Applied Pharmacogenomics in Cardiovascular Medicine

Peter Weeke¹,² and Dan M. Roden¹

Peter Weeke: peter.e.weeke@vanderbilt.edu; Dan M. Roden: dan.roden@vanderbilt.edu

¹Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee

²Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark

Abstract

Interindividual heterogeneity in drug response is a central feature of all drug therapies. Studies in individual patients, families, and populations over the past several decades have identified variants in genes encoding drug elimination or drug target pathways that in some cases contribute substantially to variable efficacy and toxicity. Important associations of pharmacogenomics in cardiovascular medicine include clopidogrel and risk for in-stent thrombosis, steady-state warfarin dose, myotoxicity with simvastatin, and certain drug-induced arrhythmias. This review describes methods used to accumulate and validate these findings and points to approaches—now being put in place at some centers—to implementing them in clinical care.

Keywords

personalized medicine; genetics; polymorphisms; clopidogrel; warfarin; statin

INTRODUCTION

Half of all Americans take at least one prescription drug monthly (1). Variability in efficacy is nearly universal across drugs. Also variable is susceptibility to serious adverse drug reactions (ADRs), which have been implicated as a leading cause of death in the United States (2).

Pharmacogenomics is the science of understanding interindividual variation in drug response as a function of underlying genetic architecture. The field has its roots in traditional translational medicine—identifying the mechanisms of unusual responses to drug therapy in individual subjects. Recent advances in informatics, genetics, and sequencing throughput are increasing our understanding of the molecular, cellular, and genetic determinants of drug responses and hold the promise of realizing a vision of genome-enabled healthcare. Furthermore, discovery of genetic variants that modulate human physiology or drug
response can point to targets for development of new drugs. These advances are having an impact across multiple disciplines in medicine (see sidebar, Pharmacogenomics Beyond the Heart); the present review describes progress in understanding genomic variability in response to commonly used cardiovascular drugs (Figure 1), and how this knowledge may be used in clinical care.

PRINCIPLES

Hippocrates stated that “when a patient’s unique idiosyncrasia is known, then it is feasible to custom tailor the treatment” (3). Rather than a “one size fits all” approach, personalized medicine involves a tailoring of diagnostic and treatment strategies based on individual patient characteristics. Clinicians have been personalizing care for centuries in response to features such as patient attitudes, age, comorbid conditions and therapies, and educational levels. A modern vision of personalized medicine builds on these principles and incorporates genetic information into clinical decision making to improve the precision, safety, and efficacy of drug therapy.

Common modulators of variable drug responses include genes affecting a drug’s plasma or tissue concentrations (pharmacokinetics) or its effects (pharmacodynamics). In addition, variation in specific genes involved in the disease being treated can also affect drug outcomes. Two approaches are commonly used to identify the contribution of underlying genetic variation to a given drug-response phenotype. The first, a hypothesis-driven “candidate gene” approach, is one in which an understanding of underlying pharmacokinetics or pharmacodynamics drives selection of specific genes and variants to be tested for association with the variable drug response. The second, an agnostic “hypothesis free” approach, interrogates large sets of genomic variants without regard to a priori knowledge and tests these for association with the drug response. The most widely used hypothesis-free approach is the genome-wide association study (GWAS), in which a large number (now usually >1,000,000) of common single-nucleotide polymorphisms (SNPs) are genotyped in hundreds or thousands of patients and the association with a phenotype such as drug response analyzed. The emerging approach of resequencing whole genes, pathways, or genomes may identify rarer SNPs and other genetic variants associated with drug response.

ANTITHROMBOTICS

Warfarin

The widely used vitamin K antagonist warfarin is administered as a racemate, and the more potent (S)-enantiomer is bioinactivated by the cytochrome P450 (CYP) enzyme CYP2C9. Carriers of common CYP2C9 SNPs that reduce enzymatic activity require lower average warfarin dose requirements (4, 5). In Caucasians, two common loss-of-function polymorphisms in CYP2C9 are associated with impaired ability to metabolize warfarin (~30% impairment with *2, rs1799853 and ~90% with *3, rs1057910) compared with the *1 reference allele (6). Moreover, a higher risk of bleeding and lower warfarin dose requirements have been reported in carriers of the *2 or *3 alleles compared to noncarriers (5, 7, 8).
Vitamin K epoxide reductase subunit 1 (encoded by *VKORC1*) is the target protein with which warfarin interacts to produce its therapeutic effect. Two common SNPs, rs9923231 (−1639G>A) and rs9934438 (−1173C>T), located in the promoter region of the gene and in almost perfect linkage disequilibrium in Caucasians, modulate hepatic *VKORC1* mRNA transcript abundance, and individuals with lower *VKORC1* expression require lower warfarin dosages to achieve stable anticoagulation, whereas individuals with SNPs leading to greater expression require greater steady-state dosages (9–13). Up to 60% of the variability in a steady-state warfarin dose requirement can be explained by clinical factors plus common variants in *CYP2C9* and *VKORC1*. In addition, rare *VKORC1* polymorphisms that cause a change in the amino acid sequence of the protein (“nonsynonymous polymorphisms”) are associated with increased warfarin dose requirements (14).

Warfarin pharmacogenomics also highlights the critical role of ancestry in drug responses. Steady-state doses are generally lower in Asian subjects largely because the *VKORC1* reduced-function variants are common, whereas greater dosages are required in African subjects because increased-function *VKORC1* promoter variants are more common. In addition, *CYP2C9* *2/*3 variants are less common in subjects of African descent and thus explain less of the overall dosing variability in these subjects than in Caucasians; other *CYP2C9* SNPs (*CYP2C9* *5, *6, *8, and *11) may contribute in African subjects (15).

GWAS have also implicated the V433M variant in *CYP4F2* as an independent predictor of warfarin dosing variability (16, 17). *CYP4F2* catalyzes the metabolism of reduced vitamin K by removing vitamin K from the vitamin K cycle and acts as a counterpart to *VKORC1* in limiting excessive accumulation of vitamin K (18).

Two small randomized controlled trials (RCTs) (19, 20) and a nonrandomized cohort study using historical controls (21) have provided evidence of improved outcomes such as time to steady-state dosing when genetic information is incorporated into prediction algorithms compared to standard dosing (21–24). The National Heart Lung and Blood Institute has completed enrollment in COAG, an RCT comparing warfarin outcomes in patients treated conventionally and those treated with a pharmacogenomically driven algorithm; initial results should be available in late 2013 (25).

Newer factor Xa and direct thrombin inhibitors have been developed to improve efficacy, reduce bleeding risk, and increase convenience of dosing by eliminating a need for dose adjustment. One of these, dabigatran, is a prodrug bioactivated by carboxylesterase, and an analysis of genomic data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial has implicated a common variant in carboxylesterase 1 (*CES1*, rs2244613) as a modulator of bleeding risk (26).

**Clopidogrel**

Clopidogrel (Figure 2), widely used in diverse settings including percutaneous coronary intervention (PCI), is a prodrug that requires hepatic biotransformation via multiple CYPs, notably CYP2C19, to form the pharmacologically active metabolite(s) that binds irreversibly to the adenosine diphosphate receptor encoded by *P2RY12*, thereby inhibiting platelet aggregation (27).
Genetic variation within *CYP2C19* is consistently associated with variable clopidogrel response (28). The strongest evidence is related to the common loss-of-function allele *CYP2C19*\(^*2\) [681 G>A, rs4244285, which encodes a cryptic splice variant with no enzymatic activity in vivo (29)]. *CYP2C19*\(^*2\) is associated with impaired clopidogrel bioactivation (30–32), decreased antiplatelet activity (30, 33–36), and increased risk of adverse cardiac events (31, 37–41). A large meta-analysis (31) identified an increased risk of major adverse cardiovascular events in carriers of the *CYP2C19*\(^*2\) variant undergoing PCI. Carriers of the *CYP2C19*\(^*2\) allele had a greater risk of the composite endpoint of cardiovascular death, myocardial infarction, and stroke [heterozygous carriers: hazard ratio (HR)=1.55, 95% confidence interval (CI) 1.11–2.17; homozygous carriers: HR=1.76, CI 1.24–2.50] (39). The risk of in-stent thrombosis was especially increased [heterozygous carriers: HR=2.67, CI 1.69–4.22; homozygous carriers: HR = 3.97, CI 1.75–9.02]. Although this and some other studies have reported findings suggestive of a graded gene-dose relationship between the number of *CYP2C19*\(^*2\) alleles and the risk of sustaining a cardiovascular event (31, 36, 37), others have not replicated the finding; this may reflect small study numbers, since homozygotes for the *2 allele are uncommon (~2%) in Caucasian populations (42, 43). Another large meta-analysis included more subjects but with diverse indications for clopidogrel, and did not identify a strong signal with *CYP2C19*\(^*2\) (44). One possibility is that the effect of the drug is greatest in patients undergoing PCI, and therefore the effect of genomic variation is also most easily detected in this group (45). A GWAS in a large Amish population estimated that inhibition of platelet aggregation by clopidogrel was ~75% heritable but that *CYP2C19*\(^*2\) accounted for only ~12% of the overall variation in platelet aggregation among clopidogrel-treated subjects (36). The extent to which the *3 (rs498693), *4 (rs28399504), and *5 (rs72552267) alleles contribute is unknown; these loss-of-function alleles have minor allele frequencies (MAFs) below 1% in Caucasians, but *3 is common in Asian populations (MAF 2%–9%). The *17 (rs1248560) variant has been implicated as a gain-of-function allele, and carriers exhibit increased CYP2C19 activity, greater platelet inhibition, and possibly increased bleeding risk (46, 47). Variants in *ABCB1* and *P2YR12* (see Figure 2) have been associated with variable clopidogrel responsiveness, but the findings have been inconsistent or not reproduced. One very small study also associated *PON1* variants with impaired clopidogrel response, but multiple other reports have failed to replicate this finding (48).

In 2010, the US Food and Drug Administration (FDA) revised the clopidogrel label to include a black box warning of decreased efficacy in *CYP2C19*\(^*2\) homozygotes. However, an American College of Cardiology/American Heart Association task force decided not to recommend routine *CYP2C19* testing (49), arguing the evidence was insufficient. Recognizing that genetic testing—including preemptive testing described below—is becoming increasingly widespread, the Clinical Pharmacogenetics Implementation Consortium (CPIC) provides guidelines, including for clopidogrel (48), on how to treat patients in whom genetic-variant data have already been obtained (Table 1).

**CHOLESTEROL-LOWERING THERAPY**

There is substantial interindividual variability in response to treatment with 3-hydroxy-3-methylglutaryl HMG-CoA reductase (HMGCR) inhibitors, commonly known as statins. One-
third of statin-treated patients do not obtain clinically desired reductions in low-density lipoprotein cholesterol (LDLc) (50). In addition, rare severe adverse drug reactions can occur (51). Important factors affecting statin outcomes include genetic variability, as well as environmental factors and compliance (52).

Variability in Statin Response

Variants in HMGCR and LDLR have been associated with a decrease in LDLc lowering (53–56). Variation in other genes has also been associated inconsistently with variability in statin responsiveness. These include APOE, encoding a protein that interacts with the LDL receptor; CYP3A4, encoding a key drug metabolizing enzyme; and ABCB1 and ABCG2, encoding drug transporters. Multiple reports associated a missense variant, Trp719Arg (rs20455), in kinesin-like protein 6 (encoded by KIF6) with increased risk of coronary events, improved LDLc response to pravastatin, and a ~30% reduction in relative risk of cardiovascular events compared to noncarriers who were also treated with pravastatin (57, 58). However, these associations have been questioned (59, 60). Rare variants in PCSK9 have been associated with low LDLc and decreased coronary disease, and the protein is now being targeted to develop new cholesterol-lowering agents (61).

The most common ADR during statin therapy is muscle pain or myalgia (1%–5%), which is sometimes accompanied by increases in plasma creatine kinase (CK) levels. True statin-induced rhabdomyolysis is much rarer (incidence~ 1/1,000,000) and carries a 10% mortality rate (52, 62). Risk factors include high statin doses (e.g., 80 mg/day simvastatin), drug interactions, and genetic factors. Early candidate studies implicated variants in CYP3A5 (63) and SLCO1B1 (64). SLCO1B1 encodes the polypeptide organic anion transporter OATP1B1, involved in hepatic statin uptake (52). A GWAS that compared 85 individuals who developed myalgia and elevated CK while on high-dose simvastatin (80 mg/day) to 90 controls tolerating high doses identified a signal at genome-wide significance for a SNP near SLCO1B1 that was in linkage disequilibrium with rs4149056, a previously studied nonsynonymous variant resulting in V174A (65). In an additive model, heterozygous carriers of the rs4149056 risk allele had an odds ratio (OR) of 4.5 (CI 2.6– 7.7) per risk allele for developing myalgia over five years and homozygous carriers had an OR of 16.9 (CI 4.7–61.1), compared to noncarriers. Sixty percent of the myalgia risk identified was attributable to rs4149056, and most cases occurred in the first year of treatment. Subsequently, rs4149056 was also shown to influence simvastatin adherence, suggesting that some patients stop the drug due to myalgia (66). In 2011 the FDA announced an update to the simvastatin product label recommending that the 80-mg/day dose not be used because of the risk of myalgia.

Given the FDA warning against high-dose simvastatin unless the patient has tolerated >12 months of treatment, which is when the majority of simvastatin-related myalgia is encountered, routine screening for V174A prior to simvastatin initiation seems impractical. However, if genotype information is available before simvastatin initiation, the CPIC recommends that CK levels be monitored among heterozygous and homozygous risk allele carriers in conjunction with a reduced simvastatin dose (20 mg/day) (67). Alternatively,
carriers should be placed on another statin, as the evidence is strongest regarding simvastatin (68).

### β-Blockers

Two common nonsynonymous polymorphisms in the β-1-adrenergic receptor gene (ADRB1), resulting in S49G (rs1801252) and R389G (rs1801253), are associated with the clearest evidence for modulating β-blocker action (69). In vitro, G49 is more susceptible to agonist-promoted downregulation than S49 (70), and the R389 form of the receptor couples more efficiently to G protein than does the G389 variant (71, 72). In vivo, one study reported that homozygous carriers of the R389 genotype experienced greater improvements in left ventricular ejection fraction following β-blocker therapy (carvedilol and metoprolol) than did individuals with other genotypes (73). Improved outcome in R389 homozygotes was also reported in the β-Blocker Evaluation of Survival Trial (BEST), a large study of bucindolol in heart failure patients (74, 75). As a result, a superiority trial designed to assess the safety and efficacy of bucindolol in ~3,200 homozygous R389 heart failure patients is planned. Improved antihypertensive response to β-blockers was also reported among homozygous R389 carriers (76, 77).

The β-2-adrenergic receptor is encoded by ADRB2. Two common ADRB2 polymorphisms, R16G (rs1042713) and Q27G (rs1042714), are resistant to agonist-mediated downregulation (78). Associations between common ADRB2 polymorphisms and altered clinical cardiovascular outcomes have been reported but have not been replicated (79, 80).

CYP2D6 metabolizes some commonly used β-blockers (e.g., propranolol, timolol, and metoprolol) and propafenone, an antiarrhythmic with β-blocking properties. There are many loss-of-function variants in the gene, and individuals who carry two loss-of-function alleles, ~7% of Caucasians and Africans, are termed poor metabolizers. Rarer individuals carry multiple functional copies of the gene and are termed ultrarapid metabolizers, and the remainder are extensive metabolizers. Poor metabolizers have higher metoprolol and propafenone concentrations than extensive metabolizers (81), a difference associated with increased risk for bradyarrhythmias or bronchospasm. There is some evidence that the poor metabolizers may be at increased risk for ADRs (82), and the FDA has added a statement to the metoprolol and carvedilol labels to this effect.

G protein–coupled receptor kinases (GRKs) desensitize β-adrenergic receptors. The L41Q variant in GRK5 blunts the effects of catecholamines and is associated with improved outcomes in heart failure compared to noncarriers (Q41Q) (83). Although L41 is more common among individuals of African ancestry, the benefit associated with the polymorphism is seen across multiple ancestries (84).

### ANTIHYPERTENSIVES

Among patients treated with angiotensin-converting enzyme inhibitors (ACEi), homozygous carrier status for a common insertion/deletion (I/D) (rs4646994) in ACE has been associated with improved 10-year outcomes compared to noncarriers (I/I), but this association has not been replicated (85, 86). ACEI-related angioedema is commoner in African than in
Caucasian subjects, and initial studies have implicated a variant in \textit{XPNPEP2} (rs3788853, C-2399A), encoding aminopeptidase P (87). Among thiazide users, a common nonsynonymous variant in the adducin gene (\textit{ADD1}, Gly460Trp) has been inconsistently associated with thiazide response (88). Genetic variants producing large signals for variability in responses to antihypertensives have not yet been identified, and so clinical implementation would be premature.

**ARRHYTHMIAS**

Exaggerated drug-induced QT interval prolongation is a predictor of the malignant arrhythmia torsades de pointes (TdP) and is a common cause of drug relabeling or withdrawal. Variation in genes associated with the congenital form of the long QT syndrome (cLQTS) appears overrepresented in acquired long QT cases (89–93). A large candidate-gene study found that the D85N variant in the potassium channel subunit gene \textit{KCNE1} conferred an odds ratio of 9–12 for this ADR (90). Another study implicated variants in \textit{NOS1AP}, a gene known to modulate baseline QT interval, as risk factors for amiodarone-induced TdP (94).

**CONCLUSIONS**

A rapidly growing set of data links genetic variation to variable drug responses. Key factors in establishing the strength of such associations are allele frequency, effect size, and population size (Figure 1). The strongest evidence is obtained when large numbers of subjects are studied, and this may not be possible for some drug-response phenotypes. Establishing an association between a drug response and a genetic variant may be especially problematic if the drug response is uncommon, like some ADRs, and the risk alleles are rare. Most studies to date have concentrated on subjects of Caucasian ancestry, although risk alleles may be different, and have different frequencies, in other ancestries. Once a potential association is identified, replication in larger numbers is desirable; networks using electronic medical records (EMRs) have been proposed as one potential approach (95). The advent of cheap sequencing technologies is showing that most human genetic variants are rare, and establishing the functions of rare variants will be a challenge to genomics and pharmacogenomics going forward.

A very appealing idea is that pharmacogenomic data can be used to individualize therapy. Physicians can select drugs and drug dosages based on anticipated therapeutic responses and risks for ADRs. It has been argued that this approach will be valid only after RCTs demonstrate its utility. A common counterargument is that for many decisions in clinical medicine, such as adjusting the dose of a renally excreted drug in a patient with renal dysfunction, RCTs have never been done to demonstrate utility; furthermore, expecting an RCT for each of hundreds or thousands of potentially actionable variants is unrealistic.

Logistics and cost are also considerations. Obtaining a genotype relevant to a single drug when that drug is prescribed may add considerably to the cost for all patients prescribed the drug, to potentially benefit only the few who carry a risk allele. An alternative is a preemptive strategy, such as the Vanderbilt PREDICT project (96). The idea is first to
identify subjects who are “at risk” for receiving drugs that have clinically important variable effects due to genetic variants. Efforts to identify subjects at risk can use informatics tools developed by examining large numbers of subjects (96) or can simply use the disease being treated, e.g., subjects about to undergo joint replacement are “at risk” for receiving warfarin and subjects about to have coronary arteriography are “at risk” for receiving clopidogrel. Once subjects are identified, they are genotyped on a platform that includes many pharmacogenomic variants relevant to many drugs, and the data are stored in a genetic archive. Those variants with the strongest levels of evidence (determined by CPIC guidelines and institutional oversight) are displayed in the EMR, and informatics-based decision support is delivered when a patient with a relevant genetic variant is prescribed a target drug. As new evidence accumulates, more drug-gene pairs are deployed from the archive into the EMR. This preemptive approach has the potential advantages of bringing down costs and recognizing that pharmacogenomic considerations will not be relevant for most patients receiving most drugs but that all patients carry potentially deleterious alleles, some of which will be highly relevant to some drugs.

New sequencing technologies have brought the cost of sequencing whole genomes below $2,000, but how to use these data to better care for patients is an ongoing question (97). Although it seems likely that drug therapy will be one of the first areas to benefit from this genomic revolution, continued rigorous scientific discovery in individual subjects, families, and large cohorts remains the major challenge and opportunity in the field.

Acknowledgments

DISCLOSURE STATEMENT

Work on this review was supported in part by a grant from United States Health Services U19 HL065962. Peter Weeke is funded by an unrestricted grant from the Tryg Foundation (J.nr. 7343–09, TrygFonden, Denmark).

Glossary

ADR       adverse drug reaction

CPIC      Clinical Pharmacogenetics Implementation Consortium

References


Anna Rev Med. Author manuscript; available in PMC 2014 July 04.
*3 require lower steady-state dosages and have an increasing risk of bleeding during long-term therapy; the latter observation remains unexplained.


The scenarios outlined here for cardiovascular therapies are being repeated across multiple disciplines: varying levels of evidence and replication, common variants with modest to large effects, rarer variants with very large effects. HLA-B variants conferring high risk for serious adverse drug reactions have now been identified for allopurinol, carbamazepine, and abacavir. Cancer is a disease of genomic instability, and variants in tumor genomes are serving not only as biomarkers for prognosis but also as targets for new drugs that can provide surprising efficacy. Tumor genotyping is becoming standard of care for drug selection in certain cancers. The influence of the microbiome on development of a range of diseases—cancer, atherogenesis, obesity, and asthma and other immune conditions, to name a few—is only now being appreciated and exploited for individualized therapy. Pharmacogenomics is emerging from its adolescence and is poised to contribute to improved drug therapy across medicine.
SUMMARY POINTS

1. Interindividual variability in drug response exists for all types of drug therapy.
2. For some drugs, single common variants with large effect sizes contribute to variable drug actions.
3. Polymorphisms in CYP2C19 modulate cardiovascular outcomes, particularly risk of instent thrombosis, among patients undergoing treatment with clopidogrel.
4. Polymorphisms in VKORC1 and CYP2C9 modulate steady-state warfarin dose requirements.
5. Polymorphisms in SLCO1B1 are associated with myotoxicity among simvastatin-treated patients.
6. Genotyping for common variants modulating drug response is entering practice at some centers.
7. Pharmacogenomic signals may represent potential targets for drug discovery.
FUTURE ISSUES

1. Response to drug therapy is multifactorial. Examples to date focus on single common variants, and the warfarin example shows that variants in more than one gene can be analyzed. How can we predict the effects of multiple variants, especially if they have directionally differing predicted effects?

2. Serious adverse drug reactions are uncommon, and risk alleles may have large effect sizes but be rare. Thus, methods to accrue enough samples to identify these variants need to be refined.

3. The randomized controlled trial (RCT) is the gold standard for defining efficacy of new drugs or therapeutic approaches. However, RCTs in pharmacogenomics require participation by many subjects in order to identify the few who carry variants being evaluated. It seems unrealistic to propose RCTs for hundreds of target variants. Although potential advantages of implementation may seem self-evident, hidden risks (e.g., withholding an effective drug) also need to be evaluated. Thus, the optimal way in which to evaluate the utility of pharmacogenomic implementation remains in flux.
Figure 1.
The continuum from initial scientific discovery to evidence development and consolidation, with the ultimate goal of implementing new knowledge in clinical care. The position of the arrows is a rough indicator of progress for each of the listed drug responses. Abbreviations: LDLc, low-density lipoprotein cholesterol; ACEi, angiotensin-converting enzyme inhibitor.
Figure 2.
Pharmacogenomic basis for variability in clopidogrel action. (a) There is variability in the extent to which ADP results in platelet aggregation at baseline (left). With exposure of platelets to clopidogrel (right), the effect of ADP is blunted as expected, but variability in response persists. Reproduced from Reference 36 with permission. (b) Potential genetic mechanisms underlying variability in clopidogrel action. Clopidogrel is a prodrug and undergoes bioactivation in the liver using the enzymes shown, notably CYP2C19. The active metabolites interact with the ADP receptor on platelets to inhibit ADP-induced
platelet aggregation. (c) Data on distribution of loss-of-function variants (predominantly CYP2C19*2) in a cohort of 12,451 subjects in the Vanderbilt PREDICT program described in the text.
## Table 1
Genotype-phenotype assignment and suggested clinical implications of common *CYP2C19* variants for clopidogrel therapy (adapted from Reference 46 with permission)

<table>
<thead>
<tr>
<th>Carrier genotype</th>
<th>Inferred metabolizer phenotype</th>
<th>Implication</th>
<th>Clinical Pharmacogenetics Implementation Consortium guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/*2, *2/*3, *3/*3</td>
<td>poor</td>
<td>significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>*2/*2: prasugrel or other alternative therapy unless clinically contraindicated</td>
</tr>
<tr>
<td>*1/*2, *1/*3</td>
<td>intermediate</td>
<td>increased residual platelet aggregation;</td>
<td>*1/*2: prasugrel or other alternative therapy unless clinically contraindicated</td>
</tr>
<tr>
<td>*1/*1</td>
<td>extensive</td>
<td>normal platelet inhibition and residual platelet aggregation</td>
<td>standard dosing of clopidogrel</td>
</tr>
<tr>
<td>*1/*17, *17/*17</td>
<td>ultra-rapid</td>
<td>increased platelet inhibition; decreased residual platelet aggregation;</td>
<td>standard dosing of clopidogrel</td>
</tr>
</tbody>
</table>