
CARDIOVASCULAR DRUGS AND THE GENETIC RESPONSE

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Abstract

The emergence of personalized medicine mandates a complete understating of DNA sequence variation that modulates drug response. Initial forays have been made in the cardiac arena, yet much remains to be elucidated in the pharmacogenetics of cardiac drugs. Most progress has been made in describing DNA sequence variation related to the anticoagulant warfarin and the antiplatelet drug clopidogrel. This includes a description of DNA sequence variation that underlies pharmacokinetic and pharmacodynamic variability, the impact of such variation on predicting hard outcomes, and the ability of genotype-guided prescription to facilitate rapid titration to a therapeutic range while avoiding unnecessary high plasma levels. Nuanced prescription will require a complete inventory of DNA sequence variants that underlie drug-related side effects.

Introduction: Cardiovascular Drugs and the Genetic Response

Recent advances have been made in defining DNA sequence variations that modulate one's response to drug administration. Much of this information has been clarified with respect to warfarin, an anticoagulant, and clopidogrel, an antiplatelet agent. This includes identification of single nucleotide polymorphisms (SNPs) that affect drug metabolism, an analysis to enable prediction of clinical outcomes in prospective settings, and a description of how genotype-directed prescription could potentially decrease the frequency of drug-related adverse events.

Information has been garnered with respect to polymorphisms that increase individual susceptibility for drug-related side effects (Table 1). One such example is the description of a polymorphism in the ion transporter *SLCO1B1* that increases the probability of statin-induced myopathy by at least one order of magnitude.¹

- Clopidogrel alleles of the cytochrome P450 system, particularly allele CYP2C19*2.
- Warfarin alleles of the cytochrome P450 system, particularly CYP2C9*2 and CYP2C9*3, and alleles of the gene *VKORC1*.
- Statin therapy allele of the *SLCO1B1* gene, in particular rs4149056C.

Table 1. Pharmacogenetic variants under assessment in the clinical arena.

The Pharmacogenomics of Clopidogrel

STARS demonstrated the efficacy of dual antiplatelet therapy following coronary artery stenting.² Studies such as CAPRIE have also demonstrated its efficacy as a single-agent therapy.

The thienopyridines exert their effects by antagonizing the

ADP receptor of the P2Y₁₂ subtype. Through a series of oxidative steps, clopidogrel is metabolized to its active form—the first of which leads to formation of 2-oxo-clopidogrel and the second to the active metabolite. Studies have indicated that cytochromes P450 1A2, P450 2C9, and P450 2C19 are involved in the first step while cytochromes P450 3A4, P450 2C9, P450 2C19, and P450 2C19 are involved in the second. While cytochrome P450 2C19 is involved in both steps, cytochrome P450 3A4 is the major enzyme responsible for conversion to its active metabolite. There exists evidence that paraoxonase 1 may also be involved in transforming 2-oxo-clopidogrel to its active metabolite.

Mega et al. hypothesized that patients taking clopidogrel who were also carriers of polymorphisms in cytochrome P450 carry an increased risk of ischemic events.⁷ These authors assessed the effects of functional polymorphisms in cytochromes on clopidogrel-mediated platelet inhibition in a small series of healthy subjects. They subsequently genotyped patients who were enrolled in the treatment arm of TRITON-TIMI 38 for polymorphisms in cytochromes P450 2C19, P450 2C9, P450 2B6, P450 3A5, and P450 1A2 and assessed the rate of stent thrombosis in carriers versus noncarriers. They observed that carriers of cytochrome P450 2C19 polymorphisms demonstrated the most profoundly altered pharmacodynamic and pharmacokinetic profiles. Consistent with this, carriers of loss-of-function (LoF) alleles were unique in demonstrating primary endpoint event rates that were statistically significantly different from noncarriers in that carriers of the *2 (rs4244285) LoF allele were found to have primary endpoint event rates that were more frequent (hazard ratio 1.53; 95% CI, 1.07-2.19). Moreover, the frequency of stent thrombosis, an endpoint that carries a high mortality, was significantly higher among carriers of this allele (hazard ratio 3.33; 95% CI, 1.28-8.62). Pare et al. examined the role of the same series of CYP P450 2C19 polymorphisms in the CURE population and was unable to demonstrate a significant effect on outcomes among those taking clopidogrel⁸ as an adjunctive therapy for acute coronary syndromes. It should be

noted that only a minority of patients received coronary stents in this population.

Inconsistent data exists with respect to polymorphisms in ABCB1, an efflux pump involved in clopidogrel transport and bioavailability. While, TRITON-TIMI 38 demonstrated an association between the TT variant and major adverse cardiac events (MACE) but not stent thrombosis,⁹ analysis of the PLATO study was unable to replicate this finding.¹⁰

One study correlated the presence of the PON1 QQ192 with significantly lower PON1 activity, lower levels of clopidogrel active metabolite, attenuated platelet inhibition, and an increased risk of stent thrombosis.¹¹ Subsequent studies have failed to correlate QQ192 with MACE; however, the same studies have demonstrated the association of CYP P450 2C19 *2 allele carriage and adverse events.¹²

While the pharmacogenetics of the newer P2Y12 antagonists such as ticagrelor and prasugrel has not been investigated, it is clear that the efficacy of neither of these agents is affected to the same degree. While data regarding tailored therapy is limited, several studies are underway to assess the role of genotype-tailored therapy in reducing MACE. Until the results of such trials are available, routine genotyping and assessment of platelet function cannot be recommended.

Pharmacogenomics of Aspirin

The definition of aspirin resistance is variable, therefore estimates of its prevalence vary.¹⁴ Aspirin exerts its action by irreversible acetylation of cyclooxygenase-1 (COX-1), inhibiting its activity with a resultant reduction in the production of thromboxane A2. Sequence variation in COX-1 as it relates to aspirin response has been investigated, with studies yielding inconsistent data.^{15, 16} Similar studies have been concluded with respect to SNPs that reside within the glycoprotein IIIa gene. These too have led to contradictory findings.^{17, 18} In a large meta-analysis, however, it was concluded that in healthy subjects the PIA1/A2 variant is associated with aspirin resistance,¹⁹ potentially implying that the effect of this SNP in inhibiting aspirin-mediated platelet inhibition may be reduced by the coadministration of drugs that are commonly prescribed in the context of CAD. Relatively common side effects to aspirin include gastrointestinal hemorrhage and aspirin-induced urticaria. Studies of DNA sequence variants that may alter the frequency of such endpoints have been investigated with variable results.^{19, 20}

The Pharmacogenomics of Warfarin

Warfarin is an effective anticoagulant and has been applied as thrombosis prophylaxis in settings including atrial fibrillation, venous thromboembolic disease, and metallic prosthetic valves. Warfarin acts by inhibiting vitamin K epoxide reductase (VKORC1), the enzyme responsible for maintaining vitamin K in its reduced state. It is under this condition that its catalytic property is preserved; in its oxidized state, it is unable to catalyze the gamma-carboxylation of the vitamin-k dependent clotting factors (II, VII, IX, X) and proteins C and S. Warfarin is metabolized by cytochrome P-450.²²⁻²⁴ Genome-wide association studies (GWAS) have subsequently identified rs2108622 in CYP4F2 to be associated with increased warfarin requirement; other SNPs have not met stringent genome-wide statistical thresholds.²⁵⁻²⁸

In retrospective studies, carriage of the two most common reduced-function CYP 2C9 variants, *2 (rs1799853) and *3

(rs1057910), predisposes one to an increased risk of an out-of-range international normalized ratio (INR), delay in the time-to-therapeutic INR, and increased bleeding.^{29, 30} Carriage of the A allele of VKORC1³¹ and the T allele of CYP4F2³² have been associated with both out-of-range INR and increased time-to-therapeutic INR but not an increased propensity to bleed. Pharmacogenetic-centered modelling has been developed to predict warfarin requirement. Such modelling incorporates CYP P450 2C9 and VKORC1 genotype, smoking status, relevant medications, age, sex, and body mass index.³³ The application of these algorithms has been investigated in several prospective studies demonstrating efficacy.^{34, 35}

Standard dosing regimens have been compared with genotype-guided algorithms. Primary outcomes were the percent out-of-range INRs and time in the therapeutic range at 3 months.³⁶ The combined genotype-guided prescription cohort demonstrated superior outcomes with respect to both primary endpoints—percent out-of-range INRs and time in the therapeutic range at 3 months. Moreover, serious events were significantly less frequent in the genotype-guided cohort (4.5% vs. 9.4% of patients ($P < .001$)).³⁶

Cost-effectiveness analyses need to be undertaken to document broad application of genotype-guided prescription, and they should be done in multiple racial cohorts as variant allele frequencies are disparate among racial groups.³⁰ In the meantime, niche application may be warranted in groups that have high thrombosis risk (e.g., individuals with metallic prosthetic valves) or those who pose elevated bleeding risk (e.g., those who are prescribed dual antiplatelet therapy in concert with warfarin).

Pharmacogenomics of Hydroxymethylglutaryl (HMG) Coenzyme A Reductase Inhibitors and Statin-Induced Myopathy

Hydroxymethylglutaryl coenzyme A reductase inhibitors or statins are frequently prescribed drugs that have been shown to reduce mortality in both primary and secondary prevention settings, as they reduce the frequency of myocardial infarction, cerebrovascular accident, and revascularization procedures by approximately 20% for every 1 mmol/L fall in the level serum low-density lipoprotein.¹ However, there is marked interindividual variability in response to statin administration.³⁷ REGRESS (Regression Growth Evaluation Statin Study) examined the Taq1 B variant in the cholesterol transfer protein and demonstrated that CAD progresses more slowly in individuals with the B2B2 genotype. In B1B1 individuals, however, the response to statin administration is associated with a greater decrease in serum LDL-C. Therefore, while B1B1 individuals carry an elevated baseline coronary risk, this may be offset by an improved response to statins.³⁸ It should be noted that a meta-analysis analyzing patients both with and without antecedent CAD was not able to demonstrate such an interaction with the statin response.³⁹

Ambiguous data exists with respect to the epsilon² variant of the apolipoprotein (APO) E gene and statin response.^{40, 41} A meta-analysis of three GWAS results showed that a SNP in the calman gene was associated with the response to statin therapy,⁴² yet this remains to be confirmed. DNA sequence variation in APOC1, adjacent to APOE, was also associated with the response to statin therapy.⁴²

Kinesin-like protein 6 was associated with improved outcomes in three large randomized controlled trials examining the role of pravastatin treatment.^{43, 44} This improvement in outcomes appeared

to be independent of the lipid-lowering activity of pravastatin. A cross-sectional GWAS found that the relevant SNP (rs20455) was not associated with CAD.⁴⁵ Moreover, a recent meta-analysis combining 19 similar studies did not demonstrate an association with CAD. However, these studies were not designed to evaluate the pravastatin effect.

Statin-induced myopathy is associated with statin administration, although the pathogenesis of this condition is not well understood. The SEARCH trial (Study of the Effectiveness of Additional Reductions of Cholesterol and Homocysteine) was a GWAS that used high-density gene chips to evaluate 85 cases and 90 controls, both of which were prescribed simvastatin. The study showed that a SNP in *SLCO1B1*, which encodes the organic anion-transporting polypeptide OATP1B1, was very strongly associated with statin-induced myopathy.¹ Each copy of the variant allele conferred an odds ratio of 4.5. The odds ratio was 16.9 for homozygotes relative to the non-risk genotype. It was estimated that carriers of the variant allele accounted for 60% of all statin-induced myopathy cases. While the association with simvastatin-induced myopathy has been confirmed, it is not evident among individuals prescribed atorvastatin or pravastatin.⁴⁶

The Pharmacogenomics of Beta-Blockers

Beta-blocker pharmacogenomics has focused on polymorphisms in both the beta-1 and beta-2 receptors (*ADRB1* and *ADRB2*), angiotensin-converting enzyme, and cytochrome P450 2D6.⁴⁷ One study demonstrated that homozygosity for the Arg389 mutation in *ADRB1* was associated with a 3-fold greater response in daytime diastolic pressure following metoprolol administration.⁴⁸ However, the association of *ADRB1* mutations and blood pressure response to other beta-blockers has not been established. Genotype-driven variable response to beta-blockers may help to explain race-specific response to the drug class since the minor allele frequency for these polymorphisms is discrepant between African Americans and Caucasians.⁴⁷ Other genes in beta-blocker response including *ADRB2*, G-protein beta3 subunit gene, and G-protein alpha unit gene have all been analyzed, but a consistent modulation of response to beta-blocker administration has not been demonstrated.⁴⁷ The data with respect to beta-blocker therapy and the modulation of negative chronotropic effect by similar polymorphisms is somewhat underwhelming, where even the codon 389 *ADRB1* polymorphism does not demonstrate consistent effect.^{49, 50}

Since the late 1990s, beta-blockers have been central in the treatment of heart failure and have shown substantial benefits in mortality. Healthy subjects who carry two copies of the variant allele Arg389Gly (rs1801253) in the beta-1 adrenergic receptor have greater chronotropic and blood pressure response following prescription of metoprolol. Consistent with this observation, patients with systolic dysfunction who carry two copies of this variant have greater improvements in ejection fraction after administration of metoprolol than noncarriers. While this has been also demonstrated with carvedilol, it is not the case with bucindolol. Cytochrome P450 2D6 is central in the metabolism of metoprolol and its polymorphisms have a profound influence on metoprolol pharmacokinetics. However, despite a genotype-based change in pharmacokinetic profile, changes in efficacy or the frequency of adverse effects have not been demonstrated.

Thus far, there are certain aspects of beta-blocker pharmacogenetics that provide hope for the future. However, consistent effect, and perhaps a more complete inventory of genetic variation that affects beta-blocker effect, needs to be described before personalized titration of this drug class can take place.

The Pharmacogenomics of Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE inhibitor pharmacogenetics has focused on the insertion/deletion polymorphism (rs4646994), a strong determinant of ACE plasma concentration. However, the GenHAT (Genetics of Hypertension-Associated Treatment) study did not demonstrate association of this polymorphism with MACE.⁵¹ Furthermore, PROGRESS (Perindopril Protection Against Recurrent Stroke Study) did not find an association between the presence of this polymorphism and the risk of MACE, neurological events, or blood pressure response.⁵²

The Rotterdam study reported association of rs699 or Met235Thr in angiotensinogen with myocardial infarction and stroke among ACE inhibitor users.⁵³ However, in a Chinese population, neither blood pressure response nor atherosclerosis risk appeared to correlate with presence of the variant allele.⁵⁴

PERGENE (Perindopril Genetic Association Study) was designed to assess the viability of genetic analysis in the prescription of perindopril and the association of 52 SNPs with predetermined EUROPA endpoints.⁵⁵ This study identified two SNPs in the *AGTR1* gene and one SNP in the bradykinin 1 receptor associated with perindopril treatment benefit, and a genetic risk score combining these SNPs was able to discriminate poor responders. Interestingly, five SNPs in linkage disequilibrium with the ID polymorphism (rs4646994) did not appear to influence response to the drug.⁵⁵

Conclusion

In conclusion, the greatest body of work regarding genome-tailored drug prescription has been performed on the oral anticoagulant warfarin. The use of certain algorithms has demonstrated that tailored prescription after genotyping has led to more effective control of INR and freedom from adverse events. While much has been elucidated with respect to the pharmacogenetics of commonly prescribed agents in the cardiovascular arena, there remains much work to validate the role of genetic testing in drug prescription. A more complete inventory of the genetic variation responsible for the efficacy of drug action and the frequency of adverse events would likely yield data that is more reproducible and therefore of greater clinical relevance.

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