Canadian Agency for Drugs and Technologies in Health

Issues in Emerging Health Technologies

Issue 123 • March 2013

Point-of-Care Phenotypic and Genetic Testing for Patients with Acute Coronary Syndrome

Summary

- ✓ **Clopidogrel is recommended as part of dual antiplatelet therapy (DAT) for clot prevention in patients with acute coronary syndrome (ACS). Clopidogrel is a prodrug that requires activation by CYP2C19 enzymes in the liver. It is expected that 16% to 50% of clopidogrel-treated patients who have ACS may not fully benefit from the protective effect of clopidogrel, potentially remaining at an increased risk of experiencing a major adverse cardiovascular event (MACE), because loss-of-function (LOF) mutations in the CYP2C19 gene prevent them from fully metabolizing clopidogrel.[1-3] The CYP2C19*2 LOF mutation accounts for 5% to 20% of the variability in response to clopidogrel.[4] Compliance, age, gender, body mass index, diabetes, clopidogrel loading dose, and platelet count also influence platelet reactivity.[4]**
- ✓ **Point-of-care (POC) genotyping and phenotyping, using Spartan RX and VerifyNow respectively, are designed to help guide antiplatelet therapy without requiring the time, training, and access that is required for central laboratory testing.[5]**
- ✓ **The Spartan RX genotyping assay identifies carriers of the LOF mutation CYP2C19*2 within 60 minutes based on a buccal swab. One proof-of-concept study involving 200 patients shows that CYP2C19*2 carriers who received prasugrel instead of clopidogrel after percutaneous coronary intervention (PCI) had lower on-treatment platelet reactivity than patients undergoing standard therapy with clopidogrel.[6] However, no definitive conclusions can be made because of the small sample size and use of surrogate end points in this study.[6]**
- ✓ **The VerifyNow phenotyping assay identifies patients with high on-treatment platelet reactivity (HPR) who could benefit from using an alternate clopidogrel dosing strategy or a different antiplatelet drug to reduce the risk of a MACE.[7,8]**
- ✓ **The association between CYP2C19 genotype and cardiovascular events is still uncertain. Further trials are needed to define optimal thresholds for POC phenotyping. Trials using a combined genotyping and phenotyping approach are underway to better define the role of such tests in guiding antiplatelet therapy in clinical practice.**
- ✓ **While not currently approved for use in Canada, Spartan RX CYP2C19 has regulatory approval in Europe and is working toward Food and Drug Administration (FDA) clearance in the United States.[9] VerifyNow is available in more than 70 countries worldwide and was approved for use in Canada in August 2012.[10,11]**

Background

DAT with acetylsalicylic acid (ASA) and clopidogrel is recommended to prevent blood clots in patients with ACS and those undergoing PCI or stenting.[12] The prodrug clopidogrel is activated by the cytochrome P450 enzyme CYP2C19. Patients with LOF mutations in CYP2C19 achieve lower levels of active drug, less platelet inhibition, and are at an increased risk of MACEs, including heart attack, stroke, and death.[13,14] Each named star (*) allele is defined by the genotype at one or more specific single-nucleotide polymorphisms.[2] With the LOF mutation the CYP2C19*1 allele remains functional, while the CYP2C19*2 and CYP2C19*3 variants have reduced enzyme activity, and CYP2C19*17 increases enzyme activity.[2] Approximately 25% to 50% patients with ACS carry one[1] or two copies of the LOF allele CYP2C19*2, conferring an increased risk of a MACE and stent thrombosis.[2,14,15] A significant increased risk of experiencing MACEs is found in carriers of one (hazard ratio [HR] 1.55, 95% CI, 1.11 to 2.27, $P = 0.01$) and two (HR 1.75, 95% CI, 1.24 to 2.50, $P = 0.002$) CYP2C19 LOF alleles.[1] Similarly, there is a significantly increased risk of stent thrombosis in carriers of one (HR 2.67, 95% CI, 1.69 to 4.22, $P < 0.0001$) and two (HR 3.97, 95% CI, 1.75 to 9.02, $P = 0.001$) CYP2C19 LOF alleles.[1] Phenotyping using platelet function testing identifies patients with HPR. In 2010, the United States FDA issued a boxed warning informing health care professionals to test for CYP2C19 status and use alternative clopidogrel dosing strategies or other antiplatelet drugs to treat poor clopidogrel metabolizers.[5] No guidance was provided regarding the choice of platelet function test to be used or the management strategy for poor metabolizers.[16] POC CYP2C19 genotyping and phenotyping tests are designed to help guide antiplatelet therapy, without the time, training, and access required for central laboratory testing.

The Technology

The Spartan RX CYP2C19 assay (Spartan Bioscience, Ottawa, Canada) identifies CYP2C19*2, *3, and *17 genotypes from genomic DNA with a buccal swab sample.[17] POC genotype results, obtained within 60 minutes of testing, are used to guide personalized DAT.[6] According to validity tests, POC genotyping was 100% concordant with laboratory confirmed DNA sequencing.[6]

The VerifyNow (Accumetrics, San Diego, US) phenotyping test is designed to help monitor antiplatelet therapy.[16] The three-minute POC assay measures altered light transmission after adding a known platelet aggregation agonist to a sample of whole blood. As platelets bind to fibrinogen-coated beads, they aggregate and precipitate, allowing the light transmitted through the solution to be measured. Platelet reactivity is reported as P2Y12 reaction units (PRUs). Low clopidogrel responsiveness is defined as > 235 PRUs to 240 PRUs based on studies measuring MACEs at one year.[6,18,19] While VerifyNow results were strongly correlated with those derived through standard adenosine diphosphate (ADP) aggregometry,[18] there is evidence to suggest there is a lack of correlation in patients with stable coronary artery disease (CAD).[20] The specificity of the P2Y12 cartridge has been evaluated in a study investigating response to clopidogrel therapy in healthy volunteers and compared with ADP-induced laboratory aggregometry methods. The percentage platelet inhibition measured using VerifyNow was 93%, while that measured using standard ADP aggregometry was 95%. [18]

Regulatory Status

Spartan RX CYP2C19 has been submitted for FDA approval in the United States. The system has Conformité Européenne (CE) IVD Mark regulatory approval for Europe and other countries recognizing the CE Mark, including the Middle East, Africa, Latin America, and Asia-Pacific regions.[9]

In August 2012, Health Canada licensed VerifyNow for clinical use.[10] The system is used in more than 800 facilities in the United States and is available in more than 70 countries worldwide.[11]

Patient Group

In 2009, approximately 10,000 Canadians were hospitalized for ACS, classified as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA).[21] STEMI and NSTEMI patients may undergo PCI, stenting, bypass grafting, or medical management.[21] While DAT with ASA and clopidogrel is standard treatment,[12] the prevalence of clopidogrel non-response ranges from 16% to 50%, depending on the platelet function test used.[3] For the VerifyNow assay, in seven studies that defined clopidogrel non-response as greater than 240 PRUs, the prevalence of clopidogrel non-responders ranged from 12% to 59%.[3] Approximately 9% of patients taking clopidogrel go on to experience a MACE.[13] On the other hand, enhanced clopidogrel response in ultrarapid metabolizers causes major bleeding in approximately 1.5% of patients.[13] Genotyping and phenotyping for CYP2C19 may help to guide antiplatelet treatment, preventing MACEs and serious adverse bleeding events.[22]

Current Practice

Canadian practice guidelines recommend DAT with ASA and clopidogrel for patients with ACS, but ASA combined with prasugrel or ticagrelor may be considered for some groups depending on the clinical presentation.[12] The FDA advises health care professionals to test for CYP2C19 and alter dosing or to use another antiplatelet drug to minimize MACEs in poor clopidogrel metabolizers.[5] Recent American and European guidelines recommend genotyping or phenotyping testing if test results could alter the management strategy.[23] Laboratory-based DNA sequencing or TaqMan genotyping is used to genotype CYP2C19 variants, but results are usually not ready soon enough for acute patients undergoing PCI who need to start antiplatelet therapy.[24,25] Residual on-treatment platelet reactivity is measured using aggregometry, platelet counting, vasodilator-stimulated phosphoprotein (VASP), phosphorylation flow cytometry, thromboelastography, the cone and platelet analyzer, and platelet function analyzers.[16,25] The various tests, based on different principles, are sensitive to different aspects of platelet activation and correlate poorly with each other.[24,26-28] For example, a change in light transmission is used as a measure of platelet aggregation using platelet aggregometry; whereas, the VASP assay measures a cascade of events leading to the degree of P2Y12 antagonism in the presence of prostaglandin E1 and ADP.[25] Current clinical laboratory methods are time-consuming, labour-intensive, and

require technical training.[18] In contrast, bedside POC assays provide rapid results without demanding sample processing and with reduced training and access requirements.[25] This makes testing for genotype and phenotype clinically applicable in the context of ACS. However, there is a lack of consensus on the optimal method to quantify HPR, the cut-off value associated with clinical risk, and there are limited data to support that altering therapy based on platelet function measurements will improve outcomes.[29-32]

Methods

Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, The Cochrane Library (2012, Issue 8), ECRI (Health Devices Gold), and the University of York Centre for Reviews and Dissemination (CRD) databases. Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist.[33] No methodological filters were applied. The search was limited to English language documents published between January 1, 2007 and August 31, 2012. Conference abstracts were excluded from the search results. Regular alerts were established on MEDLINE and PubMed, and information retrieved through alerts was current to December 13, 2012.

Selection Criteria

Eligible studies for inclusion in "The Evidence" section of this report included randomized controlled trials (RCTs) or systematic reviews of RCTs that evaluated the performance of either the Spartan RX or the VerifyNow POC testing devices in patients using P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor).

The Evidence

A Canadian prospective, randomized, proof-of-concept study identified CYP2C19*2 carriers using Spartan RX CYP219 and assessed personalized DAT after PCI.[6] Two hundred patients undergoing PCI, with a mean age of 61 years (range 18 to 75 years) were randomly assigned to POC genotyping or standard treatment. Carriers received 10 mg of prasugrel daily while non-carriers and standard care patients received 75 mg of clopidogrel daily.[6] While the antiplatelet prasugrel requires biotransformation by carboxylesterases, there are fewer reports of non-responsiveness. The study reported the proportion of LOF CYP2C19*2 carriers with HPR (P2Y12 PRUs > 234) after one week of DAT. Of the 91 Spartan RX patients, 23 (25%) had one copy of CYP2C19*2 compared with 23 (24%) of 96 patients treated with standard therapy. Of the individuals carrying a CYP2C19*2 allele, four (4%) Spartan RX patients and three (3%) standard care patients carried two alleles. Compared with direct DNA sequencing, one Spartan RX patient was incorrectly identified as a carrier.[6] None of the 23 carriers in the Spartan RX group had a PRU > 234 at seven days, compared with seven (30%) in the standard therapy group (0.0092). Spartan RX had a sensitivity of 100% (95% confidence interval [CI] 92.3 to 100) and a specificity of 99.3% (96.3 to 100).[6] The authors concluded that POC genetic testing after PCI can be done at the patient's bedside, and treatment of CYP2C19*2 carriers can be altered to use prasugrel, which reduces HPR.[6] The authors stated that this is clinically important as high-dose clopidogrel and ticlopidine did not improve cardiovascular outcomes in patients with HPR in the Gauging Responsiveness with a VerifyNow Assay — Impact (GRAVITAS) and Responsiveness to Clopidogrel and Stent Thrombosis 2-ACS (RECLOSE 2-ACS) studies. While results of this proof-of-concept study suggest the potential for personalized medicine, no definitive conclusions can be made because it reports surrogate end points for 200 patients.[6] Furthermore, there may be differences in the validity of CYP2C19 typing and prasugrel efficacy between Caucasians and East Asians.[30,31] Study details are outlined in Table 1.

A 2012 Japanese meta-analysis investigated whether HPR, using the VerifyNow assay and CYP2C19 genotype, were associated with a MACE within 12 months of PCI in clopidogrel-treated patients with cardiovascular disease.[7] Eight studies involving 4,817 patients were meta-analyzed to assess the association between HPR and MACEs.[7] The mean patient age was 65 years, 74% were male, and 4,748 (99%) underwent PCI, while the remainder underwent coronary artery bypass grafting or medical management.[7] Patients received 75 mg of clopidogrel and 75 mg to 325 mg of ASA daily.[7] Overall, 2,237 (46%) patients had HPR and a significantly higher risk of experiencing a MACE compared with patients without HPR (odds ratio [OR] 3.05, 95% CI, 2.33 to 3.98, $P < 0.001$). The risk of all-cause death (OR 2.00, 95% CI, 1.22 to 3.27), heart attack (OR 3.07, 95% CI, 2.19 to 4.31), and stent thrombosis (OR 3.26, 95% CI, 1.63 to 6.51) in patients with HPR were significantly higher than those of patients without HPR.[7] The authors state that while publication bias may exist, it probably does not affect overall results because ORs in large-scale studies were consistent. HPR, assessed using

VerifyNow, is associated with MACEs in clopidogrel-treated patients with cardiovascular disease.[7]

Seven observational studies involving 5,307 patients were meta-analyzed to assess the association between the CYP2C19 genotype and MACEs.[7] The test used to determine genotype was not reported. The mean patient age was 62 years, 74% were male, 1,926 (36%) had at least one CYP2C19*2 allele and 364 (7%) of all patients had a MACE.[7] The OR of MACEs between CYP2C19*2 carriers and non-carriers showed heterogeneity (Cochran's Q test, $P = 0.01$, $I^2 = 57\%$). The OR of the seven studies ranged from 0.58 to 16.60.[7] This is a limitation of the meta-analysis, as population heterogeneity may have resulted in differences of the antiplatelet effect or patient prognosis across the study population.[7] The risk of stent thrombosis in CYP2C19*2 carriers was significantly higher than that of non-carriers (OR 2.65, 95% CI, 1.46 to 4.84).[7] While HPR, assessed using VerifyNow, was associated with increased all-cause death, myocardial infarction, and stent thrombosis, CYP2C19*2 carrier status through genotyping was associated only with an increased risk of stent thrombosis.[7]

Similarly, a meta-analysis of individual patient data demonstrated that HPR, assessed using VerifyNow, is associated with higher risks of MACEs within two years of PCI.[8] Six studies involving 3,059 patients showed those in the highest quartile for platelet reactivity had a higher rate of experiencing a MACE than those in the lowest quartile (OR 2.62, 95% CI, 1.78 to 3.87).[7] In addition, they considered a PRU value of 230 as the most effective threshold for predicting a MACE.[8] The impact of genotype on platelet function and clinical outcomes could not be assessed as genotyping was not performed.[8]

In contrast, two recently published RCTs found no independent association between platelet function and ischemic outcomes in medically treated ACS patients.[34,35] The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) substudy evaluated MACEs associated with platelet reactivity among 2,564 patients with ACS who were treated with clopidogrel or prasugrel.[34] At 30 months, no significant difference was noted between groups as prasugrel recipients had 160 MACEs, while clopidogrel recipients had 180 events ($P = 0.29$).[34]

The ARCTIC study found no significant improvements in MACEs with platelet function testing and antiplatelet treatment adjustment following coronary stenting compared with standard antiplatelet therapy without monitoring.[35] MACEs occurred in 34% of patients who were phenotyped compared with 31% of patients who received standard antiplatelet therapy (HR 1.13, 95% CI, 0.98 to 1.29; $P = 0.10$).[35] Stent thrombosis or urgent revascularization occurred in 4.9% of phenotyped patients and 4.6% of standard treated patients (HR 1.06, 95% CI, 0.74 to 1.52; $P = 0.77$).[35] The ARCTIC study authors concluded that the data does not support routine use of platelet function testing in patients undergoing coronary stenting.[35]

The Agency for Healthcare Research and Quality is currently conducting a systematic review and meta-analysis to evaluate the association between LOF CYP2C19 variants and increased risk of MACEs based on genotypic and phenotypic testing.[36]

There are currently three ongoing RCTs using the SPARTAN RX to guide treatment after PCI,[37-39] and at least three RCTs using the VerifyNow phenotyping test to monitor oral antiplatelet therapy.[40-42]

Adverse Effects

No clinical adverse ischemic outcomes, such as heart attack or stroke, were noted in either RCT group at seven or 30 days following Spartan RX genotyping or standard care.[6] A thrombolysis in myocardial infarction (TIMI) minor bleed was seen in five (6%) of 91 Spartan RX patients compared with two (2%) of 96 standard therapy patients ($P = 0.27$).[6] A TIMI major bleed occurred in two (2.2%) of Spartan RX patients and one (1%) standard therapy patient ($P = 0.61$). One of the patients in the Spartan RX group who had a TIMI major bleed was receiving clopidogrel.[6]

Neither of the meta-analyses evaluating HPR, using VerifyNow, reported additional adverse events other than the primary outcomes of interest.[7,8] Neither meta-analysis reported any information regarding adverse events related to testing, such as infection at the collection site.

Administration and Cost

The Spartan RX CYP219 POC assay is indicated to aid clinicians in guiding antiplatelet therapy.[17] A nurse acquires a buccal swab from the patient, inserts it into a cartridge, adds a reaction solution, and genotype results

are available within 60 minutes.[6] According to the manufacturer, the Spartan RX POC DNA testing system costs US$15,000 and the test kits cost US$200 per test.[17] The device can be set up in an area that is close to the patient where it can be started and run within four minutes of collecting a patient sample.[17] Sample collection kits must be stored between –80°C and –15°C in a non–frost-free freezer.[17]

The VerifyNow POC test can be conducted in the catheterization lab. Approximately 20% of cases likely undergo testing twice to evaluate a response to a change in therapy.[43] Within an hour of blood collection, two millilitre samples of whole blood are anticoagulated with sodium citrate, inserted into a disposable P2Y12 cartridge containing fibrinogen-coated beads, a platelet agonist, a buffer, and preservative. As agglutination occurs following stimulation of the platelet agonist, light transmission through the sample increases and is converted into PRUs and the per cent inhibition using an algorithm.[16] Patients with > 240 PRUs and less than 20% to 30% inhibition are considered clopidogrel non-responders. The VerifyNow instrument costs US$8,000 and test kits cost US$60 per test.[44]

Concurrent Developments

The Verigene CYP2C19 (CLO+) Nucleic Acid test (Nanosphere, Northbrook IL) identifies a patient's CYP2C19*2 and *3 and *17 genotypes directly from a whole blood sample in approximately 2.5 hours.[16,45] According to validity tests, Verigene POC genotyping was 100% concordant with TaqMan systems.[16]

PlaCor PRT (PlaCor Inc., Plymouth, MN) uses blood from a finger prick to measure platelet reactivity based on high shear conditions within a disposable cartridge.[16] Phenotype results are available in less than 10 minutes and correlate with whole blood aggregometry.[16]

Rate of Technology Diffusion

An FDA warning has increased awareness about the diminished effectiveness of clopidogrel in LOF CYP2C19 carriers and identified the need for personalized antiplatelet therapy through genotyping.[5,46] While some hospitals initiated CYP2C19 genotyping and prescribe alternative antiplatelet drugs for CYP2C19*2 carrying patients undergoing PCI, prospective randomized trials evaluating patient outcomes are few.[46] One proof-of-concept study involving 200 patients showed that Spartan RX genotyping can be performed at the bedside after PCI, and reported that treatment of identified CYP2C19*2 carriers with prasugrel reduces HPR, compared to treatment with clopidogrel.[6] The ongoing Genotyping Infarct Patients to Adjust and Normalize Thienopyridine Treatment (GIANT study) is expected to determine whether genotyping-guided antiplatelet selection improves outcomes for PCI patients.[24] The Thrombocyte Activity Reassessment and GEnoTyping for PCI (TARGET-PCI) trial combined genotyping and phenotyping to provide greater certainty to guide and monitor antiplatelet therapy, but has been stopped based on neutral results.[24] Further studies are needed to validate individual tests and determine whether genotyping and/or phenotyping for screening and monitoring will become widely used in clinical practice.[14,16]

Implementation Issues

While POC genotyping can be performed at any time and in the absence of clopidogrel, LOF CYP2C19 alleles account only for approximately 5% to 12% of observed variability in responsiveness.[16,46] Other genes and factors such as ABCB-1, PON-1, esterase, diet, smoking, and proton pump inhibitors may influence the responsiveness of clopidogrel.[16,22]In contrast to phenotyping, the results of genotyping do not vary over time and they have the potential to guide other types of drug therapy.[46] While there is an association between CYP2C19 genotype and clopidogrel responsiveness, there remains uncertainty regarding the association between genotype and cardiovascular events.[47,48]

While VerifyNow produces POC phenotype results that correlate with results obtained using standard laboratory light transmission aggregometry, without the need for sample preparation, access, or special training; hematocrit and platelet count ranges are moderately reproducible.[4,18] Studies assessing the efficacy of POC assays have shown a good correlation with laboratory methods, but no single test has been shown to consistently correlate with post-procedural outcomes.[18,49,50] Further trials are needed to define optimal thresholds of inhibition to identify non-responders and guide therapy.[18,51] Adequately powered RCTs incorporating data from POC genotyping and phenotyping would help in determining the role of such testing in the management of patients on antiplatelet therapy.[18] While the ARCTIC study concluded that platelet function testing should not be performed routinely in patients undergoing coronary stenting, it may play a role in identifying patients at high risk of a major bleeding event or stent thrombosis.

Table 1: Spartan RX and VerifyNow Identification of Poor Clopidogrel Metabolizers				
Technology	**Spartan RX**	**VerifyNow**		
Study	Roberts 2012 et al.[6]	Yamaguchi 2012 et al.[7]		Brar et al. 2011[8]
Design	RCT	SR, MA (2 RCTs, 6 observational studies for MACEs; 7 observational studies for STh)		MA (patient-level data)
Inclusion Criteria	NSTEMI or CAD undergoing PCI	Clopidogrel-treated patients with cardiovascular disease, MACEs within 12 months, VerifyNow phenotype, CYP2C19 genotype, (method not reported), observational study or RCT.		Clopidogrel-treated patients after PCI, MACEs, ≥ 30-day follow-up, VerifyNow phenotype.
Intervention	Spartan RX genotyping (N = 97), 23 CYP2C19*2 carriers received prasugrel; 74 non-carriers received clopidogrel.	VerifyNow phenotyping (8 studies); genotyping (7 studies).		VerifyNow phenotyping (6 studies).
Comparator/Comparison	Standard treatment with clopidogrel (N = 98)	Carrier versus non-carrier		Reduced platelet reactivity (normal) versus HPR.
Population Completed/Randomized	N = 187 Clopidogrel bolus, Undergoing PCI 187/200	Phenotyping N = 4,817 NA	CYP2C19*2 N = 5,307 NA	N = 3,059 Clopidogrel-treated post PCI NA
Outcome	Proportion of CYP2C19*2 carriers with a PRU ≥ 234 after 7 days of therapy.	MACEs: all-cause death, MI, STh, stroke, target vessel revascularization within 12 months of PCI.		MACEs: death, MI, STh, at least 30-day follow-up (outcomes stratified based on quartile [Q] with Q1 representing the patients with the lowest on-treatment platelet reactivity and Q4 the highest).
Duration	30 days	NA		NA
Efficacy	CYP2C19*2 allele: 23/91 (25%) of genotyped patients and 23/96 (24%) of standard patients. Sensitivity: 100% (95% CI, 92.3 to 100); specificity: 99.3% (95% CI, 96.3 to 100). 7-day HPR: 0/23 (0%) of carriers in prasugrel group; 7/23 (30%) in standard treatment group (P = 0.0092).	HPR phenotype and MACEs: Patients with HPR had significantly higher odds of MACE than those without HPR (OR 3.05, 95% CI, 2.33 to 3.98) All-cause death (OR 2.00, 95% CI, 1.22 to 3.27) MI (OR 3.07, 95% CI, 2.19 to 4.31) STh (OR 3.26, 95% CI, 1.63 to 6.51) Stroke (OR 1.99, 95% CI, 0.74 to 5.31) Genotype and MACEs: 1,926 (36%) patients with ≥ 1 CYP2C19*2 allele The odds of STh in carriers was significantly higher than in non-carriers (OR 2.65, 95% CI, 1.46 to 4.48)		Q1 85 ± 37 PRUs Q2: 171 ± 19 PRUs Q3: 230 ± 17 PRUs Q4:301 ± 33 PRUs; P < 0.001. MACE HR for Q2, Q3, and Q4 > Q1 (referent) Q2 HR: 2.62, 95% CI, 1.77 to 3.87. Q3 HR: 1.13, 95% CI, 0.72 to 1.78. Q4 HR: 1.82, 95% CI, 1.77 to 3.87; P < 0.001. Groups were stratified as above or below 230 PRUs. Death HR: 1.66; 95% CI, 1.04 to 2.68; P = 0.04.

Table 1: Spartan RX and VerifyNow Identification of Poor Clopidogrel Metabolizers			
Technology	**Spartan RX**	**VerifyNow**	
		HPR using VerifyNow identifies patients at risk of a MACE, while CYP2C19*2 carrier status was associated with STh.	STh HR: 3.11, 95% CI, 1.50 to 6.46; $P = 0.002$. MI HR: 2.04; 95% CI, 1.51 to 2.76; $P < 0.001$).
Safety	TIMI minor bleed: 5/91 (6%) of genotyped patients, 2/96 (2%), standard patients ($P = 0.2693$). TIMI major bleed 2/91 (2%) of genotyped patients, 1/96 (1%) standard treatment patients.	Bleeding events NR	Bleeding events NR.
Limitations Possible Bias	Surrogate end points, small sample size.	Publication bias may exist but OR of 2 large-scale trials consistent; heterogeneous population.	Lack of genotype and bleeding events data.

CAD = coronary artery disease; CI = confidence interval; DES = drug-eluting stent; HPR = high on-treatment platelet reactivity; HR = hazard ratio; MA = meta-analysis; MACE = major adverse cardiovascular event; MI = myocardial infarction; NA = not applicable; NR = no reported; NSTEMI = non-ST-segment elevation myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PRU = P2Y12 reaction unit; RCT = randomized controlled trial; SR = systematic review; STh = stent thrombosis; TIMI = thrombolysis in myocardial infarction.

References

1. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 2010 Oct 27;304(16):1821-30.
2. Scott SA, Sangkuhl K, Gardner EE, Stein CM, Hulot JS, Johnson JA, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther [Internet]. 2011 Aug [cited 2012 Sep 27];90(2):328-32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3234301
3. Mallouk N, Labruyere C, Reny JL, Chapelle C, Piot M, Fontana P, et al. Prevalence of poor biological response to clopidogrel: a systematic review. Thromb Haemost. 2012 Mar;107(3):494-506.
4. Bouman HJ, Harmsze AM, van Werkum JW, Breet NJ, Bergmeijer TO, Ten CH, et al. Variability in on-treatment platelet reactivity explained by CYP2C19*2 genotype is modest in clopidogrel pretreated patients undergoing coronary stenting. Heart. 2011 Aug;97(15):1239-44.
5. Postmarket Drug Safety Information for Patients and Providers [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2012. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug; 2010 Mar 12 [cited 2012 Sep 20]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm
6. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet. 2012 May 5;379(9827):1705-11.
7. Yamaguchi Y, Abe T, Sato Y, Matsubara Y, Moriki T, Murata M. Effects of VerifyNow P2Y12 test and CYP2C19*2 testing on clinical outcomes of patients with cardiovascular disease: A systematic review and meta-analysis. Platelets. 2012 Jul 3.
8. Brar SS, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim HS, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. J Am Coll Cardiol. 2011 Nov 1;58(19):1945-54.
9. PRWeb [Internet]. Herndon (VA): Vocus, Inc.; 2012. Spartan Bioscience achieves ISO 13485 Certification for Manufacturing of first point-of-care DNA testing system; 2012 Aug 14 [cited 2012 Oct 2]. Available from: http://www.prweb.com/releases/2012/8/prweb9788743.htm

10. Medical Devices Active Licence Listing (MDALL) [Internet]. Ottawa: Health Canada. Verifynow PRUtest; Licence no. 89108; 2012 Sep 19 [cited 2012 Sep 20]. Available from: http://www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic-eng.php

11. VerifyNow [Internet]. San Diego: Accumetrics; 2012. Press release, Accumetrics' VerifyNow System receives Health Canada license for clinical use; 2012 Aug 8 [cited 2012 Oct 2]. Available from: http://www.accumetrics.com/investors-media/press-releases/79-prutest-comes-to-canada

12. Love MP, Bergin P, Paddock V, Rose B, Adams L, Callaghan M, et al. Atlantic Canadian guidelines for the acute use of oral anti--platelet therapy in patients with acute coronary syndromes [Internet]. Saint John (NB): Atlantic Cardiovascular Society; 2012 Apr 14. [cited 2012 Sep 27]. Available from: http://ac-society.org/cms/sites/default/files/AAPI%20Guidelines_0.pdf

13. Ned Mmsc Phd RM. Genetic testing for CYP450 polymorphisms to predict response to clopidogrel: current evidence and test availability. Application: pharmacogenomics. PLoS Curr [Internet]. 2010 [cited 2012 Sep 7];2. Available from: http://pubmedcentralcanada.ca/articlerender.cgi?artid=1714093&report=printable

14. Singh M, Shah T, Adigopula S, Molnar J, Ahmed A, Khosla S, et al. CYP2C19*2/ABCB1-C3435T polymorphism and risk of cardiovascular events in coronary artery disease patients on clopidogrel: Is clinical testing helpful? Indian Heart J. 2012 Jul;64(4):341-52.

15. Sofi F, Giusti B, Marcucci R, Gori AM, Abbate R, Gensini GF. Cytochrome P450 2C19*2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. Pharmacogenomics J. 2011 Jun;11(3):199-206.

16. Harrison P. Advances in the monitoring of anti-P2Y(12) therapy. Platelets. 2012 Aug 23;23(7):510-25.

17. Published studies for Spartan RX CYP2C19 point-of-care DNA testing system. Ottawa: Spartan Bioscience Inc.; 2012.

18. Patni R, Nawaz MA, Macys A, Chan KMJ, Punjabi P. Assessment of Platelet Function in Patients on Antiplatelet Therapy Undergoing Cardiac Surgery: A Review. Heart Lung and Circulation. 2012;21(8):456-62.

19. Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. Circulation [Internet]. 2009 Jan 20 [cited 2012 Sep 17];119(2):237-42. Available from: http://circ.ahajournals.org/content/119/2/237.full.pdf+html

20. Lordkipanidze M, Pharand C, Nguyen TA, Schampaert E, Palisaitis DA, Diodati JG. Comparison of four tests to assess inhibition of platelet function by clopidogrel in stable coronary artery disease patients. Eur Heart J [Internet]. 2008 Dec [cited 2012 Nov 29];29(23):2877-85. Available from: http://eurheartj.oxfordjournals.org/content/29/23/2877.full.pdf+html

21. Kanichay R, Wilsdon T, Connolly S, Sauri L. The economic and societal burden of acute coronary syndrome in Canada [Internet]. London: Charles River Associates; 2010 Nov. [cited 2012 Oct 2]. Available from: http://www.crai.com/uploadedFiles/RELATING_MATERIALS/Publications/files/CRA%20%20Methodology%20Report_131210%20(2).pdf

22. Sibbing D, Bernlochner I, Kastrati A, Pare G, Eikelboom JW. Current evidence for genetic testing in clopidogrel-treated patients undergoing coronary stenting. Circ Cardiovasc Interv. 2011 Oct 1;4(5):505-13.

23. Gurbel PA, Tantry US. Do platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents?: platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents. Circulation. 2012 Mar 13;125(10):1276-87.

24. Cuisset T, Frere C, Poyet R, Quilici J, Gaborit B, Bali L, et al. Clopidogrel response: head-to-head comparison of different platelet assays to identify clopidogrel non responder patients after coronary stenting. Arch Cardiovasc Dis. 2010 Jan;103(1):39-45.

25. Michelson AD. Methods for the measurement of platelet function. Am J Cardiol. 2009 Feb 2;103(3 Suppl):20A-6A.

26. Gremmel T, Kopp CW, Seidinger D, Koppensteiner R, Panzer S, Sunder-Plassmann R, et al. Differential impact of cytochrome 2C9 allelic variants on clopidogrel-mediated platelet inhibition determined by five different platelet function tests. Int J Cardiol. 2011 Nov 8.

27. Paniccia R, Antonucci E, Maggini N, Miranda M, Gori AM, Marcucci R, et al. Comparison of methods for monitoring residual platelet reactivity after clopidogrel by point-of-care tests on whole blood in high-risk patients. Thromb Haemost. 2010 Aug;104(2):287-92.

28. Gaglia MA, Torguson R, Pakala R, Xue Z, Sardi G, Suddath WO, et al. Correlation between light transmission aggregometry, VerifyNow P2Y12, and VASP-P platelet reactivity assays following percutaneous coronary intervention. J Interv Cardiol. 2011 Dec;24(6):529-34.

29. Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol. 2010 Sep 14;56(12):919-33.

30. Morita H, Nagai R. Pharmacogenetic guidance for antiplatelet treatment. Lancet. 2012 Aug 25;380(9843):725-6.

31. Jeong YH, Bliden KP, Park Y, Tantry US, Gurbel PA. Pharmacogenetic guidance for antiplatelet treatment. Lancet. 2012 Aug 25;380(9843):725-6.

32. Alexopoulos D, Dimitropoulos G, Davlouros P, Xanthopoulou I, Kassimis G, Stavrou EF, et al. Prasugrel overcomes high on-clopidogrel platelet reactivity post-stenting more effectively than high-dose (150-mg) clopidogrel: the importance of CYP2C19*2 genotyping. JACC Cardiovasc Interv. 2011 Apr;4(4):403-10.

33. Canadian Agency for Drugs and Technologies in Health. Grey matters: a practical search tool for evidence-based medicine [Internet]. Ottawa: The Agency; 2008 Apr. [cited 2012 Jan 4]. Available from: http://www.cadth.ca/media/pdf/Grey-Matters_A-Practical-Search-Tool-for-Evidence-Based-Medicine.doc Updated 2011 Jan.

34. Gurbel PA, Erlinge D, Ohman EM, Neely B, Neely M, Goodman SG, et al. Platelet Function During Extended Prasugrel and Clopidogrel Therapy for Patients With ACS Treated Without Revascularization: The TRILOGY ACS Platelet Function Substudy. JAMA. 2012 Nov 7;308(17):1785-94.

35. Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S. Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting. N Engl J Med. 2012 Nov 29;367(22):2100-9.

36. Testing of CYP2C19 variants and platelet reactivity for guiding antiplatelet treatment [draft] [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2012. [cited 2012 Sep 18].

    Available from: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=854

37. Clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01452139, Pharmacogenetic approach to anti-platelet therapy for the treatment of ST-segment elevation myocardial Infarction (STEMI) (RAPID STEMI); 2012 Jul 5 [cited 2013 Mar 22]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01452139?term=01452139&rank=1

38. Clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01742117, Tailored antiplatelet therapy following PCI (TAILOR-PCI); 2012 Dec 3 [cited 2013 Mar 22]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01742117?term=01742117&rank=1

39. Clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01477775, Customized choice of oral P2Y12 receptor blocker (GENE-MATRIX); 2012 Nov 5 [cited 2013 Mar 22]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01477775?term=01477775&rank=1

40. Clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01538446, Tailored antiplatelet therapy versus recommended dose of Prasugrel (ANTARCTIC); 2012 Jun 21 [cited 2013 Mar 22]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01538446?term=verifynow+accumetrics&rank=17

41. Clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT00827411, Double randomization of a monitoring adjusted antiplatelet treatment versus a common antiplatelet treatment for DES implantation, and interruption versus continuation of double antiplatelet therapy (ARCTIC); 2012 Sep 6 [cited 2013 Mar 22]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00827411?term=verifynow+accumetrics&rank=12

42. Clinicaltrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01062516, Influence of esomeprazole on antiplatelet action of clopidogrel associated with aspirin; 2010 Oct 2 [cited 2013 Mar 22]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01062516?term=verifynow+accumetrics&rank=14

43. Use of the VerifyNow point of care test to detect non-responsiveness to clopidogrel and aspirin [Internet]. Montreal: McGill University Health Centre; 2011 Jul 19. Report No.: 53. [cited 2012 Sep 14]. Available from: http://www.mcgill.ca/tau/sites/mcgill.ca.tau/files/muhc_tau_2011_53_verifynow_a.pdf

44. Pollack A. Eli Lilly pitches blood test to aid sales of blood thinner [Internet]. In: Prescriptions Blog. New York: The New York Times; 2010 Jul 12 [cited 2012 Oct 10]. Available from: http://prescriptions.blogs.nytimes.com/2010/07/12/eli-lilly-pitches-blood-test-to-aid-sales-of-blood-thinner/

45. Nanosphere [Internet]. Northbrook (IL): Nanosphere, Inc; 2012. CYP2C19; 2012 [cited 2012 Sep 20]. Available from: http://www.nanosphere.us/product/cyp2c19-0

46. Trenk D, Zolk O, Fromm MF, Neumann FJ, Hochholzer W. Personalizing antiplatelet therapy with clopidogrel. Clin Pharmacol Ther. 2012 Oct;92(4):476-85.

47. Bauer T, Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of CYP2C19 variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. BMJ [Internet]. 2011 Aug 4 [cited 2012 Oct 1];343:d4588. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191560/pdf/bmj.d4588.pdf

48. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA [Internet]. 2011 Dec 28;306(24):2704-14.

49. Woo KS, Kim BR, Kim JE, Goh RY, Yu LH, Kim MH, et al. Determination of the prevalence of aspirin and clopidogrel resistances in patients with coronary artery disease by using various platelet-function tests. Korean J Lab Med [Internet]. 2010 Oct [cited 2012 Sep 7];30(5):460-8. Available from: http://pdf.medrang.co.kr/Kjlm/2010/030/Kjlm030-05-02.pdf

50. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA. 2010 Feb 24;303(8):754-62.

51. Godino C, Mendolicchio L, Figini F, Latib A, Sharp AS, Cosgrave J, et al. Comparison of VerifyNow-P2Y12 test and Flow Cytometry for monitoring individual platelet response to clopidogrel. What is the cut-off value for identifying patients who are low responders to clopidogrel therapy? Thromb J [Internet]. 2009 [cited 2012 Sep 7];7(4). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683811/pdf/1477-9560-7-4.pdf

Cite as: McGahan L. *Point-of-Care Phenotypic and Genetic Testing for Patients with Acute Coronary Syndrome* [Issues in emerging health technologies, Issue 123]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2013.

CADTH thanks the external reviewer who kindly provided comments on an earlier draft of this bulletin.

****

ISSN: 1488-6324 (online)