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Atherothrombosis as a Leading Cause of Acute Coronary Syndromes and Stroke: The Main Killers in Developed Countries

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Additional information is available at the end of the chapter

Abstract

Worldwide, cardiovascular incidents are estimated to cause 17.5 million deaths, 80% of which are ischemic strokes or acute coronary syndromes. Cardiovascular disease results in a significant financial burden for healthcare system—namely, in 2009, it was 9% of the gross health service expenditure in the European Union. Therefore, the development of the knowledge about atherosclerosis—initially thought to be solely degenerative disorder but now considered a multifactorial inflammatory state—is essential. Acute coronary syndrome (ACS) is usually a manifestation of severe reduction in coronary blood flow caused by atherosclerotic plaque and thrombus. The pathology of the atherosclerotic plaque is complex. Essentially, it is disease of the arterial intima that, through subsequent stages, results to luminal narrowing. Over the years, various theories regarding the genesis growth and vulnerability of atherosclerotic lesions have been promoted, usually focusing on endothelial injury, smooth muscle cell proliferation, lipid accumulation, and, more recently, inflammatory reactions.

Keywords: atherothrombosis, atherosclerotic plaque, intravascular thrombus, acute coronary syndrome, cardiovascular events, ischemic heart disease, vulnerable plaque, plaque erosion

1. Introduction

Ischemic heart disease, despite the significant progress of drug therapy as well as coronary revascularization techniques, still represents the most common cause of death in developed countries [1]. Social significance of the problem is reflected by analyzing the results of the

randomized controlled trials (POLSCREEN, EURO-ACTION, POLCARD, DART, GISSI). The above-mentioned trials, as well as other carried out so far, including autopsy studies and clinical and experimental studies, have shed new light on the pathogenesis of atherosclerosis, which for years was believed to be a disease solely degenerative. It is now known that it is a condition characterized by systemic low-grade inflammation [2, 3]. This process begins peri-natally [4]. Lipid disorders that occur in the mother increase the sensitivity of the fetus to the risk factors for atherosclerosis. Moreover, the low birth weight correlates positively with an instance of the metabolic syndrome in adulthood [5, 6].

Inflammation affects the compliance of the arteries. It is a response of vascular walls to agitation and injury of vascular endothelium (*response-to-injury hypothesis*) [2, 7]. It has been shown that endothelial cells are the main component of the vessel wall that is responsible for empowerment of the process of atherogenesis. It has also been suggested that they participate in various stages of development, destabilization and cause for plaque rupture [8]. Under physiological conditions, the cells of proper endothelium produce substances that regulate vascular smooth muscle tension, adhesion and aggregation of platelets and the migration of monocytes and polymorphonuclear leukocytes. Damage to the vascular endothelium, also considered for activation of the inflammation, is characterized by a reduced bioavailability of endothelial vascular distending substances (mainly nitric oxide [NO] and prostacyclin [PGI]), increased permeability of plasma lipoprotein vessel intima and changing the properties from anti-adhesive to pro-adhesive [9, 10]. The state of endo-thelial cells depends, among other things, on vascular endothelial NO formed under the influence of L-arginine NO synthase [10]. This is the endothelial substance responsible for the anti-atherosclerotic, vascular distention, anti-inflammatory and anti-coagulant activity of vascular endothelium [9, 11]. Factors responsible for endothelium dysfunction include elevated LDL cholesterol, high homocysteine, hypoxia, diabetes, oxidative stress (due to excessive formation of free radicals of oxygen), bacterial and viral infections (Chlamydia pneumoniae, Helicobacter pylori, Herpes virus, Cytomegalovirus). These components of atherogenesis cause mainly functional but also morphological damage. Moreover, shear stress variability in hypertension causes mechanical injury of endothelial cells [9, 12]. Increased sensitivity to the damage is shown in the endothelium of the diabetic patients, as its cells can be stimulated, under the influence of the increased concentration of glu-cose and the accumulation of advanced glycation end-products. These substances, acting through the receptors for glycation end products, may induce proinflammatory molecule expression in endothelial cells [13].

2. Epidemiology and impact of life style on atherothrombosis

Atherothrombosis is a complication of atherosclerosis. The essence of this process con-sists of closing or narrowing vessel lumen, which is caused by a clot formation following exposure of thrombogenic, lipid rich necrotic core, of the ruptured plaque. Depending

on the affected vascular bed, it can manifest as a heart attack or unstable coronary artery disease, transient ischemic episode or stroke, as intermittent claudication or acute limb ischemia [14].

About 80% of deaths from cardiovascular events occur as a result of a stroke or a heart attack. Approximately 17.5 million people die every year due to cardiovascular disease, which is approximately 31% of general mortality in the world. Atherothrombosis is the main cause of mortality due to cardiovascular diseases (CVD). Approximately 75% of the cases of heart attack and approximately 90% of strokes associated with carotid arteries atherosclerosis are caused by thrombosis [15].

CVD is a big financial burden for healthcare systems. In 2009, CVD-related costs totaled 106 billion euros, which was approximately 9% of the total expenditure on health care in the European Union [16]. There exists global trend towards the increase in the incidence of lifestyle diseases and a decrease in cases of premature death as compared to years on disability. In the context of lost years of life and life years on disability, ischemic heart disease (IHD) and stroke are, respectively, in the first and third place in the world [17]. About 85–90% of strokes are of ischemic etiology [18].

In accordance with meta-analysis, based on an analysis of studies involving a total of more than 250,000 people, the risk of death due to CVD in the course of lifetime is approximately 30%, and taken into account the risk of death and all cardiovascular events dating back to it, 50% for both sexes, in each age group [19]. Among diabetics, most of whom die due to CVD, 8 of 10 deaths are due to atherothrombosis [20].

According to the findings of the Global Burden of Disease Study from 2010 onwards, adjusted for age, the mortality due to CVD has fallen approximately 20% during the last 80 years of the twentieth century [21]. The success of the reduction of mortality due to CVD is associated with the development of methods of treatment and better organization of healthcare, as well as preventive activities, including non-pharmacological interventions. To the above, one can also add changes in tobacco legislation, which can lead to a 15% reduction in the risk of hospitalization and a 16% reduction in mortality from coronary heart disease and stroke [22]. Not less important are the lifestyle changes, including eating habits. It has been demonstrated that appropriate physical activity and dietary intervention can contribute to approximately 35% reduction in the risk of death already accepted with adjustment of pharmacologic medication [23]. Proper diet contributes to the reduction of cardiovascular events (CVE) in patients after 55 years of age diagnosed with diabetes or a history of CVE irrespective of the use of drugs in secondary prevention [24].

In terms of cardiovascular risk reduction, the introduction of statin therapy was the pharmacological milestone. This has proven effective in reducing CVE and mortality due to CVD [25]. What's more, their use in low-risk populations decreased by approximately 30% the relative risk in this population. In addition, for patients intolerant of statins or for those who despite optimal therapy fail to achieve their therapeutic goal, Ezetimibe or

Evolucumab can be currently used, new drugs of proven efficacy and safety of therapy [26, 27]. Ezetimibe connects with Niemann-Pick C1-like 1 (NPC1L1) proteins preventing absorption of cholesterol from the gastrointestinal tract. Used together with simvastatin, it significantly reduced the risk of mortality compared to statin monotherapy. Evolocumab is a monoclonal antibody interacting with enzyme PCSK9 (proprotein convertase subtilisin kexin type-9) and significantly lowering LDL-cholesterol and total cholesterol and reducing CVE rate in combination with a statin as compared to statin monotherapy [26, 27].

Very important element of therapy is patient's compliance. Adherence of the patient affects the effectiveness of the therapy. The review of approximately 20 studies involving a total of over 375,000 patients showed only 42–61% of adherence to treatment in patients receiving cardiovascular drugs as primary prevention and 62–76% adherence in secondary prevention [28].

There are some differences in CVD mortality among different races. Black people have a higher risk of death from coronary heart disease and 2–4 times higher risk of ischemic stroke than white people. The Asian race and the people of the Pacific Islands are at the highest risk for hemorrhagic stroke [29].

Appropriate prevention would reduce the CVD cases by 80% [19, 30]. Unfortunately, there are still inequalities between countries. About 80% of deaths from CVD take place in countries with low-to-moderate prosperity, in which the frequency of multiple risk factors, especially obesity and diabetes mellitus (DM), tends to increase significantly [16]. Interestingly, despite the general decline in the consumption of tobacco products, there currently exists three times higher risk for smoking in women because of the trend to start the habit at a younger age.

Among patients with CAD, the most common manifestations of atherothrombosis are myocardial infarctions with ST segment elevation (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI). In-hospital mortality in STEMI varies, according to a variety of records, around 6–14%. Despite the development of pharmacotherapy and the invasive therapy, the mortality rate in 6 months after STEMI is still approximately 12%. Over the last decade, the proportion of STEMI has been reduced as compared to NSTEMI. Although, in the early years, the population of patients with NSTEMI acute coronary syndrome is characterized by lower mortality; after about 2 years, it is similar as in patients with STEMI [31].

3. The role of inflammation in the process of the formation of atherosclerosis

Atherosclerosis is a chronic inflammatory disease [9, 32–34]. Due to the damage to the vascular endothelium and the development of inflammatory lesions in the vessel wall, there is a tendency to create blood clots leading to the occurrence of the thromboembolism evolving from atherosclerotic plaques or closing of the artery lumen at the site of inflamed plaque rupture, i.e. thrombotic vessel occlusion. Acute coronary syndromes (ACS) are in the form of unstable coronary artery disease (unstable angina—UA) and acute myocardial infarction

(AMI)—which includes STEMI and NSTEMI or sudden cardiac death (SCD). Atherosclerosis in carotid arteries can lead to transient ischemic attacks (TIA) or ischemic stroke. The cause for these complexes, known as cardiovascular syndromes, is a blood thrombosis, forming on the surface of the damaged endothelium, a narrowed coronary artery or carotid artery, most frequently internal carotid artery (ICA) [9, 32].

Pathophysiological studies have shown that the most common cause of formation of a blood clot is rupture of the fibrous cap, which separates the contents of the plaque from the blood [9, 13, 33, 35]. This was confirmed in intravascular ultrasound (IVUS) with virtual histology (VH-IVUS), optical coherence tomography (OCT) and magnetic resonance imaging (MRI) [36, 37]. This mechanism applies to approximately 55–60% (in some studies dating back to the 80%) cases of ACS [33, 35, 36]. Other mechanisms are damage of endothelial cells known as erosion on the surface of atherosclerotic plaque (plaque erosion) consisting of 30–35% of the ACS and of approximately 2–7% endovascular calcifications (calcified nodules) [33, 35]. Inflammatory changes ongoing in the atherosclerotic plaque cause a loss of stability making it vulnerable to rupture, the so-called unstable atherosclerotic plaque (vulnerable plaque). Unstable plaque is characterized by a thin fibrous cap (thin cap fibroatheroma—TCFA) covering the big necrotic core around which revolves the inflammatory process and positive remodeling of the artery [9, 32, 33, 35]. A similar transformation in the atherosclerotic plaque has also been observed in the ICA. This location is responsible for TIA and strokes [9]. Positive remodeling of the artery proves that narrowing of its lumen does not have to be relevant, and it may not exceed 50–70% [9, 33]. The widespread use of statin drugs, especially atorvastatin and rosuvastatin, also likely ACE inhibitors, and lifestyle changes in developed countries have resulted in better control of inflammatory changes ongoing inside atherosclerotic plaque. This results in reduction in the incidence of strokes (primary stroke prevention) and ACS in the form of STEMI, but higher prevalence of NSTEMI and UA [9, 13, 32]. As a result, this has led to decreased cardiovascular mortality in many countries. It cannot be excluded that control of inflammation in the vessel wall by commonly used statins lowers the incidence of share in causes for destabilizing plaque rupture leading to occlusion of the artery. Because the total number of ACS and cerebral ischemic events remains at a similar level, this finding probably reveals other mechanisms leading to intravascular thrombosis with a smaller share of acute inflammation within the plaque rupture-induced accumulation of oxygen-modified LDL cholesterol (oxy-LDL) leading to destabilization. These mechanisms include endothelial injury by vascular flow disorders caused by artery stenosis, abnormal healing processes of the damaged endothelium, infectious pathogens as well as autoimmune responses against modified plaque components [9, 13, 35, 38, 39].

4. The evolution of stable coronary artery disease to ACS

4.1. Vulnerable plaque

Endocrine endothelial function, which consists in the synthesis and secretion of NO and PGI, is a prerequisite for the preservation of its integrity and correct relationship between

it and flowing blood. Known atherosclerotic risk factors may interfere with this function of encouraging the penetration of lipoproteins, monocytes and lymphocytes into the vessel wall. Currently, there is no doubt that atherosclerosis is a chronic inflammatory disease involving many immunological processes. Some researchers of these medical conditions compare them with other chronic inflammatory disorders, in which immune and autoimmune reactions play an important role [40, 41].

Inflammation in connexion with the accumulation of cholesterol, principally oxygen-modified LDL cholesterol (oxy-LDL), causes the proliferation of monocytes from peripheral blood, which is then converted into macrophages. It also stimulates the recruitment of myofibroblasts producing proteoglycans—the main substrate of extracellular matrix. Changes are conducive to the occurrence of the vasoconstriction and activation of the endovascular inflammatory and prothrombotic mechanisms. Gradual increase of the volume of the emerging plaque leads to abnormal blood flow, which in turn causes the oscillating shear stress and intensifies the atherothrombotic mechanisms stimulating further plaque growth [35, 42, 43]. The resultant atherosclerotic plaque is made of fibrous cap of smooth muscle cells and connective tissue. The cap separates the lumen of vessels from the contents in which necrotic core is surrounded by inflammatory infiltrates containing macrophages, foam cells and lymphocytes. The core of the plaque also contains the oxy-LDL cholesterol, free cholesterol crystals and calcium deposits [13, 43–46]. A part of the atherosclerotic plaques also contains foci of hemorrhage arising from the damage to the proliferating blood vessels, stimulated by inflammation [37, 47, 48]. Angiogenesis plays an important role in the pathophysiology of plaque instability and plaque rupture. New blood vessels rarely penetrate from the main lumen, but more often from the vasa vasorum [47, 48]. They lack the cells constituting the vessel wall which are fragile and porous, so that they become a source of local extravasation plasma protein and blood cells. Such bleedings in the plaque are frequent, may increase the volume of necrotic core and cause sudden progression of artery stenosis [49]. A central role both in the development and destabilization of plaque was attributed to macrophages, which, through their surface scavenger receptors, absorb oxy-LDL and transform into foam cells. Cytokines produced by macrophages infiltrates would lead to the degradation of the connective matrix tissue and smooth muscle cell necrosis and, consequently, to fibrous cap rupture. It leads to a thrombus formation responsible for acute ischemic syndromes. It has been repeatedly described for years as a mechanism of emergence and rise of the plaque volume, as well as its destabilization, is simplistic and does not actually translate the complex changes taking place in its interior.

Currently, a greater role in initiation of changes is attributed to lymphocytes and mutual relations between lymphocytes and macrophages, which cause varying degrees of inflammation activity. The main antigen that initiates and maintains inflammation in the vessel wall is oxy-LDL [13, 32, 41, 50]. It is toxic to the vessel wall cells causing the immune system to try eliminating it. The presence of oxy-LDL-derived antigens on the surface of the dendritic cells, macrophages and different types of lymphocytes regulates the activity of inflammation [13, 41, 50, 51]. Antigen can also be protein of bacterial cells, viral, heat shock protein 60 or β2glycoprotein 1 [3].

Naïve T-cells maturating in the thymus gland under the influence of natural antigens differentiate into the cells of total immune memory, slow reacting (central memory—T_{CM}) long remaining in circulation and storing the memory of antigens (e.g. cancer, HIV) and effector cells (effector memory—T_{EM}) rapidly responsive and likely to produce cytokines [52]. The T_{CM} have the molecule CD27 on their surface. After contact with nominal antigens, they irreversibly lose surface molecule and can settle in the lymph nodes where they acquire the characteristics of T_{EM} [52]. These cells differentiate into the lymph nodes in the direction of various cell lines—helper (Th) and regulatory (Treg) [53]. Antigen-presenting cells (APC) play key role in direction of differentiation of T cells by stimulating their surface receptor (T-cell receptor—TCR). Under their influence, functionally differentiated Th cells arise, which are classified according to the type of produced cytokines, surface markers and expression of lineage specifying transcription factors. The direction of the differentiation of T cells depends on the antigen quantity and intensity of TCR stimulation and on cytokine-inducing specific types of cells [39, 53]. It has been shown that circulating T lymphocytes, CD4+ and CD8+, differentiate preferentially in the direction of Th_1, Th_2 and Th_{17}, which promotes the transformation from stable atherosclerotic plaque into unstable vulnerable plaque [9, 50, 51, 54]. Arising Th cells produce different cytokines, including interleukin 2 (IL-2), which controls immune processes by influencing the maturation of lymphocytes Treg demonstrating immunosuppressive reactivity [13, 42, 50, 51, 53, 54]. It is now suspected that cell response (Th_1, Th_{17}) and its mediators: tumor necrosis factor-α (TNFα), interferon-γ (INFγ) and interleukins (IL)—IL-1β, IL-12, IL-17, IL-18 are responsible for promoting the development of atherosclerosis, whereas humoral immune response (Th_2) and its mediators: IL-2 IL-4, IL-5, IL-10, IL-13 have an inhibitory effect on this process [3]. Propagators of the ongoing inflammation are increased levels of proinflammatory cytokines (i.e. TNF-α, IL-6); soluble adhesion-intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), L-selectin and so-called acute-phase proteins—inflammation C-reactive protein (CRP), amyloid A and fibrinogen [2].

The mechanism of lymphocytes penetration into the arterial wall is not exactly known. Probably this is done with the participation of chemokines and L-selectin [50]. Because most chemokine receptors are found on different cell types, research to clarify the mechanisms of lymphocytes homing in the atherosclerotic plaque is mostly inconclusive.

Th_1 and Th_{17} cells produce large amounts of IFNγ that activates inflammatory processes and expresses the transcription factor β (T-bet). These factors play a decisive role in the destabilization of atherosclerotic plaque. IFNγ activates APCs and macrophages, reduces collagen synthesis and increases production of cytokines degrading extracellular matrix. An important role in the degradation of the extracellular matrix is also played by matrix metalloproteinases (MMP) [9, 55, 56]. A strong factor in boosting the activity of MMP-9 (an enzyme that breaks down collagen type IV, which is component of the fibrous cap) is TNFα (**Figure 1**) [57].

Treg cells inhibit the inflammatory reactions by IL production such as IL-10 and similarly acting transforming growth factor beta (TGFβ) [9, 13, 39, 50, 60]. They reinforce simultaneously the fibrous cap by stimulating the proliferation of smooth muscle cells and the production
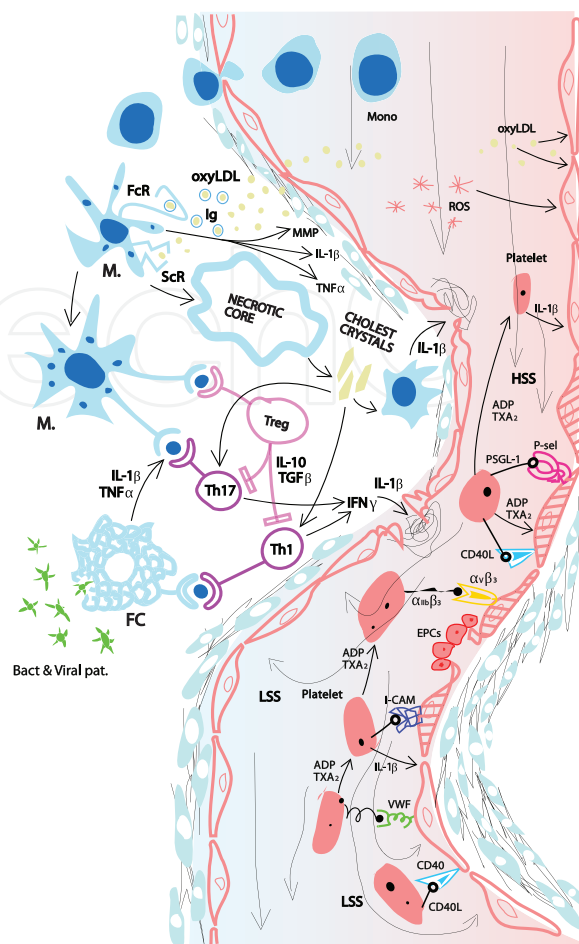
Figure 1. Possible mechanisms of plaque vulnerability (left) and plaque endothelial erosion (right). *Vulnerability*: oxy-modified LDL (oxy-LDL) causes inflammation by the proliferation of monocytes from peripheral blood, which is then converted into macrophages (M). The excess oxy-LDL in the blood penetrating into plaque results in the formation of the complexes with immunoglobulin (Ig). These complexes combine with Fc receptors (FcR) on the surface of macrophages stimulate the secretory activity for MMP, IL-1β and TNFα. Presentation of the oxy-LDL on the surface of macrophages stimulates Treg lymphocytes, which slows the inflammation by reducing the activity of the Th lymphocytes. Cell response (Th$_1$, Th$_{17}$) and its mediators—tumor necrosis factor-α (TNFα), interferon-γ (INFγ) and interleukins (IL-1β)—are responsible for promoting the development of atherosclerosis and activating inflammatory processes. IFNγ activates macrophages, reduces collagen synthesis and increases production of cytokines degrading extracellular matrix. Treg cells inhibit the inflammatory reactions by IL production (IL-10) and similarly acting transforming growth factor beta (TGFβ). The binding of oxy-LDL to scavenger receptor (ScR) located on macrophages, which is not subject to feedback, results in overloading of these cells leading to their death, releasing the free cholesterol and increasing volume of necrotic core. Such antigens, when released, trigger mechanisms of the vicious circle by stimulation of the Th$_1$ and Th$_{17}$ instead of Treg lymphocytes. *Endothelial erosion*: both low (LSS) and improperly high shear stress (HSS) interfere with endothelial functions and can produce prothrombotic state. Shear stress fluctuations increase tendency of endothelial cells covering the atherosclerotic plaque to apoptosis. Damage to the endothelial cells activates endothelial progenitor stem cells (EPCs) derived from bone marrow, which proliferate at the place of damage, and may prevent the described processes that leading to the thrombus formation. Endothelial cells increase their adhesion properties in relation to the platelets which by releasing granulation substances (IL-1β) activate the endothelial cells creating a mutual feedback. Reactive oxygen species (ROS) and circulating lipoprotein (oxy-LDL) also express endothelial surface adhesion proteins as selectins (P-sel) and von Willebrand factor (VWF), which supports the mutual relationships between them and platelets. Platelet CD40 ligand (CD40L) binds CD40 on endothelial cells, resulting in upregulation of adhesive molecules (ICAM-1, VCAM-1, P-sel), cytokines, and TF release, leading to reduction in NO synthesis. Surface platelets glycoprotein-1 receptors for P-selectin (PSGL-1) allow for adhesive bond and rolling platelets but not strict binding to the endothelium. Glycoprotein surface receptor GPVI and αvβ3 bind vascular walls collagen causing the activation of receptors αIIbβ3 and release of ADP and thromboxane A2 (TxA2). The combination of glycoprotein platelet receptors αIIbβ3 with VWF and fibrinogen stabilizes the platelet clot. This initiates a platelet thrombus protruding into artery lumen and is essential for the later stages of thrombus formation.

of collagen [39]. Functional balance between these T-cell types provides the stability of atherosclerotic plaque. The excess oxy-LDL in the blood penetrating into plaque results in the formation of the complexes with immunoglobulin. These complexes combine with Fc receptors (FcR) on the surface of macrophages and stimulate the secretory activity for MMP, IL-1β and TNFα. At the same time, the presentation of the oxy-LDL on the surface of macrophages stimulates Treg lymphocytes, which slow the inflammation down by reducing the activity of the Th lymphocytes. Such control system works well in people with low levels of risk factors. The binding of oxy-LDL to scavenger receptor located on macrophages, which is not subject to mentioned feedback, results in overloading of these cells leading to their death, releasing of free cholesterol and increasing volume of necrotic core [13, 58]. The release of such antigens triggers the mechanisms of the vicious circle by stimulation of the Th$_1$ and Th$_{17}$ instead of Treg lymphocytes [9, 13, 39, 42, 50].

Lately, attention is focused on the role of receptor programmed target death protein-1 (PD-1) presented on the naive CD8+ cells. It bears the responsibility for the so-called immune exhaustion observed in chronic inflammatory states (tbc, HIV) and cancer. There are suggestions that chronic stimulation of TCR by oxy-LDL leads to increased presentation of PD-1. The presence of PD-1 correlates inversely with the level of IL-2 produced by Th$_2$. This can interfere with the CD8+ cell differentiation in the direction of Treg and potentiate their apoptosis leading to competitive advantage mechanisms acting as pro-inflammatory and destabilizing factors in the plaque [41].

Probably within a plaque, there are three subtypes of macrophages. The most common are classically activated macrophages M1 induced by INFγ or Th$_1$ and Th$_{17}$ lymphocytes cytokines. The second group are macrophages M2 induced by cytokines of helper lymphocytes Th$_2$ (IL-4 and IL-13). They produce the anti-inflammatory acting cytokines—IL-10 and TGFβ [59]. Probably, there is a third group of macrophages presenting CD163+, activated by hemoglobin, which do not produce pro-inflammatory cytokines and have reduced ability to produce inducible nitric oxide synthase (iNOS). A decrease in the levels of intracellular iron ions within the macrophage probably plays a leading role in the transcription of genes protecting these security cells from the accumulation of lipids. This is done by increase in the levels of ferroportin-1 leading to reduction of free radicals (-OH) production as result of iron ions accumulation and depletion. One of the key regulators of atherosclerotic plaque stability may prove to be hepcidin, responsible for ferroprotein-1 degradation, resulting in the accumulation of iron ions, the accumulation of intracellular lipids and apoptosis of macrophages. Hepcidin blockage inhibits the development of atherosclerosis by regulating ATP-binding protein subfamily G [59, 60].

A significant role in the weakening of the fibrous cap, consequently causing it to rupture, is played by T-cells CD4 + CD28[nul]. They produce a significant amount of INFγ and TNFα, strongly stimulating macrophages. They also have cytotoxic properties in relation to fibrous cap, smooth muscle cells and are apoptosis resistant. These cells are presenting cytotoxic immunoglobulin (killer immunoglobulin) on their cell membrane that acts as cytotoxic receptors (Ig-like receptors).

They also produce cytolytic enzymes against the endothelial cells that directly kill them, such as perforins, granzyme A and granzyme B, which are usually present in killer T cells (KTC) and natural killer cells (NK) [13, 39, 61, 62]. It has been shown that the number of these cells in the circulation is an important prognostic for occurrence and course of ACS [61].

Production of proinflammatory proteins, such as IL-1β, chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-C motif) ligand 3 (CCL3), E-selectin (SELE), ICAM-1, MMP-3 and the MMP-9, involved in the process of destabilizing atherosclerotic plaque denotes a genetic profile connected with polymorphism of many genes. Polymorphism of this plays an important role in the susceptibility to risk factors for atherosclerosis and to changes in already existing atherosclerotic plaque. What's more, single nucleotide polymorphisms located within the regions of functional genes for these proteins may affect their concentration and activity causing further clinical implications [63].

By examining the mechanisms leading to the development of atherosclerosis, it was shown that in these processes, beyond the stimulated endothelial cell and cells of the immune system, also vascular smooth muscle cells (VSMC) are involved [64]. VSMC function is not just limited to the production of extracellular matrix in the vessel wall. It has been shown that in response to a stimulus, these cells may change the type of produced extracellular matrix and thus affect the lipid content in the vessel wall and the multiplication of other cells. Under specific conditions, they can also take over the function of other cells, for example macrophages, and due to the expression of the relevant receptors acquire absorption capacity of fat by mimicking foam cells. While taking over some functions of endothelial cells, they can produce cell adhesion molecules, VCAM-1 or ICAM-1. In addition, being a component of atherosclerotic plaque, they can also produce cytokines—platelet-derived growth factor (PDGF), TGFβ, IFN and monocyte chemoattractant protein 1 (MCP-1) [64].

Under the influence of these cytokine, extracellular matrix degradation occurs into fibrous cap. It is weakened further due to result of the apoptosis of smooth muscle cells and cell death due to primary necrosis (oncosis) [9, 44].

Contact of the flowing blood with the content of the ruptured plaque activates processes of coagulation, which can occur rapidly. A large amount of tissue factor (TF) liberated by inflammation tissue activates plasma factor VII, which runs the enzymatic coagulation cascade. TF forms a complex with factor VII, activating it to active form (VIIa). The complexes TF/VIIa activate factors IX and X, leading to thrombin generation. The consequence of this cascade of activation is rapid formation of the intravascular thrombus [9, 35, 65].

4.2. Erosion on the surface of the atherosclerotic plaque as a cause of ACS and stroke

Epidemiological studies have shown that myocardial infarction may occur in people with normal levels of LDL cholesterol. In addition, as demonstrated by pathomorphological and clinical studies using optical coherence tomography, 30-40% of patients with vascular thrombosis atherosclerotic plague have no inflammatory features [13, 45, 46]. The morphology of such plaques is completely different from the above, subjected to the inflammatory changes. The blood clot formed on its surface is in direct contact with the intima at a place completely devoid of the endothelium. Fibrous cap is well demarcated and includes numerous smooth muscle cells and an extensive connective tissue forming an extracellular matrix [33, 46]. The interior of the well-demarcated plaque contains few macrophages and lymphocytes. As well, the profile of patients with ACS, who have been found to have this

type of plaque, differed from the profile of patients who suffered vulnerable plaque. In available reports, these patients were younger, 80% of these were premenopausal women, and frequent tobacco smokers [9, 33, 45]. The mass of the plaque, which was the basis of thrombosis, was less than in the case of plaque rupture and often it was nonconcentric [9, 13, 33, 45]. In contrast to the inflammatory plaques that show positive remodeling, arteries affected by erosion are characterized by negative one [45]. Demonstrated characteristics suggest a different mechanism in formation of a blood thrombus, which, like in the case of plaque rupture, can cause both the closure of an artery and peripheral embolism, more often associated with such morphology of the intravascular changes [9, 13, 33, 45]. However, the mechanism of the formation of this type of inter arterial thrombosis has not been fully understood. It is suspected that a decisive role in its formation plays abnormal blood flow due to arterial plaque stenosis, which causes changes in shear stress, endothelial dysfunction that covers plaque affecting its anti-inflammatory and anti-thrombotic signals of the endothelium [9, 13]. Laminar flow disorders more often occur in places of bifurcation and in the folds of the arteries. The correct endocrine function of the endothelium creates normal shear stress, which is the force of friction between the flowing blood and cellular layer covering the interior surface of the vessel. Both low and improperly high shear stress interfere with endothelial functions and can produce pro-thrombotic state. In the case of atherosclerotic narrowing of the artery, both pre- and post-stenosis flow are slowed down—shear stress is low, whereas at the apex of the plaque, the flow is accelerated—shear stress is abnormally high. This creates conditions conducive to damaged endothelium. Low shear stress and turbulent blood flow facilitate the accumulation of lipids, the recruitment of inflammatory cells and increased expression of adhesion molecules and proteases [59]. The correct vascular flow—valid shear stress induces the enzyme systems that prevent the expression of pro-inflammatory and pro-thrombotic genes and at the same time promote the layout security by activating the endothelial NO synthase. Simultaneously, high shear stress stimulates the synthesis of several types of microRNAs that interact with Krüppel-like factor 2 (KLF2) and nuclear factor erythroid cell-specific 2-related factor2 (Nrf2), which support the interaction of anti-inflammatory and anti-thrombotic pathways [13]. Accelerated flow of blood within the largest narrowing and supra-physiologically high shear stress suppresses these systems, which prevent inflammation and activate the prothrombotic processes, and may be the reason for damage to the endothelial cells and the activation of inflammation with further consequences of thrombosis [9, 13]. These biomechanical force fluctuations associated with shear stress are particularly apparent in people with hypertension and their effects are intensified under the influence of other atherosclerotic risk factors, such as hypercholesterolemia, advanced glycation end-products in diabetes, tobacco smoking, vasoactive amines and immune complexes. These factors in terms of alternating shear stress can lead to endothelial dysfunction [35].

In areas of damaged vascular endothelium and high shear stress, there are abnormal interactions between thrombocytes and endothelial cells, which is the basis for the pathogenesis of endovascular thrombosis and activates the processes leading to instability of the atherosclerotic plaque. Another suggested mechanism that can coexist with described above is increased tendency of endothelial cells covering the atherosclerotic plaque to apoptosis. It is

associated with the possibility of presentation by so-called pattern recognition receptor—toll-like receptor 2 (TLR2). It contains a hyaluronian molecules in its structure, identical to that found in Gram+ bacteria, which can result in the recognition of these cells as foreign by the immune system, leading to their destruction, and thus initiating thrombotic processes. This may lead to identification of these cells by the immune system as foreign, leading to damage and thus initiating the processes of thrombosis [9].

In the event of existence of some pro-inflammatory agents, endothelial cells increase their adhesion properties in relation to the platelets which by releasing granulation substances activate the endothelial cells creating a mutual feedback. Platelets associated with endothelial cells become very effective in recruiting leukocytes in blood by promoting their adhesion and transmigration within the atherosclerotic plaque. They play such an important role due to the interaction of numerous cell types such as endothelial cells, neutrophils, monocytes, dendritic cells and cytotoxic T-cells. Under physiological conditions, platelets circulate in the blood remaining in close contact with the endothelial cells. However, their adhesion is prevented by a specific phenotype of endothelium cells controlled by three intracellular ways: way of NO, trace ectoADPase/CD39/NTPDase and eicosanoids-arachidonic acid-prostacyclin pathway (PGI2), which inhibit the activation of platelets on the way of synthesis of cAMP and cGMP stimulation [59]. Impairment of these three mechanisms causes the expression of cell adhesion particles and then a multistep process coagulation cascade activation involving bondage, translocation and strict adhesion of platelets to the inner layer of the vessel [65]. Activated blood plate increases its volume, which denotes cardiovascular risk, and is used in the clinical trial identification of inflammation and accompanying prothrombotic state [66, 67].

Activation of endothelial cells, arising not only under the influence of flow disorders but also under the influence of reactive oxygen species (ROS), and circulating lipoprotein leads to the expression of surface adhesion proteins—P-i L-selectin and von Willebrand factor (VWF), which support the mutual relationships between endothelial cells and platelets [65]. Endothelial cells present selectin on their surface, such as selectin-P, which stimulate platelets to produce glycoproteins, including glycoprotein-1. Complex selectin-P-glycoprotein-1 (PSGL-1) allows platelet adhesion and rolling but not tight binding of endothelial cells. Glycoprotein surface receptors GPVI and $\alpha v\beta 3$ bind vascular walls collagen, which activates the channels for intracellular calcium flux, causing the activation of receptors $\alpha IIb\beta 3$ and release of ADP and thromboxane A2 (TxA2). This initiates a platelet thrombus protruding into artery lumen and is essential for the later stages of thrombus formation. The combination of glycoprotein platelet receptors $\alpha IIb\beta 3$ with VWF and fibrinogen stabilizes the platelet clot, which in clinical practice becomes the target of preventing thrombolysis by pharmacological interventions (**Figure 1**) [65]. Impregnation of so-formed platelets conglomerate on the inner surface of the artery by fibrin finally decides the formation of a stable thrombus [9, 65].

Mutual activation of endothelium and platelets largely depends on the IL-1β, accumulated in granules of platelets and activated by mRNA already several hours after thrombin stimulation or adhesion-dependent integrins. Stimulation of platelets by IL-1β induces secretion of IL-6 and IL-8 and the expression of surface adhesion molecules-ICAM-1, $\alpha v\beta 3$ and hemotactic monocyte's protein-1 (MCP-1). Due to these mechanisms, platelets are

capable of recruiting monocytes and neutrophils from blood and then causing them to migrate and participate in the above described pathophysiology of atherosclerotic plaque vulnerability. Presented mechanisms ensure the presence of activated thrombocytes in the center of the pathophysiology of the process, not only with the thrombus formation but also as an important part in the activation and maintenance of the inflammatory process. Human platelets are capable of producing all types of toll-like receptors (TLR). It has been shown that higher TLR expression in women may be responsible for differences in cardiovascular risk profile, as well as the tendency for a higher incidence of ACS in the superficial thrombosis mechanism, without active inflammatory features in the atherosclerotic plaque [9, 59, 65].

Damage to the endothelial cells activates endothelial progenitor stem cells (EPCs) derived from bone marrow, which proliferate at the place of damage and may prevent the described processes that leading to the thrombus formation. These repair mechanisms are defective in patients with diabetes, characterized by a general weakness of repair capacity of damaged tissues [13, 33].

4.3. Artery calcification

Calcification in the arteries is especially visible in the carotid arteries. The relationship of calcification with instability of atherosclerotic plaques was not proven and is rather dubious [33]. It is suspected that calcifications are the result of increased apoptosis of smooth muscle cells and bleeding inside the atherosclerotic plaque [33].

Previously, it was thought that the calcification in the arterial walls increases the risk of cardiovascular complications [68]. Research in recent years has not shown; however, that calcifications increase the risk of plaque destabilization, and even reversely, calcified atherosclerotic plaques are now considered to be more stable [66, 67, 69, 70].

It has been shown that in the process of vascular calcification same changes occur as in the process of mineralization of bone tissue [33, 68]. Calcification of arteries in atherosclerosis is an active process and a complicated arrangement of mediators and calcification inhibitors is involved in it. This process includes participation of many cells (monocytes/macrophages, smooth muscle cells, vascular endothelial cells) and a variety of substances and transcription factors that are specific to bone rebuilding [71].

Emphasis is placed on separate pathomechanism of calcification of the arteries in patients with DM2 as compared with non-diabetic patients [2]. It has been proved that serum proteins like glycosylated albumin, through nuclear factor kappa-lightchain-enhancer of activated B cells (NFkB), mitogen-activated protein kinase (MAPK) and p38 kinase MAPK, leads to activation of vascular smooth muscle cells, which leads to the induction of inflammatory response, proliferation and migration of cells [72].

The dependence of calcifications on age and their predominance in men gender is underlined. The current prevailing opinion is that the presence of calcification demonstrates the extent and progress of atherosclerosis and identifies the risk of the patient generally associated with atherosclerosis and not directly related to the acute cardiovascular risk [70].

5. Summary

Progress within understanding the causes of the described disorders and the mechanisms leading to the formation of a blood clot opens up new therapeutic possibilities now and in the future to prevent acute cardiovascular incidents. The importance of the anti-inflammatory activity of statins as shown in many studies proving their clinical efficacy has already been mentioned. Similar importance has been demonstrated for other forms of therapy to lower LDL cholesterol with the help of ezetimibe or evolocumab. Controlling inflammation with patient behavior and statin drugs administration reveals other mechanisms leading to desta-bilization of atherosclerotic plaques. It cannot be ruled out that statins act on different levels of ongoing inflammation. In patients with HIV, there exist demonstrated beneficial effects of rosuvastatin, which reduced the presentation of PD-1 receptor on the surface of naïve-CD8+ [41]. It cannot be ruled out that it may be an indirect effect of its activity, by lowering levels of LDL cholesterol. Similar effects, including other pathways, leading to increased production of IL-2 and the intensification of differentiate naïve-CD8+ lymphocytes in the direction of Treg can restore the immunological balance and prevent destabilization of inflammatory athero-sclerotic plaque [41].

Understanding of the immunological mechanisms, vulnerability of atherosclerotic plaque creates the chance to obtain antibodies against antigens involved in this process. The mul-titude of these antigens operating at different stages of development is currently an impor-tant difficulty. There exist attempts to gain effective antibodies against oxy-LDL, the key antigen for activation of inflammation and atherosclerosis. Research is directed into the efficacy and safety of antibodies directed against interleukins active in generating plaque instability. Some hopes are in the direction of tocilizumab, that is, IL-6 antagonist. The disadvantage to the trials that use anti-inflammatory medications is due to accompany-ing increase in metabolic disorders of the lipid fraction which can negatively affect the progression of atherosclerotic lesion [34]. In the last published results of CANTOS study, it has been shown to reduce the risk of several percent in recurrent cardiovascular events after the monoclonal antibody—canakinumab application, which is the antagonist of IL-1β, and reduce the level of highly sensitive C-reactive protein without affecting the level of cholesterol. The result of this study was considered inflammatory confirmation theory of atherosclerosis and a new perspective in its treatment [73, 74]. An interesting sugges-tion for therapy is in trying to influence the MMP family. Some of them, like MMPs-8; 10; 12; 13, are the enzymes responsible for the destruction of the fibrous cap as well as plaque rupture, its stabilization and reconstruction. MMPs are an interesting target for therapy of acute coronary syndromes; however, their general inhibition may lead to oppo-site effects [75].

Strong anti-inflammatory and anti-atherogenic effects have apoA-I, which is a protein com-ponent of high-density lipoprotein HDL. HDL is responsible for the reverse transport of cho-lesterol contained in the atherosclerotic plaque into the bloodstream. Change in aspect ratio of apoB/apoA-I can change the course of the atherosclerotic process. Significant in this regard are clinical studies [35].

The chances of stabilizing atherosclerotic plaques also connect with the future possibility of affecting the subpopulations of T lymphocytes. Controlling activity of Th by increasing the impact of immunosuppressive Treg may foster chronicity process atherosclerosis and avoid exacerbations associated with inflammation [34].

Another investigation directed towards controlling the course of the disease is the effect on macrophages. Control of their pro-inflammatory function could prevent destabilization of atherosclerotic plaque by reducing their in-plaque activity [34].

Recognizing the importance of external antigens (bacterial and viral infections) in activating inflammatory process, it is proposed to use vaccination as a prevention of exacerbations [13, 34].

Ongoing attempts to intensify healing processes within using pluripotent stem cells and activate endothelial progenitor cells derived from bone marrow. Getting progress in this regard would be an opportunity to control endothelial dysfunction in the early stages of atherosclerosis, particularly in patients with diabetes mellitus [13].

Above mentioned studies, as well as other ongoing multidirectionally experimental and clinical studies, offer hope that in the future one will be able to better understand and control the processes leading to the initiation and progression of atherosclerosis and mechanisms of activation and worsening inflammatory changes that lead to intravascular thrombosis—direct causes of acute cardiovascular syndromes.

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