American Journal of Biology and Natural Sciences
https://biojournals. us/index. php/AJBNS
**ISSN: 2997-7185**

# Review Article: Physiological and Immune Alterations in Atherosclerosis: From Endothelial Dysfunction to Chronic Inflammation

**Tamarah H. Ahmed [1] Noor H. Al-Mousawi [2]**
[1] Department of Physiology, College of Veterinary Medicine, Wasit University, Iraq
[2] Department of Pathological Analysis, College of Science, Wasit University, Iraq

**Received:** 2025, 15, Sep
**Accepted:** 2025, 21, Oct
**Published:** 2025, 01, Nov

Copyright © 2025 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4. 0).
Open Access
http://creativecommons. org/licenses/ by/4. 0/

**Annotation:** Atherosclerosis is an arterial wall disorder which is a chronic and progressive disease and has interrelations immunological and physiological events. The endothelium begins to malfunction and initiate a cascade of metabolic and biomechanical alterations, including a reduction in the bioavailability of nitric oxide, oxidative stress, and the lipoprotein retention of the intima. Also, recruitment and polarization of innate and adaptive immune cells are then increased, which increases inflammation, foam-cell generation, as well as, remodeling of the extracellular matrix, eventually causing plaque and instability. The recent discoveries (2019-2025) in vascular physiology and immunology, relevant to atherogenesis, are outlined in this review, which takes into consideration the understanding of endothelial shear stress, cholesterol handling, cytokine network, also, clonal hematopoiesis of unknown potential. As well as, clinical implications are also discussed with respect to the development of biomarkers and treatment

strategies that focus on lipids, inflammation, and thrombosis, and new biological agents. Although, an appreciation of the interplay between physiological pathways and immunological circuits gives an integrative framework that can prevent the development of atherosclerotic cardiovascular events by stopping the formation of a plaque, promoting stabilization, and reducing the frequency of such events.

**Keywords:** atherosclerosis; cytokines, endothelial dysfunction; clonal hematopoiesis.

### 1.1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in the world. Also, is the cause of close to one-third of all the deaths. It is a big burden to both the developing and the industrialized societies, both financially and health wise **(1)**. Also, atherosclerosis, which has historically been considered a passive lipid deposition disease and only a result of cholesterol deposition in the arterial wall, as well as is currently known to be a dynamic and complex systemic condition with a sustained interaction between the physiology of the vascular wall, metabolic dys- and immune-activation. **(2)**. The metabolism of lipoproteins, the endothelial cell biology, the local hemodynamic pressures, and the innate and adaptive immune reactions are all of them involved in the disease process and begins decades before clinical manifestation. Furthermore being a barrier to mechanical and chemical stimuli, the endothelium is a complex sensor and transducer of such stimuli. Besides that it regulates the hemostasis, trafficking of leukocytes, the vascular tone and permeability. In addition the decrease in the nitric oxide (NO) bioavailability, the augmentation of reactive oxygen species (ROS) production, augmented expression of adhesion molecules (VCAM-1, ICAM-1, E-selectin) and augmented permeability are all indicators of dysfunctional endothelium induced by regions of disrupted shear stress (in particular arterial bifurcations and curvatures). **(3)**. Through these changes, apolipoprotein B-carrying lipoproteins and low-density lipoproteins (LDL) are able to enter the subendothelial space. Also in that point, they are oxidatively altered and accumulate to produce epitopes that engage scavenger receptors on resident vascular cells and infiltrating leukocytes and the pattern-recognition receptor (TLR) Atherogenesis experiences a radical change with this immunological activation. Moreover the chemokines (MCP-1/CCL2) recruit monocytes which become macrophages that ingest oxidized lipids to form foam cells which are signs of early lesions of the atherosclerosis. **(4)**. Furthermore, chronic inflammation facilitates the formation of necrotic cores, extracellular matrix remodeling and phenotypic flipping of vascular smooth muscle cells (VSMCs), besides that the result in thrombosis and instability of the plaque. The local vascular events are not the only ones that are influenced by systemic variables and determine the onset and progression of atherosclerosis. In addition risk factors that are well-known to modify endothelial functioning and immunological tone are: smoking, obesity, diabetes, hypertension and Dyslipidemia. The environmental factors that also influence the vascular-immune interface are added by nutrition, exercise, psychological stress, and even the gut microbiota. **(5)**. Although

atherosclerosis is taken as an example in this paper as a typical example of a disorder that occurs when immunology and vascular physiology interact. Thus we are looking to provide a deep understanding of the processes involved in plaque formation, development and destabilization by examining how mechanical stresses, oxidative stress, lipid metabolism and immunological activation interact to create a positive feedback mechanism of the pathological network.

### 1.2. Vascular Physiology and the Arterial Wall Atheroprone

In the context of vascular physiology, which promotes atherogenesis, atherosclerosis is preferentially developed at arterial arch points that experience disturbed or oscillatory shear stress (OSS) at the arch curvatures and bifurcations **(6)**. Also, protective phenotype of endothelial cells is also characterized by high nitric oxide (NO) bioavailability, antioxidant production, and low adhesion marker expression in response to laminar flow and is mainly regulated by the transcription factors KLF2 and KLF4 **(7)**. Wherease, OSS enhances reactive oxygen species (ROS), reduces NO synthesis owing to uncoupling of eNOS, and activates pro-inflammatory signaling, including NF- mB, leading to the upregulation of VCAM-1, ICAM-1 and E-selectin **(8)**. In addition these changes improve leukocyte adhesion, endothelial permeability, subendothelial retention of low-density lipoproteins (LDL) which are oxidatively modified and produce local inflammation. **(9)**. Also, hyperglycemia and oxidative stress increase the permeability and weaken the glycocalyx, increasing the invasion of lipoproteins and exacerbating endothelial homeostasis **(10)**. These physiological abnormalities when coupled together convert the endothelium into a vascular remodeler and an inflammatory player rather than being a passive barrier. Furthermore, atherosclerotic plaques are governed by the vascular physiology, i. e., shear stress patterns, NO signaling, and redox balance, which renders them targets of early intervention. **(6–10)**.

### 2.3. Endothelial Dysfunction: Mechanisms and Physiological Impact

Essentially important in atherogenesis is the loss of the endothelial vasodilatory, anti-inflammatory, and antithrombotic properties; this loss is called the endothelial dysfunction **(7)**. In addition the diminished availability of nitric oxide (NO) is one of the main elements of this mechanism that are induced by the enhancement of reactive oxygen species (ROS) generation through the NADPH oxidase and mitochondrial pathways and endothelial nitric oxide synthase (eNOS) uncoupling. **(8)**. Also,ROS oxidizes Tetrahydrobiopterin (BH4) and worsens the uncoupling of eNOS and stimulates the formation of peroxynitrite, which damages cell constituents. In addition, the inhibition of leukocyte migration is enhanced through the stimulation of adhesion molecules (VCAM-1, ICAM-1) and chemokines by the activation of transcription factors (NF-KB) **(9)**. Vasoconstrictors like endothelin-1 take the lead over vasodilators and endothelial cells are also altered to a pro-thrombotic phenotype by increasing tissue factor and plasminogen activator inhibitor-1 (PAI-1) levels. **(10)**. Furthermore one factor of the development of plaque and fibrotic remodeling is endothelial-to-mesenchymal transition (EndMT). In a clinical setting, the endothelial dysfunction is associated with predicting cardiovascular events and it precedes detectable lesions in atherosclerotic disease even in patients with controlled cholesterol levels **(11)**. Whereas, the key goals of the prevention and treatment of atherosclerosis include restoring NO signaling, reduced oxidative stress, and endothelial integrity. **(7–11)**.

### 2.4. Plaque Development, Foam Cells, and Lipid Metabolism

Lipoprotein retention and change in its subendothelial location, particularly, low-density lipoprotein (LDL), is one of the most important features of atherosclerosis. In addition the CD36 and SR-A scavenger receptors of Macrophages recognize oxidized LDL (oxLDL) that is formed when LDL is deposited in the intima and subsequently subjected to oxidative and enzymatic changes **(11)**. Besides OxLDL invokes local inflammation. As a result the foam cells that are formed when these macrophages ingest oxLDL are the early atherosclerotic lesions. **(12)**. The foam cells enhance the leukocyte recruitment and migration of the vascular smooth muscle cell (VSMC) by producing growth factors and pro-inflammatory cytokines. Moreover the presence of plaque is facilitated by the phenotypic transition of VSMCs between a contractile and a synthetic

state and its ability to form foam-like **(13)**. The accumulation of apoptotic cells is owing to the inability of the phagocytosis process to be effective, forming a necrotic core and weakening the plaque. Also, overexpression of matrix metalloproteinases (MMPs) degrades collagen in the fibrous cap increasing the risk of rupture and thrombosis **(14)**. Although, lipid retention, foam cell generation, and ineffectual clearance will result in a loop of chronic inflammation and structural remodelling, and drive the progression of plaque and clinical repercussions. **(11–14)**.

### 2.5. Immune Mechanisms and Chronic Inflammation

The immune system plays a significant role in all stages of atherosclerosis making the lipid-mediated condition a chronic inflammatory disease. Also, chemokines and adhesion molecules lead monocytes to the intima where it becomes macrophages and produces cytokines such as TNF- alpha, IL-6, and interleukin- 1beta (IL-1 beta) that enhance inflammation. **(14)**. When the NLRP3 inflammasome is activated, lipid accumulation and innate immune activation are associated and leads to the production of IL-18 and IL-1B more **(15)**. Besides adaptive immunity is also another crucial parameter. Th1 cells secrete interferon- 7(IFN- 7) that suppresses collagen synthesis and stimulates macrophages, after that Tregs (regulatory T cells) secrete TGF- 7 and IL-10 which have anti-inflammatory properties. **(16)**. The B cells can be pro-atherogenic and preventive depending on their subsets. Furthermore, neutrophil extracellular traps (NETs) worsen thrombosis as well as plaque instability **(17)**. The newer systems, which do not lower the lipid levels but instead maintain the inflammation, are the trained immunity and clonal hematopoiesis **(18)**. In addition the relevance of the immune-targeted therapy in reducing atherosclerotic risk is also emphasized by the interaction of these immune responses that results in a vicious cycle of vascular injury, inflammation, and remodeling. **(14–18)**.

### 2.6. Crosstalk Between Physiological and Immune Pathways

Atherosclerosis is often caused by the continuous interaction between immunological reactions and vascular physiology. DAMPs are delivered to endothelial cells through broken shear stress and oxidative stress, and they cause innate immune signaling and pattern-recognition receptor activation **(2)**. On the other hand, pro-inflammatory cytokines including interleukin-1 (IL-1), IL-6, also tumor necrosis factor- alpha (TNF- alpha) boost tissue factors expression, impede endothelial nitric oxide (NO) signaling, and stimulate the phenotypic flipping of vascular smooth muscle cells (VSMC) **(18)**. This is a two-way connection, which creates a feed-forward loop: physiological impairment leads to immunological stimulation, and inflammation exacerbates the state of vascular functioning. Also, oxidized LDL (oxLDL) also connects lipid metabolism to immunological signaling in that it activates the macrophages and dendritic cells as well as accumulates due to increased permeability. NF-KB activation and augmentation of inflammatory pathways are often caused by the production of reactive oxygen species (ROS) by endothelial cells. **(19)**. Besides the therapeutic potential of targeting this interaction is also demonstrated by the fact that anti-inflammatory treatments lead to improvements in endothelial function, lipid-lowering treatments lead to a decrease in lipoprotein retention, and anti-inflammatory treatments indirectly cause a decrease in inflammation **(20)**. In addition to minimize the atherosclerotic development and the clinical outcomes, it is urgent to understand such interaction and develop therapies that touch upon both vascular and immunological factors. **(2-18-20)**.

### 2.7. Biomarkers and Imaging of Vascular-Immune Dysfunction

Imaging techniques and biomarkers provide significant novel data on the immunological and vascular pathways underlying atherosclerosis. Furthermore to lipid concentrations, systemic inflammatory activity in the form of tumor necrosis factor-alpha (TNF- 0), interleukin- 6 (IL- 6), and high-sensitivity C-reactive protein (hsCRP) is also reflected in the circulating levels of inflammatory indicators **(19)**. Endothelial dysfunction can be determined noninvasively by both peripheral arterial tonometry and flow-mediated dilatation (FMD), which is an NO-dependent vasodilation and is also associated with atherosclerotic load. **(20)**. In addition the inflammation of the vascularity and the susceptibility of the plaque can be observed directly due to the advanced

imaging tools. Although the marker 18F-sodium fluoride (18F-NaF) determines regions of micro calcification, which is a marker of active disease, PET by 18F- fluorodeoxyglucose (18F-FDG) determines actively inflammatory cells within plaques. **(21)**. The Computed tomography angiography (CTA) of the coronary is also used to describe the shape of the plaque and high-risk factors like poor attenuation and thin-cap fibroatheromas **(22)**. Addition emerging single cell RNA sequencing and spatial transcriptomics also define immune cell heterogeneity in plaques, which are also new biomarkers and therapeutic targets. **(23)**. Such techniques increase the early detection of atherosclerotic disease, besides risk-assessment, and personalized therapy by the combination of physiological and immunological data. **(19–23)**.

### 2.9. Treatment Views: Thrombosis, Inflammation, and Lipids

The primary factors of atherosclerosis, thrombosis, inflammation, and accumulation of cholesterol are dealt with in the management of atherosclerosis. Also, intensive LDL-C reduction remains the mainstay with statins and ezetimibe as the first-line therapy and PCSK9 inhibitors or siRNA as additional agents to lower apoB as the first line of therapy in high-risk patients **(21)**. In addition the effectiveness of icosapent ethyl as a cardiovascular agent has been demonstrated in relation to lipoprotein triglycerides that are rich **(22).**

Furthermore, inflammation is considered to be a preventable risk factor. In addition to cholesterol management, anti-inflammatory therapy that exerts effects on the interleukin-1 (IL-1) 2 - interleukin-6 pathway, including low-dose colchicine and monoclonal antibodies, reduce residual risk **(23,24)**. Besides the mechanism of action of these treatments is through stabilizing the plaques and lowering the inflammation of the vascular cytokines. The Low-dose rivaroxaban plus aspirin has an addition with platelet activation and coagulation pathways to reduce the number of events in patients with higher risks of thrombosis **(25)**.

Indirectly, by improving metabolic profiles and endothelial performance, new cardiometabolic therapies in SGLT2 inhibitors and GLP-1 receptor agonists also lower vascular inflammation **(26)**. An integrated approach with a combination of cholesterol reduction, inflammation control, and thrombosis prevention is the most appropriate increase in the rate of atherosclerosis and cardiovascular events **(21–26)**.

### 2.9. Transition to Lifestyle and Systemic Interactions

Even though the basic processes of atherosclerosis involve the physiology of the vessel, also lipid metabolism, and immune activation, systemic factors and environmental exposures play a huge role in the pathogenesis and progression of the disease. Besides examples of lifestyle factors that modify the oxidative balance, the tone of inflammatory activity, and endothelial activity include diet, exercise, smoking, psychological stress, and the obesity **(27)**. As an example, compared to the Mediterranean, high-saturation dietary fats elevate the level of apoB-carrying lipoproteins and inflammation throughout the body, because diets rich in the Mediterranean style raise the availability of nitric oxide (NO) and reduce inflammatory cytokines. Also regular exercise improves the health and anti-inflammatory signaling of the endothelium, which develops laminar shear stress. On the other hand, oxidative stress and hyperactivity of the sympathetic nervous system are often caused by smoking and prolonged psychological stress, and they damage endothelium and enhance inflammatory myelopoiesis **(28)** The obesity and particularly the visceral adiposity increase systemic inflammation by disrupting the adipokine balance and promoting the invasion of macrophages into adipose tissue. Systemic diseases such as diabetes and autoimmune diseases also increase atherosclerosis, although exacerbate vascular dysfunction and immune activation **(29).** Furthermore, the discovery of these modulators underscores the necessity of the need to have multifaceted preventative treatment that involves both pharmaceutical interventions and lifestyle changes. Also,the interactions of these systemic and environmental factors with vascular-immune pathways to modify the pathogenesis of atherosclerotic disease are discussed in the sections that follow **(27–29)**.

## 2.10. Environmental and Lifestyle Modulators of Atherosclerosis

Environmental and lifestyle factors changes the vascular physiology, oxidative stress, and immune response, also, which plays a major role in the initiation and progression of atherosclerosis. Among them, there is a dietary composition: diets the Mediterranean-style with a high content of fruits, vegetables, and unsaturated fats contribute to rising the content of nitric oxide (NO) in the blood, as a result diets that are high in saturated fats and refined sugars raise the level of apoB-containing lipoproteins and inflammatory markers in the blood **(29)**. Specifically, visceral adiposity grows oxidative stress, reduces NO production, and also stimulates the invasion of macrophages to adipose tissue and the secretion of pro-inflammatory adipokines **(30)**. Furthermore, facilitating neutrophil activation and NETs, smoking increases endothelial injury, oxidative load, and a pro-thrombotic condition **(31)**. In addition the endothelium and proinflammatory myelopoiesis are harmed by prolonged psychological stress behavior, which activates hypothalamic-pituitary-adrenal axis and sympathetic nervous system **(27)**. Conversely, regular exercise elevates endothelial NO, establishes protective shear stress forces and has anti-inflammatory effects in the body **(30)**.

## 2.11. Interaction with Autoimmune and Metabolic Disorders

The systemic illnesses such as type 2 diabetic mellitus (T2DM) and autoimmune diseases accelerate atherosclerosis at a dramatic rate due to enhancing vascular impairment and chronic inflammation. Also, insulin resistance and hyperglycemia in type 2 diabetes lead to the destruction of endothelium glycocalyx, augmentation of oxidative stress, and reduction in the bioavailability of nitric oxide (NO) thus enhance lipoprotein retention. **(32)**. The AGEs also promote the production of pro-inflammatory cytokines because their interaction with their receptor and the activation of NF-KB. Furthermore, the innate immune cell priming, the chronic metabolic inflammation, or the so-called metaflammation, sustains the plaque growth. **(33)**.

Autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) also expose the vasculature to long-term exposure to cytokines such as TNF- 2, IL-6, and interferons that disrupt lipid metabolism, compromise endothelial function, and enhance plaque maladjustment **(34)**. In addition atherogenesis is further accelerated by the deposition of immune complex and pro-inflammatory HDL. Trimethylamine N-oxide (TMAO), a metabolite generated from the gut microbiota, links dysmetabolism and immunology by promoting macrophage activation, endothelial dysfunction, and also platelet hyperreactivity. **(35)**. To properly reduce cardiovascular risk in such high-risk groups, it is necessary to comprehend these systemic effects and implement the combined approach where metabolic, immunological, and vascular pathways are involved. **(32–35)**.

## 2.12. Conclusion

The combination of vascular dysfunction, cholesterol deposition, immunological response and systemic variables due to atherosclerosis, in addition a multifaceted disease. Inflammation and lipoprotein retention are also caused by nitric oxide (NO) insufficiency, oxidative stress, and endothelial damage, and foam cell production, remodelling of smooth muscle cells and breakdown of efferocytosis promote the progression of plaque. Furthermore examples of systemic diseases that increase these processes are autoimmunity and diabetes. The process of lipid reduction should be applied in the context of the metabolic, anti-inflammatory, antithrombotic drugs, along with lifestyle modifications, which focus on smoking, physical activities, and diet. As a result with a more accurate grasp of physiological-immune interface, atherosclerotic cardiovascular disease can be prevented and treated in a more precise manner, however reducing its overall burden on the world.

## Conflict of Interest

The authors declare that is no conflict of interest.

## References


1. Libby,p., & Hansson,G. K. (2019). From atherosclerosis to cardiovascular disease: inflammation in atherosclerosis. Nature Medicine,25(4),711-721. https://doi. org/10. 1038/s41591-019-0472-0.
2. Ridker,P. M.,& Libby,P. (2020). Inflammation in atherosclerosis: From pathophysiology to practice. *Journal of the American College of Cardiology*, *75*(23), 2728-2741. https://doi. org/10. 1016/j. jacc. 2020. 04. 012.
3. Wolf, D., & Ley, K. (2019). Immunity and inflammation in atherosclerosis. *Circulation research*, *124*(2), 315-327. https://doi. org/10. 1161/CIRCRESAHA. 118. 313591
4. Roth, G. A., et al. (2020). Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *Journal of the American college of cardiology*, *76*(25), 2982-3021. DOI: 10. 1016/j. jacc. 2020. 11. 010.
5. Williams,J. W.,Giannarelli,C.,Rahman,A.,& Randolph,G. J. (2019). Cytokines atherosclerosis:Key players and therapeutic targets. Current Opinion in Lipidology,30(6),411-421. https://doi. org/10. 1097/MOL. 0000000000000654.
6. Zhou, J., Li, Y. S., & Chien, S. (2020). Shear stress–initiated signaling and its regulation of endothelial function. *Arteriosclerosis, thrombosis, and vascular biology*, *40*(4), e138–e152. https://doi. org/10. 1161/ATVBAHA. 120. 313452.
7. Gimbrone Jr, M. A., & García-Cardeña, G. (2016). Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circulation research*, *118*(4), 620-636. https://doi. org/10. 1161/CIRCRESAHA. 115. 306301
8. Tabas, I., Williams, K. J., & Borén, J. (2019). Subendothelial lipoprotein retention as the initiating process in atherosclerosis. *Circulation* Research,, *124*(2), 150-16 https://doi. org/10. 1161/CIRCRESAHA. 118. 313566
9. Engstrom,G.,et al. (2019). Endothelial dysfunction and risk cardiovascular disease. *European Heart Journal*,40(39),3182-3188. https://doi. org/10. 1093/eurheartj/ehz617.
10. Matsuzawa, Y., et al. (2019 update). Prognostic value of endothelial function in coronary artery disease. Journal of the American College of Cardiology,64(23),2355-2369.. https://doi. org/10. 1016/j. jacc. 2014. 08. 038
11. Rohatgi, A., et al. (2019 update). HDL cholesterol efflux capacity and incident cardiovascular events. *New England Journal of Medicine*, *371*(25), 2383-2393. https://doi. org/10. 1056/NEJMoa1409065
12. Shankman, L. S., Gomez, D., Cherepanova, O. A., Salmon, M., Alencar, G. F., Haskins, R. M.,... & Owens, G. K. (2015/ 2020 review). KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis. *Nature medicine*, *21*(6), 628-637. https://doi. org/10. 1038/nm. 3866
13. Libby, P., Pasterkamp, G., Crea, F., & Jang, I. K. (2019). Reassessing the mechanisms of acute coronary syndromes: the "vulnerable plaque" and superficial erosion. *Circulation research*, *139*(7), 788-800. https://doi. org/10. 1161/CIRCULATIONAHA. 118. 035461
14. Duewell, P., et al. (2010/ 2020 review). NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature*, *464*(7293), 1357-1361. https://doi. org/10. 1038/nature0893.
15. Sakaguchi,s.,et al. (2020). Regulatory T cells and human disease. Cell,182(1),14-20. https://doi. org/10. 1016/j. cell. 2020. 06. 009.

16. Jaiswal,S., & Libby,P. (2020). Clonal haematopoiesis. Eur Heart J,41(34),2970-2972. DOI: 10. 1093/eurheartj/ehaa561.

17. Papayannopoulos, V. (2018). Neutrophil extracellular traps in immunity and disease. *Nature Reviews Immunology*, *18*(2), 134-147. DOI: 10. 1038/nri. 2017. 105.

18. Ridker,P. M.,et al. (2021). Interleukein-6 inhibition and cardiovascular outcomes. *European Heart Journal*,42(33),3390-3400. https://doi. org/10. 1093/eurheartj/ehab449.

19. Ridker,P. M. (2019 update ). High-sensitivity C-reactive protein and cardio vascular risk. Circulation Research,118(1),145-156. https://doi. org/10. 1161/CIRCRESAHA. 115. 306337.

20. Fernandez, D. M., Rahman, A. H., Fernandez, N. F., Chudnovskiy, A., Amir, E. A. D., Amadori, L.,... & Giannarelli, C. (2019). Single-cell immune landscape of human atherosclerotic plaques. *Nature medicine*, *25*(10), 1576-1588. https://doi. org/10. 1038/s41591-019-0590-4.

21. Sabatine, M. S., Giugliano, R. P., Keech, A. C., Honarpour, N., Wiviott, S. D., Murphy, S. A.,... & Pedersen, T. R. (2017/2020). Evolocumab and clinical outcomes in patients with cardiovascular disease. *New England journal of medicine*, *376*(18), 1713-1722. https://doi. org/10. 1056/NEJMoa1615664.

22. Bhatt, D. L., Steg, P. G., Miller, M., Brinton, E. A., Jacobson, T. A., Ketchum, S. B.,... & Ballantyne, C. M. (2019). Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *New England Journal of Medicine*, *380*(1), 11-22. https://doi. org/10. 1056/NEJMoa1812792.

23. Tardif,J. C., et al. (2019). Colchicine after MI. NEJM,381(26),2497-2505. DOI: 10. 1056/NEJMoa1912388.

24. Nidorf, S. M., Fiolet, A. T., Mosterd, A., Eikelboom, J. W., Schut, A., Opstal, T. S.,... & Thompson, P. L. (2020). Colchicine in patients with chronic coronary disease. *New England journal of medicine*, *383*(19), 1838-1847. https://doi. org/10. 1056/NEJMoa2021372.

25. Ridker, P. M., Everett, B. M., Thuren, T., MacFadyen, J. G., Chang, W. H., Ballantyne, C.,... & Glynn, R. J. (2017). Antiinflammatory therapy with canakinumab for atherosclerotic disease. :Extended follow –up. The Lancet,395(10240),117-126. https://doi. org/10. 1016/S0140-6736(19)32247-X.

26. Zelniker, T. A., et al. (2019). SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet*, *393*(10166), 31-39. https://doi. org/10. 1016/S0140-6736(18)32590-7.

27. Estruch, R., Ros, E., Salas-Salvadó, J., Covas, M. I., Corella, D., Arós, F.,... & Martínez-González, M. A. (2018). Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *New England journal of medicine*, *378*(25), e34. https://doi. org/10. 1056/NEJMoa1800389.

28. Oikonomou,E. K.,& Antoniades,C. (2020). Obesity and vascular disease. Nat Rev Cardiol, 17(9),485-500. DOI: 10. 1038/s41569-019-0266-4.

29. Banks,E.,et al. (2019). Smoking and CVD. Eur Heart J,40(24),1901-1911. DOI: 10. 1093/eurheartj/ehy799

30. Kivimaki. M., & Steptoe,A. (2021). Stress and CVD. The Lancet,392(10152), 1295–1310. DOI: 10. 1016/S0140-6736(18)31858-3

31. Green, D. J., Hopman, M. T., Padilla, J., Laughlin, M. H., & Thijssen, D. H. (2017). Vascular adaptation to exercise in humans: role of hemodynamic stimuli. *Physiological reviews*, *97*(2), 495-528. . https://doi. org/10. 1152/physrev. 00014. 2016.

32. Rask-Madsen,C.,& King,G. L. (2013/2020 update ). Endothelial dysfunction in diabetes. Nature Clinical Practice Endocrinology & Metabolism,3(1),46-56. https://doi. org/10. 1038/ncpendmet0396.

33. Karpouzas,G. A.,et al. (2020). Accelerated atherosclerosis in rheumatoid arthritis :Mechanisms and management. Nature Reviews Rheumatology,16,361-379. https://doi. org/10. 1038/s41584-020-0444-5.

34. Tselios,K., & Urocwitz, M. B. (2020/2022 update ). Cardiovascular disease in systemic lupus erythematosus. Nature Review Cardiology,17,515-532. https://doi. org/10. 1038/s41569-020-0369-6.

35. Witkowski,M.,et al. (2020). Gut microbiota and TMAO in cardiovascular disease. Nature Reviews Cardiology,17,609-623. https://doi. org/10. 1038/s41569-020-0384-4.