Pharmacogenetics in Cardiovascular Disease: The Challenge of Moving From Promise to Realization

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Philip G. Joseph, MD; Guillaume Pare, MD; Stephanie Ross, MSc; Robert Roberts, MD; Sonia S. Anand, MD, PhD

Population Health Research Institute (Joseph, Pare, Ross, Anand), Hamilton Health Sciences, McMaster University, Hamilton; Department of Pathology (Pare), McMaster University, Hamilton; Population Genomics Program (Pare, Anand), Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton; University of Ottawa Heart Institute (Roberts), Ottawa; Department of Medicine (Anand), McMaster University, Hamilton, Ontario, Canada

Address for correspondence:

Philip Joseph, MD
Population Health Research Institute
McMaster University,
Hamilton General Hospital Campus
DB-CVSRI,
237 Barton Street East, Rm C3102
Hamilton, Ontario, Canada L8L 2X2
philip.joseph@phri.ca

ABSTRACT

Pharmacogenetics in cardiovascular medicine brings the potential for personalized therapeutic strategies that improve efficacy and reduce harm. Studies evaluating the impact of genetic variation on pharmacologic effects have been undertaken for most major cardiovascular drugs, including antithrombotic agents, β -adrenergic receptor blockers, statins, and angiotensin-converting enzyme inhibitors. Across these drug classes, many polymorphisms associated with pharmacodynamic, pharmacokinetic, or surrogate outcomes have been identified. However, their impact on clinical outcomes and their ability to improve clinical practice remains unclear. This review will examine the current clinical evidence supporting pharmacogenetic testing in cardiovascular medicine, provide clinical guidance based on the current evidence, and identify further steps needed to determine the utility of pharmacogenetics in cardiovascular care.

Introduction

Pharmacologic effects can vary significantly between individuals, leading to reduced drug efficacy, decreased adherence, or increased adverse events. Identifying individuals who are at risk for poor therapeutic responses may be useful for amending treatment decisions to optimize benefit and minimize harm.¹ Many factors influence the effectiveness of a given pharmacologic agent, including adherence, pharmacologic and environmental interactions, and genetic effects.² Genetic markers have been proposed as stratification tools to predict therapeutic effects, such that pharmacologic regimens are tailored to specific genetic profiles to maximize efficacy and minimize harm. Although this approach could herald an innovative departure from current clinical cardiology practice, significant limitations in the current literature exist that make the realization of this practice difficult.

This review will evaluate the clinical evidence examining pharmacogenetics in the management of cardiovascular

(CV) disease (CVD) across major drug classes. We will focus on common drugs used for the treatment of CVD and thrombosis: warfarin, aspirin, clopidogrel, β -blockers, statins, and angiotensin-converting enzyme (ACE) inhibitors (ACEis). Moreover, based on the current evidence, we will provide clinical guidance regarding the current use of pharmacogenetic testing in CVD and outline future directions in research.

Warfarin Response

Warfarin is among the most effective agents to prevent thromboembolic events in patients with atrial fibrillation. However, the efficacy of warfarin is highly dependent on achieving and maintaining a narrow therapeutic window (usually an international normalized ratio [INR] between 2 and 3). Through the inhibition of vitamin K epoxide reductase complex 1 (VKORC1), warfarin limits the generation of the vitamin K hydroquinone, a necessary cofactor to sustain vitamin K-dependent coagulation factors II, VII, IX, and X.³ Metabolism of warfarin to its inactive metabolites occurs through the cytochrome p450 (CYP) system.

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Table 1. Select Genes and Their Effects on Thrombotic Agents

Treatment	Gene	Chromosome	Polymorphisms	Minor Allele ^a	Minor Allele Frequency ^a	Effect
Warfarin	<i>VKORC1</i> ^{5,6}	16	rs9923231	T	0.40	Polymorphisms were combined to form haplotypes. <i>VKORC1</i> "A" haplotype associated with lower warfarin dose requirement
			rs2884737	C	0.26	
			rs9934438	A	0.26	
			rs8050894	G	0.37	
			rs2359612	A	0.40	
			rs7294	T	0.36	
			rs17880887	A	0.15 ^{b,d}	
	<i>CYP4F2</i> ¹²	19	rs2108622	T	0.23	Variability in warfarin dose
	<i>CYP2C9</i> ⁷⁻⁹	10	<i>CYP2C9</i> *2 (rs1799853)	T	0.10	Lower warfarin dose and increased bleeding
			<i>CYP2C9</i> *3 (rs1057910)	C	0.06	Lower warfarin dose and increased bleeding
Clopidogrel	<i>CYP2C19</i> ^{18,19}	10	<i>CYP2C19</i> *2 (rs4244285)	A	0.14	Reduced clopidogrel activity but limited impact on clinical outcomes
			<i>CYP2C19</i> *3 (rs4986893)	A	0.01 ^{b,d}	
Aspirin	<i>PEAR1</i> ³¹	1	rs2768759	A	0.39 ^{b,d}	Variability in platelet response
	<i>ITGB3</i> ³²	17	PIA1/A2	PIA2	0.15 ^{b,c}	Variability in platelet response

^aMinor allele and frequencies are reported from the HapMap white population unless otherwise specified.⁷² ^bReported from a multiethnic population.
^cReported or estimated from the referenced study population. ^dMinor allele frequency reported from the 1000 Genomes Project.⁷³

Several genetic polymorphisms exist in the *VKORC1* loci that influence warfarin dosage and INR response (Table 1).⁴⁻⁶ Rieder et al evaluated the impact of several *VKORC1* polymorphisms, grouped into 2 distinct haplotypes (designated A and B), on warfarin dose requirements, and observed a significant difference in the warfarin dose needed to maintain effective anticoagulation: 2.7 ± 0.2 mg/d for the A/A haplotype group, 4.9 ± 0.2 mg/d for the A/B group, and 6.2 ± 0.3 mg/d for the B/B group ($P < 0.001$). Overall, *VKORC1* variability accounted for 21–25% of the variation in warfarin dose between individuals.⁴

Approximately 6% to 10% of the variability in warfarin dose is attributable to polymorphisms within the *CYP2C9* locus.⁴ Compared to the *CYP2C9**1 reference allele, warfarin metabolism is reduced by 30% to 50% in carriers of the *CYP2C9**2 allele and 90% in carriers of the *CYP2C9**3 allele, resulting in lower warfarin dose requirements and increased bleeding risk in *CYP2C9**2 and *3 carriers.⁷⁻¹⁰ In a meta-analysis of 9 studies involving 2775 patients, the *CYP2C9**2 variant was associated with a 17% reduction in warfarin dose and a 1.91 (95% confidence interval [CI], 1.16–3.17) increased relative risk of bleeding, whereas in *CYP2C9**3 carriers, the relative risk of bleeding increased by 1.77 (95% CI = 1.07–2.91), despite carriers of both

risk alleles requiring lower doses of warfarin.¹¹ Additional polymorphisms in the *CYP4F2* loci have also been associated with warfarin dose variability in several studies, although the mechanism is unclear, and may be mediated by indirect influences on vitamin K metabolism.¹² The impact of *CYP4F2* polymorphisms appears to be significantly less than that of *CYP2C9* mutations or clinical factors, accounting for approximately 1% of the variability in warfarin dose.¹³

Several algorithms combining genetic and clinical criteria have been generated to help improve dose prediction. Klein et al demonstrated improved dose prediction using a pharmacogenetic-clinical algorithm compared to a clinically based algorithm ($R^2 = 0.47$ vs 0.27 , $P < 0.001$) or a fixed dose approach ($R^2 = 0.47$ vs 0 , $P < 0.001$) in 5052 patients treated with warfarin, with fewer overestimations of dosage in those receiving ≤ 21 mg of warfarin per week, and fewer underestimations in those receiving ≥ 49 mg of warfarin per week.⁶ Randomized control studies have observed improvements in surrogate markers of treatment efficacy with genetic-based algorithms, such as increased time in the therapeutic range, reduced out-of-range INRs, and decreased dose adjustments.^{14,15} Although the US Food and Drug Administration (FDA) currently mandates drug labels informing clinicians that genetics

can assist in warfarin dose prediction, there is lack of clinical outcome data from randomized control trials (RCTs) to provide clinical guidance. In a meta-analysis of 3 RCTs involving 521 participants, pharmacogenetically based dosing was associated with a 0.69 (95% CI = 0.16–2.9) relative risk of bleeding, with no significant difference in thromboembolic events.¹⁶ Despite a point estimate favoring a reduction in major bleeding, the effect was nonsignificant, emphasizing the need for larger studies adequately powered to detect clinical outcomes, which are currently underway. Finally, novel antithrombotic agents such as dabigatran, rivaroxaban, and apixaban, which demonstrate equivalent or superior efficacy compared to warfarin in atrial fibrillation, may overtake warfarin use, thereby rendering tailored methods to improve warfarin dosing less important.

Clopidogrel Response

Dual antiplatelet therapy following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) has been shown to significantly reduce CV events, with the most common antiplatelet regimen combining aspirin with clopidogrel, a thienopyridine that inhibits the P2Y₁₂ receptor. The most common adverse effect of clopidogrel therapy is bleeding, with a major bleeding event occurring in 3.7% of patients receiving long-term therapy.¹⁷ Given that clopidogrel is a prodrug, of which only 15% is converted to the active metabolite via oxidative transformation by CYP enzymes, the pharmacokinetics of clopidogrel can vary significantly with polymorphisms in the *CYP2C19* gene, with lower plasma drug concentrations in *CYP2C19**2 or *3 allele carriers, and increased drug concentrations in *CYP2C19**17 carriers.

Regulatory agencies, such as the FDA, have issued a black box warning cautioning clopidogrel use in reduced function allele carriers. However, there are conflicting clinical outcome data and a lack of clear strategies on how to manage poor responders. The most recent evidence suggests that although *CYP2C19* polymorphisms appear to significantly impact clopidogrel metabolism and platelet activity, these effects do not significantly impact clinical events. In a meta-analysis of 32 studies evaluating the impact of the *CYP2C19* polymorphisms in 42 016 patients, the presence of a reduced function allele was significantly associated with lower clopidogrel metabolite concentration and increased platelet activity. However, the overall clinical impact on bleeding risk or CVD events was small, and when analysis of clinical events was limited to larger studies, no significant differences in clinical events were observed. Moreover, analysis of studies with genotyped placebo controls demonstrated no significant modification of clinical effects with clopidogrel compared to placebo.^{18,19} Overall, the current data suggest that *CYP2C19* polymorphisms have a limited impact on clinical events in those receiving clopidogrel. Further supporting the notion that personalized approaches to clopidogrel dosing may have limited clinical impact are the results of clinical trials utilizing platelet testing, which have failed to demonstrate any significant differences in clinical outcomes when compared to usual care.^{20,21} Nonetheless, some studies have evaluated methods utilizing pharmacogenetic testing to direct patient care as a proof of concept. Recently, a strategy of identifying *CYP219**2

carriers through point-of-care genetic testing, and selective treatment with prasugrel, was associated with improved platelet inhibition in patients with ACS undergoing PCI. Although this demonstrates that going directly from genetic testing to pharmacotherapy is feasible, the clinical benefits of this approach should be proven prior to its adoption.²²

Associations between other genes and clopidogrel response have been studied less extensively. Polymorphisms of the *ABCB1* gene, which encodes the p-glycoprotein efflux pump involved in the metabolism of several drugs, have been shown to influence active metabolite levels, platelet reactivity, and CV outcomes in participants receiving clopidogrel.^{23–25} Haplotypes of the *P2RY12* gene, encoding the P2Y₁₂ receptor, have been shown to influence platelet function in patients receiving clopidogrel who are undergoing percutaneous coronary intervention, although further studies are needed to evaluate clinical outcomes.^{26,27} Moreover, with newer antiplatelet agents, such as prasugrel or ticagrelor, demonstrating improved efficacy compared to clopidogrel, the need to test for clopidogrel response may diminish with the broader adoption of newer agents. In a substudy including 10 285 participants from the Platelet Inhibition and Patient Outcomes (PLATO) trial that compared CV outcomes with clopidogrel and ticagrelor, several *CYP2C19* polymorphisms associated with normal CYP function (*1), reduced function (*2–*8), and gain-of-function (*17) were analyzed based on the presence or absence of a reduced-function allele. Ticagrelor was associated with a significant reduction in the composite outcome of CV death, myocardial infarction, or stroke compared to clopidogrel irrespective of genotype, without a significant contribution from genetic factors that influence clopidogrel response.²⁴

Aspirin Response

Aspirin remains the cornerstone of antithrombotic therapy in those with CVD; it is associated with an 18% relative risk reduction in serious vascular events. Although the doses of aspirin used in clinical practice for CVD (ie, 80–325 mg) are 2.5- to 10-fold larger than what is required to fully inhibit cyclooxygenase-1 activity, variability in platelet aggregation is still observed at these doses.^{28,29} Although the clinical impact of factors influencing aspirin response remains debated, some studies have demonstrated increased CV events in poor responders.³⁰

Pharmacogenetic studies have evaluated several genes associated with platelet activation and aggregation pathways, focusing on intermediate endpoints of platelet function. Although further data are needed, promising polymorphisms impacting aspirin response have been identified within the gene encoding the platelet endothelial activation receptor-1 (PEAR-1), which is stimulated by platelet-to-platelet contact, causing the activation of tyrosine phosphorylation-mediated signaling pathways and platelet aggregation.³¹ This locus is of particular interest because PEAR-1 is not directly involved in aspirin pharmacokinetics, or as a target receptor, but instead demonstrates how downstream, indirect effects on platelet aggregation impact drug efficacy. In a candidate gene study of *PEAR1*, Herrera-Galeano et al observed a significant association between the rs2768759 single nucleotide polymorphism (SNP) and

Table 2. Select Genes and Their Impact on Statin Efficacy

Gene	Chromosome	Polymorphisms	Minor Allele ^a	Minor Allele Frequency ^a	Effect
<i>SLCO1B1</i> ⁴⁹	12	SLCO1B1*5 (rs4149056)	C	0.15	Increased risk of myopathy
<i>APOE</i> ^{23,39–42}	19	rs7412	T	0.07 ^c	Polymorphisms form three haplotypes: ϵ 3, ϵ 2 and ϵ 4. Associated LDL reduction is greatest with ϵ 2 haplotype, and lowest with ϵ 4 haplotype.
		rs429358	C	0.15 ^c	
<i>HMGCR</i> ^{36,42}	5	rs10474433	C	0.36	Modification of statin effect on LDL
		rs17244841	T	0.04 ^c	(nothing to put under gene, chromosome or effect)
		rs17671591	T	0.36	
<i>LDL-R</i> ³⁸	19	AVA II (rs5925)	C	0.43 ^c	Modification of statin effect on LDL
<i>ABCB1</i> ^{39,43}	7	rs2032582	A	0.47	Smaller reduction in LDL
		rs2235067	T	0.15	Modification of MI risk
<i>PCSK9</i> ⁴²	1	rs11591147	T	0.01	Modification of statin effect on LDL
<i>KIF6</i> ⁴⁶	6	rs20455	G	0.37	Modification of death or major CV event risk
<i>LIPC</i> ⁴³	15	rs8192701	T	0.15	Modification of stroke risk
		rs12914035	G	0.13	
		rs1968685	G	0.47	
		rs7163555	G	0.10	
<i>CETP</i> ⁴³	16	rs5883	T	0.07	Modification of stroke risk
<i>ADAMTS1</i> ⁴⁵	21	rs402007	C	0.24 ^b	Modification of MI risk
<i>GNB3</i> ⁴⁴	12	C825T	T	0.31 ^b	Modification of stroke risk
<i>TLR4</i> ⁴⁷	9	Asp299Gly	NR	NR	Modification of CV event risk

Abbreviations: CV, cardiovascular; LDL, low-density lipoprotein; MI, myocardial infarction; NR, not reported.
^aMinor allele and frequencies are reported from the HapMap white population unless otherwise specified.⁷² ^bReported or estimated from the referenced study population. ^cReported from the 1000 Genomes Project.⁷³

platelet response to collagen, adenosine diphosphate, or epinephrine, with carriers of the C allele demonstrating greater native platelet aggregation before and after receiving aspirin therapy. Results were consistent in whites and individuals of African descent, accounting for 2.5% and 6.9% of the variation in aspirin-induced platelet response, respectively.³¹

Genetic studies evaluating other candidate genes associated with aspirin resistance have reported inconsistent results, partially due to heterogeneity in study designs, sample sizes, and assays used to define the phenotype. In a systematic review of 31 candidate gene studies (not including *PEAR1*) evaluating the effect of various genetic

polymorphisms on aspirin resistance, only the P1A1/A2 polymorphism in *ITGB3* encoding the glycoprotein IIIa receptor demonstrated a significant association with aspirin resistance. Moreover, the P1A2 variant was only associated with aspirin resistance in healthy subjects (odds ratio [OR] = 2.36, 95% CI = 1.24–4.49, $P = 0.009$), whereas no effect was observed in those with CVD (OR = 0.92, 95% CI = 0.65–1.30, $P = 0.64$).³² Although additional genes were not significant, the evaluated studies had small sample sizes, and were likely underpowered to detect small to moderate effects. Moreover, there was significant heterogeneity between assays used to detect platelet resistance, which may have impacted results.

3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibitors: Low-Density Lipoprotein Response, Clinical Outcomes, and Adverse Effects

Serum low-density lipoprotein (LDL) reduction with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) has greatly improved CV outcomes among individuals with established coronary artery disease, or those at increased risk for CV events.³³ With several studies demonstrating incremental CV risk reduction with high-dose statins, clinical guidelines support aggressive lipid lowering in secondary prevention or high-risk primary prevention. However, statin-related side effects are an important cause of nonadherence. Myalgia affects 5% of individuals on statins, and rhabdomyolysis occurs in 1:10 000 patients, with the risks of developing these adverse effects increased at higher doses.³⁴

A significant proportion of patients receiving statins do not achieve LDL values targeted in CVD guidelines, emphasizing the need to address interindividual variability in statin response and treatment adherence.³⁵ Genetic studies have identified several genes associated with LDL reduction (Table 2), although most lack consistent replication.^{36–42} In a large, candidate gene study, Chasman et al examined the impact of polymorphisms from 10 loci on lipid changes in 1536 participants receiving 40 mg/d pravastatin over a 24-week period.³⁶ Polymorphisms in the gene encoding HMG-CoA reductase (*HMGCR*) were associated with a reduced response to the statin, with heterozygotes of one polymorphism achieving a 22% lower reduction in total cholesterol ($P = 0.001$) and a 19% lower reduction in LDL ($P = 0.005$) compared to non-carriers of the risk allele. Neither polymorphism impacted lipid levels in 649 participants not receiving statins, suggesting that resistance to lipid lowering was statin related, rather due to confounding. Several studies have reported an association between statin response and polymorphisms in the *APOE* locus, with a greater reduction in LDL seen in e2 allele carriers and a diminished response in e4 carriers, although the overall impact on LDL appears modest.^{39–41}

Although LDL is strongly related to CV events, the impact of genetic polymorphisms on statin response cannot be fully realized without examining clinical outcomes. In a small number of studies, differences in CV outcomes have been observed with several genes in participants receiving statins, although these results require further replication (Table 2).^{43–47} There is the potential for an additional approach to the pharmacogenetics of lipid disorders. Recently, a genome-wide association study (GWAS) involving >100 000 individuals detected and confirmed 95 genetic variants regulating plasma levels of lipids, of which 59 are novel, explaining 10% to 12% of the total variance in LDL, high-density lipoprotein, and triglyceride levels.⁴⁸ Although further study is required for clinical application, these lipid genetic variants regulating plasma levels may partially determine the dose of a statin needed to optimize treatment effects.

Genetic variability also significantly impacts the development of myopathy in those who receive a statin. In a recent GWAS conducted by the Study of the Effectiveness of Additional Reductions in Cholesterol

and Homocysteine (SEARCH) collaborative group, a polymorphism of the *SLCO1B1* gene (rs4149056) explained 60% of the variability in simvastatin-induced myopathy ($P = 2 \times 10^{-9}$), with 0.15% of the population possessing the C risk allele.⁴⁹ Similar results have been observed in several additional studies examining the relationship between *SLCO1B1* and myopathy associated with different statins.⁵⁰ Voora et al examined the impact of selected polymorphisms in 99 patients (with matched controls) who discontinued statins due to any side effect, experienced myalgias, or had creatine kinase elevations $>3 \times$ the upper limit of normal. The rs149056 polymorphism was associated with increased adverse events (37% vs 25%, $P = 0.03$), with an observed gene-dose response, characterized by an adverse event incidence of 19%, 27%, and 50% for 0, 1, or 2 risk alleles, respectively (trend $P = 0.01$).⁵¹ With novel-lipid lowering agents such as PCSK9 inhibitors being studied that may become effective alternatives to statins, future genotyping strategies may inform tailored approaches to statin therapy, or alternative treatments, in those at high risk for myopathy.

ACE Inhibitors

Significant reductions in CV events have been demonstrated with inhibition of the renin angiotensin aldosterone system (RAAS) in patients with established heart disease, or at high risk for vascular events, with the use of ACEis. Secondary stimulation of the bradykinin pathway uncommonly results in cough or angioedema, occurring in 4.1% and 0.3% of patients receiving ACEis, respectively.⁵²

Polymorphisms in several genes encoding critical enzymes or receptors involved in the RAAS pathway have been evaluated. Although some studies have demonstrated a significant association between the *ACE* gene insertion/deletion (I/D) polymorphism and CV outcomes, the impact of this polymorphism on ACEi response not well understood.^{53–55} McNamara et al studied the impact of the *ACE* (I/D) polymorphism on 479 participants with heart failure treated with ACE inhibitors, and observed an increased risk of death or transplantation in carriers of the *ACE-D* polymorphism.⁵⁶ Conversely, a larger study of 37 939 hypertensive patients treated with various antihypertensive agents, including ACEis, failed to demonstrate a relationship between the *ACE* gene I/D polymorphism, and either CV event risk or pharmacologic treatment response.⁵⁷ Although these opposing results may be due to different participant characteristics, with the lack of consistent replication, it is difficult to conclude from the current data whether *ACE* polymorphisms result in clinically significant differences in ACEi response. Without additional studies, the impact of *ACE* polymorphisms on ACEi efficacy remains uncertain.

To explore the premise that genes regulating the RAAS pathway may have cumulative effects on ACEis, a gene score comprised of polymorphisms within the AT1 receptor and bradykinin type 1 receptor genes was evaluated in a genetic substudy of 8907 participants from the European Trial on Reduction of Cardiovascular Events with Perindopril in Stable Coronary Artery Disease (EUROPA). An increasing genetic risk score (ranging from 0 to 4 risk alleles) was associated with increased CV events in participants receiving perindopril.⁵⁸ Observations from this analysis

highlight that, for drugs with complicated pharmacokinetic or pharmacodynamic pathways, understanding the impact of multiple polymorphisms together may be necessary to fully characterize pharmacogenetic effects.

Limited studies have evaluated genetic polymorphisms affecting side effects related to ACEis such as cough or angioedema. Candidate gene studies have not consistently demonstrated an association between *ACE* or bradykinin receptor 2 (*BK2*) polymorphisms and angioedema, despite these being crucial genes in the RAAS and bradykinin pathways respectively.^{59,60} Initial analysis of *XPNPEP2*, which encodes membrane-bound aminopeptidase, has indicated correlation with reduced aminopeptidase activity and ACEi-related angioedema ($P = 0.036$).⁶¹ *ACE-D* and *BK2* polymorphisms have been associated with ACEi-induced cough in East Asian populations.^{62–64} Overall, several polymorphisms of the RAAS have been shown to influence ACEi efficacy and the risk of adverse events, with multiple alleles potentially acting together to impact drug pharmacology. However, many of these results require replication in additional studies for more generalizable conclusions to be made about their pharmacogenetic effects.

β-Adrenergic Receptor Blockade

Studies demonstrate a significant reduction in CV mortality and morbidity with β-adrenergic receptor blockers

(β-blockers) after myocardial infarction or in the long-term treatment of heart failure. Polymorphisms of the *ADRB1* and *ADRB2* genes have been shown to influence adenylyl cyclase activity through β1- and β2-adrenergic receptors. Although studies have identified several genetic polymorphisms influencing β-blocker response and impacting surrogate heart failure endpoints, data evaluating clinical outcomes have been less conclusive, making it difficult to draw strong conclusions about the clinical impact of these polymorphisms (Table 3).^{65–70} For example, Liggett et al observed a significant mortality reduction in *ADRB1* Arg389 carriers treated with bucindolol therapy compared to placebo (hazard ratio [HR] = 0.62, 95% CI = 0.40–0.96, $P = 0.03$), whereas Gly389 carriers did not demonstrate any response to bucindolol treatment compared to the placebo (HR = 0.90, 95% CI = 0.62–1.30, $P = 0.57$), although interaction testing was insignificant.⁶⁹

Genes encoding downstream effectors of the β-adrenergic pathway, such as *GRK5* and *GNAS*, have also been implicated in β-blocker efficacy. In a study of 1554 African American and 591 white participants, the effect of β-blocker treatment on mortality was significantly modified by the presence of the *GRK5-L41* variant (rs17098707) in African American participants with heart failure ($P = 0.036$) and ACS ($P = 0.023$).⁷⁰ No effect was observed in whites, although the L41 allele frequency was lower in

Table 3. Select Genes and Their Effects on ACEis and β-Blockers

Drug Class	Gene	Chromosome	Polymorphism	Minor Allele ^a	Minor Allele Frequency ^a	Effect
ACEi	<i>ACE</i> ^{56,62,63}	17	ACE-D	Deletion allele	0.50 ^{b, c}	Increased death or transplantation risk in heart failure patients treated with low-dose ACEi. Increased ACEi-induced cough.
	<i>AT1R</i> ⁵⁸	3	rs275651	A	0.22	Modification of CV death or MI risk.
			rs5182	C	0.48	
	<i>BK-1</i> ⁶²	14	rs12050217	G	0.19	Modification of CV death or MI risk.
	<i>BK-2</i> ⁵⁵	14	–58T/C	T	0.44 ^d	Increased ACEi-induced cough.
	<i>XPNPEP2</i> ⁶¹	X	C2399A	A	0.40 ^b	Increased ACEi-related angioedema.
β-Blocker	<i>ADRB1</i> ⁶⁹	10	Arg389Gly (rs1801253)	G	0.31	Lower mortality with Arg-389 carriers in CHF.
	<i>ADRB2</i> ⁶⁸	5	Arg16Gly (rs1042713)	A	0.36	Increased mortality or transplantation risk with Arg16Gln27 haplotype in CHF.
			Gln27Glu (rs1042714)	G	0.46	
	<i>GRK5</i> ⁷⁰	10	rs17098707	T	0.01 ^b	Modified mortality risk based on β-blocker usage. Only observed in African Americans with CHF or ACS.
					0.23 ^{b, e}	
	<i>GNAS</i> ⁷¹	20	rs6123837	A	0.41	Association between polymorphisms and mortality following cardiac surgery.
			rs15754	G	0.29 ^f	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction.

^aMinor allele and frequencies are reported from the HapMap white population unless otherwise specified. ^bReported or estimated from the referenced study population. ^cReported from a multiethnic population. ^dReported from an East Asian population. ^eReported from an African American population.

^fReported from the 1000 Genomes Project.⁷³

that ethnic group, reducing the study's power to detect a significant pharmacogenetic interaction. A gene-gene interaction between adrenergic receptor coding *ADRB* variants and *GNAS*, encoding *Gas*, was also reported in a small study of 185 participants undergoing cardiac surgery, with the presence of both *GNAS* and *ADRB2* risk alleles significantly increasing cardiac specific mortality (HR = 2.3, 95% CI = 1.5–3.5) compared to no risk alleles.⁷¹ Thus far, studies have identified several promising loci that may influence β -blocker efficacy and clinical outcomes through direct effects or gene-gene interactions. However, further studies are needed to provide more conclusive evidence of these effects prior to adapting any pharmacogenetic strategies into clinical practice.

Judging the Population Impact of Personalized Pharmacogenetic Strategies

Even if personalized approaches based on genetic screening succeed in improving clinical outcomes in those at increased genetic risk, these strategies may have limited impact from a population perspective if only a small proportion of individuals derive benefit. For example, although the *CYP2C9**2 genetic variant is associated a 30% to 50% reduction in warfarin metabolism and increased bleeding, the allele frequency of the risk allele is 10% in the white population. Heterozygous carriers of the risk allele would comprise approximately 18% of the population, and homozygous carriers (who would be at the greatest bleeding risk) would comprise approximately 1% of the population. Although personalized medicine is focused on tailoring therapies to optimize individual responses to treatment, given that healthcare resources are finite in most countries, the cost effectiveness of genetic guided screening strategies requires careful consideration prior to their implementation in clinical practice.

Summary of Evidence and Clinical Guidance

Currently there is a lack of evidence supporting the use of genetic testing to guide pharmacologic treatments in CVD management. The most promising evidence is related to warfarin therapy, where several landmark studies have now demonstrated an association between *CYP2C9* and *VKORC1* polymorphisms and clinically important outcomes such as bleeding. Moreover, incorporating genetically based algorithms appears to result in improved warfarin dosing over routine practice. However, the impact of these strategies on clinical outcomes remains uncertain and needs to be proven. Currently, we do not recommend a role for warfarin pharmacogenetic testing in clinical practice, but anticipate the results of clinical outcomes studies that are currently underway.

The association between *SLCO1B1* polymorphisms and statin-induced myopathy has also been clearly established through pharmacologic studies. However, it remains unclear how to incorporate this knowledge into routine clinical care. Further studies are needed to test the clinical impact of strategies that use *SLCO1B1* testing to influence lipid management, particularly in groups that are at increased risk for myopathy, such as those receiving high-dose statins.

Despite significant interest in the role of *CYP2C19* on clopidogrel response, results of the recent meta-analysis by Holmes et al suggest there is limited impact on clinical outcomes associated with these polymorphisms.¹⁸ Accordingly, we see no current role for routine genetic testing to aid clinical decisions regarding clopidogrel therapy. Among the other CV drug classes reviewed, most identified polymorphisms require replication in additional studies to provide further evidence supporting their pharmacogenetic effects.

Future Directions

Significant challenges need to be overcome to better understand the utility of genetic testing in CV care. Thus far, most pharmacogenetic studies have relied on pharmacokinetic or pharmacodynamics endpoints to evaluate the impact of genetic polymorphisms. Although this approach is useful to first identify gene-drug interactions, further evaluations are required in studies that are adequately powered to examine relevant clinical outcomes. Furthermore, replication studies are needed to confirm whether initial effects are generalizable, or represent false-positive findings.

Another major limitation of many pharmacogenetic studies is that analysis of treatment effects are limited to those who received the studied medication, without a comparative (eg, control, usual care) group. In this study design, it is difficult to distinguish whether a significant association is due to a true gene-drug interaction, to the polymorphism itself, or confounding. For example, several treatment-only studies solely analyzing patients on clopidogrel have observed a significant association between *CYP2C19* loss of function alleles and clinical events. However, in studies that also analyzed comparator groups, similar effects were shown in those not treated with clopidogrel, suggesting that the association is related to an alternative mechanism rather than a genetic interaction with clopidogrel response.¹⁸ Therefore, significant interactions identified in treatment-only studies should only be considered hypothesis generating, and need confirmation in studies using comparator groups. Ideally, this would be in the setting of randomized control trials comparing pharmacogenetically guided treatments to alternate strategies. Moreover, despite the cost of genetic tests decreasing substantially, routine testing in patients receiving these medications can lead to significantly increased costs for health providers. Economic analyses of clinically beneficial pharmacologic strategies would also be valuable to guide health policy decisions.

Conclusion

Currently, the promise of a personalized genetic approach to improve CV care has yet to be reached. In some instances, genetic testing may provide valuable additional information to guide treatment decisions, but clinical outcome data are lacking. Although the available data may give us pause as to whether the hope of personalized CV pharmacogenetics will become realized, what is clear is that more detailed investigations are required to fully understand the potential of pharmacogenetics in CV care.

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