Clinical Application of Cardiovascular Pharmacogenetics

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Pharmacogenetics primarily uses genetic variation to identify subgroups of patients who may respond differently to a certain medication. Since its first description, the field of pharmacogenetics has expanded to study a broad range of cardiovascular drugs and has become a mainstream research discipline. Three principle classes of pharmacogenetic markers have emerged: 1) pharmacokinetic; 2) pharmacodynamic; and 3) underlying disease mechanism. In the realm of cardiovascular pharmacogenetics, significant advances have identified markers in each class for a variety of therapeutics, some with a potential for improving patient outcomes. While ongoing clinical trials will determine if routine use of pharmacogenetic testing may be beneficial, the data today support pharmacogenetic testing for certain variants on an individualized, case-by-case basis. Our primary goal is to review the association data for the major pharmacogenetic variants associated with commonly used cardiovascular medications: antiplatelet agents, warfarin, statins, beta-blockers, diuretics, and antiarrhythmic drugs. In addition, we highlight which variants and in which contexts pharmacogenetic testing can be implemented by practicing clinicians. The pace of genetic discovery has outstripped the generation of the evidence justifying its clinical adoption. Until the evidentiary gaps are filled, however, clinicians may choose to target therapeutics to individual patients whose genetic background indicates that they stand to benefit the most from pharmacogenetic testing. (J Am Coll Cardiol 2012;60:9–20) © 2012 by the American College of Cardiology Foundation

“The right dose of the right drug to the right person” is one of the goals of pharmacogenomics and personalized medicine. The need for pharmacogenomics in clinical practice is underscored, for example, by the improved ischemic outcomes with newer platelet P2RY12 receptor inhibitors which also have higher risk of adverse events compared to clopidogrel (1,2). Therefore, there is a critical need to target therapeutics to individual patients who stand to benefit the most and suffer the least.

Principles of Pharmacogenetics

A prerequisite for pharmacogenetics is heterogeneity in drug response. The definitions of drug response are varied and can include surrogate measurements measured in the laboratory (e.g., international normalized ratio [INR] for warfarin) or clinical endpoints (e.g., stent thrombosis for clopidogrel).

A genetic basis for drug response is suggested when responses are similar within family members (and therefore are heritable) or significantly different in across ethnic backgrounds. Underlying genetic variation can be determined either using a targeted approach where known variants in candidate genes are hypothesized to influence drug response or genome-wide association—an “unbiased” screen for common variants across the entire genome. Rare genetic variants missed by genome-wide association studies (GWAS) can be identified through sequencing candidate genes, exomes, or the entire genome in the case of rare drug-induced adverse events.

Three broad classes of genetic variants influence drug response: 1) pharmacokinetic; 2) pharmacodynamic; and 3) those associated with the underlying disease mechanism (Table 1, Fig. 1). This review will discuss specific drugs, and in each case, we will apply these pharmacogenetic principles followed by potential clinical implications.

Statins

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase [HMGCR] inhibitors) can elicit 4 types (at least) of “responses”: 1) low-density lipoprotein cholesterol (LDLc) lowering; 2) protection from cardiovascular events; 3) musculoskeletal side effects; and 4) statin adherence.

LDLc lowering. The majority of patients respond with 30% to 50% LDLc reduction; however, there is wide (10% to 70%) variation (3). Two loci appear to affect LDLc lowering: HMGCR and APOE (Table 2).

HMGCR. Carriers of a minor haplotype (defined by 3 single nucleotide polymorphisms [SNPs]: rs17244841, rs17238540, and rs3846662) of HMGCR experience a 5%
to 20% reduced LDLc lowering with pravastatin (4) or simvastatin (5) due to an alternatively spliced HMGCR transcript that produces a version of HMGCR that is less sensitive to simvastatin inhibition (6). This haplotype was not identified in a GWAS with atorvastatin (7), and therefore, whether this association holds for other statins is unclear.

**APOE.** Two variants, rs7412 and rs429358, define 3 haplotypes, namely, e2, e3, and e4, that are associated with lipid, cognitive, and thrombotic traits. In general, the magnitude of LDLc lowering is greatest for carriers of e2, followed by e3, and e4 haplotypes, respectively. The influence of APOE haplotypes appears to be consistent across variety of statin types (4,7,8) and doses (8), and results in mild (<15%) attenuations of LDLc lowering.

**Additional loci.** Information on ABCE1 and ABCG2 can be found in the Online Appendix.

**Reduction in cardiovascular events.** Statins prevent cardiovascular disease by lowering LDLc and potential pleiotropic effects. There are few genetic predictors of these pleiotropic benefits, but the rs20455 polymorphism in kinesin-like protein 6 (KIF6, an underlying disease gene) may be a candidate. Carriers of the risk allele may receive a greater benefit from statin therapy compared to noncarriers despite equal LDLc, triglycerides, or C-reactive protein reduction (9,10). However, subsequent genome-wide meta-analysis of large randomized placebo-controlled statin trials found no evidence for association with coronary artery disease (11) or any differential treatment benefit with statin therapy (12,13).

**Statin-induced musculoskeletal side effects.** Statins have a well-defined safety profile, but come with a small risk of musculoskeletal side effects (14). Genetic variants in the hepatic transporter, SLCO1B1, influence the risk of adverse events (Table 2); it does not appear that cytochrome P450 (CYP) SNPs influence statin-induced side effects.

**SLCO1B1.** The solute carrier organic anion transporter family, member 1B1 gene (SLCO1B1, also referred to as SLC21A6, OATP-C, or OATP1B1) harbors many genetic variants, and each variant is numerically and sequentially labeled beginning with the unmutated copy of the gene, *1* (referred to as “star 1”) followed by *2*, *3*, *4*, and so forth. The *5* variant (rs4149056, Val174Ala) interferes with the localization of this transporter to the hepatocyte plasma membrane (15) and leads to higher plasma statin concentrations (16–18). In candidate gene and GWAS, carriers of *5 are at 4- to 5-fold increased risk of severe, creatine kinase (CK)- positive simvastatin-induced myopathy and 2- to 3-fold increased risk of CK- negative myopathy (19,20).

In trials of randomly assigned statins as well as in observational studies, the risk for myopathy with *5 depends on the statin type: the risk is greatest for simvastatin > atorvastatin > pravastatin, rosuvastatin, or fluvastatin (20–23). These effects parallel the influence of the *5 allele on the clearance of these statins (16–18,24) and thus appear to be statin-specific.

**Adherence to statin therapy.** Often, statin therapy is hampered by nonadherence. Although the genetics of adherence to statins has not been studied in any great depth, 2 studies (a clinical trial and observational cohort) observed that carriers of the SLCO1B1*5 allele have a higher rate of statin nonadherence (20,25).

**Clinical implications for statin pharmacogenetics.** It is unlikely that genetic testing for statin efficacy will enter clinical care since the magnitude of associations is small (~10% to 15% differences in LDLc lowering), and physicians can reasonably forecast the magnitude of LDLc lowering based on statin type, dose, and baseline LDLc.

In contrast, statin-induced side effects and nonadherence are less predictable. While the current level of evidence surrounding SLCO1B1*5 may not support prospective genotyping at this time, the test is currently offered on consumer-directed whole genome genotyping platforms (e.g., 23andMe, deCODEMe, and so on). A potential strategy for prospective SLCO1B1*5 testing might offer carriers either pravastatin or rosuvastatin or fluvastatin as first-line

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**Table 1 Sources of Pharmacogenetic Variation**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Types of Genes</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Pharmacokinetic       | Variability in concentration of drug at site of drug effect | Drug-metabolizing enzymes | Warfarin: CYP2C9  
Clodigrel: CYP2C19  
Simvastatin: SLCO1B1  
Metoprolol: CYP206 |
|                       |                                       | Drug transporters                   |                                               |
| Pharmacodynamic       | Variability in drug ability to influence its target | Transmembrane receptors | Clodigrel: P2RY12  
Simvastatin: HMGCR  
Metoprolol: ADRB1 |
|                       |                                       | Intracellular enzymes               |                                               |
| Underlying disease mechanisms | Variability in disease being treated | Often downstream or independent of drug target | Hydrochlorothiazide: ADD1  
Simvastatin: APOE |

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agents, which seem to depend the least on SLCO1B1 for their clearance.

**Thienopyridines**

Thienopyridines are effective in patients with acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI); however, some patients remain at risk for death, myocardial infarction (MI), and stent thrombosis. Platelet function in response to clopidogrel is variable (26), heritable (27), and reduced inhibition predicts future events (28); therefore, clopidogrel is a prime candidate for pharmacogenetics. Clopidogrel pharmacogenetics centers around 2 loci, CYP2C19 (pharmacokinetic) and ABCB1 (pharmacokinetic); other loci, CYP2C9 (pharmacokinetic), PON1 (pharmacokinetic), and P2RY12 (pharmacodynamic) may also influence response (Table 3).

**Platelet function in response to clopidogrel. CYP2C19.** Clopidogrel is an inactive prodrug activated by several enzymes, including CYP2C19, to an active metabolite that inhibits the platelet adenosine diphosphate receptor, P2RY12 (29). CYP2C19 *2 (rs4244285) is the most common reduced-function (RF) variant; additional, rare variants mimic the *2 allele: *3 [rs4986893], *4 [rs28399504], *5 [rs56337013]) (30). An individual person’s genotype can be characterized in 3 ways: 1) presence of at least 1 RF allele (carrier vs. noncarrier); 2) the number of RF alleles (i.e., 0, 1, 2); or 3) the predicted, total CYP2C19 enzymatic activity (Table 4). Carriers of *2—also referred to as intermediate metabolizers or poor metabolizers—produce lower active metabolite and have attenuated platelet inhibition (31). In general, there is a gene-dose effect where increasing number of RF alleles (i.e., 0, 1, 2, or extensive metabolizers, intermediate metabolizers, and poor metabolizers) predicts a decreasing amount of platelet inhibition (27,31,32). Carriers of another variant *17 (rs3758581, ultrametabolizers) exhibit increased CYP2C19 activity, produce more active metabolite, and improved platelet inhibition, in most reports (33,34).

Higher loading and maintenance doses (e.g., 1,200 mg and 150 mg/day) appear, in part, to overcome the effects of the *2 allele (30,32,35,36), although not completely (37), and can require up to 300 mg/day (38). Ticlopidine (39), prasugrel (31,40,41), and ticagrelor (42) all produce uniform platelet inhibition in *2 carriers and noncarriers.

**ABCB1.** The adenosine triphosphate-binding cassette, subfamily B (MDR/TAP), member 1 (ABCB1) gene encodes an apical membrane protein in enterocytes and hepatocytes and serves to reduce bioavailability. Clopidogrel appears to be handled by this transporter, and 3 SNPs—C1236T (rs1128503), G2677T (rs2032582), and C3435T (rs1045642)—capture the common genetic variation at this locus. Persons who carry a T allele at each SNP (i.e., the T-T-T haplotype) produced reduced active metabolite (43) in an initial report. Despite this initial observation, the link to reduced platelet inhibition has been difficult to establish (27,30), although may be present for persons who carry 2 copies of the T-T-T haplotype (44). As with CYP2C19 variants, prasugrel-
induced platelet inhibition is not affected by T-T-T haplotype (44).

**Additional loci.** Using GWAS, investigators have unsuccessfully searched for additional variants for clopidogrel (27). An additional discussion of genetic variation at ABCB1, P2RY12, CYP2C9, and PON1 can be found in the Online Appendix.

**Clinical response to clopidogrel. CYP2C19.** In parallel with the platelet function data, the CYP2C19*2 allele is associated with a graded risk of death, MI, or stroke. Carriers of 1 allele (intermediate metabolizers) have a ~1.5-fold increased risk, and carriers of 2 alleles (poor metabolizers) experience a ~1.8-fold increase. This pattern also extends to stent thrombosis as well with a ~2.6- and ~4-fold increased risk in those with 1 and 2 *2 alleles, respectively (32,45–49). Therefore, the CYP2C19 genetic associations with platelet function are mirrored in the clinical response to clopidogrel in the setting of PCI. These observations formed the foundation for updating the clopidogrel label by the Food and Drug Administration to include pharmacogenetic information. Similarly, the gain of function variant, CYP2C19*17, is associated with increased risk of bleeding (50), and protection from ischemic events (51) CYP2C19*2 carriers treated with prasugrel or ticagrelor do not show a heightened risk of cardiovascular death, MI, stroke, or stent thrombosis (40,52).

**ABCB1.** Carriers of 2 copies of the ABCB1 T-T-T haplotype treated with clopidogrel are at an increased risk for subsequent death, MI, or stroke compared to persons who carried none, thus mirroring the platelet function data (44,45,52). Genetic variation at the ABCB1 locus does not appear to influence prasugrel- or ticagrelor-treated patients (40,52).

**Clinical implications.** The current state of evidence reflects a strong and consistent association with the CYP2C19*2 allele and an increased risk for cardiovascular outcomes in ACS/PCI patients treated with clopidogrel, although not other settings (51). Alternative antiplatelet agents (i.e., prasugrel and ticagrelor) mitigate the adverse risk of CYP2C19*2-associated adverse events. Although CYP2C19 genotyping is commercially available, whether genotype-guided therapy will improve outcomes or reduce costs is unknown. Consensus statements (53) currently do not recommend routine testing. However, there is sufficient evidence to support physicians who may choose to pursue CYP2C19*2 testing in selected patients: 1) for diagnosis in patients with complications of clopidogrel therapy such as stent thrombosis in compliant clopidogrel users; or 2) for the choice of dual antiplatelet therapy in the ACS/PCI setting where the physician believes that additional information regarding the risk/benefit profile for clopidogrel will influence the choice of drug therapy (54). Outside of these scenarios, the ACS/PCI setting, or situations where there are ample data to guide drug choice (e.g., ST-segment elevation MI [55], diabetic patients [56], age >75 years, or prior
transient ischemic attack/stroke), there is minimal rationale to support CYP2C19 testing. Based on the available data, it is reasonable that if a person is found to be a poor metabolizer (Table 4), 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 (57–59). The greatest uncertainty is in the intermediate metabolizer group (i.e., those with 1 loss of function allele) and is where integration of other clinical risk factors such as diabetes, body mass index, cost, and other bleeding and thrombosis risk factors need to be considered in determining the therapy with the optimal risk:benefit profile.

### Aspirin

Aspirin irreversibly inhibits prostaglandin G/H synthase 1 (PTGS1, or COX-1) and the conversion of arachidonic acid to thromboxane. With adequate dosing and compliance, aspirin is capable of completely inhibiting COX-1 in >99% of persons; thus, true “aspirin resistance” is rare (60). However, alternate agonists such as adenosine diphosphate and collagen can produce robust aggregation in the face of complete COX-1 inhibition (61), a response that demonstrates wide interindividual variability (62), heritability (63,64), and at high levels, association with future cardiovascular events (65,66), therefore making aspirin a candidate for pharmacogenetic discovery. Because aspirin uniformly inhibits its target, COX-1, there are no pharmacokinetic or pharmacodynamic genetic considerations. Instead, investigators have focused on platelet function loci (underlying disease) and LPA (underlying disease).

Variants in several platelet genes, namely, PEAR1, ITGB3, VAV3, GPVI, F2R, and GP1BA, are associated with platelet function in response to aspirin (67–70). One with moderate evidence is rs5918 in ITGB3 where carriers of the risk allele have heightened platelet function on aspirin (71–73). Recent GWAS of platelet function in response to aspirin have identified additional genetic loci that have yet to be replicated (74). Finally, the most robust association comes from a large study that found carriers of the minor allele for an intronic SNP, rs12041331, in PEAR1 have higher PEAR1 platelet protein content and heightened platelet function in response to aspirin (75).

The link to an increased risk of clinical events in aspirin users has not been established despite several large studies (76,77), although the PEAR1 variant rs12041331 has not yet been tested. An uncommon variant in LPA (rs3798220) seems to modify the protective effects of aspirin: carriers of the minor allele have a more than 2-fold reduction in the risk for cardiovascular disease with aspirin, whereas noncarriers (>95% of Caucasians) had none in a large placebo-controlled clinical trial (78).

### Clinical implications

Because of the lack of consistent or preliminary associations with the variants described in the preceding text, there is currently no role for genetic testing for aspirin.

### Warfarin

Three loci contribute to the heterogeneity in response: CYP2C9 (pharmacokinetic), VKORC1 (pharmacodynamic), and CYP4F2 (pharmacodynamic) (Table 5).

#### Warfarin dose requirements

CYP2C9. CYP2C9 is responsible for S-warfarin (the more active enantiomer) clearance. The 2 most common reduced-function variants are

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### Table 3

Main Genetic Associations With the Response to Clopidogrel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant(s)</th>
<th>Risk Allele/Haplotype Frequencies</th>
<th>Effect of Variant With Risk Allele</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>*2 (rs4244285)</td>
<td>16% 14% 27% Drug concentration, platelet function, recurrent MI, stent thrombosis/GWAS, DMET, GG</td>
<td>Active metabolite concentration</td>
<td>31,32,45–47,52</td>
</tr>
<tr>
<td></td>
<td>*2/*3/*4/*5/*6 and *1/*17 Intermediate metabolizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*2/*3/*4/*5/*6 Poor metabolizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*2/*3/*4/*5/*6 and *2/*3/*4/*5/*6 Poor metabolizer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*1/*17 or *17/*17 Ultrametabolizer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mi = myocardial infarction; DMET = drug metabolizing enzyme and transporter panel; other abbreviations as in Table 2.

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### Table 4

CYP2C19 Diplotype Classification*

<table>
<thead>
<tr>
<th>Alleles</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1 and *1</td>
<td>Extensive metabolizer</td>
</tr>
<tr>
<td>*2/*3/*4/*5/*6 and *1/*17</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>*2/*3/*4/*5/*6 and *2/*3/*4/*5/*6</td>
<td>Poor metabolizer</td>
</tr>
<tr>
<td>*1/*17 or *17/*17</td>
<td>Ultrametabolizer</td>
</tr>
</tbody>
</table>

*Adapted from Ingelman-Sundberg et al. (147) and Scott et al. (148).
*2 (rs1799853) and *3 (rs1057910). The CYP2C9*2 allele reduces warfarin clearance by 30% and the *3 allele by 90% (79), which translate into 19% and 33% reductions per allele in warfarin dose requirements compared to noncarriers (80).

**VKORC1.** Vitamin K epoxide reductase complex, subunit 1 (VKORC1) is warfarin’s target (81,82), and resequencing this gene identified 2 haplotypes (A and B defined by the alleles at 5 SNPs: rs7196161, rs9923231, rs9934438, rs8050894, and rs2359612) that influence VKORC1 gene expression and predict warfarin dose requirements (83). Of these 5 SNPs, an A allele at rs9923231 (also referred to as −1639 G>A and the 3673 SNP) in the promoter region is responsible for reducing: VKORC1 gene expression (84). Therefore, carriers of an A allele at rs9923231 (or the A haplotype) require a 30% per allele reduction in warfarin dose requirements (85).

**CYP4F2.** Several GWAS have not only confirmed the observations above but also have identified a novel association between rs2108622 in CYP4F2 and reduced hepatic CYP4F2, higher levels of hepatic vitamin K, and higher warfarin dose requirements (86–89). Additional loci. Additional information regarding CALU and GGCX can be found in the Online Appendix.

### Clinical response to warfarin. RETROSPECTIVE STUDIES

Standard dosing algorithms (i.e., a 5 mg or 10 mg loading dose followed by titration based on the INR) lead to an increased risk of an out-of-range INR (>4.0) or a delay in the time-to-therapeutic range INR in carriers of the CYP2C9*2 or CYP2C9*3 alleles (91,92), the A haplotype or A allele of the −1639 SNP in VKORC1 (93), or the T allele in CYP4F2 (94). Importantly, only variants in CYP2C9 have been linked to the risk of bleeding (91,92).

### Prospective studies of tailored warfarin therapy

Small randomized pilot studies, parallel cohort studies, and single arm studies with or without historical controls have prospectively explored genetically guided warfarin therapy. Whereas some studies suggest a benefit over standard therapy (95–97), others failed to show any significant advantage (98) except for smaller and fewer dosing changes and INR measurements (99). Definitive clinical trials are ongoing to assess the benefit of incorporating genetics into warfarin therapy.

### Clinical implications

There are strong genetic associations surrounding CYP2C9, VKORC1, and CYP4F2 variants that influence the response to warfarin. Commercial testing and algorithms that assist in the interpretation of genotypes are available. Therefore, there is evidence to justify and tools to enable genotype-guided warfarin therapy. Until large scale trials demonstrate a benefit for routine testing, physicians may choose to pursue testing in selected patients who feel may benefit by: 1) diagnosing those with complications from warfarin therapy (e.g., hemorrhage); 2) predicting dose for those at high risk of bleeding (e.g., “triple-therapy” with aspirin, clopidogrel, and warfarin); or 3) weighing the costs of newer anticoagulants against warfarin.

### Diuretics

**Blood pressure–lowering response.** The adducin 1 (alpha) gene (ADD1, underlying disease) is implicated in animal and human sodium handling (100), and persons with a Gly460Trp substitution are more salt sensitive and have enhanced blood pressure (BP) lowering with thiazide diuretics (100).

### Clinical outcomes

In an observational study, patients with Trp460 who were treated with thiazide diuretics experienced a greater protection from MI and stroke than patients with Gly460 (101). However, this difference in the protective effects of diuretics could not be replicated in several larger studies (102–104).

### Clinical implications

Given the inconsistent associations and lack of a commercially available test, the use of this genetic variant in guiding treatment options in hypertension is limited.
Beta-Blockers

Beta-adrenergic receptor antagonists (or beta-blockers) are a diverse class of agents that primarily antagonize the beta-1 adrenergic receptor, encoded by \(\text{ADBR1}\). Accordingly, changes in heart rate (HR), BP, and left ventricular ejection fraction (LVEF) are considered the surrogate responses in place of clinical responses such as protection from MI, death, or heart failure. Variation in \(\text{CYP2D6}\) (pharmacokinetic) and \(\text{ADRB1}, \text{ADRB2},\) and \(\text{GRK5}\) (all pharmacodynamic) have received the most attention (Table 6).

**Heart rate and blood pressure reduction. CYP2D6.** Beta-blockers are substrates for CYP, and metoprolol is extensively metabolized by hepatic CYP2D6. The most common RF variant \(\text{CYP2D6}^*4\) (rs3892097) results in the absence of CYP2D6 activity. Carriers have a higher systemic exposure to metoprolol (105), which translates into a greater reduction in HR and BP (106,107). Beta-blockers such as atenolol and carvedilol (108) do not require \(\text{CYP2D6}\) for their metabolism.

**ADRB1.** Ethnic differences in the dose response for propranolol (109) motivated pharmacodynamic genetic investigations of beta-blockers. Two variants in \(\text{ADRB1}\), the Ser49Gly (rs1801252) and Arg389Gly (rs1801253), lead to impaired down-regulation (110) and higher signal transduction, respectively (111). Therefore, carriers of either variant have enhanced, beta-1-receptor activity and more beta-blocker sensitivity. Healthy volunteers and patients with hypertension who carry 2 Arg389 variants have a greater HR (112) or BP (113) reduction mainly with metoprolol, although not with all beta-blockers (114).

In patients with systolic heart failure treated with either metoprolol or carvedilol (115), but not bucindolol (116), carriers of 2 copies of the \(\text{ADRB1}\) Arg389 variant had significantly greater improvements in LVEF compared to the Gly389 carriers.

**ADRB2.** Genetic variation in the beta-2 adrenergic receptor \(\text{ADBR2}\) centers around 2 variants: Arg16Gly (rs1042713) and Glu27Gln (rs1042714). Receptors with Gly16 versus Arg16 have enhanced down-regulation of \(\text{ADBR2}\). In contrast, receptors with Glu27 appear to be resistant to down-regulation (117). Extension to variation in BP or HR lowering in response to beta-blocker therapy has not been demonstrated (114).

**GRK5.** Downstream of the beta-1-adrenergic receptor are G-protein coupled receptor kinases responsible for desensitization of the beta-1-adrenergic receptor. A Glu41Leu genetic variant in 1 of these kinases, G protein-coupled receptor kinase 5 \(\text{GRK5}\), is more prevalent in African Americans. The Leu41 more effectively uncoupled isoproterenol-stimulated responses than GRK5-Q41, thus producing a pharmacological-like “beta-blockade” in mice (118), although with no differences in atenolol-induced HR reduction in humans (119).
Clinical benefit in patients with cardiovascular disease. **ADRB1.** In heart failure patients, when compared to placebo, **ADRB1** Arg389 homozygotes had a greater reduction in the time to first hospitalization or death when treated with bucindolol (116) but not carvedilol or metoprolol (120–125) compared to Gly389 carriers. Whether these differences are due to drug specific effects (i.e., bucindolol vs. metoprolol) or the play of chance has not been adequately tested. In patients with chronic coronary artery disease randomly assigned to verapamil or atenolol, carriers of at least 1 copy of the Ser49/ Arg389 haplotype had a 9- versus 2-fold worsened prognosis when assigned to verapamil versus atenolol (126) despite equivalent BP and HR control in both groups.

**ADRB2.** One study examined the influence of genetic variation at **ADRB2** and its influence on ACS patients and found those homozygous for both the Arg16 and Gln27 alleles had a 20% rate of subsequent death versus 6% of those homozygous for both Gly16 and Gln27 (125). This trend has been observed in some studies of patients with heart failure (124), although not all (122,123,126).

**GRK5.** Extension of the associations of the Glu41Leu variant to clinical outcomes of patients was demonstrated in 1 study where Leu41 carriers exhibited improvement in survival compared to Glu41 carriers (118), although not in another, larger study (121).

**Adverse events.** Metoprolol-induced adverse events (e.g., bradycardia) are associated with CYP2D6*4 in 2 studies, each numbering >1,000 treated patients (127,128), although not in another, larger study (121).

**Clinical implications.** In general, carriers of the Arg389 variant have: 1) enhanced reduction in HR and BP; 2) larger improvements in LVEF; and 3) longer survival when treated with chronic beta-blocker therapy compared to persons with the Gly389 variant. Although it is unlikely that beta-blocker therapy will ever be withheld for carriers of the Gly389 variant, a potential application of these findings would be to consider advanced heart failure therapies (e.g., left ventricular assist devices, biventricular pacing, or transplantation) at an earlier stage in patients with the Gly389 variant.

Because certain beta-blockers such as atenolol and carvedilol are minimally handled by CYP2D6 (131), these may be reasonable alternates for carriers of CYP2D6*4 with metoprolol-induced bradycardia. Commercial testing for CYP2D6*4 is available (e.g., Labcorp).

**Antiarrhythmic Drugs**

**Digoxin and calcium-channel blockers.** Many antiarrhythmics are known ABCB1 (described in preceding text) substrates including verapamil, diltiazem, and digoxin. Genetic variation in ABCB1 is inconsistently associated with altered pharmacokinetic profiles (132–134), and there are no reports of different clinical outcomes.

**Procainamide.** Procainamide is rapidly converted by acetylation into N-acetylprocainamide (NAPA, an active metabolite) by hepatic acetyltransferases (NAT2, primarily). Variability in hepatic acetylation capacity has long been observed (135), and “slow acetylators” produce less NAPA. Common genetic variants that decrease NAT2 activity are *5/rs1801280, *6/rs1799930, *7/rs1799931, and *14/rs1801279 (136,137). Although efficacy does not appear to be related to variation in its pharmacokinetics, the induction of drug-induced lupus-associated autoantibodies (138,139), but not symptomatic, drug-induced lupus (138,139) has been linked to the slow acetylator status.

**Propafenone.** The hepatic hydroxylation by CYP2D6 of propafenone into 5-hydroxypropafenone demonstrates wide interindividual variability (140). Carriers of CYP2D6*4 (a reduced function allele) have reduced propafenone clearance compared to noncarriers (140–142).

**Antiarrhythmic efficacy.** At low doses of propafenone, CYP2D6*4 carriers have greater reduction in exercise- or isoproterenol-induced HR compared to noncarriers (143), although not with higher doses or without the “stress” of exercise/isoproterenol (140,142,143). Further, CYP2D6*4 carriers have enhanced suppression of atrial and ventricular arrhythmias compared to noncarriers in some studies (141,144), although not in all (140,142). Therefore, there are insufficient data to make any conclusions regarding CYP2D6 genotype and antiarrhythmic efficacy.

**Toxicity.** Central nervous system side effects with propafenone, as well as excessive beta-blockade, are correlated with a higher concentration of systemic propafenone and, accordingly, the CYP2D6 genotype (140).

**Clinical implications.** Antiarrhythmic drug pharmacogenetics represents a mixed collection of associations that do not sufficiently translate to consistent associations of meaningful clinical outcomes. Therefore, there is currently no role for pharmacogenetic testing in the clinical use of these medications.

**Future Directions**

The data to date support many common variants that alter the pharmacologic properties of cardiovascular agents. Newer medications such as prasugrel, ticagrelor, and apixaban as well as older medications such as enalapril, spironolactone, and angiotensin-receptor blockers that have variable clinical effects are also candidates for a pharmacogenetic approach. Novel systems approaches may elucidate additional determinants of drug response. Broad “omics” approaches have several advantages over traditional genetics-based research, for example, 1) responding to the environment, and 2) elucidating how the activity of entire pathways, instead of individual genes, influence drug response.

The field of pharmacogenomics would benefit from the development of thresholds of evidence for testing and coverage by insurance. With the expanding number and complexity of “omic” markers of drug response is an equally
profound evidentiary gap between association studies and those that demonstrate clinical utility. It may be unrealistic to wait (or to require) a prospective, events-driven randomized controlled trial of each drug-marker combination. Even when such trials are conducted, the results may be made obsolete by new observations and/or approval of new drugs. Therefore, genetic substudies of clinical trials and registries may become the highest levels of evidence for the potential benefits of using pharmaco genetic testing. Such standards are common in many fields of medicine where there is often a lack of randomized clinical trial data. Observational studies and comparative effectiveness research will lay the foundation for broad-based recommendations and translation of pharmaco genetic observations into a clinical paradigm of personalized medicine to improve health outcomes.

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