Abstract—Over the past decade, personalized medicine has received considerable attention from researchers, drug developers, and regulatory agencies. Personalized medicine includes identifying patients most likely to benefit and those most likely to experience adverse reactions in response to a drug, and tailoring therapy based on pharmacokinetics or pharmacodynamic response, as well. Perhaps most exciting is finding ways to identify likely responders through genetic, proteomic, or other tests, so that only likely responders will be treated. However, less precise methods such as identifying historical, demographic, or other indicators of increased or reduced responsiveness are also important aspects of personalized medicine. The cardiovascular field has not used many genetic or proteomic markers, but has regularly used prognostic variables to identify likely responders. The development of biomarker-based approaches to personalized medicine in cardiovascular disease has been challenging, in part, because most cardiovascular therapies treat acquired syndromes, such as acute coronary syndrome and heart failure, which develop over many decades and represent the end result of several pathophysiological mechanisms. More precise disease classification and greater understanding of individual variations in disease pathology could drive the development of targeted therapeutics. Success in designing clinical trials for personalized medicine will require the selection of patient populations with attributes that can be targeted or that predict outcome, and the use of appropriate enrichment strategies once such attributes are identified. Here, we describe examples of personalized medicine in cardiovascular disease, discuss its impact on clinical trial design, and provide insight into the future of personalized cardiovascular medicine from a regulatory perspective. (Circulation. 2015;132:1425–1432. DOI: 10.1161/CIRCULATIONAHA.114.009761.)

Key Words: biological markers ■ cardiology ■ clinical trial ■ individualized medicine ■ pharmacogenetics

Personalized medicine, also referred to as individualized or precision medicine, is the practice of tailoring medical treatment to the individual characteristics of each patient. The enormous potential of personalized medicine, to improve clinical outcomes by moving away from a one-size-fits-all approach and toward treatment strategies that are most likely to benefit each individual, has led to high expectations from both physicians and patients. Personalized medicine covers a lot of territory. Perhaps the most exciting prospect is discovery of genomic or proteomic biomarkers that reveal the underlying cause of a disease and can be directly targeted. Such targeted treatments have, of course, long been available for the treatment of infectious diseases, and have recently become common in oncology where broadly cytotoxic agents have increasingly been replaced by drugs directed at critical pathways driven by specific tumor mutations or aberrant gene expression. These include epidermal growth factor receptor tyrosine kinase inhibitors for lung cancer, human epidermal growth factor 2 inhibitors for breast cancer, and v-raf murine sarcoma viral oncogene homolog B inhibitors for melanoma. Recently, we have approved medications targeting other genetically defined subsets of patients, including ivacaftor for the treatment of patients who have cystic fibrosis with certain genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that affect the channel’s gating activity, and specific genetically distinct hepatitis C viruses. In all of these cases, the responsive patient subsets can be distinguished from the nonresponders with laboratory tests before treatment.

In addition to diseases that are clearly distinct because of specific genetic abnormalities or diseases that are caused by infectious organisms with specific properties, diseases that appear generally similar can have pathophysiological hallmarks that could provide a basis for specific drug targeting. Some such hallmarks are present in cardiovascular diseases, although they are less widely used to direct treatment. For example, there is a clear mechanistic distinction between high- and low-renin hypertension that can predict responsiveness...
and be used in drug selection. Nevertheless, assessment of renin activity has not been a common practice. In most cases, race or age are used as markers for renin activity, and practitioners empirically try 1 drug and add a second if needed. Perhaps more surprisingly, only recently has the clear mechanistic distinction between systolic and diastolic heart failure been incorporated into drug development programs. In both cases, however, a priori assessment could lead to better targeted treatments. In addition to well-understood distinctions among individuals based on genetic or pathophysiological features, empirically described differences such as the early response of a biomarker to treatment (eg, blood pressure, as noted above) might predict the long-term response and be used to identify patients to receive long-term treatment, as initial tumor response can be used in oncology.

Apart from mechanistically, genomically, or empirically targeted therapies, there are 2 other important personalizing approaches. First, individuals can be identified who will have a variety of distinct pharmacokinetic (PK) properties, either because of variations in excretory or metabolic function, or because they are taking another drug that affects excretion or metabolism of the drug of interest. Second, for reasons that may not be recognized or pathophysiologically understood, some demographic or other characteristics may significantly affect the performance of a treatment, such that these factors may have a role in empirical individualization.

Identifying the probable responders or tailoring therapy in any of the above ways can improve the benefit-risk profile of a drug. However, personalizing cardiovascular medicine has a major impact on clinical trial design issues and other drug development considerations. In this review, we describe current examples of personalized medicine in cardiovascular disease, discuss the impact of such methods on drug development, and provide insight into the future of personalized cardiovascular medicine from a regulatory perspective.

**Current Examples of Personalized Cardiovascular Medicine**

**Subgroup Analyses**

Probably the crudest, but most broadly available, attempt to support personalized medicine, routine in published reports of outcome trials and increasingly included in labeling for cardiovascular drugs, is to show the treatment effects in subgroups (most often the primary benefit measure, but sometimes a prominent safety measure). An example of a forest plot showing such analyses is shown in the Figure, taken from the recently approved drug ticagrelor. There is a relatively long history of using forest plots like these for meta-analyses of multiple trials; use in subgroup analyses of single trials is a more recent development, and has become common for large cardiovascular outcome studies.

Although the value of subgroup analyses is generally appreciated, it is also recognized that they suffer from an inherent multiplicity problem and need to be interpreted cautiously. There are, for example, numerous subgroups of interest, based on demographic factors, disease-related characteristics, and concomitant medications. Moreover, cut points for continuous variables, such as age and creatinine clearance, may not be prespecified. Although the effect in each subgroup is usually shown with its 95% confidence interval, these intervals are not adjusted for the fact that there are multiple analyses. In addition, formal tests of statistical interaction are rarely conducted, and, when they are performed, they typically have poor power to detect a statistical interaction, even if one truly exists.

Another problem is that the various factors being examined are generally not independent of one another. For example, there will surely be relationships among age, sex, weight, and renal function, and single factors could, and probably should, be subjected to covariate analyses. A third problem is that there is sometimes little insight into the mechanism by which these factors impact treatment effects. Thus, subgroup analyses must be interpreted with care; the many analyses can lead to spurious differences or give unwarranted confidence that subgroup differences are not present. In the case of a trial that fails to meet its primary end point, findings of efficacy in ≥1 subgroups, even if such analyses are prespecified in the trial’s statistical plan, should ordinarily be considered as hypothesis generating, not as hypothesis confirming.

In some cases, unanticipated issues arise that lead to unplanned, yet important, subgroup analyses. When the US Food and Drug Administration (FDA) approved ticagrelor in 2011, there was a strong interaction between geographic region and dose of aspirin, with higher (>150 mg) aspirin doses used in almost half of US patients but in <10% of patients elsewhere. Indeed, analyses suggested there was, in fact, no actual regional difference in effect but that higher aspirin doses decreased the effectiveness of ticagrelor in both the United States and elsewhere, and did so for both mortality and heart attacks (ie, both end point components). The consistency of findings related to aspirin dose in both the United States and elsewhere, and for individual components of the composite end point, helped provide a credible basis for the approval of ticagrelor.

**Pharmacokinetics**

Although considering blood concentrations (ie, exposure) for various subgroups to personalize treatment does not generate the level of excitement that identifying responders genetically or pathophysiologically does, it is a well-understood and highly justified example of personalized medicine. The PK of drugs is altered when there are changes in the function of organs responsible for absorption, distribution, or elimination. The changes in function of these critical organs (eg, liver, kidney) are generally correlated with patient attributes such as age, body weight, or comorbidities. Drug development programs today almost always investigate the PK impact of abnormal renal and hepatic function, of sex and age, and of concomitant treatments that could affect metabolism. In addition, population PK, now routine, allows assessment of the impact of other factors, such as weight, which would be expected to affect blood concentrations of a drug, but may have other unanticipated effects. These characterizations allow for dose adjustments in specific subgroups, either to decrease the frequency of adverse events or to improve efficacy. To do this, of course, it is important to know the concentration-response relationship for effectiveness and toxicity. Drugs given on the plateau of a concentration-response curve are not likely to be
greatly affected by modest PK differences, but if doses are below the plateau, eg, to avoid dose-related toxicity, exposure adjustment for groups or, possibly, using blood concentration data, could be important.

In a recent case, population PK analyses of late-phase data demonstrated that body weight was an independent predictor of exposure to the active metabolite of prasugrel and that exposure to the active metabolite increased with decreasing body weight.4 Moreover, the increase in exposure in patients with low body weight was also associated with an increase in bleeding risk. Specifically, Thrombolysis in Myocardial Infarction major bleeding was higher in patients weighing <60 kg than in patients with higher body weight, but efficacy was similar across body weight groups. These data provided the rationale for reducing the exposure to prasugrel active metabolite in patients weighing <60 kg by reducing the maintenance dose of prasugrel from 10 mg to 5 mg daily in such patients. Similar approaches have been used to provide dosing adjustment for renal function for digoxin and dabigatran, and for many other drugs, that are predominantly cleared by the kidneys. For example, in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial of dabigatran, subjects with atrial fibrillation were randomly assigned to either of 2 doses of dabigatran (110 mg twice daily or 150 mg twice daily) or to warfarin.5 The dabigatran dose was not titrated during the study, nor was there a dose reduction for factors that might be associated with increased exposure, such as low body weight or impaired renal function. However, blood was obtained for dabigatran plasma level determinations (trough) from all consenting patients randomly assigned to dabigatran (>70% of the ≈6000 subjects in each arm). This large collection of PK data, coupled with the clinical outcomes data, allowed the FDA to characterize concentration-response relationships for both bleeding and thrombotic events. The available data indicated that no dose adjustment was needed for renal function in the range permitted in the study (only patients with a creatinine clearance <30 mL/min were excluded). However, based on PK modeling, there was enough information to support a dose of 75 mg twice daily (which was not used in RE-LY) for patients with severe renal impairment (ie, creatinine clearance of 15–30 mL/min). The 75 mg dose would yield plasma dabigatran plasma levels in patients with severe renal impairment similar to those in patients with moderate renal impairment (ie, creatinine clearance 30–50 mL/min) treated with dabigatran 150 mg twice daily.6

Genomic factors and drug-drug interactions can also affect drug exposure. A classic example is the 8-fold higher desipramine blood concentrations in cytochrome P450 (CYP) 2D6 poor metabolizers or in people receiving concomitant fluoxetine, a strong CYP2D6 inhibitor.7 Clopidogrel represents a cardiovascular case. Clopidogrel is an inhibitor of platelet aggregation that is converted to its active metabolite

**Figure.** Forest plot included in the US drug labeling for ticagrelor. ASA indicates aspirin; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; TIA, transient ischemia attack.
by multiple CYP isoforms including CYP2C19, a polymorphic drug-metabolizing enzyme. Individuals with 2 reduced-function CYP2C19 alleles are referred to as poor metabolizers, and PK studies have demonstrated that genetically reduced CYP2C19 function is associated with reduced conversion of clopidogrel to its active metabolite and considerably reduced platelet inhibition. Studies evaluating the impact of CYP2C19 genotype on clinical outcomes have demonstrated that, in patients treated with clopidogrel following percutaneous coronary intervention, poor metabolizers are at higher risk of major cardiovascular events. Collectively, the PK, pharmacodynamic (platelet inhibition), and post hoc clinical outcomes analyses provide compelling evidence that CYP2C19 genotype impacts the efficacy of clopidogrel, so that current clopidogrel prescribing labeling recommends that physicians “consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.” Another example is the cardioselective β-adrenergic inhibitor metoprolol. About 8% of whites and 2% of others lack activity of CYP2D6, the primary enzyme involved in the oxidation of this drug. At recommended doses, these patients will have both increased β-blockade and a decreased extent of cardioselectivity in comparison with extensive metabolizers. Also, patients taking concomitant medications that inhibit CYP2D6 have 2 to 5 times the exposure to metoprolol as persons without these characteristics at recommended doses.

Sometimes none of these factors are adequate to predict drug exposure in an individual patient. For certain drugs, particularly when the therapeutic index is narrow, we resort to therapeutic drug monitoring (blood concentrations) to guide dosing. For example, the dosage of some anticonvulsants can be guided by therapeutic drug monitoring (eg, phenytoin, phenobarbital, carbamazepine), and a well-known example in cardiovascular medicine is digoxin. Many other drugs are titrated to effect or tolerability in ordinary practice, another standard individualization approach.

Pharmacodynamics

Genomic factors may also affect the pharmacodynamic (PD) effect of a drug, independent of exposure. Warfarin is an oral anticoagulant that exerts its pharmacological effect through inhibition of vitamin K epoxide reductase (VKORC). Warfarin’s PD effect is altered by a common genetic variant in the VKORC1 promoter that is associated with a lower warfarin dose requirement. Moreover, dosing algorithms that incorporate VKORC1 and CYP2C9 (a polymorphic drug-metabolizing enzyme that affects warfarin exposure) genotypes perform significantly better in predicting a stable warfarin dose than do algorithms that rely on only clinical information and fixed-dose approaches. Accordingly, the warfarin prescribing labeling includes dosing recommendations based on VKORC1 genotype to assist prescribers in titrating warfarin to the goal international normalized ratio of the patient. Apart from adjusting the initial warfarin dose regimen according to genetic characteristics, warfarin effects are also monitored by measuring the effect on international normalized ratio, a measure of the desired PD effect of coagulation inhibition, and adjusting dose accordingly to optimize the treatment effect.

Safety Versus Effectiveness

Many of these examples of individualization relate to effectiveness, but some have safety implications as well, such as increased blood concentrations when a drug is given to people who metabolize it poorly or are taking an enzyme-inhibiting concomitant medication. A classic example of this is the calcium channel blocker mibebradil, which inhibits CYP3A4 and CYP2D6, and caused severe muscle damage (rhabdomyolysis) when used with simvastatin and torse de pointe arrhythmias when used with astemizole, cisapride, and terfenadine. In some cases, population subsets have appeared to be at increased risk as was the case with individuals >75 years of age, or who weighed <60 kg, each of whom had an increased risk of bleeding when taking prasugrel, as noted in labeling.

Impact of Drug Labeling

The level of evidence required for information to be included in labeling generally differs from the level of evidence required to impact clinical practice. Many factors are considered when deciding whether to include information in labeling; the purpose of the label is to provide adequate instructions for use for the prescriber. Thus, labeling information, although comprehensive, is necessarily limited to the effects of a particular drug, both beneficial and harmful, and its proper use. In contrast, clinical practice is shaped by a myriad of factors that go far beyond a particular drug or group of drugs.

Designing Clinical Trials in the Era of Targeted Therapies and Personalized Medicine

Enrichment

Genomic or pathophysiological markers can also be used to improve the efficiency of clinical trials, by identifying the most appropriate patients to include. The power of a study designed to test preventive therapy can be enhanced in 2 distinct ways, by enrolling a population with higher risk, in whom the number of events is expected to be higher (prognostic enrichment) and by identifying a population with a larger effect size (predictive enrichment). Prognostic enrichment is widely practiced in cardiovascular outcome trials, but predictive enrichment is far less common in the cardiovascular therapeutic area.

Prognostic enrichment is frequently used in cardiovascular outcome trials. The first angiotensin-converting enzyme inhibitor trial to show a survival advantage, Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), was performed in New York Heart Association class IV patients and needed just 253 patients because the 6-month mortality was 44% on placebo. The reduction in mortality was quickly observed and the trial was stopped early. Later trials in less ill patients were much longer and had to use a composite end point of death plus hospitalization, because the mortality rate was much lower. Similarly, the first outcome trial of 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, the Scandinavian Simvastatin Survival Study, required a low-density lipoprotein (LDL) cholesterol between 213 and 310 mg/dL for entry and entered patients with a history of angina (21%) or a recent acute myocardial infarction (79%), recognized predictors of cardiovascular risk, and showed a clear
survival effect. Later trials in less ill patients had to be larger and used composite end points. In the recent Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study of a lower-risk population (LDL <130 mg/dL), patients had to have elevated C-reactive protein of ≥2 mg/L to ensure a reasonable event rate.19

Predictive enrichment, in contrast, has not been common in cardiovascular studies, largely because mechanisms (genomic, prognostic, etc) that might predict effectiveness have not been identified. Conditions where predictive enrichment would seem appropriate include heart failure, where the systolic and diastolic subtypes would be expected to respond differently to different treatments, and hypertrophic cardiomyopathy, where patients with obstructive and nonobstructive physiologies could respond differently. In fact, this has only infrequently been attempted, although interest appears to be increasing.

Even if there is no identified marker, a predictive biomarker response could be used to identify likely responders, a so-called pragmatic or empirical enrichment. This was actually attempted in the Cardiac Arrhythmia Suppression Trial (CAST), a study of arrhythmias to reduce mortality in postinfarction patients with increased premature ventricular depolarization rates (known to predict mortality).20 Only patients who had at least a 70% reduction in ventricular premature depolarization rates on initial screening were randomly assigned to antiarrhythmic or placebo. Unfortunately, despite this effort at predictive enrichment (studying only ventricular premature beat responders), the trial failed to show benefit, indeed showing a 2-fold increased risk of death. Despite the failure of the trial, the enrichment plan was appropriate.

Recent cardiovascular drug development programs have followed up on positive post hoc findings in subgroups where the overall trial did not show a treatment effect. For example, the combination of isosorbide dinitrate and hydralazine was prospectively shown to demonstrate clinical benefit in self-identified blacks (only blacks were studied)21 following a post hoc analysis of 2 previous controlled trials that showed no overall mortality benefit, but significantly reduced mortality in black patients.22 Similarly, although the Beta-Blocker Evaluation of Survival Trial (BEST) did not demonstrate a significant mortality reduction in patients with advanced heart failure who were assigned the β-blocker bucindolol in comparison with placebo, a post hoc pharmacogenetic analysis suggested that a common variant in the gene encoding the β1-adrenergic receptor (ADRB1 Arg389Gly) was associated with worse clinical outcomes in patients who received bucindolol.23 Bucindolol-treated patients who were homozygous for the Arg genotype appeared to have significantly higher survival rates and lower hospitalization rates than placebo-treated patients, whereas Gly carriers were not significantly different from placebo-treated patients.24 Bucindolol is now being evaluated specifically in patients with the ADRB1 Arg389Arg genotype (NCT 01970501).

These examples used prerandomization biomarker results or post hoc findings from nonenriched trials to identify possible responder populations, which were then studied. If the pathophysioloogy of the disease and mechanism of action of the drug were well understood, however, such demographic or genetic factors could be used prospectively to enrich the study population for likely responders. For example, elevated lipoprotein-associated phospholipase A2 activity is associated with higher risk of coronary heart disease.25 However, clinical trials evaluating the lipoprotein-associated phospholipase A2 inhibitor darapladib in patients with coronary heart disease did not enrich for patients with high levels of lipoprotein-associated phospholipase A2 activity (although patients with very low activity were excluded), and the drug did not significantly reduce cardiovascular events in this population.26 Such cases where the drug target drives disease pathophysiology and is prospectively known to have variable activity may represent opportunities for enriched clinical trials. In cases where exploratory data suggest that population subsets may respond differently, adaptive trial designs that use interim analyses may be useful to enrich the patient population.27 Modifications of the study population may also be made based on safety data from interim analyses. For example, following an interim analysis of the antiplatelet agent vorapaxar, patients with a history of stroke were discontinued from the study treatment because they were experiencing a higher risk of intracranial hemorrhage and were not benefiting from vorapaxar.28 More information on the considerations of adaptive trial designs, including statistical issues, is included in the FDA Draft Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologics.27

**Surrogate End Points**

In some cases, data demonstrating improved clinical outcomes are limited or would take a great deal of time to obtain, and effects on surrogate end points are relied on to make decisions related to approval of drugs used in personalized medicine. Although the FDA usually requires demonstration of a beneficial effect on a clinical end point – ie, one that assesses how a person feels, functions, or survives – to support the conclusion that a drug is effective for its intended indication, the FDA has based many cardiovascular drug approvals based on an effect on a well-established surrogate end point, in general, one shown to predict clinical benefit for ≥1 treatments.29 The FDA has defined a surrogate end point as “a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point … and is expected to predict the results of therapy.”30 The FDA has granted full approval to drugs on the basis of an effect on a surrogate end point considered to predict a clinical benefit, but under the regulations for “Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses,” the FDA can also approve a drug for a serious life-threatening disease that fulfills an unmet medical need on the basis of its effects on a surrogate end point that is less certain (ie, reasonably likely) to predict benefit.

Surrogate end points have been fully acceptable bases for the approval of antihypertensive drugs, drugs that lower LDL cholesterol (eg, statins and ezetimibe, among others), and antidiabetic drugs. The end points that were accepted in these cases were blood pressure, LDL cholesterol levels, and hemoglobin A1c levels, respectively. A demonstration of improvement in cardiovascular outcomes was not required in these cases because we were convinced from the totality of the
evidence that was available at the time of approval that the surrogate effects predicted a clinical outcome benefit. Similarly, drugs that raise or lower serum electrolytes – potassium, calcium, or phosphate – have also been approved largely on the basis of electrolyte effects.

Reliance on a surrogate poses 2 potential problems. One is that the surrogate may not in fact predict outcome. The second is that the drug may have an off-target effect that is harmful. The first problem can be mitigated by experience with other drugs with similar effects, but the second is difficult to anticipate. In the case of torcetrapib, both of these problems were suggested as possible reasons for why this drug, which substantially increased blood levels of high-density lipoprotein (HDL) cholesterol, was associated with worsened cardiovascular outcomes in a large randomized trial. For example, it was suggested that merely raising levels of HDL cholesterol without improving HDL function might not beneficially affect the course of atherosclerosis or prevent its associated adverse cardiovascular outcomes. There was also speculation that the off-target, hypertensive effect of torcetrapib may have increased the rate of cardiovascular events. Another interesting example is the previously noted CAST study of the use of antiarrhythmics to suppress ventricular premature beats in patients with recent myocardial infarction. CAST did not rely on a surrogate marker but it illustrates the risks of doing so, because the dramatic effect on a potential surrogate end point (ventricular premature beat suppression) was not accompanied by a favorable effect on survival but by an adverse effect, which probably represents an unanticipated manifestation of the drug’s on-target effects on ion channels. This unexpected effect might not have been detected in a trial that assessed only the effects of antiarrhythmic drugs on premature ventricular contractions.

Another example involves the use of inotropic drugs for heart failure. One would expect a drug that favorably affects cardiac output and improved exercise ability to improve outcomes in patients with heart failure. However, several inotropic drugs with seemingly beneficial effects on cardiac function and short-term clinical benefit have proven to increase cardiovascular mortality in longer trials. Consequently, the FDA typically requires convincing, preapproval evidence that any drug for heart failure either improves survival or at least is neutral in terms of survival and provides some other benefit for patients.

Nonetheless, there may be some novel settings in which the FDA might consider the use of a surrogate end point to support regular or accelerated approval for a drug for a cardiovascular indication. For example, congenital long-QT syndrome type 3 (LQT3) is a rare genetic disorder associated with prolongation of the QT interval in children and adults, caused by gain-of-function mutations in SCN5A, the gene coding for the sodium channel hNa1.5. These mutations result in the expression of sodium channels whose inactivation is delayed, leading to an increase in late flux of sodium (late $I_{Na}$) into the cardiomyocyte, with manifestations of QT prolongation on the surface ECG and increased risk of torsade de pointes and symptoms of syncope and sudden death. The pathophysiology of LQT3 seems well understood, and the abnormal ion flux that causes QT prolongation on the surface ECG is believed to be the underlying cause for the increased risk of ventricular arrhythmia. Thus, if a hypothetical drug suppressed late $I_{Na}$ in preclinical studies in models of LQT3 and shortened the QT interval in studies in patients with QT prolongation and increased risk of arrhythmia associated with LQT3, it may be reasonable to expect that the drug will provide a clinical benefit to patients with LQT3 and increased arrhythmia risk. The use of this surrogate end point would thus allow this hypothetical and possibly life-saving drug to be available to patients years before an outcomes trial could be completed in the very small population of patients with LQT3. QT prolongation is, of course, currently used as a safety surrogate for indicating the risk of fatal arrhythmias and affects both labeling and, in some cases, drug approval.

**Discussion and Future Perspective**

Personalized medicine has the potential to change the standard of care for cardiovascular diseases. Although few examples of personalized cardiovascular medicine based on molecular profiling exist to date, other methods have been used. Certainly, normalization of drug exposure across different subsets of individuals is 1 form of personalized medicine that is well established and commonly implemented. Differences in exposure may be driven by body size, organ function, and genetic factors among other causes, and prospective adjustment of therapy based on any of these factors is an example of personalized medicine. This is of growing interest in dealing with the important concentration-response relationship of oral anticoagulants and this approach has, of course, long been the norm for using warfarin. It appears likely that many factors can affect response to a drug independent of exposure, but such differences in response are more difficult to anticipate and assess prospectively than exposure.

When it is suspected that drug response is altered in a demographic or genetic subgroup, a reliable PD predictor of drug response may facilitate mechanistic understanding of the association and provide supporting evidence of its validity. Notable drug classes with PD markers include antiplatelet agents and anticoagulants. Despite the relative scarcity of predictive markers, cardiovascular medicine is heavily influenced by many prognostic markers – factors that are known to increase risk. These include previous cardiovascular events, concomitant illnesses such as diabetes mellitus, family history, and levels of HDL cholesterol, LDL cholesterol, and C-reactive protein. Given effective medications, patients at higher risk reap a greater likelihood of benefit.

The development of personalized medicine strategies based on genetic or physiological biomarkers for cardiovascular diseases such as atherosclerosis, heart failure, and hypertension is challenging because of the multifactorial etiology of these diseases. Thus, the current state of personalized medicine in cardiovascular disease is largely limited to classical approaches such as PK adjustments and dose titration to a PD marker. A greater fundamental understanding of these complex disorders will facilitate more precise disease classification based on underlying pathophysiology and may lead to the development of personalized medicine strategies. Meanwhile, the greatest source of information on potential intergroup
differences will continue to be the subgroup analyses regularly conducted.

One potential opportunity for personalized medicine in cardiovascular disease appears to be hypertension, where patients are typically treated to a goal blood pressure irrespective of the factors driving blood pressure elevation, and the particular treatment is generally not thought to matter. Nonetheless, current hypertension guidelines recommend different initial first-line antihypertensive treatment options based on race (reflecting prevalent renin status) and the presence of chronic kidney disease, and suggest different blood pressure goals based on age. Race and age, however, would seem to be crude classifications for more fundamental patient and disease characteristics that seem likely to be shared by individuals across race and age spectra. For treatment to become truly personalized, we need to understand these fundamental characteristics better and develop individualized treatment strategies. Several clinical trials have suggested that some antihypertensive regimens improve clinical outcomes more than others, despite similar blood pressure lowering effects, but, in general, differences are seen in all subsets, the exception being the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), where the incidence of stroke was not reduced by losartan in comparison with atenolol in the black population. It remains to be seen whether correcting the underlying pathophysiology rather than treating the clinical manifestation of elevated blood pressure is a potential personalized medicine approach to improve clinical outcomes in patients with hypertension.

Genetic polymorphisms can also alter the biological activity of critical pathways and drive disease pathophysiology. Moreover, genetic association studies have discovered that variants in numerous genes impact cardiovascular disease risk. Functional evaluation of these genetic loci to characterize their impact on disease pathology at the individual patient level may reveal opportunities for the development of targeted therapies. Current and future clinical trials will determine whether or not these findings will translate into successful therapeutic strategies for cardiovascular disease and increased implementation of personalized medicine approaches.

In conclusion, there are currently few examples of personalized cardiovascular medicine that identify patients with greater responses, although there are many ways to identify high-risk patients for treatment. The complex etiology of common cardiovascular diseases makes the development of targeted therapies and personalized medicine approaches difficult. This problem is further confounded by classification of cardiovascular diseases based on the observed clinical phenotype rather than on the underlying mechanism driving the disease. As our mechanistic understanding of complex cardiovascular diseases grows and we are able to identify causative factors at the individual patient level, opportunities for personalized medicine and the development of targeted therapies should emerge. The development of targeted therapies that directly mitigate the underlying cause of disease in patients where a single factor appears to be the driver, rather than treating the resulting clinical symptom, may lead to greater clinical implementation of personalized medicine for common cardiovascular diseases.

Disclosures
None. This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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