



Prasugrel, Maori, and personalised medicine in New Zealand

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The response to thienopyridine antiplatelet therapy is heterogeneous and is in part explained by clinical and genetic factors. A recent meta-analysis has demonstrated the clinical significance of a genetic polymorphism in the cytochrome P450 2C19 gene. Carriers of this polymorphism have a higher incidence of stent thrombosis and cardiovascular death, whilst on the thienopyridine clopidogrel. The polymorphism and rarer variants display higher carrier frequencies in ethnic groups with disproportionate cardiovascular mortality, such as Māori. Knowledge of an individual's genetic status may assist in optimising antiplatelet therapy, thereby reducing the cost of adverse events, expenditure on new medicines, and the ethnic disparities seen in healthcare outcomes. A demonstration of the cost-effectiveness of genetic testing, on a population basis, and a proven alternative, personalised strategy is required before the adoption of this technology can be advocated.

Pharmacogenetics has long held the promise of individualising pharmacological therapy using genetic biomarkers. Within the last year pharmacogenetic tests predicting adverse reactions to the antiepileptic drug carbamazepine and HIV medication abacavir have entered routine clinical practice.^{1,2} With ever growing healthcare costs, new pharmaceuticals providing only a modest incremental benefit over current therapies, and the world-wide economic downturn there has never been a greater need to match treatment to those who have the most to gain from it.³

Cardiovascular medicine is well positioned to benefit from rapid advances in this field. Potential genomic biomarkers for drugs in clinical use include a genetic test for warfarin to predict the treatment maintenance dose,⁴ for simvastatin to predict the likelihood of myopathy/myositis,⁵ for bucindolol to predict potential efficacy in heart failure⁶ and for clopidogrel to predict increased recurrent thrombotic events, including stent thrombosis.⁷⁻⁹

Elucidation of the genetic markers predicting response to clopidogrel, the second most-prescribed drug in the world, is of particular importance as a reduced antiplatelet effect with clopidogrel is associated with adverse clinical outcomes including cardiovascular death, myocardial infarction, stroke and additional healthcare costs.

Clopidogrel is attractive for pharmacogenetic study as it is a pro-drug that requires conversion to an active derivative, catalyzed by cytochrome P450 (CYPs). The functional polymorphisms within the CYP genes have been relatively well characterised, with those of interest including 3A4 and 3A5, 2C19, 2C9, 2B6 and 1A2 enzymes.¹⁰⁻¹²

Several studies have shown that the loss of function allele *CYP2C19**2 is associated with adverse vascular outcomes in those taking clopidogrel. While other rarer variants such as the *CYP2C19* *3 and *4 alleles are also associated with reduced function of

the enzyme, the *CYP2C19*17* variant is associated with ultrarapid enzyme activity.¹³ In contrast the third generation thienopyridine prasugrel is not as dependent on the *CYP2C19* and *CYP2C9* enzymes for biotransformation into its active metabolite.¹¹

Genotypes that code for a phenotypic poor response to clopidogrel are more frequently found in some ethnic groups than others. The *CYP2C19*2* loss of function variant occurs in 13% of Caucasians, 18% of African Americans and 29% of East Asians. It also occurs in higher frequency in Māori (24%) than NZ Europeans (15%).¹⁴

*CYP2C19*3* is four to five times more frequent in Polynesians and Māori (1.8%) than Europeans (0.4%).^{14,15} This variant codes for a truncated protein and, together with the *2 allele, accounts for 99% of poor metabolisers in Asian populations.¹⁶

These ethnic disparities have two potential important clinical consequences. Firstly, these differences should be considered when interpreting trial data. For example, the largest trial evaluating clopidogrel and its effect on mortality was undertaken in 46,000 Chinese patients presenting with ST elevation myocardial infarction (COMMIT-CCS trial).¹⁷ While the response to clopidogrel found in this study might reasonably be extrapolated to a Māori and Pacific Island population, the magnitude of benefit observed may have been greater in other ethnic groups with a lower prevalence of *CYP2C19*2*.

Secondly, using pharmacogenetics to individually tailor treatment may improve outcomes to a greater extent in some ethnic groups than others. Taking this hypothesis one step further, it is possible that therapy guided by genomics may help reduce the disparity in treatment outcome in populations such as Māori where cardiovascular disease is highly prevalent and clinical outcomes on treatment are poor.

Pre-determining poor-responders to clopidogrel may aid in optimising antiplatelet therapy in these patients by either giving a higher dose of clopidogrel or using alternative therapy such as prasugrel. While prospective clinical trials are necessary to assess this theoretically-attractive approach, pharmacogenetic data from TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction), a comparison of prasugrel with clopidogrel in patients undergoing percutaneous coronary intervention, give some insights.

Patients with the reduced-response allele *CYP2C19*2* on clopidogrel treatment had a higher incidence of vascular events, stent thrombosis and death, whereas those with the same variant on prasugrel had no increased events and, interestingly, no increase in bleeding.^{18,19} Further large population outcome studies have confirmed the association between the *2 allele and adverse outcomes in those taking clopidogrel.^{7,9,20,21}

Although this individualised genetic approach to therapeutics may improve the patient's response to treatment, it does not address the lifestyle changes that need to be implemented to prevent disease, issues such as reduced access to healthcare resources, and socio-economic, educational or cultural influences on treatment choices. Further understanding of the molecular basis of disease may well bring us effective tailored preventative therapies targeted at currently unmodifiable risk

factors. We can hope that these are affordable to the healthcare system, and accessible to disadvantaged ethnic groups.

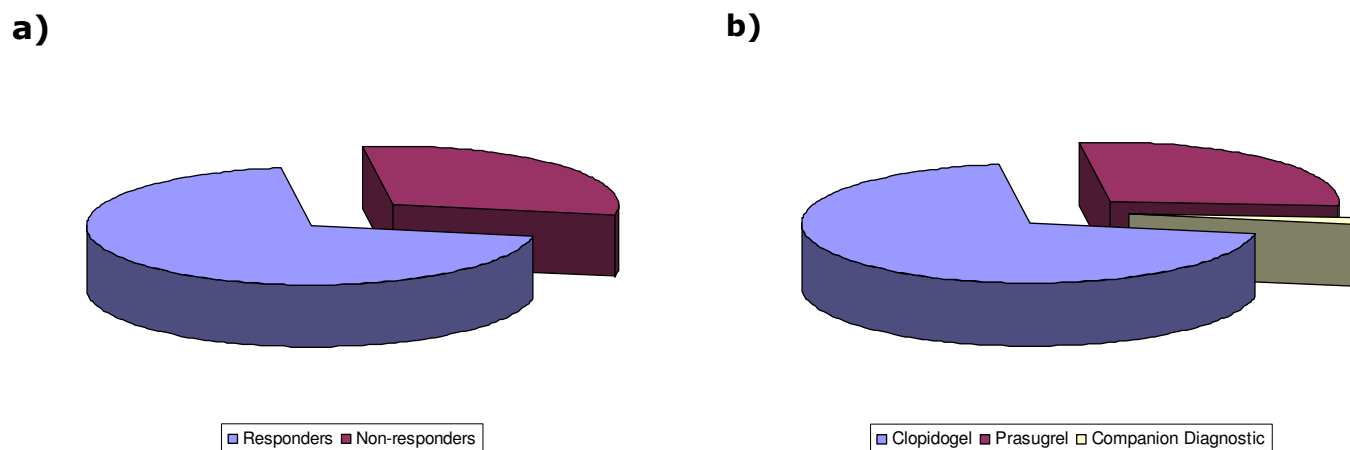
Genotyping prior to drug administration may be of particular importance for drugs like clopidogrel, which is often started in the acute setting with the need for a clinical benefit from a rapid and effective antiplatelet effect. It may also help predict the clinical importance of drug interactions, such as with omeprazole^{22,23} and other CYP2C19 inhibitors. Although phenotyping, using platelet function testing, provides a more integrated assessment of drug response, testing can only be performed after a drug is administered. There is some evidence that combining genotyping and phenotyping may be more effective in predicting clinical outcomes than either alone.²⁴

The US Food and Drug Administration (FDA) has recently updated the package insert for clopidogrel, to include information on pharmacogenetic testing. Testing is not officially advocated and the cost utility of testing, in terms of preventing adverse events, has not yet been proven. Recent analysis has shown that a simple three SNP test for warfarin is not cost effective under current average test prices.²⁵ However the costs of genotyping are reducing exponentially and the era of the \$1000 genome is not far away.

A shift from treating everyone with a particular condition to individualizing treatment based on genomic or proteomic biomarkers promises to improve safety, efficacy and allocate expensive treatments to those who have the most to gain. The concept of rationing treatment in the current economic climate appears appealing but reduced expenditure will only be achieved if the incremental cost of the diagnostic test can be recouped (Figure 1).²⁶

With appropriate safeguards in place, a once in a lifetime genetic test could soon be part of every patient's medical record. Busy physicians may need to integrate this "companion diagnostic" information into their day-to-day clinical decision-making, when they use the information from clinical trials, patient comorbidities and potential drug interactions to apply evidence-based practice in the individual patient.

Figure 1. Microeconomics of Personalised Medicine



a) Displays current expenditure on a pharmaceutical agent, with substantial portion of spending wasted on treating non-responders. **b)** Future expenditure based on personalised approach where therapeutic diagnostic ('theranostic') constitutes a fraction of total expenditure. The objective of the targeted approach is to maximise benefit of next generation pharmaceutical and minimise potential harm. A cost-effectiveness analysis is required prior to adoption of the new model, taking into account savings from prevented events.²⁶ (Adapted from Personalized Medicine: The Emerging Pharmacogenomics Revolution. A 2005 monograph by Price Waterhouse Coopers.)

Competing interests: PG has founded a company offering genetic tests to consumers/doctors.

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