# Using Pharmacogenetics to Tailor Cardiovascular Treatment in Women

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*At the forefront of precision medicine, integrating pharmacogenetics into clinical practice holds promise for increasing treatment efficacy and reducing adverse drug reactions. By understanding the relationship between medications and genetic variability, pharmacogenetics can help tailor cardiovascular treatment in women, avoiding the trial-and-error approach and improving cardiovascular health outcomes. This article provides a review of factors that influence the therapeutic benefit of drugs and the risks for toxic effects. Pharmacogenetics, as one of these factors, is highlighted with examples of its role in the use of three common medications (clopidogrel, warfarin, and HMG-CoA [3-hydroxy-3-methylglutaryl-CoA] reductase inhibitors, commonly known as "statins") for treatment of cardiovascular disease.*

**Keywords:** cardiovascular pharmacogenetics, pharmacogenomics, precision medicine, women's cardiovascular health, nurse practitioners, primary care

Cardiovascular disease (CVD) continues to be the leading cause of death in women globally.[1] At least two out of three women in the United States possess one significant risk factor for coronary disease and 34.6% of deaths in women were from CVD-related causes in 2019.[1,2] CVD refers to a number of complex genetically diverse and environmentally influenced conditions that affect the heart and blood vessels, including atherosclerosis, coronary artery disease (CAD), myocardial infarction (MI), ischemic and hemorrhagic stroke, peripheral vascular disease, rheumatic and congenital heart disease, conduction abnormalities, cardiomyopathies, valvular disorders, and clotting disorders.[2-4] Between 2015 and 2018, 44.4% of adult women had CVD, with the highest prevalence in non-Hispanic Black women at 58.8%.[5] Being one of the most common risk factors for CVD, 40.4% of adult women have elevated total cholesterol levels of 200 mg/dL or greater.[4,5] Rates of hypertension increase dramatically in women after the age of 65, with 80% of women aged 75 or older having hypertension.[3,5] Of the 9.1 million women living with CAD, 3 million have had an MI. In 2019, 57.1% of individuals who died of stroke were women.[5] Early identification, prevention, and intervention are crucial to reduce morbidity and mortality.

Women have faced disparities in the treatment of CVD due to underrepresentation in research and the generalization of results from men to women, resulting in the use of treatment modalities for women that may not be as appropriate or effective as they are when used to treat men.[2,6] For example, women experience higher in-hospital mortality from an MI than men and a higher post-MI 5-year mortality of 47% compared with men at 36%.[5,6] There are differences in cardiac remodeling post-MI among women and men. Cardiac remodeling is defined as the structural, molecular, and interstitial changes that occur as a result of an injury to the heart that manifest clinically as changes in size, shape, and function of the heart.[7] Postmenopausal women are more likely to develop heart failure with a preserved ejection fraction, while men of the same age are more likely to develop heart failure with reduced ejection fraction.[6] Most of our medical therapies are aimed at treating heart failure with reduced ejection fractions, with few options targeted at heart failure with preserved ejection fractions.[6] Awareness of the misrepresentation of women in clinical trials has increased, and understanding of the differences and implications that biological sex has on disease processes and outcomes is improving.[6]

Another growing discipline, pharmacogenetics, holds promise for increasing treatment efficacy and reducing adverse drug reactions by studying the relationship between medications and genetic variability.[8] Pharmacogenetics will help tailor CVD treatment in women by providing personalized medicine: "the right





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drug to the right patient at the right time and dosage."[9] The purpose of this article is to provide a review of factors that influence the therapeutic benefit of drugs and risks for toxic effects with a focus on pharmacogenetics, as one of these factors. Examples highlight the role of pharmacogenetics in choosing and monitoring the use of three common medications for treatment of CVD. The implications of pharmacogenetics in all therapeutic areas, including those related specifically to women's health, are expanding as we learn how to use information on genetic variations effectively.

## CVD Risk and Recommended Screening

Well-established CVD risk factors include obesity, hypertension, diabetes, smoking, kidney disease, lipid abnormalities, and family history.[1,10] Other risk factors include chronic inflammatory diseases, such as rheumatoid arthritis, lupus, or HIV/acquired immunodeficiency syndrome, and chronically elevated inflammatory markers.[1,2,10] Female-specific CVD risk factors related to pregnancy history and reproductive health have been identified. Pregnancy-related conditions such as gestational diabetes, gestational hypertension or preeclampsia, premature delivery, stillbirth, and giving birth to an infant that is small or large for gestational age have been associated with a higher risk for CVD.[3,11–13] Other female-specific CVD risk factors include early menarche before the age of 10 or 11 and early onset of menopause before the age of 50.[3,11–13] Breastfeeding has been identified as providing protection against CVD.[3] These female-specific factors have been linked to increasing or decreasing cardiovascular risk and are included in the risk calculators for purposes of early detection. Unfortunately, with the addition of pregnancy and reproductive factors, the predictive value of these calculators in determining CVD risk in women has not improved significantly.[1] Women aged 20–75 years should be screened for risk of CVD.[10] The Framingham Heart Study recommends using the American College of Cardiology (ACC)/American Heart Association (AHA) Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator[A] to predict 10-year CVD risk.[14] Younger women between 20 and 39 years of age should be screened for traditional risk factors (ie, high blood pressure, high low-density lipoprotein cholesterol, obesity, diabetes, smoking, too much alcohol use, stress/depression, physical inactivity, and unhealthy diet) every 4–6 years.[10] At 40 years of age, routine screening for 10-year CVD risk is recommended; however, risk calculators may overestimate or underestimate risk, may not accurately represent every ethnicity or gender, and may not consider strong familial history or other social demographics.[1,10,15] For example, in the Multi-Ethnic Atherosclerosis Study, 32% of women considered "low-risk" based on the Framingham ASCVD risk assessment were found to have coronary artery calcium.[15] The presence of coronary artery calcium in those low-risk women was determined to be predictive of future CVD and cardiovascular events.[15] Coronary calcium scores are determined by taking a computed tomography scan of the chest and measuring the amount of calcium deposited in the coronary arteries.[16] Coronary artery calcium is the single most predictive risk marker for CVD in asymptomatic people.[16] Thus, it is necessary to consider the specific patient population being screened to determine the most appropriate predictor scale and treatment to use. In patients with borderline or intermediate 10-year ASCVD risk or with uncertainty of evidence, evaluating the coronary artery calcium score or other clinical factors can help further assess risk and guide treatment.[10]

## Factors Influencing Response to Medications

There are many factors that affect how people respond to medications, including genetics, sex, age, weight, diet, herbal supplements, environmental factors, gastrointestinal microbiome, drug–drug interactions, kidney function, and liver size and function.[17,18] Women have a higher risk of developing adverse drug reactions than men.[18] This could be for many reasons, including clinical trials without adequate female participants leading to drug safety, efficacy, and dosing protocols based on male-dominated findings.[19] In addition, adverse reactions may be attributed to biological differences in pharmacodynamics and pharmacokinetics (eg, differences in absorption, distribution, metabolism, and excretion), smaller body size and higher body fat, and biological processes involving hormonal changes, including the menstrual cycle, pregnancy, and menopause.[17–19] There are known genetic variations among ethnicities; however, there is a lack of representation of non-Hispanic Black and Hispanic women in pharmacogenetic research, placing these populations at even higher risk for adverse events.[18] Older adults usually have decreased or altered drug metabolism. Commonly known drug–herb and drug–food interactions include grapefruit and statins, vitamin K and warfarin, and St. John's wort and oral contraceptives. For example, grapefruit juice inhibits the enzymes that metabolize statins, increasing plasma statin concentration.[20]

## Pharmacogenetics

Pharmacogenetics is an advancing area of pharmacology that studies the impact of genetics on drug responses.[4] A list of defined terms commonly associated with pharmacogenetics is provided in the Table. Pharmacogenetics emerged after a study completed in 1958 attributed notable differences in systemic blood concentrations of the antibiotic isoniazid among European and East Asian patients to genetic variations in the metabolism of the antibiotic.[8]

Its clinical use has increased over the last decade and is applicable to many areas of medicine, including oncology,



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**Table.** Terminology Associated With Pharmacogenetics[17]

| TERM | DEFINITION |
|---|---|
| Pharmacogenetics | The study of genetic factors and how they influence the pharmacodynamics and pharmacokinetics of a drug |
| Pharmacodynamics | The effects that drugs have on the body, including how the drug interacts with its biological receptor (eg, binding affinity, agonism, and antagonism) to elicit a biological effect; pharmacodynamics play a role in determining what drug to use to treat a disease or symptom |
| Pharmacokinetics | The effects that the body has on drugs, including absorption, distribution, and elimination; pharmacokinetics play a role in determining dosage and administration of a drug |
| Allele | One of two or more forms of a gene found at the same genetic locus |
| Allele variations | Different forms of a gene that can result in varied phenotypic expression of that gene; for example, the extent to which the CYP2D6 enzyme functions is a result of which CYP2D6 variant alleles a person has in their genotype |
| Genotype | The genetic makeup of an organism, including what allelic variations for a specific gene the organism has |
| Phenotype | The expression of an organism's genotype |
| Phenotype variant | One of two or more possible expressions of a gene |
| Metabolizer phenotype | Determines the extent to which an enzyme will transform a drug; metabolizer phenotypes include poor metabolizers, intermediate metabolizers, rapid metabolizers, and ultra-rapid metabolizers |
| Inherited genetic variants | Genes inherited from parent to child that may affect the pharmacologic relationship between a drug and a human; for example, certain inherited variations in the HLA genes gene can predispose a person to drug-induced hypersensitivity reactions, such as Stevens–Johnson syndrome |
| CYP450 enzymes | Enzyme family responsible for the majority of drug metabolic reactions; enzymes that can metabolize a drug from an inactive to an active form or vice versa; over 50 CYP450 enzyme genes identified; each enzyme gene's name reflects family designation, subfamily, and individual enzyme within subfamily, for example, CYP2C19 |
| Prodrug | Drugs that must be metabolized to become pharmacologically active; developed to improve stability, increase absorption, or prolong duration of drug activity; for example, valacyclovir used in the treatment of herpes genitalis is not effective, but its active metabolite acyclovir is |

*Abbreviations:* CYP450, cytochrome P450; HLA, human leukocyte antigen.

cardiology, neurology, psychiatry, gastroenterology, and infectious diseases.[8] Inherited genetic variations influence the expressions and functions of proteins, which in turn alter an individual's response to drug metabolization.[8] These genetic variants can cause an increase, decrease, or inactive function of the proteins that metabolize, transport, and bind drugs, producing an alternate or unintended response.[8,9] For example, the cytochrome P450 (CYP450) enzymes are responsible for most drug metabolism in the liver. Over 50 CYP450 enzyme genes have been identified. Genetic variants result in ultra-rapid, rapid, normal, intermediate, and poor metabolizers for enzymatic drug metabolism.[4,8] Normal metabolization is the population average. Intermediate and poor metabolizers metabolize drugs poorly, increasing the risk of drug toxicity, while rapid and ultra-rapid metabolizers metabolize drugs rapidly, increasing the risk of insufficient drug efficacy.[8] However, whether the patient experiences increased toxicity or decreased efficacy from a drug ultimately is dependent on whether the drug is activated or deactivated by metabolism.[8]

Most of the population possess at least one clinically significant pharmacogenetic variant.[8] Pharmacogenetic testing helps predict drug responses and can be completed preemptively to help guide and direct drug dosing and selection to optimize therapy and improve outcomes.[4] Preemptive pharmacogenetic testing is a one-time test that can be used throughout the life of the patient to guide prescribing decisions, as opposed to reactive pharmacogenetic testing, which refers to genotyping performed following the use of a drug to explain the response to the drug and which may only include a specific gene–drug association.[8] The pharmacogenetic test can be ordered once by the primary care provider and shared with the



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entire health care team for future reference as it gives information about drugs from all specialties and eliminates the need for additional testing.

Some barriers, misconceptions, and concerns may influence the implementation of pharmacogenetics in clinical practice, including lack of education, knowledge, and understanding of how to interpret results; insurance reimbursement; cost; privacy and confidentiality; and accuracy of results. The Clinical Pharmacogenetics Implementation Consortium (CPIC), the U.S. Food and Drug Administration (FDA), and the AHA/ACC are leading organizations in the field of pharmacogenetics and cardiovascular treatment. The CPIC[B] publishes clinical practice guidelines and recommendations that provide useful information for clinicians who wish to incorporate the use of pharmacogenetic testing into their practice.[8] The CPIC was founded by the National Institutes of Health and PharmGKB (Pharmacogenomics Knowledge Base) and consists of a group of international pharmacogenetic experts who evaluate the current research and publish detailed practice guidelines and recommendations for gene–drug interactions based on the strength of evidence.[8] Gene–drug associations classified as levels A and B have the strongest level of evidence to support clinical action and should guide the choice of therapy, while levels C and D signify a weak level of evidence that should not direct clinical action.[8] The pharmacogenetic information released by the FDA and the AHA/ACC does not endure the same austerity in the evaluation process as CPIC guidelines and can be incongruent or outdated at times.[8] However, they do serve as a valuable secondary resource and hold a necessary role in the progress of pharmacogenetics. The AHA and ACC are leaders in establishing and presenting up-to-date recommendations to guide cardiovascular treatment, while the FDA regulates drug labeling and direct-to-consumer testing to ensure quality and safety. The FDA drug labels include pertinent pharmacogenomic information, with some drugs having boxed warnings for clinically significant genetic variations and drug efficacy.[8] As insurance reimbursement for pharmacogenetic testing increases, out-of-pocket costs are declining, so more individuals may seek specific FDA-approved direct-to-consumer pharmacogenetic testing. Thus, providers should be able to provide counseling on genetics or have resources for patients on where they can access genetic counseling because patients will need assistance in understanding and interpreting their results. Cost will vary depending on insurance coverage; Medicare will often completely cover the cost of testing for medications demonstrated to have clinically actionable pharmacogenetics. The Genetic Information Nondiscrimination Act (GINA) prevents most health insurance and employment discrimination based on test results. However, GINA protections do not extend to certain life, long-term care, or disability insurance types.[8] Finally, there is the risk of inaccurate genotyping, which could affect health outcomes. For example, lowering or stopping statin therapy based on inaccurate genotyping can increase CVD risk.[21] Monitoring lipid levels to evaluate treatment efficacy and switching to an alternate statin as necessary may help reduce the risk of CVD in the event of an error in allele genotyping.[21]

Utilizing pharmacogenetics to tailor treatment in CVD provides individualized person-centered care that can improve treatment efficacy, decrease adverse reactions, and reduce costs in women.[4,8] Pharmacogenetic testing can be completed preemptively to help guide and direct drug dosing and selection to optimize therapy and improve outcomes.[4] To expand on the application of pharmacogenetics for the treatment of women with CVD, the authors present three cardiovascular drug classes with the highest level of evidence supporting their recommendations, including clopidogrel, statins, and warfarin.[22]

## Clinical Guidelines and Recommendations

Clopidogrel is a platelet inhibitor used for prevention of blood clots in the treatment of acute coronary syndrome, including percutaneous intervention and stent placement.[22] It is a prodrug metabolized to its active form by the CYP2C19 enzyme.[8] A prodrug is an inactive drug that must be metabolized by the body to its active form to become effective. Clopidogrel has a boxed warning because poor or intermediate metabolizers have a decreased ability to activate this drug, rendering it less effective and placing those individuals at an increased risk for adverse cardiovascular events.[8,22] These patients should avoid taking clopidogrel and instead should use a different P2Y12 inhibitor, such as ticagrelor or prasugrel.[8]

HMG-CoA (3-hydroxy-3-methylglutaryl) reductase inhibitors, known as "statins," are a class of lipid-lowering medications used in the treatment of hypercholesterolemia and CVD.[20] They inhibit the enzyme HMG-CoA reductase, which is responsible for cholesterol synthesis in the liver.[20] Pharmacogenetics can be used in the selection and dosing of statins to decrease the risk of statin-associated musculoskeletal symptoms (SAMS), which include myalgia, myopathy, and rhabdomyolysis.[8,21] SAMS are one of the driving factors negatively impacting long-term compliance and effectiveness of the lipid-lowering agents.[8,21] Genetic variations in the SLCO1B1, ABCG2, and CYP2C9 genotypes are associated with increased systemic drug exposure and are relevant to consider for the risk of SAMS.[21]

SLCO1B1 is a protein transporter that promotes statin uptake in the liver.[21] When this transporter has reduced or poor function, the body is exposed to a higher drug concentration.[21] In a patient with poor or decreased function of the SLCO1B1 protein, the CPIC guidelines provide an algorithm to substitute the high SAMS risk statins with low SAMS risk statins to provide effective lipid-lowering



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treatment.[21] For example, a patient may have an indication for atorvastatin 80 mg, yet is at risk for SAMS due to decreased SLCO1B1 function. The provider may substitute for rosuvastatin 20 mg to reduce the risk.[21] The provider should consistently monitor lipids to evaluate for effective treatment. This algorithm can be found in the 2022 CPIC Statin Guidelines for further reference.[21]

The ABCG2 phenotype variant is associated with increased plasma concentration of rosuvastatin.[21] Therefore, it is recommended to initiate rosuvastatin at a 20-mg dose or less for patients with poor ABCG2 function. If additional lipid-lowering effects are needed, the clinician should consider switching statins or adding combination therapy with a statin and ezetimibe.[21]

The CYP2C9 enzyme is important in metabolizing many drugs, including statins.[15] The intermediate and poor metabolizer phenotypes are associated with increased systemic fluvastatin concentration.[21] Thus, it is recommended to prescribe 40 mg or less for intermediate metabolizers and 20 mg or less for poor metabolizers.[21]

While pharmacogenetics helps guide statin therapy to reduce SAMS risk, it is paramount to ensure patients receive statin therapy regardless of genotype results to reduce their risk for cardiovascular events.[21–23] Statin selection will be based on which statin intensity and dose the patient needs, considering their metabolizer phenotype.

Warfarin is an anticoagulant utilized in the prevention and treatment of blood clots in people with disorders such as atrial fibrillation, venous thromboembolism, or prosthetic heart valve replacement.[24] It decreases thromboembolism by inhibiting epoxide reductase from activating vitamin K, which activates clotting factors.[22] It has a narrow therapeutic index, making appropriate dosing critical, and can be heavily influenced by dietary intake. Genotype-guided warfarin therapy considers how the allele variations in the CYP2C9 and VKORC1 enzyme genotypes influence dose requirements.[8] People with variants in VKORC1 that cause increased sensitivity to warfarin require decreased doses of the drug. Allele variations in CYP2C9 decrease warfarin metabolism, thus increasing drug concentration and placing the patient at risk for hemorrhage and adverse events.[22] These allele variations typically decrease dose requirements and should be considered when dosing warfarin, especially in patients of African descent.[23]

## Implications for Women's Health Care Providers

Pharmacogenetics is a developing field with promising advances and implications for future CVD treatment as well as pharmacologic interventions for other health indications. Most of the population has at least one clinically actionable pharmacogenetic variant predisposing them to toxicity or subtherapeutic drug effects.[8] At the forefront of precision medicine, pharmacogenetic testing can be used to guide selections for individualized drug regimens. One very practical potential benefit of having genetic testing to inform treatment plans is having information to support requests for prior authorization from insurance companies. Being able to use pharmacogenetic testing to demonstrate how one drug may not be an appropriate choice even though it may be the preferred first-line treatment by the payer could decrease medication costs for patients. Avoiding the trial-and-error process with drugs decreases the risk of adverse side effects.

This article provides an illustration of incorporating pharmacogenetics to tailor therapy with clopidogrel, statins, and warfarin, which can help improve CVD outcomes and reduce adverse events. Women's health care providers can draw implications for practice from the information provided in at least two aspects. First, CVD is the leading cause of morbidity and mortality for women in the United States and worldwide. Prevalence increases with age, but 11% of women have some form of CVD before the age of 60. While the women's health care provider might not prescribe the medications described, they will see women who are taking these medications as they collaborate with cardiovascular specialists in their care, so they will want to be knowledgeable about factors that can influence efficacy and drug toxicity. Second, the application of pharmacogenetics is growing. Drugs related to the treatment of specific women's health conditions will be identified as having efficacy and drug toxicity affected by genetic variants. Utilizing pharmacogenetics allows clinicians to make predictions of how patients will respond to medications based on their genotype, thereby creating individualized treatment plans that maximize effectiveness and minimize adverse reactions. As evidence accumulates, clinical utility and integration into care planning will evolve. Precision medicine will undoubtedly improve cardiovascular health outcomes for women.

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## Web Resources

A. https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate
B. https://cpicpgx.org

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