Special Topics In Interventional Cardiology
Ischemic and Haemorrhagic Risk in Acute Coronary Syndromes

Α-Δ. ΜΑΥΡΟΠΙΑΝΗ
ΚΑΡΔΙΟΛΟΓΟΣ
ΑΙΜΟΔΥΝΑΜΙΚΟ ΕΡΓΑΣΤΗΡΙΟ
Γ.Ν.Θ. «Γ. ΠΑΠΑΝΙΚΟΛΑΟΥ»
ΘΕΣΣΑΛΟΝΙΚΗ
Disclosure Statement of Financial Interest

none whatsoever…
An 82 Years Old Lady with STEMI:

- Chest pain 2hr. duration
- ST ↑ V1-V6
- EF 35% hypokinetic anterior wall
- CRF: previous smoker
  - positive family history
  - hypertension (controlled)
  - mild renal failure (CKD stage 2)
  - no DM
- Medical Cardiac History: Paroxysmal Afib on Dabidatran

Antithrombotic drugs during PCI:
- NOAC was still active (radial approach)
- 2500 IU Heparin (to avoid catheter thrombosis)
- Clopidogrel 300 mg at arrival and additional dosing in the Cath.Lab
- Aspirin 500mg sl. at arrival
Choosing Between Skylla and Charybdis
## Risk Score Comparison

<table>
<thead>
<tr>
<th></th>
<th>PURSUIT</th>
<th>TIMI</th>
<th>GRACE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>&gt; 3 risk factors</td>
<td>Cardiac arrest during presentation</td>
</tr>
<tr>
<td></td>
<td>Worst CCS class in last 6 weeks</td>
<td>Known CAD</td>
<td></td>
</tr>
<tr>
<td><strong>Exam</strong></td>
<td>SBP</td>
<td>ASA within 7 days</td>
<td>SBP</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>Recent &lt;24h angina</td>
<td>HR</td>
</tr>
<tr>
<td></td>
<td>Rales</td>
<td></td>
<td>Killip class</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>↓ST</td>
<td>ST↓ &gt;0.5 mm</td>
<td>ST deviation</td>
</tr>
<tr>
<td><strong>Labs</strong></td>
<td>↑cardiac markers</td>
<td></td>
<td>↑cardiac markers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Creatinine</td>
</tr>
</tbody>
</table>
## Factors Associated With Appropriate Selection

| Immediate invasive (within 2 h) | • Refractory angina  
|                                | • Signs or symptoms of HF or new or worsening mitral regurgitation  
|                                | • Hemodynamic instability  
|                                | • Recurrent angina or ischemia at rest  
|                                | • Sustained VT or VF  

| Ischemia-guided strategy | • Low-risk score (e.g., TIMI [0 or 1], GRACE [<109])  
|                         | • Low-risk Tn-negative female patients  
|                         | • Patient or clinician preference in the absence of high-risk features  

| Early invasive (within 24 h) | • None of the above, but GRACE risk score >140  
|                            | • Temporal change in Tn (Section 3.4)  
|                            | • New or presumably new ST depression  

| Delayed invasive (within 25-72 h) | • None of the above but diabetes mellitus  
|                                | • Renal insufficiency (GFR <60 mL/min/1.73 m2)  
|                                | • Reduced LV systolic function (EF <0.40)  
|                                | • Early postinfarction angina  
|                                | • PCI within 6 mo.  
|                                | • Prior CABG  
|                                | • GRACE risk score 109–140; TIMI score <2  

---

Bleeding and Mortality

Major Bleeding

- Hypotension
- Cessation of ASA/P2Y12

- Ischemia
- Stent Thrombosis

- Transfusion
- Inflammation

Mortality

Bhatt DL.
In Braunwald EB, Harrison’s Online. 2005.
Impact of In-hospital Bleeding in ACS
34,146 pts. with ACS in the OASIS 1/2 and CURE

Major bleeding occurred in 2.3% of pts

First 30 days

P<0.0001

Adj. HR [95%CI] = 5.37 [3.97, 7.26]

Landmark analysis, 1-6 mo

P=0.002

Adj. HR [95%CI] = 1.54 [1.02, 2.36]

Eikelboom JW. et al.
Adverse impact of bleeding on prognosis in patients with acute coronary syndromes.
Circulation. 2006 Aug 22;114(8):774-82
Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials.

## Definitions of Major/Severe Bleeding in Randomized Controlled Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>PLATO</th>
<th>ACUITY Horizons</th>
<th>STEEPLE</th>
<th>CURE</th>
<th>OASIS-5 ESSENCE</th>
<th>REPLACE-2</th>
<th>TIMI phase II</th>
<th>TIMI phase I</th>
<th>GUSTO</th>
<th>Type of bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Intracranial/ intracerebral</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Intraocular</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Retro peritoneal</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Bleeding causing hemodynamic compromise</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Bleeding requiring surgical intervention</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Hematoma &gt;5cm at the puncture site</td>
</tr>
<tr>
<td>≥4</td>
<td>≥1</td>
<td>≥1</td>
<td>≥2</td>
<td>≥2</td>
<td>≥2</td>
<td>≥2</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
<td>Transfusion, units</td>
</tr>
<tr>
<td>≥5.0</td>
<td>≥3.0</td>
<td>≥3.0</td>
<td>≥2</td>
<td>≥2</td>
<td>≥2</td>
<td>≥3.0</td>
<td>≥3.0</td>
<td>≥5.0*</td>
<td>-</td>
<td>Decrease in Hgb with overt bleeding, g/dL</td>
</tr>
<tr>
<td>-</td>
<td>≥4.0</td>
<td>-</td>
<td>≥5.0</td>
<td>-</td>
<td>≥4.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Decrease in Hgb without overt bleeding, g/dL</td>
</tr>
</tbody>
</table>

- Decrease in Hgb with overt bleeding, g/dL
- Decrease in Hgb without overt bleeding, g/dL
Bleeding Definitions

TIMI Major
- Bleeding with >5 g/dL fall in hgb
- Intracranial bleeding
- Intraocular bleeding
- Access site bleed requiring intervention
- ≥ 5 cm hematoma at puncture site
- Reoperation for bleeding
- Blood product transfusion
- Hgb ↓ ≥3g/dL with an overt source
- Hgb ↓ ≥4g/dL w/o overt source
- Retroperitoneal bleeding
- Gross hematuria or hematemesis

TIMI Minor

ACUITY/HORIZONS Major Bleeding
<table>
<thead>
<tr>
<th>Type 0</th>
<th>No bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional</td>
</tr>
<tr>
<td>Type 2</td>
<td>Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, (3) prompting evaluation</td>
</tr>
<tr>
<td>Type 3a</td>
<td>Overt bleeding plus haemoglobin drop of 3 to &lt; 5*g/dL (provided haemoglobin drop is related to bleed) Any transfusion with overt bleeding</td>
</tr>
<tr>
<td>Type 3b</td>
<td>Overt bleeding plus haemoglobin drop ≥ 5*g/dL (provided haemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) Bleeding requiring intravenous vasoactive drugs</td>
</tr>
<tr>
<td>Type 3c</td>
<td>Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal) Subcategories; confirmed by autopsy or imaging or LP Intra-ocular bleed compromising vision</td>
</tr>
<tr>
<td>Type 4</td>
<td>CABG-related bleeding Perioperative intracranial bleeding within 48 h Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period* Chest tube output ≥ 2 L within a 24 h period If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as ‘not a bleeding event’</td>
</tr>
<tr>
<td>Type 5a</td>
<td>Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious</td>
</tr>
<tr>
<td>Type 5b</td>
<td>Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation</td>
</tr>
</tbody>
</table>

Mehran R. et al.  
Circulation. 2011 Jun 14;123(23):2736-47
Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE).
Eur Heart J. 2003 Oct;24(20):1815-23
ACS and Bleeding: Frequency and in Hospital Mortality

Major Bleeding

Overall ACS
UA
NSTEMI
STEMI

In Hospital Mortality ± Bleeding

Patients %

Overall ACS
UA
NSTEMI
STEMI

Moscucci M. et al.
Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE).
Eur Heart J. 2003 Oct;24(20):1815-23
There is No Free Meal: Detrimental Effects of Transfusions

Bleeding

Transfusion

effect of prolonged storage

activation of Inflammatory cascade

THROMBOSIS

vasoconstriction

Platelet activation aggregation

TISSUE ISCHEMIA

effect independent of storage duration

Hill SR. et al.

Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2002;(2):CD002042
Non-CABG Major Bleeding in PCI Treated ACS Patients

Mehran R.
SCAI Proceedings 2011
Sources and Incidence of Bleeding Among 17,393 PCI Patients

Verheugt FW, et al.
Incidence, prognostic impact, and influence of antithrombotic therapy on access and non access site bleeding in percutaneous coronary intervention. JACC Cardiovasc Interv. 2011 Feb; 4(2):191-7
Relative Risk of 1-year Mortality Associated with Bleeding and Source (unadjusted)

P < .001 for all bleeding versus none

12 RCTs of DAPT Duration After Stenting

Timing of ASA only vs. DAPT

- RESET n 2177
- OPTIMIZE n 3119
- EXCELLENT n 1448
- ISAR SAFE n 4000
- I LOVE IT 2 n 1829
- ITALIC n 1850
- PRODIGY n 2014
- ARCTIC INT. n 1259
- DAPT BMS n 1687
- DAPT DES n 5961
- DES LATE n 5045
- OPTIDUAL n 1885

35,709 Randomized Patients
Stent Thrombosis with Extended Duration DAPT after DES: A Pairwise and Bayesian Network Meta analysis of 10 RCTs and 31,666 Patients

Palmerini T. et al.
Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials.
Lancet. 2015 Jun 13;385(9985):2371-82
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Lancet. 2015 Jun 13;385(9985):2371-82

22% ↑ mortality with prolonged DAPT p .02
## Extended DAPT Duration after DES:
Second vs. First Generation DES

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second Generation DES</strong></td>
<td></td>
</tr>
<tr>
<td>DAPT</td>
<td>2.64 (1.74, 5.98)</td>
</tr>
<tr>
<td>ITALIC</td>
<td>7.01 (3.63, 15.86)</td>
</tr>
<tr>
<td>SECURITY</td>
<td>0.70 (0.12, 4.20)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>0.25 (0.03, 2.25)</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>3.01 (0.31, 28.99)</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>1.08 (0.49, 2.37)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>Heterogeneity: p = 0.21</td>
</tr>
<tr>
<td></td>
<td>1.54 (0.96, 2.47)</td>
</tr>
</tbody>
</table>

**P for Interaction = 0.008**

<table>
<thead>
<tr>
<th><strong>First Generation DES</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT</td>
<td>4.44 (2.22, 8.87)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>2.30 (0.70, 7.56)</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>7.12 (0.37, 138.77)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>Heterogeneity: p = 0.59</td>
</tr>
<tr>
<td></td>
<td>3.94 (2.20, 7.03)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Overall</strong></th>
<th>Heterogeneity: p = 0.59</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.33 (1.63, 3.34)</td>
</tr>
</tbody>
</table>

Giustino G. et al.
Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials.
J Am Coll Cardiol. 2015 Apr 7;65(13):1298-1310
Leaders Free: Multivariate Predictors of Primary Safety Endpoint and Major Bleeding (BARC 3-5)

<table>
<thead>
<tr>
<th></th>
<th>Cardiac death/MI/ST</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1.61 (1.23-2.11) p=0.001</td>
<td>-</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.66 (1.27–2.18) p&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Number of stents per patient</td>
<td>1.20 (1.09–1.32) p&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>BMS vs DCS</td>
<td>1.28 (1.03–1.59) p=0.027</td>
<td>-</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>1.56 (1.23–1.97) p&lt;0.001</td>
<td>1.52 (1.13–2.06) p=0.006</td>
</tr>
<tr>
<td>Hb ( per 1 mmol/ l lower )</td>
<td>1.32 (1.19–1.46) p&lt;0.001</td>
<td>1.73 (1.52–1.96) p&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine &gt;150 μmol/ l</td>
<td>-</td>
<td>1.58 (1.10–2.27) p=0.012</td>
</tr>
<tr>
<td>Planned Oral Anticoagulants</td>
<td>-</td>
<td>2.01 (1.51–2.68) p&lt;0.001</td>
</tr>
</tbody>
</table>

Garot P. et al.
2-Year Outcomes of High Bleeding Risk Patients After Polymer-Free Drug-Coated Stents.
J Am Coll Cardiol. 2017 Jan 17;69(2): 162-171
### Treatment Effect According to AMI Presentation Status at 12–36 Months:

All Randomized Patients (n=11,648)

3.576 (30.7%) Presented with MI 47% STEMI 53% NSTEMI

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Continued Thieno</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent Thrombosis</td>
<td>0.4</td>
<td>1.1</td>
</tr>
<tr>
<td>MACCE</td>
<td>4.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Severe/Moderate Bleeding</td>
<td>2.6</td>
<td>1.7</td>
</tr>
<tr>
<td>All cause Death</td>
<td>2.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Yeh RW. et al.
Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction.

J Am Coll Cardiol. 2015 May 26;65(20):2211-21
Treatment Effect According to AMI Presentation Status at 12–36 Months:
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Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction.
J Am Coll Cardiol. 2015 May 26;65(20):2211-21
**PRECISE DAPT Score**

- Hemoglobin (1gr/Dl decrease): 0-15
- WBC ($10^3$ units /μmol increase): 0-15
- Age (10 years increase): 0-19
- Creatinine (10mL/min decrease): 0-25
- Prior bleeding: 0-26
- **TOTAL**: 100

**DAPT Score**

- Age ≥ 75: -2
- Age 65-74: -1
- Age < 64: 0
- Cigarette smoking: 1
- Diabetes Mellitus: 1
- MI at presentation: 1
- Prior PCI or MI: 1
- PES: 1
- Stent diameter < 3mm: 1
- CHF or LVEF < 30%: 2
- SVG stenting: 2
- **TOTAL**: -2 to 10

**PCI**

- No high bleeding risk (score <25)
- Standard DAPT

- High bleeding risk (score >25)
- Shorter DAPT

- **Uneventful Patients**
  - DAPT Score <2
  - Stop DAPT

- DAPT Score ≥2
  - Prolong DAPT

**DAPT Duration After Drug Eluting Stent Implantation: No News Is Good News**

Vaglimigli M., Gargiulo G.

JACC Cardiovasc Interv. 2017 Jun 26; 10(12): 1211-1214
2016 ACC/AHA Guidelines:
Updated Algorithm for DAPT Duration in CAD

CAD  
SIHD

Acute/recent ACS (N STEACS or STEMI)

Medical Therapy  
Lytic (STEMI)  
PCI (BMS DES)  
CABG

Class I:
At least 12 mo (clopidogrel, ticagrelor)

Class I:
Minimum 14 d and ideally at least 12 mos

Class I:
At least 12 mo (clopidogrel, prasugrel)

Class I:
After CABG, resume P2Y12 inhibitor to complete 1 y of DAPT

No high risk of bleeding and no significant overt bleeding on DAPT
Class IIb:
>12 mo may be reasonable

DAPT Duration: Factors to be Weighed

HIGH BLEEDING RISK
- Clinically significant bleeding on DAPT
- Bleeding diathesis
- Prior bleeding
- Female gender
- Elderly
- Liver disease
- Chronic renal dysfunction
- Anemia or thrombocytopenia
- Chronic anticoagulation
- Diabetes
- Second generation DES

LOW ISCHEMIC RISK
- Stable CAD
- Troponin negative ACS
- Single vessel disease
- Simple stenting (single, short, large stent)

INTERMEDIATE ISCHEMIC RISK
- Troponin positive ACS

HIGH ISCHEMIC RISK
- Troponin positive ACS

Favors 3 or 6-month DAPT
Favors 1-year DAPT
Favors > 1-year DAPT

Palmerini T., Stone GW.
Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: conceptual evolution based on emerging evidence.
Eur Heart J. 2016 Jan 21;37(4):353-64
An 82 Years Old Lady with STEMI: Revisited

- **Index to 12 months:**
  - Dabigatran 110 mg twice daily
  - Clopidogrel 75 mg once daily

- **After 12 months:**
  - Dabigatran 150 mg twice daily
Ischemia and Bleeding: The Yin and Yang of ACS

In Chinese philosophy, yin and yang (\(\text{yín} / \text{yǎng}\); Chinese: 阴阳, lit. "dark-bright", "negative-positive") describes how seemingly opposite or contrary forces may actually be complementary, interconnected, and interdependent in the natural world, and how they may give rise to each other as they interrelate to one another.