PHARMACOGENOMIC DETERMINANTS OF RESPONSE TO CARDIOVASCULAR DRUGS

Karmen M. STANKOV1,2, Bojan G. STANIMIROV1,3 and Momir M. MIKOV1,3

Summary
Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. Despite considerable advances in cardiovascular pharmacology, significant inter-individual variability in response to drugs affects both their efficacy and safety profile. Drug-gene associations have emerged as important factors determining a spectrum of response to therapy. Pharmacogenomic interactions in cardiovascular medicine are also involved in etiology of adverse effects that may be life-threatening, such as statin-induced myopathy or a hemorrhage/thrombosis event during anticoagulant therapy. Introduction of genetic tests prior to the initiation of therapy and implementation of genetically-guided therapy represent a step forward to achieving a goal of individualized medicine in cardiology, already present in recommendations for warfarin and clopidogrel. However, further investigations addressing genomic predictors of variability in response to drugs are still needed and translating these findings into routine clinical practice remains a substantial challenge.

Key words: Cardiovascular Agents; Pharmacogenetics; Individualized Medicine; Treatment Outcome; Drug-Related Side Effects and Adverse Reactions; Practice Guideline; Polymorphism, Genetic; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Thienopyridines; Warfarin; Adrenergic beta-Antagonists; Angiotensin-Converting Enzyme Inhibitors; Anti-Arrhythmia Agents; Genetic Testing

Introduction
As a leading cause of morbidity and mortality, cardiovascular diseases represent one of the most pervasive and expensive disorders worldwide [1]. Significant inter-individual variability in response to cardiovascular drugs affects both their efficacy and safety profile [2, 3]. This may occur as a result of either perturbations in drug pharmacokinetics or pharmacodynamics. Various factors underlie the inter-individual variability to therapy, including clinical (age, comorbidities, pregnancy, etc.), environmental (drug-drug and drug-food interactions) and genetic factors, including intestinal microbiota composition [4, 5]. Pharmacogenomics is a discipline that studies the genetic determinants of individual variation in response to a given drug, aiming to facilitate the personalization of ther-

Sažetak
Kardiovaskularna oboljenja predstavljaju vodeći uzrok morbidi-teta i mortaliteta širom sveta. Upkros značajnom napretku u ra-zvoju kardiovaskularnih lekova, pojava interindividuale razlike u odgovoru na terapiju utiče i na efikasnost i na bezbednosni profil ovih lekova. Genetski polimorfizmi predstavljaju značajan faktor koji utiče na odgovor na primenu lekova. Farmakogenetske interakcije u kardiovaskularnoj medicini se često nalaze u osno-vi neželjenih dejstava koja mogu biti potencijalno fatalna kao što je statinima indukovanom miopatijama, krvarenje ili tromboembolijski događaji tokom terapije antikoagulantnim ili antiagregacionjim agensima. Izvođenje genetskih testova pre primene lekova i implementacija terapijskih smernica u skladu sa farmakogenet -skin profilom predstavlja korak napred ka dostizanju personali-zovane terapije u kardiologiji, a već je prisutno u smernicama za terapiju varfarinom i klopidogrelo. Međutim, neophodna su dalja istraživanja u definisanju genetskih prediktora koji utiču na terapijski odgovor, uz brojne faktore koji utiču na brzinu transla-cije ovih rezultata u svakodnevnu kliničku praksu.

Ključne reči: Kardiovaskularni lekovi; Farmakogenetika; Individualizovana medicina; Ishod lečenja; Komplikacije i neželjeni efekti izazvani lekovima; Vodiči u praksi; Genetski polimorfizmi; Statin; Klopidogrelo; Varfarin; Beta blokatori; ACE inhibitori; Antiaritmici; Genetsko testiranje

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Corresponding Author: Prof. dr Karmen M. Stankov, Medicinski fakultet, 21000 Novi Sad, Hajduck Veljkova 3, E-mail: stankov_karmen@uns.ac.rs
Relevance of Pharmacogenomics in Cardiology

Abbreviations

- ABCBI – ATP binding cassette sub-family B member 1
- ACE I/D – Angiotensin converting enzyme insertion/deletion
- ACEI – Angiotensin converting enzyme inhibitors
- ACS – Acute coronary syndrome
- ADR – Adverse drug reaction
- CPLIC – Clinical Pharmacogenetics Implementation Consortium
- GWAS – Genome-wide association studies
- HMGCR – 3-hydroxy-3-methylglutaryl-coenzyme A reductase
- INR – International normalized ratio
- OATP1B1 – Organic Anion Transporting Polypeptide 1B1
- PCI – Percutaneous coronary intervention
- RAAS – Renin-angiotensin-aldosterone system
- SLCO1B1 – Solute carrier organic anion transporter family, member 1B1
- SNP – single nucleotide polymorphism
- TdP – Torsade de Pointes
- VKORC1 – Vitamin K-epoxide reductase subunit 1
- DNA – deoxyribonucleic acid
- LDLc – low-density lipoprotein cholesterol
- CYP – cytochrome P 450

A Brief Review of Commonly Used Terminology

The deoxyribonucleic acid (DNA) sequence represents the unique genotype of an individual, whereas a trait resulting from the protein product encoded by the gene is a phenotype. The genotype is formed from two alleles per autosomal gene, one maternal and one paternal. Heterozygotes possess two of the same alleles, while heterozygotes possess two different alleles. A haplotype is a combination of alleles or polymorphisms at nearby locations on a chromosome that are inherited together. The most common allele in population is referred to as the wild-type allele. Several types of genetic variations are relevant to pharmacogenomics. The most common form is single nucleotide polymorphism (SNP), a substitution of a single DNA base pair within a genome. SNPs may occur within introns, the regions that are not translated to messenger ribonucleic acids (RNA) and proteins. However, SNPs also occur within exons, the protein-coding regions of the gene, in which they do not cause an alteration of the amino-acid sequence in protein (synonymous polymorphisms), or SNPs lead to a change in amino-acid sequence (non-synonymous polymorphisms) [9]. The identification of genomic variation can be performed by focused studies of genes or genomic regions of interest or through genome-wide association studies (GWAS) that are performed with high-density SNP genotyping platforms in thousands of subjects with important potential to discover the novel genetic associations.

Statins

Cholesterol-lowering agents - statins, the most commonly prescribed class of medicines worldwide, are indicated for both primary and secondary prevention of cardiovascular disease. Their pharmacological action is based on a competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a rate-limiting enzyme in endogenous, hepatic cholesterol synthesis pathway [10]. Besides decreasing cholesterol synthesis, statins up-regulate the hepatic expression of low-density lipoprotein receptor (LDLR), which results in increased clearance of low-density lipoprotein cholesterol (LDLc). Inter-individual variability in the extent of LDLc lowering by statins, resulting in the increased risk of cardiovascular events for the patients with specific genotype despite the multiple dose adjustments, is influenced by genetic heterogeneity. Moreover, genetic variants have been associated with statin-induced myopathy as a serious side effect. Therefore, pharmacogenomics contributes to identification of genetic polymorphisms that may influence the pharmacokinetics and pharmacodynamics of statin therapy, being relevant to the efficacy of treatment, prevention of adverse drug reactions as well as for the patient’s compliance [11].

Simvastatin, atorvastatin and lovastatin are inactivated by cytochrome P 450 (CYP3A4); therefore, polymorphisms in gene encoding this enzyme modify the pharmacokinetics of these statins and affect the dosing requirements. The carriers of loss-of-function allele variant, CYP3A4*22, require only 20–60% of the statin dose compared to the non-carriers taking stable doses of atorvastatin, simvastatin, or lovastatin for the optimal lipid control [12]. About 7% of Caucasian population possess at least one CYP3A4*22 allele [13]. Genetic variation of HMGCR can also result in significantly attenuated responses to statin pharmacotherapy. H7 haplotype of HMGCR, including three intronic SNPs: rs17244841, rs3846662, and rs17238540, is thought to be involved in production of HMGCR isoform through alternative splicing of transcript. The rs# code refers to the unique identification number for genetic polymorphism recorded in SNP Database, maintained by the National Centre for Biotechnology Information (NCBI) in collaboration with the Human Genome Research Project and the 1000 Genomes projects have profound impact on our knowledge of genetic architecture and polymorphisms in the human genome. The translation of genetic association to clinical practice has been generally slow and its impact is most profound in the field of oncology [6–8]. However, the substantial progress in cardiovascular pharmacogenomics during the past decade improved our understanding of genetic determinants influencing the response to certain cardiovascular medicines including statins, warfarin and clopidogrel, enabling the realization of the vision of genomics-based healthcare and personalized medicine.
Carriers of H7 haplotype have an attenuated reduction of LDLc following simvastatin and pravastatin therapy; however, this effect was not observed in studies with other statins [15]. Another HMGCR haplotype, H2 (rs3846662), as well as L5 haplotype of LDLR, diminish the sensitivity to statins, particularly in African population. Genetic variations in apolipoprotein-E (haplotypes e2, e3, and e4 defined by two SNPs: rs7412 and rs429358) have been shown to attenuate the statin effectiveness [16, 17].

Solute carrier organic anion transporter family, member 1B1 (SLCO1B1) gene encodes the statins influx transporter, an organic anion-transporting polyepptide 1B1 (OATP1B1). Regarding the statin adverse effects, the pharmacogenomic association of greatest magnitude found so far is between SLCO1B1 non-synonymous SNP polymorphism rs4149056 and statin-induced muscle toxicity [521C>T, Val174Ala amino-acid change from valine to alanine, defining SLCO1B1*5 variant). The association between SLCO1B1*5 polymorphism and muscle toxicity exists for multiple statins (such as pravastatin and pitavastatin); however, the evidence is strongest for simvastatin, whereas the currently available data do not support the clinical translation of SLCO1B1*5 for the prediction of atorvastatin- or rosuvastatin-induced myopathy [19]. The rs4149056 polymorphism causes the perturbation of the OATP1B1 localization in the cell membrane of hepatocytes reducing its transport activity, which consequently results in increased plasma concentration and systemic exposure of simvastatin, thus leading to the increased risk of muscle toxicity [13]. Fifteen percents of the population are the carriers of rs4149056 and 60% of patients with myopathy have been shown to be the carriers of risk allele [20]. Since the OATP1B1 transports statins from the circulation into the hepatocytes, representing the primary cholesterol-lowering site of statins action, this polymorphism has been expected to result in lower statin efficacy. However, significant reductions in efficacy have not been reported yet. In addition, some statin-treated patients develop an immune-mediated necrotizing myopathy that continues even after discontinuation of statin. This myopathy is characterized by forming HMGCR auto-antibodies. This sub-phenotype of myopathy has been associated with HLA-DRL*11:01 polymorphism [21].

Based on the highly prevalent use of simvastatin, Clinical Pharmacogenetics Implementation Consortium (CPIC) generated the guidelines in October 2014 with clinical recommendations regarding the implementation of genetic information on SLCO1B1 genotype in order to reduce the potential risk of myotoxicity and to guide the therapeutic decisions in rs4149056 carriers. For patients with a modest risk, the recommendations include the use of lower doses of simvastatin and routine creatine kinase monitoring. If myotoxicity occurs or desirable LDLc level is not achieved, the use of an alternative statin is recommended [22].

**Warfarin**

Being the most frequently prescribed oral anticoagulant agent worldwide, warfarin is widely used in the treatment and prevention of thrombo-embolic events. Warfarin is administered as a coumarin-derived racemic mixture that antagonizes vitamin K-epoxide reductase subunit 1 (VKORC1) and inhibits the activation of vitamin K-dependent coagulation factors II, VI, IX and XI. The degree of anticoagulant action is monitored by measuring the international normalized ratio (INR); however, due to significant inter-individual dose-response variability and narrow therapeutic window, the INR is frequently outside the target therapeutic range, which increases the risk of thromboembolism and bleeding [23]. Clinical factors such as age, weight, diet and interacting drugs account for 26% of inter-individual therapeutic dose warfarin variability [24]. However, clinical factors associated with genetic factors are considered to be implicated in 60% of warfarin maintenance dose variability [25]. Genetic polymorphisms at three loci have been associated with variable response to warfarin dosing [26].

CYP2C9 enzyme catalyzes the predominant reaction of hydroxylation, which results in the transformation of more active enantiomer S-warfarin into an inactive metabolite. CYP29C genotype accounts for up to 10% of warfarin dosing variability [27]. More than 30 allelic variants of CYP2C9 gene are recognized. Two most common minor loss-of-function allele variants in Caucasian population are CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) with frequencies of 0.13 and 0.07, respectively [23]. CYP2C9*2 and CYP2C9*3 polymorphisms result in the production of proteins with enzymatic function reduced by 40 and 90%, respectively [28]. This results in the prolonged half-life of warfarin, elevated warfarin concentrations and increased susceptibility to hemorrhagic complications during treatment. A large meta-analysis confirmed that, compared to wild-type homozygotes (*1 allele), the heterozygous carriers of CYP2C9*2 and CYP2C9*3 need reduction in warfarin dosing by 19% and 33%, respectively, whereas in homozygous carriers even great-
er dose reductions are required, up to 36% and up to 78%, respectively, in order to achieve a steady state [29]. Since CYP2C9 is also responsible for the bioactivation of losartan and other angiotensin-receptor blocking agents, the presence of loss-of-function alleles could also result in reduced anti-hypertensive effects [30].

VKORC1 is a rate limiting enzyme of vitamin K cycle which converts the oxidized, inactive form of vitamin K into the active form, and represents a pharmacological target of warfarin. SNPs in the non-coding promoter region of VKORC1 gene, rs9923231 (-1639G>A) and rs9934438 (-1173C>T) result in reduced promoter activity, decreased enzyme expression and lower warfarin dose requirements [23]. On the other hand, several rare non-synonymous VKORC1 polymorphisms resulting in a changed amino-acid protein sequence confer warfarin resistance, thus resulting in higher dose requirements to achieve the stable anticoagulation.

CYP4F2 also metabolizes the reduced, epoxide form of vitamin K to an inactive form, hydroxy-vitamin K. GWAS have identified a non-synonymous polymorphism rs2108622 (1297G>A, Val433Met) as a predictor for higher warfarin dose requirement [31].

Despite six decade-long clinical experience, warfarin has been identified as the second leading cause of drug-related emergency room visits due to its ADRs: thrombo-embolism and hemorrhage. Numerous warfarin dosing algorithms that include genetic information (predominantly CYP2C9, VKORC1) with or without CYP4F2 have been designed and clinically evaluated in order to facilitate the clinical implementation of genetic information [32]. The International Warfarin Pharmacogenetics Consortium (IWPC) pharmacogenetic algorithm is one of the high-performing and validated algorithms, recommended by the CPIC guidelines, with the aim to predict warfarin dose based on available information on genomic variation [23]. Patients may benefit from incorporation of pharmacogenomic information into the warfarin dosing algorithms by reducing the time to achieve the initial therapeutic and stable INR values, optimizing time spent within therapeutic range and reducing ADRs. The ongoing clinical trials aimed at genotype-guided dosing will provide more clinically-relevant information.

**Clopidogrel**

Clopidogrel is a second generation thienopyridine. Its active metabolite binds to P2Y12 receptors located on the platelet membrane and antagonizes the adenosine diphosphate-mediated platelet aggregation throughout their life time. As a pro-drug, clopidogrel undergoes multiple bioactivation processes mediated by CYP1A2, CYP3A4/5, CYP2B6, CYP2C9, and CYP2C19 enzymes to generate pharmacologically-active metabolite. Clopidogrel is indicated in the prevention of thrombo-embolic events including myocardial infarction and stent thrombosis. However, cardiovascular events occur in 12% of patients with acute coronary syndrome (ACS) on clopidogrel. Considerable inter-individual variability in its anti-platelet response has been shown to be associated with certain genotypes [33].

Polymorphisms in CYP2C19 are associated with decreased or increased function of this enzyme, which is mainly responsible for clopidogrel bioactivation. The most common loss-of-function SNP defining CYP2C19*2 variant (rs4244285; 681G>A) is associated with the reduced enzymatic activity and subsequently impaired clopidogrel activity [34]. Carriers of this polymorphism have a significantly increased risk of adverse cardiac events, particularly the stent thrombosis following percutaneous coronary intervention (PCI), compared to non-carriers (*1/*1) [35]. The risk is high for heterozygous genotype variant carriers (*1/*2, “intermediate metabolizers”), which is found in 25%, and even higher in homozygous allele carriers (*2/*2, “poor metabolizers”) which was found in 2% of Caucasian population [36]. Other loss-of-function alleles including CYP2C19*3 (rs4986893), CYP2C19*4 (rs28399504), and CYP2C19*5 (rs72552267) have minor allele frequency in Caucasians. On the other hand, CYP2C19*17 variant (rs12248560; -806C>T) is the most frequent polymorphism that results in enhanced transcription and increased enzymatic activity [36]. Carriers of this allele, the so called “ultra-rapid metabolizers”, have an increased risk of hemorrhage [37].

Another significant polymorphism that affects a response to clopidogrel treatment represents a variant of ABCB1, gene encoding P-glycoprotein - an extensively distributed efflux transporter with broad substrate specificity. Common 3435 C>T polymorphism in ABCB1 gene (rs1045642) has been associated with reduced intestinal absorption and bioavailability of clopidogrel, and higher rates of adverse cardiovascular outcomes, particularly in homozygous TT carriers [38]. Moreover, a missense Gln192Arg variant of paraoxonase-1, an enzyme responsible for bioactivation of clopidogrel, is thought to be associated with a higher risk of stent thrombosis [39]. Carboxylesterase-1 is an enzyme responsible for inactivation of clopidogrel’s active metabolite. Non-synonymous minor allele variant Gly143Glu (rs71647871) impairs the catalytic activity of this enzyme, resulting in a higher level of clopidogrel active metabolite [40].

Although a routine CYP2C19 genotyping in clinical practice for clopidogrel therapy was not recommended by the American Heart Association consensus guidelines due to insufficient amount of convincing data, CYP2C19 genotyping should be considered in the patients believed to be at high risk to have poor prognosis (e.g. patients undergoing PCI for extensive coronary ischemic disease) before introducing clopidogrel therapy [41]. According to CPIC guidelines, the patients with ACS managed with PCI and available CYP2C19 genotype status should be administered an alternative antiplatelet therapy (prasugrel or ticagrelor) if loss-of-function
CYP2C19 allele is present [36]. Investigators at Vanderbilt University have already described the program implementing the pre-emptive CYP2C19 genotyping in candidate patients for clopidogrel therapy [42].

**Beta–Adrenergic Antagonists**

Beta–adrenergic antagonists (β-blockers) are indicated for the management of numerous conditions including hypertension, angina pectoris, ACS, arrhythmias and heart failure. β-blockers act by antagonizing the endogenous catecholamine action at β-adrenergic receptors, β1 and β2 receptor subtypes being the most important for cardiovascular pharmacology. Inter-individual variability in response to β-blocker therapy has raised the question of genetic components associated with β-blocker response.

Two common non-synonymous polymorphisms in β-1-adrenergic receptor gene, ADRB1: rs1801252 (Ser49Gly), and rs1801253 (Arg389Gly) result in the modulation of β-blocker action. Arg389 variant common in Caucasian population is associated with enhanced agonist-mediated G-protein-coupled signaling and provides increased β-blocker responsiveness. In patients with heart failure, homozygous carriers of this polymorphism, therapy with β-blockers (carvedilol, metoprolol, and bucindolol) has been shown to result in a significantly greater improvement in the left ventricular ejection fraction compared to non-carriers [43]. Similarly, improved anti-hypertensive response to β-blockers has been reported among homozygous carriers of rs1801253 [25].

Two common polymorphisms in β-2-adrenergic receptor gene, ADRB2: rs1042713 (Arg16Gly), and rs1042714 (Gln27Glu) result in the resistance to agonist-mediated down-regulation; however, the majority of studies have not confirmed the associations between these polymorphisms and clinical outcomes so far [19].

Common deletion in α2C-adrenergic receptor gene, ADRA2C (ADRA2C Del 322-325), results in the loss of four amino-acids. Patients with heart failure, carriers of this genotype have been found to have worse disease-related outcomes [44]. However, carriers of this genotype have a greater improvement of left ventricular function during treatment with metoprolol but not with bucindolol [45].

Several β-blockers, including propranolol, metoprolol, timolol, and carvedilol, are metabolized by CYP2D6, whose loss-of-function polymorphisms are common among Caucasian population. Polymorphisms underlying a poor metabolizing phenotype have been shown to result in significantly elevated plasma concentrations of metoprolol, potentiating its hypotensive effects and increased risk of bradyarrhythmias [46]. On the other hand, carvedilol is also CYP2D6 substrate; however, clinical effects have not been observed in poor metabolizers; therefore, it is not necessary to consider dose adjustments in these patients [25]. The United States Food and Drug Administration (FDA) recommendations suggest that caution should be exerted among heart failure patients treated with β-blockers who are the carriers of CYP2D6 loss-of-function polymorphism in order to avoid adverse drug reactions [47].

**Angiotensin-Converting Enzyme Inhibitors**

Angiotensin-converting enzyme inhibitors (ACEI) antagonize the renin-angiotensin-aldosterone system (RAAS) and are indicated in the therapy of hypertension, chronic heart failure, ACS and diabetic nephropathy. A common polymorphism in ACE gene, an insertion/deletion (ACE I/D) within intron 16 (rs4646994) correlates with plasma enzyme levels [48]. An observational study reported a significantly higher mortality risk among homozygous carriers of D allele (D/D) compared to those with I/I genotype [49]. However, neither of these findings were replicated in other prospective studies nor the pharmacogenomic interaction between ACE I/D polymorphism and ACEI therapy has not been confirmed so far. Other candidate genes in RAAS have been examined; however, only two polymorphisms in angiotensin-II receptor type I and one in the bradykinin type-1 receptor gene were associated with beneficial effects during therapy with perindopril [50]. A rare adverse drug reaction following therapy with ACEI is angioedema, which manifests in 0.1-0.7% of population, most commonly long after ACEI initiation. A recent GWAS found no significant SNP associations for ACEI-induced angioedema [51]. Furthermore, no association between ACE I/D genotype and ACE-induced cough has been found in recently performed meta-analysis [52]. Due to the insufficiency and inconsistency of the results, there is no clear candidate gene of RAAS for clinical implementation of routine pharmacogenomic testing.

**Antiarrhythmics**

Drug-induced ventricular arrhythmias are unpredictable and present the potentially fatal adverse drug reactions. Antiarrhythmic drugs act by perturbing the cardiomyocytes repolarization and causing prolongation of QT interval, which may be associated with an increased risk of developing the malignant arrhythmia Torsade de Pointes (Tdp). Tdp is a common cause of drug relabeling and withdrawal. Most drug induced-TdPs are related to antiarrhythmic drugs including amiodarone, flecainide, and sotalol, as well as to non-cardiovascular drugs such as erythromycin, domperidone, and chlorpromazine. In addition to clinical factors including electrolyte imbalances, co-medication or cardiac disease, multiple polymorphisms in at least 13 genes encoding ion channels or proteins that modulate channel function significantly contribute to inducing prolonged QT interval and TdPs [53]. Non-synonymous SNP in gene that encodes the potassium channel subunit, potassium voltage-gated channel subfamily E member 1 (rs1805128), leads to an amino acid substitution from aspartic acid to asparagine at position 85 of the translated protein (Asp85Asn; D85N). This polymor-
phism, relatively common in population (minor allele frequency 1-2%), has been associated with significantly increased risk of TdPs [54]. In addition, SNP polymorphism in nitric oxide synthase 1-adapter protein, rs10919035, a protein which interacts with neuronal nitric oxide synthase and accelerates cardiac repolarization, increases the risk for amiodarone-induced TdPs [55].

Conclusion

Introduction of genetic tests prior to the initiation of therapy and implementation of genetically-guided therapy represents a step forward to achieving a goal of individualized medicine in cardiology, providing a potential to identify the patients who are likely to respond to therapy but who require lower or higher doses, as well as the patients who should be given an alternative therapy (those likely to be non-responders and those at an increased toxicity risk). This approach is already present in recommendations for warfarin and clopidogrel. Despite the increasing number of established drug-gene associations, further investigations addressing genomic predictors of variability in response to drugs are still needed and substantial challenge remains in translating these findings into routine clinical practice. Incorporation of pharmacogenomic research findings into clinical practice and development of evidence-based guidelines represent the fundamentals of personalized therapy concept, enabling clinicians to individualize cardiovascular drug therapy based on anticipated response of the patient.

References


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