Henry Ford Health
Henry Ford Health Scholarly Commons

Cardiology Articles | Cardiology/Cardiovascular Research

1-1-2016

Cardiovascular Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics for the Clinical Practitioner

Anna T. Sleder
Henry Ford Health

James Kalus
Henry Ford Health, JKALUS1@hfhs.org

David Lanfear
Henry Ford Health, dlanfea1@hfhs.org

Follow this and additional works at: https://scholarlycommons.henryford.com/cardiology_articles

Recommended Citation
Sleder AT, Kalus J, Lanfear DE. Cardiovascular pharmacokinetics, pharmacodynamics, and pharmacogenomics for the clinical practitioner. J Cardiovasc Pharmacol Ther. 2016 ;21(1):20-6.

This Article is brought to you for free and open access by the Cardiology/Cardiovascular Research at Henry Ford Health Scholarly Commons. It has been accepted for inclusion in Cardiology Articles by an authorized administrator of Henry Ford Health Scholarly Commons.

Check for updates

Journal of Cardiovascular Pharmacology and Therapeutics
2016, Vol. 21(1) 20-26
© The Author(s) 2015
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1074248415590196
cpt.sagepub.com
SAGE

Cardiovascular Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics for the Clinical Practitioner

Anna T. Sleder, MD, MS[1], James Kalus, PharmD[2], and David E. Lanfear, MD, MS[3]

Abstract

Current clinical cardiovascular practice requires a clinician to have a strong foundation in multiple aspects of pharmacology. Modern cardiovascular regimens are complex, and optimal management, application of evolving guidelines, and adoption of new therapies build off a more basic understanding of pharmacokinetics and pharmacodynamics. In addition, it is likely time to add a third pillar into this discussion, the expanding field of *pharmacogenomics* referring to the genetic influences on drug response. This field has increasing applications in medicine and clearly holds significant promise for cardiovascular disease management. Awareness of pharmacogenomic advances and the fundamentals of pharmacokinetics and pharmacodynamics can help the clinician more easily deliver great care. Here we attempt to briefly summarize and simplify key concepts of pharmacokinetics, pharmacodynamics, and pharmacogenomics relevant to the cardiovascular disease practitioner.

Keywords

cardiovascular pharmacology, cardiovascular pharmacogenetics

Introduction

Cardiovascular disease requires the practicing clinician to have a strong foundation in multiple aspects of pharmacology including that of pharmacokinetics, pharmacodynamics, and pharmacogenomics. Here we attempt to briefly summarize and simplify some of these key concepts with application to current clinical cardiovascular disease practice.

Cardiovascular Pharmacokinetics

Understanding the effect a medication may have on the cardiovascular system necessitates an understanding of how the drug will reach the desired target. The term *pharmacokinetics* refers to the action the body takes on a medication; this is broken down into absorption, distribution, metabolism, and elimination. Having a framework for interpreting a patient's response to a drug is crucial, and understanding the pharmacokinetic parameters that vary between drug, host, and disease state is important for clinical practice and can help decrease the likelihood of adverse effects by avoiding drug interactions and anticipating likely onset and duration of action.

Absorption

Absorption is the movement of a drug from its site of administration into the bloodstream. A medication can be absorbed from the gastrointestinal (GI) tract, through the oral mucosa (sublingual nitroglycerine), through the skin (transdermal clonidine), or subcutaneously (enoxaparin). Absorption is not relevant in the setting of intravenous administration since drug is administered directly into the bloodstream. Oral medications are generally less expensive, easy to administer, and are the cornerstone for outpatient management of cardiovascular disease. Bioavailability refers to the fractional amount of a given dose of a drug that is measured in the blood after administration. All medications have an inherent bioavailability related to efficiency of absorption. For example, the bioavailability of oral amiodarone is approximately 50% because half as much drug is available after taken by mouth as compared to intravenous administration.

Drugs can be formulated to modify absorption (eg, immediate-release forms vs extended-release/sustained-release formulations), which can greatly impact its duration of effect and ideal dosing interval. An example is nifedipine, which is

[1] Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA
[2] Department of Pharmacy, Henry Ford Hospital, Detroit, MI, USA
[3] Heart and Vascular Institute, Henry Ford Hospital, Detroit, MI, USA

Manuscript submitted: February 12, 2015; **accepted:** May 05, 2015.

Corresponding Author:
David E. Lanfear, Heart and Vascular Institute, Henry Ford Hospital, 2799 W Grand Blvd K14, Detroit, MI 48202, USA.
Email: dlanfea1@hfhs.org

available as an extended-release and immediate-release formulation, each carrying different clinical implications; the extended-release formulation can be given once daily, while the immediate-release formulation must be administered 3 times daily and can cause rapid hemodynamic changes and in certain situations has been associated with increased adverse effects.[1] Absorption of a drug is also affected by a variety of factors extrinsic to the medication itself. Transdermal absorption of a medication administered through a patch can be altered if the patch has been cut. Subcutaneous drug absorption is affected by changes in cutaneous blood flow (eg, high dose of vasopressors causing reduced cutaneous perfusion).[2] Within the GI tract, the presence or absence of food, anatomical abnormalities, and/or coadministration of other medications that may bind the medication (eg, antacids) can impact absorption rates as well as the presence of heart failure.[3]

Bioavailability of oral medications is impacted by numerous pathways within the digestive system, a key one being drug transporters within the GI tract. For example, P-glycoprotein (P-gp), an adenosine triphosphate (ATP)-dependent intestinal transporter, can efflux a drug back intraluminally within the intestine and can be inhibited or induced with coadministration of other medications. Since P-gp affects, and is affected by, many medications, it is important to note which drugs are P-gp inhibitors, inducers, and substrates in order to anticipate these interactions. For example, a clinically relevant P-gp interaction occurs when digoxin and amiodarone are coadministered. P-gp efflux of digoxin into the GI tract is inhibited by amiodarone, leading to a doubling of the digoxin concentration; thus, the digoxin dose should be decreased by half when initiating amiodarone. It should also be noted that P-gp induction can also occur, although less commonly. One example of a drug interaction that occurs due to P-gp induction is the clinically significant interaction between rifampin (P-gp inducer) and the new oral anticoagulant, dabigatran, whose bioavailability may thus be reduced with coadministration due to the P-gp on its prodrug dabigatran etexilate.[4]

Distribution

After a drug is absorbed (reaches systemic circulation), it is distributed within the interstitial and intracellular compartments. The volume of distribution (Vd) mathematically relates the total amount of drug administered to the concentration achieved within the target compartment (usually measure in blood) and is expressed as a volume (L) or volume/body weight (L/kg). Understanding a drug's Vd can be important for estimating the optimal dose of some drugs. Generally, large Vd reflects the wide distribution of drug, while a small Vd reflects relative containment in the vascular space.

The Vd can differ from population estimates due to numerous factors including age, body habitus, disease states, nutritional status, pregnancy, and critical illness.[5,6] For example, selection of the appropriate bolus dose of lidocaine is based on Vd and can be affected by these factors with typical loading doses varying between 1 mg/kg and 1.5 mg/kg. The 1-mg/kg dose is often used in the elderly patients or in patients with heart failure since they may have a lower Vd compared to younger patients or those with normal ventricular function.

A drug exists within the body in either bound or unbound forms, most often to proteins such as albumin, lipoproteins, and globulins. This binding may influence Vd because an increase or decrease in binding of drug to proteins can lead to a corresponding alteration in the amount of free drug and on transport across membranes. This concept is important as drugs are active in their free form (also discussed further under Pharmacodynamics).

Metabolism

Drug metabolism (also referred to as biotransformation) occurs primarily through the liver via phase I (oxidation, hydrolysis, and reduction) and phase II (conjugation) reactions. Phase I reactions include those mediated by the cytochrome P (CYP) 450 enzyme system, estimated to act on over 90% of all medications. Induction and inhibition of this critical system helps account for many drug–drug interactions and also features functional genetic variation, resulting in clinically significant differences in drug metabolism (discussed later in Pharmacogenomics).

Phase 1 reactions can also include the conversion of a *prodrug*, a pharmacologically inactive compound, to its active form. Prodrugs are employed for a variety of reasons such as stability, absorption, or other particular advantages. For example, enalapril is a prodrug that is rapidly metabolized in the liver into enalaprilat, the active form that inhibits angiotensin-converting enzyme (ACE). Enalaprilat itself can be administered intravenously, but when using the oral route the prodrug, enalapril maleate is administered. In order to allow for better systemic absorption and thus serum concentration, the prodrug of enalapril maleate is converted by hydrolysis of an ethyl ester to enalaprilat, which can then inhibit ACE. More often, metabolism via the CYP system leads to formation of inactive/less active metabolites; indeed this is part of the pathway of inactivation for most medications. Another key example of a prodrug is clopidogrel, which has received recent and widespread attention due to this characteristic and the potential for interactions.[7] Clopidogrel remains inactive until a complex hepatic activation occurs, this activation utilizes several CYP enzymes that will be discussed further under Pharmacogenetics as they are implicated in an individual's response to the drug.

Changes in the rate of drug metabolism via the CYP enzymatic system are affected by genetics, hepatic function, and other drugs, which can result in increased or decreased exposure to a medication. The most common CYP enzyme involved with drug interactions is CYP3A4. Numerous cardiac medications are either inhibitors or substrates of CYP3A4, including amiodarone, most statins, and several calcium-channel blockers. When a CYP3A4 inhibitor is administered with a CYP3A4 substrate, this could result in increase in medication exposure, resulting in potential toxicities. Table 1 summarizes important

Table 1. Selected Substrates and Inhibitors of the CYP450 System.[4]

	Group/Class	Medications	Cytochrome P-450 System
Substrates	HMG-CoA reductase inhibitors	Lovastatin, simvastatin	3A4
	β-Blockers	Metoprolol	2D6
	Calcium-channel blockers	Nifedipine and nisoldipine	3A4
	Antithrombotic	Warfarin	2C9
	Selective aldosterone receptor antagonists	Eplerenone	3A
	Proton pump inhibitors	Omeprazole and lansoprazole	2C19
Inhibitors	Calcium-channel blockers	Diltiazem	3A4
		Verapamil	3A4
	Antiarthymics	Amiodarone	2C9, 3A, 2D6
	Antilipemics	Gemfibrozil	2C8

Abbreviation: CYP, cytochrome P; HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.

CYP450 enzyme system substrates and inhibitors that the cardiac clinician should recognize.

Drug–drug interaction is a constant consideration for the practicing clinician; many arise from pharmacokinetic properties and can thus be anticipated and avoided with solid pharmacokinetic knowledge. A recent example is ranolazine and simvastatin. Ranolazine is a unique antianginal medication, whose mechanism of action is not completely understood but is known to be metabolized predominantly by CYP3A and less so by CYP2D6; it is also a weak inhibitor of CYP3A. Ranolazine has an extensive list of drug interactions including statin drugs, particularly simvastatin. One pharmacokinetic study of coadministration of simvastatin and ranolazine showed a roughly doubling of simvastatin concentration.[8] Relevant to these concerns, the Food and Drug Administration revised dosing recommendations such that if simvastatin is coadministered with ranolazine, it should be at doses no greater than 20 mg daily due to concern of myopathy. The evidence for interaction of statin with ranolazine is most abundant with simvastatin, but reasonable concern could be extrapolated to other agents in the class that are cleared by CYP3A. Alternative statins that are not metabolized significantly by CYP3A such as pravastatin or rosuvastatin could then be considered in the setting of patients on ranolazine.

Another drug interaction that has received attention that involves the CYP enzymatic system is clopidogrel and its interaction with omeprazole. Clopidogrel is an antiplatelet drug crucial in multiple areas of cardiovascular medicine and is also a prodrug processed by the CYP isoenzymes, namely CYP2C19. Omeprazole, a proton-pump inhibitor (PPI), often used for patients at high risk or with known upper GI bleeding, is also processed by the CYP2C19 enzyme; when used in combination, the interaction of omeprazole with CYP2C19 results in inhibition of clopidogrel with proven effect on platelet activity.[9] The clinical importance of the interaction between clopidogrel and omeprazole remains controversial but to note this alleged interaction is not a class effect of PPIs.[10]

Elimination

Elimination refers to how the medication exits the body. This could be the drug in its original form or after being converted to active or inactive metabolites. Elimination is usually either through renal excretion in urine or the hepatic route into stool. Renal clearance is a crucial mechanism of drug elimination; patients with renal dysfunction have reduced clearance of drugs with renal excretion and are often at greater risk of toxicity from medications. For example, the patient with atrial fibrillation on rivaroxaban with reduced creatinine clearance (30-49 mL/min) requires a dose adjustment to 15 mg daily from 20 mg, and its use is contraindicated with creatinine clearance of less than 30 mL/min due to increased bleeding risk.[11] Another example is dabigatran, used for the same purpose of anticoagulation for atrial fibrillation, the dose is 150 mg twice daily, but with renal impairment (creatinine clearance of 15-30 mL/min), the dose is 75 mg twice daily due to the increased half-life secondary to the nature of dabigatran's renal elimination.[12] Most renal elimination occurs via glomerular filtration and secretion into the renal tubules; dysfunction within these mechanisms, either through drug effect or innate function, can have consequences for drug exposure. For example, dofetilide, an antiarrhythmic, undergoes glomerular filtration as well as secretion in renal tubules. Agents that block tubular secretion such as hydrochlorothiazide, cimetidine, and ketoconazole can result in accumulation of dofetilide with potential for toxicity including QT prolongation and ventricular arrhythmias.

A key pharmacokinetic parameter relevant for the practicing clinician is half-life, which is the amount of time required for the concentration of drug to be reduced by half. Steady state is the point at which drug administration is equal to drug elimination. When discontinuing a medication, it generally takes 4 to 5 half-lives for the drug to be nearly completely removed from the body, conversely when initiating a drug, 4 to 5 half-lives will also be required to achieve steady-state concentrations.

Cardiovascular Pharmacodynamics

The term *pharmacodynamics* refers to the relationship between the drug concentration at the site of action and the biological effect. Medications generally interact with a specific target in the body, this interaction enhances, suppresses, or changes the function of the target and thus produces an effect. Macromolecules within the body, such as neurohormonal signaling receptors (eg, adrenergic receptors), enzymes (eg, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase [HMG-CoA-reductase] and vitamin K 2,3-epoxide reductase [VKORC1]), and ion channels (eg, calcium channels) serve as the target for many medications. Medication interactions with specific target receptors may vary across the population, this concept will be discussed in more detail under Pharmacogenomics.

Cardiac medications frequently stimulate or block a signaling receptor. For example, the β-adrenergic receptor is stimulated by dobutamine, thus termed an *agonist*, while medications that block the action of β-adrenergic receptor such as metoprolol are called *antagonists*. Antagonists can be further qualified as competitive, taking the place of a naturally occurring ligand (eg, epinephrine) to block activity, or noncompetitive, which bind elsewhere on the receptor and thus are less affected by the concentration of the usual ligand.

Another common type of cardiovascular drug is that which has a pharmacodynamic effect by inhibiting the action of an ion channel. Calcium-channel blockers inhibit the influx of calcium into cardiac and other muscle cells, which in the cardiac pacemaker cells reduces chronotropic activity, in other myocardium can result in reduced inotropy, and in vascular smooth muscle can lead to vasodilatation. Vaughn-Williams class III antiarrhythmics inhibit efflux of potassium through potassium channels. A notable pharmacodynamic effect of the class III antiarrhythmic drugs is prolongation of the QT interval. Concomitant use of more than one medication that prolongs the QT interval could result in a pharmacodynamic drug interaction, increasing the patient's risk for developing Torsades de Pointes.

Enzyme inhibition is another important target of many important cardiovascular medications. The HMG-CoA-reductase inhibitors are a class that produces a pharmacodynamic response through enzyme inhibition. The HMG-CoA-reductase inhibitors block the enzyme responsible for the final step of cholesterol formation, leading to the pharmacodynamics effect of reduced intracellular cholesterol levels in the liver, which then causes enhanced reuptake of low-density lipoprotein (LDL) particles from plasma to liver, subsequently lowering plasma LDL levels. Another example is VKORC1, which is the target of warfarin. Warfarin inhibits VKORC1 from reducing vitamin K leading to the pharmacodynamic effect of a decrease in production of vitamin K-dependent clotting factors.

Targets of drugs may also be specific proteins where the drug may enhance or impair a protein-dependent physiologic process. For example, within the coagulation cascade, both unfractionated heparin and bivalirudin are good examples. Unfractionated heparin exploits the action of the protein antithrombin through binding and altering the structure slightly, which subsequently enhances its action of inactivating activated thrombin; thus, unfractionated heparin produces an antithrombotic effect due to greater inactivation of thrombin. On the other hand, bivalirudin is a direct thrombin inhibitor, it binds to thrombin and prevents thrombin from converting fibrinogen to fibrin, resulting in the antithrombotic effect.

An understanding of pharmacodynamics may be useful in understanding differences in patient outcomes between medications with a similar mechanism of action. For example, the adenosine receptor antagonists all inhibit platelet activation through blockade of the $P2Y_{12}$ receptor. However, prasugrel and ticagrelor produce faster and more extensive inhibition of platelet activation than clopidogrel.[13,14] This difference in pharmacodynamic response could be one potential explanation for greater efficacy with both prasugrel and ticagrelor or greater bleeding risk with prasugrel, as compared to clopidogrel.[15,16]

As discussed previously, drug interactions can often arise via pharmacokinetics, but interactions can also occur via pharmacodynamic considerations. Examples include the impaired response to dobutamine in patients receiving β-blockers mentioned earlier or additive heart rate lowering when nondihydropyridine calcium-channel blockers and β-blockers are coadministered.

An awareness of the interplay between pharmacokinetics and pharmacodynamics is important in practice. Aspirin irreversibly inhibits the action of cyclooxygenase (COX) enzyme in the platelets, leading to prevention of platelet activation. While the pharmacodynamic effect of most drugs will not be present 4 to 5 half-lives after discontinuation, the pharmacodynamic effect of aspirin persists long after 4 to 5 half-lives have passed (approximately 12-24 hours for aspirin). This is because the *irreversible* inhibition of the COX enzyme in platelets renders those platelets permanently inactive. Therefore, the antiplatelet effect of aspirin does not normalize until new functional platelets have been generated, which generally takes approximately 1 week.

Cardiovascular Pharmacogenetics

There are many factors that contribute to individual variation in response to medications; the study of relation between genotypic and the phenotypic response to a medication is *pharmacogenetics*. The terms pharmacogenetics and pharmacogenomics are often used interchangeably, though *pharmacogenomics* technically should be used to describe the study of gene-based differences in drug response using a broad or even genome-wide approach, whereas pharmacogenetics would technically apply in discussions of specific genes or variants.[17] There are numerous barriers to implementing pharmacogenomics into clinical practice, one of which is the current knowledge base.[18] As discussed in the previous sections on Pharmacokinetics and dynamics, many nongenetic factors (eg, age, organ function, and drug interactions) influence medication response; thus, it is important to view pharmacogenetic factors within this larger framework, supplementing (not supplanting) other more conventional predictors. Moreover, pharmacogenetic factors generally operate through and interact with pharmacokinetics and pharmacodynamics; thus our knowledge of these is a necessary basis in which to incorporate the contribution of genetics.

Previously solely a research field, evidence that genetic polymorphisms alter the pharmacokinetics, pharmacodynamics, and thus the clinical response to a medication is now well established.[17] Although progress has been slower in cardiovascular disease, pharmacogenetics is being used very commonly clinically in the field of oncology. However, examples of clinical use in cardiovascular disease are occurring despite adoption being uneven and slow, and promise remains as research techniques and our knowledge base continue to expand. Also, real-life clinical challenges exist, which can be potentially mitigated via personalized medicine,

thus the potential profit remains high. At this time in cardiovascular disease, an exhaustive knowledge of all previous associations is not worthwhile, but an understanding of the general principles and the current (and near future) clinical applications are warranted, and can help the clinician to avoid toxicity or treatment failure.

Variation in DNA sequences leading to alterations in phenotype, termed *mutations*, is rare, occurring generally <1%. Some of these can lead to clinical and genetic phenotypes such as hypertrophic cardiomyopathy, familial Wolff-Parkinson–White syndrome, or congenital long QT syndrome; not all rare variants are disease causing and some more common variants can be associated with phenotypic changes. More common variants (roughly ≥1%) are called *polymorphisms*, can come in several subtypes, and are widespread throughout the genome. There are insertions, deletions, repeats, and copy-number variants, but the most common type is the single-nucleotide polymorphism (SNP), essentially a substitution of one nucleic acid for another at a particular locus in the genome. Single-nucleotide polymorphisms are thought to have 300 to 1000 nucleotides with estimates totaling up to 30 million, depending on the population.[19]

Genetic components of drug response were described in the literature as early as the 1950s; first with the observation that individuals when given succinylcholine (a suxamethonium derivative) resulted in what we now know as malignant hyperthermia and led to the discovery of pseudocholinesterase deficiency.[20] Initial applications of pharmacogenetics were related to altered pharmacokinetics, specifically drug metabolism, and this remains one of the more common areas of application today. Early examples were limited to medications with very narrow therapeutic indices; a classic example being azathioprine and the gene thiopurine methyl transferase (*TPMT*). Azathioprine is an anticancer and immune-suppressing agent (can be used in heart transplantation), and TPMT is primarily involved in the inactivation of 6-mercaptopurine (the active metabolite of azathioprine) into an inactive by-product. Polymorphisms in the gene *TPMT* can disable this enzyme, thus exposing the patient to higher than anticipated levels and causing toxicity, typically bone marrow suppression. Clinical testing for genotype allows for identification of patients with those polymorphisms and for whom reduced doses of azathioprine should be used, avoiding bone marrow toxicity.

Developments within cardiac pharmacogenomics have progressed with discoveries that variants are associated with modified effect or metabolism of many commonly prescribed cardiovascular medications such as β-blockers, ACE inhibitors, statins, and antiplatelet and anticoagulant drugs.[21] The clinical applications of these discoveries have been slower but there are a few that, while controversial, could be used today, particularly clopidogrel, warfarin, and statin pharmacogenetics (Table 2). Platelet response to clopidogrel is highly heritable with multiple SNPs implicated affecting pharmacokinetics and pharmacodynamics.[22] As described previously, clopidogrel ingested in its inactive form and is activated largely by CYP2C19, after which it blocks the adenosine diphosphate receptor. Genotype at functional SNPs impacting CYP2C19 identifies subgroups of patients at higher risk of ischemic events after percutaneous intervention (PCI) while on clopidogrel.[23,24] As noted, clopidogrel is also subject to efflux via P-gp; variants in the gene ATP-binding cassette, sub family B member 1 (*ABCB1)* which encodes P-gp, lead to altered expression of P-gp, which impact bioavailability of the drug and were associated to increased bleeding post PCI.[25] As part of the Escalating Clopidogrel by Involving a Genetic Strategy–Thrombolysis In Myocardial Infarction 56 (ELEVATE–TIMI 56) trial, they investigated the effect of escalating maintenance doses of clopidogrel on platelet reactivity (PR) in patients with coronary artery disease, taking into account the *CYP2C19* genotype, numerous observations with clinical implications have been discovered including variation in PR over time in individuals.[26] These findings carry great clinical implications of clopidogrel use, much like TPMT activity measurement prior to initiating azathioprine, measurement of PR prior to initiating clopidogrel may be considered.

Table 2. Summary of Cardiovascular Pharmacogenetics With Known Clinical Implications.[31]

Drug	Gene	Variants	Clinical Phenotype
Warfarin	*CYP2C9*	*2,*3	Lower dose requirements
	VKORC1	1639G>A	Lower dose requirements
		D36Y	Greater dose requirements
Simvastatin	*SLCO1B1*	rs4149056 T>C	Increased risk of myopathy
Clopidogrel	*CYP2C19*	*2,*3, *4-*8	Higher platelet reactivity, worse outcomes after stenting.

Abbreviations: *CYP*, cytochrome P; *VKORC1*, vitamin K 2,3-epoxide reductase 1; *SLCO1B1*, solute carrier organic anion transporter family, member 1B1.

A patient may thus be genetically ''resistant'' to clopidogrel. While it is not in widespread use today, some centers are indeed genotyping patients planned for long-term clopidogrel. One study which tested higher dose clopidogrel to resistant genotype patients was not able to show that this intervention overcame the effect.[27] However newer, more potent (and more expensive) antiplatelet agents are now available, presenting another possible strategy to perform genotype testing and then assign patients with the resistant genotype to an alternate agent while keeping patients with the wild-type genotype on clopidogrel. Clopidogrel ''resistance'' can thus be a result of genetic variation and also drug interactions; both etiologies result in platelets maintaining their functional ability which may have fatal consequences for an individual.

Another cardiac medication that has undergone much pharmacogenetic investigation is warfarin. Variants in the gene coding for vitamin K 2,3-epoxide reductase complex (*VKORC1)* and a CYP enzyme (*CYP2C9)* have been convincingly associated with differences in steady state warfarin dosing, time to therapeutic international normalized ratio (INR), and time in therapeutic range. It has not been proven that clinical outcomes are improved with pharmacogenetic dosing of warfarin with 2 recent trials showing differing

results.[28] One of the main reasons for this discrepancy appears to be the larger number of African descendent patients in the American study. Among African Americans, genotype guidance actually worsened INR control, and it has subsequently become clear that there are differing prevalence of some functional variants within *VKROC1* and *CYP2C9* between European versus African ancestry groups, and these differences likely contributed to the differing results seen in the studies. Thus, the totality of available data suggests that for patients of European ancestry, genotype-guided warfarin dosing offers some clinical advantage over standard practice, but additional work would be needed to try to extend this to other ancestral groups particularly African Americans.[28] Another large outcome study is ongoing through the same investigators.

Another potential application today is in regard to simvastatin. There is an increased risk of simvastatin-induced muscle toxicity in patients with variants in solute carrier organic anion transporter family, member 1B1 (*SLCO1B1)*. Similar to that mentioned previously, some centers have started performing this testing routinely to inform the risk of simvastatin (patients homozygous for the risk variant have a 15%-20% risk of myopathy). On the other hand, with the availability of newer agents in the class that have less risk, including atorvastatin, which is now generic, the pragmatic impetus for pharmacogenetic direction of treatment is much less but does highlight the role of pharmacogenomics. For example, in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) study, a genome-wide association study on patients receiving simvastatin 80 mg daily, revealed patients with variants in *SLCO1B1* genotype had an associated increase in odds of simvastatin-induced myopathy.[29] The same findings in the Statin Response Examined by Genetic Haplotype Markers (STRENGTH) study with atorvastatin, simvastatin, and pravastatin with effects negligible for atorvastatin and pravastatin and most pronounced among female participants taking simvastatin.[30]

Conclusions

Clinical cardiovascular practice needs great attention to medication effects, both desired and dreaded, requiring a clinician to have a strong foundation of knowledge in multiple aspects of pharmacology. Here we provided a review of pharmacokinetics, pharmacodynamics, and pharmacogenomics tailored for the cardiovascular disease practitioner. Continued self-education with attention to the evolving research and entity that is pharmacogenomics is necessary in this ever-changing practice with a goal of personalized medicine.

Authors' Contributions

Lanfear, D contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Sleder, A contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; and gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Kalus, J contributed to analysis and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Dr Lanfear's time is supported by NHLBI (R01HL103871).

References

1. Jung SY, Choi NK, Kim JY, et al. Short-acting nifedipine and risk of stroke in elderly hypertensive patients. *Neurology*. 2011; 77(13):1229-1234.
2. Dorffler-Melly J, deJonge E, Pont AC, et al. Bioavailability of subcutaneous low-molecular weight heparin to patients on vasopressors. *Lancet*. 2002;359(9309):849-850.
3. Berkowitz D, Droll MN, Likoff W. Malabsorption as a complication of congestive heart failure. *Am J Cardiol*. 1963;11: 43-47.
4. Food and Drug Administration. Drug Development and Drug Interactions. Web site. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency. Accessed May 27, 2015.
5. Wilkenson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med*. 2005;352(21):2211-2221.
6. Buxton IO, Benet LZ. Chapter 2. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12e; 2011. Retrieved May 27, 2015 from http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266207.
7. Depta JP, Lenzini PA, Lanfear DE, et al. Clinical outcomes associated with proton pump inhibitor use among clopidogrel-treated patients within CYP2C19 genotype groups following acute myocardial infarction. *Pharmacogenomics J*. 2015;15(1):20-25.
8. Jerling M, Huan BL, Leung K, Chu N, Abdallah H, Hussein Z. Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem, or simvastatin during combined administration in healthy subjects. *J Clin Pharmacol*. 2005;45(4):422-433.
9. Arbel Y, Birati EY, Finkelstein A, et al. Platelet inhibitory effect of clopidogrel in patients treated with omeprazole, pantoprazole, and famotidine: a prospective, randomized, crossover study. *Clin Cardiol*. 2013;36(6):342-346.
10. Wedemeyer RS, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. *Drug Saf*. 2014;37(4): 201-211.
11. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and Safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban

once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation*. 2014; 130(2):138-146.
12. Stangier J, Tahgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet*. 2010;49(4):259-268.
13. Jernberg T, Payne CD, Winters KJ, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J*. 2006; 27(10):1166-1173.
14. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50(19): 1852-1856.
15. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
16. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
17. Cres KR, Hicks JK, Pui CH, Relling MV, Evans WE. Pharmacogenomics and individualized medicine: translating science into practice. *Clin Pharmacol Ther*. 2012;92(4)467-475.
18. Turner RM, Pirmohamed M. Cardiovacular Pharmacogenomics: expectations and practical benefits. *Clin Pharmacol Ther*. 2014; 95(3)281-293.
19. Frazer KA, Ballinger DG, Cox DR, et al. International HapMap consortium. A second generation human haplotype map of over 3.1 million SNPs. *Nature*. 2007;449(7164):851-861.
20. Lehmann H, Ryan E. The familial incidence of low psuedocholinesterase level. *Lancet*. 1956;271(6934):124.
21. Roden DM. Cardiovascular pharmacogenomics. *Circulation*. 2003; 108(25):3071-3074.
22. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009;302(8): 849-857.
23. Tang XF, Wang J, Zhang JH, et al. Effect of the CYP2C19 2 and 3 genotypes, ABCB1 C3435T and PON1 Q192R alleles on the pharmacodynamics and adverse clinical events of clopidogrel in Chinese people after percutaneous coronary intervention. *Eur J Clin Pharmacol*. 2013;69(5):1103-1112.
24. Giusti B, Gori AM, Marcucci R, et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. *Am J Cardiol*. 2009;103(6):806-811.
25. Zang JH, Tang XF, Zhang Y, et al. Relationship between ABCB1 polymorphisms, thromboelastography and risk of bleeding events in clopidogrel-treated patients with ST-elevation myocardial infarction. *Thromb Res*. 2014;134(5):970-975.
26. Hochholzer W, Ruff CT, Mesa RA, et al. Variability of individual platelet reactivity over time in patients treated with clopidogrel. *J Am Coll Cardiol*. 2014;64(4):361-368.
27. Mega JL, Hochholzer W, Frelinger AL, et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. *JAMA*. 2011; 306(20):2221-2228.
28. Kimmel SE, French B, Kasner SE, et al. The COAG investigators. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013;369(24):2283-2293.
29. SEARCH Study Collaborative Group, Bowman L, Armitage J, Bulbulia R, Parish S, Collins R. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12064 myocardial infarction survivors. *Am Heart J*. 2007;154(5):815-823.
30. Voora D, Shah SH, Spasojevic I, et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. *J Am Coll Cardiol*. 2009;54(17):1609-1616.
31. Johnson JA, Cavallari LH. Pharmacogenetics and cardiovascular disease—implications for personalized medicine. *Pharm Rev*. 2013;65(3):987-1009.