Safety of Drug-Eluting Stents in Acute Coronary Syndromes

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Bern University Hospital, Switzerland
Scientific Advances and Cardiovascular Mortality


1958
Coronary arteriography (Sones)

1961
Risk factors defined

1961
First coronary care unit developed (Julian)

1969
First description of CABG (Favolaro)

1972
NHBPEP

1977
Coronary angioplasty (Grüntzig)

1976
First HMG CoA reductase inhibitor described (Endo)

1980
First implantable cardioverter-defibrillator developed (Mirowski)

1983
CASS

1985
TIMI 1

1986
GISSI and

1992
SAVE

1993
Superiority of primary PCI vs. fibrinolysis in acute MI

2002
Efficacy of drug-eluting vs. bare-metal stents

2009
Left-ventricular assist device as destination therapy in advanced heart failure shown to be effective

2009
Genomewide association in early-onset MI described

2009
Deep gene sequencing for responsiveness to cardiovascular drugs performed
Mortality and Repeat Revascularization with Early Generation DES versus Bare Metal Stents


**Mortality**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES vs BMS</td>
<td>1.00 (0.82-1.25)</td>
</tr>
<tr>
<td>PES vs BMS</td>
<td>1.03 (0.84-1.22)</td>
</tr>
<tr>
<td>SES vs PES</td>
<td>0.96 (0.83-1.24)</td>
</tr>
</tbody>
</table>

**Repeat Revasc**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES vs BMS</td>
<td>0.30 (0.24-0.37)</td>
</tr>
<tr>
<td>PES vs BMS</td>
<td>0.42 (0.33-0.53)</td>
</tr>
<tr>
<td>SES vs PES</td>
<td>0.70 (0.56-0.84)</td>
</tr>
</tbody>
</table>

NNT=7 (CI 6-8)

NNT=8 (CI 7-10)

NNT=35 (CI 23-65)
Drug-Eluting vs. Bare Metal Stent in Acute MI

**Propensity Score Matched Pair Comparison of DES and BMS in Patients Undergoing PCI for acute myocardial infarction in Massachusetts**

*N=7,217 Patients (04/2003-09/2004)*

**Mortality**

<table>
<thead>
<tr>
<th></th>
<th>DES 8.5%</th>
<th>BMS 11.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>8.5%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Change</td>
<td>3.1%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

**Recurrent MI**

<table>
<thead>
<tr>
<th></th>
<th>DES 7.0%</th>
<th>BMS 8.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent MI</td>
<td>7.0%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Change</td>
<td>1.0%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>
Early Generation Drug-Eluting Stents versus Bare Metal Stents in Patients With STEMI

Kalesan B et al. *Eur Heart J* 2012

15 RCTs Comparing DES and BMS in 7,843 STEMI Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>DES</th>
<th>BMS</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>14.1%</td>
<td>15.7%</td>
<td>0.91</td>
<td>(0.71-1.15)</td>
<td>0.63</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>7.5%</td>
<td>7.9%</td>
<td>1.01</td>
<td>(0.73-1.40)</td>
<td>0.90</td>
</tr>
<tr>
<td>MI</td>
<td>9.2%</td>
<td>9.1%</td>
<td>0.94</td>
<td>(0.78-1.14)</td>
<td>0.98</td>
</tr>
<tr>
<td>TVR</td>
<td>8.7%</td>
<td>15.4%</td>
<td>0.51</td>
<td>(0.43-0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Definite ST</td>
<td>4.1%</td>
<td>3.2%</td>
<td>1.08</td>
<td>(0.82-1.43)</td>
<td>0.46</td>
</tr>
</tbody>
</table>
Stent Choice in ACS

- Vessel Size in ACS
- Thrombus Burden in ACS
- Newer Generation DES and ACS
- Discontinuation of Antiplatelet Therapy
- Vessel Remodelling and Inflammation in ACS
### Impact of Vessel Diameter and Late Loss on Restenosis

<table>
<thead>
<tr>
<th>RVD</th>
<th>4.0 mm</th>
<th>3.5 mm</th>
<th>3.0 mm</th>
<th>2.5 mm</th>
<th>2.0 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late loss (BMS)</td>
<td>0.9 mm</td>
<td>0.9 mm</td>
<td>0.9 mm</td>
<td>0.9 mm</td>
<td>0.9 mm</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>23%</td>
<td>26%</td>
<td>30%</td>
<td>36%</td>
<td>45%</td>
</tr>
<tr>
<td>Late loss (DES)</td>
<td>0.2 mm</td>
<td>0.2 mm</td>
<td>0.2 mm</td>
<td>0.2 mm</td>
<td>0.2 mm</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>5%</td>
<td>6%</td>
<td>7%</td>
<td>8%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Vessel Size in Patients With Acute Myocardial Infarction

Mean Reference Vessel Diameter (mm)
Paclitaxel-Eluting Stents versus Bare-Metal Stents in Acute Myocardial Infarction: HORIZONS-AMI


**In-Stent**

<table>
<thead>
<tr>
<th></th>
<th>PES</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1081</td>
<td>0.41</td>
<td>0.64</td>
</tr>
<tr>
<td>N=332</td>
<td>0.82</td>
<td>0.70</td>
</tr>
</tbody>
</table>

**In-Segment**

<table>
<thead>
<tr>
<th></th>
<th>DES</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1081</td>
<td>0.30</td>
<td>0.56</td>
</tr>
<tr>
<td>N=332</td>
<td>0.59</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*P* < 0.001
Drug-Eluting Stent Safety in Large Vessels

BASKET-PROVE: DES vs BMS


**Death or MI**

**Repeat Revasc**

![Graph showing outcomes for Drug-Eluting Stent Safety in Large Vessels](image)

2,314 Patients

2,314 Patients
Newer Generation Drug-Eluting Stents versus Bare Metal Stents in Patients with STEMI

**EXAMINATION**  
**EES** versus **BMS**  

**COMFORTABLE AMI**  
**BES** versus **BMS**  

1 yr HR  
0.28 (0.13-0.59)  
P < 0.001
Stent Choice in ACS

- Vessel Size in ACS
- Newer Generation DES and ACS
- Thrombus Burden in ACS
- Discontinuation of Antiplatelet Therapy
- Vessel Remodelling and Inflammation in ACS
Acute Coronary Syndrome as Predictor of Stent Thrombosis

- Park et al, Am J Card 2006: OR=12.4 (1.7-89.7)
- Daemen et al, Lancet 2007: OR=2.3 (1.3-4.0)
- Urban et al, Circulation 2006: OR=1.8 (1.1-2.7)
- De la Torre et al, JACC 2008: HR=2.6 (1.3-4.9)
Impact of Thrombus Burden on Risk of Stent Thrombosis With DES in Patients With STEMI

**Independent Predictors of ST**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.6</td>
<td>0.4-0.8</td>
</tr>
<tr>
<td>Index ST</td>
<td>6.2</td>
<td>2.1-18.9</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>4.1</td>
<td>1.6-10.0</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>0.1</td>
<td>0.01-0.8</td>
</tr>
<tr>
<td>Large thrombus</td>
<td>8.7</td>
<td>3.4-22.5</td>
</tr>
</tbody>
</table>

![Graph showing cumulative IRA-ST rate (%) over months of follow-up for LTB and STB.]
Risk of Ischemic Events and Stent Thrombosis Stratified According to Time and Stent Type (DES vs BMS) in STEMI

15 RCTs Comparing DES and BMS in 7,843 STEMI Patients

Death
0 to 1 year: RR (95% CI) = 0.89 (0.68-1.15), p-inter = 0.91
1 to max FU: RR (95% CI) = 0.91 (0.65-1.26)
0 to max FU: RR (95% CI) = 0.91 (0.71-1.15)

Cardiac death
0 to 1 year: RR (95% CI) = 1.09 (0.75-1.59), p-inter = 0.46
1 to max FU: RR (95% CI) = 0.81 (0.40-1.64)
0 to max FU: RR (95% CI) = 1.01 (0.73-1.40)

MI
0 to 1 year: RR (95% CI) = 0.73 (0.57-0.94), p-inter = 0.006
1 to max FU: RR (95% CI) = 1.30 (0.95-1.78)
0 to max FU: RR (95% CI) = 0.94 (0.78-1.14)

Definite ST
0 to 1 year: RR (95% CI) = 0.79 (0.56-1.10), p-inter = 0.0046
1 to max FU: RR (95% CI) = 2.10 (1.20-3.68)
0 to max FU: RR (95% CI) = 1.05 (0.79-1.39)

Definite/Probable ST
0 to 1 year: RR (95% CI) = 0.81 (0.60-1.11), p-inter = 0.0092
1 to max FU: RR (95% CI) = 2.04 (1.16-3.60)
0 to max FU: RR (95% CI) = 1.03 (0.80-1.32)

Kalesan, Windecker
Stent Choice in ACS

- Vessel Size in ACS
- Newer Generation DES and ACS
- Thrombus Burden in ACS
- Discontinuation of Antiplatelet Therapy
- Vessel Remodelling and Inflammation in ACS
Arterial Healing at Culprit Sites after DES Implantation in Patients with Acute MI and Stable Angina – An Autopsy Study

Nakazawa et al. *Circulation* 2008; 118:1138-1145

Correlation between fibrous cap thickness and % uncovered struts

Correlation between fibrous cap thickness and % uncovered struts

\[ p = 0.0006, r = -0.60 \]

AMI lesions (with Plaque Rupture)

Stable Lesions (with Fibroatheroma and thick cap)
Stent Malapposition/Vessel Remodeling

I. Incomplete stent apposition due to positive arterial remodelling

A. Inflammation

B.

II. Incomplete stent apposition due to thrombus dissolution

A. Thrombolysis

B.

III. Incomplete stent apposition due to stent underexpansion

A. Fulcrum

B.

Cook S et al. Circulation 2007
Arterial Healing at Culprit Sites after DES Implantation in Patients with Acute MI and Stable Angina – An Autopsy Study

Nakazawa et al. *Circulation* 2008; 118:1138-1145

**Neointimal thickness**

- Acute MI culprit site (N=25): 0.04 (0.02–0.09) mm
- Stable angina culprit site (N=26): 0.11 (0.07–0.21) mm

\[ P = 0.008 \]

**Struts with fibrin**

- Acute MI culprit site (N=25): 63%
- Stable angina culprit site (N=26): 36%

\[ P = 0.008 \]

**Struts with inflammation**

- Acute MI culprit site (N=25): 35%
- Stable angina culprit site (N=26): 17%

\[ P = 0.003 \]

**Uncovered struts**

- Acute MI culprit site (N=25): 49%
- Stable angina culprit site (N=26): 9%

\[ P = 0.01 \]
Association of Eosinophilic Infiltrates of Thrombus Aspirates With Vessel Remodeling
Cook S, Ladich E, Virmani R, Windecker S. *Circulation* 2009

**Eosinophilic Infiltrates**

**Vessel Remodeling**

---

Eosinophils 25.2%
Late Acquired Stent Malapposition in HORIZONS-AMI

Guo N et al. Circulation 2010;122:1088-84

Independent predictors of LASM:
- plaque/thrombus protrusion at baseline (OR=5.6, 95% CI 2.3-13.5)
- PES use (OR=6.3, 95% CI 2.2-18.6)
OCT 5 yrs after STEMI

STEMI @ BL

Stent Thrombosis @ 5.5 yrs

Courtesy Räber/Windecker, SIRTAX OCT
Strut Coverage, Malapposition and Protrusion in HORIZONS-AMI – OCT Substudy @ 13 Months

Guagliumi G et al. Circulation 2010;123:274-81

- Malapposed and Uncovered Struts: 0.1% BMS, 0.9% PES
- Uncovered Struts: 1.1% BMS, 5.7% PES
- Protruding Struts: 1% BMS, 6.3% PES

P-values: P=0.0003, P<0.0001, P<0.0001
Stent Choice in ACS

- Vessel Size in ACS
- Newer Generation DES and ACS
- Thrombus Burden in ACS
- Vessel Remodelling and Inflammation in ACS
- Discontinuation of Antiplatelet Therapy
Discontinuation of Antiplatelet Therapy as Predictor of Stent Thrombosis

- HR = 19.2 (5.6-65.5)
- OR = 4.8 (2.0-11.1)
- HR = 13.7 (4.0-46.7)
- HR = 13.8 (8.8-21.6)
- HR = 4.6 (1.4-15.35)
Premature Discontinuation of Thienopyridine Therapy After DES Implantation
Spertus JA et al. Circulation 2006;113:2803-9

Multicenter, prospective PREMIER registry in patients admitted with myocardial infarction
- 500 DES patients enrolled at 19 sites
- 68 (14%) patients d/c thienopyridine

Factors associated with premature Thienopyridine discontinuation
- older age
- lower socioeconomic status
- preexisting cardiovascular disease
- inadequate discharge instructions
- lack of referral to cardiac rehab

Mortality Between 30 Days and 1 Year

<table>
<thead>
<tr>
<th></th>
<th>Off Thienopyridine</th>
<th>On Thienopyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Rehosp.</td>
<td>23</td>
<td>14</td>
</tr>
</tbody>
</table>
Death, MI, or Stroke

>1 Year vs. ≤1 Year

- REAL / ZEST (N=2,701)
  - 1.73 (0.99-3.00)
- PRODIGY (N=2,701)
  - 1.02 (0.78-1.35)
- Overall (N=4,671)
  - 1.25 (0.76-2.07)

>6 Months vs. ≤6 Months

- REAL / ZEST (N=1,443)
  - 1.12 (0.77-1.67)
- PRODIGY (N=2,701)
  - 1.02 (0.78-1.35)
- Overall (N=4,671)
  - 1.05 (0.85-1.31)

Bleeding

>1 Year vs. ≤1 Year

- REAL / ZEST (N=2,701)
  - 2.93 (0.31-28.46)
- PRODIGY (N=2,701)
  - 2.17 (1.44-10.00)
- Overall (N=4,671)
  - 2.19 (1.46-3.28)

>6 Months vs. ≤6 Months

- REAL / ZEST (N=1,443)
  - 2.56 (0.79-8.33)
- PRODIGY (N=2,701)
  - 2.17 (1.44-10.00)
- Overall (N=4,671)
  - 2.21 (1.50-3.25)

Adapted from Kastrati A. ESC Congress 2011, Paris
**Pt oriented Outcome stratified by stent from 6 up to 24 months**

<table>
<thead>
<tr>
<th></th>
<th>HAZARD RATIO (95% CI)</th>
<th>P-VALUES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Superior</td>
<td>Interaction</td>
</tr>
<tr>
<td><strong>6-mo Landmark Death/MI/CVA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS</td>
<td>1.04 (0.56-1.95)</td>
<td>0.90</td>
<td>0.05</td>
</tr>
<tr>
<td>ENDEAVOR SPRINT</td>
<td>2.55 (1.19-5.47)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>TAXUS</td>
<td>0.63 (0.35-1.14)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>XIENCE V</td>
<td>1.06 (0.53-2.11)</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td><strong>6-mo Landmark Death/MI</strong></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>BMS</td>
<td>0.83 (0.43-1.58)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>ENDEAVOR SPRINT</td>
<td>2.07 (0.94-4.53)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>TAXUS</td>
<td>0.59 (0.30-1.14)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>XIENCE V</td>
<td>1.18 (0.52-2.68)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td><strong>6-mo CV Death/MI</strong></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>BMS</td>
<td>0.86 (0.49-1.51)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>ENDEAVOR SPRINT</td>
<td>2.33 (1.20-4.53)</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>TAXUS</td>
<td>0.73 (0.49-1.31)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>XIENCE V</td>
<td>0.58 (0.26-1.33)</td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>

24-month DAPT better 6-month DAPT better

*Courtesy: M Valgimigli*
Stent Choice in ACS

Vessel Size in ACS
Newer Generation DES and ACS
Thrombus Burden in ACS
Discontinuation of Antiplatelet Therapy
Vessel Remodelling and Inflammation in ACS
Struts Coverage 9 Months After Implantation of Everolimus- and Sirolimus-Eluting Stents
Choi et al. *Int J Cardiovasc Imaging* 2011

Lesions With >10% Uncovered Struts

(A) EES  (B) SES

Bar chart showing:
- EES (N=40): 10%
- SES (N=70): 34.3%
# Everolimus-Eluting Stent versus Early Generation DES

**DES Safety – Risk of Stent Thrombosis**

<table>
<thead>
<tr>
<th>Trials</th>
<th>EES</th>
<th>SES</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-TEST 4</td>
<td>4/652</td>
<td>9/652</td>
<td>0.44 (0.14, 1.44)</td>
</tr>
<tr>
<td>SORT-OUT 4</td>
<td>2/1390</td>
<td>9/1384</td>
<td>0.22 (0.05, 1.02)</td>
</tr>
<tr>
<td>BASKET-PROVE</td>
<td>2/774</td>
<td>3/775</td>
<td>0.67 (0.11, 3.98)</td>
</tr>
<tr>
<td>RESET</td>
<td>5/1597</td>
<td>6/1600</td>
<td>0.83 (0.26, 2.73)</td>
</tr>
<tr>
<td>ESSENCE-DIABETES</td>
<td>0/149</td>
<td>0/151</td>
<td>(Excluded)</td>
</tr>
<tr>
<td>Burzotta et al.</td>
<td>0/75</td>
<td>0/75</td>
<td>(Excluded)</td>
</tr>
</tbody>
</table>

**Overall**  
(I-squared = 0.0%, p = 0.579)

- **Favors EES**: 0.51 (0.26, 0.99)

---

<table>
<thead>
<tr>
<th>Trials</th>
<th>EES</th>
<th>PES</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIRIT II</td>
<td>1/223</td>
<td>2/777</td>
<td>0.17 (0.02, 1.88)</td>
</tr>
<tr>
<td>SPIRIT III</td>
<td>6/669</td>
<td>2/333</td>
<td>1.49 (0.30, 7.36)</td>
</tr>
<tr>
<td>SPIRIT IV</td>
<td>8/2458</td>
<td>12/1229</td>
<td>0.33 (0.14, 0.81)</td>
</tr>
<tr>
<td>COMPARE</td>
<td>5/897</td>
<td>24/903</td>
<td>0.21 (0.08, 0.55)</td>
</tr>
</tbody>
</table>

**Overall**  
(I-squared = 34.6%, p = 0.205)

- **Favors EES**: 0.35 (0.16, 0.77)

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**N = 11,167**  
**N = 6,789**

Kalesan, Windecker
Bern-Rotterdam Cohort Study

Very Late Definite ST (1-4 yrs)

Räber et al. Circulation 2012; 125:1110-21

EES vs. SES HR* = 0.33, 95% CI 0.15 – 0.72, P=0.006
EES vs. PES HR* = 0.24, 95% CI 0.13-0.47, P <0.0001

*from Cox proportional hazards model
Biolimus Eluted from Biodegradable Polymer versus Sirolimus Eluted from Durable Polymer

Barlis P et al. Eur Heart J 2010

Lesions With At Least 5% Uncovered Struts

-45.5
(-76.9 to -14.3)

P<0.01

N=29

N=35

Biolimus Stent
Sirolimus Stent

29 Lesions
35 Lesions
Biodegradable Polymer DES versus Durable Polymer Sirolimus Eluting Stents

Stefanini G et al. Lancet 2011

**DES Safety – Risk of Stent Thrombosis**

<table>
<thead>
<tr>
<th></th>
<th>BP-DES</th>
<th>DP-SES</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-TEST 3</td>
<td>1/202</td>
<td>2/202</td>
<td>0.50 (0.05, 5.47)</td>
</tr>
<tr>
<td>ISAR-TEST 4</td>
<td>9/1299</td>
<td>9/652</td>
<td>0.50 (0.20, 1.26)</td>
</tr>
<tr>
<td>LEADERS</td>
<td>20/857</td>
<td>32/850</td>
<td>0.62 (0.36, 1.08)</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p=0.92)</td>
<td></td>
<td></td>
<td><strong>0.58 (0.37, 0.93)</strong></td>
</tr>
</tbody>
</table>

**Definite ST Meta-Analysis**

**Definite ST LEADERS trial @ 4 years**

Risk ratio

- Favours biodegradable polymer DES
- Favours durable polymer SES

0 to 1 year*

RR 0.99 (95% CI 0.51-1.95)  
p=0.98

1 to 4 year*

RR 0.20 (95% CI 0.06-0.67)  
p=0.004

* RR 0-1 vs RR 1-4 p for interaction=0.017
Biodegradable Polymer BES vs Durable Polymer SES

Association of Cardiac Events With Definite ST


### NOT ASSOCIATED with ST

<table>
<thead>
<tr>
<th>Event</th>
<th>BES</th>
<th>SES</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>P-inter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death, MI, or ci-TVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>78/857</td>
<td>87/850</td>
<td>0·89 (0·65-1·20)</td>
<td>0·44</td>
<td></td>
</tr>
<tr>
<td>1 to 4 years</td>
<td>67/749</td>
<td>79/738</td>
<td>0·81 (0·59-1·12)</td>
<td>0·21</td>
<td></td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>48/857</td>
<td>47/850</td>
<td>1·02 (0·68-1·53)</td>
<td>0·94</td>
<td></td>
</tr>
<tr>
<td>1 to 4 years</td>
<td>43/779</td>
<td>52/781</td>
<td>0·80 (0·54-1·21)</td>
<td>0·30</td>
<td></td>
</tr>
<tr>
<td>Clinically-indicated TVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>37/857</td>
<td>45/850</td>
<td>0·81 (0·52-1·25)</td>
<td>0·33</td>
<td></td>
</tr>
<tr>
<td>1 to 4 years</td>
<td>39/776</td>
<td>40/760</td>
<td>0·94 (0·60-1·45)</td>
<td>0·77</td>
<td></td>
</tr>
</tbody>
</table>

### ASSOCIATED with ST

<table>
<thead>
<tr>
<th>Event</th>
<th>BES</th>
<th>SES</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>P-inter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death, MI, or ci-TVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>13/857</td>
<td>15/850</td>
<td>0·86 (0·41-1·80)</td>
<td>0·68</td>
<td></td>
</tr>
<tr>
<td>1 to 4 years</td>
<td>2/749</td>
<td>11/738</td>
<td>0·17 (0·04-0·78)</td>
<td>0·009</td>
<td></td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>11/857</td>
<td>11/850</td>
<td>1·00 (0·43-2·30)</td>
<td>0·99</td>
<td></td>
</tr>
<tr>
<td>1 to 4 years</td>
<td>3/779</td>
<td>11/781</td>
<td>0·27 (0·08-0·95)</td>
<td>0·029</td>
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</tr>
<tr>
<td>Clinically-indicated TVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>13/857</td>
<td>15/850</td>
<td>0·85 (0·41-1·80)</td>
<td>0·68</td>
<td></td>
</tr>
<tr>
<td>1 to 4 years</td>
<td>2/776</td>
<td>10/760</td>
<td>0·19 (0·04-0·87)</td>
<td>0·017</td>
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</tr>
</tbody>
</table>
DES Thrombosis in Perspective

Very Late Definite ST in All-Comers Trials @ 3 Years

Early Generation DES

Newer Generation DES

%
Definite Stent Thrombosis among Patients with Stable Coronary Artery Disease and Acute Coronary Syndromes @ 4 Years

*Bern-Rotterdam Cohort Study*

**Stable CAD**

- **PES**: 2.3
- **SES**: 1.8
- **EES**: 0.4

\[P = 0.0001\]

\[N = 5,138\]

**ACS**

- **PES**: 3.7
- **SES**: 3.2
- **EES**: 1.4

\[P = 0.0001\]

\[N = 7,201\]
Clinical Outcomes With Everolimus- and Paclitaxel-Eluting Stents in Patients With ACS


A Pooled Analysis of SPIRIT II, III, IV, and COMPARE Trials @ 2 Years

Cardiac death, MI, TLR
Cardiac death or MI
Cardiac death
MI
TLR

Pooled analysis comparing EES (N=1393) and PES (N=988) stents:
- Cardiac death, MI, TLR: P=0.04
- Cardiac death or MI: P=0.01
- Cardiac death: P=0.38
- MI: P=0.01
- TLR: P=0.04
Stent Thrombosis With Everolimus- and Paclitaxel-Eluting Stents in Patients With ACS


A Pooled Analysis of SPIRIT II, III, IV, and COMPARE Trials @ 2 Years

$P = 0.01$  $P = 0.0002$

Definite ST  Definite or Probable ST

EES (N=1393)  PES (N=988)

<table>
<thead>
<tr>
<th>Time in Months</th>
<th>EES</th>
<th>PES</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>30dy</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>1yr</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>2yr</td>
<td>2.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Number at risk:

- EES: 1393, 1380, 1365, 1339, 1318, 1152
- PES: 988, 968, 956, 935, 917, 841
EXAMINATION Trial - Everolimus-Eluting Stents vs Bare Metal Stents in STEMI @ 12 Months

Sabaté M. Presented at ESC Congress 2011

**P=0.16**

**P=0.003**

**P=0.01**

**P=0.01**

<table>
<thead>
<tr>
<th>Category</th>
<th>EES - Xience (N=751)</th>
<th>BMS - Vision (N=747)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, any Revasc</td>
<td>14.4%</td>
<td>12%</td>
</tr>
<tr>
<td>TLR</td>
<td>2.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Definite ST</td>
<td>0.5%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Definite/Probable ST</td>
<td>0.9%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>
Definite/Probable Stent Thrombosis

EXAMINATION trial

p = 0.01

Sabaté M. ESC Congress 2011
COMFORTABLE AMI Trial

Biolimus-Eluting Stent vs Bare Metal Stent in STEMI

Primary Endpoint – MACE

@ 1 Year

1 yr HR
0.49 (0.30-0.80)
P=0.004

BMS 8.7 %

BES 4.3 %

MACE= Cardiac death, TV-MI, ci-TLR – Clinical outcomes were adjudicated by an independent and blinded CEC
COMFORTABLE AMI Trial - Biolimus-Eluting Stents vs Bare Metal Stents in STEMI @ 12 Months

P=0.004  P=0.53  P=0.01  P<0.001  P=0.10

Räber L Presented at EuroPCR 2012

Cardiac Death, TV-MI, TLR

BES-BioMatrix (N=575)  BMS - Gazelle (N=582)
Target vessel MI up to 30 days

Target vessel MI between 30 days and 1 year
Stent Thrombosis With Everolimus-Eluting Stents and Bare Metal Stents

A Network Meta-Analysis

Short and Long-Term Outcomes with Drug Eluting and Bare Metal Stents

A Mixed Treatment Comparison of 77 RCTs and 117,762 Patient-Years Fup

Bangalore S et al. Circulation 2012, in press

### 0 to 1 Year

<table>
<thead>
<tr>
<th>Control</th>
<th>Treatment</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>95%</th>
<th>Crl</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS (Ref) Sirolimus</td>
<td>0.97</td>
<td>0.74</td>
<td>1.21</td>
<td></td>
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</tr>
<tr>
<td>Paclitaxel</td>
<td>0.97</td>
<td>0.74</td>
<td>1.25</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>0.87</td>
<td>0.64</td>
<td>1.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zotarolimus</td>
<td>1.28</td>
<td>0.85</td>
<td>1.80</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Zotarolimus-R</td>
<td>0.66</td>
<td>0.36</td>
<td>1.18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Long Term

<table>
<thead>
<tr>
<th>Control</th>
<th>Treatment</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratio</th>
<th>95%</th>
<th>Crl</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS (Ref) Sirolimus</td>
<td>0.89</td>
<td>0.79</td>
<td>1.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.89</td>
<td>0.78</td>
<td>1.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>0.81</td>
<td>0.64</td>
<td>1.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zotarolimus</td>
<td>0.94</td>
<td>0.73</td>
<td>1.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zotarolimus-R</td>
<td>0.71</td>
<td>0.31</td>
<td>1.09</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Short and Long-Term Outcomes with Drug Eluting and Bare Metal Stents
A Mixed Treatment Comparison of 77 RCTs and 117,762 Patient-Years Fup

Bangalore S et al. Circulation 2012, in press

Definite or Probable ST
Target Lesion Revasc

0 to 1 Year

Long Term
**Table 35** Relative clinical contraindications to the use of drug-eluting stents

<table>
<thead>
<tr>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical history difficult to obtain, especially in the setting of acute severe clinical conditions (STEMI or cardiogenic shock).</td>
</tr>
<tr>
<td>• Expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy.</td>
</tr>
<tr>
<td>• Non-elective surgery required in the short term that would require interruption of DAPT.</td>
</tr>
<tr>
<td>• Increased risk of bleeding.</td>
</tr>
<tr>
<td>• Known allergy to ASA or clopidogrel/prasugrel/ticagrelor.</td>
</tr>
<tr>
<td>• Absolute indication for long-term anticoagulation.</td>
</tr>
</tbody>
</table>
ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

Use of Drug-Eluting Stents

- No safety concerns
- Consistent reduction in repeat revascularization with the use of DES

As there are no safety concerns related to the use of DESs in ACS, DESs are indicated based on an individual basis taking into account baseline characteristics, coronary anatomy, and bleeding risk.
Newer Generation Drug-Eluting Stents...What Have We Achieved?

- **Improved safety in all-comers**
  - Reduced risk of stent thrombosis
  - Reduced risk of cardiac death or MI associated with ST

- **New Generation Drug-Eluting Stents**
  - Reduced risk of TLR

- **Improved efficacy in all-comers**
  - Reduced risks of TLR and ST, translating into a lower risk of MI at 1 year

- **Improved efficacy and safety in STEMI compared with BMS**
  - Revascularization procedures

- **Target Lesion Revascularization (TLR)**
  - Biodegradable polymer 1.3%
  - Durable polymer 2.8%

- **Target Vessel MI between 30 days and 1 year**
  - Biodegradable polymer 12.0%
  - Durable polymer 13.7%

- **Restenosis and Stent Thrombosis**
  - Overall (p-value) = 0.029

Favors EES  Favors SES
Questions for Tomorrow

- Are newer generation DES safer than BMS during long-term follow-up?

- Are biodegradable polymer based DES superior to newer generation durable polymer based DES?

- Will BVS outperform newer generation DES?