ST-Elevation MI: Update on Bivalirudin and DES

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Disclosure

- Research grant to Institution
- The Medicines Co
- Sanofi, BMS
- Eli Lilly, Daichi-Sankyo
Relationship Between Myocardial Salvage and Survival

- **Mortality reduction (%)**
  - Median U.S. Sx-ER: 2°
  - Lytic given: 30’
  - Lytic works: 60’

- **Extent of salvage (% of area at risk)**
  - Median U.S. PCI Sx-bal: 3.5°

- **Modifying factors**
  - Collaterals
  - Ischemic preconditioning
  - MVO₂

- **Treatment objectives**
  - Time to treatment is critical
  - Opening the IRA (PCI)

- **Median U.S. Sx-ER: 2°**
- **Lytic given: 30’**
- **Lytic works: 60’**
- **Median U.S. PCI Sx-bal: 3.5°**
Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

R 1:1

UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)

Bivalirudin monotherapy (± provisional GP IIb/IIIa)

Emergent angiography, followed by triage to...

CABG – Primary PCI – Medical Rx

3006 pts eligible for stent randomization

R 3:1

Paclitaxel-eluting TAXUS stent

Bare metal EXPRESS stent

Clinical FU at 30 days, 6 months, 1 year, and then yearly through 5 years; angio FU at 13 months
Primary Outcome Measures (ITT)

<table>
<thead>
<tr>
<th>Event</th>
<th>Heparin + GP IIb/IIIa inhibitor (N=1802)</th>
<th>Bivalirudin monotherapy (N=1800)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Net adverse clinical events</strong></td>
<td>DIFF = -2.9% [-4.9, -0.8] RR = 0.76 [0.63, 0.92] P_{NI} ≤ 0.0001 P_{sup} = 0.006</td>
<td>DIFF = -3.3% [-5.0, -1.6] RR = 0.60 [0.46, 0.77] P_{NI} ≤ 0.0001 P_{sup} ≤ 0.0001</td>
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<td><strong>Major bleeding</strong></td>
<td>DIFF = -2.9% [-4.9, -0.8] RR = 0.76 [0.63, 0.92] P_{NI} ≤ 0.0001 P_{sup} = 0.006</td>
<td>DIFF = -3.3% [-5.0, -1.6] RR = 0.60 [0.46, 0.77] P_{NI} ≤ 0.0001 P_{sup} ≤ 0.0001</td>
</tr>
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<td><strong>MACE</strong></td>
<td>DIFF = -0.0% [-1.6, 1.5] RR = 0.99 [0.76, 1.30] P_{sup} = 1.00</td>
<td>DIFF = -3.3% [-5.0, -1.6] RR = 0.60 [0.46, 0.77] P_{NI} ≤ 0.0001 P_{sup} ≤ 0.0001</td>
</tr>
</tbody>
</table>

*Not related to CABG
**MACE = All cause death, reinfarction, ischemic TVR or stroke
Rapid Reversal of Bivalirudin is the Key
Inactivated by Thrombin Itself and Metabolized by Plasma Esterases

Plasma concentrations versus time

Bolus 1mg/kg  Infusion 2.5 mg/kg/h
Bolus 0.75 mg/kg  Infusion 1.75 mg/kg/h

Shown to reduce risk of ischemia in PCI (6.5 mcg/mL)

25 minute half-life

Three-Year All-Cause Mortality

- **Bivalirudin alone (n=1800)**
  - 1-yr HR [95%CI] = 0.71 [0.51, 0.98]
  - P = 0.04
  - 3-yr HR [95%CI] = 0.75 [0.58, 0.97]
  - P = 0.03

- **Heparin + GPIIb/IIIa (n=1802)**
  - 1-yr HR [95%CI] = 0.75 [0.58, 0.97]
  - P = 0.04

**Number at risk**
- **Bivalirudin alone**
  - 1800, 1689, 1660, 1633, 1611, 1574, 1098
- **Heparin+GPIIb/IIIa**
  - 1802, 1670, 1643, 1593, 1568, 1525, 1043
Methods

Study Flow Chart

3602 Horizons AMI STEMI patients

Pre-treated with Heparin N=2357 (65%)

Randomization stratified according to Pretreatment with Heparin

Bivalirudin Switch Group N=1,178

Heparin plus GPIIb/IIIa Control Group n=1,179

Dangas et al, JACC 2011
HORIZONS SWITCH
2 year NACE, cardiac mortality, major bleeding and stent thrombosis

Dangas et al, JACC 2011
3602 STEMI pts enrolled in the HORIZONS AMI trial

- Ticlopidine loading
  - N=13

- Data missing
  - N=108

- Pre-randomization thienopyridines
  - N=143

- Clopidogrel other loading dose
  - N=27

- 300 mg clopidogrel loading dose
  - N=1153 pts

- 600 mg clopidogrel loading dose
  - N=2158 pts

Dangas et al, SCAI-ACCi2 2008
The impact of Biv was independent of the dose of clopidogel loading. Interaction P values for the above 3 endpoints = 0.48 (NACE) 0.41 (Major bleeding), and 0.75 (MACE).
Radial Access in HORIZONS

Genereux et al; Eurointerv 2012
Clinical Outcomes Following Stent Thrombosis Occurring In-Hospital versus Out-Of-Hospital: Results from HORIZONS-AMI

George D Dangas, MD, PhD; Bimmer E Claessen, MD, PhD; Roxana Mehran, MD; Sorin Brener, MD; Bruce R Brodie, MD; Dariusz Dudek, MD; Bernhard Witzenbichler, MD; Jan Z Peruga, MD; Giulio Guagliumi, MD, PhD; Jeffrey W Moses, MD; Ke Xu, PhD; Gregg W Stone, MD

JACC 2012;59(20):1752-9
Results
Mortality according to ARC timing definitions

- **Acute**: 7.1%
- **Subacute**: 50.0%
- **Late**: 3.3%
- **Very late**: 8.0%

**In-Hospital ST**
- Acute: 7.1%
- Subacute: 50.0%
- Late: 3.3%
- Very late: 8.0%

**Out-of-Hospital ST**
- Acute: 0%
- Subacute: 27.6%
- Late: 3.3%
- Very late: 0%
Conclusion

• Following primary PCI for STEMI, more than one-third of all ST events during 3-year follow-up occurred during the index hospital phase.

• Mortality and major bleeding were significantly higher after in-hospital ST compared with out-of-hospital ST.

• Although bivalirudin was associated with more acute stent thrombosis, it was also associated with lower mortality after a stent thrombosis event.
Development and Validation of a Stent Thrombosis Risk Score In Patients With Acute Coronary Syndromes

George D Dangas; Bimmer E Claessen; Roxana Mehran; Ke XU; Martin Fahy; Helen Parise; José PS Henriques; E Magnus Ohman; Harvey D White; Gregg W Stone

Jacc interventions; in press
<table>
<thead>
<tr>
<th>Variable Calculation</th>
<th>Integer Assignment for Stent Thrombosis Risk Score</th>
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</thead>
<tbody>
<tr>
<td>Type of Acute Coronary Syndrome</td>
<td>NSTE-ACS w/o ST changes +1 NSTE-ACS with ST deviation +2 STEMI+4</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>Yes: +1 No: +0</td>
</tr>
<tr>
<td>Insulin treated diabetes mellitus</td>
<td>Yes: +2 No: +0</td>
</tr>
<tr>
<td>History of PCI</td>
<td>Yes: +1 No: +0</td>
</tr>
<tr>
<td>Baseline Platelet Count</td>
<td>&lt;250K/ul: +0 250K/ul-400K/ul: +1 &gt;400K/ul: +2</td>
</tr>
<tr>
<td>Absence of pre-PCI Heparin</td>
<td>Yes: +1 No: 0</td>
</tr>
<tr>
<td>Aneurysm or Ulceration</td>
<td>Yes: +2 No: 0</td>
</tr>
<tr>
<td>Baseline TIMI flow grade 0/1</td>
<td>Yes: +1 No: 0</td>
</tr>
<tr>
<td>Final TIMI flow grade &lt; 3</td>
<td>Yes: +1 No: 0</td>
</tr>
<tr>
<td>Number of Vessels Treated</td>
<td>1 vessel: +0 2 vessels: +1 3 vessels: +2</td>
</tr>
</tbody>
</table>
Stent Thrombosis after primary PCI for STEMI in relation to non-usage of dual antiplatelet therapy over time: Results of the HORIZONS-AMI trial

George D Dangas, Bimmer E Claessen, Roxana Mehran, Ke Xu, Gregg W Stone

*EuroIntervention; in press*
Results According to DAPT d/c

Events under 30 days

- Thienopyridine: 14.9%, P=0.006
- Aspirin: 6.3%, P=0.012
- Thienopyridine or Aspirin: 6.6%, P=0.003
- Thienopyridine and Aspirin: 8.0%, P=0.025

Events from 30 days to 6 months

- Thienopyridine: 44.4%, P=0.016
- Aspirin: 11.9%, P=0.046
- Thienopyridine or Aspirin: 9.4%, P=0.004
- Thienopyridine and Aspirin: 13.8%, P=0.144

Events from 6 to 12 months

- Thienopyridine: 50.0%, P=0.22
- Aspirin: 31.9%, P=0.36
- Thienopyridine or Aspirin: 16.7%, P=0.23
- Thienopyridine and Aspirin: 9.0%, P=0.30

Events beyond 1 year

- Thienopyridine: 43.8%, P=0.014
- Aspirin: 34.4%, P=0.0008
- Thienopyridine or Aspirin: 11.7%, P=0.056
- Thienopyridine and Aspirin: 28.1%, P=0.005
Conclusion

- the relationship between ST and non-usage of DAPT was complex and varied overtime
- It was strong during the 1-6 month timeframe, but not between 6 and 12 months
- Hereafter, very late ST was associated with non-usage of aspirin but not of a thienopyridine
Primary PCI
CADILLAC: 30-Day MACE

- PTCA, no abciximab
- PTCA, abciximab
- Stent, no abciximab
- Stent, abciximab

Days to event

P=0.02

Stone et al, NEJM 2001
Use of Drug-Eluting Stents in Acute Myocardial Infarction
A Systematic Review and Meta-Analysis

Somjot S. Brar, MD, Martin B. Leon, MD, Gregg W. Stone, MD, Roxana Mehran, MD, Jeffrey W. Moses, MD, Simerjeet K. Brar, BS, George Dangas, MD, PhD
New York, New York

Objectives
The primary aim of the analysis was to compare outcomes by stent type for death, myocardial infarction (MI), target vessel revascularization (TVR), and stent thrombosis in randomized trials of ST-segment elevation myocardial infarction (STEMI). A secondary analysis was performed among registry studies.

Background
It is not known whether there are differences in outcomes between drug-eluting stents (DES) and bare-metal stents (BMS) for STEMI.

Methods
We searched MEDLINE, EMBASE, the Cochrane Library, and Internet sources for articles comparing outcomes between DES and BMS among patients with STEMI between January 2000 and October 2008. Randomized controlled trials and registries including patients 18 years of age and older receiving a DES or BMS were included. We extracted variables related to the study design, setting, participants, and clinical endpoints.

Results
Thirteen randomized trials were identified (N = 7,352). Compared with BMS, DES significantly reduced TVR (relative risk [RR]: 0.44; 95% confidence interval [CI]: 0.35 to 0.55), without increasing death (RR: 0.89; 95% CI: 0.70 to 1.14), MI (RR: 0.82; 95% CI: 0.64 to 1.05), or stent thrombosis (RR: 0.97; 95% CI: 0.73 to 1.28). These observations were durable over 2 years. Among 18 registries (N = 26,521), DES significantly reduced TVR (RR: 0.54; 95% CI: 0.40 to 0.74) without an increase in MI (RR: 0.87, 95% CI: 0.62 to 1.23). Death was significantly lower in the DES group within 1 year of the index percutaneous coronary intervention, but there were no differences within 2 years (p = 0.45).

Conclusions
The use of DES appears safe and efficacious in randomized trials and registries of patients with STEMI. The DES significantly reduce TVR compared with BMS, without an increase in death, MI, or stent thrombosis within 2 years of the index procedure. (J Am Coll Cardiol 2009;53:1677–89) © 2009 by the American College of Cardiology Foundation
DES in AMI Meta-Analysis

Mortality (RCTs)

- Di Lorenzo et al.
- STRATEGY
- PASSION
- TYPHOON
- BASKET-AMI
- SELECTION
- SESAMI
- Diaz de la Llera et al.
- DEDICATION Stent
- HAAMU-STENT
- MISSION
- HORIZONS-AMI Stent
- MULTISTRATEGY

Overall

Relative Risk (95% CI)
0.89
(0.70 - 1.14)

I² = 0%

Favors DES
Favors BMS

Brar et al. JACC 2009; 53(18)
DES in AMI Meta-Analysis
Myocardial Infarction (RCTs)

Di Lorenzo et al.
STRATEGY
BASKET-AMI
PASSION
TYPHOON
SELECTION
SESAMI
Diaz de la Llera et al.
DEDICATION Stent
HAAMU-STENT
MISSION
HORIZONS-AMI Stent
MULTISTRATEGY

Overall

Relative Risk (95% CI)
0.82
(0.64 - 1.05)

Favors DES  Favors BMS

Brar et al. JACC 2009; 53(18)
Target Vessel Revascularization (RCTs)

- STRATEGY
- BASKET-AMI
- PASSION
- TYPHOON
- SELECTION
- SESAMI
- Diaz de la Llera et al.

DEDICATION Stent
HAAMU-STENT
MISSION
HORIZONS-AMI Stent
MULTISTRATEGY

Overall

Favors DES  Favors BMS

Relative Risk (95% CI)
0.44
(0.35 - 0.55)
p < 0.001

56%

Di Lorenzo et al.

Brar et al. JACC 2009; 53(18)
Di Lorenzo et al.
STRATEGY
BASKET-AMI
PASSION
TYPHOON
DEDICATION Stent
HAAMU-STENT
MISSION
SELECTION
Diaz de la Llera et al.
HORIZONS-AMI Stent
MULTISTRATEGY

Overall

Relative Risk (95% CI)
0.97
(0.73 - 1.28)

Brar et al. JACC 2009; 53(18)
EXAMINATION trial
(A Clinical Evaluation of Xience-V stent in Acute Myocardial Infarction)

12 centers - 3 countries
M. Sabate et al
Study Design = All-comer RCT

Patients suffering from an AMI, presenting within 48 hours after Onset of Symptoms Requiring Emergent PCI of a Native Coronary Artery

Randomization 1:1 (n=1504)

Everolimus-eluting Stent (751 patients)

6 pts withdrew consent

Cobalt-chromium stent (747 patients)

Everolimus-eluting Stent (737 patients-98.1%)

Cobalt-chromium stent (732 patients-98%)

1-YEAR FOLLOW-UP
Dual Antiplatelet Regimen

EXAMINATION trial

Discharge 1 month 6 month 1 year
Xience-V Vision
Primary Endpoint:
Composite of all-cause death, any MI or any revascularization

Survival, %

<table>
<thead>
<tr>
<th></th>
<th>Xience-V</th>
<th>Vision</th>
<th>Log-Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival, %</td>
<td>88.0</td>
<td>85.6</td>
<td>0.16</td>
</tr>
</tbody>
</table>

EXAMINATION trial
Secondary Endpoints: Cardiac Death

Survival, %

<table>
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<th>Xience-V</th>
<th>Vision</th>
<th>Log-Rank P-value</th>
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<tbody>
<tr>
<td>Survival, %</td>
<td>96.8</td>
<td>97.2</td>
<td>0.68</td>
</tr>
</tbody>
</table>

EXAMINATION trial
Secondary Endpoints:
Target Vessel Revascularization

- **XIENCE-V**
- **Vision**
- **Log-Rank P-value**

<table>
<thead>
<tr>
<th>Freedom from event, %</th>
<th>Xience-V</th>
<th>Vision</th>
<th>Log-Rank P-value</th>
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<tr>
<td>96.1</td>
<td>93.0</td>
<td>0.007</td>
<td></td>
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</table>

**EXAMINATION trial**
Definite/Probable Stent Thrombosis

EXAMINATION trial

$p = 0.01$
My “Bottom Line”

- In patients with acute STEMI who are at high risk for bleeding:
  - Move swiftly!
  - Early treatment with IV heparin (weight adjusted bolus pre-transfer to cath lab).
  - Early administration of antiplatelets orally
    - High loading dose of clopidogrel
- In the Cath Lab:
  - Radial Approach
  - Switch to bivalirudin
    - Statistically Lower cardiac mortality
    - Major savings in Major Bleeding
  - Thrombectomy
  - Bare Metal Stent to reduce abrupt closure and avoid obligatorily prolonged DAPT
  - DES (EES specifically) for routine use otherwise.