How does hemostasis occur and when is it not desired?

Adapted from Ferguson JJ et al. Antiplatelet Therapy in Clinical Practice. 2000:15-35
When is “Normal” Hemostasis not Desirable?

How can hemostasis be inhibited in at-risk individuals?

FDA Approved Oral Antiplatelet Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Half-Life</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Salicylates</td>
<td>Irreversible inactivation of COX-1</td>
<td>5-8 hours</td>
<td>Pain, fever, inflammation, prevention of MI, &amp; stroke</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Thienopyridine</td>
<td>P2Y12 receptor antagonist</td>
<td>24 hours</td>
<td>Stroke prevention &amp; steal thrombosis</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Thienopyridine</td>
<td>P2Y12 receptor antagonist</td>
<td>8 hours</td>
<td>Prevention of ischemic events in patients with: History of MI, stroke, or PAD and in ACS patients with U/A/NSTEMI or STEMI</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Thienopyridine</td>
<td>P2Y12 receptor antagonist</td>
<td>7 hours</td>
<td>Prevention of ischemic events in ACS patients managed with PCI</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Cyclopentyl-triazolopyrimidine</td>
<td>P2Y12 receptor antagonist</td>
<td>7 hours</td>
<td>Prevention of ischemic events in patients with ACS</td>
</tr>
</tbody>
</table>

ACS=Acute coronary syndrome, COX-1=Cyclooxygenase-1, MI=Myocardial infarction; NSTEMI=Non-ST-segment elevation myocardial infarction, PAD=Peripheral artery disease, PCI=Percutaneous coronary intervention, STEMI=ST-segment elevation myocardial infarction, UA=Unstable angina

Antagonizing the Platelet Side of Hemostasis

What are the benefits and limitations of using antiplatelet therapy in at-risk individuals?

What is the Efficacy of Aspirin in Secondary Prevention?

Effect of antiplatelet treatment* on vascular events**

<table>
<thead>
<tr>
<th>Category</th>
<th>% Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Acute CVA</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td></td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td></td>
</tr>
<tr>
<td>Other high risk</td>
<td></td>
</tr>
<tr>
<td>CVD (e.g. unstable angina, heart failure)</td>
<td></td>
</tr>
<tr>
<td>PAD (e.g. intermittent claudication)</td>
<td></td>
</tr>
<tr>
<td>High risk of embolism (e.g. Afib)</td>
<td></td>
</tr>
<tr>
<td>Other (e.g. DM)</td>
<td></td>
</tr>
<tr>
<td>All trials</td>
<td></td>
</tr>
</tbody>
</table>

*Aspirin was the predominant antiplatelet agent studied. **Include MI, stroke, or death

Antithrombotic Trialist Collaboration. BMJ 2002;324:71-86

<table>
<thead>
<tr>
<th>Category</th>
<th>% Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>1.0</td>
</tr>
<tr>
<td>Acute CVA</td>
<td>0.5</td>
</tr>
<tr>
<td>Prior MI</td>
<td>0.0</td>
</tr>
<tr>
<td>Prior CVA/TIA</td>
<td>1.5</td>
</tr>
<tr>
<td>Other high risk</td>
<td>2.0</td>
</tr>
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<td>CVD (e.g. unstable angina, heart failure)</td>
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</tr>
</tbody>
</table>

What is the Efficacy of Dual Antiplatelet Therapy?

Rates of Ischemic Events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>CVD, MI, CVA</td>
<td>9.3%</td>
<td>11.4%</td>
<td>&lt;0.001</td>
<td>48</td>
</tr>
<tr>
<td>CREDO</td>
<td>CVD, MI, CVA</td>
<td>8.5%</td>
<td>11.5%</td>
<td>0.02</td>
<td>33</td>
</tr>
<tr>
<td>COMMIT</td>
<td>CVD, MI, CVA</td>
<td>9.2%</td>
<td>10.1%</td>
<td>0.002</td>
<td>111</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>CVD, MI, CVA</td>
<td>6.8%</td>
<td>7.3%</td>
<td>0.22</td>
<td>--</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>CVD, MI, CVA</td>
<td>12.1%</td>
<td>9.9%*</td>
<td>0.0004</td>
<td>45</td>
</tr>
<tr>
<td>PLATO</td>
<td>CVD, MI, CVA</td>
<td>11.7%</td>
<td>9.8%</td>
<td>&lt;0.001</td>
<td>53</td>
</tr>
</tbody>
</table>

What are the Risks of Antiplatelet Therapy?

Rates of Major Bleeding

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aspirin Dose</th>
<th>A + C</th>
<th>A + P (T)</th>
<th>P-value</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>75-325 mg</td>
<td>3.7%</td>
<td>2.7%</td>
<td>0.001</td>
<td>100</td>
</tr>
<tr>
<td>&lt;100 mg</td>
<td>2.6%</td>
<td>2.0%</td>
<td></td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>100-200 mg</td>
<td>3.5%</td>
<td>2.3%</td>
<td></td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>&gt;200 mg</td>
<td>4.9%</td>
<td>4.0%</td>
<td></td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>81-325 mg</td>
<td>1.2%</td>
<td>0.8%</td>
<td>0.28</td>
<td>--</td>
</tr>
<tr>
<td>COMMIT</td>
<td>162 mg</td>
<td>0.58%</td>
<td>0.53%</td>
<td>0.59</td>
<td>--</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>75-162 mg</td>
<td>1.7%</td>
<td>1.3%</td>
<td>0.09</td>
<td>--</td>
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<tr>
<td>PLATO (TIMI)**</td>
<td>75-325 mg</td>
<td>7.7%</td>
<td>7.9%</td>
<td>0.57</td>
<td>--</td>
</tr>
</tbody>
</table>

*Risks in at-risk individuals

**Effects of clopidogrel vs placebo

**Among patients not undergoing CABG, the TIMI rates of major bleeding were 2.2% (clopidogrel) vs. 2.8% (placebo), p<0.02, NNH=67

The CURE Trial Investigators. NEJM 2001;344:494-502
Steinhubl S et al. JAMA 2002;288:2411-20
Sabatine MS et al. NEJM 2005;352:1179-1189
Bhatt DL et al. NEJM 2006;354:1716-17

CVA=Stroke, CVD=Cardiovascular death, MI=Myocardial infarction, UR=Urgent revascularization
Do These Results Apply Equally to Everyone?

- Good Outcome
- Intermediate Outcome
- Bad Outcome

Outcomes from a Study

Mean Treatment Difference

What risks are associated with antiplatelet withdrawal?

Risks Associated with Aspirin Withdrawal

Prospective cohort of 1,358 patients with an acute coronary syndrome stratified by oral antiplatelet status as a non-user, prior user, or recent withdrawer*

Withdrawal of aspirin is associated with increased CV risk

Risks Associated with Clopidogrel Withdrawal

Retrospective cohort of 3,137 patients with an acute coronary syndrome treated with clopidogrel after discharge

Withdrawal of clopidogrel leads to early increased CV risk

*CVD=Cardiovascular, PCI=Percutaneous coronary intervention

Outcomes from a Study

Mean Treatment Difference

Do These Results Apply Equally to Everyone?

Outcomes from a Study

Mean Treatment Difference

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Mean Treatment Difference

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Outcomes from a Study

Mean Treatment Difference

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Outcomes from a Study

Mean Treatment Difference
**Risks Associated with Antiplatelet Withdrawal**

**Stent Thrombosis**
- Most cases (60%) occur within the first 30 days, regardless of stent type
- Stable angina
  - 30 day: 0.3-0.5%
  - 1 year: 0.6-1.7%
- ACS
  - 30 day: 1.2-3.1%
  - 1 year: 4.3-5.8%

**Perioperative Management of Antiplatelet Therapy**

**How should antiplatelet therapy be managed perioperatively?**

**What is the optimal duration of dual antiplatelet therapy?**

---

POBA = Plain old balloon angioplasty
BMS = Bare metal stent
DES = Drug eluting stent
OR = Operating room

BMS=Bare metal stent, DES=Drug eluting stent, OR=Operating room, POBA=Plain old balloon angioplasty.
Observational study of 4,666 patients undergoing percutaneous coronary intervention stratified by type of stent and self-reported use of clopidogrel at 6 and 12 months

**Longer term clopidogrel provides benefit following a DES**

DAP=Dual antiplatelet therapy, DES=Drug-eluting stent, MI=Myocardial infarction

Gwon HC et al. JAMA 2007;297:159-68

**Three separate randomized trials evaluating varied durations of dual antiplatelet therapy following PCI: EXCELLENT (6 vs 12 months), REAL-LATE/ZEST-LATE (12 vs 24 months), PRODIGY (6 vs 24 months), and RESET (3 vs 12 months)**

DAP=Dual antiplatelet therapy, PCI=Percutaneous coronary intervention


Park SJ et al. NEJM 2010;362:1374-82


Kim BK et al. JACC 2012;60:1340-8

**Three separate randomized trials evaluating varied durations of dual antiplatelet therapy following PCI: EXCELLENT (6 vs 12 months), REAL-LATE/ZEST-LATE (12 vs 24 months), PRODIGY (6 vs 24 months), and RESET (3 vs 12 months)**

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Park SJ et al. NEJM 2010;362:1374-82


Kim BK et al. JACC 2012;60:1340-8

**Should a P2Y₁₂ Inhibitor be Used for >1 Year?**

**Dual Antiplatelet Therapy (DAPT) Trial**

Drug-Eluting Stents (n=15,000)
Bare Metal Stents (n=5,000)

N=20,000 patients

Treated for 12 months with either Clopidogrel or Prasugrel in addition to aspirin

Placebo
Clopidogrel or Prasugrel for an extended 18 months of therapy

33-month follow-up

Co-primary end point: Stent thrombosis
Co-primary end point: MACCE
Major safety end point: Major bleeding

**What role do drug-drug interactions play in contributing to variance in response to antithrombotic therapy?**
Assessment of platelet inhibition among a group of patients treated each morning with aspirin (81 mg) administered two hours before ibuprofen (400 mg) and the same medications administered in the reverse order.

Ibuprofen competitively inhibits platelet inhibition by aspirin.

Catella-Lawson F et al. NEJM 2001;345:1809-17

Retrospective cohort of 8,205 patients after an ACS

Survival free of Composite CV Events

Bhatt DL et al. NEJM 2010;363:1909-1917

Is there variability in how individuals respond to antiplatelet therapy?
**Do These Results Apply Equally to Everyone?**

Outcomes from a Study

Mean Treatment Difference

Risk Stratification

---

**There Exists Variability in Response to Aspirin**

Assessment of platelet responsiveness among 131 individuals with coronary artery disease treated with low dose (75 mg) enteric coated aspirin

*All cases of aspirin nonresponsiveness were eradicated by exogenous higher dose aspirin*

Maree AO et al. JACC 2005;46:1258-63

---

**There Exists Variability in Response to Clopidogrel**

Assessment of ex vivo platelet aggregation among 2040 patients undergoing elective coronary angiography following a clopidogrel 600 mg loading dose


---

**Do genetic differences underlie variability in response to antiplatelet therapy?**
Is There a Genetic Basis for Aspirin Variance?

- COX-1 C22T
- COX-1 C50T/A842G
- COX-1 G128 A
- COX-1 C644A
- COX-1 C714A
- COX-1 C10427 A
- COX-1 G1446A
- COX-2 G765C
- GP1a C807T
- GP1b α C5T
- GPIIIa T196C
- GPVI T13254C
- FxII G34T
- P2Y1 C893T
- P2Y1 C993T
- P2Y1 A1622G
- P2Y12 H1H2


Is There a Genetic Basis for Clopidogrel Variance?

- ABCB1 3435CÆT
- CYP2C19*2
- CYP2C19*17

1. Loss of function allele
2. Mixed data whether TT homozygotes face increased CV risk
3. Impaired antiplatelet effect
4. Increased CV risk


Is There Benefit to Genetic Testing with Aspirin?

Meta-analysis of 2,834 patients in whom candidate gene analyses were performed to assess for response to aspirin

There is no polymorphism that predicts response to aspirin

Holmes MV et al. JAMA 2011;306:2704-2714

Meta-analysis of 4,341 patients reporting CYP2C19 genotype and platelet reactivity after a 600 mg loading dose of clopidogrel

Clopidogrel concentration* | Platelet reactivity
--- | ---

*The expected mean active clopidogrel metabolite concentration in a white population for all individuals treated with 75 mg and for individuals with loss-of-function and normal/increased-function CYP2C19 alleles

Mega JL et al. JAMA 2010;304:1821-1830

A meta-analysis of 9,685 patients (91% underwent PCI and 55% had an ACS) who were treated with clopidogrel and in whom the carrier status of a mutant CYP2C19*2 allele* was measured and clinical outcomes were tracked

CV death, MI, or ischemic stroke | Stent thrombosis
--- | ---

*Noncarrier (72%), 1 reduced function allele (26%), 2 reduced function alleles (2%)

ACSAcute coronary syndrome, CV=Cardiovascular, PCI=Percutaneous coronary intervention

Mega JL et al. JAMA 2011;305:1821-1830

Is There Benefit to Genetic Testing with Clopidogrel?

ELEVATE-TIMI 56

333 patients with stable CV disease and known CYP2C19*2 genotype randomized to different maintenance doses of clopidogrel (75 mg vs 150 mg for noncarriers and 76 mg vs 150 mg vs 226 mg vs 300 mg for noncarriers) to assess the response to platelet reactivity

Mega JL et al. JAMA 2011;305:2221-2228

Is phenotyping of platelet function the answer?
## Gold Standard to Assess Platelet Reactivity

![Image of Optical Platelet Aggregometry: Born Principle](image)


## Other Tests to Assess Platelet Reactivity

**Available Tests to Assess Aspirin and P2Y12 Responsiveness**

<table>
<thead>
<tr>
<th>Test</th>
<th>Able to Monitor Aspirin</th>
<th>Able to Monitor Thienopyridines</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFA-100</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>VerifyNow</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Plateletworks</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Impact cone and platelet analyzer</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboelastogram</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Activated platelet surface proteins (i.e., P-selectin)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>VASP phosphorylation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum thromboxane B2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Urinary 11-dehydromethane B2</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

NR=Not recommended

Gurbel PA et al. *JACC* 2007;50:1822-34

## Is There Benefit to Platelet Phenotyping?

A cohort of 683 patients presenting with an ACS and treated with PCI in whom point of care platelet function testing was performed

![Graph showing Hazard Ratios for CV Death and MI](image)

ACS=Acute coronary syndrome, PCI=Percutaneous coronary intervention


## What more is needed to usher in the era of personalized medicine for antithrombotic therapy?
Patients with low pre-treatment function and low inhibition have low post-treatment function and may be at Low Risk (overestimation of risk based on low responsiveness).

Patients with high pre-treatment function and inhibition may still have high post-treatment function and may be at High Risk (underestimation of risk based on normal responsiveness).

Post-treatment platelet function is a better predictor of ischemic events than platelet inhibition (responsiveness).

Misconceptions About Antiplatelet Responsiveness

Lack of Inhibition (Responsiveness) = High Risk

Post-treatment platelet function is a better predictor of ischemic events than platelet inhibition (responsiveness).

Platelet Phenotyping to Tailor Antiplatelet Therapy

ARCTIC Study

2,440 patients with high on-treatment platelet reactivity following elective PCI with a DES randomized to standard therapy with clopidogrel versus tailored therapy* periprocedurally and at 2-4 weeks post PCI

Tailored therapy does not reduce risk in those with HPR after

*Includes aspirin dose adjustment, clopidogrel dose adjustment, use of prasugrel and/or a GP IIb/IIIa inhibitor

DES=Drug eluting stent, PCI=Percutaneous coronary intervention

Price MJ et al. JAMA 2011;305:1097-1105

Is such a personalized approach even needed?
**Clinical Benefit of Greater Platelet Inhibition in ACS**

13,608 patients with high-risk ACS scheduled for PCI randomized to clopidogrel (300 mg LD and 75 mg MD) or prasugrel (60 mg LD and 10 mg MD) for a median of 12 months

<table>
<thead>
<tr>
<th>CV death, MI, or stroke (%)</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT=46</td>
<td>12.1 (781)</td>
<td>9.9 (643)</td>
</tr>
</tbody>
</table>

**Bleeding Events: Safety Cohort**

<table>
<thead>
<tr>
<th>TIMI major</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Threatening</td>
<td>1.8</td>
<td>2.4</td>
<td>.03</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>0.9</td>
<td>1.1</td>
<td>.23</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.1</td>
<td>0.6</td>
<td>.002</td>
</tr>
<tr>
<td>ICH</td>
<td>0.3</td>
<td>0.3</td>
<td>.74</td>
</tr>
</tbody>
</table>

**Clinical Benefits of Greater Platelet Inhibition in ACS**

18,624 patients with a moderate to high risk ACS randomized to clopidogrel (300-600 mg LD and 75 mg MD) or ticagrelor (180 mg LD and 90 mg twice daily MD) for 12 months

<table>
<thead>
<tr>
<th>CV death, MI, or stroke (%)</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT=53</td>
<td>9.8</td>
<td>11.7</td>
</tr>
</tbody>
</table>

**Rates of Ischemic Events in ACS patients undergoing PCI**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>A + C</th>
<th>A + P (T)</th>
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<td>45</td>
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<td>PLATO**</td>
<td>CVD, MI, CVA</td>
<td>10.7%</td>
<td>9.0%</td>
<td>0.0025</td>
<td>59</td>
</tr>
</tbody>
</table>

**Rates of Major Bleeding in ACS patients undergoing PCI**

<table>
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<tr>
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<td>0.02</td>
<td>167</td>
</tr>
</tbody>
</table>

---

**Clinical Benefits of Greater Platelet Inhibition in ACS**


**Clinical Benefits of Greater Platelet Inhibition in ACS**

*Not currently approved by the FDA

**No statistically significant differences were observed in bleeding rates overall

ACS=Acute coronary syndrome, LD=Loading dose, MD=Maintenance dose

---

**So what's a clinician to do?**
What do we know?

- Long term aspirin therapy is important in secondary prevention
- Dual antiplatelet therapy should be used after an ACS or PCI
  - Current guidelines recommend at least 1 year of a P2Y₁₂ inhibitor
  - Dual antiplatelet therapy increases the risk of bleeding
  - Low dose aspirin (81 mg) should be used preferentially when given in conjunction with a P2Y₁₂ inhibitor
  - Withdrawal of antiplatelet therapy increases CV risk
  - Attention to perioperative antiplatelet therapy is key to reduce CV risk

What do we know?

- There is variability in patient response to antiplatelet therapy
  - For aspirin
    - Routine genotyping and phenotyping is not recommended
  - For clopidogrel
    - Genotyping for CYP2C19*2 can identify at risk individuals
    - Platelet phenotyping can identify at risk individuals
    - A higher LD/MD can achieve greater platelet inhibition
  - Tailored therapy, however, hasn't been shown to improve CV outcomes
  - More potent antiplatelet therapy in ACS improves outcomes

Questions