PRACA POGLĄDOWA

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Pathogenesis, prevention and treatment of peripheral artery disease

Patogeneza, profilaktyka i leczenie choroby tętnic obwodowych

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ABSTRACT

The aim of the article is to present an overview of recent findings on the etiology, pathogenesis and methods of diagnosis and treatment of atherosclerosis and a chosen specific syndrome caused by this polyvascular disease.
The author considers pathogenic mechanisms like cellular dysfunction, inflammation and coagulation disorders and also inquires about the primary cause of endothelium damage. The links between the state of vascular endothelium and lifestyle are emphasized. The author notes that the primary causes of endothelial damage should be traced, as originally suggested many years ago to such factors as heightened anger, hostility, aggression, impulsiveness and depression.
The author points out that lipid abnormalities are associated with the occurrence of vascular endothelial inflammation. It is highlighted that even though the family predisposition to the disease has long been known – genetic studies have failed to identify critical gene variants and that the notion of so-called "missing heredity" should be noted. The author also accentuates that determining so-called classical risk factors does not enable reliable prediction of the disease and therefore many researchers are looking for so-called novel biomarkers.
The performed discussion on the specific features of peripheral arterial disease makes physicians aware how to combine treatment of the generalized disease with proceedings indicated for particular local lesions. Apart from pharmacological and surgical procedures, the recent attempts to stimulate the development of collateral vessels are interesting. The considerations and conclusions presented in this overview seem of great importance for the prevention and treatment of peripheral artery disease.

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KEY WORDS
atherosclorosis, revascularisation, pathophysiology

STRESZCZENIE

Autor dokonuje przeglądu najnowszych ustaleń dotyczących etiologii, patogenezy oraz rozpoznawania i leczenia miażdżycy, a także specyfiki obranego wtórnego zespołu. Prócz przypomnienia istoty takich mechanizmów patogenetycznych,

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jak zaburzenia funkcji makrofagów, procesy zapalne i zaburzenia krzepnięcia rozważane są możliwe pierwotne przyczyny uszkodzenia śródbłonka naczyń.
Podkreśla się powiązania pomiędzy stanem śródbłonka naczyniowego a stylem życia. Autor zwraca uwagę, że poszukując pierwotnych przyczyn uszkodzenia śródbłonka należy rozważyć zaproponowane już wiele lat temu czynniki osobowościowe i behawioralne, takie jak wrogość, agresywność, impulsywność i depresja.
Autor wskazuje, że zaburzenia lipidowe są powiązane z występowaniem zapalenia śródbłonka. Podkreśla także, że choć znana jest już od dawna predyspozycja rodzina, to dotychczasowe badania genetyczne nie określiły krytycznych chorobotwórczych wariantów genów, co skłoniło do sformułowania pojęcia tzw. brakujących wyznaczników dziedziczności. Podkreślono także, że wykazanie tzw. klasycznych czynników ryzyka nie umożliwia precyzyjnego prognozowania wystąpienia choroby, stąd współczesne poszukiwania tzw. nowych biomarkerów miażdżycy. Przedstawienie specyfiki choroby tętnic obwodowych ułatwia autorowi uświadomienie klinicystom sposobów łączenia zwalczania uogólnionych objawów choroby z leczeniem miejscowych, zlokalizowanych zmian naczyniowych.
Oprócz farmakologicznych i chirurgicznych sposobów leczenia autor omawia także rozpoczęte niedawno próby stymulowania rozwoju naczyń obocznych.
Przedstawione rozważania i wnioski mają duże znaczenie dla procesu dydaktycznego dotyczącego tego najbardziej rozpowszechnionego schorzenia.

SŁOWA KLUCZOWE
miażdżyca, patofizjologia, rewaskularyzacja

INTRODUCTION

Atherosclerosis is the most common medical condition. Usually it applies to the majority of arteries of the body, but in different individuals, it manifests in the form of a particular syndrome whose symptoms result from engagements of certain vessels [1].
Because of the high prevalence of this clinical condition, it is important for physicians and their patients to be acquainted with the current state of research on the etiology of this disease and in particular with the knowledge of contemporary treatment options [2,3].
The treatment of syndromes caused by atherosclerosis should take into account the current knowledge of the possible impacts of modifying the general disorder and specific therapeutic procedures applied in the course of peripheral manifestations of the disease. One of the syndromes is peripheral artery disease. From this example, it can be seen how the therapy for this generalized disorder should be followed up by treatment of the most troublesome syndrome which develops in a patient. It is preferable, however, to treat any patient as a person affected by a polyvascular disease [4,5].
An analytical, in depth presentation of the theory would require discussion of a number of factors and mechanisms like cellular dysfunction, inflamation and coagulation disorders. However, the interesting question is what the primary cause of the damage to the endothelium is, which seems to be the starting point for the whole pathogenetic process.
The manifestation and development of the disease depends not only on family and genetic predispositions, but also environmental influences. In addition, many researchers believe that there are links between the state of the vascular endothelium and lifestyle [6,7].
Thus, the development of this disease, because of the significance of lifestyle is dependent on behavioral factors, is determined by a specific state of mental health. Therefore, this article aims to present considerations which explore the root causes of this disease in light of recent experimental findings and give an overview of contemporary indications for prevention and treatment useful for teaching purposes.

Definition and general characteristics of the disease

Atherosclerosis is a clinical state caused by artery obturations. The artery wall thickens as a result of the accumulation of lipids i.e. cholesterol and triglycerides and as a result of a chronic inflammatory response in the artery walls, caused by the accumulation of macrophages and enhanced by low-density lipoprotein molecules which carry cholesterol and triglycerides [2,3]. These pathogenetic mechanisms cause the formation of multiple plaques within the arteries [2].
Three kinds of plaque are discerned: 1. Atheroma, which is the accumulation of a soft material near the lumen of the artery, 2. Areas of cholesterol crystals, 3. Calcifications at the outer base of arteries. So-called stable and unstable plaques are also discerned. Stable plaques are rich in extracellular matrix and smooth muscle cells. Unstable plaques are rich in macrophages. There are plaques prone to ruptures which release thrombogenic material into circulation and can induce the formation of thrombi. Intraluminal thrombi can

occlude arteries and also detach and move into circulation, sometimes occluding smaller branches of arteries causing thromboembolism. When artery lumen stenosis becomes severe, ischemia symptoms occur. Atherosclerosis can be asymptomatic for decades. The most frequent complications are myocardial infarction, stroke (often caused by formation of thrombus or plaque rupture in carotid arteries) or claudication as result of insufficient blood supply to the legs. Atherosclerosis affects all the arteries, but most frequently high-pressure vessels, that is to say the coronary, carotid, cerebral, femoral and renal arteries.

Symptoms

Atherosclerosis is a generalized illness, however, in a particular person the disease manifests itself primarily by symptoms resulting from a lesion mainly in certain arteries, such as coronary arteries, carotid and cerebral arteries, peripheral arteries of the limbs, renal arteries and the celiac trunk [1]. Hence the disorder may be manifested mainly by the symptoms of a heart attack, stroke, intermittent claudication, impaired kidney function and high blood pressure or characteristic abdominal pain. For the majority of men and half of women, the first symptom of the artheriosclerosis is heart attack or sudden cardiac death.
We discuss in this paper the symptomatology of the disease in more detail of one of these syndromes, namely of peripheral arterial disease.

Etiology

The cause of the disease cannot be explained by pointing to one etiological factor. The etiology of this illness can be described only by describing the interaction of many factors [2]. Atherosclerosis is a disease whose etiology should be considered, as illustrated by Figure 1. Nevertheless, we can be tempted to indicate which factors are primarily involved in the development of the disease.
According to Williams et al., atherosclerosis is initiated by inflammatory processes in the endothelial cells of the vessel wall in response to retained low-density lipoprotein molecules [8]. Their theory can be explained as follows: probably only low density lipoproteins (LDL) are able to get behind the cellular monolayer of the endothelium. LDL particles are susceptible to oxidation by free radicals. Once inside the vessel wall, LDL particles can be trapped and be more susceptible to oxidation. The damage caused by oxidized LDL molecules triggers a cascade of immune responses which over time can produce plaque. The immune system responds to damage of the artery wall, caused by oxidized LDL, through the activation of macrophages and T-lymphocytes. Subendothelial accumulation of fatty substances occurs in vessel walls, triggering more white blood cells and the artery becomes inflammed. The cholesterol plaque causes the muscle cells to enlarge and form a so-called cover. This hard cover causes narrowing of the artery.
The contribution of different etiological factors can be described in many different ways. It is impossible to prove that one of these particular theories is more appropriate. For this reason, it is appropriate to describe the pathogenesis of this disease by enumerating and discussing so-called risk factors.

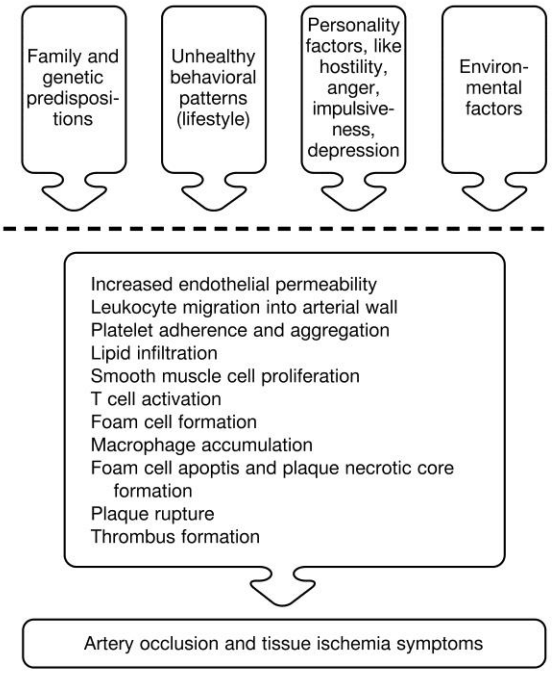

Fig. 1. Atherosclerosis is caused by numerous etiological factors that trigger a complex process of pathogenesis of the disease.
Ryc. 1. Czynniki etiologiczne miażdżycy, które uruchamiają złożony proces patogenetyczny tej choroby.

Brief description of basic mechanisms of pathogenic process

A number of theories have been proposed to explain the pathogenesis of atherosclerosis [2].
Comprehensive presentation of the theory would require the discussion of a number of factors and mechanisms. Consideration should be given, among other things, to pro-inflammatory factors like: chemokines, adhesion molecules, cytokines, toll-like receptors, penatraxins or peroxisome-proliferator-activated receptors [2]. Attention should also be paid to proteases, that is to say metalloproteinases, catepsins, mast cell proteases and the plasmid system [1]. We should also discuss the role of oxidative stress, especially the role of NADPH oxidase, heme oxygenase and the infuence of nitric oxide on endotelium. A separate, important sphere of issues is the significance of hyperlipidemia. These deliberations come down among other things to

the discussion of the dysregulated function of monocytes and macrophages. Macrophage foam cell formation and smooth muscle cell heterogeneity should be included.

Since the purpose of this article is, however, to facilitate the clinician to grasp the whole problem of atherosclerosis, we must rather present the intuitive descriptions of general features of these mechanisms. The most important mechanisms are illustrated intuitively by Figure 2.

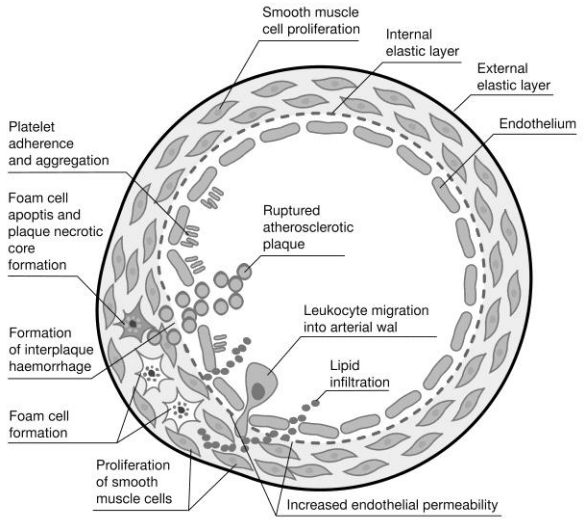

Fig. 2. Intuitive illustration of most important mechanism of atherosclerosis pathogenesis.
Ryc. 2. Intuicyjne zobrazowanie najważniejszych mechanizmów patogenetycznych miażdżycy.

To mentally order the sequence of pathogenic mechanisms, we usually assume that the sequence of adverse events leading to the development of atherosclerosis begins as a response to injury [9]. This theory encompasses the essential elements of all earlier hypotheses and states that atherosclerosis begins with endothelial injury making it susceptible to the accumulation of lipids and deposition of them [8,9].

Atherogenesis consists in remodeling arteries caused by the subendothelial accumulation of lipids and formation of so-called plaques [2]. Plaques are formed through a series of cellular activities occurring within the arterial wall [2]. Monocytes and basophils infiltrate arteries endothelium causing the development of inflammation and leading to the formation of plaques in the arterial tunica intima, that is the layer located between the endothelium and the tunica media. Plaques are formed from lipids, collagen and elastin. In the beginning of this process, plaques grow and the artery wall thickens without narrowing. Stenosis occurs later as a result of repeated plaque rupture and healing responses, not due to the atherosclerotic process itself.

The pathogenic mechanisms of the disease in more detail consist of cellular processes, changes in lipid metabolism and the formation of calcifications.

The cellular process can be described briefly as follows: As we already mentioned, first low-density lipoproteins invade the endothelium and become oxidized. Some enzymes regulate the oxidation of these lipoproteins. In the early stages of the atherosclerotic process, blood circulating monocytes adhere to the vascular endothelium. Then they migrate to the subendothelial space and transform themselves into macrophages. Afterwards, the macrophages transform themselves into large "foam cells". Their changed appearance results from the occurrence of cytoplasmic vesicles and lipid content. The foam cells decay and further propagate advancement of the inflammatory process. There is also smooth muscle proliferation. This causes the formation of a fibrous capsule covering the plaque lipid core.

Calcifications develop between the vascular smooth muscle cells in the vessel muscular layer, especially in the muscle cells adjacent to plaques and on the surface of plaques and tissue. The necrosis of these cells leads to extracellular calcium deposits between the muscular wall and the outer portion of atheromatous plaques. Cholesterol is released from low-density lipoprotein particles and oxidized inside of the vessel wall. This begins the inflammatory process. This mechanism can be prevented by high density lipoproteins which can remove cholesterol from the tissues. The foam cells and platelets stimulate the proliferation of smooth muscle cells, which are replaced by collagen. The lipid deposits contained in 'atheromas' induce the production of enzymes that cause the artery to enlarge. If the artery enlarges sufficiently to compensate for the extra thickness of the atheroma, narrowing of the vessels does not happen, but when the enlargement is out of proportion with the atheroma thickness, then an aneurysm is formed.

The disease develops slowly over decades and usually remains asymptomatic until an atheroma ulcerates. This leads to blood clotting at the site of an atheroma ulcer. It may obstruct the flow of blood. A complete blockage leads to ischemia. When occlusion occurs in the coronary arteries, myocardial infarction occurs.

If the infarction is not fatal, fibrous organization of the clot is formed. It covers the rupture but also evokes vessel stenosis. Repeated ruptures result in persistent localized vessel stenosis, which can be progressive.

If the fibrous cap separating the atheroma from the bloodstream ruptures, tissue fragments are exposed and released. These tissue fragments containing collagen promote clots. It also activates platelets and activates the arteries system. This leads to the formation of a thrombus, which can obstruct the blood flow. Obstruction of the blood causes tissue ischemia.

Risk factors

The risk factors can be divided in different ways i.e. congenital or acquired, modifiable or unmodifiable, classical or non-classical. Some authors suggest ways to calculate the overall risk on the basis of finding particular factors. Some of them argue that the risk factors multiply. Two different major factors increase the risk four times [10]. Hyperlipidemia, hypertension and smoking increase the risk seven times [10]. The so-called Framingham Risk Score and similar indexes can be calculated [11,12].

***The primary Framingham risk factors are*:** hyperlipidaemia, hypertension, smoking, family history of premature coronary disease, low physical activity and diabetes mellitus.

Considering hyperlipidema, it should be emphasized that elevated serum cholesterol, triglyceride and low density lipoproteins with decreased high density lipoprotein levels are of particular importance.

Important modifiable risk factors are also

1. Hyperthyroidism
2. Hyperhomocysteinaemia
3. Dietary factors like high intake of saturated fat and high carbohydrate intake
4. Most of these risk factors have their own genetic conditioning and independent genetic contribution to the disease and behave variably in different environments.

It may be noted that the so-called risks do not occur completely independently. They occur together in the form of sets of factors bound by some more general causes. Therefore we discuss below the most important sets of pathogenethic influences.

Behavioral and psychosocial factors influencing development of atherosclerosis

The most frequently cited behavioral factors influencing the occurrence and development of atherosclerosis are unhealthy behavioral patterns such as smoking, inappropriate diet and low physical activity. An unhealthy diet may lead to hypercholesterolemia.

It should be noted that low physical activity predisposes one not only to coronary heart disease but also to peripheral artery disease (PAD). Maintaining physical activity is particularly important for those people who have already developed PAD symptoms.

Cunningham et al. state that people with intermittent claudication are at an increased risk of death from heart attack and stroke compared to the matched controls [13]. They state that increasing physical activity can reduce claudication symptoms and may improve cardiovascular health [13]. They are convinced that surgery for intermittent claudication is for symptom management and does not reduce the risk of cardiovascular morbidity and mortality [13]. They remark that a brief psychological intervention can lead to increased physical activity, improvement in quality of life, and a reduction in the demand for surgery, for patients with intermittent claudication. This team in their next paper presents very positive results of a randomized clinical trial of a brief psychological intervention, which increase walking in patients with intermittent claudication [14].

Ram et al. discern so-called modifiable and preventable behavioral risk factors. They performed a "paired matched case control study" and also found obesity and high alcohol consumption among the risk factors for the development of atherosclerosis [15].

Early approaches to concept of stress

The formulation of the concept of stress by Selye was important for the consideration of behavioral and psychosocial factors influencing the development of atherosclerosis [24,25]. Although this concept was later criticized by opponents of the so-called psychosomatic approach, it is however, recognized by clinicians [24,25]. Trigo et al. write that "despite its critics, stress clearly plays a mediating role between psychosocial pressures and coronary heart disease, triggering various hemodynamics, neuroendocrine and/or immunological changes" [26]. These authors emphasize that stress is known to stimulate the release of catecholamines and corticosteroids, inducing cardiovascular reactivity, it means increases in heart rate, oxygen consumption, blood pressure, pressure on vascular lesions, platelet aggregation, coagulation and vasoconstriction [25,26].

Coronary prone behavior

One of the challenges of the psychosomatic approach was to try to define specific signs and symptoms that surpass the notion of stress. This was achieved in the 1960s and 1970s by Meyer Friedman and Ray Rosenman who introduced the concept of the Type A behavior pattern [27]. In the beginning, the postulated influence was defined as a behavioral pattern that could be observed in people struggling to control their environment in a chronic and aggressive manner. People manifesting this pattern usually want to achieve “more and more in less and less time” and display a hostile attitude . Subsequently, in the 1990s, Friedman refined the diagnostic criteria for type A behavior [28]. He proposed considering the two hidden components of this pattern i.e. insecurity and low self-esteem, the precursor of the disorder, and two overt components i.e. time urgency and free-floating hostility. This opened new ways for research into other psychosocial factors. From the 1980s, type A

behavior began to be supplanted by the concept of coronary-prone behavior [29].
Rose remarks that since that time the researchers have begun to focus on subcomponents of the type A behaviour pattern, particularly hostility and anger, that appear to be more reliable predictors of coronary artery disease [16].

Hostility – anger – aggression and depression syndrome

Therefore, in the last 20 years, a wide range of research has been done which attempts to establish the influence of hostility, anger and aggressiveness on the formation of atherosclerosis [16,17,18]. The endeavors of Hillbrand et al. are consistent with these postulates [7]. They remark that total serum cholesterol appears to be negatively associated with physical aggression in humans [7]. They also discuss the possible association for non-overt forms of aggression like "verbal" aggression. An example of a tool that can be used to discern the sub-components of hostility and aggression is Buss and Perry's Aggression Questionnaire [7,18]. Hillebrand et al revealed that anger, hostility and verbal aggression effectively predict total serum cholesterol. They postulate that these factors should be targets of behavioral interventions like anger management training [7].
Recently, experimental results have been published on the effect of stimulating the hypothalamus and the role of the amygdala and cerebral spinal centers on the action of the hypothalamic-pituitary-adrenal axis and the release of pro-inflammatory cytokines [23]. Some authors have also noted the influence of the sympathetic nervous system for the regulation of lipid metabolism [103]. The importance of the above hidden behavioral risk factors such anger, hostility, verbal aggression, impulsivity, perhaps explain the concept discussed earlier by Gutstein [6]. He published a paper entitled "The central nervous system and atherogenesis: endothelial injury". Gutstein cites experiments which consisted of electrical stimulation of the lateral hypothalamus in conscious, unrestrained animals on normal diets. He states that such stimulation induced severe endothelial damage in both the aorta and coronary arteries. He maintains that the mechanism by which stimulation leads to endothelial injury consists in the induction of vasospasm [6].
Gutstein's hypothesis has been taken up again recently by Serano at al. who concentrated on the association of depression and its behavioral components with the development of coronary heart disease [19].
Serrano et al. formulate hypotheses explaining the relationship between depression and vascular endothelial damage [19]. There are some underlying behavioral mechanisms like frequently present and combined lifestyle factors such as smoking, heavy alcohol use, and physical inactivity. Depression also causes reduced adherence to prescribed regimens and recommended lifestyle changes. The relationship of an unhealthy lifestyle with the occurrence of damages to the vascular endothelium was also noticed by other authors [20,21,22].
Serrano at al. also indicate other independent mechanisms linking depression and heart disease including autonomic imbalance, platelet-endothelial interaction, neurohumoral activation, inflammation, and polymorphism in the serotonin gene [19]. They remember earlier works which emphasized that disproportionate sympathetic and vagal activation leads to an absence of heart rate variability and are associated with a higher incidence of morbidity and mortality [23].
They also remark that the association between depression and CAD may also be mediated by changes in platelet activation. Platelets play a role in the development of atherosclerosis and thrombosis by means of its interaction with vessel subendothelial components and coagulation factors. Increased platelet reactivity is common among depressed patients [19].
Serrano et al. recall that high cortisol blood levels also induce endothelial injury. Sympathoadrenal activation leads to catecholamine production and subsequent tachycardia, vasoconstriction, and platelet activation [19]. Depressed patients have higher levels of C-reactive protein and inflammatory cytokines. It seems that depression can alter immune functioning and enhance inflammation [19].

Family predispositions to atherosclerosis

Family predispositions to atherosclerosis and coronary heart disease are an established risk factor from early twin studies [30]. The family predisposition to the development of atherosclerosis and coronary artery disease has been emphasized especially since the Framingham study [12,31]. In the last decade it was reinforced by Scheuner, Johansen et al. and Hurrell et al. [31,32,33,34,35,36]. Scheuner emphasized that many family and twin studies, animal models and gene association studies support the thesis of a genetic basis for coronary artery disease [31]. He maintains that genetic predisposition contributes to the development and progression of this disease, and a positive response to risk factor modification and lifestyle choices [31]. He maintains that family history reflects not only genetic susceptibility, but also interactions between genetic, environmental, cultural, and behavioral factors [32]. He emphasizes that the level of risk can be evaluated by considering the number of affected relatives, the degree of relationship, their ages and gender as well as their age at the onset of the disease [32]. This author justifies the trial of estimating the degree of predisposition by practical therapeutic and prevention needs, because persons with an increased

familial risk should be targeted for aggressive risk factor modification [32]. Scheuner in his next paper emphasizes that the systematic interpretation of family history information is the most appropriate screening approach to identifying individuals with genetic susceptibility to coronary artery disease [33].
Hurrell et al. consider the significance of the high prevalence of major cardiovascular risk factors in first-degree relatives of individuals with familial premature coronary artery disease [36]. This team found that hypertension, obesity and hypercholesterolemia are highly prevalent among first-degree relatives. It was not found among the spouses of patients with familial premature coronary artery disease [36]. These authors stress that persons with familial premature coronary artery disease deserve special attention due to their familial and genetic susceptibility to atherogenic metabolic abnormalities [36].
These findings have recently been confirmed and used by the authors of an interesting paper dedicated to the concept of a novel protective family history category which allows better profiling of cardiovascular risk and atherosclerotic burden in the general population [37].

Current state of research on genetic background of atherosclerosis

In addition to the above-discussed data concerning familial predisposition to atherosclerosis and its complications, increasingly more information being collected by researchers involved in genetic research. Concrete data on the subject has been obtained by different types of genetic research only in the last few years. We try to present in this section of our article a review of the most important results and conclusions of these investigations.
The first reports about the discovery of the genetic determinants of coronary heart disease were published in 2000 [34]. Pajukanta et al. and Johansen et al. signal the discovery of genetic variants in chromosome locus 9p21.3, which is associated with coronary artery disease [34,35]. The authors speculated on the possibility of a genotype-based risk prediction, however, they question whether assessment on the basis of genotype estimation could be superior predictors of risk evaluated through family history [35].
Liu et al. note that over the past decades, great efforts have been made to elucidate the underlying genetic basis of coronary artery disease (CAD) [38]. They developed the CADgene database, which is a collection of information related to the results of genetic investigations in the realm of coronary artery disease [38]. The purpose of this database is to integrate this information and to provide a useful resource for researchers. These authors have manually extracted relevant data for ~ 300 candidate genes for CAD from over 1300 publications. They classified these candidate genes into 12 functional categories. They extracted detailed information for each gene with the found variant [38]. In addition, CADgene provides cumulative data from 11 publications of CAD-related genome-wide association studies. CADgene is freely available at http://www.bioguo.org/CADgene/. A similar endeavor was undertaken by Preuss et. al [39]. They formed a so-called consortium called Coronary ARtery DIsease Genome-wide Replication And Meta-analysis (CARDIoGRAM) [39]. The team collected and analyzed data from all published genome-wide association studies (GWAS) in 22 000 affected persons and 60 000 controls [39].
Hernesniemi et al. also combined data from three large genome-wide association studies, which identified a large number of variants (SNPs) associated with an increased risk of coronary artery disease [40]. They have also taken into account the results of the aforementioned CARDIoGRAM consortium. Hernesniemi et al. examined whether the genetic profiling of the discovered genetic variants improves prediction of subclinical atherosclerosis – i.e. carotid intima-media thickness and carotid artery elasticity – beyond classical risk factors. They conclude that their genetic profiling does not improve risk stratification for subclinical atherosclerosis beyond conventional risk factors among healthy young adults [40].
Bis et al. present the results of yet another meta-analysis based on the data collected by the so-called CHARGE consortium, which focused on the identification of genetic variants associated with carotid intima media thickness and plaque [41]. These authors have also taken into account the data gathered by the CARDIOGRAM consortium. Bis et al. argue that the associated mapped SNPs are related to cellular-signaling, lipid metabolism, and blood pressure homeostasis [41].
Another initiative addressing the review of papers on genetic research related to coronary artery disease has been undertaken by Padmanabhan et al. [42,43].
They note that genome-wide association studies have been successful in identifying some associations of single nucleotide polymorphisms (SNP) with CAD. However, they note that it is a challenge to bind the discovered genetic variants with particular elements of pathogenetic mechanisms. The researchers of a paper published in 2010 wrote that "despite extensive studies, strong evidence of a molecular genetic association with coronary artery disease or myocardial infarction remains elusive" [42]. They are convinced that elaboration of the theoretical framework for the joint effects of genes and environment require technologies from whole genome sequencing, proteomics, transcriptomics and metabolomics [42].
Pranavchand et al. in their next review conclude that till now about 300 genes influencing the development

of atherosclerosis have been identified in the so-called candidate gene approach [43]. According to their review, an additional 32 loci have been identified through genome-wide association studies [43]. Many of these genes were found in the locus 9p21.3 [43]. Pranavchand et al. note, however, that these studies still show a relative lack of consistency in the association pattern across populations [43].

Roberts et al. in another review paper recall that the first gene for CAD was simultaneously identified by 2 independent groups in 2007 [44]. The subsequent 23 loci linked to increased risk for CAD were mapped in the following years. These authors emphasize that the results of these studies confirm that CAD is caused by multiple genes, each contributing to minimal risk and that these loci do not act through known risk factors for CAD [44].

A. J. Marian drew critical conclusions from all the previous genome-wide association studies [45]. He stresses that GWA studies have successfully led to the identification of over 100 different loci for susceptibility to coronary atherosclerosis [45]. A. J. Marian states that the significant outcome of GWA study is modest. He justifies his opinion by the fact that the identified SNPs account for a relatively small fraction of heritability of coronary atherosclerosis [45]. It raises the question of "missing heritability" [46]. He hypothesises that a plausible explanation might be the presence of uncommon and rare variants in the genome that have not been discovered by the performed GWAS but that might have a great effect on the risk of atherosclerosis. He also mentions possible alternative mechanisms which might in part account for the heritability of coronary atherosclerosis. It could consist in transgenerational epigenetics regulated in part by specific microRNAs [45]. A. J. Marian concludes that "the genetic etiology of coronary atherosclerosis will remain enigmatic in the foreseeable future" [45].

Marian and Kaprio discuss in several other papers the concept of "missing heredity" [46,47]. This concept is revealed to be useful in continuing discussions on the pathogenesis of other diseases of complex etiology [48]. Indeed, some other authors use it for considering the pathogenesis of other illness like Parkinson's disease [49].

The authors of manuals and papers considering the genetic conditioning of atherosclerosis and coronary heart disease usually mention, at the beginning of their inference, the Mendelian forms of syndromes like familial hypercholesterolemia. Its pathogenesis is explained, however, the difficult challenge remains – to explain the mechanisms of genetic impacts observed in the majority of people affected by atherosclerosis. The investigations of this problem during the past two decades consisted of a so-called candidate gene approach and genome-wide scans. Hence, it is useful to examine the essence of these studies and the obtained results.

Candidate gene approach

The candidate gene approach is an assessment of the association between the occurence of a particular allele or polimorfism of a gene and a particular manifestation of the disease. This approach requires choosing a candidate's gene polymorphism and testing its frequency distribution in random samples of affected cases and in control individuals.

More than 300 candidate genes associated with coronary artery disease have been identified by this approach. These genes contribute to a wide range of metabolic pathways like lipid metabolism, blood coagulation, blood pressure, inflammation and cell cycle regulation [43]. The interested reader can check data in many publications related to the involved genes like: gene symbol, gene name, chromosomal loci and metabolism pathway [39,43].

It is possible to draw a simple diagram which illustrates the relative proportion of studies showing a significant typical 'candidate gene study' association for each CAD candidate gene [43]. We will find in the first ten places of this diagram genes identified by the symbols: ACE, LPL, APOE, PON1, NOS3, MTHFR, CETP, APOB, APOA5, AGT [43]. As an example, we will mention the APOE gene. It is one of the candidate genes whose role in pathogenetic mechanisms is well understood and which is widely studied in different populations. It is involved in the removal of LDL cholesterol, coding for apolipoproteins, lipases and ATP binding proteins. APOE is a ligand for the receptor-mediated clearance of chylomicrons, chylomicron remnants and excess cholesterol, so it has a prominent role in determining plasma cholesterol levels [43]. The association with susceptibility to the development of atherosclerosis has been demonstrated for many genes, however, it is not easy to link their function with intelligible, recognized pathogenetic mechanisms. Pranavchand et al. conclude that the ultimate aim of providing a simple diagnostic test by candidate gene approach screening remains unfulfilled for CAD or any other complex disease [43].

A newer method of genetic testing is genome-wide scanning (GWAS). There are two variants of this method. Primary GWAS was used in family-based linkage analysis for microsatellite markers.

Genome-wide scanning used in family-based linkage analysis for microsatellite markers

Microsatellites are two, three or four nucleotide tandem repeats in DNA sequences. The number of repeats is variable in populations and within the alleles of an individual.

Genetic linkage is the tendency of two allele to be inherited together as a unit. Linkage is determined based upon an analysis of families. When allele are close on a chromosome, there is a higher likelihood that they will be inherited together and familial recombination will not interfere. The likelihood that allele will be inherited together is measured as a logarithm of odds ratio (LOD) e.g. 100:1 or a LOD of 2. The statistical reliability of measuring linkage depends on the number of tested families so that one can determine whether allele are inherited together because they are linked or whether they are inherited together by chance.
When two features (allele) occur together as an intact unit within a population, we say the features are in linkage disequilibrium. Features that occur randomly are in linkage equilibrium. Allele in linkage disequilibrium are much closer together than those that are linked within families because in every generation there is an opportunity for them to become unlinked by genetic recombination.
An example of the results obtained by this method is the discovery of a significant linkage peak, which is defined by the LOD score 3.5, which indicates a gene near or within the marker that is in linkage disequilibrium with the disease [43]. The first genome-wide linkage scan encompassed the screening of 303 microsatellite markers in 156 Finnish families including two individuals with premature CAD [43]. The analysis of the population yielded two point LOD scores of 3.7 and 2.9 for the chromosomal regions 2q21.1-22 and Xq23-26 [43].
Pranavchand et al. estimate, however, that whole genome microsatellite linkage analysis till now has not been successful [43].

Genome-wide association studies based on SNPs

Genome-Wide Association Study (GWAS) is a method developed in some past years. It is an examination of many genetic variants in different individuals to verify if such a variant is correlated with a pathogenetic feature. In the course of the study, people with the disease are compared with control individuals.
A sample of DNA is taken from many persons included in the study. GWA studies investigate the entire genome. Using so-called microarray technology, millions of possible genetic variants called SNP are checked. GWAS focus on associations between single-nucleotide polymorphisms (SNPs) and different disease traits. A single nucleotide polymorphism (SNP) is the most frequent type of variation in the genome. There are around 50 million SNPs that have been identified in the human genome.
If a variant is more frequent in people with the disease, the SNP is said to be "associated" with the disease. The associated SNPs are then considered to mark a region of the human genome which influences the risk of a disease. GWA studies identify SNPs of the genome which are associated with a disease, but do not indicate which genes are causal. Pleiotropism, meaning the production of multiple phenotypic effects by a single gene, is a characteristic feature of many GWAS-identified variants.
Employing this approach to coronary artery disease resulted first in the identification of 9p21.3 as a locus significant for determining CAD [43]. Since then, 32 other loci have been identified by teams like the Wellcome Trust Case Control Consortium, the Ottawa Heart Study, German Myocardial Infarction Family Studies and the Myocardial Infarction Genetics Consortium [43,50].
Pranavchand et al. conclude that GWAS is a usful method in the search of possible new genetic markers for CAD. They point out, however, that pleiotropic effects, the existence of subclinical phenotypes and genetic heterogeneity are limiting factors in using the method for developing a genetic risk profile test [43].
Pranavchand et al. summarize the results of all kinds of genetic studies performed so far that unlike diabetes, Alzheimer's disease and other complex diseases, where GWAS demonstrated major genes responsible for the disease (like TCF7L2, CFH, ApoE-like major genes), the results of CAD genetic research are quite unsatisfactory in the sense that no major gene has yet been identified.

Novel biomarkers of the disease

Since the known Framingham Heart Study, several commonly accepted clinical risk factors for cardiovascular disease have been identified i.e. male sex, elevated low-density lipoproteins, smoking, hypertension, family history of premature coronary disease, and diabetes mellitus [51,52].
These risk factors do not account for all the coronary disease risks. Large trials and meta-analyses have shown that approximately 90% of people who have an acute coronary syndrome have at least one of the major risk factors [47]. About 10%–15% of people who develop an acute coronary syndrome do not have any of these known traditional risk factors. It is also known that patients with traditional risk factors may not develop cardiovascular disease. These facts explain the efforts of many researchers who are endeavouring to find novel biomarkers of the disease.
Montgomery defines biochemical markers as "characteristics that are objectively measured and evaluated as an indicator of normal biological processes". They can be measured in body fluids e.g. blood, urine or via medical imaging or testing [53]. He states that such a factor could be causally related to the outcome of a risk marker or risk factor [53]. At present, a risk marker is considered as risk factor if an intervention

exists, which results in a change of risk. Therefore hypertension is a risk factor for coronary artery disease because when the blood pressure decreases, the coronary artery disease risks also decrease [54].

There are three criteria that should be fulfilled by a biomarker: (1) it must be easy to measure; (2) it must provide new information, (3) it must help the clinician to manage patients [53].

Thus, the proposed novel biomarker should be relatively simple to obtain, it should add new information that other available tests do not and it should be demonstrated that patients live longer, better, or have fewer hospitalizations as a result of screening with the discussed biomarker [56,57,58]. Although many biomarkers may be useful for predictions, very few have been shown to improve the treatment of patients with cardiovascular disease when implemented in a clinical setting. The third criterion has precluded many biomarkers from reaching the clinical realm [53]. It is also important to realize that we should keep in mind the factors affecting the primary or secondary prevention of a particular atherosclerotic syndrome [53].

Many authors are considering whether some combination of these novel biomarkers of the disease affect the overall ability to predict consequences evaluated for primary or secondary prevention. Montgomery presents ten extensive studies verifying the overall prognostic efficiency of particular sets of novel risk factors [53,59].

The authors of all of these studies have included into such sets of biomarkers the C-reactive protein. Sets of substances intended to assess the overall risk have often also encompassed interleukin IL-6, lipoprotein-associated phospholipase A2, B-type natriuretic peptide, high-sensitivity troponin T, homocysteine and fibrinogen. It seems to us that it is worth providing data on novel, and the most effective new biomarkers because such knowledge is useful for contemporary clinician practice .

C-reactive protein

CRP was discovered by Tillett et. al. in 1930 [53]. Its name comes from the fact that it reacts with the C polysaccharide of Pneumococcus. CRP is a 224--residue protein. It was found in the serum of patients with acute inflammation. CRP is an acute-phase substance produced by hepatocytes in response to stimulation from interlukin-6 and tumor necrosis factor-α [60]. CRP binds to the surface of decaying cells and activates the complement system [60]. It is thought to increase the uptake of LDL by macrophages and to enhance surface adhesion of molecules, therefore it plays a role in the inflammatory processes involved in atherosclerosis [60]. CRP concentrations can increase within 48 h up to 50 000–fold in acute inflammation infection.

Previous measurement methods have enabled detection levels > 10 mg /L, which signified an acute phase of inflammation. New methods, so-called high-sensitivity CRP (hsCRP) facilitate stratifying the level of risk for atherosclerosis. One assumes that that a level > 3 mg/L indicates a high risk and < 1 mg/L low risk while those between 1 and 3 mg/L are considered as intermediate risk [61].

The arguments for the value of CRP as a biochemical markers comes from several clinical trials. One of the best known is a prospective case–control study known as the Women's Health Study [63]. The participants in this investigation with CRP levels > 3 mg/L had a double frequency of coronary heart disease [64]. Similar data was obtained in the course of The Physicians' Health Study [47].

In the past 15 years, more than 20 epidemiological studies have demonstrated a significant association between increased CRP concentrations (hs-CRP) and the risk of a first cardiovascular event among asymptomatic patients [54]. A metaanalysis of 22 studies indicated that hs-CRP concentrations greater than 3 mg/L were associated with a 60% increased risk of cardiovascular disease [62]. Researchers pursuing several large studies on the impact of new derivatives of statins on lipid concentration and risk of myocardial infarctions demonstrated that the obtained results were acompanied by a reduction in the CRP level. In the course of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) and the Reversal of Atherosclerosis with Aggressive Lipid-lowering Therapy trial (REVERSAL), atherosclerotic regression measured by intravascular ultrasound was accompanied by both LDL and CRP lowering [64]. Hence, the authors of these investigations argue that there may be a decrease in cardiovascular events if statin therapy is based on CRP values [64]. JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) was a large prevention study with a potent statin medication (rosuvastatin) [64], in which nearly 18 000 individuals were enrolled. The hs- CRP level was one of the inclusion criteria. The study is therefore one of the few major randomized controlled trials which incorporate a biomarker to evaluate the results of therapy. The results of this study demonstrated that treatment with use of statins can significantly lower the rate of a first major cardiovascular event among those with baseline LDL levels less than 130 and lower CRP by 37% when compared with a placebo [64].

Lipoprotein-associated phospholipase A2

Lp-PLA2 is a 441–amino acid protein – produced by inflamatory cells. It circulates with LDL. It is responsible for hydrolyzing oxidized phospholipids in LDL,

catalyzing the degradation of the'platelet activating factor' to inactive products [65]. It is present in atherosclerotic plaques and may be directly involved in the development of atherosclerosis and plaque ruptures [68,70]. Some researchers argue that Lp-PLA2 is more specific for vascular inflammation than other inflammatory markers because it is produced by macrophages and foam cells in the vascular intima [71].
In vivo studies demonstrated that individuals with increased concentrations of circulating Lp-PLA2 have a higher plaque burden in the coronary arteries than those with normal concentrations [65]. It also has been shown that inhibiting Lp-PLA2 leads to a reduction in atherosclerotic lesions in hyperlipemic rabbits [65]. Taking into account its specificity for vessels and presence when there is accumulated atherosclerotic plaque, Lp-PLA2 has been proposed as a biomarker for identifying individuals at increased risk of cardiovascular disease [66].
Several clinical trials assessing the role of Lp-PLA2 in primary prevention have been performed. One of the best known is the West of Scotland Coronary Prevention Study. The authors indicate that both hs-CRP and Lp-PLA2 were significantly associated with increased cardiovascular risk [66]. The investigators who performed the Atherosclerosis Risk in Communities study found that the Lp-PLA2 and hs-CRP means were higher in those who suffered from coronary events than in those who did not [67].

Hyperhomocysteinemia

Many authors argue that hyperhomocysteinemia promotes atherosclerosis [72,73,74,75]. Its level increases when there is a deficit of B vitamins, especially folic acid, B6, and B12 and also in circumstances of renal impairment or during treatment using certain drugs [72]. Elevated homocysteine promotes atherosclerosis through increased oxidant stress, impaired endothelial function, and the induction of thrombosis [72]. Humphrey et al. reviewed 26 articles about prospective cohort studies which took into account the measurements of homocysteine and estimation of the Framingham risk factors in populations assessed also in terms of the incidence of CHD [72]. The metaanalysis leads to the conclusions that any increase in the homocysteine level of 5 micromol/L augments the risk of CHD events by approximately 20% – independent of traditional CHD risk factors [72].
Sen et. al. performed a cohort study of 307 consecutive hospitalized stroke or TIA patients. They estimated changes in the aortic arch atheroma plaque thickness and found a correlation between the level of homocystein and progression of aortic atheroma [75].
Kosar et al. made a comparison of 37 patients with coronary artery ectasia, 36 patients with coronary artery disease and 32 patients in a control group [76]. They found that the patients with coronary artery ectasia and coronary artery disease have increased plasma hyperhomocysteine levels compared with the controls [76]. Asfar et al. discovered that elevated homocysteinemia was found in 40.7% of patients suffering from peripheral vascular disease [77]. Aksoy et al. performed a non-randomized prospective study which included 56 patients who were admitted with occlusive arterial disease and 39 control patients without occlusive arterial disease [78]. They found that the incidence of hyperhomocysteinemia was higher in the patients with occlusive vascular disease than in the control patients [78]. Thus, different kinds of studies have demonstrated that elevated concentrations of homocysteine increase the risk of cardiovascular disease. It seems that hyperhomocysteinemia is an independent risk factor of atherosclerosis [72,73,74, 75,76,77,78,79].

High-sensitivity troponin T

Troponin was discovered by Ebashi et al. in 1963 [80]. It was established that this myofibrillar protein is common to skeletal and cardiac muscle [81]. Troponin has three subunits: troponin C, I, and T. Troponin C responds to the presence of calcium. Troponin T has an afinity for tropomyosin, forming the troponin––tropomyosin complex. Troponin I binds to actin in thin myofilaments [81].
Cardiac troponins have become the standard biomarker in the diagnosis of acute myocardial infarction. Its concentration above the normal range is considered as a sufficient diagnostic criterion of infarction. Troponin is undetectable in the majority of healthy individuals. The newer so-called high-sensitivity assay of cardiac troponin I and T permit the detection of concentrations significantly lower than the normal range. It increased the sensitivity of acute myocardial infarction diagnosis and opened other clinical applications [82,83].
Several cohort studies investigated the clinical utility of hs-troponins. de Lemos et al. measured troponin T concentrations using both standard and highly sensitive assays in over 3500 adults in the Dallas Heart Study [84]. These investigators found in over 6 years of follow up that hs-troponin T concentrations were associated with structural heart diseases and all causes of cardiovascular mortality [84].
deFilippi et al. investigated the prognostic value of hs-troponin T concentrations in more than 4200 older adults [85]. Increased hs-troponin T concentrations were associated with the development of heart failure and cardiovascular death.
The researchers from the Atherosclerosis Risk in Communities study found that hs-troponin T concentrations were associated with incidents of CHD, heart failure and mortality assessed in nearly 10 000 indi-

viduals [75]. The addition of hs-troponin T to traditional risk factors improves the prediction of first major cardiovascular events and death [41].
As we mentioned, many research teams have tried to evaluate the use of several biomarkers in order to gain a better predictive ability [87,88,89,90,91,92]. The use of such sets of biomarkers generally increases the predictive ability, however, it is a complicated and costly procedure of prevention.

Indications for prevention and treatment

We briefly present below the main guidelines for the prevention and treatment of atherosclerosis which usually manifests mainly by one of the secondary syndromes like coronary heart disease or peripheral artery disease [93,94]. These rules should be drawn from knowledge of the etiological and pathogenetic factors. Because the pathogenesis is not fully understood, prevention and treatment focus on diminishing the so-called risk factors. Therefore in general, efforts should be made to normalize hypertension and components of hyperlipidemia. Sometime it is necessary to reduce body weight and control hyperglicemia. Lifestyle changes should include quitting smoking, the introduction of a healthy diet and increased physical activity.
It seems to us that it is also worth remembering that one of the possible factors primarily influencing the susceptibility of arterial endothelium to injury are personality traits and the pattern of response to stress. We emphasize below only some important arguments and guidelines for prevention and treatment.

Hyperlipidaemia normalization and vessel inflammation reduction

For a long time, statins were used to reduce hypercholesterolemia [95]. For several years, many authors recommended using Rosuvastatin, which is efficient, potent and rather safe [64,96,97,98]. It slows the progression and induces the regression of atherosclerotic coronary lesions.
It seems that inflammation is involved in all phases of atherosclerosis. C-reactive protein is a well-studied, nonspecific marker of inflammation which may reflect a general health risk [60,61,62,63]. Considerable evidence suggests CRP is an independent predictor of future cardiovascular events [62]. Rosuvastatin also lowers CRP levels significantly [96]. It was shown by the large Intervention Trial Evaluating Rosuvastatin (JUPITER) [64,99,100]. The authors of this trial noted that when both low density lipoprotein and CRP were reduced, patients improved better than when only LDL was lowered.
It should be noted that when the use of statins led to a reduction in cholesterol and low density lipoproteins (LDL) but did not normalize the level of triglycerides or sufficiently increase high density lipoproteins (HDL), then so-called fibrates should to be added for treatment.

Healthy diet

The essential indications consist in reducing the consumption of saturated fatty acids (< 7% of energy demand, < 15 g /day) by substitution with monounsaturated fatty acids and a low cholesterol diet. An appropriate diet is particularly important in the cases of concomitant obesity.
At the same time, Kones notes that nearly 70% of adult Americans are overweight or obese [93]. At the same time, 55% of the population is on a weight-loss diet, and almost all fail [93]. He also points out that 34% of children in North America is overweight or is obese [93]. Obesity in childhood causes the early development of atherosclerosis [101]. The reduction of obesity is a very important element of prevention because it also affects blood pressure, lipid profiles, glucose metabolism, inflammation, and atherothrombotic disease progression [102]. Obesity evokes the dysregulation of a number of adipocyte-derived factors including free fatty acids and "adipo"-cytokines, which favors atherosclerosis [103].
It seems that the mechanisms by which obesity targets the vascular system consist of consequences of the metabolic syndrome of insulin resistance, which is caused by obesity [103].

Lowering homocysteine blood level by folates

We mentioned above the opinions of several authors who formulate arguments that hyperhomocysteinemia is an independent risk factor of atherosclerosis and coronary heart disease [72,73,74,75,76,77,78,79]. Thus, it seems that attempts to normalize hyperholecysteinemi are justified as a preventive and treatment procedure. The level of homocysteine can be lowered by a folate-rich diet or pharmacological supplementations [109,110].

Management of negative emotional status

It seems that attempts to apply behavioral interventions and management of negative emotions should be an important element of prevention and treatment. We should remember that the most convincing theory to explain the pathogenesis of atherosclerosis consists of a specific kind of response to primary vascular endothelial damage [6,7,8,9]. As we tried to show, this primary vascular endothelial damage cannot be explained fully and convincingly by genetic predispositions (see so called "missing heredity"). This is why we must carefully consider the importance of the in-

fluences of psychological stress and personality traits such as hostility, anger, aggression, impulsivity [104,105,106]. Therefore, we should take into account the application of different kinds of behavioral interventions and methods of corrective training [107,108].

Specific feature of peripheral arterial disease

Definition and clinical presentation of the syndrome

Peripheral arterial disease occurs when significant narrowing of arteries distal to the arch of the aorta is present [111]. PAD most often commonly affects the lower limbs as a result of arterial narrowing distal to the aortic bifurcation. The most prevalent symptom of the syndrome is so-called intermittent claudication [115]. It is reproducible lower extremity muscular pain induced by exercise and relieved by short periods of rest. It is an expression of the inability of the lower limb vessels to maintain adequate tissue perfusion and oxygenation during physical activity. The syndrome initially is asymptomatic. The slight narrowing of peripheral arteries does not cause the symptomatic syndrome.

Epidemiology and natural development of the disease

The prevalence of peripheral arterial disease varies across populations and depends on the groups studied and the detection methods used [116]. A sensitive tool for PAD screening diagnosis is the ankle-brachial index (ABI) [117]. It is a more sensitive method for detecting PAD than paying attention to intermittent claudication. About 10–30% of patients diagnosed on the basis of the ankle-brachial index do not have evident symptoms of claudication. The prevalence of peripheral arterial disease increases with age and in persons with diabetes or a history of smoking. The prevalence is also elevated in persons with hyperlipidemia, hypertension or chronic kidney disease. Peripheral arterial disease, defined by an elevated ABI factor < 0.90, is associated with elevated cardiovascular mortality.
Peripheral arterial disease affects approximately 20% of persons above the age of 55 years. In the United States, Canada and Europe the disease affects 27 million people [117]. Leng et. al. who refer to the so-called Edinburgh Artery Study, failed to demonstrate a significant difference in the prevalence of peripheral arterial disease between men and women [114]. About 10% of persons with asymptomatic peripheral arterial disease develop intermittent claudication over 5 years. However, 75% of these persons experience symptom stabilisation or improvement over their lifetime without intervention [115]. The stabilization occurs despite arteriographic evidence of disease progression in the majority of patients. Symptoms may then deteriorate in the remaining 25%. The progression of PAD is usually slow, however, 25% of patients die within 5 years because of of coronary heart disease or stroke [111].

Risk factor of the syndrome

The risk factors for peripheral arterial disease are largely the same as for the primary condition, which is atherosclerosis.

Specific diagnostic examinations

Each of the syndromes developing as result of atherosclerosis requires a specific set of examinations. In the following brief outline, we enumerate only indispensable elements of the diagnostic procedure, describing more broadly only the key, specific requirements for these studies, if they are less known [117].
1. Risk factors should be evaluated.
2. Vascular flow should be investigated.
Preliminary assessment of peripheral blood flow consisting in non-invasive estimation of so-called ankle-brachial pressure index [117].

Ankle-Brachial Pressure Index (ABPI)

The Ankle-Brachial Pressure Index (ABPI) is evaluated by comparing the systolic pressures on the posterior tibial and dorsalis pedis arteris measured using cuff occlusion by a sphygmomanometer and Doppler ultrasound.
When the ABPI index < 0.90, haemodynamically significant arterial stenosis is very probable . It is the essential criterion of PAD diagnosois. An ABPI index < 0.5 is acompanied by moderate to severe claudication while an ABPI < 0.3 indicates the possibility of a critical ischaemia occurring. An ABPI < 0.90 also indicates also the very probable existence of arteriograph-positive lesions.
Significant calcification, which occurs usually in the course of diabetes or renal insufficiency may result in a false elevation of ABPI > 1.4. In these patients, angio-arteriography can show the multiple sites of stenosis in the lower limb. It may indicate a haemodynamically significant lesions. The disease may also be demonstrated by the characteristics of Doppler waveforms which range from normal triphasic waveforms to atherosclerotic biphasic and monophasic patterns.

Non-invasive angioghraphy

Contemporary non–invasive angiography is posssible on the basis of computerised tomography and magnetic resonance imaging. These techniques are known

as Magnetic Resonance Angiography and Computerized Angio-Tomography. Sometimes complications can occur due to gadolinium-based contrast agents or iodinated contrast. The interpretation of Computerized Angio – Tomography results should be done carefully because of calcifications.

Transarterial Angiography

Invasive Transarterial Angiography remains the golden mean to assess the state of arteries. The examination can be combined with therapeutic intervention.

Assessment of functional capacity. The evaluation of functional capacity consists of a subjective assessment of the quality of life combined with quantitative walking distances on a treadmill.

The evaluation of Quality of Life can be performed through the use of well-known generic questionnaires like QoL – Short Form-36. Morgan et al. elaborated recently the so-called Disease-specific QoL instrument for patients with PAD like the Walking Impairment Questionnaire (WIQ) and the VascuQoL Questionnaire [118].

Treadmill Testing objectively measures walking capacity using the machine, which enables calibration of the performed effort. The time of of claudication pain onset is called the initial claudication distance (ICD) or claudication onset time (COT). The maximal walking performance till the moment when the patient stops due to pain is called absolute claudication or maximal walking distance (ACD or MWD). Patients suffering because of PAD usually have reduced walking capacities, with a 50% to 60% reduction in peak treadmill performance compared to age-matched healthy controls [117].

Treatment of peripheral arterial disease

Treatment should take into account modification of the risk factor. One of the most important goals is lipid lowering. It should be done according to the rules described above. Pharmacological treatment usually involves the administration of drugs necessary to reduce blood pressure. Antiplatelet drugs are also included (Aspirin, Clopidegrol) [119]. A specific type of treatment for PAD is the use of vasodilators, combined with efforts to intensify walking [109]. Traditional vasodilators such as naftidrofuryl, pentoxifylline, α-blockers, papaverine, nylidrin and nifedipine were used but not effectively. Some authors emphasise the possibility of this kind of treatment by cilostazol [121].

Invasive therapeutical interventions

Revascularisation should be considered in patients with critical limb ischaemia or severe claudication, which persist despite conservative treatment. Operative arterial bypasses have a better long term potency. However, the risks of surgery are greater in comparison to endovascular interventions in terms of mortality and return to normal daily activities [122].

Endovascular Revascularisation by percutaneous transluminal angioplasty (PTA) with stentingis for lesions in the iliac artery is effective in about 90% of cases [123]. Five year patency rates range between 64% and 75%. The clinical success rate of PTA for femoropopliteal stenoses exceeds 95%. PTA reduces the symptoms at 6 months in patients with claudication, but longer term benefits are limited with no significant difference in walking distances or quality of life at 2 or 6 years post-PTA. The clinical effects depend on the circumstances prior to surgery, the length of the obstructed segment and the distal outflow of the artery. The recent performance obtained by endovascular revascularization procedures constitute a significant advance in the treatment of PAD. Sometimes the achieved clinical improvement is astonishing.

Surgical interventions

Surgical interventions are necessary for patients with critical limb ischaemia when it is imperative to relieve pain and prevent limb loss and increase the chance of survival [124].

Surgical intervention may also be indicated for claudicating patients with proximal lesions with deteriorating symptoms. Although surgical procedures improve the outcome rates compared to endovascular intervention, they threaten the occurrence of major complications after surgery [124].

An aortobifemoral arterial bypass is usually recommended for diffusing aortoiliac disease with critical decreased patency.

In higher risk patients, less typical bypasses are performed, such as femoro-femoral or axillo-femoral arterial conections. However, these types of interventions have a lower success rate for a 5 year patency range. An infrainguinal arterial bypass requires effective inflow at the proximal anastomosis. A satisfactory distal outflow is the most important determinant of longer-term patency. After five years, the vessel is unobstructed in 35% of cases for prosthetic material, rising to 60% for vein grafts [124].

Attempts to treat by stimulating development of collateral vessels

Peripheral arterial disease is associated with significant morbidity and mortality. It can lead to critical limb ischemia, often resulting in a need for major amputation and subsequent death. About 30% of patients cannot be treated by surgical interventions due

to the high operative risk or unfavorable vascular involvement. Therefore, recently a new strategy for treatment is has been tested. It consists in trialling stimulation of the development of collateral vessels. I Increased blood flow could be achieved by increasing the number of vessels that supply the ischemic tissue with blood. The use of pharmacological agents to induce new blood vessel growth has been called therapeutic angiogenesis.

There are three posssible strategies for realizing therapeutic angiogenesis: the utilization of stem cells, biomaterials or growth factors [125]. An example of biomaterials are such substances as alginate hydrogel or polyethylene glycol hydrogel [126].

So-called cell therapy is possible since the identification of endothelial progenitor cells [128,129]. Hence, bone-marrow derived stem and progenitor cells have been identified as a potential new therapeutic option to induce angiogenesis. Till now, several small clinical trials have been performed [130,131,132,133,134]. Clinical benefits were reported including improvement of the ankle-brachial index, reduction of pain and decreased need for amputation [132]. Current literature is supportive of intramuscular bone marrow cell administration as a relatively safe, feasible, and possibly effective therapy for patients with PAD who are not subjects for conventional revascularization [131,132,133,134].

Moazzami K et. al. emphazise, however, that the evidence from larger randomised controlled trials are needed in order to assess the role of intramuscular mononuclear cell implantation. Further basic research which will improve understanding of the mechanisms governing homing and incorporation of endothelial progenitor cells is necessary to optimize cell therapy methodology [135].

We would also like to draw attention to the fact that some new insights can be drawn from the observation that the above-mentioned growth factors (basic fibroblast growth factor – bFGF and vascular endothelial growth factor-VEGF), stimulating the development of collateral vessels are enhanced by hypoxia [137,138].

Conclusions

It seems to us that the presented overview of the current knowledge about atherosclerosis should indicate to clinicians some points important for the realization of prevention and treatment.

Clinicians considering specific symptoms manifested by a particular patient should be aware that they are dealing with polyvascular disease. Although symptoms usually result from damage in one group of arteries, injury always applies to all vessels.

From the knowledge about the pathogenesis of atherosclerosis, some practical consequences emerge. The considerations of many pathogenic mechanisms like cellular dysfunction, inflammation and coagulation disorders should be concluded by a question about what the most primary causes of damage to the endothelium are, which seems to be the starting point for all pathogenetic processes. It is useful to see links between the state of the vascular endothelium and lifestyle. The development of the disease because of the significance of lifestyle is dependent on behavioral factors, which is determined by a specific state of mental health.

In the light of some recent papers, it appears that the primary causes of endothelial damage should be traced – as originally suggested already in the 1970s – in such factors as raised anger, hostility, aggression, impulsivity and depression. These conclusions are of great importance for prevention and treatment.

Clinicians should be aware that lipid abnormalities are associated with the occurrence of vascular endothelial inflammation. Rovustatin, a drug which effectively lowers the cholesterol level and LDL also simultaneously reduces inflammation, which can be assessed by determining the levels of CRP.

It is important for clinicians to know that even though the family predisposition to atherosclerosis and coronary artery disease have long been known, genetic studies have failed to identify the critical gene variants. The notion of so-called "missing heredity" should be noted.

It should also be known that the determination of so-called classical risk factors does not allow reliable prediction of the disease and therefore many researchers are looking for so-called novel biomarkers. The most useful discovered biomarkers of atherosclerosis are C-reactive protein, lipoprotein-associated phospholipase A2, homocysteine and high-sensitivity troponin T. Clinicians could also use in practice the possibility of evaluating the risk of occurrence of the disease through the whole set of these new biomarkers.

The presented discussion of specific features of peripheral arterial disease demonstrates how to combine treatment of the generalized disease with proceedings indicated for particular local lesions. Apart from pharmacological and surgical procedures, the recent attempts to stimulate the development of collateral vessels are interesting. It is remarkable that such attempts are made not only by the use of appropriate biomaterials, growth factors, but also the use of bone-marrow derived progenitor stem cells.

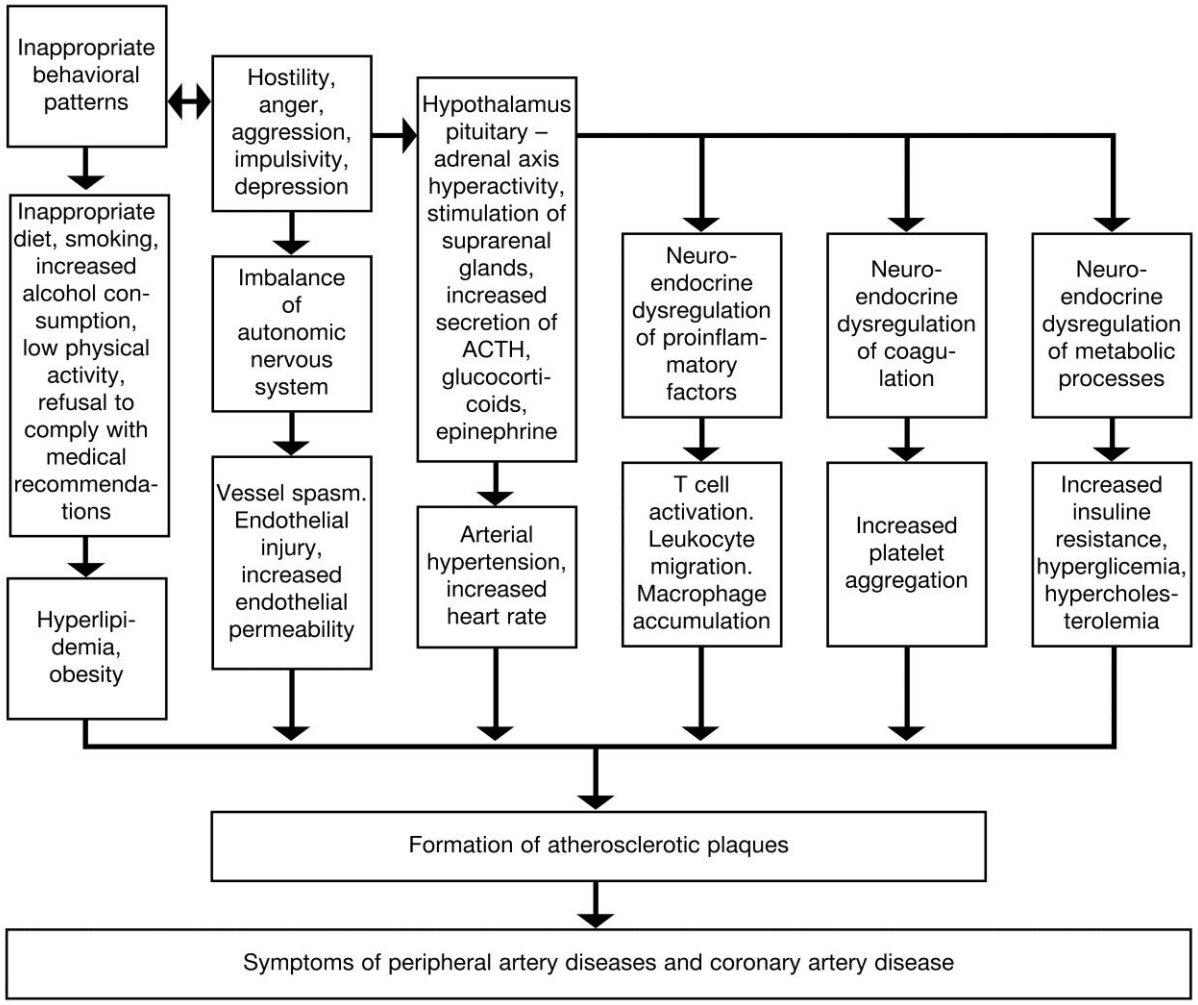

Fig. 3. Influence of negative emotional and behavioral factors on development of atherosclerosis.
Ryc. 3. Wpływ negatywnych czynników emocjonalnych i behawioralnych na rozwój miażdżycy tętnic.

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