Thrombelastograph® (TEG®) Overview

Laurel Omert MD, FACS
Medical Director
Haemostasis Management
Objectives

- Is there a need for TEG?
- How does it work?
Clinical Practice: A Constant Struggle……
Upsetting the Balance

• Surgery
  • Devices – LVADs, CPB, ECMO
• Trauma
• Drugs
• Stents
• Flights – DVT
• Smoking

Plavix is a trademark of Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership.
How do we know where we are?

- Thrombosis
- Traditional hemostasis tests
- Bleeding
- TEG
Traditional Hemostasis Monitoring

- Platelet plug forms
- Fibrin strands form
- Clot grows
- PT/INR
- PTT
- Bleeding Time
- Platelet Count
- D-dimer
- FDP
- Clot forms
- Maximum clot forms
- Clot degradation takes over
- Clot dissolved
- Damage repaired

Traditional Hemostasis Tests

Do not define the overall process, just provide pieces of the process!
What does the literature say about traditional coagulation testing?

“Elevated activated partial thromboplastin time does not correlate with heparin rebound following surgery”


Key point
No relation between aPTT and anti-Xa activity following CPB
A little coagulation knowledge can be dangerous!
Bruce D. Spiess, MD

Key Question
“Why do we persist in using the aPTT and PT tests when our cardiac textbooks teach that these tests do not predict bleeding?”
What happens in the ICU?

Prevalence, management, and outcomes of critically ill patients with prothrombin time prolongation in the UK intensive care units

Timothy S. Walsh, MD; Simon J. Stanworth, MD; Robin J. Prescott, PhD; Robert J. Lee, MSc; Douglas M. Watson, MSc; Duncan Wynncoll, FRCA; Writing Committee of the Intensive Care Study of Coagulopathy (ISOC) Investigators

Key points
1. 30% have abnormal INR
2. Associated with greater ICU mortality
3. Clinical uncertainty in how to treat
Prolongation of prothrombin time in the critically ill: Is it time for decisive action?

Balraj Appadu, MD, FRCA; Peterborough, UK

Key points

- Coagulation tests such as PT and aPTT poorly reflect in vivo hemostasis
- A better approach to individual bleeding risk should be sought; newer global tests of hemostasis such as the thromboelastogram….have been effective in guiding transfusion therapy in the surgical setting.
Hemostasis Monitoring with the TEG System

Measures entire clotting process

Measures: $\Delta$Clot strength / time (min)

- Rate of clot formation
- Strength of clot
- Stability of clot

$\sum$ Hemostatic status
TEG Analyzer: Mechanics of Sample Measurement
TEG® 5000 Analyzer
Test Simulation
TEG Tracing and Clotting Process

- Continuous monitoring of clotting process
- Generates parameters that relate to each phase

- Platelet plug forms
- Fibrin strands form
- Initiation
- Clot grows
- Maximum clot forms
- Time (min)
- Clot degradation takes over
- Clot dissolved
- Damage repaired
- Time (min)
Analytical Software
Graphical Representation

- **Coagulation**
  - Kinetics of clot development
  - Reaction time, first significant clot formation
  - Achievement of certain clot firmness

- **Fibrinolysis**
  - Angle
  - Maximum amplitude – maximum strength of clot
  - Percent lysis 30 minutes after MA

- **LY30**
  - LY30

- **MA**
  - MA

- **R**
  - R

- **K**
  - K
TEG Parameters: R

Reaction time
(4 – 8 min)
TEG Parameters: K and angle ($\alpha$)
Rate of clot growth

- $\alpha$: Angle (47 - 74°)
- K: Clot kinetics (0 - 4 min)
# TEG Parameters: MA

## Maximum clot strength

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clot time</th>
<th>Clot rate</th>
<th>Maximum clot strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostatic Activity</td>
<td>IIa generation</td>
<td>Fibrin X-linking</td>
<td>Platelet – fibrin interactions</td>
</tr>
<tr>
<td>Hemostatic Component</td>
<td>Coagulation pathways</td>
<td>Coag pathways platelets</td>
<td>Platelets (~80%) Fibrin (~20%)</td>
</tr>
</tbody>
</table>

### Dysfunction

<table>
<thead>
<tr>
<th>Hypocoagulable</th>
<th>Hypercoagulable</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ R (min)</td>
<td>↓ R (min)</td>
</tr>
<tr>
<td>↑ K (min)</td>
<td>↓ K (min)</td>
</tr>
<tr>
<td>↓ α (deg)</td>
<td>↑ α (deg)</td>
</tr>
</tbody>
</table>

**Maximum amplitude**

(54 – 72 mm)
# TEG Parameters: LY30 Clot Breakdown

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clot time</th>
<th>Clot rate</th>
<th>Maximum clot strength</th>
<th>Clot stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostatic Activity</td>
<td>IIa generation</td>
<td>Fibrin formation</td>
<td>Platelet – fibrinogen interactions</td>
<td>Reduction in clot strength</td>
</tr>
<tr>
<td>Hemostatic Component</td>
<td>Coagulation pathways</td>
<td>Coag pathways platelets</td>
<td>Platelets (~80%) Fibrinogen (~20%)</td>
<td>Fibrinolysis</td>
</tr>
</tbody>
</table>

- **Dysfunction**
  - Hypocoagulable: ↑ R (min)  
    - ↑ K (min)  
    - ↓ α (deg)  
    - ↓ MA  
    - LY30 > 7.5%  
    - EPL > 15%
  - Hypercoagulable: ↓ R (min)  
    - ↓ K (min)  
    - ↑ α (deg)  
    - ↑ MA  
    - N/A

- **Lysis at 30 minutes** (0 – 8%)
For the non-verbal among us......

Normal Hemostasis

Hemorrhagic

- Low clotting factors
- Low platelet function
- Low fibrinogen level
- Primary fibrinolysis
- Hypocoagulable state

Thrombotic

- Platelet hypercoagulability
- Enzymatic hypercoagulability
- Platelet & enzymatic hypercoagulability
- Secondary fibrinolysis
TEG and Clot Morphology: What do all the letters really mean?

Panel I  
R time  
Fibrin and platelet filopods

Panel II, III, IV  
K time and alpha angle  
Fibrin build-up and X-linking

Panel V  
MA  
RBCs packed with fibrin strands

Panels VII-X  
Addition of Reopro

Electron Microscopic Evaluations of Clot Morphology During Thrombelastography  
Kawasaki et al Anesthesia Analgesia 2004;99
## TEG Technology
### Blood sample types

<table>
<thead>
<tr>
<th>Sample type (ST)</th>
<th>Activator</th>
<th>Sample timing (minutes)</th>
<th>Cup &amp; Pin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K</strong></td>
<td>Kaolin</td>
<td>&lt; 5 POC</td>
<td>Clear</td>
</tr>
<tr>
<td><strong>CK</strong></td>
<td>Kaolin CaCl₂</td>
<td>15* - 120 Lab</td>
<td>Clear</td>
</tr>
</tbody>
</table>
What else can TEG do?

- Heparin reversal
- Platelet inhibition (PlateletMapping ®)
- Functional fibrinogen assay
- Faster: (RapidTEG ™)
## TEG Technology: Heparin reversal

### Blood sample types

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</tr>
</thead>
<tbody>
<tr>
<td>KH</td>
<td>Kaolin</td>
<td>&lt;5 POC</td>
<td>Heparinase (blue)/(6 IU)</td>
</tr>
<tr>
<td>CKH</td>
<td>Kaolin CaCl₂</td>
<td>15* - 120 Lab</td>
<td>Heparinase (blue)</td>
</tr>
</tbody>
</table>
Testing for presence of heparin:
Patient post-protamine and bleeding

Green = kaolin with heparinase (KH)
Black = kaolin only (K)

R value for KH = K
Suggests no heparin present

R value for KH < K
Suggests presence of heparin
What else can TEG do?

- Heparin reversal
- Platelet inhibition (PlateletMapping ®)
- Functional fibrinogen assay
- Faster: (RapidTEG ™)
Conversation with my aunt

Aunt: Hi Laurel, you know the doctor put me on a new drug to help my heart beat called Plavix

Me: Great, it’s really to keep your blood from clotting to protect your heart….What dose are you taking, 75 mg?

Aunt: Well, whatever, it’s pink and I think it upsets my stomach.

Me: It doesn’t usually do that.

Aunt: Well, that’s okay, I just don’t take it for a day or two if that happens. Yesterday I think I skipped it….

Me: You really shouldn’t do that.

Aunt: You know actually, I haven’t taken it since Saturday, I forgot yesterday because I went to the bridge game

Me: That was 3 days ago!
What is Plavix doing to our patients?


Clinical Research

Interventional Cardiology

Increased Risk in Patients with High Platelet Aggregation Receiving Chronic Clopidogrel Therapy Undergoing Percutaneous Coronary Intervention

Kevin P. Bliden and Paul A. Gurbel MD

Key Facts

1. 20% PCI patients have recurrent ischemic/thrombotic events
2. Variation in platelet aggregation due to ADP stimulation was ~60%
Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.

Patients with variants in cytochrome P-450 2C19 (CYP2C19) have:
- Lower levels of the active metabolite of clopidogrel,
- Less inhibition of platelets
- 3.58 times greater risk for major adverse cardiovascular events such as death, heart attack, and stroke
- Risk is greatest in CYP2C19 poor metabolizers.
Ideal Clot = Fibrin mesh + Platelets

- Fibrin – strands formed from biochemical reactions in the blood
- Platelet – cellular element in blood
Assessing *specific* platelet function with PlateletMapping

1. Define overall platelet contribution to clot strength
2. Define clot without platelets

![Diagram](image)

- Thrombin-induced platelet contribution ($MA_T$)
- Clot without platelets ($MA_A$)

<table>
<thead>
<tr>
<th>SP</th>
<th>R</th>
<th>K</th>
<th>Angle</th>
<th>MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>min</td>
<td>min</td>
<td>N/A</td>
<td>deg</td>
<td>mm</td>
</tr>
<tr>
<td>0.8</td>
<td>1.7</td>
<td>N/A</td>
<td>32.4</td>
<td>8.7</td>
</tr>
</tbody>
</table>
Assessing specific platelet function with PlateletMapping

3. Define effect of agonist on platelet contribution to clot strength
   - ADP (Plavix ®)
   - AA (Aspirin)

   Agonist-induced platelet contribution ($MA_{ADP}$)
   Clot without platelets ($MA_A$)

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<td>deg</td>
<td>mm</td>
</tr>
<tr>
<td>0.8</td>
<td>1.4</td>
<td>3.9</td>
<td>48.7</td>
<td>36.6</td>
</tr>
</tbody>
</table>
Assessing *specific* platelet function with PlateletMapping: Let’s subtract.
Interventional Cardiology

Adenosine diphosphate-induced platelet-fibrin clot strength: A new thromboelastographic indication of long-term post-stenting ischemic events

Paul A. Gurbel, MD; Kevin P. Bliden, BS, Irene A. Navickas, BS; et al
American Heart Journal 2010

Key points
1. Therapeutic range for $MA_{ADP} = 31-47$
2. TEG can serve to personalize antiplatelet treatment to reduce ischemic events and bleeding
Personalized Platelet Analysis

- Patient A: 50% platelet inhibition does not provide sufficient reduction of the risk of a thrombotic or ischemic event.
- Patient B: 50% platelet inhibition provides antithrombotic protection without risk of bleeding.
- Patient C: 50% platelet inhibition increases risk of bleeding.
What else can TEG do?

- Heparin reversal
- Platelet inhibition (PlateletMapping®)
- Functional fibrinogen assay
- Faster: (RapidTEG™)
Functional fibrinogen

- Used for determination of fibrinogen level
- Partitions clot strength into two components
  - Contribution of platelets ($MA_P$)
  - Contribution of fibrin ($MA_{FF}$)

$$MA = MA_P + MA_{FF}$$
Functional fibrinogen

Figure 4. Superimposed Functional Fibrinogen and kaolin test results.

MA = 47 (low)
MA_{FF} = 6.3 (low)

Patient may benefit from FFP, cryoprecipitate or fibrinogen concentrate (Haemocomplettan®)
What else can TEG do?

- Heparin reversal
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<td>15* - 120 Lab</td>
<td>Kaolin +TF</td>
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RapidTEG (TEG ACT Test)

- A faster TEG assay; ACT in < 1 minute
- Activates both extrinsic and intrinsic coagulation pathways
- Cleared by FDA for ACT
Case # 1 - Resuscitation

46 year old status post MCC, arrived in the ED pulseless due to profound hemorrhagic shock*
TEG # 1 Coagulopathic bleeding

TEG (White): Primary fibrinolysis

Treatment: Amicar (and other products)
TEG # 2 Coagulopathic bleeding slows

TEG (Green): Primary fibrinolysis improving
TEG # 3 Coagulopathic bleeding stops

TEG (Pink): Normal
# Patient Profile

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS</td>
<td>25</td>
</tr>
<tr>
<td>RBC 0-6 hrs</td>
<td>23</td>
</tr>
<tr>
<td>FFP 0-6 hrs</td>
<td>12</td>
</tr>
<tr>
<td>PLT 0-6 hrs</td>
<td>2</td>
</tr>
<tr>
<td>Cryo 0-6 hrs</td>
<td>4</td>
</tr>
<tr>
<td>pH in ED</td>
<td>7.08</td>
</tr>
<tr>
<td>Temp in ED (°C)</td>
<td>34.7</td>
</tr>
</tbody>
</table>
Case #1 – Recovery

Pre-op

Post-op pelvic fracture stabilization
The hypercoagulable side.....
TEG is not just for bleeding......
Why do some (2-22%) patients on “DVT prophylaxis” get VTE?

Thrombelastography Versus AntiFactor Xa Levels in the Assessment of Prophylactic-Dose Enoxaparin in Critically Ill Patients

Philbert Y. Van, MD, S. David Cho, MD, Samantha J. Underwood, MS, Melanie S. Morris, MD, Jennifer M. Watters, MD, and Martin A. Schreiber, MD

J Trauma. 2009;66:1509–1517

Key point

1. TEG R time differentiated enoxaparin treated patients who developed DVT from those who did not

2. Antifactor Xa levels were not significantly different when comparing patients with DVT and without DVT
Anesthesia Analgesia (1999; 88:312-319)

Thromboelastography-Guided Transfusion Algorithm Reduces Transfusions in Complex Cardiac Surgery

Linda Shore-Lesserson MD, Heather E. Manspeizer MD, Marietta DePerio RN, Sanjeev Francis BS, Frances Vela-Cantos RN, and M. Arisan Ergin MD

Departments of Anesthesiology and Cardiothoracic Surgery, Mount Sinai Medical Center, New York, New York

Objective

Prospective, randomized trial to compare bleeding and transfusion requirements in cardiac surgical patients at moderate to high risk of bleeding using a TEG-guided algorithm or standard laboratory coagulation testing.
Shore-Lesserson Data

Table 4. Bleeding and Transfusion Requirements

<table>
<thead>
<tr>
<th></th>
<th>Intraoperative</th>
<th>Postoperative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEG</td>
<td>Control</td>
<td>TEG</td>
</tr>
<tr>
<td>Packed red blood cells (mL)</td>
<td>267 ± 423</td>
<td>346 ± 449</td>
<td>0.4</td>
</tr>
<tr>
<td>Fresh-frozen plasma (mL)</td>
<td>22 ± 101</td>
<td>113 ± 407</td>
<td>0.4</td>
</tr>
<tr>
<td>Platelet concentrates (mL)</td>
<td>22 ± 75</td>
<td>41 ± 122</td>
<td>0.6</td>
</tr>
<tr>
<td>Autologous reinfusion volume (mL)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6-h MTD + reinfusion volume (mL)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>24-h MTD + reinfusion volume (mL)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Packed red blood cells</td>
<td>17/53</td>
<td>23/52</td>
<td>0.2</td>
</tr>
<tr>
<td>Fresh-frozen plasma</td>
<td>3/53</td>
<td>8/52</td>
<td>0.1</td>
</tr>
<tr>
<td>Platelet concentrates</td>
<td>5/53</td>
<td>8/52</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Values are mean ± so or proportion of patients transfused. Nonparametric statistics performed for all data not conforming to normal distribution. TEG = thromboelastography, MTD = chest tube drainage.

Key points
1. Less blood tx intraop, post op and ICU (NS)
2. Volume of FFP tx significantly lower with TEG
3. FFP tx to significantly lower proportion of patients
4. Platelets tx to significantly lower proportion of patients
Our immediate goals...

- Expand the use of TEG in cardiac surgery
- Find the TEG “niche” in trauma / critical care
Publications List

Application of the TEG® has been documented in over 3000 highly esteemed and prestigious peer-reviewed journals such as:

- Anesthesiology
- Anesthesia and Analgesia
- Anesthesia and Intensive Care
- Annals of Thoracic Surgery
- British Journal of Anesthesia
- British Journal of Urology
- Journal of Cardiothoracic and Vascular Anesthesia
- Journal of Clinical Anesthesia
- Journal of Clinical Monitoring
- Journal of Heart and Lung Transplantation
- Journal of Neurology, Neurosurgery and Psychiatry

Applications also appear in medical texts and in proceedings of various professional organizations.
Questions?
Causes of Bleeding after Cardiopulmonary Bypass

Common (95-99%)
- Defective surgical hemostasis
- Acquired transient platelet dysfunction

Less common (1-5%)
- Other platelet dysfunction
- Thrombocytopenia
- Vitamin K deficiency
- DIC
- Inherited hemostatic defects
- Systemic fibrinolysis
- Heparin
- Protamine excess

RapidTEG (TEG ACT Test)

- A faster TEG assay
- Activates both extrinsic and intrinsic coagulation pathways
- Cleared by FDA for ACT
A Novel Thrombelastograph® Tissue Factor/Kaolin Assay of Activated Clotting Times for Monitoring Heparin Anticoagulation During Cardiopulmonary Bypass

Jack J. Chavez, MD*, Donald E. Foley, MD*, Carolyn C. Snider, MT*, James C. Howell, CCP*, Eli Cohen, PhD†, Robert A. Muenchen, MS‡, and Roger C. Carroll, PhD*

*Department of Anesthesiology, University of Tennessee Graduate School of Medicine, Knoxville, Tennessee; †Haemoscope Corporation, Niles, Illinois; and the ‡Statistical Consulting Center, University of Tennessee at Knoxville

Key points
1. TEG ACT correlated with Hepcon and Hemochron
2. Less effect of hemodilution than Hemochron
3. ACT in < 1 minute
Hemochron vs. TEG® ACT

- Comparison testing was done at 2 clinical sites
- The results demonstrate a strong correlation

**Regression Analysis**

\[ y = 1.057x - 17.274 \]

\[ r = 0.905 \]
Three facts about DVT/PE

1. DVT occurs in ~60% untreated trauma patients, 1.13% of treated

2. In treated patients, incidence of pulmonary embolus is 0.45%*

3. VTE is 3rd most common cause of death in trauma patients; mortality rate is 8.9%

*2,332/519,268 pts
Knudson et al; UCSF ASA 2011 data
TEG is not just for bleeding......
TEG and ECMO and LVAD

- PubMed Search over 10 years
  - 8 citations “thrombelastography and ECMO”
  - 2 citations “thrombelastography and LVAD”
Thrombelastography and LVAD

- Bleeding and thromboembolic complications are common
- High shear rates cause platelet dysfunction
- Dysfunction resembles acquired von Willebrand syndrome associated with formation of microaggregates and bleeding
- Case study shows:
  - Hypercoagulability by ROTEM and PFA-100
  - Hypocoagulability by routine coags
  - Thrombus formation on cannula, so Plavix started

Steinlechner et al, Ann Thorac Surg 2009; 87(1)131
Fries et al, Ann Thorac Surg 2003; 76(5)1593
Baseline
Pre ECMO

Kaolin with heparinase

Sample: 7/20/2007 07:53-09:02

<table>
<thead>
<tr>
<th>R (min)</th>
<th>K (min)</th>
<th>Angle (deg)</th>
<th>MA (mm)</th>
<th>G (d/sc)</th>
<th>Cl</th>
<th>EPL (%)</th>
<th>LY30 (%)</th>
<th>PMA</th>
<th>A (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-8</td>
<td>0-4</td>
<td>47-74</td>
<td>54-72</td>
<td>6.0K</td>
<td>-3</td>
<td>3</td>
<td>0-15</td>
<td>0</td>
<td>50.8</td>
</tr>
<tr>
<td>25.8</td>
<td>12.3</td>
<td>15.9</td>
<td>33.9</td>
<td>2.6K</td>
<td>-23.9</td>
<td>0</td>
<td><em>0</em></td>
<td>1.0</td>
<td>35.9</td>
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</tbody>
</table>
ECMO (1 Hour)

ECMO 1HR

2 Kaolin with heparinase

Sample: 7/20/2007 09:03-10:37

10 millimeters

<table>
<thead>
<tr>
<th>SP min</th>
<th>R min</th>
<th>K min</th>
<th>Angle deg</th>
<th>MA mm</th>
<th>G d/sc</th>
<th>Cl</th>
<th>EPL %</th>
<th>LY30 %</th>
<th>PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.8</td>
<td>7.6</td>
<td>3.0</td>
<td>52.2</td>
<td>53.5</td>
<td>5.7K</td>
<td>-3.4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>4 - 8</td>
<td>0 - 4</td>
<td>0 - 4</td>
<td>47 - 74</td>
<td>54 - 72</td>
<td>6.0K - 13.2K</td>
<td>-3 - 3</td>
<td>0 - 15</td>
<td>0 - 8</td>
<td>0.0</td>
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<th>K min</th>
<th>Angle deg</th>
<th>MA mm</th>
<th>G d/sc</th>
<th>Cl</th>
<th>EPL %</th>
<th>LY30 %</th>
<th>PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.6</td>
<td>38.7</td>
<td>46.9</td>
<td>4.5</td>
<td>20.2</td>
<td>1.3K</td>
<td>-47.9</td>
<td>0.0</td>
<td><em>0</em>*</td>
<td>1.0</td>
</tr>
<tr>
<td>4 - 8</td>
<td>0 - 4</td>
<td>0 - 4</td>
<td>47 - 74</td>
<td>54 - 72</td>
<td>6.0K - 13.2K</td>
<td>-3 - 3</td>
<td>0 - 15</td>
<td>0 - 8</td>
<td>0.0</td>
</tr>
</tbody>
</table>
### ECMO (4 Hour)

**kaolin with heparinase**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Date</td>
<td>7/20/2007 12:17-13:04</td>
</tr>
<tr>
<td>10 millimeters</td>
<td></td>
</tr>
</tbody>
</table>
Plavix and the Black Box

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)