

Improving Cardiovascular drug Therapy Through Pharmacogenomics?

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Parmacogenetics and pharmacogenomics are terms that are being seen with increasing frequency in both the scientific literature and the lay press. They are terms used to describe a field that aims to understand the genetic basis for variable drug response^{1,2}. The practical application of the field may range from use of a patient's genetic information to determine their most appropriate therapy to using knowledge about the genetic basis of disease to discover new drug targets, and drugs that act on those targets. Pharmacogenetics and pharmacogenomics hold the promise of improving drug therapy by optimizing efficacy and reducing toxicity through genetically guided, individualized therapy.

There is some confusion at present about the distinctions between pharmacogenetics and pharmacogenomics, with many different definitions available in the literature. Definitions that are consistent with the distinctions between genetics and genomics describe pharmacogenetics as a field focused on describing the contribution of variability in a single gene to variable drug response. In contrast, pharmacogenomics describes the contribution of multiple genes, or the entire genome, to interpatient variability in drug response^{1,2}. Using these definitions, most work in the field to date would be described as pharmacogenetics, whereas future studies that focus on multiple genes or gene chips, or

use of genomic information in drug discovery would be described as pharmacogenomics.

Cardiovascular disease is a particularly interesting and appropriate focus for pharmacogenetics and pharmacogenomics research. The review by Boudoulas on page 1 highlights a number of genes whose polymorphisms have been associated with variable response to cardiovascular drugs. Pharmacogenomics has the potential to enhance drug efficacy, by allowing patients with the greatest likelihood for benefit to be identified and to reduce toxicity by identifying those at greatest toxicity risk. The examples provided by Boudoulas touch on both of these general principles.

Cardiology is a field that has the luxury of practicing evidence based medicine, as there are solid clinical trials data that guide practice in nearly all settings. Nonetheless, clinicians recognize that not all patients derive benefit from drugs that may have been shown useful in large patient populations. For example, a certain percentage of appropriately treated hypertensives will still develop acute myocardial infarction or stroke and far too many appropriately treated heart failure patients still die. These facts indicate that our drug therapy is not perfect and that some patients derive greater benefits than others from specific drugs. Pharmacogenomics has the potential to improve upon current cardiovascular drug therapy in several respects³. First, it holds the promise of allowing

patients with the greatest benefit from a certain drug to be identified and targeted for therapy. Those with a lower likelihood for benefit or increased toxicity risk can be treated with alternative therapy, which in them, might be highly beneficial. Additionally, pharmacogenomics has the potential to lead to discovery of important new therapeutic agents that might further reduce the burden of cardiovascular disease³.

In the practice of cardiology, there are two general approaches to treatment of disease with drug therapy, both of which have the potential to be improved through pharmacogenomics. First is a trial and error approach, which is commonly used in the treatment of hypertension, lipid disorders, angina, and atrial fibrillation. For these diseases there are multiple drugs that might be beneficial to the patient and the selection of a specific agent is often based on certain patient demographics, the physician's personal preferences, and/or clinical trials data suggesting superiority to other drugs used for the condition.

Treatment of hypertension may be the best example of the trial and error approach, where diuretics, ACE inhibitors, AT₁-receptor blockers (ARBs), β -blockers, calcium channel blockers and α_1 -blockers are considered appropriate first line therapy⁴. How a physician selects from among these many drug classes is based on many factors. However, certain statistics in the literature would suggest that the trial and error approach in hypertension is far from optimal. For example, NHANES III data suggest that only 27% of hypertensives have their blood pressure adequately controlled and 43% are not currently treated⁴. In many cases the untreated patients have been treated in the past, but are no longer on therapy. Communication with these patients indicates that for many, failure of the first drug to control their blood pressure or bothersome adverse effects is the reason they are no longer taking an antihypertensive drug. Through pharmacogenomics, it might be possible to identify a priori a drug or drugs most likely to reduce a patient's blood pressure, based on the patient's genetic make-up. While not proven, it seems probable that successful blood pressure control with the initial drug would increase the patient's likelihood of remaining on their prescribed therapy. Additionally, such a genetic prediction should reduce the number of physician visits needed to achieve blood pressure control and result in shorter periods of uncontrolled hypertension, potentially leading to reduced health-

care expenditures and improved patient outcomes. The likelihood that such predictive tests will be available in the next decade seems high as there are already data linking genetic polymorphisms with response to ACE inhibitors, diuretics, β -blockers and ARBs⁵⁻¹³.

The other typical treatment approach leads to all patients with a certain disease being treated similarly. Management of patients with heart failure, acute coronary syndromes and post-myocardial infarction are examples of this treatment approach. For example, current treatment guidelines recommend that essentially all patients with systolic heart failure should be on an ACE inhibitor, a β -blocker, a diuretic, and possibly digoxin and spironolactone¹⁴. While the benefits of these treatments have been well documented in clinical trials, it seems clear that not all patients obtain benefit from all of the medications. The difficulty in this scenario is that for several of the drugs, the primary benefit of therapy is mortality reduction, an endpoint that cannot be measured in individual patients. Thus, all patients are treated with the same cadre of medications. Determination of the genetic profiles associated with the best outcomes with these therapies could lead to targeted therapy. This might be particularly beneficial in heart failure since most of the heart failure therapies lead to a reduction in blood pressure, sometimes limiting the ability to add other therapies that also have potential for benefit. Should it be determined that a patient is unlikely to derive substantial benefit from a certain drug (e.g. β -blocker), then this drug class might be withheld, allowing other potentially beneficial therapies to be given. The more recently conducted clinical trials (e.g. MERIT-HF) and most ongoing clinical trials involve collection of genetic samples. Thus, it is hoped that such insights into the genetic basis for benefit will be revealed in the upcoming years.

The cardiovascular disease state that is probably least likely to benefit in the near future from genetically guided therapy is ischemic heart disease and more specifically, the acute coronary syndromes. This is because treatment decisions for patients with acute coronary syndromes must be made immediately, and there wouldn't be time to run a genetic test. However, it is conceivable that individuals with angina, or a previous history of acute coronary events might be genotyped so that such information could be utilized at the time of a second acute coronary event.

The final manner in which pharmacogenomics might improve patient care is through identification of patients at risk for toxicity with cardiovascular medications. Fortunately, most cardiovascular medications are very safe and serious toxicities are rare. Nonetheless, there are certain cardiovascular medications that have serious toxicities, for which a priori identification of risk would be helpful.

The best example of ongoing research in this area is the genetic basis for drug-induced Torsades de Pointes (TdP)¹⁵⁻¹⁸. This is a serious adverse effect of many antiarrhythmic drugs and numerous other non-cardiovascular drugs. Most studies to date have focused on the genetic mutations that are associated with congenital long QT syndrome. While they have shown some association with drug-induced QT prolongation and TdP, the associations are typically weak. Studies in this area are also quite difficult since drug-induced TdP is relatively rare, thus compiling a sufficient number of patients to test genetic associations is a challenge. Nonetheless, there is great hope that pharmacogenomics might be able to unravel the presumed underlying genetic basis for this adverse drug effect. If this were to happen, then patients who are being considered for QT prolonging drugs could undergo genetic screening. Those at risk for QT prolongation and TdP based on their genetic profile could receive alternative therapy and the drug could then be used with greater confidence in the remainder of the population.

Another example where pharmacogenetics might reduce toxicity risk is for drugs that have toxicities associated with high plasma drug or metabolite concentrations. For example, genetic polymorphisms in the enzyme responsible for metabolism of S-warfarin (the active stereoisomer) have been associated with reduced enzyme activity, increased bleeding risk (particularly early in the course of therapy), need for reduced doses of warfarin and prolonged time to a therapeutic INR or stable dose¹⁹⁻²². Should a genetic test be developed that could predict those at risk for impaired warfarin metabolism, then warfarin dosing might be individualized from the outset of therapy, as opposed to the current practice, where most patients are started on the same dose (e.g. 5 mg), with adjustments made based on the patient's INR. Such predictive ability should reduce the risk of over-anticoagulation and bleeding early in the course of therapy and also lead to more rapid attainment of a stable warfarin dose. Numerous studies in this area are ongoing and it

seems likely that a point of care genetic test will be available in the next decade.

The discussion to this point has focused on the benefits of pharmacogenetics and pharmacogenomics in the patient care setting, with medications that are part of the current armamentarium. Another important potential benefit of pharmacogenomics is in the area of drug discovery. While there are no examples at present of cardiovascular drugs developed through genomic technologies, it is expected that it is only a matter of time until this occurs. The basic tenet is that through genomics, the array of genes that are involved in cardiovascular (or any other) disease might be identified²³⁻²⁵. It is anticipated that for many diseases, this might represent hundreds of different genes, many of which we currently know nothing about, or which have never been linked with the disease of interest. Through such efforts, new protein targets for drugs might be revealed and important new drug classes developed.

Nearly all cardiovascular diseases show patterns of inheritance (i.e. run in families), suggesting that genetics play an important role in the various cardiovascular diseases. However, except in rare exceptions, like hypertrophic cardiomyopathy, it is believed that numerous genes contribute to risk of a given disease and there are no cardiovascular diseases for which the constellation of "disease genes" has yet been well defined. Additionally, environmental factors play an important role in risk of most cardiovascular diseases. Thus, cardiovascular diseases are what are known as common complex diseases, meaning that numerous genes, along with environmental factors contribute to disease risk. This makes the challenge of understanding the genetic basis for disease somewhat daunting.

The complexity of cardiovascular diseases also makes it likely that numerous genes will best define the interpatient variability in response to a specific drug. Thus, while most studies to date have focused on a single gene, it is likely that evaluation of a constellation of genes will be necessary to provide the predictive power necessary for pharmacogenomics to enter clinical practice^{1,3,24}. However, it seems highly likely that this will occur, and that the next decade will see the clinical availability of genetic "drug responder" tests that will allow cardiologists to further individualize the drug therapies they prescribe.

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