What hematologists should know about VerifyNow

Hematology fellows conference 12/13/2013
Presenter: Christina Fitzmaurice, MD, MPH
Discussant: Daniel Sabath, MD, PhD
HMC consult patient

• 54 yo woman admitted with SAH 2/2 ICA aneurysm
• Underwent stent placement by IR
• Pre-procedurally clopidogrel 150 mg and aspirin 325 mg were started
• Follow up angiogram on day 3 showed almost complete thrombosis of the aneurysm
HMC consult patient

• Repeat angiogram on day 7 showed recanalization of aneurysm
• Concern that patient has too much platelet inhibition
• VerifyNow was ordered
• Clopidogrel changed to qod
• Hematology was consulted
Verify WHAT???

1. What does it measure?
2. Is it predictive of bleeding or thrombosis?
3. Can it be used to adjust platelet inhibitors?
1. What does VerifyNow measure?
VerifyNow

• Measures platelet response to major antiplatelet agents (P2Y12 inhibitors, aspirin, GP IIb/IIIa inhibitors)
• Measures platelet reactivity by the rate and extent of light changes in whole blood as platelets aggregate
VerifyNow P2Y12 assay

Chamber 1: TRAP to determine baseline platelet function (agonist for platelet activation independent of aspirin and clopidogrel)

Chamber 2: ADP and Prostaglandin E1 (PGE1 added to suppress ADP activation through P2Y1-receptor)
P2Y12 assay

- Results reported as P2Y12 reaction units (PRU)
- PRU <194 has 98% specificity and 72% sensitivity that effect is due to drug
- Other cutoffs have been used
HMC patient

• PRU=5 (repeated twice)
Clopidogrel metabolism

Influence of genotype on clopidogrel metabolism

- Different isotypes of CYP2C19 have been associated with response:
  - CYP2C19*1 wildtype
  - CYP2C19*2 loss of function
  - CYP2C19*17 gain of function

- 20-40% of patients are non-responders or poor-responders to clopidogrel

Correlation between PRU and genotype

Cytochrome P450 2C19 Genotype (performed at Mayo) [Code: 415]

Cross References
CYP, CYP2C19, Clopidogrel, Plavix

Specimen Type
whole blood

CPOE Name
Order Using 'Lab Undefined Order'

General Information

Note:
1. Bone marrow and liver transplants will interfere with testing. Call Mayo Medical Laboratories at 800-533-1710 or 507-266-5700 for instructions.
2. Recent transfusions with non-leukocyte-reduced blood will interfere with testing. Wait 4 to 6 weeks until transfused cells have left the patient's circulation before drawing the patient's blood specimen for genotype testing.
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)
Clinical pharmacogenetics implementation consortium guidelines 2013

UM: Ultrarapid metabolizer
EM: Extensive metabolizer
IM: Intermediate metabolizer
PM: Poor metabolizer

Benefit of platelet function testing

- Genetics (e.g. CYP2C19)
- Non-compliance
- Concomitant diseases (e.g. diabetes)
- Concomitant medications (e.g. PPIs, warfarin)

Platelet inhibitor effect (e.g. Clopidogrel)

Platelet function testing measures pharmacodynamic effect
2. Are *VerifyNow* results predictive of bleeding or thrombosis?
VerifyNow predicting bleeding or thromboses after cerebral aneurysm stenting

- Retrospective analysis of 48 patients after cerebral aneurysm stenting
- Preoperative dual antiplatelet therapy started and adjusted based on PRU

<table>
<thead>
<tr>
<th></th>
<th>Thromboembolic complications</th>
<th>Hemorrhagic complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRU&lt;60 (n=13)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>PRU 60–200 (n=32)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PRU&gt;240 (n=3)</td>
<td>2</td>
<td>1</td>
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Protocol to adjust antiplatelet therapy in neuro-interventional procedures

<table>
<thead>
<tr>
<th>Initiation of DAT</th>
<th>17 Days before procedure</th>
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<tbody>
<tr>
<td>Target P2Y12 receptor inhibition</td>
<td>PRU 60–240</td>
</tr>
<tr>
<td>Target aspirin inhibition</td>
<td>≥50%</td>
</tr>
<tr>
<td>Initial aspirin dose</td>
<td>81 mg daily</td>
</tr>
<tr>
<td>Initial clopidogrel dose</td>
<td>75 mg daily</td>
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<tr>
<td>Preprocedural aspirin inhibition testing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>After ten 81-mg aspirin doses or the day before procedure</td>
</tr>
<tr>
<td>Preprocedural P2Y12 receptor-inhibition testing</td>
<td>After ten 75-mg clopidogrel doses and the day before procedure</td>
</tr>
<tr>
<td>Hyporesponse to aspirin (&lt; 50% inhibition)</td>
<td>Aspirin, 325 mg daily</td>
</tr>
<tr>
<td>Clopidogrel dosing schedules</td>
<td>0) 150 mg daily&lt;sup&gt;b&lt;/sup&gt;; 1) 75 mg daily; 2) 75 mg QOD; 3) 75 mg Q3D; 4) 75 mg Q5D; 5) 75 mg Q7D; 6) 75 mg PRN to reach PRU 60</td>
</tr>
<tr>
<td>Hyporesponse to clopidogrel (PRU &gt; 240)</td>
<td>Go back 1 step in clopidogrel dosing schedule</td>
</tr>
<tr>
<td>Hyper-response to clopidogrel (PRU &lt; 60)</td>
<td>PRU 40–59: advance 1 step in clopidogrel dosing schedule</td>
</tr>
<tr>
<td>Reschedule procedure</td>
<td>PRU 10–39: advance 2 steps in clopidogrel dosing schedule</td>
</tr>
<tr>
<td>Postprocedural P2Y12 receptor-inhibition testing</td>
<td>PRU &lt; 10: advance 3 steps in clopidogrel dosing schedule</td>
</tr>
<tr>
<td>PRU &lt; 60 or &gt;240 on the day before procedure</td>
<td>7–10 and 30–40 Days after any clopidogrel dose adjustment, after changes to medications that may affect clopidogrel metabolism, or at any time if symptomatic with abnormal bruising/bleeding or focal neurologic deficits</td>
</tr>
</tbody>
</table>

<sup>a</sup> or PRU > 240 can also be used as the basis for adjusting aspirin and/or clopidogrel therapy.

<sup>b</sup> For oral aspirin, the adult daily dose is 150 mg for those >65 years of age and >100 mg for those <65 years of age.
ADAPT-DES study

“Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents”

- Prospective, multicenter registry of 8665 patients
- Patients with coronary DES on aspirin and clopidogrel
- Platelet reactivity measured with VerifyNow

GRAVITAS TRIAL

“Gauging Responsiveness with a VerifyNow assay- Impact on Thrombosis And Safety”

- RCT of 2214 patients after PCI with PRU>235
- Randomized to either standard dose clopidogrel or repeated loading with 150 mg maintenance dose
- Composite endpoint of death, MI, stent thrombosis

GRAVITAS TRIAL

• Underpowered study
• Even patients with high dose clopidogrel did not achieve PRU<208
• Switching to a second generation P2Y12 inhibitor might be needed
TRIGGER-PCI

“Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel”

- RCT of 423 elective PCI patients with PRU>208
- Randomized to prasugrel or clopidogrel

TRIGGER-PCI

CV death, MI, stroke, or rehospitalization for cardiac ischemic event
TRIGGER-PCI

Risk of bleeding

Hazard Ratio 1.517
(95% CI, 0.428-5.376)
p=0.516

Event rate, %

Days from randomization

Number at Risk
Prasugrel 207 193 177 164 149 137 66 3 2
Clopidogrel 206 195 179 168 154 140 81 1 0
TRIGGER-PCI

- Terminated prematurely due to lower rate of ischemic events
- Possible selection bias (30% of patients declined randomization)
ARMYDA-BLEEDS

“Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Bleeding Study”

- Prospective study of 310 consecutive clopidogrel-treated patients who underwent PCI
- PRU value ≤189 predicts 30-day bleeding (sensitivity 87%, specificity 70%)

Patti et al: Am J Cardiol. 2011 Apr 1;107(7):995-1000
12.4. Antithrombotic Therapy
The optimum choice of P2Y$_{12}$ receptor inhibitor and anticoagulant agents for patients with STEMI can be challenging. Individual genetic variability in drug absorption, metabolism, and effectiveness has been highlighted by the experience with clopidogrel in patients with ACS (285,637). The risks of bleeding also may vary across racial and ethnic groups (12). The roles of platelet function testing and genetic screening for clopidogrel metabolism in the acute phase of STEMI care are uncertain (289), especially with the availability of alternative P2Y$_{12}$ receptor inhibitors. More information specific to patients with STEMI is needed with regard to the use of prasugrel, ticagrelor, novel factor Xa and IIa antagonists, and platelet protease–activated receptor 1 antagonists (638,639).
Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on P2Y12 receptor inhibitor therapy may be considered if results of testing may alter management.

*Level of Evidence: B, Class IIb*
E. Monitoring Platelet Function

Class IIb Recommendation

a. Because of their high negative predictive value, preoperative point-of-care testing to assess bleeding risk **may be useful** in identifying patients with high residual platelet reactivity after usual doses of antiplatelet drugs, and who can undergo operation without elevated bleeding risk. (Level of evidence B)

b. Point-of-care testing to assess perioperative platelet function **may be useful** in limiting blood transfusion. (Level of evidence B)

Conclusion

• Platelet function testing may be most appropriate in high-risk clopidogrel-treated patients with current or prior ACS or history of stent thrombosis
• Newer antiplatelet agents can be considered in patients with high platelet reactivity
• Evidence is sparse for using PRU to adjust dosing of antiplatelet agents
• Few data in patients undergoing neurointerventional procedures
Thank you