THE PHARMACOGENETICS OF CARDIOVASCULAR DRUGS

FARMAKOGENETIKA KARDIOVASKULARNIH LEKOVA

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Summary: This article will primarily summarize the current knowledge of the pharmacogenetics of commonly used drugs for the cardiovascular system: oral anticoagulants, antiplatelet therapy and statins. Coumarin anticoagulants are widely used to treat and prevent thromboembolisms. Variations in the CYP2C9 and VKORC1 genes influence the pharmacodynamic response to coumarins. Genetic variation makes an important contribution to the variation in the response to clopidogrel, the most commonly prescribed antiplatelet treatment. Genetic polymorphisms in the CYP2C19 gene as in the paraoxonase 1 gene are associated with clopidogrel effectiveness and have shown an association with excess of ischemic events such as myocardial infarction and stent thrombosis, but also with serious threat of bleeding. Statin pharmacogenetics has the potential to improve the safety and effectiveness of lipid-lowering therapy by statins. Genetic variations in apolipoprotein E, cholesterol ester transfer protein, kinesin-like protein 6, statin transporter OATP1B1 etc. could partly explain the interindividual variation in statins therapeutic response and adverse reactions. Finally, we comment on the pharmacogenetics of other cardiovascular drugs that have been extensively studied, but for which data are conflicting or that have not yet seen clinical implementation. Based on the available data, it could be expected that in the future genome-tailored drug prescription and use of defined algorithms will contribute to the successful drug action, lowering the frequency of adverse events, and will have greater clinical relevance.

Keywords: cardiovascular drugs, drug therapy, pharmacogenetics

Kratak sadržaj: Ovaj rad će prvenstveno sumirati sadašnja saznanja o farmakogenetici najčešće korišćenih kardiovaskularnih lekova i to oralne antikoagulantne i antiagregacione terapije i terapije statinima. Kumarini su antikoagulansi sa širokom primenom u lečenju i prevenciji tromboembolizma. Varijacije u CYP2C9 genu i genu za VKORC1 utiču na farmakodinamski odgovor na kumarine. Genetska varijabilnost značajno doprinosi varijabilnosti u odgovoru na klopidogrel, najčešće propisivanu antiagregacionu terapiju. Genetski polimorfizmi u genu za CIP2C19 i paraoksonazu 1 povezani su sa efektivnošću terapije, kao i sa pojavom ishemijskih događaja kao što su infarkt miokarda i tromboza stenta, ali i sa ozbiljnim rizikom od krvarenja. Farmakogenetika statina mogla bi značajno da doprinese poboljšanju efektivnosti terapije statinima, kao i smanjenju neželjenih efekata. Genska varijabilnost u apolipoproteinu E, proteinu koji transportuje holesterol estre, kinezinu sličnom proteinu 6, transporteru za statine OATP1B1 itd. može donekle da objasni interindividualne varijacije u odgovoru na terapiju statinima i pojavu neželjenih efekata. Na kraju, komentarisaćemo farmakogenetiku drugih kardiovaskularnih lekova koji su intenzivno proučavani, ali za koje su dobijeni kontradiktorni podaci ili za koje se još ne vidi jasno klinička primena. Na osnovu raspoloživih podataka, može se očekivati da će u budućnosti propisivanje lekova na osnovu genetike i korišćenje definisanih algoritama doprineti boljem delovanju leka, smanjenju učestalosti neželjenih reakcija na lek, kao i da će imati veći klinički značaj.

Ključne reči: kardiovaskularni lekovi, terapija lekovima, farmakogenetika

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Introduction

The drug effects vary from patient to patient. Usual doses can result in inefficacy of drugs, adverse reactions and toxic effects. In addition to the fact that the effects of treatment depend on many nongenetic factors, there is considerable evidence that the sequence variants in the genes encoding drug-metabolizing enzymes, drug transporters, transmembrane receptors, intracellular enzymes and molecular targets for the action of drugs are responsible for interindividual differences in the response to therapy. It is estimated that genetic factors affect 20–95% of variations in the effects of the applied treatment. A genetic basis for drug response can be determined using the candidate genes approach or genome-wide association studies. Pharmacogenetics is the study of the effect of variation in a single gene on drug response, including both efficacy and toxicity, with the aim to provide the adequate dosage for each patient with maximum clinical benefit and minimal side (1–4). Sources of pharmacogenetic variation could be divided into three broad categories: pharmacokinetic (variability in concentration of drug at site of drug effect), pharmacodynamic (variability in drug ability to influence its target) and those related with the underlying disease mechanism (variability in disease being treated).

At present, we are witnessing the use of genetic information in guiding cardiovascular therapy. It is of great importance, because cardiovascular disease is the leading cause of death worldwide. Using drugs that inhibit coagulation, disrupt platelet function, reduce cholesterol levels, control blood pressure levels, etc. can reduce mortality in these patients. Although the first results were mainly related to the use of anticoagulant and antiplatelet therapy, the pharmacogenetic evidence is accumulating with other cardiovascular drugs. This article will summarize the current knowledge of the pharmacogenetics of drugs for the cardiovascular system and will focus on antiplatelet therapy, oral anticoagulants, statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and diuretics.

Antiplatelet therapy

Antiplatelet medications are known to decrease adverse effects in patients with atherothrombotic disease. However, despite ongoing antiplatelet medication, a considerable number of patients suffer from atherothrombotic events. Genetic variations contribute to interindividual heterogeneity in response to antiplatelet therapy (aspirin, thienopyridine derivates (clopidogrel, prasugrel, ticagrelor) and GP IIb/IIIa receptor inhibitors).

Aspirin is the most widely used antithrombotic agent. Aspirin irreversibly acetylates the cyclooxygenase (COX)-1 enzyme, leading to the suppression of thromboxane A2 and related metabolites (5). Despite taking aspirin, 5–40% of patients can experience a serious vascular event because of aspirin resistance. Several genetic polymorphisms are proposed to influence aspirin response and contribute to bad prognosis. Among them, the most studied are:

– COX-1 (C50T, rs3842787) and COX-2 (G-765C) polymorphisms (6, 7). COX-1 C50T polymorphism is associated with higher thromboxane B2, the marker of thrombotic events before and after aspirin treatment. Significant association was found between the COX-2 G-765C and higher reduction of thromboxane B2 levels after aspirin treatment. But, there is no clinical data about the role of COX-1 and COX-2 polymorphisms in thromboembolic disease of patients on aspirin therapy.

– GP IIIa PlA polymorphism (Pro33Leu) (8–11). Carriers of PlA2 allele require a greater dose of aspirin to experience the same antiaggregant effect as PlA1 homozygous. Also, these patients carry an increased risk of thrombosis and complications after coronary angioplasty and percutaneous coronary intervention (PCI).

– C807T, G873A polymorphisms (12). GP Ia C807T polymorphism is associated with the expression of this collagen receptor on the platelet membrane surface and both polymorphisms are related with greater platelet reactivity in patients receiving dual antiplatelet therapy.

– Polymorphism in the ADP subtype P2Y1 receptor (C893T) (13) is associated with reduced platelet aggregation after aspirin intake, but there is no clinical data that will strongly confirm this. The literature data suggests that hemostatic factors may affect platelet function. Leu34 carriers (Val34Leu polymorphism of factor XIII) on therapy with low-dose aspirin are at lower risk for acute myocardial infarction compared with Leu34-negative subjects (14).

Thienopyridine derivates

Clopidogrel is the most commonly prescribed antiplatelet treatment. Clopidogrel is a thienopyridine derivate that exerts its effect through binding irreversibly to the platelet P2RY12 purinergic receptor, selectively blocking ADP-dependent platelet activation and aggregation. Clopidogrel is a prodrug. Cytochrome P450 (CYP) 1A2, CYP2C19, CYP2B6 catalyze conversion of prodrug to 2-oxo-clopidogrel, and CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4/5 and paraoxonase 1 catalyze generation of the active metabolite. The active clopidogrel metabolite irreversibly binds to platelet ADP P2Y12 receptors. Up to 21% of patients undergoing PCI exhibit clopidogrel non-response, which corresponds to an 8-fold

increase in the risk of adverse cardiovascular events postprocedure (15).

CYP2C19 is the primary isoform responsible for clopidogrel activation (16). Carriers of loss of function alleles CYP2C9*2 and CYP2C9*3 have impaired ability to metabolize clopidogrel. The consequence is decreased inhibition of platelet aggregation and increased cardiovascular risk. Four large-scale studies (17–20) have confirmed the prognostic implications of the CYP2C19 polymorphism in clopidogrel-treated patients. Eight meta-analyses of CYP2C19-clopidogrel outcome studies revealed following conclusions: significantly increased risk for stent thrombosis in *2 carriers, with the median hazard ratio of 2.58; major adverse coronary event (MACE) after PCI with the median hazard ratio of 1.26.

The US Food and Drug Administration (FDA) in 2010 drew special attention of clinicians to the diminished effectiveness in poor clopidogrel metabolizers. Different guidelines suggest that it is reasonable to consider CYP2C19 genotyping in patients at high risk for poor outcomes after PCI and that alternative antiplatelet therapy should be considered in those for whom the genotype poses potential risk for reduced antiplatelet efficacy. Genotyping should not be recommended for routine use in patients at lower risk.

CYP2C19*17 allele is associated with increased enzyme transcription and better response to clopidogrel. Carriers of this allele could be protected from MACE, but are at increased risk of bleeding (21).

Paraoxonase 1 (encoded by PON1) is the rate-limiting enzyme responsible for the conversion of 2-oxo-clopidogrel to the active metabolite (22). Carriers of 192Gln allele have lower paraoxonase 1 activity, lower concentrations of the active metabolite of clopidogrel and lower platelet inhibition. Bouman et al. (22) found that the Gln192Arg (rs662) polymorphism was associated with clopidogrel-associated stent thrombosis, and patients with the Gln192Gln polymorphism had a hazard ratio of 12.9 for risk of stent thrombosis versus patients with an Arg192Arg polymorphism. Further studies did not confirm this result (23–25). A recently published meta-analysis (26) that included 12 studies also concluded that the PON1- Gln192Arg polymorphism has no major impact on the risk of MACE and does not alter the biological response to clopidogrel in clopidogrel-treated patients.

CYP3A4 plays a pivotal role in the CYP system; therefore, the role of five genetic variants of this enzyme on clopidogrel response was the first to be evaluated, but only the IVS10+12G>A CYP3A4 polymorphism was associated with platelet activation but not aggregation (27).

A growing number of studies have investigated the effect of pharmacokinetic variables–intestinal absorption, metabolic activation, on response to clopidogrel. It is well known that ABCB1 is involved in the intestinal absorption of clopidogrel. Influence of the C3435T variant (rs1045642) in ABCB1 on clopidogrel absorption was found in patients with cardiovascular diseases (18, 28). Carriers of 2 copies of the ABCB1 T-T-T haplotype (T allele at C1236T (rs1128503), G2677T (rs2032582), and C3435T (rs1045642)) treated with clopidogrel were at an increased risk for subsequent death, myocardial infarction or stroke compared to persons who carried none, thus mirroring the platelet function data (29).

Reduced platelet aggregation with clopidogrel in the acute phase of treatment was noticed in PlA2 carriers compared with the carriers of PlA1/A1 genotype. The T allele of the GP Ia gene was shown to modulate platelet aggregation and clopidogrel antiplatelet effects. In T-allele carriers increased platelet reactivity related to enhanced reactivity to fibrillar collagens was noticed and they are at higher risk of thrombosis (30).

Based on the available data, it is reasonable to advise that if a person is found to be a poor metabolizer, then an alternative to clopidogrel, such as prasugrel or ticagrelor, should be considered. This seems preferable over increased clopidogrel doses, which have not shown benefit over standard dose clopidogrel.

The GP IIb/IIIa receptor inhibitors

Intravenous GP IIb/IIIa receptor inhibitors as potent antiplatelet drugs are administrated in patients treated by early PCI. Few studies evaluated the association of PIA polymorphism of the GP IIIa subunit of GPIIb/IIIa platelet receptor with antiplatelet effects of inhibitors to this receptor. The obtained results are quite controversial. Some reports suggest that carriers of the PlA2 allele exhibit lower platelet-inhibiting effects, worse clinical outcomes and the greatest rates of in-stent restenosis (31, 32). In contrast, some other studies (33, 34) found no significant effect of the PIA genotype in platelet inhibition or in myocardial reperfusion. Also, oral GP IIb/IIIa inhibitors have not demonstrated any beneficial effect in acute coronary syndrome.

Oral anticoagulants

Coumarin derivates (warfarin, acenocoumarol, phenprocoumon) (vitamin K antagonists) are widely prescribed anticoagulants for the treatment of thrombotic disorders. They have a very narrow therapeutic range and wide interindividual variability. Defining an appropriate dose can take weeks. Meanwhile, many adverse events are noticed. A low dose can induce thromboembolism, and a high dose can induce bleeding. Except patient-related and clinical factors, individual response to anticoagulant therapy is influ-

enced by genetic factors. About 50% of the variability in coumarin derivates maintenance dose requirements could be explained by genetic polymorphisms in the following genes: a) CYP2C9 – the principal metabolizing enzyme of all coumarines; b) VKORC1 (vitamin K epoxide reductase complex subunit 1) – the pharmacologic target of coumarins; c) CYP4F2 (vitamin K1 oxidase).

CYP2C9 metabolizes S-warfarin enantiomer. CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) variant alleles result in decreased CYP2C9 enzyme activity compared with CYP2C9*1. The consequence is the influence on coumarin pharmacokinetics, and increasing risk of bleeding. The results of a meta-analysis showed that carriers of the CYP2C9 *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3 genotypes require lower warfarin doses (19.6, 33.7, 36.0, 56.7, 78.1%, respectively) to achieve a similar level of anticoagulation compared with those homozygous for CYP2C9*1 respectively and require more time to achieve stable INR (35).

In addition to CYP2C9, the polymorphic vitamin K epoxide reductase subcomplex 1 (VKORC1) gene is an important determinant of warfarin dose requirement. Polymorphisms in the VKORC1 (-1639G > A, rs9923231; and 3730G > A, rs7294) gene have been found associated with required warfarin dose. Carriers of −1639A require lower initial doses of warfarin compared with −1639G carriers. The −1639G>A polymorphism alters a VKORC1 transcription factor binding site, leading to lower protein expression (36). The first meta-analysis of 19 studies confirmed the impact of VKORC1 gene polymorphism on interindividual warfarin dose requirement variation, and showed different effects in different ethnic groups (37). Data from two large comparative effectiveness studies are available to support genotype-guided warfarin therapy (38, 39). Many dosing algorithms have been developed with the aim to predict initial and maintenance doses. This has led to changes in the warfarin drug label in 2007 by the FDA and introduction of dosing tables in 2010. After that, pharmacogenetics-based dosing algorithms were developed (40). When computer access is unavailable, the pharmacogenetic table in the FDA-approved warfarin label may serve as an alternative guide to dosing.

The single nucleotide polymorphism of CYP4F2 (rs2108622, Val433Met) has a moderate effect on the stable warfarin dose. A recent review/meta-analysis (41) in 9470 participants better defined the impact of CYP4F2 SNP on coumarin dose requirement.

Genetic variation in several other genes, apolipoprotein E, glutamyl carboxylase, calumenin, epoxide hydrolase 1, and factor VII, may also influence warfarin dosage requirements (42).

Statins

With the increasing incidence of cardiovascular disease, obesity, metabolic syndrome increases the need to use statins 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) inhibitors. Statins lower total and low-density lipoprotein cholesterol up to 55% and reduce cardiovascular risk by 20–30% (43, 44). Increased statin concentrations correlate with increase in toxicity causing myopathy and rarely rhabdomyolysis. There is large interindividual variability in the clinical response to statin treatment, in the efficacy of statin therapy as well as risk of adverse effects. Polymorphisms in the genes involved in cholesterol synthesis, absorption, transport can affect statin efficacy. Important genes involved in the lipid-lowering response to statin therapy and variation in clinical events after statin therapy identified by candidate gene studies (pharmacokinetic and pharmacodynamic candidate genes) or genome-wide association studies include the HMGCR (target of statin therapy), lipid metabolism genes such as apolipoprotein E (APOE), apolipoprotein B (APOB), cholesteryl ester transfer protein (CETP), LDL receptor (LDLR), 2 cholesterol transport adenosine triphosphate–binding cassette proteins (ABCG5/8, ABCG2), kinesin-like protein 6 (KIF6), solute carrier organic anion transporter 1B1 (SLCO1B1) genes, calmin (CLMN), cytochrome P450 family metabolizing enzymes (42, 45).

The literature data indicate an association between statin myopathy and genetic polymorphisms (c521T > C, rs4149056 and 388A>G, rs2306283) of the solute carrier organic anion transporter (SLCO1B1) gene. This gene encodes organic anion transporting polypeptides B1 (OATP1B1) expressed on the sinusoidal membrane of hepatocytes that facilitate the hepatic uptake of many statins. This association was first reported by the SEARCH consortium in Genome-Wide Association Study (GWAS) and replicated by several research teams. Compared with the TT carriers, individuals who are carriers of a CC genotype are at increased risk of myopathy. But, myopathy can occur in the absence of a risk SLCO1B1 allele, indicating that some other variants of the same gene or other genes can be important. Strong association between a noncoding polymorphism (rs4363657) and statin-induced myopathy in patients treated with high-dose simvastatin was noticed in a GWAS (46, 47). Haplotypes are associated with statin responsiveness. The c388A-c521T haplotype is known as *1A (reference haplotype), c388G-c521T as *1B, c388A-c521C as *5 and c388G-c521C as *15. Carriers of *5 are at 4- to 5-fold increased risk of severe, creatine kinase-positive simvastatin-induced myopathy and 2- to 3-fold increased risk of creatine kinase-negative myopathy (46, 48).

Genetic variants in CYP3A4, which metabolizes simvastatin, atorvastatin and lovastatin, have been associated with variability in statin therapy response.

Polymorphism (M445T) and the CYP3A4*4 haplotype were associated with lower low density lipoprotein cholesterol levels with atorvastatin. In carriers of the CYP3A4 promoter polymorphism (A290G) or CYP3A4*1G haplotype the lipid-lowering effect of statins is not demonstrated (49, 50).

Many statins are substrates for efflux transporters multidrug resistance protein MDR1 (gene name ABCB1) or another efflux protein from the same family (gene name ABCG2). ABCB1 variants influence the efficacy of simvastatin in hypercholesterolemic patients and ABCB1 variants (1236T, 2677 non-G and 3435T) were less frequent in patients with adverse muscle effects. ABCG2 variants alter the pharmacokinetics of atorvastatin and rosuvastatin. Participants carrying a CC genotype at rs2231142 (ABCG2 polymorphism) had greater reduction in LDL cholesterol levels compared to those with AA genotypes (51, 52).

Kinesin-like protein 6 is a member of the molecular motor superfamily and is a protein involved in the intracellular transport of different molecules, including mRNA. Some studies have found an association between the rs20455 polymorphism in the kinesin-like protein 6 (KIF6) (Trp719Arg) gene and coronary artery disease, and also a protective effect of statin administration in Trp719Arg carriers (53, 54). Unfortunately, a meta-analysis of 19 studies did not replicate the association between the kinesin-like protein 6 (KIF6) Trp719Arg polymorphism (rs20455) and nonfatal coronary artery disease (55).

The calmin gene polymorphism (rs8014194) explained only 1% of the variability in statin response. Carriers of this polymorphism in the calmin gene had a significantly greater reduction in total cholesterol compared with noncarriers (56).

APOE gene is polymorphic with three common alleles: e2, e3 (wild-type) and e4. Several studies demonstrated an association between e2 carriers and an increased reduction in low-density lipoprotein, reduced nonfatal myocardial infarction and mortality compared with the e4 when treated by lipid-lowering therapy, but the other studies did not find significant associations (57). The first genome-wide association study (GWAS) on statin effects showed a significant association between the APOE polymorphisms and low density lipoprotein cholesterol (LDL-C) lowering (58), but a recent meta-analysis did not confirm this association (59).

Several pharmacogenetic studies examined the gene encoding the cholesterol ester transfer protein (CETP) involved in cholesterol metabolism and, in particular, the TaqIB variant (rs708272). Patients with a B1B1 genotype on statin treatment showed lower progression of CAD than B2B2 carriers. Boekholdt et al. (60) in their meta-analysis did not find an interaction between the TaqIB polymorphism and pravastatin treatment. On the contrary, Regression Growth Evaluation Statin Study (REGRESS) reported possible pharmacogenetic interactions between the CETP polymorphism and statin treatment, and found significantly higher 10-year mortality in statin-treated male patients carrying the B2 allele, compared with the B1B1 genotype (61).

We can expect that in the future the mechanism of statins' action will be fully explained, for instance, the variability in response. A recent GWAS identified new loci that influence lipid concentration and can be associated with statin therapy (62).

Angiotensin-converting enzyme inhibitors

ACE inhibitors are routinely used in patients with cardiovascular and renal disorders. There are interindividual differences in response to equivalent doses of ACE inhibitors. The polymorphisms related to the ACE gene result in the presence (I) or absence (D) of a 287 bp product (Alu) in intron 16. It accounts for approximately 50% of the genetic variance in serum ACE levels. Mean ACE activity concentrations in DD carriers are around twice those found in II carriers. The ACE DD genotype is associated with higher circulating levels of angiotensin II involved in peripheral vasoconstriction, aldosterone secretion, pressure responses, renal tubular sodium transport, norepinephrine release from sympathetic nerve endings and inactivation of bradykinin, a vasodilator and natriuretic substance (63).

The effect of the ACE I/D polymorphism was examined in patients treated with ACE inhibitors. The study of Bleumink et al. (64) tested the possible interaction of ACE inhibitors in patients with hypertension and the ACE I/D polymorphism in incident heart failure and death, and found that the ACE D allele was associated with less long term benefit from treatment with ACE inhibitors. This suggests that ACE inhibitors may be less effective in patients with a DD genotype or that higher doses of ACE inhibitors should be applied to ACE DD patients compared with ACE II patients to exert similar benefit of this therapy.

The clinical application of ACE gene polymorphisms has been tested on diuretics. In the Sciarrone et al. (65) study, the ACE D/D genotype was associated with a reduced response to hydrochlorothiazide, which could have been expected considering the polymorphism's net effect on sodium may counterbalance the pharmacologic effect of the diuretics on inhibiting sodium reabsorption.

There are other candidate genes for the pharmacogenetics of ACE inhibitors that have been analyzed, including angiotensinogen (AGT) and angiotensin II receptor types I and II (AGTR1 and AGTR2). Angiotensinogen 235Met/Thr polymorphism is also

associated with renin–angiotensin system activity and drug responses. In 634 middle-aged subjects on ACE inhibitor monotherapy with 235Thr allele the response is higher than in the control group. Carriers of the T235 allele had higher systolic and diastolic blood pressures (BP) and the likelihood of using two or more antihypertensive medications was 2.1 times higher (66). Ten years later, Schelleman et al. (67, 68) in two different cohorts of the Rotterdam study (4097 subjects/4097 subjects) analyzed the Met235-Thr (rs699) polymorphism of AGT. In the first study, the Thr allele increased the risk of MI and stroke in ACE inhibitor users, while in the second study the risk of myocardial infarction was increased in current use of ACE inhibitors with the MT or TT genotype compared to ACE inhibitors with the MM, but significant drug–gene interaction was not found on the risk of stroke in ACE inhibitor users or between current use of beta-blockers and the AGT M235T polymorphism on the risk of myocardial infarction or stroke.

Some studies examined the association of the angiotensin AT1 receptor (AGT1R) gene polymorphisms and ACE inhibitor therapy. Angiotensin AT1 receptor mediates the major biological actions of angiotensin II. The 1166C allele of AGT1R has been associated with increased arterial responsiveness to angiotensin II in ischemic heart disease and increased aortic stiffness in hypertension. During ACE inhibitor treatment, reduction in aortic stiffness was reported to be three times greater in carriers of the 1166C allele than in 1166A homozygotes (69, 70). Su et al. found that AGT SNP rs7079 (C/T) SNP (3'-untranslated region) and AGTR1 haplotypes are associated with BP reduction in response to ACE inhibitor therapy in hypertensive Chinese patients and could serve as genetic markers for prediction of the hypertensive response to therapy with ACE inhibitors (71).

Schelleman et al. (72) investigated the interaction between ACE inhibitors or beta-blockers and the ACE I/D polymorphism or AGTR1 573C/T (rs5182) polymorphism and its influence on the risk of myocardial infarction or stroke. The risk of myocardial infarction was reduced in current users of ACE inhibitors with at least one copy of the AGTR1 573C allele compared to ACE inhibitors with the AGTR1 573TT genotype.

Perindopril Genetic Association study (PER-GENE) (73) evaluated 12 genes from the pharmacodynamic pathway of ACE inhibitors with the main aim – prediction of the outcome of treatment with these drugs. A total of 8907 patients with stable coronary artery disease treated with perindopril or placebo were included. Results of the PERGENE study indicated that carriage of three or more risk alleles of rs275651 A>T (AGTR1), rs5182 C>T (AGTR1), and rs12050217 A >G (bradykinin type I receptor) were significantly associated with increased risk of myocardial infarction, cardiovascular mortality, and

resuscitated cardiac arrest during follow-up. In this way, persons who do not have benefit from therapy would not take ACE inhibitors.

Beta-blockers

Beta-blockers through binding to β-adrenergic receptors (BAR) subtype 1 and 2 antagonize the binding of endogenous agonists. Major indications for drug administration are: cardiac arrhythmias, heart failure, hypertension, stable angina pectoris and acute myocardial infarction. There is evidence about interindividual variability in the response to beta-blockers administration. The literature data suggest that beta-blockers are cardiovascular drugs that are closest to the clinical utility of pharmacogenetics. Variations in the genes involved in the synthesis of proteins for the beta-1 and beta-2 adrenergic receptors (ADRB1, ADRB2), and the gene that codes for associated regulatory proteins such as G protein-coupled receptor kinase 4 and 5 involved in signal transduction (GRK4, GRK5) could influence the treatment outcome.

Two functionally important polymorphisms have been identified in the beta-1 adrenergic receptor (ADRB1) gene. A common polymorphism Arg389Gly (rs1801253) is a critical point for G protein coupling, until the Ser49Gly polymorphism (rs1801252) that is located on the extracellular region of the receptor is connected with a higher activity of the receptor and greater desensitization and downregulation with long-term stimulation. Arg389Gly polymorphism in the ADRB1 gene affects the patient's response to beta-blockers therapy. A few studies found that 389 Arg carriers exhibit markedly greater heart rate and blood pressure reductions, significantly greater improvement in left ventricular ejection fraction in response to beta-blockers compared to Gly 389 carriers in healthy volunteers, patients with hypertension, patients with systolic heart failure (74, 75).

Two functionally important polymorphisms have been identified in the beta-2 adrenergic receptor (ADRB2): Arg16Gly (rs104213) and Gln27Glu (rs1042714). A third polymorphism in ADRB2 was also identified, Thr164Ile (rs1800888). Most studies did not show association between the two common polymorphisms in the ARDB2 gene (Arg16Gly (rs104213) and Gln27Glu (rs1042714)) and improvement in left ventricular ejection fraction in response to beta-blockers (76, 77). Only small studies associated the Glu27 allele with increased left ventricular ejection fraction after beta-blocker treatment compared with the Gln27 allele.

G protein–coupled receptor kinase (GRK) family members may account for some of this variability. GRKs are a family of serine/threonine kinases that phosphorylate activated G protein–coupled receptors (GPCR), leading to subsequent receptor desensitiza-

tion, deactivation and endocytosis (78). GRK5 phosphorylates and attenuates the function of beta-1-AR and beta-2-AR and genetic variants of GRK5 can influence the functions of these two receptors. Gln41Leu polymorphism was described in GRK5. It was shown that patients receiving beta-blockers with the Gln41Gln genotype but Leu41 carriers exhibited improvement in survival compared to Glu41 carriers (79). The other larger study did not confirm this (80).

The presence of GRK4 variant alleles may be an important determinant of blood pressure response to atenolol and risk for adverse cardiovascular events. Data from the Vandells et al. (81) study suggest that 3 nonsynonymous polymorphisms in GRK4 (R65L, A142V, and A486V) diminish BP response to atenolol. The associations with GRK4 variant alleles were stronger in patients who were also ADRB1 389R homozygotes, suggesting a potential interaction between these two genes. Few studies examined the association of a deletion polymorphism in the presynaptic alpha 2C-adrenergic receptor gene ADRA2C and response to beta-blockers. Patients with heart failure and Del322–325 genotype have worse outcome (82).

Many beta-blockers are metabolized predominantly by hepatic CYP2D6. Polymorphisms in the gene coding for the CYP2D6 isoenzyme may also affect beta-blocker response, especially metoprolol. Oral bioavailability increases 2–4-fold in CYP2D6 poor metabolizers resulting in greater reductions in blood pressure and heart rate (83). Atenolol and carvedilol are minimally metabolized by CYP2D6 and could be alternative treatments for CYP2D6*4 carriers with metoprolol-induced bradycardia.

These data suggest differential responses to beta-blockers by genotype that include blood pressure response, improvement in left ventricular ejection fraction and survival differences in hypertension and heart failure. Dose adjustments should be considered in heart failure patients.

Diuretics

There is evidence that the alpha-adducin (ADD1) gene might influence the response to low-ceiling diuretics. Adducin modulates the surface expression of some pumps and transporters, such as sodium pump, Na^+-H^+ exchanger and Na^+-K^+-Cl^- cotransporter (84). A missense point mutation substituting thymine (T) for guanine at position 614 of α-adducin-gene results in wild type Gly (G) $\rightarrow$ Trp (W) alteration of α-subunit at amino acid 460. It influences changes in the structure of the submembrane cytoskeleton, that result in increased reabsorption of sodium in the proximal renal tubules, increase intravascular volume and cause high blood pressure. Hypertensive patients carrying at least one 460W-allele have a less steep pressure natriuresis slope compared with hypertensive patients who are homozygous for the 460G wild-type allele. In an observational study, Psaty et al. (85) examined the influence of the alpha-adducin genotype on long term patient outcomes in 1038 hypertensive patients treated with a variety of antihypertensive drugs. They reported that in W-allele carriers (38% of the population) the administration of hydrochlorothiazide halves the incidence of acute myocardial infarction or stroke compared with other antihypertensive treatments that produce a similar blood pressure reduction. However, Davis et al. (86) found no significant drug–gene interaction on the risk of cardiovascular disease in a trial setting. Three studies demonstrated a greater blood pressure reduction in response to hydrochlorothiazide among carriers of the ADD1 460W allele compared with the carriers of the ADD1 460G allele (87–88).

Conclusions

Pharmacogenetics aims to maximize the benefits and minimize the risks of cardiovascular drug treatment. Before the clinical implementation of pharmacogenetics, we must have consistent interpretation of pharmacogenomic test results, availability of clinical guidelines for prescribing based on test results, and knowledge-based decision support systems. It can be validated for each therapeutic indication and in different racial and ethnic groups. Given the fact that high throughput genotyping becomes less expensive, every patient can have their SNP profile. On the other hand, the FDA is very interested in new drug labeling. In the near future, we can expect that the general protocols will be replaced by individual treatment for each patient in the spirit of the concept of personalized medicine.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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