

Contents of Research Compiled on Genetic Testing for Plavix Dosing

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From Your Librarian

Summary of contents

Since I did not have an opportunity to talk with you directly, I made some assumptions as to the basis of your research project “Genetic Testing for Plavix Dosing.” Based on cursory research, I identified the Cytochrome P450 CYP family polymorphisms as a plausible subject of the genetic component of your research; if you are interested in other genes, we can reproduce this search to accommodate that. After reviewing hundreds of results from several PubMed searches, I identified approximately 30 articles that seemed to best serve as a foundation to support your research project. These include 4 highly cited articles and 2 review articles all of which are identified in the Table of Contents. In addition, I included the abstracts to approximately 20 articles that discuss differential effects of clopidogrel, genetic polymorphisms associated with these effects, and various dosage strategies. It is important that you provide feedback indicating how well these articles match your needs. It is easy to perform subsequent searches based on your suggested revisions.

Limitations of this report

The articles, controlled studies, double-blind placebo-controlled studies, reviews, and editorials suggested here are the results of searches performed in PubMed. As an applicant for this position, I do not have access to Web of Science, PsycINFO, CINAHL and other important databases needed to conduct a truly comprehensive search. If you are seeking a particular abstract, poster, presentation, or proposal, not listed here, know there are many other sources of information that can be explored.

Additional Strategies

We can establish a search alert in PubMed that will automatically search for your topic and send you an email once a week with any new citations. Additionally, I used the following MeSH terms when searching for your articles: 1) clopidogrel; 2) Cytochrome P-450 Enzyme System; 3) Platelet Aggregation Inhibitors/administration and dosage; and, 4) Polymorphism, Single Nucleotide. If you would like help performing these controlled searches on your own, let’s set up an appointment to go over what MeSH is, why it’s important, and how to use it to achieve maximum results.

Good luck, and enjoy!
Kelly Myer Polacek, MS, MLS

Highly Cited Papers

Absorption, metabolism, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel - Results of the ISAR-CHOICE (Intracoronary stenting and antithrombotic regimen: Choose between 3 high oral doses for immediate clopidogrel effect) trial.

Cited 250+ times

By: von Beckerath, N., Taubert, D., Pogatsa-Murray, G., Schomig, E., Kastrati, A., & Schomig, A. (2005).
Circulation, 112(19), 2946-2950.

For patients undergoing percutaneous coronary intervention, the administration of a clopidogrel loading dose ranging from 300 to 600 mg is currently recommended. It is unknown, though, whether loading doses higher than 600 mg exert additional suppression of platelet function. Sixty patients with suspected or documented coronary artery disease admitted to our hospital for coronary angiography were included in this trial. They were allocated to 1 of 3 clopidogrel loading doses (300, 600, or 900 mg) in a double-blinded, randomized manner. Plasma concentrations of the active thiol metabolite, unchanged clopidogrel, and the inactive carboxyl metabolite of clopidogrel were determined before and serially after drug administration. Optical aggregometry was performed before and 4 hours after administration of clopidogrel. Loading with 600 mg resulted in higher plasma concentrations of the active metabolite, clopidogrel, and the carboxyl metabolite compared with loading with 300 mg ($P \leq 0.03$) and lower values for adenosine diphosphate-induced (5 and 20 $\mu\text{mol/L}$) platelet aggregation 4 hours after drug administration ($P = 0.01$ and 0.004). With administration of 900 mg, no further increase in plasma concentrations of active metabolite and clopidogrel ($P \geq 0.38$) and no further suppression of adenosine diphosphate-induced (5 and 20 $\mu\text{mol/L}$) platelet aggregation 4 hours after drug administration was achieved when compared with administration of 600 mg ($P = 0.59$ and 0.39). Single doses of clopidogrel higher than 600 mg are not associated with an additional significant suppression of platelet function because of limited clopidogrel absorption.

Adenosine diphosphate-induced platelet aggregation is associated with P2Y₁₂ gene sequence variations in healthy subjects.

Cited 200+ times

By: Fontana, P., Dupont, A., Gandrille, S., Bachelot-Loza, C., Reny, J., Aiach, M., et al. (2003). *Circulation*, 108(8), 989-995.

The adenosine diphosphate (ADP) receptor P2Y₁₂ plays a pivotal role in platelet aggregation, as demonstrated by the benefit conferred by its blockade in patients with cardiovascular disease. Some studies have shown interindividual differences in ADP-induced platelet aggregation responses ex vivo, but the mechanisms underlying this variability are unknown. We examined ADP-induced platelet aggregation responses in 98 healthy volunteers, and we identified 2 phenotypic groups of subjects with high and low responsiveness to 2 μmol/L ADP. This prompted us to screen the recently identified Gi-coupled ADP receptor gene P2Y₁₂ for sequence variations. Among the 5 frequent polymorphisms thus identified, 4 were in total linkage disequilibrium, determining haplotypes H1 and H2, with respective allelic frequencies of 0.86 and 0.14. The number of H2 alleles was associated with the maximal aggregation response to ADP in the overall study population (P=0.007). Downregulation of the platelet cAMP concentration by ADP was more marked in 10 selected H2 carriers than in 10 noncarriers. In healthy subjects, ADP-induced platelet aggregation is associated with a haplotype of the P2Y₁₂ receptor gene. Given the crucial role of the P2Y₁₂ receptor in platelet functions, carriers of the H2 haplotype may have an increased risk of atherothrombosis and/or a lesser clinical response to drugs inhibiting platelet function.

Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects

Cited 110+ times

By: Hulot, J., Bura, A., Villard, E., Azizi, M., Remones, V., Goyenville, C., et al. (2006).. *Blood*, 108(7), 2244-2247.

*Clopidogrel, a prodrug, must be activated by hepatic cytochrome P450 (CYP) isoenzymes before being able to irreversibly block the platelet adenosine 5'-diphosphate (ADP) receptor P2Y12. Clopidogrel responsiveness is highly variable among healthy subjects and patients, and a genetic variant (CYP2C19*2), which encodes a deficient version of the drug-metabolizing enzyme CYP2C19, has been associated with a markedly subnormal response to clopidogrel in 28 healthy subjects, based on the phosphorylation state of the vasodilator phosphoprotein and platelet aggregation profile. However, an intronic polymorphism (IVS10 + 12G > A) in the gene coding for another CYP isoform (CYP3A4) has also been recently linked to clopidogrel responsiveness based on the expression of activated glycoprotein (GP) IIb-IIIa but not based on the platelet aggregation profile. Both studies were small-scale and none has been replicated so far. This study was conducted to evaluate and quantify the genetic contribution of the CYP2C19*2 and CYP3A4 (IVS10 + 12A) alleles to the variability of clopidogrel responses in an unselected population of 94 healthy volunteers. It points out the CYP2C19 (*1/*2) polymorphism as a candidate in the explanation of clopidogrel poor responsiveness as we replicate our previous findings in a larger, independent study population. The CYP2C19 (*1/*2) explained 10% of the observed variability in clopidogrel responsiveness. The impact of this genetic variant in a patient population now remains to be established.*

Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects.

Cited 130+ times

Savcic, M., Hauert, J., Bachmann, F., Wyld, P. J., Geudelin, B., & Cariou, R. (1999). *Semin Thromb Hemost*, 25 Suppl 2, 15-19.

Clopidogrel, a potent novel platelet ADP-receptor antagonist, induces a significant inhibition of ADP-induced platelet aggregation. Maximum inhibition of 40 to 50% is observed 2 to 5 hours after a single 400 mg dose. The same level of inhibition is achieved with 75 mg once daily at steady state, i.e., after 3 to 7 days of repeated dosing. Based on these data, two studies were undertaken to investigate whether a treatment regimen comprising a large initial dose (loading dose) of clopidogrel, followed by daily doses of 75 mg, might provide a sustained steady-state level of inhibition of platelet aggregation induced by 5 microM of ADP within hours after first dosing. In one study, 10 healthy male subjects received a 375 mg loading dose of clopidogrel on day 1, then daily doses of 75 mg from day 2 to day 10. Mean inhibition of platelet aggregation, already significant at 30 minutes, reached 55+/-8.2% (+/-SEM) at 60 minutes, and a maximum of 80+/-3.6% at 5 hours. No further significant change was observed between 5 hours and 24 hours, and from day 2 through day 10 with subsequent daily doses of 75 mg. In the second study, conducted according to a randomized, single-blind design, four parallel treatment groups of nine healthy male subjects received a loading dose of 75 mg, 150 mg, 225 mg, or 300 mg of clopidogrel on day 1, respectively, and 75 mg once daily from day 2 to day 5. Mean (+/-SD) inhibition of platelet aggregation over the 2 to 24 hours post-loading dose period was 22+/-14.5%, 21+/-13.4%, 35+/-20.6% and 31+/-13.3%, respectively. On day 5, it was 48+/-14.7%, 33 +/-14.1%, 51+/-15.7% and 40+/-10.9% for the 75, 150, 225 and 300 mg loading dose groups, respectively. The smallest day 1 to day 5 difference was observed for the 300 mg group and the largest for the 75 mg group, indicating that the development of the full inhibitory effect of clopidogrel was faster with the loading doses higher than with 75 mg, and fastest with the 300 mg loading dose. These data and those of previous studies indicate that a dose of 300 to 400 mg produces a rapid onset of the pharmacodynamic action of clopidogrel, with levels of inhibition close to steady-state reached within 2 hours.

Review Articles

Recent developments in clopidogrel pharmacology and their relation to clinical outcomes.

Gurbel, P. A., Antonino, M. J., & Tantry, U. S. (2009). *Expert Opin Drug Metab Toxicol*, 5(8), 989-1004.

Oral antiplatelet therapy with clopidogrel and aspirin is an important and widely prescribed strategy to prevent ischemic events in patients with cardiovascular diseases. However, the occurrence of thrombotic events including stent thrombosis is still high (> 10%). Current practice guidelines are mainly based on large-scale trials focusing on clinical endpoints and 'one size fits all' strategies of treating all patients with the same clopidogrel doses. Pharmacodynamic studies have demonstrated that the latter strategy is associated with wide response variability where a substantial percentage of patients show nonresponsiveness. Translational research studies have established the relation between clopidogrel nonresponsiveness or high on-treatment platelet reactivity to adverse clinical events, thereby establishing clopidogrel nonresponsiveness as an important emerging clinical entity. Clopidogrel response variability is primarily a pharmacokinetic phenomenon associated with insufficient active metabolite generation that is secondary to i) limited intestinal absorption affected by an ABCB1 gene polymorphism; ii) functional variability in P450 isoenzyme activity; and iii) a genetic polymorphism of CYP450 isoenzymes. Personalized antiplatelet treatment with higher clopidogrel doses in selected patients or with newer more potent P2Y(12) receptor blockers based on individual platelet function measurement can overcome some of the limitations of current clopidogrel treatment.

Resistance to clopidogrel: A review of the evidence.

Nguyen, T. A., Diodati, J. G., & Pharand, C. (2005). *J Am Coll Cardiol*, 45(8), 1157-1164.

Current available data show that about 4% to 30% of patients treated with conventional doses of clopidogrel do not display adequate antiplatelet response. Clopidogrel resistance is a widely used term that remains to be clearly defined. So far, it has been used to reflect failure of clopidogrel to achieve its antiaggregatory effect. The interpatient variability in clopidogrel response is multifactorial. It can be due to extrinsic or intrinsic mechanisms. Among extrinsic mechanisms are the possibility of clopidogrel underdosing in patients undergoing stenting or with acute coronary syndrome, and drug-drug interactions involving CYP3A4. Intrinsic mechanisms include genetic polymorphisms of the P2Y(12) receptor and of the CYP3As, accrued release of adenosine diphosphate, or up-regulation of other platelet activation pathways. Presently, there is no definite demonstration of an association between low responsiveness to clopidogrel and thrombotic events. The optimal level of clopidogrel-induced platelet inhibition, which will correlate quantitatively with clopidogrel's ability to prevent atherothrombotic events is still lacking. Furthermore, because there is no single and validated platelet function assay to measure clopidogrel's antiplatelet effect, it is not justified to routinely look for clopidogrel resistance in the clinical setting. This review discusses currently available evidence surrounding the variability in the antiplatelet response to clopidogrel.

20 Important Research Papers

Angiolillo, D. J., Fernandez-Ortiz, A., Bernardo, E., Ramirez, C., Cavallari, U., Trabetti, E., et al. (2006). Contribution of gene sequence variations of the hepatic cytochrome P450 3A4 enzyme to variability in individual responsiveness to clopidogrel. *Arterioscler Thromb Vasc Biol*, 26(8), 1895-1900.

*OBJECTIVE: Metabolic activity of cytochrome P450 (CYP) 3A4 has been associated with clopidogrel response variability. Because metabolic activity of CYP3A4 is genetically regulated, we hypothesized that genetic variations of this enzyme may contribute to clopidogrel response variability. METHODS AND RESULTS: The CYP3A4*1B, CYP3A4*3, IVS7+258A>G, IVS7+894C>T, and IVS10+12G>A polymorphisms of the CYP3A4 gene were assessed in 82 patients in a steady phase of clopidogrel therapy. Glycoprotein (platelet glycoprotein (GP) IIb/IIIa receptor activation and platelet aggregation were assessed. A cohort of 45 clopidogrel-naïve patients was studied to determine the modulating effects of these polymorphisms after loading dose (300 mg) administration. Only the IVS7+258A>G, IVS7+894C>T, and IVS10+12G>A polymorphisms were sufficiently polymorphic. During the steady phase of clopidogrel treatment, IVS10+12A allele carriers had reduced GP IIb/IIIa activation (P=0.025) and better responsiveness (P=0.02); similarly, clopidogrel-naïve patients carriers of the IVS10+12A allele had reduced GP IIb/IIIa activation during the first 24 hours after a loading dose (P=0.025), increased platelet inhibition (P=0.006), and a more optimal drug response (P=0.003). This polymorphism did not influence platelet aggregation profiles. No association was observed between the other polymorphisms and clopidogrel responsiveness. CONCLUSIONS: The IVS10+12G>A polymorphism of the CYP3A4 gene modulates platelet activation in patients treated with clopidogrel and may therefore contribute to clopidogrel response variability.*

Chen, B., Zhang, W., Li, Q., Li, Y., He, Y., Fan, L., et al. (2008). Inhibition of ADP-induced platelet aggregation by clopidogrel is related to CYP2C19 genetic polymorphisms. *Clin Exp Pharmacol Physiol*, 35(8), 904-908.

*Clopidogrel is one of the most important antithrombotic drugs but has different efficacies in different populations. The aim of the present study was to evaluate the contribution of CYP2C19 genetic polymorphisms to the inhibition of ADP-induced platelet aggregation by clopidogrel in healthy Chinese volunteers. Eighteen healthy male volunteers (six CYP2C19*1/CYP2C19*1, six CYP2C19*1/CYP2C19*2 and *3 and six CYP2C19*2/CYP2C19*2 and *3) were enrolled in the study. Each subject took 300 mg clopidogrel on the first day and then 75 mg once daily for 2 consecutive days. Blood samples were taken to measure ADP-induced platelet aggregation at baseline and 4, 24 and 72 h after administration of the first dose of clopidogrel. There were significant decrease in 2 and 5 micromol/L ADP-induced platelet aggregation at 4, 24 and 72 h after clopidogrel among the three CYP2C19 genotypes compared with baseline (P < 0.001). The change in 5 micromol/L ADP-induced platelet aggregation in subjects with the CYP2C19*1/CYP2C19*1 genotype was greater than that in subjects with the CYP2C19*2/CYP2C19*2 and *3 genotype at 4 h (49.0 +/- 15.5 vs 29.7 +/- 17.4%, respectively; P = 0.029), 24 h (48.7 +/- 20.5 vs 25.0 +/- 17.6%, respectively; P = 0.035) and 72 h (45.5 +/- 15.2 vs 26.5 +/- 15.8%, respectively; P = 0.030) after clopidogrel administration. In conclusion, CYP2C19*2 and CYP2C19*3 genetic polymorphisms reduced clopidogrel inhibition of ADP-induced platelet aggregation, with the degree of inhibition dependent on the genetic polymorphism present.*

Collet, J., Hulot, J., Pena, A., Villard, E., Esteve, J., Silvain, J., et al. (2009). Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*, 373(9660), 309-317.

*BACKGROUND: Clopidogrel and low-dose aspirin have become the mainstay oral antiplatelet regimen to prevent recurrent ischaemic events after acute coronary syndromes or stent placement. The frequent genetic functional variant 681 G>A (*2) of cytochrome P450 2C19 (CYP2C19) is an important contributor to the wide variability between individuals of the antiplatelet effect of clopidogrel. We assessed whether the CYP2C19*2 polymorphism affected long-term prognosis of patients who were chronically treated with clopidogrel. METHODS: Between April 1, 1996, and April 1, 2008, 259 young patients (aged <45 years) who survived a first myocardial infarction and were exposed to clopidogrel treatment for at least a month, were enrolled in a multicentre registry and underwent CYP2C19*2 determination. The primary endpoint was a composite of death, myocardial infarction, and urgent coronary revascularisation occurring during exposure to clopidogrel. Follow-up was every 6 months. The key secondary endpoint was stent thrombosis proven by angiography. FINDINGS: Median clopidogrel exposure time was 1.07 years (IQR 0.28-3.0). Baseline characteristics were balanced between carriers (heterozygous *1/*2, n=64; homozygous *2/*2, n=9) and non-carriers (n=186) of CYP2C19*2 variant. The primary endpoint occurred more frequently in carriers than in non-carriers (15 vs 11 events; hazard ratio [HR] 3.69 [95% CI 1.69-8.05], p=0.0005), as did stent thrombosis (eight vs four events; HR 6.02 [1.81-20.04], p=0.0009). The detrimental effect of the CYP2C19*2 genetic variant persisted from 6 months after clopidogrel initiation up to the end of follow-up (HR 3.00 [1.27-7.10], p=0.009). After multivariable analysis, the CYP2C19*2 genetic variant was the only independent predictor of cardiovascular events (HR 4.04 [1.81-9.02], p=0.0006). INTERPRETATION: The CYP2C19*2 genetic variant is a major determinant of prognosis in young patients who are receiving clopidogrel treatment after myocardial infarction.*

Fontana, P., Hulot, J., De Moerloose, P., & Gaussem, P. (2007). Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. *J Thromb Haemost*, 5(10), 2153-2155.

*Clopidogrel, a prodrug, must be activated by hepatic cytochrome P450 (CYP) isoenzymes before being able to irreversibly block the platelet adenosine 5'-diphosphate (ADP) receptor P2Y₁₂. Clopidogrel responsiveness is highly variable among healthy subjects and patients, and a genetic variant (CYP2C19*2), which encodes a deficient version of the drug-metabolizing enzyme CYP2C19, has been associated with a markedly subnormal response to clopidogrel in 28 healthy subjects, based on the phosphorylation state of the vasodilator phosphoprotein and platelet aggregation profile. However, an intronic polymorphism (IVS10 + 12G > A) in the gene coding for another CYP isoform (CYP3A4) has also been recently linked to clopidogrel responsiveness based on the expression of activated glycoprotein (GP) IIb-IIIa but not based on the platelet aggregation profile. Both studies were small-scale and none has been replicated so far. This study was conducted to evaluate and quantify the genetic contribution of the CYP2C19*2 and CYP3A4 (IVS10 + 12A) alleles to the variability of clopidogrel responses in an unselected population of 94 healthy volunteers. This study points out the CYP2C19 (*1/*2) polymorphism as a candidate in the explanation of clopidogrel poor responsiveness as we replicate our previous findings in a larger, independent study population. The CYP2C19 (*1/*2) explained 10% of the observed variability in clopidogrel responsiveness. The impact of this genetic variant in a patient population now remains to be established.*

Fontana, P., Senouf, D., & Mach, F. (2008). Biological effect of increased maintenance dose of clopidogrel in cardiovascular outpatients and influence of the cytochrome P450 2C19*2 allele on clopidogrel responsiveness. *Thromb Res*, 121(4), 463-468.

*INTRODUCTION: The first aim of this study is to evaluate the biological effect of doubling the maintenance dose of clopidogrel in pre-defined clopidogrel "low responders", compared to the biological effect of the standard dose in "responders". The second aim is to test the influence of the CYP 2C19*2 allele on clopidogrel responsiveness. MATERIALS AND METHODS: The platelet reactivity index (PRI), based on the phosphorylation status of the vasodilator phosphoprotein, was determined in 81 consecutive cardiovascular outpatients who had been taking clopidogrel 75 mg/day for at least 15 days (visit 1). Patients with PRI \geq 50% ("low responders") were then given clopidogrel 150 mg/day. All the patients were again evaluated 15 days later (visit 2) and were genotyped for the CYP 2C19*2 allele. RESULTS: At visit 1, PRI values ranged from 12.6% to 80.4%. In "low responders" (n=45), the mean PRI fell from 62.0 \pm 6.7% to 49.4 \pm 11.3% (P<0.001) after 15 days of clopidogrel 150 mg/day, while no significant change was observed in the other patients ("responders"), who remained on the standard dose (mean PRI: 37.7 \pm 10.4% and 39.9 \pm 10.8%, P=0.22, in visit 1 and 2, respectively). The CYP 2C19*2 allele was not associated with clopidogrel responsiveness. CONCLUSIONS: Increasing the maintenance dose of clopidogrel from 75 to 150 mg/day for 15 days in "low responders" is associated with a relative 20%-increase in its biological effect, independently of the CYP2C19 genotype, but without reaching the levels observed in "responders". The CYP 2C19*2 allele is not associated with clopidogrel responsiveness in our population of cardiovascular outpatients.*

Ford, N. F. (2009). Clopidogrel resistance: pharmacokinetic or pharmacogenetic? *J Clin Pharmacol*, 49(5), 506-512.

*Clopidogrel is important for the management of acute coronary syndromes and, along with aspirin, is recommended in the American College of Cardiology/American Heart Association guideline. It is also used along with aspirin, during the placement of coronary artery stents. Clopidogrel resistance was recognized in such procedures, as several patients did not have the anticipated platelet aggregation response to an ex vivo adenosine diphosphate challenge. From the EXCELSIOR study, which investigated the phenomenon, it was appreciated that it was present prior to treatment with clopidogrel and was therefore an intrinsic property of the patient's platelets. From other studies, it was appreciated that the patients who had clopidogrel resistance had a defective allele *2/ in the CYP2C19 gene. Furthermore, there was a dose response evident in that the homozygotes CYP2C19*2/*2 had platelets that responded even less well to clopidogrel than the heterozygotes CYP2C19*2 that responded less well than the wild-type homozygote. The involvement of the phenomenon with CYP2C19 led some to believe that it was a pharmacokinetic issue. However, the major oxidative metabolic pathway for clopidogrel by which the reactive intermediate is formed is CYP3A4. It is suggested that there is a linkage between a polymorphism of the platelet receptor P2Y12 and the polymorphism of CYP2C19.*

Freedman, J. E., & Hylek, E. M. (2009). Clopidogrel, genetics, and drug responsiveness. *N Engl J Med*, 360(4), 411-413.

Geisler, T., Schaeffeler, E., Dippon, J., Winter, S., Buse, V., Bischofs, C., et al. (2008). CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. *Pharmacogenomics*, 9(9), 1251-1259.

*AIMS: To investigate an association of responsiveness to clopidogrel loading dose with genotypes of cytochrome P450 (CYP) 2C19, other CYP isozymes and nongenetic factors in patients with coronary artery disease. MATERIALS & METHODS: Genotyping for CYP2C19 (*2, *3 and *17), CYP3A4*1B and CYP3A5*3 variants was performed in patients (n = 237) who underwent percutaneous coronary intervention. Adenosine diphosphate-induced platelet aggregation was determined after first administration of 600 mg clopidogrel. RESULTS: CYP2C19*2 carriers showed significantly increased residual platelet aggregation (RPA) (OR: 4.6; 95% CI: 2.5-8.7; p < 0.0001) compared with noncarriers. All other polymorphisms had no influence on RPA. For the development of a risk score for better prediction of RPA, CYP2C19*2 genotype and previously identified nongenetic risk factors (age >65 years, Type 2 diabetes mellitus, decreased left ventricular function, renal failure and acute coronary syndrome) were analyzed. Multivariable logistic regression analysis showed a significant correlation of the nongenetic factors (chi (2) = 5.32; p = 0.021) and CYP2C19*2 (chi (2) = 21.31; p < 0.0001) with high RPA, and an even higher association for the combination of both (chi (2) = 25.85; p < 0.0001). CONCLUSIONS: Prediction of responsiveness after clopidogrel loading dose may substantially be improved by adding CYP2C19*2 genotype to nongenetic risk factors.*

Giusti, B., Gori, A. M., Marcucci, R., Saracini, C., Sestini, I., Paniccia, R., et al. (2007). Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. *Pharmacogenet Genomics*, 17(12), 1057-1064.

*OBJECTIVES: The aim of this study was to evaluate the effect of polymorphisms affecting the clopidogrel metabolism (CYP3A4 IVS10+12G/A and CYP2C19*2) and the P2Y12 receptor (P2Y12 T744C) on modulating platelet function in acute coronary syndrome patients on dual antiplatelet treatment. BACKGROUND: Residual platelet reactivity (RPR) phenomenon on antiplatelet therapy requires clarification. P2Y12 T744C, CYP3A4 IVS10+12G/A and, in healthy individuals only, CYP2C19*2 polymorphisms have been investigated; however, the influence on platelet reactivity in a large population of high-risk vascular patients on dual antiplatelet treatment has not yet been elucidated. METHODS: A total of 1419 acute coronary syndrome patients on dual antiplatelet treatment were studied. Platelet function was evaluated by platelet-rich plasma aggregation. Electronic nanochips and restriction-fragment length polymorphism were used for analysis of polymorphisms. RESULTS: Only CYP2C19*2, out of the three investigated polymorphisms, is associated with higher platelet reactivity. Carriers of the *2 allele had significantly higher platelet aggregation values after arachidonic acid (AA; P=0.043), 2 micromol/l adenosine 5' diphosphate (ADP; P<0.0001) and 10 micromol/l ADP (P=0.001) stimuli. The genotype distribution of CYP2C19*2 polymorphism significantly differed between patients with and without RPR, as evaluated by 10-micromol/l ADP-induced platelet aggregation (P=0.002) and by AA-induced platelet aggregation (P=0.045). At the multivariate linear regression analysis, the CYP2C19*2 polymorphism remained a significant and independent risk factor for dual antiplatelet treatment variability. CONCLUSIONS: This*

study demonstrates, for the first time, that the *2 CYP2C19 allele is associated with higher platelet aggregability and RPR in high-risk vascular patients on dual antiplatelet treatment. These findings can have a significant impact on the future design of pharmacogenetic antiaggregant strategies for high-risk vascular patients on dual antiplatelet treatment.

Gladding, P., Webster, M., Zeng, I., Farrell, H., Stewart, J., Ruygrok, P., et al. (2008). The pharmacogenetics and pharmacodynamics of clopidogrel response: an analysis from the PRINC (Plavix Response in Coronary Intervention) trial. *JACC Cardiovasc Interv*, 1(6), 620-627.

OBJECTIVES: This study assessed the effect of pharmacogenetics on the antiplatelet effect of clopidogrel. *BACKGROUND:* Variability in clopidogrel response might be influenced by polymorphisms in genes coding for drug metabolism enzymes (cytochrome P450 [CYP] family), transport proteins (P-glycoprotein) and/or target proteins for the drug (adenosine diphosphate-receptor P2Y12). *METHODS:* Sixty patients undergoing elective percutaneous coronary intervention in the randomized PRINC (Plavix Response in Coronary Intervention) trial had platelet function measured using the VerifyNow P2Y12 analyzer after a 600-mg or split 1,200-mg loading dose and after a 75- or 150-mg daily maintenance dosage. Polymerase chain reaction-based genotyping evaluated polymorphisms in the CYP2C19, CYP2C9, CYP3A4, CYP3A5, ABCB1, P2Y12, and CES genes. *RESULTS:* CYP2C19*1*1 carriers had greater platelet inhibition 2 h after a 600-mg dose (median: 23%, range: 0% to 66%), compared with platelet inhibition in CYP2C19*2 or *4 carriers (10%, 0% to 56%, $p = 0.029$) and CYP2C19*17 carriers (9%, 0% to 98%, $p = 0.026$). CYP2C19*2 or *4 carriers had greater platelet inhibition with the higher loading dose than with the lower dose at 4 h (37%, 8% to 87% vs. 14%, 0% to 22%, $p = 0.002$) and responded better with the higher maintenance dose regimen (51%, 15% to 86% vs. 14%, 0% to 67%, $p = 0.042$). *CONCLUSIONS:* Carriers of the CYP2C19*2 and *4 alleles showed reduced platelet inhibition after a clopidogrel 600-mg loading dose but responded to higher loading and maintenance dose regimens. Genotyping for the relevant gene polymorphisms may help to individualize and optimize clopidogrel treatment. (Australia New Zealand Clinical Trials Registry; ACTRN12606000129583).

Kim, K. A., Park, P. W., Hong, S. J., & Park, J. (2008). The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance. *Clin Pharmacol Ther*, 84(2), 236-242.

We evaluated the effect of the CYP2C19 genotype on the pharmacokinetics and pharmacodynamics of clopidogrel. Twenty-four subjects were divided into three groups on the basis of their CYP2C19 genotype: homozygous extensive metabolizers (homoEMs, $n = 8$), heterozygous EMs (heteroEMs, $n = 8$), and poor metabolizers (PMs, $n = 8$). After a single 300-mg loading dose of clopidogrel on day 1, followed by a 75-mg daily maintenance dose from days 2 to 7, we measured the plasma levels of clopidogrel and assessed the antiplatelet effect as pharmacodynamics. The mean clopidogrel area under the curve (AUC) for PMs was 1.8- and 2.9-fold higher than that for heteroEMs and homoEMs, respectively ($P = 0.013$). The mean peak plasma concentration in PMs was 1.8- and 4.7-fold higher than that of heteroEMs and homoEMs,

respectively ($P = 0.008$). PMs exhibited a significantly lower antiplatelet effect than heteroEMs or homoEMs ($P < 0.001$). From these findings it is clear that the CYP2C19 genotype affects the plasma levels of clopidogrel and modulates the antiplatelet effect of clopidogrel.

Lee, J. M., Park, S., Shin, D., Choi, D., Shim, C. Y., Ko, Y., et al. (2009). Relation of genetic polymorphisms in the cytochrome P450 gene with clopidogrel resistance after drug-eluting stent implantation in Koreans. *Am J Cardiol*, 104(1), 46-51.

*Clopidogrel is a prodrug that has to be converted to an active metabolite by hepatic cytochrome P450 (CYP) isoenzymes to inhibit platelet aggregation. Individual variability of platelet inhibition by clopidogrel suggests a possibility for genetic factors having a significant influence on clopidogrel responsiveness. In this study, we sought to determine the relation of genetic polymorphisms of CYP genes to clopidogrel resistance in Koreans. Four hundred fifty patients who underwent successful percutaneous coronary intervention with drug-eluting stents were randomly assigned to treatment with dual antiplatelet regimen (aspirin plus clopidogrel) or triple antiplatelet regimen (aspirin plus clopidogrel plus cilostazol). Clopidogrel resistance using VerifyNow P2Y12 assay and genetic analysis were performed in 387 patients. Clopidogrel resistance was found in 112 patients (28.9%). In the clopidogrel-responsive group, there was a significantly higher proportion of cilostazol use. Because cilostazol showed a significant influence on clopidogrel resistance, we examined the association of single-nucleotide polymorphisms and clopidogrel resistance in the dual and triple antiplatelet therapy groups, respectively. In all subjects, the CYP2C19*3A allele was significantly more prevalent in the clopidogrel-resistant group compared with the clopidogrel-responsive group. Multiple logistic regression analysis demonstrated that CYP2C19*3 is an independent predictor of clopidogrel resistance. In conclusion, CYP2C19*3 single-nucleotide polymorphisms is an independent risk factor of clopidogrel resistance in Korean subjects with coronary artery disease.*

Malek, L. A., Kisiel, B., Spiewak, M., Grabowski, M., Filipiak, K. J., Kostrzewa, G., et al. (2008). Coexisting polymorphisms of P2Y12 and CYP2C19 genes as a risk factor for persistent platelet activation with clopidogrel. *Circ J*, 72(7), 1165-1169.

BACKGROUND: Coexisting polymorphisms of the genes affecting clopidogrel resistance may influence platelet activation. METHODS AND RESULTS: In 105 patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention, platelet function was measured and registered as closure time in the test with collagen and adenosine diphosphate (CADP-CT). Patients were followed for 12 months for death or recurrent myocardial infarction (MI). Genotyping revealed 7 carriers of both the C allele of P2Y12 and A allele of CYP2C19 (group 1), 14 carriers of the T allele of P2Y12 and A allele of CYP2C19 (group 2), 17 carriers of the C allele of P2Y12 and G allele of CYP2C19 (group 3) and 67 carriers of the T allele of P2Y12 and G allele of CYP2C19 (controls). The median CADP-CT value was significantly lower in group 1 than in group 2 or 3 ($p < 0.01$) or controls ($p < 0.002$), but did not differ between group 2 or 3 and controls. There were 2 cardiovascular deaths and 4 MI during follow-up, and the median CADP-CT value was lower in these patients ($p = 0.09$). CONCLUSIONS: Coexisting, rather than single, polymorphisms of different genes may be related to persistent platelet activation while on clopidogrel, which raises concern about harm in patients with ACS.

Mega, J. L., Close, S. L., Wiviott, S. D., Shen, L., Hockett, R. D., Brandt, J. T., et al. (2009). Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*, 360(4), 354-362.

BACKGROUND: Clopidogrel requires transformation into an active metabolite by cytochrome P-450 (CYP) enzymes for its antiplatelet effect. The genes encoding CYP enzymes are polymorphic, with common alleles conferring reduced function. METHODS: We tested the association between functional genetic variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to clopidogrel in 162 healthy subjects. We then examined the association between these genetic variants and cardiovascular outcomes in a separate cohort of 1477 subjects with acute coronary syndromes who were treated with clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38. RESULTS: In healthy subjects who were treated with clopidogrel, carriers of at least one CYP2C19 reduced-function allele (approximately 30% of the study population) had a relative reduction of 32.4% in plasma exposure to the active metabolite of clopidogrel, as compared with noncarriers ($P<0.001$). Carriers also had an absolute reduction in maximal platelet aggregation in response to clopidogrel that was 9 percentage points less than that seen in noncarriers ($P<0.001$). Among clopidogrel-treated subjects in TRITON-TIMI 38, carriers had a relative increase of 53% in the composite primary efficacy outcome of the risk of death from cardiovascular causes, myocardial infarction, or stroke, as compared with noncarriers (12.1% vs. 8.0%; hazard ratio for carriers, 1.53; 95% confidence interval [CI], 1.07 to 2.19; $P=0.01$) and an increase by a factor of 3 in the risk of stent thrombosis (2.6% vs. 0.8%; hazard ratio, 3.09; 95% CI, 1.19 to 8.00; $P=0.02$). CONCLUSIONS: Among persons treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers.

Patrono, C. (2009). The P2Y12 receptor: no active metabolite, no party. *Nat Rev Cardiol*, 6(4), 271-272.

Poor responders to clopidogrel have low levels of circulating active metabolite. However, in vitro experiments have shown that blood platelets from poor responders are fully inhibited by the active metabolite of this prodrug. Impaired platelet inhibition reflects inadequate plasma levels of active metabolites, and not differences in platelet P2Y12 receptor function.

Roden, D. M., & Stein, C. M. (2009). Clopidogrel and the concept of high-risk pharmacokinetics. *Circulation*, 119(16), 2127-2130.

Four large trials, reported in the last several weeks, have identified loss-of-function alleles in the gene encoding cytochrome P450 2C19 (CYP2C19) as important risk factors predicting apparent failure of clopidogrel efficacy. Previous studies have shown that clopidogrel is a prodrug that requires bioactivation, mediated in part by CYP2C19, to achieve its antiplatelet efficacy. All 4 trials built on this knowledge and studied the effects of CYP2C19 variants on coronary events (including death, myocardial infarction, and in-stent thrombosis) in patients receiving clopidogrel. Hazard ratios for a single CYP2C19 variant allele ranged from 1.5 to 4, depending on the end point and the specific population. We describe here how this

apparently surprising outcome could be anticipated from first principles in clinical pharmacology. We then discuss how considering this result within the context of a contemporary understanding of clinical pharmacokinetics and pharmacogenetics raises new hypotheses that require further testing.

Shuldiner, A. R., O'Connell, J. R., Bliden, K. P., Gandhi, A., Ryan, K., Horenstein, R. B., et al. (2009). Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*, 302(8), 849-857.

*CONTEXT: Clopidogrel therapy improves cardiovascular outcomes in patients with acute coronary syndromes and following percutaneous coronary intervention by inhibiting adenosine diphosphate (ADP)-dependent platelet activation. However, nonresponsiveness is widely recognized and is related to recurrent ischemic events. OBJECTIVE: To identify gene variants that influence clopidogrel response. DESIGN, SETTING, AND PARTICIPANTS: In the Pharmacogenomics of Antiplatelet Intervention (PAPI) Study (2006-2008), we administered clopidogrel for 7 days to 429 healthy Amish persons and measured response by ex vivo platelet aggregometry. A genome-wide association study was performed followed by genotyping the loss-of-function cytochrome P450 (CYP) 2C19*2 variant (rs4244285). Findings in the PAPI Study were extended by examining the relation of CYP2C19*2 genotype to platelet function and cardiovascular outcomes in an independent sample of 227 patients undergoing percutaneous coronary intervention. MAIN OUTCOME MEASURE: ADP-stimulated platelet aggregation in response to clopidogrel treatment and cardiovascular events. RESULTS: Platelet response to clopidogrel was highly heritable ($h^2 = 0.73$; $P < .001$). Thirteen single-nucleotide polymorphisms on chromosome 10q24 within the CYP2C18-CYP2C19-CYP2C9-CYP2C8 cluster were associated with diminished clopidogrel response, with a high degree of statistical significance ($P = 1.5 \times 10^{-13}$ for rs12777823, additive model). The rs12777823 polymorphism was in strong linkage disequilibrium with the CYP2C19*2 variant, and was associated with diminished clopidogrel response, accounting for 12% of the variation in platelet aggregation to ADP ($P = 4.3 \times 10^{-11}$). The relation between CYP2C19*2 genotype and platelet aggregation was replicated in clopidogrel-treated patients undergoing coronary intervention ($P = .02$). Furthermore, patients with the CYP2C19*2 variant were more likely (20.9% vs 10.0%) to have a cardiovascular ischemic event or death during 1 year of follow-up (hazard ratio, 2.42; 95% confidence interval, 1.18-4.99; $P = .02$). CONCLUSION: CYP2C19*2 genotype was associated with diminished platelet response to clopidogrel treatment and poorer cardiovascular outcomes.*

Sibbing, D., Stegherr, J., Latz, W., Koch, W., Mehilli, J., Dörrler, K., et al. (2009). Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eur Heart J*, 30(8), 916-922.

*AIMS: Several studies have demonstrated that the mutant *2 allele of the CYP2C19 681G>A loss-of-function polymorphism is associated with diminished metabolism of clopidogrel into its active thiol metabolite and an attenuated platelet response to clopidogrel treatment. It is not known whether patients carrying the mutant CYP2C19*2 allele have a higher risk of stent thrombosis (ST) compared with homozygous CYP2C19*1 wild-type allele carriers following percutaneous coronary intervention (PCI). The aim of this study was to assess the impact of the CYP2C19 681G>A loss-of-function polymorphism on ST*

following PCI performed after pre-treatment with clopidogrel. **METHODS AND RESULTS:** The study population included 2485 consecutive patients undergoing coronary stent placement after pre-treatment with 600 mg of clopidogrel. Genotypes were determined with a TaqMan assay. The primary endpoint of the study was the incidence of definite ST within 30 days following PCI. Of the patients studied, 1805 (73%) were CYP2C19 wild-type homozygotes (*1/*1) and 680 (27%) carried at least one *2 allele (*1/*2 or *2/*2). The cumulative 30-day incidence of ST was significantly higher in CYP2C19*2 allele carriers (*1/*2 or *2/*2) vs. CYP2C19 wild-type homozygotes (*1/*1) [10 patients (1.5%) in CYP2C19*2 allele carriers vs. 7 (0.4%) in CYP2C19 wild-type homozygotes (*1/*1), HR 3.81, 95% CI 1.45-10.02, P = 0.007; P = 0.006 after adjustment for confounding variables]. The risk of ST was highest (2.1%) in patients with the CYP2C19 *2/*2 genotype (P = 0.002). **CONCLUSION:** CYP2C19*2 carrier status is significantly associated with an increased risk of ST following coronary stent placement.

Simon, T., Verstuyft, C., Mary-Krause, M., Quteineh, L., Drouet, E., Méneveau, N., et al. (2009). Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*, 360(4), 363-375.

BACKGROUND: Pharmacogenetic determinants of the response of patients to clopidogrel contribute to variability in the biologic antiplatelet activity of the drug. The effect of these determinants on clinical outcomes after an acute myocardial infarction is unknown. **METHODS:** We consecutively enrolled 2208 patients presenting with an acute myocardial infarction in a nationwide French registry and receiving clopidogrel therapy. We then assessed the relation of allelic variants of genes modulating clopidogrel absorption (ABCB1), metabolic activation (CYP3A5 and CYP2C19), and biologic activity (P2RY12 and ITGB3) to the risk of death from any cause, nonfatal stroke, or myocardial infarction during 1 year of follow-up. **RESULTS:** Death occurred in 225 patients, and nonfatal myocardial infarction or stroke in 94 patients, during the follow-up period. None of the selected single-nucleotide polymorphisms (SNPs) in CYP3A5, P2RY12, or ITGB3 were associated with a risk of an adverse outcome. Patients with two variant alleles of ABCB1 (TT at nucleotide 3435) had a higher rate of cardiovascular events at 1 year than those with the ABCB1 wild-type genotype (CC at nucleotide 3435) (15.5% vs. 10.7%; adjusted hazard ratio, 1.72; 95% confidence interval [CI], 1.20 to 2.47). Patients carrying any two CYP2C19 loss-of-function alleles (*2, *3, *4, or *5), had a higher event rate than patients with none (21.5% vs. 13.3%; adjusted hazard ratio, 1.98; 95% CI, 1.10 to 3.58). Among the 1535 patients who underwent percutaneous coronary intervention during hospitalization, the rate of cardiovascular events among patients with two CYP2C19 loss-of-function alleles was 3.58 times the rate among those with none (95% CI, 1.71 to 7.51). **CONCLUSIONS:** Among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention. (ClinicalTrials.gov number, NCT00673036.)

Trenk, D., Hochholzer, W., Frundi, D., et al. (2008). Impact of cytochrome P450 3A4-metabolized statins on the antiplatelet effect of a 600-mg loading dose clopidogrel and on clinical outcome in patients undergoing elective coronary stent placement. *Thromb Haemost*, 99(1), 174-181.

Early studies suggested interactions between statins and clopidogrel. Based on the outcome and platelet data, there is now huge evidence of no interactions between statins and 75 to 300 mg clopidogrel; however, data with 600-mg loading are lacking. In a pre-specified analysis of the EXCELSIOR cohort, we investigated the interaction between statins, especially cytochrome P4503A4-metabolized atorvastatin and simvastatin, and the antiplatelet effects of a 600-mg loading dose of clopidogrel. We analyzed 1,395 patients scheduled for coronary angiography (CA). Patients received clopidogrel 600 mg at least two hours before CA and 75 mg daily thereafter in case of percutaneous coronary intervention (PCI). Statin medication on admission was continued unaltered until discharge. Platelet function was assessed by optical aggregometry and flow cytometry of adenosine diphosphate (ADP)-stimulated surface expression of CD62P, CD63 and PAC-1 before clopidogrel and immediately before CA. Residual platelet aggregation (RPA) after addition of ADP 5 μ M was similar irrespective of statin treatment at baseline ($p = 0.968$). RPA at CA was 46.2 \pm 16.8% in patients without statin ($n = 682$), 45.5 \pm 17.0% in patients with atorvastatin ($n = 255$), 45.8 \pm 16.3% with simvastatin ($n = 335$), 47.3 \pm 14.9% with fluvastatin ($n = 42$) and 45.9 \pm 16.2% with pravastatin ($n = 81$; $p = 0.962$). Consistent results were obtained by flow cytometry. In patients with PCI ($n = 553$), the one-year incidence of death, myocardial infarction and target lesion reintervention did not differ between cohorts stratified according to statin co-medication ($p = 0.645$). Thus, peri-interventional atorvastatin and simvastatin had no effect on the antiplatelet activity of a loading dose of clopidogrel 600 mg and did not affect clinical outcome after PCI.

Umemura, K., Furuta, T., & Kondo, K. (2008). The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. *J Thromb Haemost*, 6(8), 1439-1441.

Clopidogrel is a thienopyridine derivative with ADP-antagonistic activity and is widely used for the prevention of ischemic events in patients who have suffered a stroke, non-ST-segment elevation myocardial infarction and peripheral arterial disease. However, there are a substantial number of patients who do not respond to clopidogrel despite a standardized dosage regimen. Clopidogrel resistance is one of the major concerns in the management of high-risk vascular patients, especially those who have experienced acute coronary syndromes. Clopidogrel is an inactive prodrug requiring several biotransformation steps, mediated mainly by cytochrome P-450 isoforms (CYP), in order to generate an active metabolite with a thiol moiety that binds irreversibly to the platelet ADP receptor P2Y12. The conversion of clopidogrel to the active metabolite has been reported to be a two-step, CYP-dependent process. In these steps, CYP2C19, 1A2, 2B6, 2C9 and 3A4/5 may be involved in the activation of clopidogrel. Kim et al. recently reported that the CYP2C19 polymorphism affects the plasma levels of clopidogrel and modulates its antiplatelet effect. However, they did not measure the metabolite of clopidogrel. Therefore, it remains unresolved whether the plasma concentration of the active metabolite of clopidogrel may be affected by the CYP 2C19 polymorphism. In this study, we investigated whether the polymorphism of CYP2C19 would affect the formation of the active metabolite and hence the antiplatelet effects in healthy subjects. We conclude that the CYP2C19 pharmacogenomic status is a determinant for the formation of the active metabolite of clopidogrel and its antiplatelet effects to the active metabolite in healthy subjects.

Relevant Clinical Trials

PAPI

Determining Genetic Role in Treatment Response to Anti-Platelet Interventions. ClinicalTrials.gov Identifier: NCT00799396

One of the most common ways for preventing coronary heart disease (CHD) is to take aspirin or clopidogrel. However, studies have shown that not all people respond to these medications. The variance in treatment response may be linked to genetics. This study will examine the effects of aspirin and clopidogrel in a population whose genes are well known in order to determine the role that genes play in people's treatment responses.

Currently recruiting. Contact ashuldin@medicine.umaryland.edu

PICOLO

Platelet Aggregation Inhibition in Children on Clopidogrel. ClinicalTrials.gov Identifier: NCT00115375

PICOLO is a double blind placebo controlled phase II dose ranging, dose escalating study in patients of Blalock-Taussig age categories (neonates and infants/toddlers), to determine the dose providing inhibition of platelet aggregation similar to adults.

Study completed. Jennifer Li, Duke University, (919) 681-2916

PLATO

A Comparison of AZD6140 and Clopidogrel in Patients With Acute Coronary Syndrome. ClinicalTrials.gov Identifier: NCT00391872

AZD6140 is a new, reversible, anti-platelet medication. Anti-platelet medications work to prevent the formation of blood clots. AZD6140 is being developed as a treatment for patients with acute coronary syndrome (ACS). ACS is a term that is used to describe both heart attacks in progress or the imminent threat of a heart attack. ACS is usually caused by the formation of a blood clot in an artery that partially or totally blocks the blood supply to a portion of the heart muscle. AZD6140 will be compared with clopidogrel to determine which drug, when either is used in conjunction with aspirin, is better at reducing deaths from vascular causes, future heart attacks and/or strokes in patients with ACS.

Study completed. Principal Investigator Robert Harrington, Duke University, (919) 668-8749

PRINC

Plavix Response in Coronary Intervention. Australia New Zealand Clinical Trials Registry; ACTRN12606000129583