Pharmacogenetics of cardiovascular drugs

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Abstract
Pharmacogenetics is a field aimed at understanding the genetic contribution to inter-patient variability in drug efficacy and toxicity. Treatment of cardiovascular disease is, in most cases, guided by evidence from well-controlled clinical trials. Given the solid scientific basis for the treatment of most cardiovascular diseases, it is common for patients with a given disease to be treated in essentially the same manner. Thus, the clinical trials have been very informative about treating large groups of patients with a given disease, but are slightly less informative about the treatment of individual patients. Pharmacogenetics and pharmacogenomics have the potential of taking the information derived from large clinical trials and further refining it to select the drugs with the greatest likelihood for benefit, and least likelihood for harm, in individual patients, based on their genetic make-up. In this paper, the current literature on cardiovascular pharmacogenetics is emphasised, and how the use of pharmacogenetic/pharmacogenomic information may be particularly useful in the future in the treatment of cardiovascular diseases is also highlighted.

INTRODUCTION
Pharmacogenetics is a field of research aimed at describing the inherited basis for drug response variability. With the increasing magnitude of genetic information that is available, there is a burgeoning interest in pharmacogenetics, which holds the promise of allowing individualised or personalised therapy. Specifically, the goal is to be able to use genetic information to help select drugs with the greatest likelihood for benefit and least likelihood for harm in an individual patient.

Pharmacogenetics is often broken into two broad areas for focus: first, the genetic polymorphisms that alter the drug’s pharmacokinetics (eg drug metabolism, drug transport) and, secondly, those polymorphisms that affect the pharmacological action of the drug, independent of drug concentration. Cardiology is a discipline that practises by an ‘evidence-based’ approach, due to the wealth of clinical trials literature that helps guide therapy. While these clinical trials provide important insight into how to treat a broad population with a given disease, they provide less information on how to treat individual patients.

Pharmacogenetics holds the promise of allowing cardiology’s evidence-based medicine approach to improve further by providing a mechanism for individualising therapy for specific patients. There are several excellent general reviews on pharmacogenetics and pharmacogenomics already published. In this paper, the focus will be on the pharmacogenetics of cardiovascular drugs and the literature will be briefly described. How pharmacogenetics or pharmacogenomics may enter into the mainstream treatment of cardiovascular disease in the future will also be highlighted. The term ‘pharmacogenetics’ will be used in reference to studies focusing on a single gene’s variability and its contribution to differences in drug response. ‘Pharmacogenomics’ will be used to describe approaches that evaluate polymorphisms in numerous genes (or the genome) for their contribution to variable drug response. Examples of those cardiovascular drug classes for which there is evidence of an association between
genetic variability and drug response are given in Table 1.

PHARMACOGENETICS OF PHARMACOLOGICAL DRUG ACTION

Renin–angiotensin system drugs
The renin–angiotensin system (RAS) plays an important role in the pathophysiology of cardiovascular diseases, such as hypertension and heart failure. Angiotensin II promotes vasoconstriction, cardiac hypertrophy and fibrosis, and aldosterone release. Angiotensin-converting enzyme (ACE) inhibitors attenuate the detrimental effects of angiotensin II by blocking its conversion from angiotensin I. Based on clinical trial data demonstrating significant reductions in morbidity and/or mortality, ACE inhibitors are the first-line agents in heart failure, and are commonly used in hypertension and post-myocardial infarction.

Substantial variability exists among patients in their responses to ACE inhibitors. For example, less than 50 per cent of hypertensives achieve adequate blood pressure control with ACE inhibitor monotherapy, with a greater success rate in white than black patients. Recent analyses of data from two ACE inhibitor trials in heart failure also revealed racial disparity in ACE inhibitor efficacy. Specifically, enalapril reduced overall mortality and hospitalisation for worsening heart failure in white but not black patients.

Polymorphisms commonly occur in the genes encoding components of the RAS and may contribute to the response variability observed with ACE inhibitors. The most well described of these polymorphisms are the ACE insertion/deletion (I/D), angiotensinogen (AGT) M235T and angiotensin II type 1 receptor (AT1R) A1166C polymorphisms. The D allele of the ACE I/D polymorphism has been consistently associated with elevated plasma and tissue ACE activity. During treatment with ACE inhibitors, greater reductions in plasma angiotensin II levels and AT1R expression have been observed among DD homozygotes compared with I allele carriers. The ACE I/D genotype has also been correlated with the clinical effects of ACE inhibitors including blood pressure lowering, reductions in left ventricular hypertrophy, and improvements in endothelial function. Most of the data to date on the ACE gene are inconsistent and even conflicting. For example, in a study of 104 previously untreated hypertensives of Greek descent, DD homozygotes experienced significantly greater reductions in systolic and diastolic blood pressures compared with I allele carriers after 6 months’ treatment with the ACE inhibitor, fosinopril. In contrast, 21 Japanese

Table 1: Examples of cardiovascular drugs with evidence of association between genetics and efficacy or toxicity

<table>
<thead>
<tr>
<th>Drug/drug class</th>
<th>Gene(s) associated with efficacy or toxicity ¹</th>
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<tbody>
<tr>
<td>¹-agonists</td>
<td>β₂-receptors</td>
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<tr>
<td>¹-blockers</td>
<td>β₁-receptor</td>
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<td></td>
<td>Angiotensin-converting enzyme (ACE)</td>
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<td>Gs protein α subunit</td>
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<td></td>
<td>CYP2D6</td>
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<tr>
<td>ACE inhibitors</td>
<td>ACE</td>
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<td></td>
<td>Angiotensinogen</td>
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<td></td>
<td>AT₁ receptor</td>
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<tr>
<td>Anti-arrhythmics</td>
<td>Bradykinin receptor B₂</td>
</tr>
<tr>
<td></td>
<td>Various congenital long QT syndrome genes</td>
</tr>
<tr>
<td></td>
<td>N-acetyltransferase (procainamide)</td>
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<tr>
<td></td>
<td>CYP2D6</td>
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<tr>
<td>Anti-thrombotics</td>
<td>Platelet glycoprotein Ila</td>
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<td></td>
<td>Platelet glycoprotein Ila</td>
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<td></td>
<td>Platelet Fc receptor</td>
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<td>Warfarin</td>
<td>CYP2C9</td>
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<tr>
<td>AT₁-receptor blockers</td>
<td>AT₁ receptor</td>
</tr>
<tr>
<td>Diuretics</td>
<td>P-glycoprotein</td>
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<tr>
<td></td>
<td>G protein β₁ subunit</td>
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<td></td>
<td>α-adducin</td>
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<tr>
<td>Hydralazine</td>
<td>N-acetyltransferase</td>
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<td>Lipid-lowering drugs</td>
<td>Apolipoprotein E</td>
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<td></td>
<td>Cholesteryl ester transfer protein</td>
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<td>Stromelysin-1</td>
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<td>β-fibrinogen</td>
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<td>Low density lipoprotein receptor</td>
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<td>Lipoprotein lipase</td>
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<td>ACE</td>
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<td>Gemfibrozil</td>
<td>Apolipoprotein E</td>
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<tr>
<td></td>
<td>Stromelysin-1</td>
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</tbody>
</table>

¹Citations found in text
hypertensives homozygous for the ACE I allele tended to have greater reductions in diastolic blood pressure compared with 36 D allele carriers with 6 weeks of ACE inhibitor therapy (12.4 ± 2.2 mm Hg versus 7.9 ± 1.2 mm Hg: p = 0.07). It is possible that the conflicting results in these studies are due to racial differences in allele distribution or differences in treatment duration between the two studies. Alternatively, the association between the ACE I/D polymorphism and blood pressure response to ACE inhibitor therapy may be weak compared with other genetic and environmental factors that influence ACE inhibitor response.

The gene for AGT contains over 15 polymorphisms, but the substitution of methionine for threonine at codon 235 (M235T) has been the most intensely studied. The 235T allele has been associated with higher plasma AGT levels, enhanced blood pressure reduction with ACE inhibition and the need for combination anti-hypertensive therapy.

AT₁ receptors are located on vascular smooth muscle, cardiac, renal and adrenal gland cells where they mediate the effects of angiotensin II. The A1166C polymorphism has been associated with significantly greater reductions in arterial stiffness with ACE inhibitor therapy in hypertensives. In healthy individuals, a single dose of the AT₁-blocker, losartan, produced the greatest blood pressure reduction in 1166C allele carriers. A study in hypertensives failed to reveal an association between the A1166C polymorphism and the effects of ACE inhibitors on blood pressure.

To date, most of the RAS polymorphism–drug response studies have focused on polymorphisms in single genes (and often single polymorphisms in single genes). Given that multiple proteins are involved in the RAS, a polygenic (or pharmacogenomic) approach to evaluating genetic associations with RAS drugs may be more appropriate. This is supported by data from a study, published only in abstract form, in which 45 polymorphisms in the ACE, AT₁, R and AGT genes were investigated, and which revealed ten polymorphisms to provide the best prediction of anti-hypertensive response to ACE inhibitors. RAS polymorphisms may also contribute to adverse reactions during ACE inhibitor therapy. Approximately ten per cent of ACE inhibitor–treated patients develop a dry cough believed to be due to bradykinin accumulation during therapy. In separate studies, the ACE I/D variant and a single nucleotide polymorphism in the core promoter region of the bradykinin B₂ gene were found to be associated with the ACE inhibitor–related cough.

β₁-blockers, β₂-agonists and diuretics

β₁-blockers and diuretics are widely used drugs in the treatment of numerous cardiovascular diseases. β₁-blockers are used commonly in the treatment of hypertension, heart failure, post-myocardial infarction and angina, among other uses. Diuretics are a cornerstone of therapy for the treatment of heart failure and are considered to be the gold-standard therapy in hypertension. β₂-agonists also see frequent use for inotropic support in critically ill patients, and in diagnostic procedures. As with most therapies, there is significant inter-patient variability in response to these agents that may have some inherited basis.

The gene encoding the β₁-adrenergic receptor (β₁AR) has two polymorphisms (Ser49Gly and Arg389Gly) that result in an amino acid change and occur commonly in the population, whereas the β₂AR gene has three common, amino acid-changing polymorphisms (Cys19Arg, Arg16Gly and Gln27Glu). Responses to β₂-agonists appear to be influenced by polymorphisms in both the β₁AR and β₂AR genes. In vitro mutagenesis studies have shown that basal adenyl cyclase activity is nearly two-fold higher for the Arg389 form than the Gly389 form, and that there are more than three-fold differences in the maximal
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agonist-stimulated adenylyl cyclase activity. Consistent with the in vivo findings, a recent study documented that the Arg389 homozygous genotype is associated with hypertension. Studies from the authors’ laboratory also show that resting heart rate, systolic and diastolic blood pressure and double product (all of which have some control by noradrenaline) are higher in Arg389 homozygotes. These data suggest that the β1-AR codon 389 polymorphism may be an important determinant of the β-blocking and β-blocker responses, and confirmatory studies are ongoing.

The genetic polymorphisms of the β2-AR gene (specifically, Arg16) have been associated with hypertension in numerous studies, suggesting functional effects with respect to agonist (endogenous catecholamines)-mediated actions. Two studies have also shown the Arg16 form to be associated with greater agonist-mediated cardiovascular effects (e.g. heart rate, vasodilation, cardiac output). Conversely, another study showed the Gly16 genotype to be associated with the greatest agonist-mediated effects.

There are numerous possible genetic determinants of the β-blocker response. A recent report of patients with heart failure showed that β1-AR Gly49 carriers derived the greater benefit from β-blocker therapy. Another study of heart failure patients found that those with the ACE DD genotype derived the greatest survival benefits from β-blocker therapy.

Genetic influences of the anti-hypertensive response to β-blockers have also been examined. One study retrospectively tested the association between blood pressure response to β-blockers and β1-AR codon 389 genotype, and found no association. Another study investigated the association between β-blocker response and a genetic polymorphism in the β-receptor cell signalling protein, the stimulatory G protein, which is comprised of α, β and γ subunits. Individuals exhibiting good blood pressure response to β-blockade were more likely to carry the FokI+ than the FokI– allele of the Gs protein α subunit gene (62.5 per cent versus 37.5 per cent).

There is also evidence of an association between a G protein polymorphism and diuretic response. Specifically, one study has reported a significant association between the G protein β subunit C825T polymorphism and anti-hypertensive response to a thiazide diuretic. Average blood pressure declines were 10/6 mm Hg in CC homozygotes, 14/8 mm Hg in CT heterozygotes and 16/11 mm Hg in TT homozygotes. Two different studies have also shown the α-adducin Gly460Tp polymorphism to be associated with anti-hypertensive response to the thiazide diuretic, hydrochlorothiazide. Specifically, Tp460 allele carriers had about a 15 mm Hg decline in mean blood pressure compared with about a 7 mm Hg decline in the Gly460 homozygotes. Thus, it seems clear that multiple genes likely affect diuretic, and most other drug, responses.

**Lipid-lowering drugs**

A number of studies have investigated relationships between genetic polymorphisms and efficacy of lipid-lowering drugs. For example, studies have examined the associations between outcomes with either statin or gemfibrozil therapy and polymorphisms known to be associated with ischaemic heart disease progression and adverse outcomes — namely, the apolipoprotein E, cholesteryl ester transfer protein (CETP), stromelysin-1 and β-fibrinogen gene polymorphisms. These studies have consistently shown that those who carried the polymorphism associated with greater disease progression or increased risk of adverse disease outcomes derived the greatest benefits from lipid-lowering therapy, whereas the lower risk group derived less or no benefit from therapy. Associations between cholesterol lowering with statins and polymorphisms in the low density lipoprotein (LDL) receptor gene, lipoprotein lipase gene and...
ACE gene have also been
documented.\textsuperscript{35-58} Thus, there seems to be
strong evidence that there are important
genetic determinants of both the degree
of cholesterol lowering, and the effect on
outcomes that occur with lipid-lowering
therapy.

**Anti-thrombotics**

Several studies have highlighted the
potential role genetics plays with respect
to the development of adverse thrombotic
events with some drugs, such as oral
contraceptives, or the anti-thrombotic
efficacy of agents used to treat thrombotic
disorders. For example, patients with a
prothrombin gene mutation have an odds
ratio for the risk of developing a cerebral
vein thrombosis of 10.2. The odds ratio
for this same event is 13.4 in users of oral
contraceptives who lack the prothrombin
mutation. The risk for cerebral vein
thrombosis rises more than ten-fold, to
149.3, in oral contraceptive users with the
prothrombin mutation.\textsuperscript{59} Similar findings
have been shown for Factor V mutation,
oral contraceptive use and thrombosis
risk.\textsuperscript{60} Thromboembolism can also occur
as a result of heparin-induced
thrombocytopenia, a serious adverse effect
in up to five per cent of patients who
receive heparin. A recent study suggested
that a polymorphism of the platelet Fc
receptor may be associated with an
increased risk of heparin-induced
thrombocytopenia.\textsuperscript{61}

For the anti-platelet drugs, several
studies have suggested that the anti-
platelet effects of abciximab
(a glycoprotein IIb/IIIa inhibitor) or
aspirin are associated with a
polymorphism of the platelet glycoprotein
IIIa.\textsuperscript{62-65} Another study suggested that the
anti-platelet effects of oestrogen are also
associated with the PLA polymorphism in
glycoprotein IIIa.\textsuperscript{66} One would anticipate
that there are also important genetic
determinants of the drug targets of
warfarin and heparin anti-coagulant
efficacy, although no literature is available
to date in this area.

**Anti-arrhythmics**

Drug-induced QT prolongation and
Torsades de Pointes is a serious,
potentially life-threatening adverse effect
of anti-arrhythmics and numerous other
drugs. In fact, this has been the most
common reason for drugs to be
withdrawn from the market in the past
decade. As such, there is great interest in
identifying potential genetic markers for
the risk of drug-induced QT
prolongation and Torsades de Pointes. It
is well recognised that certain gene
mutations in cardiac potassium and
sodium channels are associated with
congenital long QT syndromes. Initial
data also suggest that the patients at
increased risk for developing drug-
induced Torsades de Pointes are those
with undiagnosed (or clinically silent)
mutations in these congenital long QT
syndrome genes.\textsuperscript{67-70} Given the serious
nature of drug-induced Torsades de
Pointes, and the likelihood that there is a
genetic predisposition for risk, this is a
good example of the benefits that may
result from the ability to use
pharmacogenetics to predict those
patients at serious risk. As such, intensive
investigation is now underway to gain an
increased understanding of the genetic
determinants of the highly unpredictable,
drug-induced Torsades de Pointes.\textsuperscript{71}

**Summary of the
pharmacogenetics of drug
action**

In contrast to the literature on drug
metabolism pharmacogenetics (\textit{vide infra},
literature of the pharmacogenetics of drug
action, also known as drug target
pharmacogenetics, is in its relative
infancy. For many of the drug target
genetic polymorphisms studied and
highlighted above, the literature is limited
to one or two studies. Thus, the strength
of the associations with response or
toxicity are, at present, difficult to judge
in many cases. The statistically strongest
evidence seems to reside in those
polymorphisms for those proteins that are
not the direct target of the drug (e.g.
Pharmacogenomic (polygenic) approaches are likely to provide better information than single gene studies.

CYP2A6, CYP2C9, CYP2C19 and CYP2D6 have polymorphisms with functional consequences.

receptor and enzyme), but which could be described as disease pathogenesis proteins. Disease pathogenesis proteins are those whose polymorphisms have been associated with a risk for a certain disease. The examples described above for lipid-lowering therapy, oral contraceptives and Torsades de Pointes all fall into this category. In general, these studies are highly consistent, showing that the polymorphism associated with disease risk is also strongly associated with drug response (either efficacy or toxicity).

Studies that have focused on direct drug targets or related proteins (eg signal transduction proteins) have provided intriguing data, but, in general, are less consistent in their associations between drug response and genetic variability. The most likely explanation for this is that multiple proteins are involved in the drug response (ie the direct protein target plus all signal transduction proteins and other upstream or downstream proteins). Thus, it seems likely that studies that account for polymorphisms in multiple genes will be more strongly associated with drug response. The only example of this approach in the cardiovascular literature was described briefly in the RAS section, and, to date, has only been published in abstract form. In this study, 45 polymorphisms in three genes were studied. A combination of the ten polymorphisms most strongly associated with response was identified and called a genetic signature (GS1 and GS2). When tested in a separate population, it was found that those who lacked both GS1 and GS2 had an average 8 mm Hg decrease in diastolic blood pressure. Those with GS1 or GS2 had 12.3 and 14.5 mm Hg declines in blood pressure, respectively, and those with both GS1 and GS2 had a 19.8 mm Hg decline in diastolic blood pressure. Thus, this combination of polymorphisms appeared to provide an increased level of prediction of response as compared with the single gene studies. Only 30 per cent of patients carry the genetic signatures identified, and it is well known that 50–70 per cent of patients have a good anti-hypertensive response to ACE inhibitors. A similar approach was taken with the anti-psychotic, clozapine, where 19 polymorphisms in ten different genes were considered. This polygenic (or pharmacogenomic) approach is likely to be used with increasing frequency as it becomes easier to genotype quickly, easily and inexpensively.

**DRUG METABOLISM PHARMACOGENETICS**

Polymorphisms in drug metabolising enzymes were among the first recognised genetic variants that contribute to drug response variability. Both the phase I (oxidative) and phase II (conjugative) drug metabolising enzymes exhibit genetic polymorphism that may affect drug plasma concentrations and predispose patients to drug toxicity or therapeutic failure despite treatment with normal, recommended drug doses.

Cytochrome P450 (CYP) enzymes comprise the phase I drug metabolising enzymes for which genetic variation has been extensively examined. The CYP2A6, CYP2C19, CYP2D6 and CYP2C9 enzymes display functional polymorphisms, with marked differences in allele frequencies among racial groups. These genetic variants have been shown to alter the capacity of drug metabolising enzymes, resulting in distinct drug metabolism phenotypes, often termed poor, extensive and ultra-rapid metabolisers. More recently, polymorphisms were identified in the CYP3A4 gene; however, these polymorphisms do not produce distinct phenotypes. Whether the CYP3A4 polymorphism significantly affects drug concentrations and response is currently unclear. The drug metabolism polymorphisms with cardiovascular relevance are summarised below.

**CYP2A6**

Several polymorphisms occur in the gene encoding the CYP2A6 enzyme. CYP2A6 metabolises nicotine, and
impaired nicotine metabolism has been observed in carriers of one or two variant CYP2A6 alleles. Cigarette smoking contributes significantly to the development of coronary heart disease, with a strong correlation between the number of cigarettes smoked and cardiovascular risk. Nicotine is the primary cigarette component responsible for tobacco dependency, and polymorphic metabolism of nicotine appears to be important in determining cigarette smoking behaviour. Specifically, a study has shown that cigarette smokers who carry a variant CYP2A6 allele smoke fewer cigarettes per week and are more likely to quit smoking successfully than smokers with normal nicotine metabolism. This suggests that individuals with impaired CYP2A6 metabolism may be relatively protected from nicotine addiction. Thus, inhibition of the CYP2A6 enzyme may have utility as an aid to smoking cessation and cardiovascular disease risk management.

CYP2C9

Two allelic variants have been identified for the CYP2C9 gene, with both resulting in single amino acid substitutions at positions essential for enzyme activity. As a result, these contribute to the poor metaboliser phenotype. The CYP2C9 enzyme catalyses the metabolism of S-warfarin, which possesses five times the anti-coagulant activity of the R-isomer. Several studies have recently documented that the CYP2C9 genotype is strongly associated with warfarin dose and bleeding risk early in therapy. For example, a study of European patients attending an anti-coagulation clinic compared CYP2D6 genotypes between those requiring low dose (≤1.5 mg/d) warfarin and a control group requiring higher dose warfarin to maintain an international normalised ratio (INR) of 2–3. The variant CYP2C9 alleles were significantly over-represented in the low dose group, with 81 per cent of patients on low dose warfarin possessing at least one of the variant alleles versus only 38 per cent of those requiring standard doses. The low dose group had more difficulty with warfarin initiation, experienced increased bleeding complications and required more frequent clinic visits to maintain the INR within target range. These findings suggest that CYP2C9 genotyping prior to warfarin initiation may be useful in predicting warfarin dose requirements and in reducing the risks associated with over-anti-coagulation in carriers of the variant alleles.

CYP2D6

The CYP2D6 enzyme catalyses the metabolism of β-blockers such as metoprolol, carvedilol, timolol and propranolol and anti-arrhythmics such as propafenone, mexiletine and flecainide. At least eight different alleles characterised for the CYP2D6 gene influence enzyme activity. Phenotypes for metabolism by CYP2D6 include extensive, poor and ultra-rapid metabolism, and are determined based on the genetic variants of the CYP2D6 gene a patient carries.

For drugs that have CYP2D6 as the major metabolising enzyme (eg metoprolol, propafenone), drug concentrations in poor metabolisers can be four- to five-fold higher than in extensive metabolisers. Consequently, patients are at risk of concentration-related adverse effects, and excessive prolongation in the pharmacological half-life. Thus, knowledge of a patient’s CYP2D6 genotype a priori would help to individualise selection of an initial drug dose, particularly in those people at risk of concentration-related adverse effects (eg β1-blockers in asthmatics). It should also be recognised that very low doses of quinidine (ie 50–100 mg) cause near complete inhibition of the CYP2D6 enzyme, and convert extensive metabolisers into phenotypic poor metabolisers.

CYP3A4

The CYP3A4 enzyme is responsible for the metabolism of a number of...
cardiovascular drugs including calcium channel blockers such as verapamil and nifedipine, anti-arrhythmics such as quinidine and disopyramide and cholesterol-lowering agents such as lovastatin, simvastatin and atorvastatin. A polymorphism was recently identified in the promoter region of the CYP3A4 gene.\(^{90,91}\) It is unclear if this polymorphism has functional significance, but it may contribute to the wide inter-patient variability in drug metabolism by CYP3A4. As such, future studies may reveal CYP3A4 polymorphisms to be important determinants of adverse effects that result from elevated concentrations of CYP3A4 substrates.

**N-acetyltransferase**

The N-acetyltransferase enzymes are examples of phase II enzymes that exhibit genetic polymorphism.\(^{92}\) The N-acetyltransferase 2 (NAT2) enzyme metabolises the anti-hypertensive drug hydralazine and the anti-arrhythmic drug procainamide. Six of the NAT2 polymorphisms result in amino acid substitution and contribute to the slow acetylator phenotype, while the remaining alleles contribute to the rapid and intermediate acetylator phenotypes. The prevalence of the slow acetylator phenotype varies by race, with reported frequencies of 50 per cent in African and Caucasian Americans and less than ten per cent in Asians.\(^{93}\)

Procainamide is predominately metabolised by the NAT2 enzyme to N-acetylplicarnamide (NAPA), which possesses Vaughn Williams Class III anti-arrhythmic effects. In fast acetylators, increased conversion of procainamide to NAPA may lead to supra-therapeutic NAPA levels, prolongation of the QT interval on electrocardiogram and an increased risk for developing life-threatening ventricular arrhythmias. The slow acetylator phenotype is a risk factor for the development of anti-nuclear antibodies and systemic lupus erythematosus-like syndrome during hydralazine or procainamide therapy.\(^{94,95}\)

In summary, genetic variation in drug metabolising enzymes may cause exaggerated therapeutic responses, drug toxicity or a lack of therapeutic effect when agents that serve as substrates for these enzymes are given in normal, recommended doses.

**DRUG TRANSPORTER PHARMACOGENETICS: P-GLYCOPROTEIN**

P-glycoprotein (P-gp) is an adenosine triphosphate-dependent transmembrane efflux pump originally recognised for its ability to transport anti-cancer agents out of cells and promote multidrug resistance to chemotherapy. Later, it was discovered that P-gp is also expressed in the intestine, liver, renal proximal tubule and the blood–brain barrier where it serves a protective role by transporting toxic substances or metabolites out of cells. A number of non–anti-cancer drugs, including digoxin and various calcium channel blockers, are P-gp substrates. Higher intestinal expression of P-gp reduces oral bioavailability and may prevent attainment of therapeutic plasma concentrations. Conversely, low intestinal P-gp expression, or P-gp inhibition, may enhance drug bioavailability, with the potential for supra-therapeutic or toxic plasma concentrations of P-gp substrates.

The multidrug resistance gene (MDR-1), which encodes P-gp, has at least 15 polymorphisms.\(^{96}\) At least one of these, located in exon 26 (C3435T), appears to be functional. Specifically, the TT genotype is associated with markedly lower gene expression and protein levels.\(^{97}\) As such, the C3435T polymorphism may serve as a useful marker for predicting plasma concentrations or risk of toxicity with P-gp substrates. For example, plasma digoxin levels were four-fold higher in those subjects with the TT genotype than in those with CC homozygotes, following a single oral dose.\(^{98}\) Thus, screening for the C3435T polymorphism may identify individuals at greater risk for digoxin toxicity and in whom it may be
wise to initiate digoxin in lower than normal doses. The TT genotype is rare among those of African descent (genotype frequency of zero to six per cent), but occurs frequently in Caucasian (24–36 per cent) and Asian (20–47 per cent) populations.  

CLINICAL POTENTIAL FOR PHARMACOGENETICS IN THE TREATMENT OF CARDIOVASCULAR DISEASE

In this paper, the current literature on the pharmacogenetics of cardiovascular drugs has been summarised. The studies conducted to date provide clear evidence that genetic variation contributes to the inter-patient variability in drug responses. Work in the next five to ten years will be aimed at furthering our knowledge of cardiovascular pharmacogenetics, and moving the field into the clinical arena, where the patient might obtain the benefit of optimised, personalised therapy through pharmacogenomic screening. In Figure 1, a schematic for the potential clinical use of pharmacogenetics is provided. Currently, the most common approaches to the treatment of cardiovascular disease are either trial and error (eg treatment of hypertension or hyperlipidaemias) or the giving of the same therapy to everyone with the disease (eg ACE inhibitors and β-blockers in heart failure). While there are large clinical trials that justify these approaches to the management of cardiovascular disease, it is clear that a certain percentage of patients will: obtain no beneficial response and be changed to another drug; continue long term on a drug that is providing no benefit; and/or experience a toxic effect, which may cause significant morbidity or mortality. Under the pharmacogenomics paradigm, highlighted in Figure 1, patients would be given a genetic test prior to the initiation of therapy in order to determine the likelihood for efficacy and risk of toxicity. This genetic test would likely test a large number of genes and polymorphisms, including the drug target, drug.

**Figure 1:** Clinical potential of pharmacogenomics. A representative population with a given disease, such as heart failure, is highlighted. Current treatment of heart failure results in prescription of essentially the same medications to all heart failure patients, recognising that not all patients will derive benefits from all the heart failure medications. Once the genetic polymorphisms associated with good response, toxicity risk and elevated or low plasma concentrations are identified, then pharmacogenomic testing will allow the prescription of more individualised therapy. For example, pharmacogenomic testing in the future should be able to identify likely responders and non-responders, where those identified as non-responders would be prescribed an alternative therapy. Pharmacogenomic testing should also be able to identify those who might need higher or lower than usual doses, and those who are at risk for serious toxicity (if the drug has a serious toxicity). Thus, the patients who are ultimately given the drug will get the right dose, and be at low risk of toxicity with a high likelihood for a beneficial response.
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metabolism and drug transporter genes. Through such testing, several groups of patients might be identified, including those likely to respond at a normal dose, and those who are likely to respond, but who would require a non-standard dose (i.e. lower or higher), due to genetic variability in drug metabolism or drug transport. Such testing would also identify two groups of patients who should be given alternative therapy — namely, those likely to be non-responders and those at increased toxicity risk. While current knowledge does not yet allow us to take into account all the various causes for variability in response or drug concentration, the probability of being able to predict a high degree of the genetic contribution to variability within the next decade seems high. Thus, it seems likely that pharmacogenomics will become an important tool in the practice of medicine in the near future. If it meets its potential, pharmacogenomics will lead to safer and more effective use of medications to treat cardiovascular disease.

Acknowledgments
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References


37. Bray, M. S., Krushkal, J., Li, L. et al. (2000), 'Positional genomic analysis identifies the


81. Freeman, B. D., Zehnbauer, B. A., McGrath,


