

# Pharmacogenomics in cardiovascular disorders: Steps in approaching personalized medicine in cardiovascular medicine

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**Abstract:** Some of the most commonly prescribed medications are those for cardiovascular maladies. The beneficial effects of these medications have been well documented. However, there can be substantial variation in response to these medications among patients, which may be due to genetic variation. For this reason pharmacogenomic studies are emerging across all aspects of cardiovascular medicine. The goal of pharmacogenomics is to tailor treatment to an individual's genetic makeup in order to improve the benefit-to-risk ratio. This review examines the potential pharmacogenomic parameters which may lead to a future of personalized medicine. For example, it has been found that patients with CYP2C9 and VKORC1 gene variations have a different response to warfarin. Other studies looking at  $\beta$ -blockers, ACE inhibitors, ARBs, diuretics and statins have shown some results linking genetic variations to pharmacologic response. However these studies have not impacted clinical use yet, unlike warfarin findings, as the small retrospective studies need to be followed up by larger prospective studies for definitive results.

**Keywords:** cardiovascular, pharmacogenomics, genetics, cardiovascular medicine, personalized medicine, polymorphism

## Introduction

Cardiovascular disease (CVD) is the number one cause of death, even with today's technological advancements. According to the American Heart Association, approximately 80 million people (one out of three) have one or more forms of CVD.<sup>1</sup> This places a major burden to improve the treatment of CVD. Doctors commonly use trial and error in discovering what medicine will work for each patient; but what if doctors were able to prescribe medications based on the specific genetic make up of a patient, knowing beforehand which medicine will work best for this patient and how this patient would respond.<sup>2,3</sup> There are many factors that can contribute to how a patient responds to a certain drug such as age, sex, body weight, nutrition, organ function, infections, concomitant medications, and genetic factors.<sup>4</sup> There has been a recent shift from looking at single genes (genetics) to focusing on the functions and interactions of the whole genome.<sup>5</sup> One major focus of today's pharmacogenomic research is in the field of cardiovascular medicine.<sup>6</sup> Currently there are many studies related to this topic in cardiovascular medicine, generating some statistically significant findings that are and will change the way doctors treat patients on an individual level. In this review we will focus on pharmacogenomics in: warfarin,  $\beta$ -blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics, and statins. Table 1 briefly outlines the polymorphisms reviewed.

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## Pharmacogenomics

Pharmacogenomics is the study of how a patient's genes could affect their response to a drug;<sup>2</sup> it is a way to personalize medicine and prescribe the optimal drug at the most advantageous dose for that patient, instead of a one drug fits all or trial and error theme. In the future doctors could predict who would respond to a drug and who would experience adverse reactions.<sup>7</sup> Even with our advances in medicine, not every patient will have a full response to every drug.<sup>8</sup> Another major problem with current cardiovascular medications is the adverse drug reactions, which are a major cause of hospitalizations in the United States today. Pharmacogenomics could help identify which patients would not benefit from a drug and avoid adverse effects potentially leading to toxicity and death.<sup>7</sup> Overall, pharmacogenomics could lead to the selection of the most effective, safe medicine at accurate dosing regimens, which would potentially decrease health care costs dramatically. Reducing hospitalizations due to adverse events, the number of failed drug attempts and the number of medications a patient may need to take to find an effective regimen are all reasons pharmacogenomics would not only be beneficial to patients but be cost effective.<sup>6</sup>

Genotyping technologies have shown positive advancements in comprehending the human genome and how genetic variations can have substantial effects.<sup>7</sup> The exact reason for variability in drug response is not clearly known, however there is evidence

that genetics are partially responsible at least.<sup>9</sup> Researchers have focused on single-nucleotide polymorphisms (SNPs) and DNA copy number variants (CNVs). Pharmacogenomic studies are attempting to link SNPs or CNVs to the expression of a target gene and eventually to how individual patients would respond to a medication.<sup>7</sup> Using a DNA microarray, or a DNA chip, one can determine which genes are expressed. One problem is that we know that drugs respond to genetic and nongenetic factors, but we are not sure how much each factor effects the variation in drug response.<sup>7</sup> One form of pharmacogenomics that is currently being used are the cytochrome P450 (CYP) enzymes. CYP enzymes are responsible for metabolizing many classes of medications, including cardiovascular medications. DNA variations in genes that code for these CYP enzymes could then cause either an overactive enzyme or an inactive form. If a patient had a DNA variation causing an inactive enzyme the drug could build up in the body, possibly leading to serious toxicity.<sup>4</sup> The inclusion of pharmacogenetic data such as CYP polymorphisms is starting to be seen in drug package inserts. Specifically, the package insert for warfarin provides doctors with genomic information regarding drug dosing and how people's responses may vary.<sup>10</sup>

## Pharmacogenomics with warfarin

Some of the most promising pharmacogenomic data right now is with the anticoagulant warfarin. Warfarin is the

**Table I** Polymorphisms reviewed for their association in drug response variability with cardiovascular medications

Drug or drug class	Gene	Polymorphism	Functional role	References
Warfarin	CYP2C9	CYP2C9 2* and 3* alleles	Enzymatic activity	3, 8, 10–12, 14
	VKORC1	–1639G > A and –1173C > T	Required to activate clotting factors	3, 8, 10, 11, 13, 14
Beta blockers	ADRB1	Ser49Gly	Mediate the effects of epinephrine and nor-epinephrine	8, 15, 16
		Arg389Gly		8, 9, 15–17
	ADRB2	Gly16Arg Gln27Glu	8, 15, 16 8, 15, 16	
ACE inhibitors and ARBs	ACE	I/D	Involved in converting angiotensin I to angiotensin II	8, 16, 18–20
	AGT	Met235Thr		16, 18, 19
	AT1R	A1166C		8, 16, 18, 19
Diuretics	α-adducin	Gly460Trp	Renal tubular sodium re-absorption	8, 20, 22, 23
	NPPA	T2238C	Controls electrolyte homeostasis	24
Statins	MDR1/ABC	ABCG5 and ABCG8	Cholesterol transport across the plasma membrane	25, 29
		HMGR	SNP 12 and 29 on chromosome 5	Cholesterol synthesis
	LDLR	Rs688	Receptor for plasma LDL	25, 31
	APOE	ε2, ε3, and ε4	Major binding protein for VLDL/IDL cholesterol	8, 25, 27

**Abbreviations:** ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; LDL, low-density lipoprotein; LDLR, LDL receptor; VLDL, very LDL.

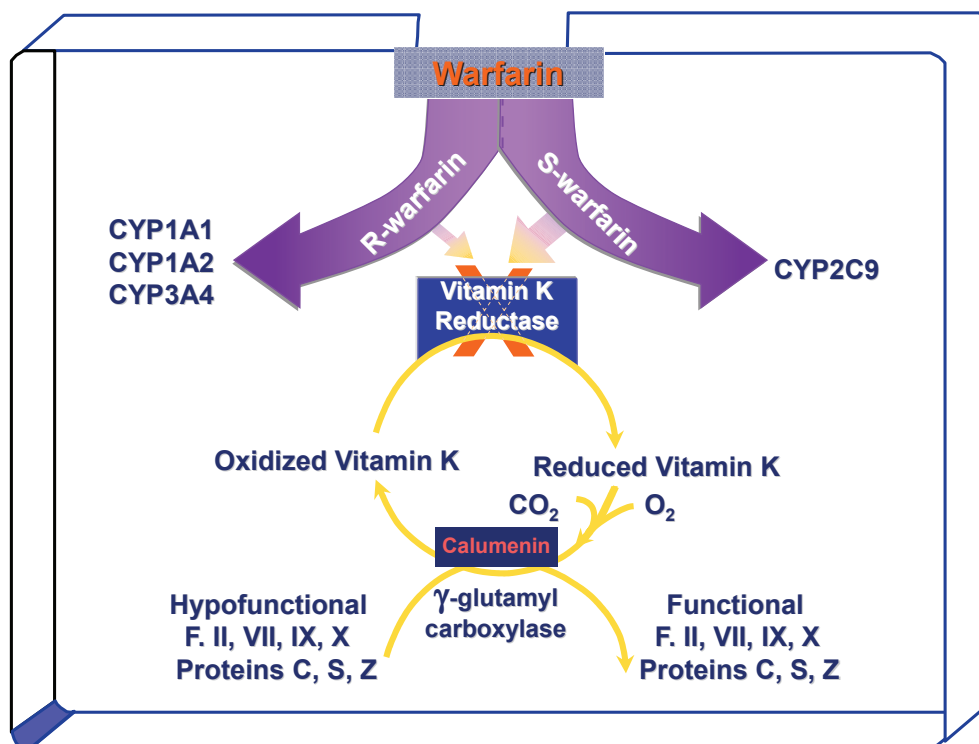
most commonly prescribed anticoagulant for the prevention and treatment of thromboembolic events.<sup>11</sup> Unfortunately, warfarin has a narrow therapeutic index, which means that even a small change in the dose could lead to adverse effects. Patients that take drugs with a narrow therapeutic index require constant monitoring to insure a safe level and uniform results. If the dose of warfarin is too high, significant bleeding events may occur. On the other hand, if the dosing is too low, thromboembolic events will not be prevented as intended. Prothrombin time and international normalized ratio (INR) are used to monitor the anticoagulation status of warfarin.<sup>12</sup> Warfarin is metabolized via the hepatic cytochrome P450 enzyme, specifically CYP2C9. Drugs either inhibiting or enhancing the CYP2C9 can have detrimental effects on warfarin since it has a narrow therapeutic index. Any variation in the CYP2C9 enzyme can also cause some patients to have a slower metabolism of warfarin, meaning the drug will stay in the body for a longer period of time, thus putting the patient at an increased risk of bleeding.<sup>12</sup> Recently a possible pharmacodynamic mechanism of warfarin resistance has been revealed with the warfarin target gene. This gene encodes vitamin K epoxide reductase complex 1 (VKORC1), which recycles reduced vitamin K. The figure below shows warfarin's CYP metabolism and the role of vitamin K reductase. Since vitamin K reductase is encoded by VKORC1 warfarin's anticoagulant effect will also be affected by polymorphisms in this gene.<sup>13</sup> Prior to pharmacogenomic studies, warfarin-dosing regimens were based on age, sex, weight and co-medication. With the advent of pharmacogenomics, variations in CYP2C9 and VKORC1 enzymes should also be considered.<sup>14</sup>

The first main gene studied for its warfarin dose-related effects is the CYP2C9 gene. Studies show that there are two main variant alleles of CYP2C9, the \*2 allele and the \*3 allele.<sup>11</sup> These alleles have been shown to cause reductions in enzymatic activity by approximately 30% and 80% respectively, thus increasing the chance of bleeding.<sup>12</sup> There have been many studies on the CYP2C9 variant alleles conferring similar results. The mean warfarin dose in the \*3 allele was significantly lower than the \*2 allele and the wildtype allele (\*1/\*1). The \*2 allele warfarin dose was also significantly lower compared to wildtype. These findings suggest that maybe there is a gene-dose relationship.<sup>14</sup> Variant alleles were also associated with an increased time to reach stable dosing as compared to wildtype<sup>12</sup> and an increased risk to have above range INR's (INR > 3.2).<sup>11</sup> Lastly, there was an increased risk of bleeding in patients

with the variant alleles when compared to the wild type. Patients with the \*3 allele had a higher risk of bleeds (above range INR's) and took a longer time to reach a stable dosing regimen compared to those with the \*2 allele, but both of these variants had a higher risk of bleeds than the wildtype. Optimistically, with the use of genotype-guided dosing, we can reduce the risk of above range INR's, bleeds, and time to reach stable dosing.<sup>12</sup>

VKORC1 codes for vitamin K reductase. Vitamin K reductase is responsible for recycling oxidized vitamin K back to its reduced form after it has carboxylated several coagulation factors and proteins. Factors II, VII, IX, and X as well as proteins C, S, and Z are dependent on these steps to become functional (Figure 1). Certain variations of the VKORC1 gene will result in reduced activity of the enzyme, which further reduces the activity of vitamin K-dependent clotting factors, thus leading to bleeds.<sup>13</sup> There have been several studies with numerous SNP's, all showing similar outcomes. Specifically studied were polymorphisms at position -1639 and -1173. For these positions, carriers of A and T required significantly lower doses of warfarin compared to G and C carriers, respectively. For both of these positions, there was a significant risk of increased INR's for variant alleles.<sup>11,14</sup> There have also been several studies looking at group A and B haplotypes. Haplotypes containing a B variant require significantly higher mean warfarin daily doses compared to group A. Although different polymorphisms have been studied, the VKORC1 genotype seems to be the most important genetic factor in establishing inconsistencies in warfarin doses.<sup>13</sup>

These two pharmacogenomic advancements have recently begun to be taken into consideration when prescribing anticoagulant regimens. Recently, there have been changes to the warfarin package insert to include information on CYP2C9 and VKORC1 gene variations, recommending considering lower doses for patients with genetic variations in these genes; as these variations may put the patient at risk for adverse events.<sup>10</sup> These changes do not tell physicians they need to change their dosing regimens. Since this is a fairly new topic, this information was added to make physicians aware of the potential variations in dose response in these patients. Currently there are genetic tests available for CYP2C9 and VKORC1 genotyping.<sup>8</sup> Unfortunately, since these tests are still relatively new, they are not being used as much as they should. This could lead to at risk patients to develop adverse effects and additional avoidable costs.<sup>3</sup> Since warfarin is very commonly prescribed and has a narrow therapeutic window, many more studies will arise in the near future. Hopefully with larger prospective studies showing



**Figure 1** Warfarin is metabolized into R-warfarin and S-warfarin, which prevent coagulation by inhibiting vitamin K reductase. Vitamin K reductase recycles oxidized vitamin K back to its reduced form after it has carboxylated several coagulation factors and proteins. These steps are necessary for factors II, VII, IX, and X as well as proteins C, S, and Z to become functional. It has been found that the more potent S-warfarin is metabolized mainly via CYP2C9 and therefore polymorphisms in CYP2C9 could account for inter-patient variability in warfarin response.

conclusive evidence, warfarin will have genotype-guided dosing regimens.

## Pharmacogenomics with beta-blockers

$\beta$ -blockers have shown to be promising in the treatment of hypertension, heart failure (HF) and myocardial infarction.<sup>8</sup>  $\beta$ -blockers block the effects of norepinephrine and epinephrine, thereby slowing nerve impulses to the heart and thus decreasing the workload of the heart. As their name states,  $\beta$ -blockers antagonize the  $\beta_1$  and  $\beta_2$  adrenergic receptors (ADRB1 and ADRB2, respectively).<sup>15</sup> Currently there are several classes of  $\beta$ -blockers that work differently; depending on whether they are selective, nonselective and if they block just  $\beta$  receptors or  $\beta$  and  $\alpha$  receptors. ADRB1 polymorphisms have been studied and Ser49Gly and Arg389Gly have been shown to possibly affect receptor function.<sup>16</sup> ADRB2 polymorphisms have also been looked at and studies show that Gly16Arg and Gln27Glu may affect receptor function.<sup>8</sup> The main focus of pharmacogenomics with  $\beta$ -blockers is to determine if these polymorphisms could be a potential factor for the variable responses to this class of medications.<sup>15</sup>

The majority of the pharmacogenomic studies in this class of medications are on ADRB1 and its potential polymorphisms including Ser49Gly and Arg389Gly.<sup>16</sup> There has been a greater overall response to  $\beta$ -blockers for the 389Arg genotype as compared to the Gly genotype. The 389Arg genotype has been found to show significant improvements in left ventricular ejection fraction (LVEF) in response to  $\beta$ -blockers,<sup>9</sup> larger reductions in heart rate and blood pressure<sup>8</sup> and significant overall decrease in hospitalizations and mortality compared to the Gly389 carriers.<sup>17</sup> Therefore, patients with the 389Arg genotype treated with  $\beta$ -blockers showed overall better results when matched up to Gly389 carriers. If we look at the Ser49Gly polymorphism, Gly49 has been associated with greater reductions in end diastolic diameter compared to the 49Ser genotype. The 49Ser genotype has also been associated with an increase in heart rate and an overall increase in mortality as compared to Gly49 carriers treated with  $\beta$ -blockers.<sup>8</sup>

There have been several studies reviewing the ADRB2 polymorphisms (Gly16Arg and Gln27Glu), but the results have not shown a large amount of conclusive evidence.<sup>16</sup> The 27Gln and 16Arg genotypes have been associated with

overall increases in mortality in patients receiving  $\beta$ -blockers as compared to the Glu and Gly carriers. Unfortunately there hasn't been a great deal of promising information in this set of polymorphisms, but this may be helpful for future pharmacogenomic research.<sup>8</sup>

Overall, many studies have shown favorable outcomes in patients with the ADRB1 Arg389 polymorphism, however there have also been studies showing inconclusive results.<sup>8,17</sup> More pharmacogenomic research needs to be completed on both ADRB1 and ADRB2 in order to determine if these mutations truly affect  $\beta$ -blocker effectiveness. Another area of interest are the CYP2D6 enzymes which metabolize the majority of  $\beta$ -blockers; potential polymorphisms in this enzyme could affect the metabolism of  $\beta$ -blockers.<sup>16</sup> Another concerning factor for future research is that there are several classes of  $\beta$ -blockers, which effect the receptors differently.<sup>16</sup> So before any general conclusions can be made, more drugs within each class must be studied. If future research shows significant beneficial effects, genotyping prior to starting  $\beta$ -blockers could be performed to see who would obtain the greatest benefit.

## Pharmacogenomics with ACE inhibitors and ARBs

Both ACE inhibitors and ARBs are universally prescribed for the treatment of hypertension and other cardiovascular problems. Both of these classes of medications work by antagonizing the renin-angiotensin-aldosterone system (RAAS). ACE inhibitors work by blocking the conversion of angiotensin I to angiotensin II and ARBs work by blocking the stimulation of angiotensin II receptors (AT1R).<sup>18</sup> Overall, both of these classes of medications are effective in reducing blood pressure; however, recent pharmacogenomic studies are assessing possible polymorphisms that may affect the end results for patients. There have been many studies looking at polymorphisms such as an insertion/deletion (I/D) polymorphism in the ACE gene, a polymorphism in the angiotensinogen (AGT) Met235Thr gene and some research with a polymorphism in the gene encoding AT1R.<sup>16,19</sup> The main focus of these studies were to determine if these genetic mutations could in fact alter the response a patient may have to a specific drug in these particular therapeutic classes.

The ACE gene is an important place for a potential polymorphism because the ACE gene plays a major role in the RAAS. Currently the majority of these studies are focusing on insertion/deletion (I/D) polymorphisms in the ACE gene.<sup>8</sup> When it comes to assessing how this polymorphism could affect blood pressure, there have been conflicting results.

Similar inconclusive results were seen in studies looking at coronary heart disease (CHD) risk for the different genes.<sup>16,20</sup> A six-year hazard rate showed no significant differences in CHD, stroke or mortality among any of the genotypes treated with ACE inhibitors.<sup>20</sup> Studies did show that there were significantly more D/D genotypes than I/D or I/I in the black population.<sup>8</sup> Studies have also looked at the affect of the I/D polymorphism with respect to ARBs, however no conclusive results were found.<sup>16</sup> Overall, there have been a wide variety of studies showing inconclusive results with the I/D polymorphism in the ACE gene. Currently there is no definitive association between this gene and CHD risk and response to ACE or ARB treatment.

A second main focus is with the angiotensinogen (AGT) Met235Thr polymorphism.<sup>18</sup> This became a focus of pharmacogenomic interest because AGT could potentially affect the mechanism of action of ACE inhibitors.<sup>16</sup> Studies have shown that people with 235Thr alleles have higher circulating levels of angiotensin in their plasma than those with Met alleles. These studies also show that there may be an association between the 235Thr allele and increased blood pressure.<sup>16</sup> Now studies are looking to see if the M or T alleles affect the response to ACE inhibitors, or are linked to stroke or myocardial infarction (MI) with conflicting results; therefore the contribution of this polymorphism to blood pressure response and any link to stroke or MI remains uncertain.<sup>16,18</sup> Larger studies need to be completed to determine the exact role, if any, this polymorphism play in blood pressure response and stroke or MI.

Another polymorphism that has been looked at is the gene encoding AT1R, especially for possibly affecting the response to ARBs.<sup>8</sup> The most common polymorphism of this gene is the A1166C. However, studies gave inconsistent results and currently there are no significant conclusions with regards to this polymorphism.<sup>16</sup>

In conclusion, the current data available does not show that polymorphisms in the ACE, AGT or AT1R genes affect blood pressure response to ACE inhibitors or ARBs.<sup>16,18,20</sup> There have been many studies in relation to these polymorphisms, nonetheless the majority have conflicting results and/or several limitations thus affecting the credibility of the results. Hopefully researchers will continue to study these genes, along with others, to find some conclusive evidence that could change the way physicians prescribe these medications.

## Pharmacogenomics with diuretics

Diuretics play a major role in the treatment of hypertension. According to the Seventh Report of the Joint National

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the majority of the compelling indications requiring hypertensive treatment(s) have thiazide diuretics listed as a first-line choice.<sup>21</sup> Diuretics are proven to be very effective in helping patients reach their blood pressure goal of <140/90 mmHg (<130/80 mmHg for patients with diabetes or chronic kidney disease).<sup>21</sup> Unfortunately there can be significant variation in blood pressure responses to diuretics depending on the individual. Therefore, diuretics pose a good place for pharmacogenomic studies to figure out whether genetic polymorphisms are, at least partially, causing this inter-patient variability in responses.<sup>22</sup> There have been several studies in regards to the adducin gene, which is a cytoskeletal protein consisting mainly of an  $\alpha$  and  $\beta$  subunit.<sup>23</sup> There are three human genes (ADD1, ADD2, and ADD3) which encode these subunits.<sup>22</sup> There has also been some research into the atrial natriuretic precursor A (NPPA) gene with regards to inter-patient responses with diuretics.<sup>24</sup>

The  $\alpha$ -adducin gene (ADD1) has specifically been researched because of its association with thiazide diuretics in patients with hypertension. ADD1 is associated with renal tubular sodium reabsorption by sodium/potassium ATPase.<sup>23</sup> Specifically, researchers have been looking at the SNP Gly460Trp in ADD1. This polymorphism has been associated with a form of salt-sensitive hypertension.<sup>8</sup> Several studies confirmed that the 460Trp variant was associated with a greater reduction in blood pressure when treated with hydrochlorothiazide as compared to the wildtype.<sup>8,20</sup> The 460Trp variant, treated with a thiazide diuretic, was also associated with a significantly lower risk of MI and stroke. However diuretic therapy with the wildtype allele was not associated with the risk of MI or stroke.<sup>23</sup> Unfortunately there have been other studies with contradicting findings, showing that there was no association between ADD1 and blood pressure lowering or CHD risk, specifically with chlorthalidone.<sup>8</sup> There has also been some thought that ADD3 G/G homozygote could also cause hypertension, however more research is needed.<sup>22</sup> Overall, these studies show that the ADD1 gene may potentially affect blood pressure responses to diuretics; however more conclusive studies need to be completed.

The NPPA gene has also been involved in pharmacogenomic studies. The NPPA gene is necessary to derive the atrial natriuretic peptide (ANP). ANP acts as a diuretic by controlling electrolyte homeostasis and extracellular fluid volume.<sup>24</sup> Keeping this in mind, a reduced ANP level could be associated with hypertension, while an increase in ANP

could result in hypotension. The SNP NPPA T2238C has been the main focus of recent studies. For the T2238C variant, the C allele carriers were associated with lower CHD event rates as well as larger reductions in blood pressure compared to the T alleles when treated with chlorthalidone vs amlodipine. The TT genotype was associated with a greater risk of MI, stroke and all-cause mortality when treated with chlorthalidone compared to amlodipine.<sup>24</sup> This study showed promising data. However, there were several limitations so further pharmacogenomic studies on the NPPA gene need to be conducted.

Even though the ADD1 and NPPA polymorphisms showed some significant positive findings, pharmacogenomic studies have yet to impact how physicians prescribe diuretics.<sup>22-24</sup> There have been too many studies with conflicting evidence to be used at this time. Given the actions of adducin and the ANP gene, the ADD1 and NPPA polymorphisms seem to be excellent areas of cardiovascular pharmacogenomics.<sup>22,24</sup> Overall, diuretics are safe and effective in treating hypertension and other complications like MI, stroke or heart failure so they will continue to be a mainstay in drug therapy. Hopefully, with further pharmacogenomic studies, diuretic adjustments can be made based on a patient's specific genetic make up.

## Pharmacogenomic with statins

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors (statins) are a class of medications that lower cholesterol levels by decreasing cholesterol production in the liver.<sup>25</sup> Statins are a first-line therapy for the prevention of coronary artery disease (CAD), which happens to be a major leading cause of death.<sup>26</sup> Statins, as their drug name states, inhibit HMG-CoA reductase, which is the rate-limiting step in the biosynthesis of cholesterol. Inhibiting the biosynthesis of cholesterol reduces the secretion of apolipoprotein B (apoB) and upregulates the low-density lipoprotein (LDL) receptor activity, thus lowering cholesterol in plasma.<sup>25</sup> Cholesterol and lipids can cause plaque build-up or atherosclerosis. Even though statins are proven to be beneficial in the majority of people, some people have varying responses to these medications.<sup>27</sup> At first, environmental and social influences were thought to cause this variation; however more recent investigations have focused on genetic variations, or polymorphisms, which could be causing this variation in drug response.<sup>28</sup> There have been approximately 30 genes studied in reference to this possible genetic contribution. Unfortunately not many of these studies have had follow up studies or similar

**Table 2** Pharmacogenomics and cardiovascular medicines**Polymorphisms affecting warfarin response**

- CYP2C9 variant alleles, \*2 and \*3, are associated with:
  - Lower mean warfarin doses
  - Increased risk of elevated INRs leading to a increased risk of bleeds
- Polymorphisms in the VKORC1 at position -1639 and -1173 require lower doses of warfarin

**Polymorphisms affecting  $\beta$ -blocker response**

- The ADRB1 Ser49Gly and Arg389Gly polymorphisms seem to positively impact the response to  $\beta$ -blockers including increasing LVEF, reducing mortality and larger reductions in heart rate and blood pressure
  - However there remains inconclusive evidence preventing its clinical use
- Current information on the polymorphisms of ADRB2, Gly16Arg and Gln27Glu, are not sufficient enough to confirm a relation to dose response variation

**Polymorphisms affecting ACE inhibitors or ARB response**

- Current information on the I/D polymorphism associated with the ACE gene has shown conflicting results
- Inconsistencies with the AGT Met235Thr polymorphism prevent its clinical use
- A small number of studies showed inconsistent results on the AT1R A1166C polymorphism

**Polymorphisms affecting diuretic response**

- The 460Trp variant of the ADD1 Gly460Trp polymorphism may be associated with greater reductions in blood pressure and lower risk of MI or stroke in patients treated with a thiazide diuretic
  - However, other studies have showed conflicting results
- The C allele of the NPPA T2238C polymorphism has been associated with lower CHD event rates and larger reductions in blood pressure when treated with a diuretic compared to the T allele

**Polymorphisms affecting statin response**

- The ABCG8 D19H polymorphism may be associated with greater reductions in LDL when treated with atorvastatin
- SNPs 12 and 29 of the HMGCR may be associated with smaller reductions in total cholesterol and LDL
- A SNP within the LDLR exon 12, rs688, may increase LDL in women
- APOE  $\epsilon$ 4 has the highest risk of CHD, while  $\epsilon$ 2 has the lowest risk of CHD and  $\epsilon$ 3 falls in between  $\epsilon$ 2 and  $\epsilon$ 4
- APOE  $\epsilon$ 2 and  $\epsilon$ 3 have greater reductions in LDL compared to  $\epsilon$ 4 when treated with a statin

**Conclusion and future perspective**

- Currently the only pharmacogenomic data that is affecting clinical use is the CYP2C9 and VKORC1 data with warfarin
- All of the other aforementioned results need further larger prospective studies to build on the results gathered in order to obtain more conclusive results

studies to compare the results to, therefore there are not many significant conclusive findings.<sup>25</sup>

One major factor potentially affecting statin responses is due to their metabolism via the cytochrome P450 system.<sup>8</sup> Lovastatin, simvastatin and atorvastatin are metabolized by CYP3A4, whereas CYP2C9 metabolizes fluvastatin. Lastly, pravastatin and rosuvastatin do not appear to be metabolized by the cytochrome P450 system. One could assume that CYP activity could cause a degree of variation in drug response and small studies have proven this. For example, lovastatin was significantly less effective in patients who expressed CYP3A5, compared to patients whom did not.<sup>25</sup>

P glycoprotein, also known as multidrug resistance-1 (MDR1) or ATP-binding cassette transporter (ABC), have been found to affect drug disposition. Several polymorphisms in the MDR1 have been examined, but further, larger studies are needed. ABC subfamilies G5 and G8 have been studied (ABCG5 and ABCG8 respectively); specifically the ABCG8 D19H polymorphism was associated with a greater reduction in LDL when treated with atorvastatin.<sup>29</sup> This polymorphism was also linked to a reduction in intestinal cholesterol absorption.<sup>25</sup> HMG-CoA reductase (HMGCR) is the target for statin therapy, so genes encoding this have been the focus of several studies. One study showed that there was a significant association between SNP 12 and 29,

both found on chromosome 5, with reduced efficacy of pravastatin therapy. Individuals who were homozygous for the minor allele had a 22% and 19% smaller reduction in total cholesterol and LDL, respectively, compared to heterozygous carriers.<sup>30</sup> LDL-receptor (LDLR) genes have been the focus of some pharmacogenomic studies because of their role in cholesterol binding and metabolism. A SNP within the LDLR exon 12, rs688, has been associated with an increase in LDL cholesterol in women.<sup>31</sup> These results should become the basis of further studies to confirm or expand the results in order for these polymorphisms to be used clinically.<sup>25</sup>

The most extensively researched pharmacogenomic topic in regards to lipid-lowering therapy is with the apolipoprotein E polymorphisms (APOE).<sup>8</sup> There are three APOE isoforms:  $\epsilon$ 2, the wildtype  $\epsilon$ 3 and  $\epsilon$ 4.<sup>25,27</sup> APOE has several roles in lipid metabolism; APOE binds to LDLR and mediates the uptake of chylomicron, very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL). This is why APOE polymorphisms can affect cholesterol and triglyceride levels.<sup>27</sup> Several studies have shown that  $\epsilon$ 4 has the poorest response to statins, while  $\epsilon$ 2 has the strongest response in regards to LDL lowering. APOE  $\epsilon$ 2 is therefore more likely to reach LDL goals. APOE also acts as a protective agent against atherosclerosis. APOE  $\epsilon$ 4 carriers have the highest risk of CHD,  $\epsilon$ 2 has the lowest risk of CHD, and  $\epsilon$ 3 is in between.<sup>25,27</sup>

Even though there have been several pharmacogenomic studies in regards to lipid lowering effects, none are currently being used clinically. Larger studies need to be completed with specific statins and for each polymorphism. Like previously mentioned, not all of the statins are metabolized in the same way, therefore each statin could be affected by different genes.<sup>25</sup> APOE and HMGCR seem to show the most promising data, however neither are currently being used clinically.<sup>27,30</sup> CYP450 enzymes have shown to be a specific area which could be useful, to help reduce the possibility for adverse effects including myalgia or rhabdomyolysis. Hopefully, in the future, pharmacogenomic studies will show clinically significant findings so they can be used to identify which statin would be best for each patient's genetic makeup.

## Conclusion

Cardiovascular medicine is perfect for pharmacogenomic studies. The main goal of pharmacogenomics is to reveal potential genetic alterations affecting the body's response to a specific drug, leading to more personalized medicine. Pharmacogenomics can prove to be cost effective by hopefully decreasing the number of patients who experience

adverse reactions. Researchers have been conducting pharmacogenomic studies on a variety of topics within cardiovascular medicine for years. Unfortunately the majorities of the studies have small sample sizes or reveal conflicting data. There needs to be larger, prospective controlled trials to build on the information already discovered. It would also be beneficial to have studies focusing on specific genes in relation to race, gender, and ethnicity, since some genes are more common in specific people. The good news for pharmacogenomics is that progresses in establishing potential genes affecting drug response have been found; the bad news is that the progression to use these findings in a clinical setting is taking a long time. As we have seen with warfarin, pharmacogenomics is not impossible. Currently there are genetic screening tests for CYP2C9 and VKORC1, which could affect warfarin dosing protocols. Changes were also made within warfarin's package insert to include this information and the United States Food and Drug Administration "highlights the opportunity for health care providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients".<sup>32</sup> Perhaps many physicians are not yet following these recommendations as they are newer; but as awareness increases, more data is collected, and gene testing becomes more commonplace, VKORC1 and CYP2C9 will begin playing a larger role in warfarin dosing. Genomic screening and the adoption of personalized medicine can help save lives and dollars. Pharmacogenomics is on the horizon and may play an important role in the near future in the way physicians prescribe medicine; it is important to stay updated as we learn and discover the role pharmacogenomics plays, in all fields of medicine. Table 2 matches pharmacogenomics with cardiovascular medicines.

## Future perspectives

Pharmacogenomics is a relatively new topic so the majority of the studies that have been conducted will provide starting points for future research. Hopefully the area of cardiovascular pharmacogenomics will continue to progress and lead to personalized medicine. Genetic screening tests will become part of standard warfarin dosing and potentially for other classes of medication. Within the next 5–10 years, more conclusive studies will hopefully unveil more specific polymorphisms that will change the way medications are prescribed.

## Disclosures

The authors report no conflicts of interest in this work.



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