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Reviews

Use of Pharmacogenetic Information in the Treatment of Cardiovascular Disease

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BACKGROUND: In 1964, Robert A. O'Reilly's research group identified members of a family who required remarkably high warfarin doses (up to 145 mg/day, 20 times the average dose) to achieve appropriate anticoagulation. Since this time, pharmacogenetics has become a mainstay of cardiovascular science, and genetic variants have been implicated in several fundamental classes of medications used in cardiovascular medicine.

CONTENT: In this review, we discuss genetic variants that affect drug response to 3 classes of cardiovascular drugs: statins, platelet P2Y12 inhibitors, and anticoagulants. These genetic variations have pharmacodynamic and pharmacokinetic effects and have been shown to explain differences in drug response such as lipid lowering, prevention of cardiovascular disease, and prevention of stroke, as well as incidence of adverse events such as musculoskeletal side effects and bleeding. Several groups have begun to implement pharmacogenetics testing as part of routine clinical care with the goal of improving health outcomes. Such strategies identify both patients at increased risk of adverse outcomes and alternative strategies to mitigate this risk as well as patients with "normal" genotypes, who, armed with this information, may have increased confidence and adherence to prescribed medications. While much is known about the genetic variants that underlie these effects, translation of this knowledge into clinical practice has been hampered by difficulty in implementing cost-effective, point-of-care tools to improve physician decision-making as well as a lack of data, as of yet, demonstrating the efficacy of using genetic information to improve health.

SUMMARY: Many genetic variants that affect individual responses to drugs used in cardiovascular disease prevention and treatment have been described. Further study of these variants is needed before successful implementation into clinical practice.

Pharmacogenetics has become a mainstay of cardiovascular science, and genetic variants have been implicated in several fundamental classes of medications used in cardiovascular medicine. In this review we discuss genetic variants that affect drug response to 3 classes of cardiovascular drugs: statins, platelet P2Y12 inhibitors, and anticoagulants. These genetic variations have pharmacodynamic and pharmacokinetic effects and have been shown to explain differences in drug response such as lipid lowering, prevention of cardiovascular disease, and prevention of stroke, as well as incidence of adverse events such as musculoskeletal side effects and bleeding.

HMG-CoA Reductase Inhibitors (Statins)

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) are the most widely used medications for the primary and secondary prevention of cardiovascular disease through the reduction of LDL cholesterol (LDL-c).[3] The clinical response to statins can generally be measured in terms of LDL-c lowering ability and cardiovascular disease (CVD) risk reduction (efficacy) and development of musculoskeletal side effects (toxicity).

LIPID-LOWERING EFFECTS

Reduction in LDL-c in response to statin therapy can range from 10% to 70% among individuals *(1)*. Genetic influences of statin-induced LDL-c lowering have been widely studied through candidate gene, resequencing, and genome-wide association studies (GWASs). Several loci have been associated with LDL-c lowering: apolipo-

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[3] Nonstandard abbreviations: LDL-c, LDL cholesterol; CVD, cardiovascular disease; GWAS, genome-wide association study; apo A, apolipoprotein A; Lp(a), lipoprotein(a); SNP, single-nucleotide polymorphism; GRS, genetic risk score; CK, creatine kinase; CPIC, Clinical Pharmacogenomics Implementation Consortium; CAD, coronary artery disease; ACD, acute coronary syndrome; PCI, percutaneous coronary intervention; ADP, adenosine diphosphate; MI, myocardial infarction; TIA, transient ischemic attack; BMI, body mass index; PT, prothrombin time; INR, international normalized ratio; COAG, Clarification of Optimal Anticoagulation Through Genetics; DOACs, direct oral anticoagulants.

protein E (*APOE*),[4] solute carrier organic anion transporter family member 1B1 (*SLCO1B1*), lipoprotein(a) (*LPA*), and sortilin 1 (*SORT1*); other genes with inconsistent associations with LDL-c response include ATP binding cassette subfamily B member 1 (*ABCB1*), ATP binding cassette subfamily G member 2 (*ABCG2*), and 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*), though these will not be covered here.

APOE encodes a lipoprotein that is a component of many lipid particles. The 2 most studied variants in the *APOE* gene are rs7412 and rs429358, which define 3 haplotypes (ε2, ε3, and ε4). In white patients treated with atorvastatin, patients who were heterozygotes for the rare allele rs7412 (belonging to the ε2 haplotype) experienced a 39.9% lowering of LDL-c compared with 36.4% in individuals with the major allele (belonging to the ε3 haplotype) *(2)*. In another study, patients randomized to receive atorvastatin, simvastatin, or pravastatin showed attenuated LDL-c lowering with the major ε3 haplotype compared with the minor ε2 haplotype: 30% vs 36% *(3)*. The effect of ε3 haplotype could not be overcome by dose escalation: even with maximally prescribed doses of the three statins, ε3 haplotype carriers continued to have diminished LDL-c lowering compared to ε2 carriers: 39% vs 45%. In a metaanalysis of over 38000 patients treated with statins, *APOE* variants in linkage disequilibrium with rs7412 emerged as the most significant in a genome-wide association study, conferring a 5% greater LDL-c lowering compared to noncarriers *(4)*. Finally, a large-scale candidate gene study of 18705 individuals revealed that rs7412 was associated with a near 3% greater reduction of LDL-c per allele in response to simvastatin therapy *(5)*.

Statins are, in part, transported into the hepatocyte from the portal circulation though the hepatic transporter OATP1B1 encoded by the *SLCO1B1* gene (discussed in more detail below). A common genetic variant, *5, in the *SLCO1B1* results in a reduced function version of the transporter that reduces hepatic HMG-CoA reductase exposure to statins, with each copy of the *5 allele conferring a 1%–2% smaller LDL-c lowering compared to noncarriers *(4)*. However, while this result is statistically significant, carriage of the *5 allele is not associated with any heightened risk of cardiovascular events despite mildly higher LDL-c *(6)*.

LPA codes for apolipoprotein A (apo A), which when linked with LDL particles form lipoprotein(a) [Lp(a)]. Lp(a) has been shown in vitro to be both atherogenic and thrombogenic. The rs10455872 and rs3798220 single-nucleotide polymorphisms (SNPs) are independently and strongly associated with the KIV-2 copy number variant in Lp(a), which encodes variability in apo A size and is responsible for approximately 30% of variance in Lp(a) levels *(7)*. Since LDL-c resides (in part) in LP(a) and statins do not lower Lp(a) levels, the component of LDL-c carried by Lp(a) is "statin resistant." Therefore, carriers of *LPA* variants that confer a larger amount of LP(a) have an approximately 5% smaller LDL-c lowering in response to statin therapy *(4)* because the available pool of statin-responsive LDL-c is diminished.

Two variants on chromosome 1p (rs646776 and rs12740374) in close proximity to 3 genes—*SORT1*, cadherin EGF LAG seven-pass G-type receptor 2 (*CELSR2*), and proline and serine rich coiled-coil 1 (*PSRC1*)—were recently identified in a metaanalysis GWAS of 38000 statin-treated patients *(4)*. The rs12740374 variant is an expression quantitative trait locus *(8)* for the 3 genes, resulting in increased transcription and in turn an approximately 1.5% greater LDL-c lowering in response to statins than noncarriers. Carriers of these 2 variants have lower levels of LDL particles that are resistant to statin lowering and as a consequence higher proportion of LDL particles that are statin responsive.

In general, the pharmacogenetic associations of LDL-c lowering with statin therapy are mild (<5% differences in LDL-c) and thus are unlikely to inform clinical decision-making around achieving LDL goals given that the average LDL-c lowering with statin therapy is much larger (30%–40%) than these effects.

CVD RISK REDUCTION

Statins primarily are effective in reducing CVD through their effects lowering LDL-c. However, statins are well known to have pleotropic effects beyond LDL-c lowering; therefore, there has been some effort to identify genetic variants that influence the magnitude of CVD risk reduction by statins. Initial efforts focused on genetic variants in kinesin family member 6 (*KIF6*) that appeared to identify patients who received a greater benefit from statins despite equal C-reactive protein and lipid lowering *(9, 10)*; however, subsequent efforts have called these findings into question *(11–13)*. Despite the questionable validity of the initial discovery, delivering *KIF6* genetic test results and expected statin benefits was associated with improved adherence and persistence to statin therapy in a nonrandomized study *(14)*. In a complementary approach, investigators have attempted to use CVD risk variants to emerge from GWAS of CVD in an attempt to identify patients with greater benefit to statin therapy.

[4] Human genes: *APOE,* apolipoprotein E; *SLCO1B1,* solute carrier organic anion transporter family member 1B1; *LPA,* lipoprotein(a); *SORT1,* sortilin 1; *ABCB1,* ATP binding cassette subfamily B member 1; *ABCG2,* ATP binding cassette subfamily G member 2; *HMGCR,* 3-hydroxy-3-methylglutaryl-CoA reductase; CELSR2, cadherin EGF LAG seven-pass G-type receptor 2; *PSRC1,* proline and serine rich coiled-coil 1; *KIF6,* kinesin family member 6; *CYP2C19,* cytochrome P450 family 2 subfamily C member 19; *P2RY12,* purinergic receptor; *CYP2C9,* cytochrome P450 family 2 subfamily C member 9; *CES1,* carboxylesterase 1; *UGT2B7,* UDP glucuronosyltransferase family 2 member B7; *VKORC1,* vitamin K epoxide reductase complex subunit 1.

Because each individual genetic variant accounts for only a small percentage of observed phenotypic variation, these variants are often combined into a genetic risk score (GRS) that typically is the sum of risk alleles weighted by their association with CVD to capture their collective risk. In a retrospective analysis of randomized clinical trials of statin therapy for primary and secondary prevention, a high CVD GRS composed of 28 variants collected from prior GWAS of coronary heart disease was not only associated with increased risk for coronary events but also identified patients who benefited the most from statin therapy in terms of both absolute and relative risk reduction *(15)*. Prospective use of this CVD GRS has recently been evaluated in a randomized clinical trial where delivery of CVD genetic risk information (though not statin efficacy) was associated with higher rates of statin initiation and lower LDL-c in patients at risk for CVD compared to usual care *(16)*.

Therefore, the available evidence suggests that selected genetic variants for CVD risk may identify patients who receive greater benefits from statin therapy with respect to CVD risk reduction. Such an approach may be useful in assisting patients and their providers in the shared decision-making process of initiating statin therapy for primary prevention where adherence to guidelines is known to lag *(17)* or to promote statin adherence where one of the most cited reasons for premature statin discontinuation is a perceived lack of benefit *(18)*.

MUSCULOSKELETAL SIDE EFFECTS

Statins have a well-defined safety profile but do carry a small but real risk of musculoskeletal side effects including myalgia [with or without creatine kinase (CK) elevation], asymptomatic CK elevations, and rhabdomyolysis *(19, 20)*. In a pharmacokinetic study, patients with atorvastatin-related myopathy had a 2.4-fold and 3.1-fold higher systemic exposures of the metabolites atorvastatin lactone ($P < 0.01$) and p-hydroxyatorvastatin ($P < 0.01$), respectively, compared to control *(21)*, and it is believed that factors such as dosing or concomitant medications that increase statin concentration in the blood are likely to increase these side effects *(22)*.

The best-studied genetic contributor to statin-induced side effects is *SLCO1B1* (also referred to as *SLC21A6*, *OATP-C*, or *OATP1B1*), which codes for a hepatic drug transporter that mediates the hepatic uptake of statins. The *5 variant is defined by the C allele of rs4149056, which encodes an alanine to valine substitution at amino acid position 174. The polymorphism interferes with the localization of the hepatic drug transporter to the plasma membrane *(23)*, resulting in increased circulating concentrations of statins *(24)*. A GWAS of severe simvastatin-induced myopathy identified a 4.4-fold increased risk in patients with the *5 variant *(25)*. The variant was then examined in a candidate gene study that focused on the more common, milder CK-negative statin-induced side effects (seen in 90% of trial participants), where each allele was associated with a 2.2-fold increased risk *(26)*. Evidence for differences in the risk of myopathy between statins exist, with simvastatin showing highest risk followed by atorvastatin and then pravastatin *(26, 27)*. Additionally, there appears to be no increased risk of myalgia among users of rosuvastatin who carry the *SLC01B1**5 allele *(28)*. These observations follow the alterations in pharmacokinetics of these statins in C allele carriers *(29)*. The *SLCO1B1**5 allele has been associated with nonadherence to statin therapy, with studies demonstrating increased risk of discontinuation or intolerance (which includes discontinuation, dose reduction, and statin switching) with the *5 allele *(26, 30)*. Therapeutic guidelines have been recently issued by the Clinical Pharmacogenomics Implementation Consortium (CPIC) for dosing based on *SLCO1B1**5 allele *(31, 32)*, and a prospective pilot study demonstrated that incorporating *SLCO1B1**5 genetic testing into the care of patients with a history of statin-induced side effects improved patients perceptions, adherence, and LDL-c *(33)*. Ongoing randomized clinical trials (NCT01894230 and NCT02871934) of *SLCO1B1**5 informed statin therapy will provide additional evidence regarding clinical utility. However even in the absence of these data, several centers have incorporated *SLCO1B1* genetic testing into their practice (either as part of research or best practice) to avoid simvastatin in carriers of *SLCO1B1**5 *(34, 35)*.

Platelet P2Y12 Inhibitors

Platelet P2Y12 inhibitors (ticlopidine, clopidogrel, prasugrel, and ticagrelor) are used in the management of patients with coronary artery disease (CAD) who experience acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI) and to prevent stroke. Despite remarkable advances in stent therapy, a significant proportion of patients still remain at risk for death, recurrent myocardial infarction, and stent thrombosis after PCI. The laboratory response to P2Y12 inhibitors is measured by platelet reactivity in response to adenosine diphosphate (ADP, the agonist for the P2Y12 receptor) with increased reactivity being associated with an increased risk for future cardiovascular events *(36)*. While ticlopidine, the first-generation drug in this class, is not in widespread clinical use, platelet function in response to the second-generation thienopyridine clopidogrel is variable and heritable, making it a prime subject of pharmacogenetic study *(37)*. The majority of the evidence surrounding clopidogrel pharmacogenetics has focused around cytochrome P450 family 2 subfamily C member 19 [*CYP2C19* (pharmacokinetic)], though there is evidence for *ABCB1* (pharmacokinetic), puriner-

gic receptor P2Y12 [*P2RY12* (pharmacodynamic)], cytochrome P450 family 2 subfamily C member 9 [*CYP2C9* (pharmacokinetic)], and carboxylesterase 1 [*CES1* (pharmacokinetic)] on drug response, which will not be discussed here.

Clopidogrel is an inactive prodrug that requires hepatic bioactivation by several enzymes, including *CYP2C19*. The prodrug is converted via a 2-step process involving several cytochrome P450 (CYP) enzymes to an active metabolite. This resulting active metabolite irreversibly inhibits the platelet ADP receptor, P2Y12 *(38)*. Genetic variants that diminish the activity of the enzyme will cause shunting of the prodrug to the esterase-mediated degradation pathway to form inactive metabolites. This will lead to decreased levels of the active metabolite and less inhibition of platelets, ultimately leading to a greater risk of cardiovascular events *(39)*.

While the *1 allele of *CYP2C19* has full enzymatic activity, the *2 (rs4244385) variant is the most common of the reduced-function variants and produces a complete loss of enzymatic activity resulting in a lower amount of active metabolite and attenuated clopidogrel-induced platelet inhibition *(39)*. With the *2 allele, a gene-dose effect is seen, where an increasing number of reduced-function alleles results in a decreasing amount of platelet inhibition *(37, 39–41)*. Apart from *2, other loss-of-function variants exist [*3 (rs4986893), *4 (rs28399504), and *5 (rs56337013)]. These variants are rare but produce similar enzymatic defects as the *2 allele *(42)*.

For carriers of *2, one potential treatment strategy is to consider higher doses of clopidogrel. A multicenter, randomized, double-blind trial showed that in patients with stable cardiovascular disease, tripling the maintenance dose of clopidogrel to 225 mg daily in *CYP2C19**2 heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75-mg dose in noncarriers; in contrast, for *CYP2C19**2 homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition *(43)*.

The association between *CYPC219* loss-of-function alleles and the risk of cardiovascular events in patients treated with clopidogrel is consistent with that seen in the associations between the alleles and platelet function. In patients who received PCI after ACS and were treated with clopidogrel, carriers of at least one *2 allele had a 1.5-fold increased risk of death, MI, and stroke in the subsequent year of follow-up compared to noncarriers *(39)*. In patients with ST-segment elevation MI who received clopidogrel, carriers of any 2 loss-of-function alleles (*2, *3, *4, or *5) had a 2-fold increase in the risk of death from any cause, nonfatal stroke, or MI in the year of follow-up *(44)*. In addition to these composite outcomes, the incidence of stent thrombosis was also found to be increased 3-fold in carriers of at least one *2 allele and up to 6-fold in carriers of 2 alleles *(39)*. Last, because clopidogrel is effective in preventing stroke, in a recent trial of Chinese patients (where the allele frequency of *CYP2C19* variants is high) with minor stroke or transient ischemic attack, reduction in the risk of new stroke was achieved by adding clopidogrel to aspirin, but this effect was apparent only in noncarriers of the *2 and *3 alleles *(45)*. In non-PCI populations, such as the CURE trial of medically-managed ACS, there was also no effect of *CYP2C19* on outcomes *(46)*. In the ACTIVE-A trial of patients with atrial fibrillation ineligible to receive warfarin, *CYP2C19* loss-of-function alleles did not affect the primary or safety (bleeding) outcomes *(46)*. Therefore, outside of the recent ACS/PCI window or recent transient ischemic attack (TIA)/stroke windows, it is unlikely that *CYP2C19* polymorphisms play an important role in influencing outcomes in clopidogrel treated patients.

Another allele, *17, is often reported as a "gain-of-function" allele. Many initial reports found an association with improved clinical outcomes compared to noncarriers (10.0% vs 11.9%) in patients with coronary artery disease. In 4 of these 6 studies, *17 carriers had an increased risk of bleeding (8.0% vs 6.5%) *(47)*. However, what is often not appreciated is that the *17 is in near perfect linkage disequilibrium with the *2 allele ($D' = 1.0$), and any analysis of *17 must account for the effects of *2 to assess its independent contribution. After adjustment for the *2 allele, the *17 allele confers no difference in the platelet response to clopidogrel *(48)*.

There are several nonclopidogrel P2Y12 inhibitors that are clinically available as alternative therapies in carriers of *CYP2C19* alleles. Ticlopidine is not impacted by the *2 or *3 *CYP2C19* polymorphisms *(49)*. However, because of the risk of potentially fatal side effects of ticlopidine compared to clopidogrel, it is no longer in widespread use *(50)*. Prasugrel (a third-generation thienopyridine), like clopidogrel, is also a prodrug, but is unique in that its bioactivation appears to be less dependent on *CYP2C19 (51)*. As a consequence, platelet function responses to prasugrel do not depend on genetic variants in *CYP2C19. (52)* Further, in contrast to clopidogrel, prasugrel is not associated with an increased risk of cardiovascular death, MI, stroke, or stent thrombosis in carriers of the *2 allele, making it a potential substitute for clopidogrel in carriers of *2 *(52)*. Ticagrelor is a nonthienopyridine P2Y12 antagonist that has been compared to clopidogrel for a variety of outcomes. Ticagrelor is administered as an orally active drug and therefore is not influenced by genetic variation at *CYP2C19 (53)*. In patients receiving ticagrelor *CYP2C19**2 does not influence platelet aggregation outcomes *(53)*. In a genetic substudy of the pivotal trial *(54)* comparing ticagrelor to clopidogrel in patients with acute coronary syndrome, clinical outcomes in patients with reduced function

alleles in *CYP2C19* were similar if randomized to ticagrelor demonstrating that ticagrelor is a viable option for these patients *(55)*. However, patients with a normal *CYP2C19* genotype benefited nearly the same from ticagrelor over clopidogrel *(55)*. Thus regardless of genotype, ticagrelor may be the best P2Y12 inhibitor to prevent ischemic outcomes; however, its higher cost and risk of bleeding require individualized decisions to be made. To identify genetic variants that may explain variation in response (efficacy or toxicity) to ticagrelor a recent GWAS of patients in PLATO identified genetic variants in *SLCO1B1* and UDP glucuronosyltransferase family 2 member B7 (*UGT2B7*) that affected ticagrelor and active metabolite levels; however, neither gene's variants were associated with bleeding or ischemic events in the ticagrelor-treated arm *(56)*.

Based on the data thus far there are several attempts to demonstrate that use of *CYP2C19* guided P2Y12 inhibitor therapy leads to improved outcomes. In a nonrandomized study, patients who carried reduced function alleles in *CYP2C19* had better clinical outcomes when treated with prasugrel or ticagrelor *(57)*. Prospective randomized clinical trials *(58, 59)* in Chinese patients where the allele frequency of *CYP2C19* variants is high demonstrates efficacy of this approach. While prasugrel and ticagrelor may eventually replace clopidogrel completely in clinical practice, clopidogrel continues to be used in many patients primarily for cost reasons. In these settings prospective genotyping for *CYP2C19* and modification of therapy may be useful.

The Food and Drug Administration has added a warning to the label of clopidogrel notifying physicians and patients that those with certain genetic differences may not receive the full benefit of clopidogrel. Despite this, genetic testing is currently not performed in standard medical practice, and consensus statements do not currently recommend routine testing. *CYP2C19**2 testing may, however, be appropriate in select situations such as for patients who develop complications such as stent thrombosis while on clopidogrel for diagnostic purposes or for patients treated with dual antiplatelet therapy (aspirin plus a P2Y12 inhibitor) after PCI who develop an indication for an anticoagulant and the preference is to maintain clopidogrel and aspirin therapy. For ACS/PCI poor metabolizers, defined as those with 2 loss-of-function alleles (*2, *3, *4, *5, and *6), the current literature supports the use of an alternative antiplatelet agent over increased doses of clopidogrel. However, for intermediate metabolizers, who have only one loss-of-function allele, other clinical factors such as diabetes, age, and body mass index (BMI) may need to be taken into consideration in determining the most effective therapy since this group has wide interindividual variability. Therapeutic guidelines based on these data have been issued by the CPIC for dosing based on *CYP2C19* genotype *(60)*. Several prospective randomized clinical trials of *CYP2C19* genotype guided P2Y12 inhibitor trials in patients with ACS treated with PCI are under way (NCT02508116, NCT01823185, and NCT01742117).

Warfarin

Warfarin is the most commonly used anticoagulant for the primary and secondary prevention of stroke in patients with atrial fibrillation and for treatment of venous thromboembolism. Warfarin is manufactured as a racemic mixture of R- and S-enantiomers, and S-warfarin is the more biologically potent form in terms of inhibiting vitamin K epoxide reductase enzyme (VKORC1) to produce warfarin's anticoagulant effect. Clinically, warfarin is characterized by a narrow therapeutic index, and there is wide interindividual variation in dose requirements. Accurate dosing is crucial for safe patient management and since clinical factors such as age and body size are limited predictors of warfarin dose requirement, there have been extensive study of genetic predictors, which have yielded the following loci: *CYP2C9*, vitamin K epoxide reductase complex subunit 1 (*VKORC1*), and *CYP4F2.*

LABORATORY RESPONSE TO WARFARIN

The laboratory response to warfarin is measured by prothrombin time (PT); the standard of care is to standardize PT measurements across laboratories using the international normalized ratio (INR), with a value between 2 and 3 representing a therapeutic warfarin dose. *CYP2C9* is part of the CYP450 system of the liver and is also responsible for S-warfarin clearance. Candidate gene associations have revealed 2 loss-of-function polymorphisms, *2 (rs1799853) and *3 (rs1057910), resulting in 30% and 90% reduced metabolism, respectively, compared to *1 (wild-type) *(61)*. Reduced metabolism results in a need for lower warfarin doses to achieve goal anticoagulation, and carriers of the *2 and *3 alleles in *CYP2C9* require, on average, a 19% and 33% reduction per allele, respectively, in warfarin dose compared to those who carry the *1 allele *(62)*. In studies of *VKORC1*, which codes for warfarin's protein target, the rs9923231 allele (also known as −1639 G>A variant) has been shown to be the most significant contributor to differences in metabolism, reducing the amount of VKORC1 produced in the liver that will require inhibition by warfarin to produce its anticoagulant effect *(63)* and reducing warfarin dose requirements by 30% *(64)*.

Despite *CYP2C9* and *VKORC1* explaining a large amount of variation in warfarin dose requirements, investigators have looked for other genetic variants. Using a specific chip that assays for all known variants that affect drug metabolizing enzymes, one study showed that

CYP4F2, an enzyme that metabolizes vitamin K, had an effect on dose requirements. Patients with the TT polymorphism in *CYP4F2* (rs2108622) were found to require a higher warfarin drug dose to achieve therapeutic anticoagulation *(65)*. A metaanalysis of 30 studies revealed that carriers of the T allele needed an 8.3% higher dose of warfarin compared with wild-type carriers ($P < 0.0001$) *(66)*.

Whereas a small number of polymorphisms in *VKORC1* and *CYP2C9* may capture most of the pharmacogenetic influence on warfarin dosing in whites these variants are rarer in Africans and do not predict dosing as well in this group. Other novel variants in or near *VKORC1* and *CYP2C9* that are enriched in those of African descent improve warfarin dose predictions *(67, 68)*.

CLINICAL RESPONSE TO WARFARIN

Clinical response can be measured in terms of efficacy, such the time to achieve a stable therapeutic dose, or in terms of adverse events (for instance, supratherapeutic INR of > 4 or hemorrhage). Carriers of *CYP2C9* and *VKORC1* variants who were initiated on warfarin using standard algorithms (usually 5 or 10 mg loading dose followed by INR-based titration) experience a higher rate of adverse clinical outcomes due to the aforementioned genetically mediated sensitivity *(69)*. *VKORC1* carriers achieve both therapeutic *(2–3)* and supratherapeutic INR more rapidly; conversely, carriers of *CYP2C9**2, *CYP2C9**3, and *VKORC1* variants require a longer time to achieve a "stable" INR *(69, 70)*. Carriers of variants in *CYP2C9* and *VKORC1* who require lower warfarin maintenance doses and whose dosing is adjusted using standard algorithms have a 2–3-fold increased risk of serious or life threatening bleeding or a supratherapeutic INR *(69, 71)*, an effect that is most prominent in the first 90 days of therapy *(72, 73)*. Mirroring the findings in adults, a study of children with heart disease found *VKORC1* polymorphisms to account for 47% of warfarin dosing variability *(74)*.

Individuals with *CYP2C9* and *VKORC1* variants may benefit from genotype-guided warfarin therapy, and prospective studies have examined whether personalized therapy can mitigate the risk of adverse events. One such study showed that *CYP2C9*-guided therapy could achieve stable INR sooner while causing less minor bleeding *(75)*; however, the reduction in out-of-range INRs was not replicated in a second study *(76)*. In a subsequent randomized trial of two pharmacogenetic dosing algorithms with a larger study size, the study cohort had favorable results in terms of in-range INR measurements and adverse bleeding events compared to a parallel historical control group *(77)*.

Because the above trials had relatively small sample sizes and limitations in study design, larger randomized controlled trials have helped to establish the potential role for pharmacogenetics testing. The Clarification of Optimal Anticoagulation Through Genetics (COAG) trial found that adding genetic testing to a clinical algorithm that incorporates early INR data did not improve INR outcomes *(78)*; however, it should be noted that genotype data was not available in more than half of trial patients before the first warfarin dose in COAG though was available for over 90% before the 2nd dose. Because *CYP2C9* and *VKORC1* genotypes were particularly important in predicting INR outcomes during warfarin initiation *(79)* adjusting warfarin dose requirements early is likely to have the greatest impact. In contrast to COAG, the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial found that a combined pharmacogenetics and clinical dosing algorithm was superior to fixed-dose warfarin initiation with respect to INR outcomes *(80)*. Additional differences in the outcomes of these 2 studies might be explained by the use of different control arms (clinical dosing algorithm vs fixed dose initiation) between the two trials and more genetic heterogeneity in the US based trials (i.e., higher proportion of non-whites for whom different *VKORC1* polymorphisms may be more important for dose prediction *(68)* vs the European trials. CPIC has published guidelines recommending the use of warfarin dosing algorithms (available at www.warfarindosing.org) incorporating *CYP2C9* and *VKORC1* genotype information when available with clinical data, with the caveats that the potential benefit of this information is seen early in the course of therapy such that adjustment of dose within the first few days of therapy is likely to have the greatest impact *(81)*.

The availability of direct oral anticoagulants (DOACs, e.g., dabigatran, rivaroxaban, endoxaban, and apixaban) has transformed the landscape of oral anticoagulation by providing viable alternatives to warfarin. Each is noninferior or, in some cases, superior to warfarin with respect to preventing thrombosis and limiting bleeding complications without the need for monitoring and with the convenience of a fixed daily dose. Because these medications are not metabolized by *CYP2C9* and do not target *VKORC1*, these medications are not susceptible to the same pharmacogenetic interactions as warfarin. As a consequence, the benefits of DOACs over warfarin are amplified in those who carry *CPY2C9*/*VKORC1* variants *(72)*. However, beyond the early initiation period, there are no differences between carriers/noncarriers with respect to the benefit of DOACs over warfarin. With this in mind, a genotype-guided approach could be used for short courses of therapy, but for long-term therapy it is likely that clinicians would use other factors to guide their drug selection.

Conclusion and Future Directions

We have outlined the considerable body of research that has identified genetic variants that alter the pharmacologic properties of widely used cardiovascular medications and affect clinical outcomes. This knowledge provides opportunity to individualize drug therapy with many implications for clinical practice; in comparison to a "blanket" approach, personalized therapy can maximize benefit, limit side effects, and potentially minimize costs.

However, there are many barriers to implementation that must be addressed. Before pharmacogenetic tests can be widely implemented, their addition to standard-of-care therapy must show clinical utility in their ability to predict outcomes. However, even after establishing clinical utility, in order for pharmacogenetic testing to be implemented in the clinical setting, it must be cost-effective, straightforward enough for general practitioners to order and interpret, and reimbursable by insurance.

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