Διαχείριση αντιθρομβωτικής αγωγής σε αιμορραγικές επιπλοκές

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ANTITHROMBOTIC THERAPY AND BLEEDING... a Catch-22 scenario
Bleeding Risk: A Comprehensive Clinical Assessment

Hematological Factors
- Anemia
- WBC
- Bleeding Diathesis

Chronic Kidney Disease

ACS Presentation

Liver Disease

Peripheral Vascular Disease

Shock Presentation

Procedural Factors
- Use of GPI
- Use of Femoral Access

Increased Risk of Mortality!

Older Age

Female Gender

Chronic Oral Anticoagulation
Risk of major bleeding 1-8% at 30d in ACS pts
Valgimigli M, et al. (TRACER) randomized trial. Eur Heart J 2017;38:804–810
Minor bleeding

PCI

Bleeding

DAPT Disruption

Coronary Thrombotic Risk

DAPT Disruption and Ischemic Risk

DAPT Cessation And Risk of Stent Thrombosis

Paris registry

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-DAPT</td>
<td>1.00 (Ref)</td>
<td>57</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0.39 (0.11, 1.35)</td>
<td>0.137</td>
</tr>
<tr>
<td>Interruption</td>
<td>0.64 (0.09, 4.82)</td>
<td>0.664</td>
</tr>
<tr>
<td>Disruption</td>
<td>2.58 (1.22, 5.46)</td>
<td>0.013</td>
</tr>
<tr>
<td>0-7 Days</td>
<td>15.94 (5.57, 45.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8-30 days</td>
<td>2.88 (0.36, 19.68)</td>
<td>0.334</td>
</tr>
<tr>
<td>31+ days</td>
<td>1.35 (0.50, 3.64)</td>
<td>0.551</td>
</tr>
</tbody>
</table>
Patients with recent bleeding have been **EXCLUDED** from most randomized trials of antithrombotic therapy
## Existing bleeding scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI</td>
<td>Laboratory-based (hemoglobin, hematocrit)</td>
</tr>
<tr>
<td>GUSTO</td>
<td>Clinical (severity)-based</td>
</tr>
<tr>
<td>GRACE</td>
<td>Simplified</td>
</tr>
<tr>
<td>Claret 2</td>
<td>Composite (clinical, lab)</td>
</tr>
<tr>
<td>ISAR-REACT 3</td>
<td>PCI-based</td>
</tr>
<tr>
<td>PLATO</td>
<td></td>
</tr>
<tr>
<td>STEEPLE</td>
<td>PCI-based</td>
</tr>
<tr>
<td>CURRENT-OASIS</td>
<td>PCI-based</td>
</tr>
</tbody>
</table>

Unmet Need of a standardized definition!!!
# BARC Bleeding Definitions

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Not actionable, does not cause unscheduled studies, hospitalization, or treatment; may include episodes leading to self-discontinuation of medical therapy</td>
</tr>
<tr>
<td>Type 2</td>
<td>Any overt, actionable sign of hemorrhage that does not fit the criteria for types 3, 4, or 5 but does meet ≥1 of the following criteria: (1) requiring nonsurgical, medical intervention; (2) leading to hospitalization or increased level of care; or (3) prompting evaluation</td>
</tr>
<tr>
<td>Type 3a</td>
<td>Overt bleeding + Hb drop of 3-5 g/dL&lt;br&gt;Any transfusion with overt bleeding</td>
</tr>
<tr>
<td>Type 3b</td>
<td>Overt bleeding + Hb drop ≥5 g/dL&lt;br&gt;Cardiac tamponade&lt;br&gt;Bleeding requiring surgical intervention or IV vasoactive agents</td>
</tr>
<tr>
<td>Type 3c</td>
<td>ICH (not including microbleeds or hemorrhagic transformation, does include intraspinal)&lt;br&gt;Subcategories confirmed by autopsy or imaging or lumbar puncture&lt;br&gt;Intraocular bleed compromising vision</td>
</tr>
<tr>
<td>Type 4</td>
<td>CABG bleeding</td>
</tr>
<tr>
<td>Type 5</td>
<td>Fatal bleeding</td>
</tr>
</tbody>
</table>

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*Acute Coronary Syndromes*


[heart.org](http://www.heart.org) | [Medscape Education](http://www.medscape.com)
WHICH DRUGS TO STOP?
WHICH TO RESTART?
WHEN?

➢ Newer P2Y$_{12}$ Inhibitors (ticagrelor, prasugrel):
  
  No data available for resumption after bleeding

➢ The risk of non-CABG/non-procedural related bleeding is significantly HIGHER compared to Clopidogrel

➢ Dose reduction (prasugrel 5 mg, ticagrelor 60mg) IS NOT RECOMMENDED

Clopidogrel Is The Drug Of Choice

Halvorsen S et al Eur Heart J 2016; 38:1455–1462
General Considerations AFTER a bleeding event

➢ The irreversible (prasugrel) and reversible (ticagrelor) binding should be taken into consideration when deciding WHEN to Restart.

LIFE-THREATENING BLEEDING
Any severe active bleeding putting patient’s life immediately at risk

- e.g. massive overt genitourinary, respiratory or upper/lower gastrointestinal bleeding,
- active intracranial,
- spinal or intraocular haemorrhage,
- or any bleeding causing haemodynamic instability.

- Immediately discontinue all antithrombotic medications.
- Once bleeding has ceased, re-evaluate the need for DAPT or SAPT, preferably with the P2Y_12 inhibitor especially in case of upper GI bleeding.
- Fluid replacement if hypotension.
- Consider RBC transfusion irrespective of HB values.
- Platelet transfusion.
- Consider i.v. PPI if GI bleeding occurred.
- Urgent surgical or endoscopic treatment of bleeding source if deemed possible.
General Considerations AFTER a bleeding event

Aspirin: Cleared from circulation within 1h

Clopidogrel/Prasugrel: Platelet transfusions can restore platelet function only 4 to 6 h after the last drug intake

Ticagrelor: 24 h-48h for drug clearance to allow transfused platelets to restore hemostatic competence

General Considerations AFTER a bleeding event

➢ Resumption of oral antithrombotic therapy in ALL situations with a clear indication
  Exclude: Life-Threatening bleeding

IF

Thrombotic Risk > Recurrent Bleeding: Continue antithrombotic therapy

Thrombotic Risk = Recurrent Bleeding: Brief or temporary interruption of antithrombotic therapy

Thrombotic Risk < Recurrent Bleeding: Consider on a case to case basis, reducing the number and/or dose of antithrombotic drug(s)

Halvorsen S et al Eur Heart J 2016; 38:1455–1462
**1st STEP: BLEEDING SEVERITY EVALUATION**

**MILD BLEEDING**
Any bleeding that requires medical attention without requiring hospitalization

e.g. not self resolving epistaxis, moderate conjunctival bleeding, genitourinary or upper/lower gastrointestinal bleeding without significant blood loss, mild haemoptysis

**MODERATE BLEEDING**
Any bleeding associated with blood loss (>3 g/dL HB) and/or requiring hospitalization, which is haemodynamically stable and not rapidly evolving

e.g. genitourinary, respiratory or upper/lower gastrointestinal bleeding with significant blood loss or requiring transfusion

**SEVERE BLEEDING**
Any bleeding requiring hospitalisation, associated with a severe blood loss (>5 g/dL HB) which is haemodynamically stable and not rapidly evolving

e.g. severe genitourinary, respiratory or upper/lower gastrointestinal bleeding

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2017 ESC focused update on dual antiplatelet Therapy
**THROMBOTIC RISK**

- **High or very high thrombotic risk**
  - ACS or PCI with newer generation DES 1-30 days ago
  - Low dose **Aspirin** without interruption
  - Restart **Clopidogrel** as soon as possible

- **Moderate thrombotic risk**
  - ACS or PCI with newer generation DES 1-12 months ago
  - Resumption of low dose **Aspirin** within 3 days (or ASAP)
  - Restart **Clopidogrel** IF: Thrombotic Risk > Recurrent bleeding risk

- **Low thrombotic risk**
  - Stable CAD (>12 months after ACS or PCI with newer generation DES)
  - Reinitiate **Aspirin** within a few days after bleeding

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**HALVOREN S et al. Eur Heart J 2016; 38:1455–1462**
<table>
<thead>
<tr>
<th>Risk category</th>
<th>Bleeding source and severity</th>
<th>Clinical setting</th>
<th>Patients clinical risk factors for bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>Intracranial bleeding where no treatment is possible or effective, Life-threatening extracranial bleeding where the source is either not identified or identified but not treated effectively</td>
<td>No precipitating or reversible factor identified (e.g. trauma, invasive procedure, hypertension, drug overdosing) Cessation of antithrombotic therapy discouraged because of very high-thrombotic risk, e.g. mechanical heart valve</td>
<td>HAS-BLED ≥ 5</td>
</tr>
<tr>
<td>High</td>
<td>Major extracranial bleeding where the source is identified but not treated effectively.</td>
<td>No reversible factor identified. Cessation of antithrombotic therapy discouraged because of very high thrombotic risk.</td>
<td>HAS-BLED 3–4</td>
</tr>
<tr>
<td>Moderate</td>
<td>Intracranial bleeding where cause of bleeding and relevant risk factors have been treated. Extracranial major bleeding where the source has been identified and treated effectively.</td>
<td></td>
<td>HAS-BLED = 2</td>
</tr>
<tr>
<td>Low-to-moderate</td>
<td>Extracranial minor bleeding</td>
<td>Bleeding caused by antithrombotic drugs which can be discontinued</td>
<td>HAS BLED = 1</td>
</tr>
<tr>
<td>Low</td>
<td>Extracranial minimal bleeding</td>
<td>Bleeding caused by antithrombotic drugs which can be discontinued</td>
<td>HAS BLED = 0</td>
</tr>
</tbody>
</table>
Acute upper GI haemorrhage in a patient using antiplatelet agent(s) (APT)

Upper GI endoscopy demonstrates a nonvariceal source of bleeding (e.g. peptic ulcer bleed)

- High risk endoscopic stigmata identified (Forrest classification: Ia, Ib, Ila, IIb)
  - APT used for secondary prophylaxis (known cardiovascular disease)
  - Patients on low dose ASA alone
    - Resume low-dose ASA by day 3 following index endoscopy
    - Second-look endoscopy at the discretion of the endoscopist may be considered
  - Patients on dual antiplatelet therapy (DAPT)
    - Continue low dose ASA without interruption
    - Early cardiology consultation for recommendation on resumption/continuation of second APT
    - Second-look endoscopy at the discretion of the endoscopist may be considered

- Low risk endoscopic stigmata identified (Forrest classification: IIc, III)
  - APT used for secondary prophylaxis (known cardiovascular disease)
  - Patients on low dose ASA alone
    - Continue low-dose ASA without interruption
  - Patients on dual antiplatelet therapy (DAPT)
    - Continue DAPT without interruption

*The Forrest classification is defined as follows: Ia spurting hemorrhage, Ib oozing hemorrhage, Ila nonbleeding visible vessel, IIb an adherent clot, IIc flat pigmented spot, and III clean base ulcer
Continue DAPT

➢ Careful consideration of bleeding/thrombotic Risk
➢ Restart Aspirin± Clopidogrel IF

Thrombotic risk Very High/High

2017 ESC focused update on dual antiplatelet Therapy
Resuming Antithrombotics in pts on Antiplatelets AND oral Anticoagulants IF MAJOR BLEEDING

STOP ASPIRIN

STOP CLOPIDOGREL IF ISCHEMIC RISK ≤ MODERATE

LOWEST EFFECTIVE DOSE OF NOAC INR: 2.0-2.5

CHA₂DS₂-VASc score:
1 for MEN
2 for WMEN
WHAT'S NEXT?
Ongoing trials in HBR patients with new generation DES

**MASTER DAPT** (Ultramaster, Terumo)

**Short DAPT Programs** (Xience, Abbott)

**ONYX ONE, ONYX ONE CLEAR** (Resolute Onyx, Medtronic)

**EVOLVE Short DAPT (SYNERGY, Boston Scientific)**

**LEADERS FREE II** (Biofreedom, Biosensors)

**COBRA REDUCE** (COBRA stent, CELONOVA)
CONCLUSIONS

✓ There is a shortage of randomized trials, describing the risks and benefits of when and how to resume antithrombotic drugs after bleeding in patients with CAD and/or AF.

✓ It is essential that clinicians be aware of the heightened risk of ischaemic events following bleeding and tailor their decisions on continuation or reinitiation of antithrombotic therapy accordingly.

✓ The results of ongoing trials for this important group of patients are eagerly awaited.
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Cardio-Cath Meeting 2019
Live Demonstration Course

27–29 June 2019
Ioannina, Greece