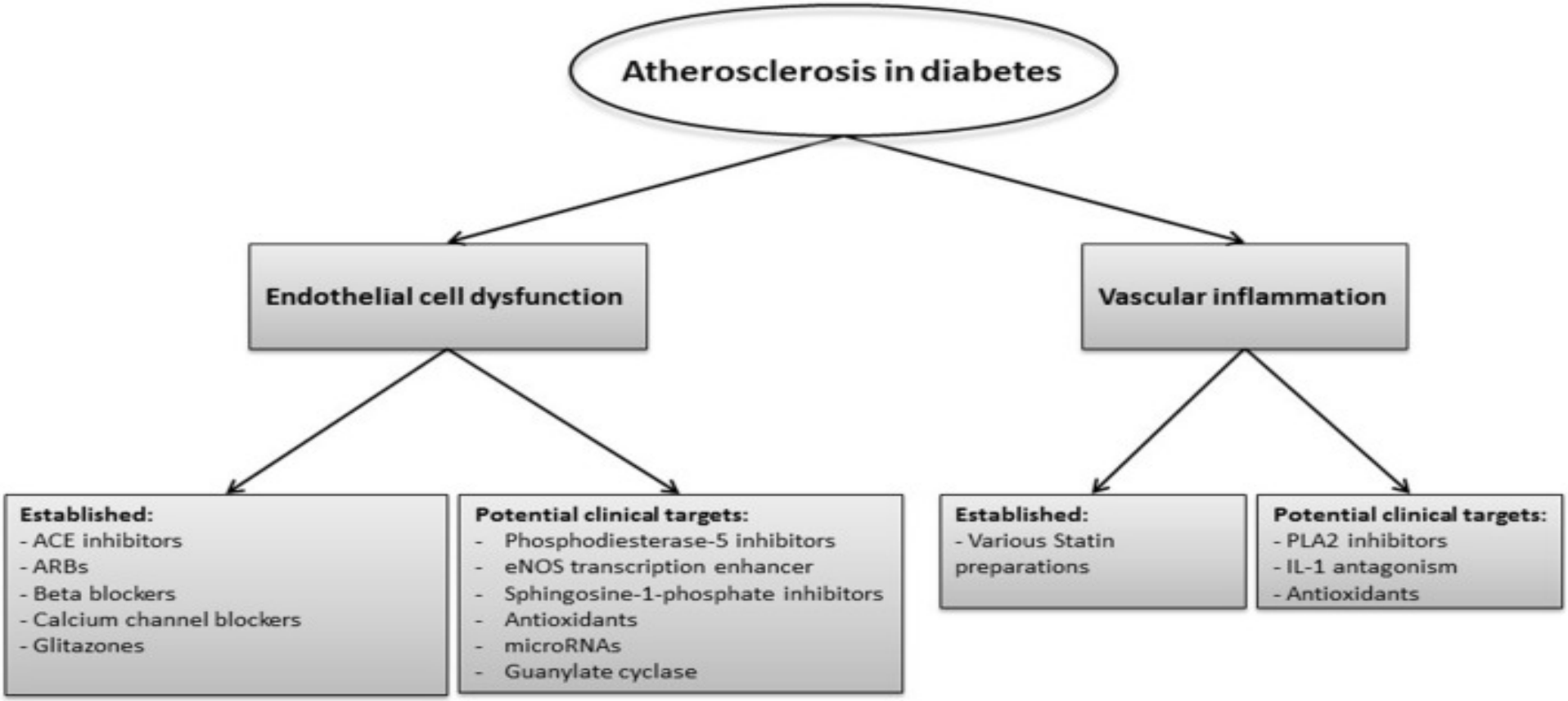
Front Cardiovasc Med. 2018; 5: 1. Published online 2018 Jan 19. doi: 10.3389/fcvm.2018.00001
PMCID: PMC5780411

Thrombosis and Vascular Inflammation in Diabetes: Mechanisms and Potential Therapeutic Targets

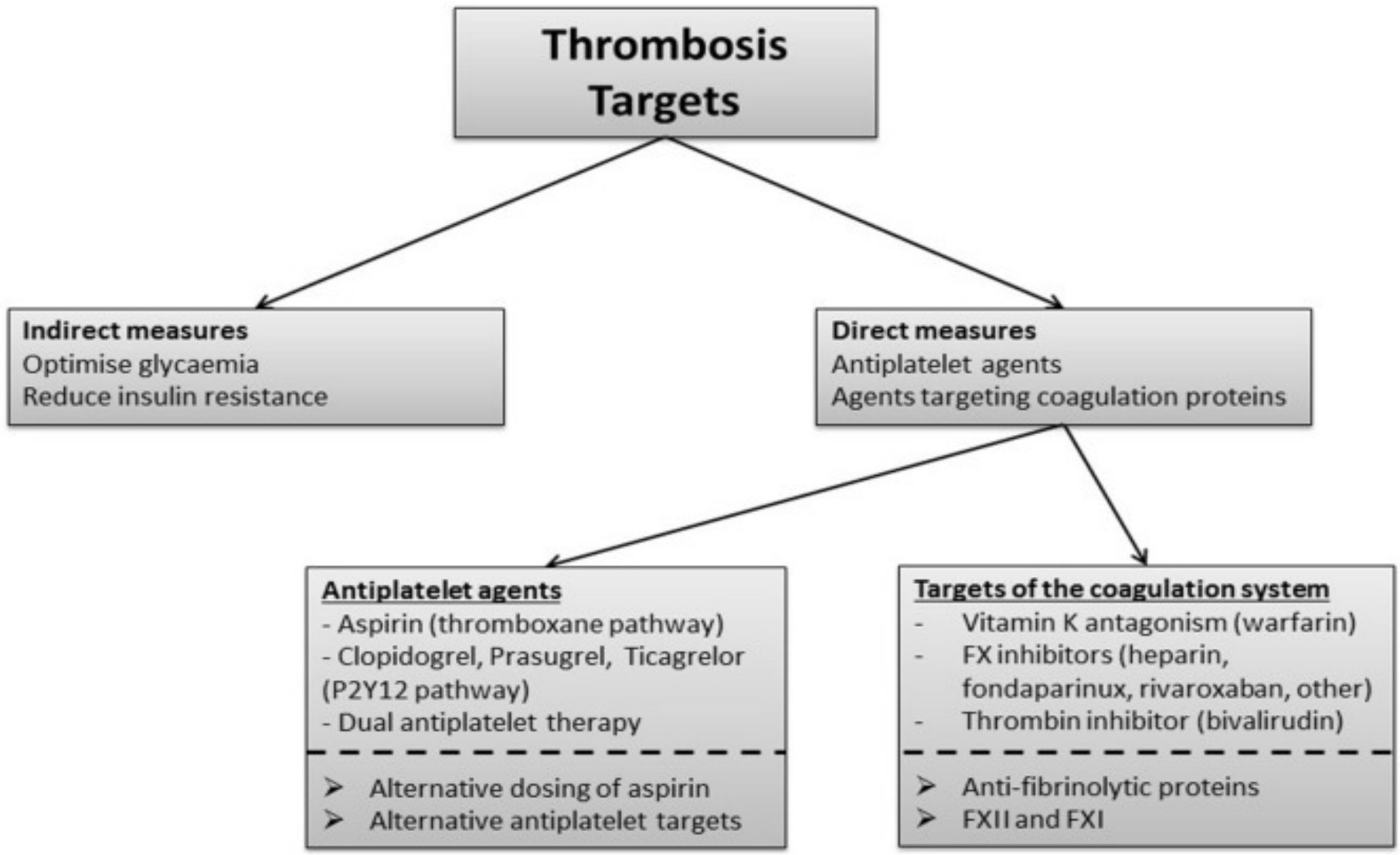
Nikoletta Pechlivani and Ramzi A. Ajjan

Abstract

Cardiovascular disease remains the main cause of morbidity and mortality in patients with diabetes. The risk of vascular ischemia is increased in this population and outcome following an event is inferior compared to individuals with normal glucose metabolism. The reasons for the adverse vascular profile in diabetes are related to a combination of more extensive atherosclerotic disease coupled with an enhanced thrombotic environment. Long-term measures to halt the accelerated atherosclerotic process in diabetes have only partially addressed vascular pathology, while long-term antithrombotic management remains largely similar to individuals without diabetes. We address in this review the pathophysiological mechanisms responsible for atherosclerosis with special emphasis on diabetes-related pathways. We also cover the enhanced thrombotic milieu, characterized by increased platelet activation, raised activity of procoagulant proteins together with compromised function of the fibrinolytic system. Potential new therapeutic targets to reduce the risk of atherothrombosis in diabetes are explored, including alternative use of existing therapies. Special emphasis is placed on diabetes-specific therapeutic targets that have the potential to reduce vascular risk while keeping an acceptable clinical side effect profile. It is now generally acknowledged that diabetes is not a single clinical entity but a continuum of various stages of the condition with each having a different vascular risk. Therefore, we propose that future therapies aiming to reduce vascular risk in diabetes require a stratified approach with each group having a "stage-specific" vascular management strategy. This "individualized care" in diabetes may prove to be essential to improve vascular outcome in this high risk population.

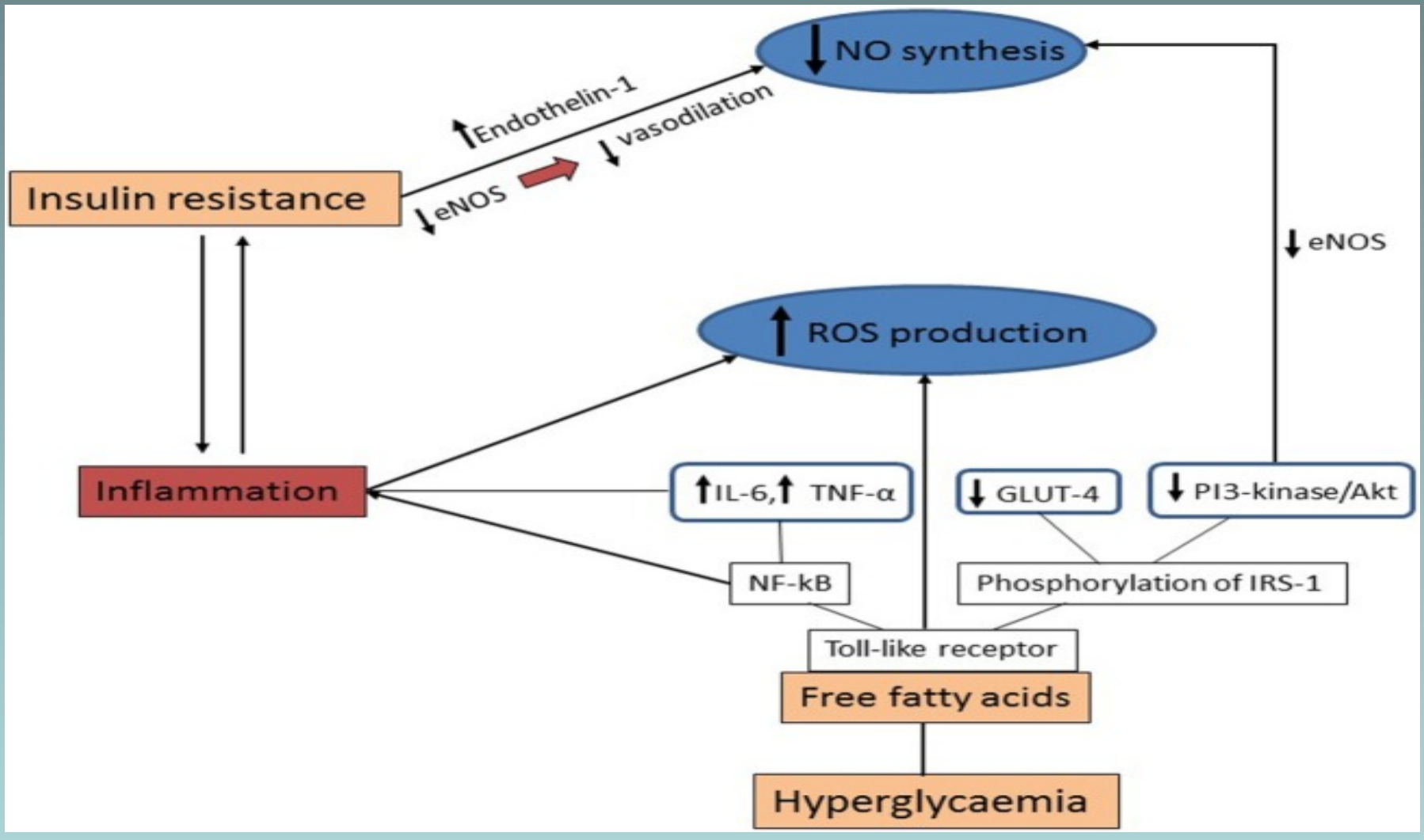


Inflammatory pathways that are currently used or may represent therapeutic targets to reduce vascular risk in diabetes. Current therapies and others in development focus on improving the endothelial cell function and reducing vascular inflammation. Established therapies to target endothelial dysfunction are ACEI's ARBs, beta blockers, CCBs and glitazones, whereas agents such as PDE-5Is, eNOS transcription enhancer, and microRNAs represent potential future therapies. Statins are widely used to reduce vascular risk and in addition to their cholesterol lowering effect they reduce vascular inflammation. Other potential targets to reduce vascular inflammation include of phospholipase A2 (PLA2) inhibitors as well as interleukin (IL)-1 antagonists and antioxidants. Front Cardiovasc Med. 2018; 5: 1. Published online 2018 Jan 19. doi: 10.3389/fcvm.2018.00001 PMCID: PMC5780411**Thrombosis and Vascular Inflammation in Diabetes: Mechanisms and Potential Therapeutic Targets** Pechlivani N[1] and Ajjan RA[1,*]



Thrombotic pathways that represent current and potential therapeutic targets in diabetes

Front Cardiovasc Med. 2018; 5: 1. Published online 2018 Jan 19. doi: 10.3389/fcvm.2018.00001
PMCID: PMC5780411**Thrombosis and Vascular Inflammation in Diabetes: Mechanisms and Potential Therapeutic Targets** Pechlivani N[1] and Ajjan RA



Mechanistic pathways for increased vascular inflammation in diabetes

Insulin resistance inhibits nitric oxide (NO) synthesis by reducing vasodilation *via* decreased activity of endothelial NO synthase (eNOS) together with increased production of vasoconstrictors such as endothelin-1 Front Cardiovasc Med. 2018; 5: 1. Published online 2018 Jan 19. doi: 10.3389/fcvm.2018.00001 PMCID: PMC5780411**Thrombosis and Vascular Inflammation in Diabetes: Mechanisms and Potential Therapeutic Targets** Nikoletta Pechlivani[1] and Ramzi A. Ajjan[1,*]

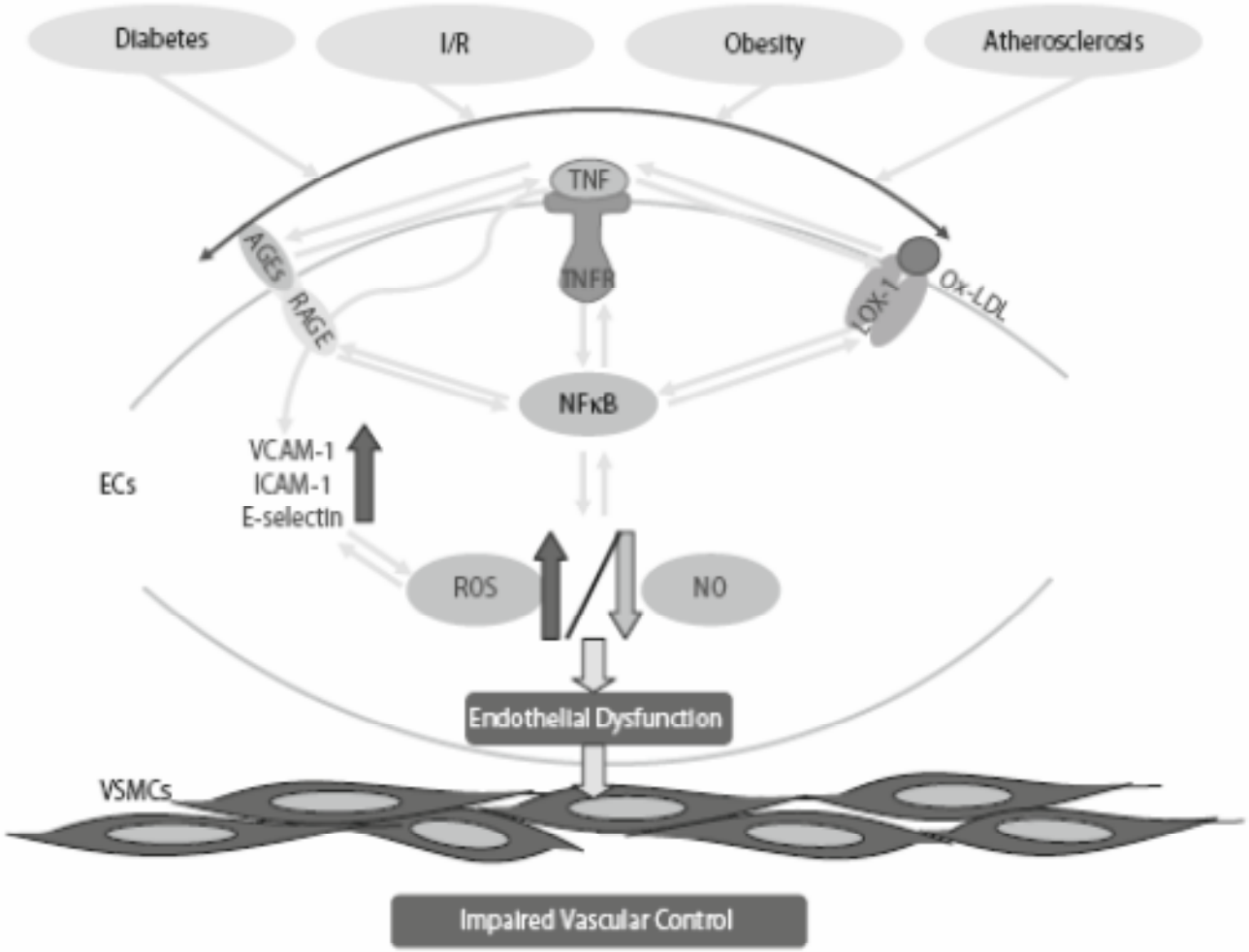
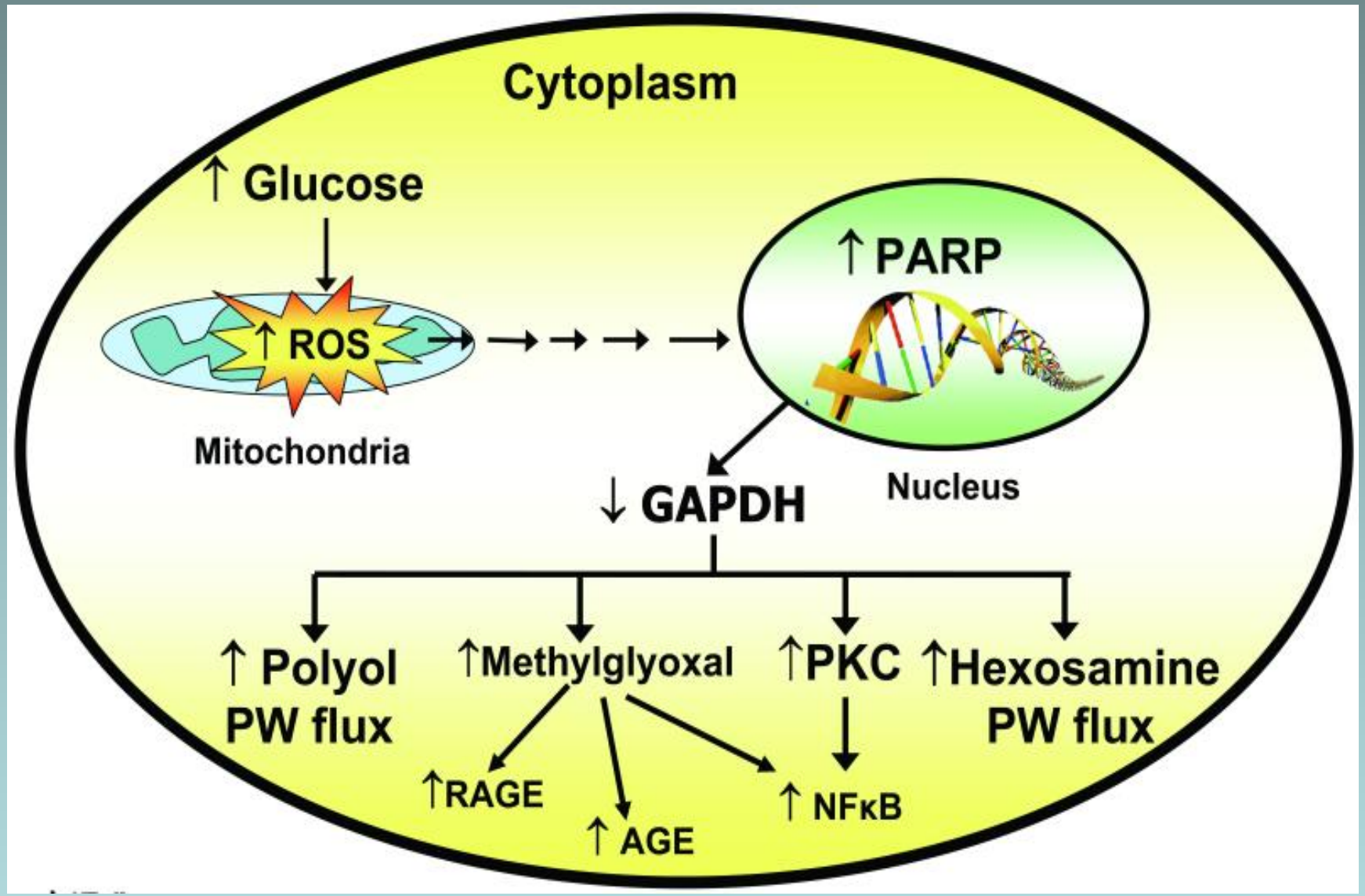
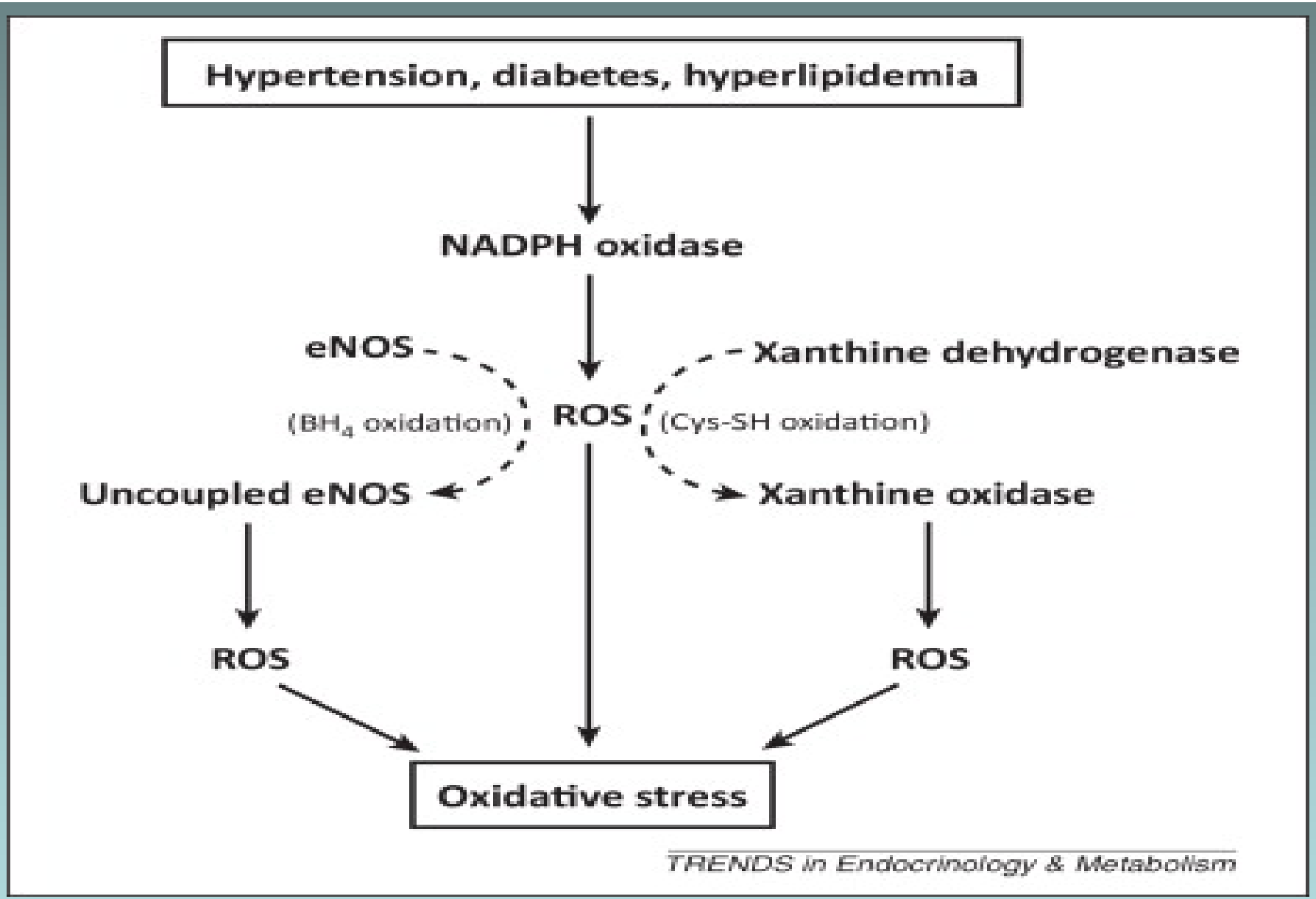


Fig. 1 The indicators of endothelial dysfunction in cardiovascular diseases (CVD) are portrayed. Normally, endothelial cells regulate the homeostasis of the vessel wall. The healthy endothelium is not leaky, anti-adhesive and is able to relax vascular smooth muscle cells. However, when risk factors (diabetes, ischemia/reperfusion, obesity and atherosclerosis etc.) disturb endothelial cells, which induce endothelial dysfunction and vascular remodelling. We have an impaired vascular control when the damaged endothelium is leaky, sticky and unable to relax vascular smooth muscle cells. In brief, central to the endothelial dysfunction is oxidative stress. The oxidative stress is induced by the production of reactive oxidative species (ROS) and this induces NF-κB. Key to the production of ROS is AGE/RAGE and TNF-α signaling, but ox-LDL/LOX-1 signaling is also involved in ROS production. The interactions among oxidative stress, AGE/RAGE, TNF-α/TNFR and ox-LDL/LOX-1 are because oxidative stress induces NF-κB, and this transcription factor can induce AGE, TNF-α and ox-LDL expression; and TNF-α can induce RAGE and LOX-1 expression. Thus, the oxidative stress of diabetes, begets more oxidative stress, eventually inducing endothelial dysfunction, because of decreased bioavailability of nitric oxide (NO, due to the reaction between NO and $O_2^{\cdot -}$)



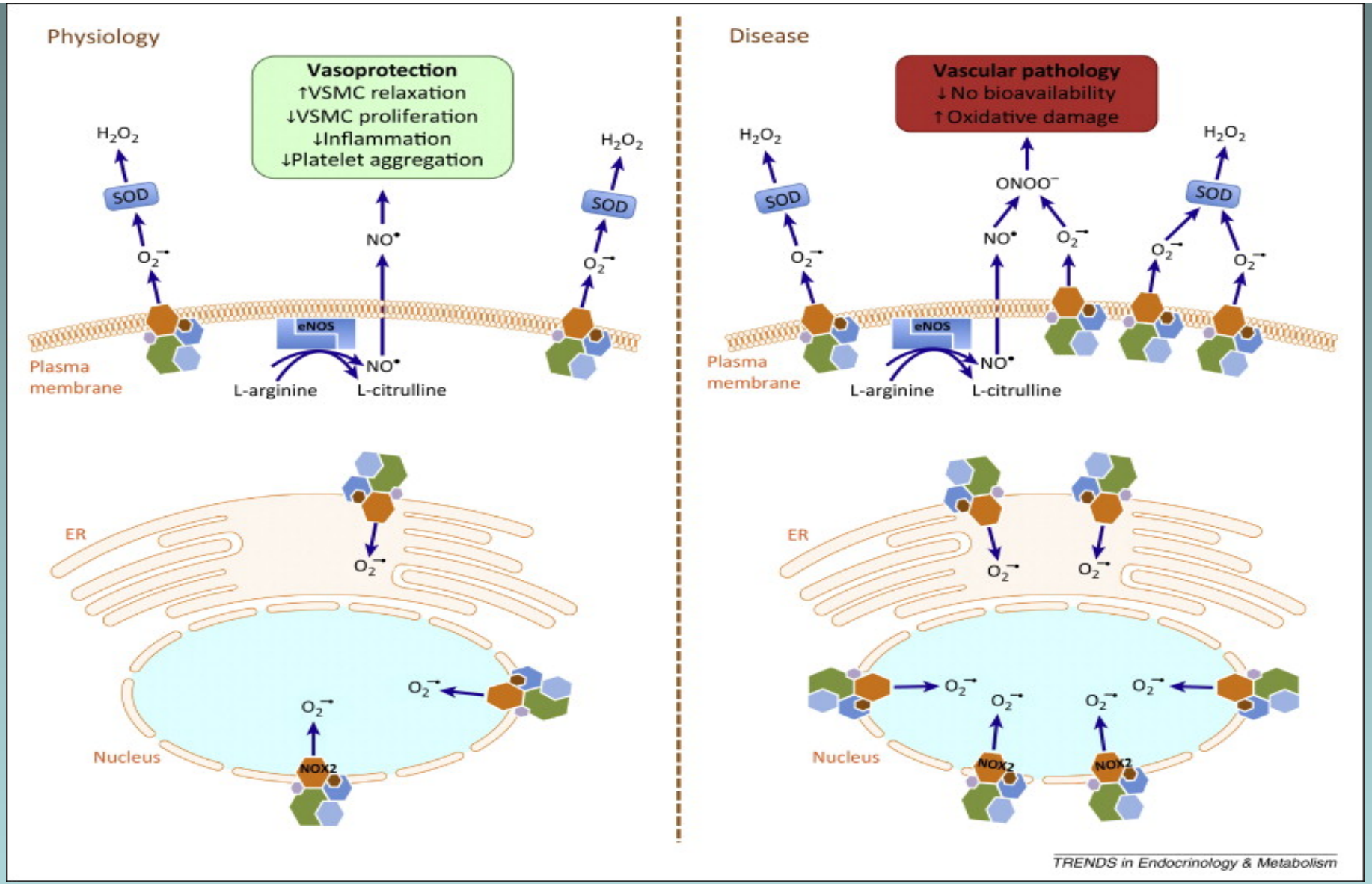
Schematic showing elements of the unifying mechanism of hyperglycemia-induced cellular damage

Circ Res. 2010.107(9):1058–1070. **Oxidative stress and diabetic complications** Giacco F and Brownlee M.



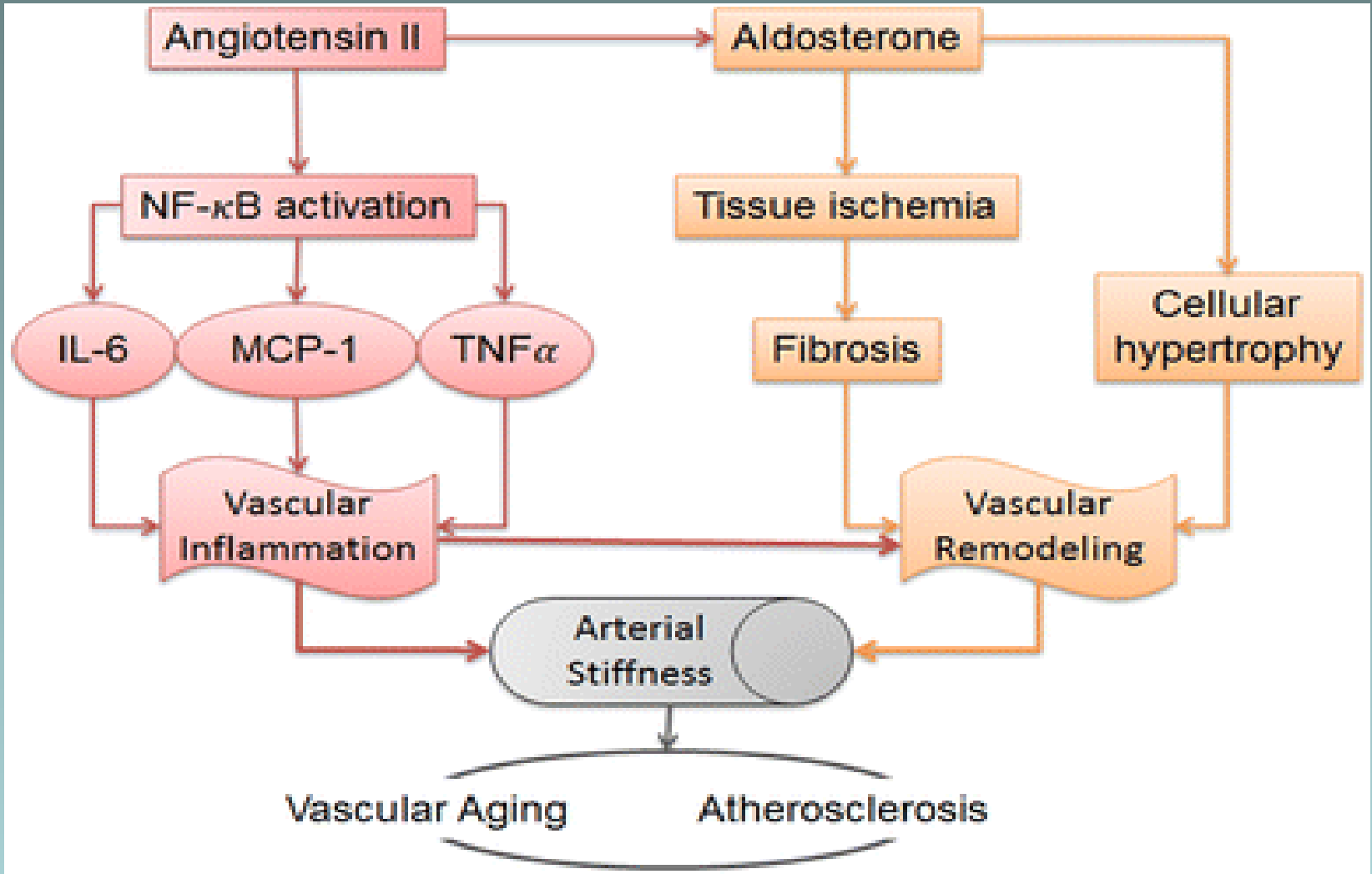
NADPH oxidase (NOX)-derived reactive oxygen species (ROS) elicit ROS production from other enzyme sources.

Trends Endocrinol Metab. 2014 25(9):452-63. ***Endothelial NADPH oxidases: which NOX to target in vascular disease?*** *Drummond GR, and Sobey CG.*



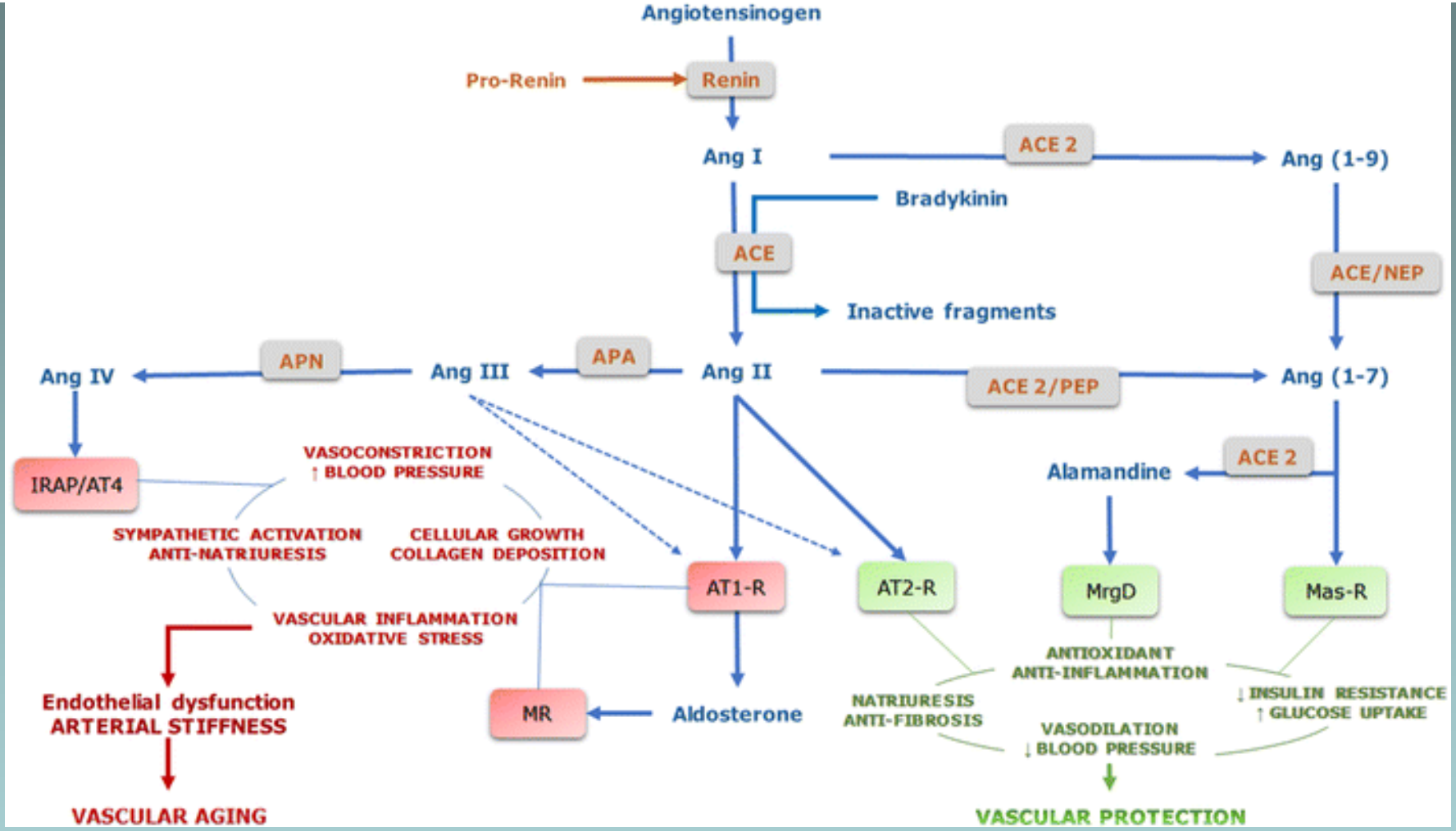
Subcellular compartments into which NADPH oxidase NOX2 generates superoxide in the endothelium in physiology and disease, and the impact on nitric oxide (NO) bioavailability.

Trends Endocrinol Metab. 2014 25(9):452-63. ***Endothelial NADPH oxidases: which NOX to target in vascular disease?*** *Drummond GR, and Sobey CG.*



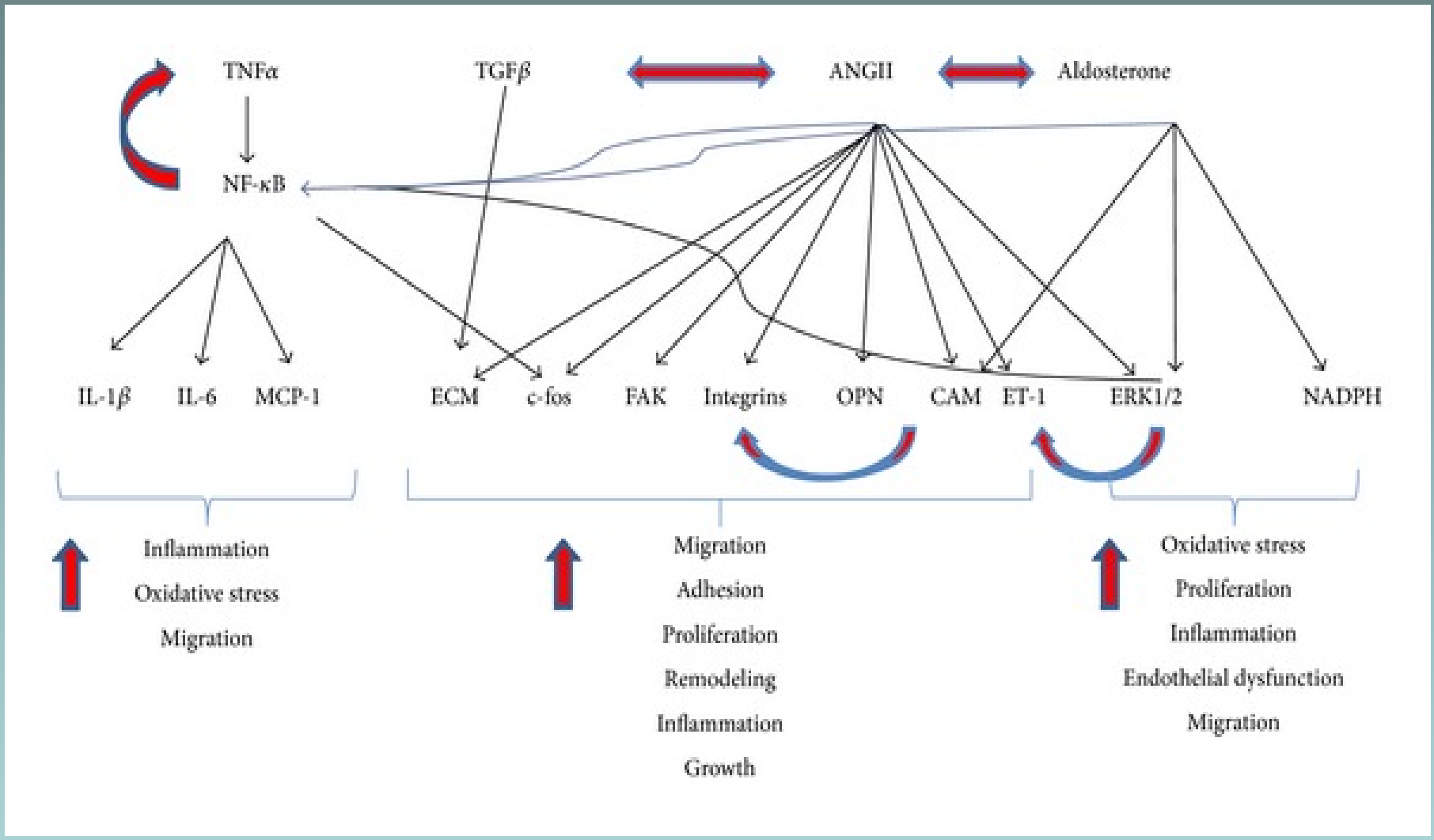
The role of angiotensin II and aldosterone in vascular inflammation and remodeling as precursor of arterial stiffness in the process of vascular aging.

High Blood Press Cardiovasc Prev. 2018 Feb 23. doi: 10.1007/s40292-018-0252-5. [Epub ahead of print] **The Role of Renin-Angiotensin-Aldosterone System and Its New Components in Arterial Stiffness and Vascular Aging.** Neves MF



The mechanisms involved in the vasoprotective axis of the renin–angiotensin–aldosterone system, mainly represented by the effects of AT2 receptor, Mas receptor and Mas-related G-protein-coupled receptor (MrgD), counteracting the deleterious effects of AT1 receptor, mineralocorticoid receptor (MR) and insulin regulated aminopeptidase (IRAP)/AT4 receptor in the vasoconstrictor axis, which contributes to the development of vascular aging. *NEP* neutral endopeptidase, *PEP* prolyl-endopeptidase, *APA*aminopeptidase A, *APN* aminopeptidase N

High Blood Press Cardiovasc Prev. 2018 Feb 23. doi: 10.1007/s40292-018-0252-5. [Epub ahead of print] ***The Role of Renin-Angiotensin-Aldosterone System and Its New Components in Arterial Stiffness and Vascular Aging.*** *Neves MF*



various molecular factors activated by RAAS effectors and cross-talk between RAAS effectors and molecular factors involved in signaling pathways with role in vascular inflammation and remodeling

Int J Inflam. 2014;2014:689360. doi: 10.1155/2014/689360. Epub 2014 Apr 6. ***The Renin-Angiotensin-aldosterone system in vascular inflammation and remodeling.*** *Pacurari M*

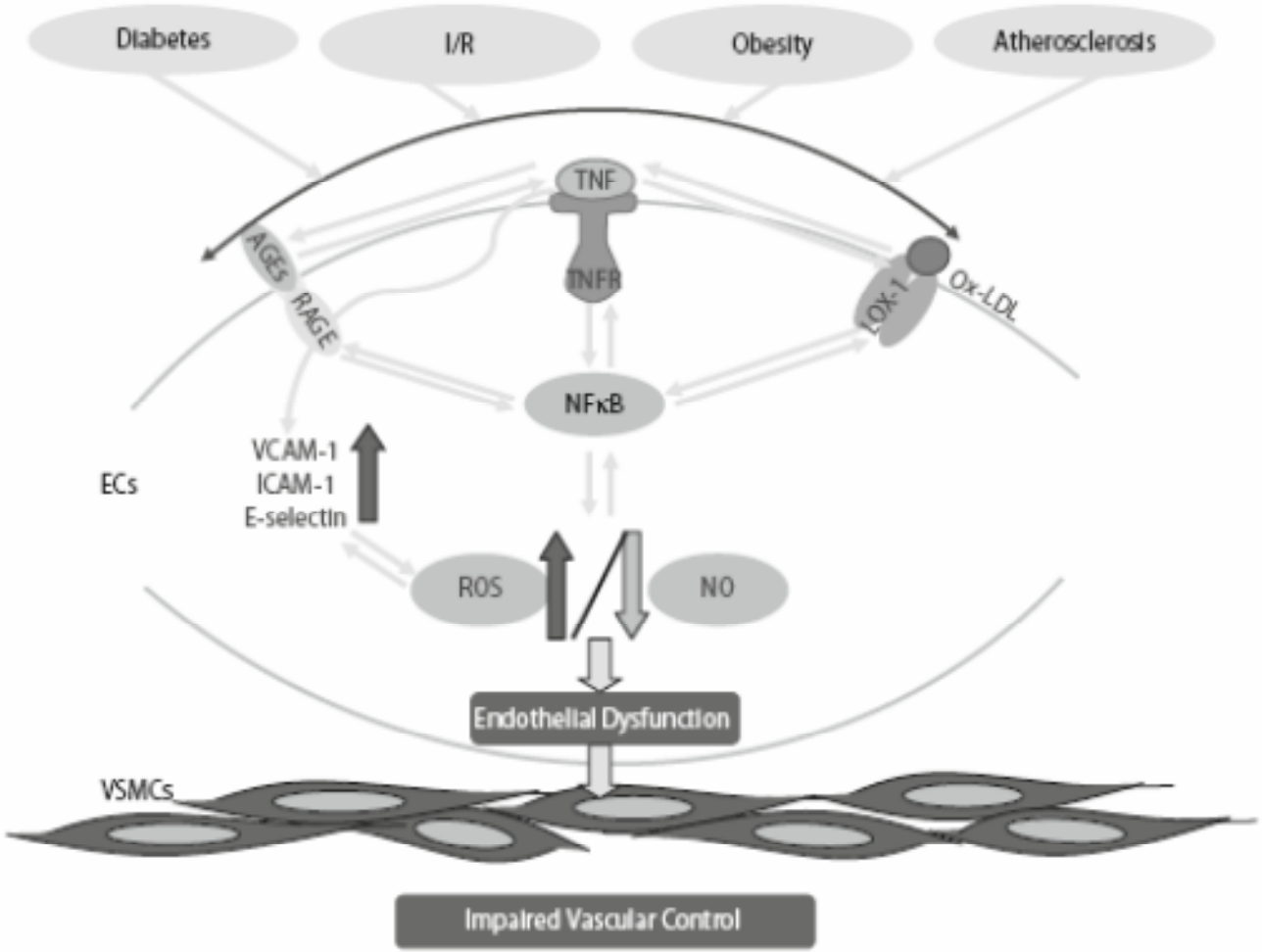


Fig. 1 The indicators of endothelial dysfunction in cardiovascular diseases (CVD) are portrayed. Normally, endothelial cells regulate the homeostasis of the vessel wall. The healthy endothelium is not leaky, anti-adhesive and is able to relax vascular smooth muscle cells. However, when risk factors (diabetes, ischemia/reperfusion, obesity and atherosclerosis etc.) disturb endothelial cells, which induce endothelial dysfunction and vascular remodelling. We have an impaired vascular control when the damaged endothelium is leaky, sticky and unable to relax vascular smooth muscle cells. In brief, central to the endothelial dysfunction is oxidative stress. The oxidative stress is induced by the production of reactive oxidative species (ROS) and this induces NF-κB. Key to the production of ROS is AGE/RAGE and TNF-α signaling, but ox-LDL/LOX-1 signaling is also involved in ROS production. The interactions among oxidative stress, AGE/RAGE, TNF-α/TNFR and ox-LDL/LOX-1 are because oxidative stress induces NF-κB, and this transcription factor can induce AGE, TNF-α and ox-LDL expression; and TNF-α can induce RAGE and LOX-1 expression. Thus, the oxidative stress of diabetes, begets more oxidative stress, eventually inducing endothelial dysfunction, because of decreased bioavailability of nitric oxide (NO, due to the reaction between NO and $O_2^{\cdot-}$)