

Special Report: Cardiovascular Pharmacogenomics



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Executive Summary

Background

Pharmacogenomics is the study of genetic influences on drug response. One of the more active areas of research in this field involves pharmacogenomics of cardiovascular disease. Given the high prevalence of cardiovascular disease and the large numbers of persons using cardiovascular drugs, pharmacogenomics has the potential to improve health outcomes.

Objective

This Special Report will survey the literature in the field of pharmacogenomics in relation to cardiovascular disease. It will highlight the particular diseases and drugs that have been studied in this field, and point out any promising areas. Areas not addressed in this Report include cytochrome P450 testing for warfarin dosage adjustment and use of genetic testing for cardiovascular disease susceptibility or outcome.

Search Strategy

A MEDLINE® search (via PubMed) for relevant review articles was completed for the period up to June 2007. The search strategy included the terms “pharmacogenetics” or “pharmacogenomics” and “cardiovascular” as text words or subject terms. The bibliographies of these review articles were also examined for other relevant review articles.

Selection Criteria

Based on the content of the review articles, it was determined that areas of this field that had sufficient research publications to discuss were pharmacogenomics of 1) statins, 2) angiotensin-converting-enzyme (ACE) inhibitors, 3) beta blockers, and 4) diuretics.

Discussion

Most studies addressing the pharmacogenomics of cardiovascular disease examine potential genetic interactions of commonly prescribed drugs for highly prevalent conditions such as hypertension, congestive heart failure, and hypercholesterolemia. Studies have focused on differential efficacy of drugs, rather than prediction of adverse effects. There are very few currently marketed tests with potential pharmacogenomic use for cardiovascular drugs.

Pharmacogenomic effects of existing and largely safe drugs may not translate into clinically useful knowledge. Such effects may not be strong or predictable enough to be clinically useful. It is difficult to prove that a particular drug previously demonstrated to be safe and effective is not effective in a particular subgroup, and demonstration of a stronger than average clinical benefit in a particular genetically identified group of persons may not change clinical decision making.

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Regarding research on statins, results are by and large unreplicated, inconsistent, or show small effects on lipid response or cardiovascular outcomes. The major review article in this field examined 41 studies. Many studies evaluated lipid response, which may not correlate with cardiovascular outcomes. ACE inhibitors have been studied many times because a known common polymorphism, the I/D polymorphism, is associated with serum ACE levels. The I/D allele and its interaction with ACE inhibitor treatment have been studied in a wide range of patients with differing indications and clinical endpoints. However, two review articles concluded that no conclusive pharmacogenomic effects have been demonstrated. Relatively fewer studies have examined beta-blockers and diuretics. Although some studies have shown pharmacogenomic interactions, such studies need to be replicated in order to confirm the associations and to assess the generalizability of the associations to other populations.

In sum, the study of pharmacogenetic interactions for cardiovascular diseases is at an early stage of development, and there are no tests that appear close to clinical utility. The literature is characterized by many exploratory findings that have not been replicated or have been contradicted. Strong and consistent associations between particular genotypes and drug response will be required for pharmacogenomics findings to be translated into clinical practice. Clinical trials may be necessary to determine whether patient outcomes are actually improved by treatment directed by genetic information.

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Introduction

Individuals vary in their response to drug therapy. Variability in patient response to treatment has always been recognized as an important factor in optimizing treatment for patients. Clinical trials commonly examine subgroup effects in order to determine patient factors associated with greater or lesser benefit of treatment. Knowledge of such subgroup effects can result in avoidance of ineffective treatments or in selection of particularly efficacious treatments. Although the exact amount of benefit or risk to an individual patient for a given treatment can never be known, knowledge of characteristics that determine greater or lesser amounts of benefit or risk can sometimes improve treatment decisions. Pharmacogenomics is the study of genetic influences on drug response. In some ways, pharmacogenomics can be viewed as a massive exercise in the discovery of clinically relevant subgroups.

Pharmacogenomics promises the potential of more specifically selecting appropriate therapy, where choice or dosage of treatments might be partially based on genetic tests in order to maximize benefit and minimize harm. Given the incidence and prevalence of cardiovascular disease throughout the world, and the high prevalence of persons taking certain classes of medications for cardiovascular conditions, there is potential for such knowledge to improve treatments and health status.

The purpose of this Special Report is to survey the field of pharmacogenomics in relation to cardiovascular disease. There have been a large number of such studies. Rather than attempting to be comprehensive, this Report will attempt to give information regarding pharmacogenetic associations that have been studied many times. Several review articles have been published attempting to summarize pharmacogenetic studies, organized by either the drug or drug class of interest or the particular genetic marker of interest (Kajinami et al. 2004; Scharplatz et al. 2005; Tsikouris and Peeters 2007). At this point in time, however, it does not appear that genetic testing to improve prescribing for cardiovascular conditions is anywhere close to clinical application because reliable genetic markers have not been found or clinical utility has not yet been demonstrated.

A number of variant alleles in cytochrome P450 (CYP450) enzyme genes are associated with variations in metabolism of many types of drugs. This has been reviewed elsewhere in a prior TEC Special Report (2004; Vol. 19, No. 9). Among the more promising uses of pharmacogenomics for cardiovascular disease previously described in that Report is the use of genotyping to aid in the determination of warfarin dosage. The American College of Medical Genetics (ACMG) commissioned a systematic review of the evidence for warfarin genetic testing in 2006; the final review is posted on the ACMG website (www.acmg.net). Therefore, CYP450 testing for this particular indication will not be addressed in this Special Report.

Use of genetic testing for cardiovascular disease susceptibility or outcome is also not addressed in this Report. Much current research is attempting to find genetic determinants of common cardiovascular conditions such as coronary heart disease and hypertension (Anderson et al. 2003). These markers, if validated and proven to be clinically useful, may affect whether a patient receives a particular preventive treatment. However, such a genetic marker may not be associated with a differential effect of treatment, and would not be considered to have a pharmacogenetic interaction. However, there is potential overlap between disease susceptibility genetics and pharmacogenomics. Certain genetic markers have been proposed to be both markers of disease susceptibility and to interact with specific treatments (Henrikson et al. 2007).

Current Scope of Cardiovascular Pharmacogenomics

Currently, most studies addressing the pharmacogenomics of cardiovascular disease examine potential genetic interactions of commonly prescribed drugs for highly prevalent conditions such as hypertension, congestive heart failure, and hypercholesterolemia. The studies have tended to focus on differential efficacy of the drugs, rather than on the prediction of adverse effects.

Prior to any consideration of genetic interactions, cardiovascular drugs such as statins and ACE inhibitors have largely been proven to be effective and safe in large broadly defined clinical trial populations and thus are in wide use. Variations in response and in risk according

to patient characteristics are often known or have subsequently been discovered, but clinical trials and long experience have generally demonstrated an overall net benefit to broad classes of patients. After taking into account known nongenetic factors that cause variation in response, the remaining variability in patient response can often be managed empirically by changing drugs or dosage. Drugs that have been associated with unpredictable severe adverse effects either do not make it to market or are likely to be withdrawn from the market. The adverse effects of available cardiovascular drugs are preventable with appropriate monitoring, or are mild and generally reversible by withdrawal of the drug.

The focus of cardiovascular pharmacogenetic research on existing effective and largely safe drugs sets a high bar of supporting evidence that would be necessary to translate findings to actual clinical practice. Regarding the efficacy of drugs, since any widely used drug is considered to be effective in the broad population of patients in whom it is being prescribed, the identification of a genetically identified patient subgroup with a differential effect of treatment might not alter clinical practice. If such a subgroup of patients achieved a substantially better outcome than the rest of patients, such knowledge may not alter clinical practice because the drug would likely still be effective in the rest of the population (i.e., if the drug had no benefit in the “wild type” majority, then the original clinical trials would likely have not shown benefit). If a genetically identified subgroup achieves worse outcomes than the wild type group, then withdrawing the drug, adding another drug or substituting with another drug is a consideration. However, it would need to be demonstrated that patient outcomes would not be harmed or would be improved by such a change. It is difficult to demonstrate definitively that a treatment otherwise known to be beneficial in the broad population is not beneficial in particular subgroups. Observational studies may not be convincing, and it might be difficult to mount a clinical trial to show that a treatment is not effective in a particular subgroup.

Regarding the safety of drugs, a genetic test would need to be sufficiently sensitive and specific in identifying persons at risk for adverse events. Such a situation would occur when the therapeutic range of a drug is relatively narrow, and significant adverse events or loss of effi-

cacy would occur when drug levels are outside that window. The genetic factor would have to account for a large proportion of the variability in drug levels. Finally, using the genetic test would need to be more efficient than current practice in preventing serious adverse effects.

Pharmacokinetics versus Pharmacodynamics

There are two broad categories of pharmacogenetic applications. The study of drug metabolism is called pharmacokinetics, and the study of pharmacologic actions independent of drug concentration is called pharmacodynamics. Genetic studies of drug metabolism have examined genetic variations in various enzyme systems that are involved in the metabolism of drugs (Anderson et al. 2003). Genetic studies of pharmacodynamics examine a variety of genetic variations involving the protein targets of drugs, proteins involved in the pathogenesis of disease, and downstream proteins (Anderson et al. 2003). Most of the research in cardiovascular pharmacogenomics has involved pharmacodynamic applications.

As described earlier in this Introduction, a major exception is the body of research examining the metabolism of warfarin. Genetic variation in the CYP450 enzyme system is one of the most extensively studied systems involved in pharmacokinetics. A number of variant alleles in CYP450 enzyme genes are associated with variations in metabolism of many types of drugs. This has been reviewed elsewhere in a prior TEC Special Report (2004; Vol. 19, No. 9). Among the more promising uses of pharmacogenomics for cardiovascular disease previously described in that report is the use of genotyping to aid in the determination of warfarin dosage. The ACMG commissioned a systematic review of the evidence for warfarin genetic testing in 2006; the final review is posted on the ACMG Web site (www.acmg.net). An ACMG recommendation statement and a summary of the systematic review will be published in *Genetics in Medicine*. Therefore, CYP450 testing for this particular indication will not be addressed in this Special Report. At this point in time, several clinical trials are enrolling patients that compare using genetic tests to usual practice in determining the proper warfarin dosage; it is hypothesized that initial dosing guided by pharmacogenetic tests will decrease the number of bleeding events compared to standard starting dose.

Examples of Available Tests for Cardiovascular Pharmacogenomic Testing

There appear to be only a few pharmacogenomic tests commercially available for cardiovascular conditions. An Internet search located only a few vendors that appeared to market tests for the general patient population (Table 1). Except for the CYP450 tests and NAT2 tests that were specifically marketed for pharmacogenetic testing for a broad range of drugs, the other tests in this table were not specifically mentioned for pharmacogenomic testing but rather for disease susceptibility testing. The principal indication for ApoE and cholesterol ester transfer protein is for prediction of cardiovascular disease. The evidence for ApoE and cholesterol ester transfer protein as pharmacogenomic tests will be discussed in a later section of this Report. Although it appears to be established that procainamide metabolism is related to NAT2 genes (perhaps based on chemical structure and knowledge based on analogous compounds), there appeared to be very little literature addressing this issue in clinical studies. A MEDLINE search using “procainamide” and “NAT2” as search terms found only one study in healthy subjects addressing this pharmacogenomic interaction, essentially confirming this association between procainamide metabolism and NAT2 genetic status (Okumura et al. 1997). Further studies addressing clinical outcomes were not found.

Methods

Search Methods

A MEDLINE® search (via PubMed) for relevant review articles was completed for the period up to June 2007. The search strategy included

the terms “pharmacogenetics” or “pharmacogenomics” and “cardiovascular” as text words or subject terms. The bibliographies of these review articles were also examined for other relevant review articles.

Study Selection

Based on the content of the review articles, it was determined that areas of this field that had sufficient research publications to discuss were pharmacogenomics of 1) statins, 2) angiotensin-converting-enzyme (ACE) inhibitors, 3) beta blockers, and 4) diuretics.

Medical Advisory Panel Review

This Special Report was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on June 28, 2007. In order to maintain the timeliness of the scientific information in this Special Report, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Special Report.

Review of Evidence

Cardiovascular Pharmacogenetic Studies

There are critical practical barriers to the discovery of important pharmacogenetic effects. The evidence regarding the efficacy of commonly prescribed cardiovascular drugs was originally proven using very large prospective clinical trials, with numbers of participants generally in the thousands in order to have

Table 1. Examples of Marketed Tests with Potential Cardiovascular Pharmacogenetic Use*

Test	Cardiovascular Drug or Drug Class	Pharmacogenetic Condition/Indication	Evidence Supporting Use
cytochrome P450 enzymes	warfarin	anticoagulation	clinical trials in progress
NAT2	procainamide	arrhythmia	nonexistent
ApoE	statins	elevated cholesterol	small associations inconsistently replicated
cholesterol ester transfer protein	statins	elevated cholesterol	contradictory associations

*tests identified on Web sites of Genelex (genelex.com), and Genosolutions (genosolutions.com)

sufficient numbers of clinical endpoints. Generating reliable subgroup effects, which is one of the goals of pharmacogenomics, requires even larger trials, particularly when the subgroup effects are not extreme. In addition, because of the numerous genetic markers that are usually analyzed in the same study, replication is always necessary to rule out false-positive findings. Replication is also necessary because genetic effects may vary across different populations due to other genetic or environmental factors (Anderson et al. 2005). Given these and other constraints, it might be difficult to gather the resources necessary for prospective pharmacogenomic studies (Haga and Burke 2004).

However, if testing can be performed from previously stored samples, subgroup analyses using genetic tests as the “exposure variable” can be done from previously collected patient groups from randomized clinical trials, prospective cohort studies, and case-control studies. The majority of cardiovascular pharmacogenetic studies with reasonable sample sizes appear to have been done using blood samples from patients from previously published studies. Thus all the treatments, measurements of exposures, confounding variables, and outcomes have generally already been completed, and the pharmacogenetic analysis is a post-hoc subgroup analysis. The genetic markers under consideration tend to be randomly distributed, because they were, of course, unknown during the original study. While this is a great convenience to researchers, it is critical to be aware of the results and limitations of the original research from which the pharmacogenetic analysis was derived. For example, when the original source study is an observational study in which patients were all receiving some treatment for a condition such as hypertension, rather than a placebo-controlled clinical trial, a pharmacogenomic interaction should be interpreted as a differential treatment effect *relative* to the other treatments used in the study and not a differential effect relative to no treatment (Psaty et al. 2002).

While post-hoc mining of existing studies can potentially provide reliable associations between genotype and treatments, they cannot prove that use of the genetic information would improve outcomes beyond current practice. The associations found would either need to be so overwhelming that the genotype information would direct patients to more appropriate treatments,

or prospective trials of clinical utility would need to be carried out. So far, only genetic testing for initiation of warfarin treatment has reached the prospective clinical trial stage.

Drug Classes Examined in Cardiovascular Pharmacogenetic Studies

Statins

Statins are among the most widely prescribed cardiovascular drugs. Large clinical trials have established their beneficial effects in the primary and secondary prevention of coronary heart disease. The effect of genotype on response to statins has been assessed in several studies. Kajinami et al. (2004) reviewed 41 studies of common genetic variants and their associations with lipid effects and clinical outcomes. Sixteen candidate genes involved lipoprotein metabolism and 3 involved pharmacokinetics of statin metabolism.

A subset of 23 studies in the review by Kajinami et al. (2004) analyzed lipid responses in patients with primary hypercholesterolemia. At the time of Kajinami and co-workers’ review, of the 20 different loci examined, only findings regarding apoE polymorphisms had been replicated. Subjects with the apoE*2 allele had greater lipid reductions with statin treatment. However, this finding was not consistent across all studies, as differences in lipid response failed to reach statistical significance in 4 out of 8 studies. The difference in lipid response across apoE genotypes was relatively small, from 3 to 6%. Other factors, such as age and gender, have been shown to have larger effects than apoE polymorphisms (Thompson et al. 2005).

Thus, most findings regarding genetic differences in lipid response were not large, had not been replicated, or were inconsistent. It should be noted that lipid response is only an intermediate outcome of statin treatment, which is easily measured after a trial of treatment. Although lipid response has been shown to be correlated with efficacy, such a correlation may not be maintained in pharmacogenomic studies. Anderson et al. (2003) in a review of several pharmacogenomic studies of statins, noted several studies in which the differential impact on outcomes was directionally opposite to that predicted by differences in lipids. They speculate that other processes occurring in persons with variant genotypes may explain the discrepancy.

Eighteen studies abstracted in the review by Kajinami et al. examined pharmacogenomic interactions of statins and cardiovascular endpoints. Significant interactions were observed in 10 of 18 studies. Most of the results had not been yet replicated, and a few studies examining the same polymorphisms contradicted each other. Maitland-van der Zee et al. (2005), in an editorial in which the review by Kajinami et al. was analyzed, showed that among the potential pharmacogenomic interactions that had been examined more than once, only the apoE findings had been replicated. They, too, noted the inconsistent replication of results for apoE. Conflicting findings were specifically noted for studies of the cholesterol ester transfer protein (Carlquist et al. 2003 versus Kuivenhoven et al. 1998).

The review by Kajinami et al. noted that pharmacogenomic studies related to adverse effects of statins had not been carried out. There had only been 2 studies relating genotype to adherence. An attempt to find additional clinical studies of genotype and adverse events of statins on MEDLINE did not turn up any.

In sum, studies of pharmacogenetic interactions of statin drugs are by and large unreplicated, inconsistent, or show small effects. Promising genetic markers, if any, are still several steps away from clinical application. Results need to be replicated, large effects need to be demonstrated, and a coherent treatment algorithm that results in improved patient outcomes needs to be developed. Lipid response may be an unreliable marker of actual clinical outcomes. It would need to be demonstrated that a pharmacogenomic approach improves upon the current approach of monitoring patients' lipid levels after a trial of therapy. Finally, there are only a few pharmacogenomic studies examining adverse events of statins (Kajinami et al. 2004).

ACE Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are widely used drugs for treatment of hypertension, heart failure, and prevention of diabetic nephropathy. Interest in possible pharmacogenomic associations with these drugs has been intense because of the existence of a common polymorphism known to cause variations in serum ACE levels (Scharplatz et al. 2005).

This polymorphism occurs in the ACE gene in which the two alleles differ by the presence (insertion) or absence (deletion) of a 287 base-pair insertion. The insertion/deletion (I/D) polymorphism has been noted to account for 47% of the variability in serum ACE levels, with DD homozygotes having the highest serum ACE levels. The DD genotype is a substantial proportion of the population, approximately one third. The I/D polymorphism has been studied as a risk factor for coronary artery disease; DD genotype may be a risk factor for myocardial infarction, albeit with only a modestly elevated relative risk of approximately 1.2 (Agerholm-Larsen et al. 2000). In addition to the I/D polymorphism, other single nucleotide polymorphisms (SNPs) of this gene have been found, which appear to have associations with ACE levels and with cardiovascular risk. Because the I/D polymorphism is both prevalent and appears to be a strong predictor of serum ACE levels, which may be a predictor of cardiovascular outcomes, interaction with ACE inhibitor treatment seems biologically plausible. Based on the possible pathophysiologic pathways involving ACE in heart disease, it is hypothesized that those with the DD genotype might be more responsive to ACE inhibitors. In fact, the ACE I/D polymorphism has also been studied in relation to other cardiovascular treatments such as statins and beta blockers. Conflicting findings regarding the I/D polymorphism and the effects of statins were noted in the editorial by Maitland-van der Zee (2005), noted previously.

The interaction of ACE gene polymorphisms and ACE inhibitors have been the subject of at least 2 recent systematic reviews. Scharplatz et al. (2005) selected only randomized, placebo-controlled trials that had examined the I/D polymorphism in relation to ACE inhibitor treatment. Eleven studies were found that studied a wide range of clinical indications and analyzed a variety of clinical endpoints. Outcomes ranged from measures of renal function in patients with renal dysfunction to coronary artery diameter in patients undergoing coronary stent implantation. The authors noted a trend toward better response to ACE inhibitors in caucasian DD carriers. On the other hand, they noted the small number of studies and stated that lack of sufficient genetic data (in terms of sufficient information from certain studies to formally examine drug interaction) from the reviewed studies precluded drawing any convincing conclusions. Studies in Asian

populations showed the opposite results with DD carriers having worse outcomes with ACE inhibitor treatment.

Another recent review article by Tsikouris and Peeters (2007) reviewed several studies of the I/D polymorphism and other polymorphisms in the ACE gene in patients with coronary artery disease. They found 11 studies that examined surrogate endpoints such as endothelial dysfunction, restenosis after revascularization, and left-ventricular remodeling. For these outcomes, findings were characterized as inconsistent and conflicting. They also reviewed 3 studies with clinical endpoints (Bis et al. 2005; Harrap et al. 2005; Bleumink et al. 2005). Of these, 2 studies examined the effect of the I/D polymorphism. One study found no pharmacogenomic interaction of I/D status and ACE inhibitor therapy (Harrap et al. 2005), and the other study actually found that those with the DD genotype had higher mortality (Bleumink et al. 2005). They characterize the findings of the studies they reviewed “when considered as a whole, ...inconclusive and in many cases conflicting.”

Perhaps the most disappointing result in the investigation of the ACE I/D polymorphism and pharmacogenomic interactions is the GenHAT study, a trial of over 37,000 persons randomized to different classes of hypertension medication (Arnett et al. 2005). It was hypothesized that those with the DD genotype randomized to ACE inhibitors would achieve superior outcomes compared to those assigned to other medications. The study appears to have been adequately powered, as fatal and nonfatal CHD outcomes occurred in 3,096 individuals during follow-up. They found that that I/D polymorphism was not a predictor of any outcome, nor was there any interaction with ACE inhibitor treatment. Even for an intermediate outcome such as blood pressure control, they found that those with the DD genotype were in fact less responsive to ACE inhibitors than other medications. The study also casts doubt on the association between genotype and cardiovascular risk in general, and whether variations in serum ACE are associated with cardiovascular disease. The association between genotype and cardiovascular disease was inconsistent across studies, but a meta-analysis was consistent with a small effect (Agerholm-Larsen et al. 2000).

Thus, even with a polymorphism with a strong association with phenotype such as the I/D

polymorphism, and a reasonable biologic rationale as to why certain subjects should have a better response to treatment, studies have not found consistent evidence. Possible reasons include an incomplete understanding of the pathophysiology or insufficient variability in ACE levels accounted for by the ACE I/D polymorphism.

Other Cardiovascular Drug Classes

Other drug classes that pharmacogenomic studies have been performed on are beta blockers and diuretics. There have been fewer pharmacogenomic studies for these drug classes, and it does not appear that findings have been replicated.

McNamara et al. (2001) examined the interaction between beta-blocker treatment and the ACE I/D polymorphism in 328 patients with heart failure. In patients not treated with beta blockers, the DD genotypes had worse transplant-free survival. However, in patients treated with beta blockers, DD genotypes did not have worse survival. Another study by Lanfear et al. (2005) examined several polymorphisms of beta-1 and beta-2 adrenergic receptors in relation to beta-blocker treatment in patients surviving an acute coronary syndrome. Differential survival was found according to whether beta-blocker therapy was given to the patients.

Although these studies identify possible differential effects of treatment based on genotype, the studies were based on observational cohorts rather than randomized clinical trials. Because of confounding of patient characteristics and prescription of beta blockers, it cannot be determined whether beta-blocker therapy is effective in all genotype groups but differs in magnitude, or whether there are some genotypes in which beta-blocker therapy is effective and in others ineffective. It would be critical to determine the absolute benefit of beta-blocker therapy in each genotype in order to determine the possible clinical strategies that would incorporate knowledge of these pharmacogenomic interactions. As stated previously, a high burden of proof is necessary to propose withholding or substituting a drug that has otherwise been shown to be beneficial.

Psaty et al. (2002) investigated the interaction between polymorphisms in the alpha-adducin gene and the risk of myocardial infarction (MI) or stroke associated with different hypertensive

medications. Genetic variants of this gene had been found to be possibly associated with hypertension or a subset of hypertensive patients with salt sensitivity. They found that those with the adducin variant genotype had a reduced risk of MI or stroke (odds ratio: 0.49) with diuretic antihypertensive medication compared to other types of antihypertensive medication. Among those with wild-type genotype, diuretic therapy was not associated with reduced MI or stroke compared to other medications. The results imply that among those with the variant allele, diuretics are particularly efficacious in reducing cardiovascular events. The effect was not dependent on degree of blood pressure control. We could not locate in MEDLINE any studies replicating these findings with clinical endpoints, but there are studies showing that those with the adducin variant gene are more sensitive to both diuretics and salt intake (Cusi et al. 1997; Glorioso et al. 1999). Psaty et al. state that blood pressure changes may not be a good surrogate for the effects of drugs on clinical endpoints, and that they do not know by what mechanism diuretic use may differentially reduce MI or stroke in those with the adducin variant.

the confirmation and characterization of a particular pharmacogenomic interaction, further study would then be required to determine whether the interaction is clinically useful. Certain patterns of pharmacogenomic interaction, even if proven true and strong, may not be clinically useful in the context of practice, given the existing treatment alternatives available. Clinical trials could then determine whether patient outcomes are actually improved based on the use of the genetic information. For the most part, for cardiovascular disease, studies are still at the early stage of discovering and confirming potential pharmacogenomic interactions. Although the cardiovascular drugs being studied in pharmacogenomic studies are relatively safe, it is surprising that there are so few studies examining genetic risk factors for adverse effects.

Discussion

Except for the use of genetic tests which may determine appropriate dosage for warfarin, there are no pharmacogenomic tests for cardiovascular conditions that appear close to clinical utility. The literature is characterized by many exploratory findings that have not been replicated or have been contradicted. Most findings involving reasonably sized samples have been generated from subgroup analyses of previously completed studies, in which numerous genotypes are simultaneously examined. These findings require replication in order to rule out false-positive findings, and to determine more precisely the nature and magnitude of the pharmacogenomic interaction. Studies must examine clinical endpoints, as surrogate intermediate measures may be misleading. Beyond

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