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Cardiovascular Pharmacogenomics – Implications for Patients with Chronic Kidney Disease

Larisa H. Cavallari, PharmD[1] and **Darius L. Mason, PharmD**[2,3]

[1]Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, Gainesville, FL 32610

[2]Division of Nephrology and Hypertension Albany Medical College, Albany, NY 12208

[3]Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, NY 12208

Abstract

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease. Thus, patients with CKD often require treatment with cardiovascular drugs, such as antiplatelet, antihypertensive, anticoagulant, and lipid-lowering agents. There is significant inter-patient variability in response to cardiovascular therapies, which contributes to risk for treatment failure or adverse drug effects. Pharmacogenomics offers the potential to optimize cardiovascular pharmacotherapy and improve outcomes in patients with cardiovascular disease, though data in patients with concomitant CKD are limited. The drugs with the most pharmacogenomic evidence are warfarin, clopidogrel, and statins. There are also accumulating data for genetic contributions to β-blocker response. Guidelines are now available to assist with applying pharmacogenetic test results to optimize warfarin dosing, selection of antiplatelet therapy after percutaneous coronary intervention, and prediction of risk for statin-induced myopathy. Clinical data, such as age, body size, and kidney function have long been used to optimize drug prescribing. An increasing number of institutions are also implementing genetic testing to be considered in the context of important clinical factors to further personalize drug therapy for patients with cardiovascular disease.

Keywords

pharmacogenomics; genotype; warfarin; clopidogrel; simvastatin

Author for correspondence and reprint requests: Larisa H. Cavallari, Department of Pharmacotherapy and Translational Research, University of Florida, 1333 Center Drive, PO Box 100486, Gainesville, FL 32610; Fax: (352) 273-6485; Tel: (352) 273-8245; lcavallari@cop.ufl.edu.

Introduction

Chronic kidney disease (CKD) affects an estimated 14% of the U.S. population.[1] The mortality burden in CKD is exceptionally high, with nondialysis CKD patients having a 36% higher mortality rate than patients without CKD. The adjusted all-cause mortality rates are 6 to 8 fold higher in the CKD population on dialysis compared to the general population. Declining kidney function is independently associated with increased cardiovascular morbidity and mortality, and cardiovascular disease is the primary cause of hospitalizations and mortality in CKD.[2] Mortality across all reported cardiovascular conditions is greater in patients with CKD compared to the general population, and CKD patients are more likely to die of CVD than reach dialysis therapy.[2, 3]

Traditional (e.g., diabetes, dyslipidemia, hypertension) and nontraditional (e.g., mineral and bone disorder, endothelial dysfunction) cardiovascular risk factors collectively contribute to the excessive cardiovascular disease burden in CKD. As such, cardioprotective measures are imperative to limit cardiovascular morbidity and mortality. Although evidence-based cardioprotective therapy is limited, pharmacotherapy that may reduce or prevent cardiovascular disease burden is an essential part of CKD management. Even less is known about the role of pharmacogenomics for personalizing cardiovascular treatment for CKD patients. However, pharmacogenomics evidence has accumulated for the mostly non-CKD population to the extent that genetic testing has entered clinical practice to assist with prescribing decisions for some cardiovascular medications. This review will describe how genetic information may be used to guide drug therapy for the treatment of CVD, including any data on patients with coexisting CKD.

Progress in the field of cardiovascular pharmacogenomics

President Obama announced a new Precision Medicine Initiative in his State of the Union address in January 2015 with the goal of accelerating progress toward personalized care that takes genetic variation into account.[4] This follows a number of other governmental programs to move genomics forward, including the Human Genome Project, International HapMap Project and Pharmacogenomics Research Network. More recently, the NIH-funded Implementing Genomics in Practice (IGNITE) Network was established to enhance and accelerate the incorporation of genomic information into clinical care.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is another initiative to facilitate the use of pharmacogenomics information into clinical care. CPIC publishes guidelines on how to use pharmacogenomic test results to choose the most appropriate drug therapy for a patient.[5] Guidelines are available for drugs that have the most evidence supporting genetic contributions to their response, and in the cardiovascular arena, this consists of clopidogrel, warfarin, and simvastatin (Table 1).[6–8] There is an increasing body of evidence to support genetic determinants of response to other cardiovascular drugs, especially for β-blockers.

Pharmacogenomics of warfarin

Place in therapy for warfarin in CKD

Warfarin, a vitamin K antagonist, has been the mainstay of oral anticoagulation therapy for the past six decades. Primarily eliminated via the liver, warfarin is commonly used for chronic anticoagulant therapy in CKD patients. While novel oral anticoagulants (NOACs) such as oral direct thrombin inhibitors (DTI) and direct acting Factor Xa antagonists are available, each has some degree of kidney elimination, and clinical trials excluded patients with advanced kidney disease. Thus, experience with these agents in the CKD population is limited, although their use has been increasing.[9]

Primary prevention against cardiogenic stroke in the setting of atrial fibrillation (AF) is a common indication for anticoagulation in CKD patients. In hemodialysis patients, the prevalence of AF is 24% compared to <10% in the general Medicare population greater than 66 years of age.[1] Warfarin therapy for stroke prevention in the general population clearly demonstrates an appropriate risk-benefit ratio when based on the CHADS2 score system.[10] Conversely, there are conflicting reports in the hemodialysis population, and scoring systems are of questionable utility.[11,12] For example, a meta-analysis of observational studies of warfarin-treated patients with AF and CKD showed a reduced risk of thrombotic events and mortality without an increased risk for bleeding with warfarin in patients without end stage CKD.[13] However, among those on renal replacement therapy, warfarin was of no benefit and increased the risk of major bleeding. In contrast, Shen et al[14] demonstrated marginal benefit of reduced ischemic stroke and mortality with warfarin in maintenance hemodialysis patients from the US Renal Data System. Clearly, more clinical trial evidence is needed to firmly establish the risk-benefit ratio of anticoagulation in the dialysis population.

Genotype-guided warfarin therapy

The *CYP2C9* and *VKORC1* genes are well recognized as contributors to the variability in warfarin dose requirements. The *CYP2C9* gene encodes for cytochrome P450 2C9, the enzyme that metabolizes the more active *S*-enantiomer of warfarin. Variants in *CYP2C9* are associated with reduced *S*-warfarin clearance and lower warfarin dose requirements.[6] The most commonly known *CYP2C9* variants are the **2* and **3* alleles, which are described in Table 2. Other alleles (**5, *6, *8, *11*) also reduce warfarin clearance and occur most often in African populations.[15] The *VKORC1* gene encodes for the target protein of warfarin, vitamin K oxidoreductase, and a single variant in the gene's regulatory region, -1639G>A, impacts sensitivity to warfarin.[16]

Numerous studies have consistently shown an association between the *CYP2C9* and *VKORC1* genotypes and warfarin dose requirements.[6] Recent data also show that *CYP2C9* and *VKORC1* genotypes contribute to bleeding risk with warfarin.[17] The FDA-approved warfarin labeling was revised in 2007 to recommend a lower starting dose for patients with a *CYP2C9*2, *3*, or *VKORC1* -1639A allele. Pharmacogenomic dosing algorithms that include *CYP2C9* and *VKORC1* genotypes in addition to important clinical factors affecting warfarin dose requirements (e.g., age, body size, amiodarone use) are publically available to

assist with warfarin dosing and recommended by CPIC for dosing when genotype information is available.[6, 18, 19]

Two clinical trials examining warfarin dosing based on the *CYP2C9*2, *3* and *VKORC1* -1639G>A genotypes were published in 2013.[20, 21] One trial, conducted in Europe, reported greater time in the therapeutic INR range (the primary endpoint) with genotype-guided dosing compared to a standard dosing approach.[21] The other trial, conducted in a diverse U.S. population, showed no difference in the time in range with dosing using a pharmacogenomic algorithm versus a clinical algorithm.[20] There are important differences between the two trials that may help explain the variable results, including lack of a loading dose for most patients in the U.S. trial and not accounting for other *CYP2C9* variants important for African Americans, who made up 28% of the U.S. trial population. Nonetheless, the disparate findings may have led many clinicians to question the utility of pharmacogenomic dosing. Guidelines for the management of anticoagulant therapy from the American College of Chest Physicians acknowledge the effect of genetic variability on warfarin dose requirements and bleeding risk, but recommend against routine use of pharmacogenetic testing to guide warfarin dosing.[10, 22] However, more recently, the American Heart Association/American Stroke Association upgraded guidelines for warfarin pharmacogenetic testing in primary stroke prevention from Class III (is not recommended) to Class IIb (may be considered).[23]

Despite the inconsistent clinical trial data, given the large body of evidence supporting genetic associations with warfarin dose requirements and bleeding risk, some institutions have started to offer genotyping to guide dose selection during warfarin initiation. An example is the University of Illinois Hospital & Health Sciences System (UI Health), where genotype-guided dosing became the standard of care in August 2012 for hospitalized patients, including those with CKD, who newly start warfarin. The process of providing genotype-guided dosing has been described, and preliminary outcome data with the service have been reported showing more efficient achievement of therapeutic anticoagulation, fewer supra-therapeutic INR values, and a shorter duration of low molecular weight heparin use with genotype-guided dosing.[24, 25]

Considerations in CKD

Warfarin is one of the few drugs for which there are data on the combined effect of genotype and kidney function. Specifically, patients with severe CKD are shown to require lower warfarin doses and have a higher risk for over-anticoagulation and bleeding with warfarin compared to those with less severe or no kidney impairment.[26] Even after accounting for other important clinical factors and genotype, kidney dysfunction remains an important contributor to low warfarin dose requirements.[26] Compared to patients with no or mild kidney impairment, patients with moderate to severe kidney dysfunction were shown to require 10% and 19% lower doses, respectively. Most pharmacogenomic dosing algorithms do not include kidney function as a variable. However, based on the data above, once a dose is calculated with an algorithm, it should be reduced by 10% in patients with moderate CKD and by approximately 20% in severe CKD.

Pharmacogenomics of P2Y12 inhibitors

Place in therapy for P2Y12 inhibitors in CKD patients

Significant opportunities exist for the improvement of acute coronary syndrome (ACS) management with antiplatelet therapy in CKD. Repeated investigations have illustrated a proportional association with the risk of mortality and stage of CKD among acute myocardial infarction (AMI) patients.[27] Dialysis patients have the worst prognosis post-AMI and are often excluded from large randomized clinical trials.[27] Furthermore, atypical clinical presentation and chronically elevated biochemical measures (e.g., troponin) often lead to incorrect diagnosis and subsequent omission of evidence-based therapy in the CKD population.[27]

There is evidence of significant reductions in prescribing of evidence-based therapies such as $P2Y_{12}$ (P2Y12) receptor inhibitors with progressively worse kidney function.[28] The concern for bleeding risk may contribute to the clinical inertia of prescribing P2Y12 inhibitors. The majority of P2Y12 inhibition studies in patients with CKD were conducted using clopidogrel, and major studies showed a decline in the efficacy of clopidogrel as kidney disease worsens.[29, 30] Although rates of bleeding were higher in CKD patients, they were not significantly greater than in individuals with normal kidney function. Prasugrel and ticagrelor are newer P2Y12 inhibitors that has been shown to be more effective than clopidogrel in patients with CKD and are acceptable for use in CKD patients who are not at high risk for bleeding.[27] Research is needed to determine the efficacy and safety of these agents in the dialysis population.

Genotyped-guided antiplatelet therapy

Clopidogrel is extensively metabolized, and the CYP2C19 enzyme is involved in the biotransformation of clopidogrel to its active thiol metabolite. The gene encoding CYP2C19 is highly polymorphic. The *CYP2C19*2* allele is the primary allele responsible for reduced enzyme activity (Table 2). Other, less common, alleles leading to deficient enzyme activity include *CYP2C19*3, *4,*5, *6, *7,* and **8*. These are referred to as loss-of-function alleles associated with complete loss or significant reduction in enzyme activity. Individuals with one loss-of-function allele are deemed intermediate metabolizers (IMs), and those with two loss-of-function alleles are deemed poor metabolizers (PM).[8] Compared to extensive metabolizers (EMs) with normal enzyme activity, clopidogrel use in IMs and PMs may result in lower concentrations of the active clopidogrel metabolite and less inhibition of platelet aggregation.[31]

Genetic substudies of a number of large clinical trials have shown that clopidogrel-treated patients with the PM or IM phenotype were at increased risk for adverse cardiovascular events, including stent thrombosis, compared with similarly treated EMs, with the strongest data in ACS patients who undergo percutaneous coronary intervention (PCI).[32] A warning is now included on the FDA-approved clopidogrel labeling about reduced effectiveness in PMs. The CPIC guidelines recommend alternative antiplatelet therapy for PMs and IMs after an acute coronary syndrome and PCI.[8] The American College of Cardiology and American Heart Association guidelines recommend the consideration of *CYP2C19*

genotyping after acute coronary syndrome and PCI if results of testing may alter management.[33] This is a Class IIb recommendation meaning that the usefulness of testing is less well established. Prasugrel and ticagrelor are alternative agents whose effectiveness is not dependent on *CYP2C19* genotype.[34, 35] Similar to clopidogrel, prasugrel is a prodrug that requires biotransformation to its active form. While CYP2C19 is involved in the biotransformation process, *CYP2C19* genotype does not compromise efficacy of the drug.[34] Unlike clopidogrel and prasugrel, ticagrelor is administered in its active form and does not require hepatic biotransformation.[35] The active prasugrel metabolite is metabolized in the liver, with inactive metabolites excreted in the urine and feces, while ticagrelor is predominately eliminated by the liver. Thus, no dose adjustment is recommended with these drugs in patients with kidney disease. However, patients with end stage kidney disease are at a higher risk for bleeding, which could potentially impact the safety of prasugrel or ticagrelor.

CYP2C19 testing to guide antiplatelet therapy after PCI was launched at the University of Florida Health (UF Health) in June 2012.[36] The genetic test order is on the post-PCI order set as the standard of care for patients undergoing PCI regardless of kidney function. Clinical decision support was built into the electronic medical record so that an alert appears when clopidogrel is ordered for a patient with the IM or PM phenotype warning the prescriber of reduced clopidogrel effectiveness and recommending substitution of prasugrel or ticagrelor in the absence of contraindications.

Considerations for clopidogrel pharmacogenetics specific to CKD

Given that clinical trials have demonstrated a reduction in clopidogrel efficacy with declining kidney function,[29, 30] patients with CKD may especially benefit from *CYP2C19*-guided antiplatelet therapy. Specifically, it would seem logical that the combination of the CYP2C19 PM or IM phenotype and CKD could place a patient at especially high risk for treatment failure with clopidogrel, though this has yet to be examined. CPIC guidelines for *CYP2C19* testing do not address kidney function, suggesting that recommendations to use prasugrel or ticagrelor in the presence of a loss-of-function allele would apply across the spectrum of kidney function.

Pharmacogenomics of statins

Place in therapy for statins in CKD patients

Over the last 15 years, clinical trials have demonstrated that HMG-CoA reductase inhibitors (i.e., statins) reduce the risk for cardiovascular events and mortality when used for primary or secondary prevention.[37] More recent evidence supports a reduction in risk regardless of baseline low density lipoprotein (LDL) levels.[37] Statin therapy in CKD has not resulted in similar outcomes, at least for primary disease prevention in dialysis patients.[38–40] Data supporting statin therapy in CKD patients with ACS are scarce overall and have largely focused on primary prevention from the excessive cardiovascular risk. For nondialysis-dependent CKD patients, recommendations supporting statin therapy are largely based on the results from the Study of Heart and Renal Protection (SHARP), which examined the efficacy of simvastatin plus ezetimibe in patients with moderate to severe CKD.[38] The

SHARP study showed a 25% reduction in the risk for major atherosclerotic events with simvastatin plus ezetimibe. These reductions were mostly driven by association in the nondialysis subjects as subgroup analysis revealed no benefits for maintenance dialysis patients. Large multicenter dialysis specific studies, with over 4000 combined patients failed to demonstrate reductions in primary outcomes of cardiovascular disease or mortality.[39, 40] These results, along with post-hoc data from the SHARP study have driven recommendations against the initiation of statin therapy in maintenance hemodialysis patients. However, continued statin therapy is recommended for dialysis patients taking statins prior to the initiation of dialysis or receiving statin therapy longer than a year.[41] Statin therapy is also recommended in kidney transplant recipients; however, polypharmacy places these patients at increased risk for drug interactions.

Pharmacogenomics of statin-induced myopathy

Myopathy is the most common side effect of statin therapy, with symptoms ranging from mild myalgias to, rarely, life-threatening rhabdomyolysis with marked elevations in creatinine kinase levels, muscle damage, and acute kidney injury. Patients with mild myalgias may not experience physical harm, but may be less likely to adhere to therapy, thus compromising the efficacy of statin therapy. Clinical factors that increase the risk for statin-induced myopathy include high statin doses, older age, low body weight, kidney dysfunction, and liver disease.[7, 42] Simvastatin, lovastatin, atorvastatin, and, to a lesser extent, fluvastatin, are metabolized by the CYP3A4 enzyme, and thus, medications that inhibit CYP3A4 (e.g. azole antifungals, macrolide antibiotics, nefazodone, cyclosporine, protease inhibitors, amiodarone, verapamil) may increase serum concentrations of these drugs and risk for myopathy. Pitavastatin, rosuvastatin, and fluvastatin are metabolized by the CYP2C9 enzyme, and pravastatin is primarily eliminated by the kidneys. Yet, cyclosporine increases exposure to these statins possibly through inhibition of efflux transporter proteins on the hepatocyte membrane. [43] Concomitant use of fibric acid derivatives also increases risk for myopathy though interference of statin glucuronidation or membrane transport.[7] The FDA-approved simvastatin labeling recommends avoiding concomitant use of azole antifungals, macrolides, protease inhibitors, and nefazodone, and prescribing lower simvastatin doses with concomitant use of other CYP3A4 inhibitors or gemfibrozil, and similar warning and precautions exists with other statins.

The solute carrier organic anion transporter family, member 1B1 (SLCO1B1) genotype, which encodes for the organic anion transporting polypeptide (OATP) 1B1, is an additional risk factor for development of statin-induced myopathy.[44] OATP 1B1 transports most statins, with the exception of fluvastatin, to the liver. The c.521T>C (p.Val174Ala) variant decreases OATP 1B1 activity and statin clearance. This effect is greatest for simvastatin with lesser effects on (in descending order) pitavastatin, atorvastatin, pravastatin, and rosuvastatin pharmacokinetics.[45] Consistent with the pharmacokinetic data, the effect of the 521T>C variant on myopathy risk is greatest with simvastatin, with a relative risk of 2.6 per C allele with the 40 mg/day dose and 4.5 per C allele with the 80 mg/day dose.[44] Modest to no association has been observed between the *SLCO1B1* genotype and myopathy risk with atorvastatin, pravastatin, and rosuvastatin.[46–48] TGiven that genetic association data are strongest with simvastatin, and CPIC guidelines are specific to simvastatin and recommend

a lower dose (e.g. 20 mg) with consideration of routine creatinine kinase monitoring or use of a different statin in patients with a 521C allele.[7] Investigators have also examined several CYP450 enzyme genes, including *CYP3A4*, but no consistent associations with statin-induced myopathy have been shown.[48]

Pharmacogenomics of statin efficacy

A number of studies have assessed genetic predictors of statin efficacy, and while a number of genes have been associated with LDL cholesterol lowering with statins, effect sizes have been small. More recently, investigators examined the genotypes of over 48,000 individuals and identified a combination of 27 variants that conferred an increased risk for coronary events.[49] The reduction in risk for coronary events with statin therapy was greatest among individuals with the highest genetic risk score. These data suggest that it may be possible to identify patients who will benefit the most from statin therapy based on their genotype.

Impact of CKD on statin pharmacogenetics

Considering the controversy with statin therapy in hemodialysis and evidence that genotype influence statin response, pharmacogenomics may offer the opportunity to identify select hemodialysis patients who will benefit from statin therapy or may be at increased risk of adverse statin-related effects. However, genotype-guided studies with statin therapy are nonexistent in the hemodialysis population. Cyclosporine is commonly prescribed after kidney transplant, and there could be potential for genotyping to identify patients at higher risk for rhabdomyolysis with combination statin and cyclosporin therapy. However, with the exception of a study showing a genetic risk for fluvastatin-induced adverse effects, there are limited pharmacogenomic data available for statin response after kidney transplant.[50]

β-Blocker pharmacogenomics

Place in therapy for β-blockers in CKD patients

Beta-adrenergic receptor antagonists (“β-blockers”) are effective agents for the treatment of hypertension, AF, and ischemic heart disease and for mortality reduction in heart failure. These same indications are valid in the CKD population. Heart failure is the second most frequently occurring cardiovascular disease in the CKD population consuming approximately $20.6 billion dollars in Medicare cost in 2012.[1] In nondialysis dependent CKD patients with heart failure, a meta-analysis by Badve et al[51] demonstrated a 28% and 34% reduction in all-cause and cardiovascular mortality with β-blocker therapy. CKD is also associated with a higher prevalence of AF and is an independent risk factor for ischemic heart disease.[37, 52]

β-blockers offer additional benefits for CKD patients such as attenuation of excessive sympathetic output. Autonomic dysfunction favors an overactive sympathetic nervous system and predisposes end stage kidney disease patients to sudden cardiac death, which accounts for 25% of all-cause mortality in dialysis patients. β-blockers are considered cardioprotective therapy in CKD and have been shown to reduce the risk for sudden cardiac death in this population.[53] While β-blockers are the most widely prescribed cardioprotective

drugs among the Medicare Part D end stage kidney disease population, they are frequently under-utilized as a cardioprotective therapy.[54]

Genetic determinants of B-blocker response

Metoprolol, carvedilol, propranolol, and nebivolol are substrates for the polymorphic CYP2D6 enzyme, whereas atenolol undergoes little to no metabolism in the liver. The *CYP2D6* gene is highly polymorphic and has implications for the disposition of CYP2D6 substrates. *CYP2D6* genotype confers four phenotypes: poor, intermediate, extensive, and ultra-rapid metabolism. Extensive metabolizers have normal enzyme activity. Poor and intermediate metabolizers, on the one extreme, have little to no enzyme activity, and ultra-rapid metabolizers, on the opposite extreme, having increased enzyme activity compared to extensive metabolizers. Significantly higher drug plasma concentrations of metoprolol and carvedilol have been reported among CYP2D6 poor metabolizers compared to those with other phenotypes.[55–58] While the poor metabolizer phenotype has also been associated with greater heart rate and diastolic blood pressure response to β-blockers, results are inconsistent.[56–61] Inconsistent associations between genotype with clinical response to metoprolol is likely a reflection of the wide therapeutic index of β-blockers where differences in plasma concentrations may or may not result in clinically significant effects.

The genes most strongly associated with response to β-blockers are the β-1 adrenergic receptor (*ADRB1)*, α-2C-adrenergic receptor (*ADRA2C)*, and G-protein coupled receptor kinase-5 (*GRK5*) genes. The *ADRB1* gene has two common nonsynonymous single nucleotide polymorphisms, p.Ser49Gly and p.Arg389Gly, that have been associated with differential responses to β-blockers in hypertension and coronary artery disease. Specifically, greater blood pressure reductions with metoprolol have been observed in patients homozygous for the Ser49-Arg389 haplotype compared to those with other haplotypes.[62] In patients with coronary heart disease, the Ser49-Arg389 haplotype was correlated with increased risk for mortality, and treatment with atenolol appeared to abolish this risk.[63] However, the data are not always consistent and have varied depending on the β-blocker under study. For example, among elderly patients with AF, the Arg389Gly polymorphism did not impact heart rate response to bisoprolol, whereas the Arg/Arg genotype was associated with a lesser heart rate response to carvedilol.[64]

There are also data with the *ADRB1* genotype in heart failure, with evidence of greater improvements in left ventricular ejection fraction in patients with the Arg389Arg genotype compared to 389Gly allele carriers.[65] Interesting outcome data come from a genetic substudy of the Beta-Blocker Evaluation of Survival Trial (BEST), which evaluated the efficacy of bucindolol, a nonselective β-blocker with sympatholytic activity, against placebo in patients with heart failure. Bucindolol-treated participants in the trial with the Arg389Arg genotype had fewer deaths and hospitalizations compared to similarly treated patients with the Arg389Gly or Gly389Gly genotype.[66] Bucindolol also appeared to protect heart failure patients with the Arg389Arg genotype against new-onset AF.[67]

A four amino acid insertion-deletion polymorphism at positons 322–325 in the *ADRA2C* gene was also associated with β-blocker response in the BEST population. The deletion allele confers a loss-of-function phenotype and was associated with worse clinical outcomes

with bucindolol.[68] Interestingly, neither the *ADRB1* nor *ADRA2C* genotype influence survival with metoprolol or carvedilol treatment for heart failure, suggesting that the interaction between these genotypes and outcomes with bucindolol may be due to the drug's unique pharmacologic characteristics.[69]

Finally, the *GRK5* p.Leu41Gln variant was shown to predict outcomes with β-blocker treatment in African American patients with heart failure. The Leu41 variant desensitizes the β-adrenergic receptor to a greater extent than the Gln41 form, thus acting somewhat as a natural β-blocker.[70] African Americans with the Leu41 allele did not appear to derive any benefit from β-blocker therapy.[71] However, β-blocker treatment was protective against adverse outcomes in patients with the Gly/Gly genotype.

Together, these data suggest that genotype may be predictive of response to β-blockers in hypertension, coronary artery disease, and heart failure. However, given that the influence of genotype on outcomes may vary according to which β-blocker is prescribed, particularly for heart failure, additional confirmation of the gene-β-blocker response association is needed to move genetic testing into practice to guide prescribing decisions. To gather such evidence, ARCA Biopharma is currently conducting a randomized trial to compare the effects of bucindolol versus metoprolol succinate on the recurrence of atrial arrhythmias in patients with heart failure and the Arg389Arg genotype (NCT01970501). There are no CPIC guidelines available addressing genotype-guided use of β-blockers, and this gene-drug pair is generally not considered clinically implementable at present.

β-blocker pharmacogenetics in patients with CKD

Despite the vast amount of information on genetic influences of β-blocker response in the general population, studies in the CKD population are largely absent. Furthermore, changes in sympathetic response in CKD may impact genetic associations with β-blocker response, and thus, β-blocker pharmacogenomics studies are warranted in the CKD population. African Americans are disproportionately affected by CKD, and opportunities exist for genotype-guided therapy, such as with the *GRK5* gene, in this subpopulation of dialysis patients with heart failure. Whether the cardioprotective benefits of β-blocker against sudden cardiac death, a common cause of death in patients with end stage kidney disease, is affected by the various genetic variations is unknown.

Immunosuppressant pharmacogenetics

While a thorough discussion of non-cardiovascular pharmacogenetics is beyond the scope of this review, the pharmacogenetics of azathioprine and tacrolimus warrant mention given their frequent use as immunosuppressants in kidney transplantation and the significant pharmacogenetic data available with these drugs. Once absorbed, azathioprine is metabolized to 6-mercaptopurine, which is activated in a series of processes to form thioguanine nucleotides responsible for immunosuppressive effects. The thiopurine methyltransferase (TPMT) enzyme inactivates 6-mercaptopurine. Up to 14% of individuals inherit a *TPMT* allele associated with loss of enzyme activity (e.g. **2, *3A, *3B, *3C*, or **4* allele) and reduced inactivation of 6-mercaptopurine so that more of the drug is available for conversion to the active thioguanine nucleotide metabolites. These individuals are at risk for

supra-therapeutic thioguanine nucleotide concentrations and moderate to severe myelosuppression with usual azathioprine doses.[72] CPIC guidelines recommend a 30% to 70% dose reduction in carriers of a single inactive *TPMT* allele and use of alternative immunosuppressant therapy in the rare individual with 2 inactive alleles.[72]

The CYP3A5 enzyme is the predominant enzyme involved in the metabolism of tacrolimus. Approximately 80% to 85% of Caucasians, but fewer African Americans and Asians, have the *CYP3A5 *3/*3* genotype associated with loss of *CYP3A5* expression and production of a nonfunctional protein. These individuals are referred to as nonexpressors.[73] Compared to expressors (with the **1/*1* or **1/*3* genotype), nonexpressors have higher trough concentrations of tacrolimus and lower dose requirements. On the other hand, expressors have lower trough concentrations and are at increased risk of transplant rejection with usual tacrolimus doses.[74] A randomized controlled trial showed that tacrolimus dosing based on *CYP3A5* genotype, with higher doses started in individuals with the **1/*1* or **1/*3* genotype, resulted in decreased time to achieve therapeutic drug concentrations compared to a traditional (non-genotype-guided) dosing approach.[75] Recent CPIC guidelines recommend starting higher tacrolimus doses (e.g. 1.5 to 2 times higher than usually recommended) in CYP3A5 expressors with the **1/*1* or **1/*3* genotype.[73]

Summary

We have long considered patient age, body size, kidney function, and concomitant diseases in choosing drug therapy for CVD. Similarly, genotype has the potential to optimize drug selection, as in the case of *CYP2C19* testing for antiplatelet therapy, and drug dosing, as in the case for *CYP2C9* and *VKORC1*, with warfarin. Furthermore, genotype information can assist in reducing drug toxicity, as in the case of *SLCO1B1* testing to predict risk for simvastatin-induced myopathy.

Our understanding of genetic determinants of other cardiovascular drug response has improved significantly over the past two decades. However, for most drugs, the combined effect of genotype and CKD on drug response has not been examined. Given the continued burden of CKD and cardiovascular disease and government initiatives to support precision medicine to reduce disease burden and improve patient outcomes, we may be moving toward the era when genotype will be routinely considered in drug prescribing for cardiovascular disease, including in the CKD population.

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Clinical Summary

- Patients with chronic kidney disease often require treatment with cardiovascular pharmacotherapies, including antiplatelet agents, anticoagulants, antihypertensives, and lipid-lowering agents. However, there is evidence of significant inter-patient variability in response to these agents which can compromise drug efficacy and increase risk for drug toxicity.
- Genotype is well recognized to contribute to response to cardiovascular agents, and evidence has accumulated to the extent that pharmacogenetic testing is being implemented in clinical care at some institutions to optimize drug therapy.
- Guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC) are available to assist clinicians with translating genotype results into actionable prescribing decisions for warfarin, clopidogrel, and statins.
- There remains a paucity of evidence on the impact of renal function on the genotype-drug response association for most drugs.

Table 1

Cardiovascular gene-drug pairs with the most evidence to date

Gene(s)	Drug	Current state of the evidence and considerations in kidney disease
CYP2C9, VKORC1	Warfarin	• Numerous studies have shown that the *CYP2C9*2, *3, *5, *6, *8, *11* and *VKORC1* -1639A alleles are associated with lower warfarin dose requirements. • CPIC guidelines recommend use of pharmacogenetic dosing algorithms to assist with warfarin dosing based on *CYP2C9* and *VKORC1* genotypes plus clinical factors.[6] • The FDA approved warfarin labeling contains a dosing table based on genotype based on the *CYP2C9* and *VKORC1* genotypes that may be used when dosing algorithms are inaccessible. • While warfarin elimination is almost entirely by hepatic metabolism, data show that moderate to severe kidney dysfunction reduces warfarin dose requirements by 10% to 20%, respectively. [26] • Most pharmacogenetic algorithms do not account for kidney dysfunction, but reducing the dose estimated by pharmacogenetic algorithms (or the FDA dosing table) by 10% to 20% for patients with moderate to severe kidney dysfunction, respectively, may prevent warfarin over-dosing in these subgroups.
CYP2C19	Clopidogrel	• CYP2C19 poor and intermediate metabolizer phenotypes are associated with reduced response to clopidogrel and an increased risk for major adverse cardiovascular events with clopidogrel treatment after PCI compared to the extensive and ultra-rapid metabolizer phenotypes. • CPIC guidelines recommend alternative treatment with prasugrel or ticagrelor after acute coronary syndrome and PCI in CYP2C19 poor and intermediate metabolizers in the absence of contraindications.[8] • The FDA approved clopidogrel label contains a boxed warning about reduced clopidogrel efficacy with the poor metabolizer phenotype. • Though no dose adjustment is necessary for prasugrel or ticagrelor in patients with kidney disease, patients with end-stage kidney disease may be at higher risk for bleeding with these agents and thus need close monitoring. [76]
SLCO1B1	Simvastatin	• The *SLCO1B1* 521C allele is associated with an increased risk of myopathy with simvastatin. • CPIC guidelines recommend avoiding simvastatin doses >20 mg or prescribing an alternative statin and consideration of creatinine kinase surveillance in patients with a 521C allele. • CPIC guidelines do not address simvastatin pharmacogenetics in patients with kidney disease. • In patients with severe kidney dysfunction, the simvastatin labeling recommends an initial dose of 5 mg. • Kidney dysfunction is a risk factor for myopathy and may could potentially further increase risk for statin-induced myopathy in patients with the 521C allele.
ADRB1	β-blockers	• There is evidence supporting associations between genes involved in β-blocker pharmacodynamics (*ADRB1, ADRA2C, GRK5*) and response to β-blockers in hypertension and coronary heart disease and response to bucindolol (not available in the U.S.), in heart failure. • No CPIC guidelines are available at present. • Atenolol is excreted by the kidneys and should be used cautiously in lower than usual doses in patients with kidney dysfunction regardless of genotype.

CPIC, Clinical Pharmacogenetics Implementation Consortium; FDA, Food and Drug Administration; PCI, percutaneous coronary intervention

Table 2

Description and prevalence of genotypes with CPIC guidelines[6–8, 15]

Allele	Genetic polymorphism	Prevalence
*CYP2C9*2*	Nonsynonymous SNP (Arg144Gly) leading to decreased enzyme activity	Present in approximately 25% of Europeans and 5% of African Americans. Usually absent in Asians.
*CYP2C9*3*	Nonsynonymous SNP (Ile359Leu) leading to decreased enzyme activity	Present in approximately 12% of Europeans, 8% of Asians, and 2% of African Americans
*CYP2C9*5*	Nonsynonymous SNP (Asp360Glu) leading to decreased enzyme activity	Present in 1–2% of African Americans. Usually absent in Europeans and Asians.
*CYP2C9*6*	Frameshift mutation leading to decreased enzyme activity	Present in about 1% of African Americans. Usually absent in Europeans and Asians.
*CYP2C9*8*	Nonsynonymous SNP (Arg150His) leading to decreased enzyme activity	Present in about 12% of African Americans. Usually absent in Europeans and Asians.
*CYP2C9*11*	Nonsynonymous SNP (Arg335Trp) leading to decreased enzyme activity	Present in about 3% of African Americans and <1% of Europeans and Asians.
VKORC1 -1639G>A	SNP in the gene regulatory region affecting gene expression	Approximately 48% of Europeans, 16% of Asians, and 20% of African Americans have the AG genotype. Approximately 15% of Europeans, 83% of Asians, and 2% of African Americans have the AA genotype.
*CYP2C19*2*	Splicing defect leading to loss of activity	Approximately 25–30% of Europeans and African Americans and 50% of Asians have the *2 allele.
SLCO1B1 521T>C	Nonsynonymous SNP	Approximately 10 to 35% of individuals carry a single 521C allele, and up to 6% have the CC genotype.