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Review

Genetic Determinants of Cardiovascular Disease: The Renin-Angiotensin-Aldosterone System, Paraoxonases, Endothelin-1, Nitric Oxide Synthase and Adrenergic Receptors

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Abstract. *Apart from conventional risk factors such as cigarette smoking, obesity, hypertension, diabetes mellitus, hypercholesterolemia, physical inactivity and metabolic syndrome, a family history of coronary artery disease (CAD) seems to be important, especially in young people. Among the genes that may potentially influence the onset and the progression of CAD, there are those controlling the following: renin-angiotensin-aldosterone system (RAAS), adrenergic receptors, paraoxonases, endothelin and nitric oxide synthase. They may modulate the risk of disease onset, as well as its progression and patient prognosis. The unravelling of genetic determinants of CAD may be the first step towards a better understanding of the pathological process involved, the early identification of those at risk and individualizing treatment.*

Abbreviations: ACE, Angiotensin-converting enzyme; ACE-I, angiotensin-converting enzyme inhibitor; AGT, angiotensinogen; AngII, angiotensin II; T1, AT2, angiotensin II type 1 and 2 receptor, respectively; CAD, coronary artery disease; COX-2, cyclooxygenase 2; *CYP11B2*, aldosterone synthase gene; eNOS, NOS-3, nitric oxide synthase; ENaC, epithelial sodium channels; ETA, ETB, endothelin receptors, types A and B, respectively; ET-1, endothelin 1; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; LDL, low-density lipoprotein; MI, myocardial infarction; MMP, metalloproteinase; MPC-1, monocyte chemoattractant protein 1; NAD(P)H, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; ox-LDL, oxidative low-density lipoprotein; PAI-1, tissue plasminogen activator inhibitor; PON, paraoxonase; RAAS, renin-angiotensin-aldosterone system; ROMK, renal outer medullary potassium channel; TF, tissue factor; TGF-β, transforming growth factor-β; TNF-α, tissue necrosis factor α; t-PA, tissue plasminogen activator; VEGFR-2, vascular endothelial growth factor 2.

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Cardiovascular disease is the main cause of mortality and morbidity in the world (1). As for example, every day 200-250 Poles die of myocardial infarction (MI) and it causes nearly 20% of deaths in people under 65 years of age (1). According to epidemiological data prepared on the basis of the Polish NATPOL PLUS study with the use of the PRECARD algorithm, the number of Poles aged 30-70 with MI in Poland will reach 740,000 during the next 10 years (2). The proportion of premature MI is constantly growing (3), and accounts for 10% of all infarcts (4). Interestingly, the phenomenon of MI without atherosclerosis, which is quite uncommon in older patients, occurs in 20% of premature MI cases (5). In up to 51% of young patients (6), MI manifests as a single-vessel disease and it may be particularly dangerous (high risk of sudden cardiac death) due to the fact that the collateral circulation, which probably helps to maintain flow within the myocardium (7), is less developed (8).

Cardiovascular disease is influenced by both environmental and genetic factors. According to Kraus *et al.* (9), genetic factors contribute to 20-60% of coronary artery disease (CAD) cases, having a more pronounced impact on disease development in young patients than do environmental factors (10). Apart from conventional risk factors such as cigarette smoking, obesity, hypertension, diabetes mellitus, hypercholesterolemia, physical inactivity and metabolic syndrome, a family history of CAD is important, especially in young people (5, 11-13). A positive family history of cardiovascular disease is defined as the occurrence of CAD or an MI event in a first-

degree relative up to the age of 55 years in men or 65 years in women (11). According to the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) study, 42% of premature acute MI (AMI) patients had a positive family history of CAD (11). Marenberg *et al.* (14) demonstrated that the risk of death from CAD at an early age is higher in monozygotic twins than in dizygotic twins, especially when one twin died before the age of 55 years in men or 65 years in women. This risk decreased with the increasing age of fatal CAD occurrence in the affected twin (14). Further research suggests that a positive sibling history is a better predictor of coronary atherosclerosis than is a parental history of premature CAD (15). However, the genetic mechanisms associated with family history of CAD remain undiscovered.

The implementation of prevention and diagnostic programs of cardiovascular diseases, which may lead to the decrease of the morbidity rate, is of high importance. Unravelling the genetic determinants of this disease may be the first step towards understanding the pathological process and may further lead to the early identification of people at risk and to personalized disease prevention and therapy. The awareness of having predisposition towards CAD may be a motivation for some people to introduce changes into their lifestyles, such as changing dietary habits or quitting smoking (16). However, the unequivocal identification of genes responsible for the genesis and progression of such disease is difficult due to the fact that disease expression depends on the cumulative effects of both genetic and environmental factors, and that the same disease in different patients may be triggered by different factors (17). According to numerous studies, single nucleotide polymorphisms (SNPs) do not usually determine the expression of CAD, but they merely predispose its progression in association with environmental factors.

Numerous genes and variants with plausible effects on the cardiovascular system have been studied; however, the results have been inconsistent. This may be explained partially by ethnic diversity, differences in experimental designs and gene by environment interactions. Among the genes which may potentially influence the onset and the progression of CAD, there are these controlling the following: renin-angiotensin-aldosterone system (RAAS), adrenergic receptors, paraoxonases, endothelin, nitric oxide synthase (NOS) and natriuretic peptides.

The Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS takes part in the pathogenesis of numerous cardiovascular diseases including MI (18), hypertrophy (19), cardiomyopathy (20), atrial fibrillation (21) and congestive heart failure (22). Activation of this system may not only lead to the occurrence of cardiovascular events but may also promote the development of heart failure after MI (16). RAAS plays an important role in the regulation of the fibrinolytic system (23), since, as was shown in both *in vitro* and *in vivo* studies, angiotensin II increases the level of tissue plasminogen activator inhibitor (PAI-1), which is the main physiological inhibitor of fibrinolysis (23-25).

Angiotensin (Ang)-converting enzyme (ACE). The enzyme responsible for cleaving AngI into vasoconstrictor peptide AngII is angiotensin-converting enzyme (ACE). Unfavourable influence of ACE on the circulatory system is caused by the fact that it generates AngII and hydrolyses bradykinin, which stimulates the production and secretion of prostacyclin, nitric oxide (NO), and tissue plasminogen activator (t-PA), thereby diminishing its beneficial vasorelaxant, antiplatelet and fibrinolytic effect on endothelium (26, 27). This enzyme, a potent vasoconstrictor, participates in the regulation of vascular tone, increases platelet activation and aggregation of platelets (23).

On the basis of studies conducted on mice with insertionally inactivated *ACE* gene in which blood pressure was lower than in mice with functional gene, Krege *et al.* (28) suggested that this enzyme is necessary for maintaining proper blood tension. The diminishing frequency of ischaemic events (29, 30) and the improvement in endothelium function (31), after the application of ACE inhibitors (ACE-I) confirm the thesis that ACE participates in the pathogenesis of cardiovascular disease. The I/D polymorphism within the *ACE* gene, characterized by the presence or absence of a 287-base pair sequence comprising all repeats, is responsible for about 50% of individual variability in the level of circulating serum ACE. The level of enzyme is about 2-fold higher in DD homozygotes than in II homozygotes, whereas the heterozygotes show intermediary concentrations (23). This polymorphism within intron 16 leads to the deletion of the gene expression 'silencer' region (32) and, as a consequence, the increase of ACE in serum and tissues (33, 34). According to Tokunaga *et al.* (35), the DD genotype is associated not only with a higher concentration of ACE in blood, but also with its higher activity in heart muscle cell. Detection polymorphism of *ACE* has been thoroughly researched and is considered a potential risk factor for cardiovascular disease. I/D polymorphism has been linked with the increased risk of MI in several studies (36-40), CAD (39), idiopathic dilated cardiomyopathy, recurrent ischaemic events (41) and left ventricle hypertrophy (42, 43).

The DD genotype has been linked with carotid intima-media thickening (44) and an elevated risk of restenosis after stenting (45). It has been suggested that the DD haplotype may increase plaque instability (46), probably through accelerating the rate of low-density lipoprotein (LDL)

particle influx into arterial walls, which results in an increased lipid content in plaque (47), as well as through promoting endothelial cell dysfunction and vascular smooth muscle cell proliferation (48, 49). On the basis of research conducted on patients who had experienced an MI event within the previous 4 to 7 months, Ohmichi *et al*. (50) concluded that the D allele influenced ejection fraction and the end-systolic volume index. McNamara *et al*. (51) suggested that the presence of the D allele is not associated with the occurrence of MI, but may modulate the rate of disease progression. The determination of *ACE* polymorphism may be important while choosing an efficient beta-blocker therapy, since, as demonstrated by McNamara *et al*. (51), only DD carriers benefited from it: their survival after transplantations was increased.

Angiotensinogen. Another part of the RAAS within which polymorphisms may contribute to the pathogenesis of CAD is angiotensinogen (AGT). It is conversed by renin into AngI and further cleaved to AngII. Being the main AngII precursor, AGT poses an important determinant of its level both in serum and tissues (52). Many polymorphisms were identified within the *AGT* gene. The most frequently studied SNPs are: M235T and T174M (in the coding region) and G(–6)A and A(–20)C (in the promoter region). Some of them are associated with an increased risk of CAD (53), extent of coronary atherosclerosis (54) and hypertension (55) in many but not all studies (56).

Angiotensinogen concentration is a factor which limits AngII generation (57), thus its increased amount may boost the AngII level, promote atherosclerosis (58) or modulate the severity of CAD (59).

According to Tsai *et al*. (60), M235T is a non-functional polymorphism which serves only as a genetic marker. This SNP is in complete linkage disequilibrium with G(–6)A polymorphism (61) located in the transcription factor binding region (62). Allele –6A (235Thr) is associated with increased gene transcription (63) and, as a consequence, with elevated levels of serum angiotensinogen (64). Azizi *et al*. (65) demonstrated that polymorphism Met235Thr leads to diminished peptide clearance. In addition, T174M was found to be in a tight linkage disequilibrium with M235T (66). Sethi *et al*. (67) showed that the 235TT genotype is linked with significantly higher blood pressure, especially among women, but it does not influence the risk of CAD. However, Tsai *et al*. (60) revealed that in women with hypertension, the risk of CAD is increased in the presence of the M235T polymorphism. The AGT haplotypes were more markedly associated with CAD in women, probably either due to the fact that the angiotensinogen gene contains an estrogen response element which stimulates this peptide's synthesis (68) or that estrogens potentiate the effect of AngII (60, 69). Met235Thr polymorphism may affect blood pressure and influence the course of cardiovascular disease. A meta-analysis conducted by Kunz *et al*. (55) showed that Met235Thr significantly increased the risk of hypertension among patients with positive family history. In a population of young Poles (under 55 years), this SNP was associated with CAD and MI (70).

Angiotensin II. AngII, the most potent element of the RAAS, takes part in the pathogenesis of atherosclerosis (71), hypertension, heart failure, cardiac hypertrophy and renal damage (72). It mediates in the onset of all the aforementioned diseases by the activation of transcription factors, redox signalling systems, and stimulation of production and secretion (73) of endogenous growth factors (*e.g*. platelet-derived growth factor, transforming growth factor-α (TGF-α), insulin-like growth factor-I), cytokines (*e.g*. interleukin-6 (IL-6), IL-1), and chemokines (*e.g*. monocyte chemoattractant protein-1 (MPC-1) and IL-8) (74). AngII exerts its detrimental effects including vasoconstriction, cell growth regulation, inflammation and fibrosis (72), pressor responses and aldosterone secretion (75) mainly through receptor AT1 (76) associated with protein Gq and phospholipase C (16). AngII may participate in the formation of atherosclerotic plaque mainly *via* the induction of adhesion molecule expression in human endothelial cells (77) and monocyte activation leading to their enhanced adhesion to endothelial cells (78) as well as in plaque development through the stimulation of the growth (79), migration (48) and matrix generation (80) in smooth muscle cells. AngII is also a chemotactic agent for T lymphocytes (80, 81). It also stimulates the activity of membrane-bound NAD(P)H oxidase which produces reactive oxygen species (ROS) (82) in vascular smooth muscle and endothelial cells (82) and induces oxidative stress in macrophages (83). ROS lead to the formation of oxidised LDL (ox-LDL) particles, which seem to be pivotal in the formation and development of the atherosclerotic plaque in coronary vessels (84).

Apart from increasing oxidative stress, AngII enhances intracellular ox-LDL uptake (85) and the differentiation of monocytes into macrophages (73). Through the stimulation of IL-6, intercellular adhesion molecule 1 (ICAM-1) and MPC-1 protein, AngII induces the inflammatory process (73). By inducing local inflammation and also by activation of metalloproteinases (MMP-1, MMP-2 and MMP-9) (74), AngII contributes to plaque instability and its rupture (86). Schieffer *et al*. (86) demonstrated the presence of AngII and its receptor next to the presumed plaque rupture site in coronary artery fragments harvested from patients who died of MI. Moreover, AngII induces the process of fibroblast proliferation and increases collagen synthesis *via* the enhancement of TGF-α synthesis (16). AngII stimulates the generation of tissue plasminogen activator inhibitor (PAI-1)

and tissue factor (TF) *via* increasing the synthesis of TNF-α (87). It triggers myocytes and vascular smooth muscle cell compensatory hypertrophy, which may lead to the limitation of blood flow and further to the development of myocardial ischaemia (88). Through the receptor AT1, AngII indirectly contributes to increased calcium inflow into myocyte interior and, as a consequence, to enhanced cardiac contractility (16). It also influences the strength of cardiac contractions by the stimulation of noradrenaline secretion from nerve terminals (89).

AT1 activation was also demonstrated to be responsible for AngII-dependent apoptosis both *in vitro* (90) and *in vivo* (91) studies. AngII takes part in the pathogenesis of arterial hypertension, which is an important risk factor for CAD, directly through smooth muscle cell vasoconstriction and indirectly by stimulation of the adrenal cortex to secrete aldosterone, which in turn leads to the increase of intravascular volume (93). Moreover, AngII influences the secretion of the potent vasoconstrictor endothelin (94) and vasopressin and reduces NO bioavailability *via* generation of ROS, which has considerable effect on endothelium-dependent vasodilatation (94). Nowadays, the two products of *N*-terminal degradation of AngII, namely Ang III and IV, are raising considerable interest. AngIV has been determined to mediate important physiological functions of the central nervous system, such as blood flow regulation, and to be associated with cognitive processes and sensory and motor functions (76). Some studies suggest that AngII has to be converted into AngIII to be able to bind with AT1 and AT2 receptors, and is further cleaved into AngIV in order to activate AT4 receptors (76).

As far as we know, no polymorphisms within the AngII gene have yet been described, probably due to the fact that most scientists concentrate on the receptor through which AngII exerts its detrimental effects. The most often studied polymorphism within the AngII type I receptor (*AT1*) gene is an adenine/cytosine (A/C) base substitution at position –1166 in the 3' untranslated region of the gene (75, 95-97). The polymorphism has been linked with essential hypertension (96), enhanced coronary artery vasoconstriction (97) and cardiac hypertrophy (98). Allele C was observed in patients who suffered from drug-resistant hypertension (96) and those with a strong family history (99). Allele –1166C has been associated in some studies with increased responses to AngII (95), which boosted the unfavourable influence of AngII on the cardiovascular system (100). However, Tiret *et al.* (101) suggested that the *AT1* C allele is in linkage disequilibrium with another functional mutation which influences AngII responsiveness *via* altering receptor down-regulation in response to AngII. According to Diez *et al.* (102), the 1166A/C polymorphism is associated with the synthesis of type I collagen and myocardial stiffness in patients suffering from hypertensive cardiovascular disease (75). In other studies, it has been demonstrated that –1166C allele influenced the hypertrophy phenotype (98), was connected with lower ejection fraction (103, 104), increased left ventricular mass index (103, 105), higher end-systolic volume (105) and higher risk of MI among concurrent carriers of *ACE* D allele (101).

The role of AT2 receptor has not yet been well studied. According to Wolf (106) activation of AT2 by AngII may, in some circumstances, stimulate *in vivo* growth and could have important pathophysiological consequences. Another study suggests that through AT2, AngII may inhibit proliferation of certain cells and induce apoptosis (107). However, the reports concerning the role of AT2 are often contradictory (108-110).

Aldosterone. Aldosterone is a steroid hormone which plays an important role in the pathogenesis of arterial hypertension (111), arteriosclerosis, left ventricle hypertrophy (112), arrhythmia (113), cardiovascular disease (114) and chronic renal disease (114). It is secreted by the *zona glomerulosa* of the adrenal gland cortex and its main function is the regulation of body water-electrolyte balance and blood pressure. At first, it was believed that aldosterone acted only in coiled duct (cortical collecting tubule) where after binding to cytosolic receptors it regulated potassium (renal outer medullary potassium channel, ROMK) and epithelial sodium (ENaC) channels thus increasing the reabsorption of sodium ions (Na^+) and the secretion of potassium ions (K^+) into the urine (115, 116). It was then found that aldosterone might also be synthesized by smooth muscle cells, endothelium and cardiomyocytes, and its actions were much more systemic (116). The overall effect of physiological levels of aldosterone is to decrease the rate of sodium ion excretion, increase the secretion of potassium and water retention, and to enhance blood pressure.

Aldosterone acts either directly through mineralocorticoid receptors (MR) or *via* enhancing AngII and endothelin expression, COX-2 activation and the increase of oxidative stress (115, 116). Recently, it has been shown that aldosterone action may be also mediated by membrane receptors and these effects occur shortly after aldosterone exposure as this pathway does not involve transcription and protein production (113).

Excessive secretion of aldosterone which binds to mineralocorticoid receptors localized in heart, blood vessels and brain may lead to myocardium and vessel hypertrophy (through type I and III collagen transcription stimulation) (117), endothelial dysfunction (through the decrease of NO release) and to severe coronary artery damage (*via* the generation of inflammatory infiltrations) (113). Studies of animal models revealed that a high concentration of aldosterone in myocardium may stimulate the formation of inflammatory infiltrations comprising macrophages, T

lymphocytes, monocytes and the proteins of the complement system, which suggest that this hormone may participate in the process of immunocompetent cell activation (118). Moreover, aldosterone may cause reduced baroreceptor sensitivity and interfere with norepinephrine uptake by myocardium and, as a consequence, may induce adverse heart rate variability and catecholamine-induced arrhythmias (113). According to Marumo *et al*. (119), aldosterone inhibits bone marrow cell differentiation by reducing the expression of vascular endothelial growth factor 2 (VEGFR-2) and in this way, it negatively influences endothelium reconstruction. The enhancement of NADPH oxidase activity by this mineralocorticoid hormone leads to higher oxidative stress which in turn stimulates proinflammatory processes and intensifies the synthesis of some growth factors (120).

The contribution of aldosterone to the pathogenesis of cardiovascular disease was confirmed in studies on transgenic mice with the increased expression of human mineralocorticoid receptor, which demonstrated their high susceptibility to arrhythmia and frequent sudden deaths (121). Moreover, promotion of aldosterone binding to mineralocorticoid receptors induced rat heart hypertrophy, fibrosis and heart failure, with no symptoms of hypertension (122). In addition, according to Cohn and Colucci (113), the local production of aldosterone, dependent on the degree of myocardial impairment and failure, increases after MI. Cardiac remodelling in which the hormone participates leads to the change of left ventricle architecture, systolic function impairment and is an indicator of unfavourable prognosis after MI (113). According to Biondi-Zoccai *et al*. (123), aldosterone directly induces myocardial apoptosis. It also promotes myocardial ischaemia and necrosis and contributes to PAI-1 regulation (113). The reduced mortality and morbidity in clinical studies of post-acute MI patients in which aldosterone blockade was used confirm the participation of aldosterone in the pathogenesis of cardiovascular disease (113).

No polymorphism influencing the risk of CAD or MI has been characterized within the aldosterone gene. However, it was demonstrated that several SNPs occur within the gene of *CYP11B2* (a key enzyme of aldosterone synthesis). Polymorphisms in aldosterone synthase may contribute to severe low-renin hypertension and left ventricle remodeling (124). The 334T/C polymorphism in the *CYP11B2* gene is located near the transcription factor SF-1-binding site and may influence the expression (125, 126) of steroid biosynthetic enzymes in the adrenal cortex (127). However, due to the fact that another SF-1 binding site located downstream from the promoter is much more important for transcriptional control, it was suggested that a site neighbouring the –344 polymorphism is essential for developmental regulation of *CYP11B2* in the adrenal or in extra-adrenal sites (124). According to Kupari *et al*. (124), the –344C allele binds in *in vitro* studies about 4 times stronger than the –344T. Carriers of the C allele have higher aldosterone concentration and increased risk of cardiovascular disease. The –344T/C polymorphism has been associated in many studies with the increase of left ventricle size and its impaired filling in young Caucasians (124) as well as with hypertension (126, 128). Healthy individuals carrying the –344C allele demonstrated up to 28% larger end-diastolic volumes and left ventricle mass 21% greater in comparison to 344TT homozygotes (124).

Paraoxonases (PON)

The defence against the detrimental effect of LDL oxidation is based on antioxidative and anti-inflammatory properties of high-density lipoprotein (HDL) and HDL-associated enzymes (129) such as: paraoxonases, apolipoprotein A-I, and Apo J (130, 131). To date, three isoforms of paraoxonases (PON) have been discovered (132), two of which are bound with HDL particles (PON1 and PON3), whereas the third is present in smooth muscle cells, endothelium and macrophages (133), where it exerts its antioxidant effect at a cellular level (134). PON1 inhibits lipoprotein oxidation and catalyses the hydrolysis of already existing lipid peroxides and other active metabolites such as organophosphate compounds (135). According to Aviram *et al*. (136), PON1 can also decompose reactive hydrogen peroxide which is generated in arterial walls during atherosclerotic plaque development. PON2 has been demonstrated to participate in the defence against LDL oxidation as well (134). Despite years of strenuous scientific research, the activity of PONs which mediate their anti-atherogenic effects has not been ascertained yet (137). It has been suggested that it is the lactonase activity preventing vessel damage *via* the degradation of toxic lactone which constitutes their main biological feature, since neither PON1 nor PON2 exhibits activity toward paraoxon (138-140). This hypothesis was confirmed by studies of PON1 mutants, in which decreased lactonase activity was associated with diminished anti-atherogenic properties (137). This activity has been shown to play a role in the inhibition of LDL oxidation as well as in the hydrolysis of oxidized lipids in macrophages (137). However, other studies demonstrated that low PON activity toward paraoxon is connected with cardiovascular risk (141, 142).

Polymorphisms lowering the expression of PONs or diminishing their activity may lead to atherosclerosis development. Numerous studies concerning the role of PONs in protection against atherosclerosis revealed the association between the *PON1* Arg192 allele and increased risk of CAD (143-145), although the results were not always consistent (146, 147). The substitution of Gln by Arg in position 192 seems to be very important in the ability of PON1 to protect

LDL from oxidation. In comparison to 192Arg, the Gln allele was associated with higher arylesterase activity (148) toward paraoxon, higher efficiency in oxidation inhibition (149) and better protection (150, 151). PON1 participation in the inhibition of ox-LDL generation may suggest that its activity modulates susceptibility to atherosclerosis and its development (152). Studies conducted on *PON1* knock-out mice demonstrated that they were more prone to the development of diet-induced atherosclerotic plaque, and the HDL isolated from them was not able to prevent lipoproteins to oxidation *in vitro* (153). The polymorphism Ser311Cys in PON2, situated in the potential active centre of oxidative lipid hydrolysis, may influence the catalytic activity of this enzyme (145). According to Martinelli *et al.* (154), *PON2* polymorphism was associated with increased risk of CAD especially among smokers. Moreover, Sanghera *et al.* (145) and Chen *et al.* (155) found a connection between Ser311Cys polymorphism and CAD risk. The latter authors demonstrated significant association between the occurrence of 192Arg and 311Cys alleles and the severity of cardiovascular disease. In their study, Arg and Cys alleles were over represented in patients with 3-vessel disease in comparison to those with lower a number of diseased vessels (155). According to Sanghera *et al.* (145) the lack of connection between Gln192Arg and Ser311Cys occurrence and the concentration of lipids and apolipoproteins may suggest that the increased risk of heart failure linked with the presence of these polymorphisms is independent of the conventional plasma lipid profile. Due to the fact that the activity and level of serum PON protein differs significantly between individuals and populations of varied ethnic backgrounds (156), some studies have suggested that not only the genotype of PONs, but also their activity and concentration influence the risk of cardiovascular disease (142, 157).

Endothelin-1 (ET-1)

Endothelial dysfunction, defined as the disturbance of the balance between vasodilatory and vasoconstrictor properties, plays an important role in the formation and progression of atherosclerotic plaque as well as in pathogenesis of heart failure (158). Both vascular relaxation impairment and increased constriction may lead to the development of hypertension, the damage of endothelium and plaque formation and rupture (159). Endothelial vasoconstrictor features depend mainly on endothelin-1 (ET-1) which is produced mainly in vascular endothelial cells in the form of pre-proendothelin-1 (160). This 212 amino acid peptide is further cleaved by furin to generate a biologically inactive 'big ET-1'. The formation of mature ET-1 requires transformation by endothelin-converting enzyme into the 21-amino acid vasoconstrictor peptide (161). Apart from being a potent vasoconstrictor, ET-1 has inotropic, chemotactic and mitogenic properties (160). The effect of ET-1 is mediated through two types of receptors: ETA located on vascular muscle cells (162), which takes part in vasoconstrictor activity of ET-1; and ETB located on endothelial cells (163), the activation of which leads to stimulation of NO and prostaglandin production, and vasodilation (159). ET-1 through the ETA receptors induces vascular smooth muscle cell proliferation (164). It favours the formation of inflammatory infiltrations through stimulation of monocyte production of cytokines (TNF, IL-1, -6 and -8, granulocyte-macrophage colony-stimulating factor) (165), the adhesion of neutrophilic granulocytes and platelet aggregation (166), which may lead to the development of ischaemic disease. ET-1 induces the release of other vasoconstrictor factors such as: vasopressin, AngII, adrenaline, noradrenaline, thromboxane A2 and aldosterone (167). The biological effects of ET-1 also include the influence on salt and water homeostasis, stimulation of both the sympathetic systems and cardiac contraction (inotropic and chronotropic effects). It was demonstrated that the concentration of ET-1 was increased in patients suffering from hypertension (168), acute coronary syndrome (169) and MI (170). ET-1 participates not only in the genesis but also in the progression of atherosclerosis: its increased levels were detected in the serum of patients in the early stage of plaque formation and in individuals with advanced, disseminated atherosclerosis. Nessler *et al.* (171) also revealed a tight correlation between this peptide concentration and the amount of atherosclerotic lesions in coronary arteries.

The effectiveness of endothelin antagonists in the treatment of vasoconstriction-induced cardiac, vascular and renal diseases including essential hypertension (172) confirms the role of ET-1 in the pathogenesis of these diseases. The functional significance of the polymorphism 198Lys/Asn localized near the *C*-terminal fragment of pre-proendothelin is not known, however, it was suggested that it may be involved in ET-1 function, as it may affect the processing of pre-proET-1 to mature ET-1 (173). The obtained protein may be non-functional and unable to exert its detrimental effect in pathological states. According to studies, this polymorphism was associated with the alteration of vascular reactivity (174), with increased resting pressure among middle-aged individuals (173, 175) and increased risk of heart failure (176).

Nitric Oxide Synthase (NOS-3, eNOS)

NO, synthesized from L-arginine by endothelial NO synthase (eNOS coded by *NOS-3*), promotes vasodilation, limits the oxidation of atherogenic LDL (177), plays a key role in reducing vascular smooth muscle cell (VSMC) proliferation, platelet adhesion (178, 179), endothelial permeability and extracellular matrix collagen synthesis. It takes part in the

maintenance of endothelial function and vascular homeostasis among others through the regulation of vascular tone (180) and blood pressure (181). NO reduces vascular smooth muscle cell mitogenesis (anti-proliferative effect), restricts chemotaxis (182) and limits leukocyte adhesion to endothelial cells (179, 183). It prevents LDL oxidation (180) and inhibits ROS release (182), thus lowering the adverse impact of oxidative LDL particles on the endothelium (180). Moreover, NO can influence blood coagulation (181) and exert anti-atherogenic effects through blunting the activity of nuclear-kappa B transcription factors leading to the decreased expression of cytokines and adhesion molecules (184). The endothelial isoform of NOS is constitutively expressed, but in for example shear stress conditions, endothelial cells respond with a compensatory increase in NOS-3 expression in order to maintain physiological functions in a pathological state (185). However, the reactive nitric species generated in inflammatory state, hypercholesterolemia, diabetes mellitus and hypertension may lead to a further damage of cellular structures (186). According to numerous studies, the impairment of NO synthesis leads to the progression of endothelial dysfunction (187), vasoconstriction and the formation of thrombi (188) and as has been observed in animal models, it promotes the formation of atherosclerotic plaque (189, 190).

This is why it was suggested that polymorphisms within the *NOS-3* gene which reduce either the expression of synthase or NO availability may contribute to the progression of cardiovascular disease (191). As yet, several polymorphisms in the *NOS-3* gene such as 786T/C, 922A/G, 894G/T, G10T, 27 bp tandem repeat in intron 4 and –1444T/A have been identified, and in some studies, but not in all (192-195), they have been linked with an increased risk of CAD (196, 197), hypertension (198,199), coronary spasm (200) and in-stent restenosis (201). The 894G/T polymorphism bringing about the 298Glu/Asp substitution, according to Tesauro *et al*. (202) leads to the formation of NOS protein more susceptible to cleavage, which in turn results in the reduction of the functional protein level. However, *in vitro* studies indicated that between various allele products, there are no differences (203) in stability or activity (204). Joshi *et al*. (205) suggested that eNOS Glu/Asp and Asp/As variants may have different caveolae localization which might influence the biological activity of NO signal molecule and signal transduction (206). According to Agema *et al*. (207), among TT homozygotes the risk of cardiovascular disease and MI is elevated. It has been also concluded that the 894G/T polymorphism may be very useful in the identification of people at high risk of atherosclerosis (208). Another polymorphism within the *NOS-3* gene, 786T/C, has been demonstrated to be associated with reduced promoter activity, reduced platelet release of NO (209) and lower response to shear stress (191). Protein A1 (replication repressor) (210) binds to the C allele and leads to diminished transcription rate and lower serum nitrite/nitrate levels in normal conditions and in hypoxia (209). This polymorphism contributed in an Italian population both to endothelial dysfunction and increased risk of CAD (211, 211), and in Japanese patients to coronary spasm (209). Joint presence of 894G/T and 786T/C was associated not only with the incidence, but also with the severity of angiographically proven congestive heart failure (213). Jeerooburkhan *et al*. (192) observed the relation between the occurrence of 786T/C and 922A/G polymorphisms. This tendency was confirmed by Nakayama *et al*. (209) who demonstrated a strong association between three polymorphisms within the *NOS-3* gene (786 T/C, 922 A/G and 1468 T/A) and coronary spasm. According to Yoon *et al*. (214) the frequency of occurrence of another polymorphism (G10T) within the intron 23 of the *NOS-3* gene is much higher in patients suffering from heart failure than in healthy individuals. Although the mechanism of this polymorphism is not known, it was suggested that due to the fact that the motif identical to the original splicing site is created in the T allele, it may lead to aberrant splicing of the primary *NOS-3* gene transcript and thus influence the enzyme activity (215).

Adrenergic Receptors

Regulatory systems, the activation of which play a role in the pathogenesis of heart failure and cardiac remodelling are the RAAS (mentioned above) and the sympathetic system (216). Prolonged stimulation of the adrenergic system in pathological states leads to further circulatory impairment and cardiovascular disease progression, since catecholamines released during activation exert a detrimental effect on the heart *via* adrenergic receptors (217). The sympathetic and RAAS systems are activated to maintain normal cardiac output, however, in the state of irreversible cardiac damage, their stimulation leads to increase in cardiac load, left ventricle geometry change and dysfunction (218). The adrenergic receptors are a class of G protein-coupled receptors that are activated by catecholamines (adrenaline, noradrenaline). The activation of β receptors through the Gs protein stimulates adenyl cyclase and leads to contractility increase, whereas α1 receptors activate Gq protein and the phospholipase C signalling pathway (217). The stimulation of α1 and β adrenergic receptors by noradrenaline may result in increased collagen synthesis and further lead to cardiac fibrosis, cardiac hypertrophy and heart remodelling (217). Prolonged stimulation of β1 receptors leads to the increase of intracellular calcium (Ca^{2+}) concentration, successive cardiomyocyte calcium overload and cell necrosis (217). Noradrenaline may modulate the process of apoptosis (219) through β1 adrenergic receptors. In contrast to β1 receptors,

β2 may exhibit cardioprotective properties. Studies on animal models demonstrated that β2 receptor activation inhibited cardiomyocyte apoptosis, probably due to the stimulation of inhibitory protein Gi (220). The β1 adrenergic receptors which are in the majority in the heart and participate in the physiological effect of noradrenaline release from sympathetic nerve endings (cardiac inotropy and chronotropy), seem to be one of the main factors taking part in the pathogenesis of cardiovascular disease (220). Stimulation of β1 receptors results in an increase in heart rate, higher cardiac contractility and renin synthesis enhancement, which in turn leads to perturbation of blood flow, increased vascular tone and finally to endothelial damage and atherosclerotic plaque rupture (221).

According to numerous studies (217, 222-224), prolonged adrenergic system activation underlies the pathogenesis of congestive heart failure. The application of β blockers in the treatment after MI reduces mortality as well as the risk of future events (225). The polymorphisms within the genes of adrenergic receptors, which either ameliorate the function of β1 receptors or diminish the expression of β2, have adverse effects on the circulatory system. The presence of hyperfunctional polymorphism in the 1165 position (Arg389Gly) within the critical point for G protein-coupling in β1 receptor localized on cardiomyocytes, according to Biolol *et al*. (226) may result in enhanced receptor function and myocyte contractile response to stimulation. However, this observation was true only in initial stages, since in older mice, the 389Arg allele was associated with reduced signalling, worse receptor binding and lower ventricular contraction (227). The Arg389 carriers were more susceptible to β-blocker treatment and their ventricular function was much more improved compared with 389Gly carriers (227).

Another polymorphism in the β1 receptor in position 49 (Ser/Gly) has been linked with higher activity of adenyl cyclase (217), higher agonist and antagonist affinity (220), better response to inhibition by metoprolol (226) and greater down-regulation and desensitization by catecholamines (226). This polymorphism is considered 'protective' as it was demonstrated to be associated with greater survival rate and lower number of cardiovascular complications in heart failure patients (217). Joint occurrence of Arg389 and a polymorphism within the α2c receptor that regulates norepinephrine release is thought to be a CAD risk factor (228). Among all polymorphisms within the β2 adrenergic receptor gene, Thr164Ile has been analysed in most studies. This substitution is associated with diminished adenyl cyclase activity (impaired binding to Gs protein) (229, 230), reduced affinity towards agonists (215) and depressed myocardial contractile function (231). According to Ligget *et al*. (232), the survival rate among patients with ischaemic or dilated cardiomyopathy carrying the 164Ile allele was much lower than in 164Thr carriers (42% *vs*. 76%, $p<0.001$). Variant 164Ile contributed to faster progression of heart failure (232). Other polymorphisms within the β2 gene such as Arg16Glu and Gln27Glu have also been linked with the course of cardiovascular disease (217). Allele 16Gly increases receptor down-regulation, whereas the Glu27 allele seems to prevent the decrease in receptor numbers during their enhanced stimulation (217).

Polymorphisms within α adrenergic receptors which regulate the norepinephrine release may lead to higher susceptibility to heart failure (233, 226). The deletion of four amino acids in α2c adrenergic receptor (Del322-325) interferes with its function and contributes to lower auto-inhibitory activity and higher norepinephrine levels (234, 226). As mentioned before, the occurrence of this polymorphism and 389Arg allele (β1 receptor) was associated with a 10-fold increased the risk of heart failure in African-American patients (228).

Conclusion

Polymorphisms within the genes of the RAAS system, ET-1, NOS and adrenergic system may contribute to the development and progression of cardiovascular disease. Although the potential functionality of some of these polymorphisms is known, the consequences of the occurrence of given alleles are not unequivocal. Current knowledge and learning supports the notion that in order to gain a more complete understanding of the mechanisms underlying cardiovascular disease initiation and progression, we need to incorporate into study designs and analyses the concept of environment genotype and genotype interactions. The unravelling of genetic determinants of vascular disease will help identify people at risk, introduce strategies for disease prevention and early-stage treatment and allow individualized treatment.

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