Cardiovascular Pharmacogenomics—Implications for Patients With CKD

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CKD is an independent risk factor for cardiovascular disease (CVD). Thus, patients with CKD often require treatment with cardiovascular drugs, such as antiplatelet, antihypertensive, anticoagulant, and lipid-lowering agents. There is significant interpatient 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 CVD, although 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 CVD.

Key words: Pharmacogenomics, Genotype, Warfarin, Clopidogrel, Simvastatin

INTRODUCTION

CKD affects an estimated 14% of the US 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 with the general population. Declining kidney function is independently associated with increased cardiovascular morbidity and mortality, and cardiovascular disease (CVD) is the primary cause of hospitalizations and mortality in CKD.[2] Mortality across all reported cardiovascular conditions is greater in patients with CKD compared with the general population, and CKD patients are more likely to die of CVD than reach dialysis therapy.[2,3]

Traditional (eg, diabetes, dyslipidemia, hypertension) and nontraditional (eg, mineral and bone disorder, endothelial dysfunction) cardiovascular risk factors collectively contribute to the excessive CVD 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 CVD 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, pharmacogenomic 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 National Institutes of Health–funded Implementing Genomics in Practice 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 pharmacogenomic 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 6 decades.

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Primarily eliminated via the liver, warfarin is commonly used for chronic anticoagulant therapy in CKD patients. Although novel oral anticoagulants such as oral direct thrombin inhibitors 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.[11]

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 aged older than 66 years.[1] Warfarin therapy for stroke prevention in the general population clearly demonstrates an appropriate risk-benefit ratio when based on the CHADS2 score system.[12] Conversely, there are conflicting reports in the hemodialysis population, and scoring systems are of questionable utility.[13,14] 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.[15] However, among those on renal replacement therapy, warfarin was of no benefit and increased the risk of major bleeding. In contrast, Shen and colleagues[16] 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.

CLINICAL SUMMARY

- Patients with CKD often require treatment with cardiovascular pharmacotherapies, including antiplatelet agents, anticoagulants, antihypertensives, and lipid-lowering agents. However, there is evidence of significant interpatient 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 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.

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 summarized in Table 2. Other alleles (**5, *6, *8, *11*) also reduce warfarin clearance and occur most often in African populations.[17] 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.[18]

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.[19] The Food and Drug Administration (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. Pharmacogenetic dosing algorithms that include *CYP2C9* and *VKORC1* genotypes in addition to important clinical factors affecting warfarin dose requirements (eg, age, body size, amiodarone use) are publically available to assist with warfarin dosing and recommended by CPIC for dosing when genotype information is available.[6,20,21]

Two clinical trials examining warfarin dosing based on the *CYP2C9*2, *3*, and *VKORC1* -1639G>A genotypes were published in 2013.[22,23] One trial, conducted in Europe, reported greater time in the therapeutic international normalized ratio (INR) range (the primary end point) with genotype-guided dosing compared with a standard dosing approach.[23] The other trial, conducted in a diverse US population, showed no difference in the time in range with dosing using a pharmacogenetic algorithm vs a clinical algorithm.[22] There are important differences between the 2 trials that may help explain the variable results, including lack of a loading dose for most patients in the US trial and not accounting for other *CYP2C9* variants important for African Americans, who made up 28% of the US trial population. Nonetheless, the disparate findings may have led many clinicians to question the utility of pharmacogenetic 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.[12,24] 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).[25]

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