The Balance of Thrombosis vs. Bleeding for PCI In HBR Patients:
insight into Patients Safety from the LEADERS FREE Trial

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Fu-Wai Hospital, CAMS & PUMC, NCCD

OCC 2016, Advances in interventional Cardiology at ACC 2016 & EuroPCR 2016
1. DES ARE SUPERIOR TO BMS

ESC-EAPCI Stent Task Force | Eur Heart J 2015

**Death**

- All-cause death (%)
- BMS: 7, Early DES: 4, New DES: 2

**MI**

- # Myocardial Infarction (%)
- BMS: 10, Early DES: 6, New DES: 2

**TLR**

- Target-lesion revascularization (%)
- BMS: 20, Early DES: 15, New DES: 12

**Definite ST**

- Definite stent thrombosis (%)
- BMS: 4, Early DES: 2, New DES: 1
2. VERY LATE ST WITH EARLY DES

**ST With Early DES**


**Recommended DAPT**

2010 ESC MR Guidelines
6-12 months post PCI

2011 ACC/AHA PCI Guidelines
12 months post PCI

**Incidence density**
1.0 / 100 pt years

Years after PCI

0 1 2 3 4 5

(%)
3. EXTENDED DAPT AND BLEEDING RISK

**Increased Bleeding Risk With Long-Term DAPT**


**Impact of Bleeding on 1 Year Mortality**

Ndrepepa G et al. *Circulation* 2012

A Network Meta-Analysis of 10 RCTs including 31,666 Patients Treated With DES

BARC type 3-5 Bleeding
4. ST IS NOT AN ISSUE WITH NEW DES

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR*</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EES vs. SES</td>
<td>0.33</td>
<td>0.15 – 0.72</td>
<td>0.006</td>
</tr>
<tr>
<td>EES vs. PES</td>
<td>0.24</td>
<td>0.13-0.47</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Paclitaxel Stent 2.4%
Sirolimus Stent 1.6%
Everolimus Stent 0.6%

*from Cox proportional hazards model
5. Long-Term DAPT May Not Be Needed With New Generation DES

Significant interaction between treatment effect of DAPT duration on ST and type of DES!

Giustino G et al. J Am Coll Cardiol 2015;65:1298-310

Meta-analysis of 10 RCT (n =32,135)

Second-generation DES: EES and ZES

First-generation DES: SES and PES
6. Limited Available Evidence on DES in High-Bleeding Risk Patients

- Patients at high-bleeding risk were not included in all-comer DES trials due to the recommended duration of DAPT in these trials.
7. AVAILABLE EVIDENCE: ZEUS TRIAL


Urgent or emergent coronary stenting in pts fulfilling ≥1 of the below:

**High Bleeding Risk**
- Need for OACs
- Previous Relevant Bleeding
- Age > 80 y/o
- Bleeding diathesis
- Known Anemia (Hb<10 gr/dl)
- Need for CCS or NSAID

**High Thrombotic Risk**
- Intolerance to ASA
- Intolerance to any P2Y₁₂
- Planned surgery w/in 1 year
- Cancer-life expectancy >1 Y
- Pro-thrombotic diathesis

**Low Restenosis Risk**
- Planned stent ≥3.0 mm, apart from LMCA and SVG intervention or for ISR lesions

Rx: 1:1, Sx: inclusion criteria

1,606 pts, 20 sites in Italy, Switzerland, Portugal and Hungary from June 2011 to September 2012

Endeavor Sprint
Zotarolimus-eluting Stent

Thin-strut
Bare Metal Stent

**Personalised DAPT duration**, i.e. modelled according to the patient clinical risk profile and not by stent type
7. Available Evidence: ZEUS Trial


Urgent or emergent coronary stenting in pts fulfilling ≥1 of the below:

**High Bleeding Risk**
- Need for OACs
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- Planned stent ≥3.0 mm, apart from LMCA and SVG intervention or for ISR lesions

---

**DAPT:**

*None if ASA/P2Y₁₂ intol.*

-Up to surgery if planned ≥ 6 mos in others

---

**DAPT:**

Stable CAD 30 days

ACS ≥ 6 mos
**Primary EP: Major Adverse Cardiovascular Events**

(Death for any cause, myocardial infarction or target vessel revascularization)

- BMS: 29.0%
- E-ZES: 22.6%

- HR 0.74  p: 0.039

Available Evidence: ZEUS Trial
7. AVAILABLE EVIDENCE: ZEUS TRIAL

Ariotti S et al. JACC Intv 2016; 9(5):426-36

Myocardial Infarction

- **BMS:** 10.4%
- **E-ZES:** 3.5%
- HR 0.33  p < 0.001

Target Vessel Revascularization

- **BMS:** 11.4%
- **E-ZES:** 5.9%
- HR 0.49  p: 0.006

Definite or Probable Stent Thrombosis

- **BMS:** 6.2%
- **E-ZES:** 2.6%
- HR 0.41  p: 0.016

Death for all causes

- **BMS:** 17.3%
- **E-ZES:** 15.8%
- HR 0.91  p: 0.57

Follow-Up (Days)
### 8. ESC Guidelines on Myocardial Revascularization 2014

**Antiplatelet therapy after stenting**

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Duration</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>At least 1 month</td>
<td>I A</td>
</tr>
<tr>
<td>DES</td>
<td>6 months</td>
<td>I B</td>
</tr>
</tbody>
</table>

- Shorter DAPT duration (<6 months) may be considered after DES implantation in patients at high bleeding risk.

**Grade and Level**

- **I**: Class I recommendation
- **B**: Class B recommendation
- **A**: Level A evidence
- **IIb**: Level IIb evidence
9. REASONS FOR BMS USE IN CLINICAL PRACTICE

Moric MC et al. J Am Coll Card 2013

- High bleeding risk: 33
- Large vessel diameter: 9
- Acute MI: 18
- Stent costs: 32
- Planned noncardiac surgery: 6
- Poor compliance: 2
WHAT WAS KNOWN BEFORE LEADERS FREE?

1. DES are superior to BMS
2. Long-term DAPT was implemented to prevent very late ST after early generation DES implantation
3. Extended DAPT is associated to higher bleeding risk, which has a negative impact on prognosis
4. Very late ST is not an issue with new generation DES
5. Short term DAPT is safe after new generation DES
6. Limited available evidence in high-bleeding risk patients
7. ZEUS, the only available RCT, showed superiority of Endeavor ZES over BMS in high bleeding risk patients
8. ESC GL 2014 considered <6 months DAPT after DES in HBR patients
9. High bleeding risk remains the most frequent reason for BMS implantation in current clinical practice
Study Objectives

For patients with a high bleeding risk, using one month DAPT, can the BioFreedom DCS be shown to be as safe and more effective than a Gazelle BMS?

2 Hypotheses: NI for safety; Sup for Efficacy
They had to be tested sequentially, to avoid splitting of the Alpha error

Was this study worth being conducted?
Yes, no data available when the study was designed;
This remains today the second study chronologically speaking which focused on HBR pts and the only study fully dedicated to this selected patient population
HBR patients....who are they?

Inclusion Criteria (One or More)

- Age $\geq$ 75 years
- OAC planned after PCI
- Baseline Hb $< 11$ g / dl or transfusion during prior 4 weeks
- Planned major surgery (within next year)
- Cancer diagnosed or treated $\leq$ 3 years
- Creatinine clearance $< 40$ ml / min
- Hospital admission for bleeding during past year
- Thrombocytopenia ($< 100,000$ / mm$^3$)
- Any prior intra-cerebral bleed
- Any stroke during the past year
- Severe liver disease
- NSAID or steroids planned after PCI
- Anticipated poor DAPT compliance for other medical reason
Multivariable-adjusted, cubic splines

Bleeding Events

Restricted cubic splines with 3 knots of the distribution (10th, 50th, and 90th percentiles)
Age ≤30 years is the reference value (HR=1)
HBR patients....who are they?

Inclusion Criteria (One or More)

- Age ≥ 75 years
- OAC planned after PCI
- Baseline Hb < 11g / dl, or transfusion during prior 4 weeks

Therefore this study included a combination of true HBR patients together with pts who did not want or could not adhere long-term to a DAPT regimen

- Thrombocytopenia (< 100,000 / mm3)
- Any prior intra-cerebral bleed
- Any stroke during the past year
- Severe liver disease
- NSAID or steroids planned after PCI
- Anticipated poor DAPT compliance for other medical reason
HBR patients:

- How frequently are these patients encountered in our practice?

≈40% among all comer PCI patients in the BERN PCI registry

Only 1% of patients with CRUSADE score > 40 would NOT fulfill these HBR criteria
Determination of Trial Size

Predicted event rates in BMS control arm

- Composite safety endpoint (cardiac death, MI and ST) 8%
- Efficacy endpoint (clinically-driven TLR) 10%

Patients per group: 1228

Endpoints

- Safety:
  > 80% power to demonstrate non-inferiority with margin 3.2%

- Efficacy:
  > 80% power to detect a 3.3% reduction in c-TLR

Both with one-sided alpha 0.025
Primary Safety Endpoint

<table>
<thead>
<tr>
<th>Primary Safety Endpoint*</th>
<th>DCS (n=1221)</th>
<th>BMS (n=1211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Death, Myocardial Infarction, or Stent Thrombosis at 390 days</td>
<td>112 (9.4%)</td>
<td>154 (12.9%)</td>
</tr>
</tbody>
</table>

Risk difference:
- -3.6% (95% CI -6.1% to -1.0%)
- HR 0.71, (95% CI = 0.56 – 0.91)
- p < 0.0001 for non-inferiority
- p = 0.005 for superiority

* 3rd Universal definition of MI, Thygesen K et al Circulation 2012;126:2020 –2035
Components of Safety Endpoint

- Cardiac death: DCS 4.2%, BMS 5.3%
  - p = 0.19
- MI: DCS 6.1%, BMS 8.9%
  - p = 0.01
- ST (def / prob): DCS 2.0%, BMS 2.2%
  - p = 0.70
## Subgroups

### Composite safety endpoint (cardiac death, MI, ST)

<table>
<thead>
<tr>
<th>Category</th>
<th>DCS: Events (%)</th>
<th>BMS: Events (%)</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80</td>
<td>No: 65 (8.3)</td>
<td>Yes: 47 (11.5)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>No: 34 (9.6)</td>
<td>Yes: 78 (9.3)</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
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<tr>
<td>ACS at admission</td>
<td>No: 82 (9.4)</td>
<td>Yes: 30 (9.3)</td>
<td>0.04</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>No: 65 (8.3)</td>
<td>Yes: 47 (11.5)</td>
<td>0.90</td>
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<tr>
<td>Renal failure at admission</td>
<td>No: 73 (8.3)</td>
<td>Yes: 31 (14.7)</td>
<td>0.46</td>
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<td></td>
<td></td>
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<tr>
<td>Planed OAC at randomization</td>
<td>No: 66 (8.7)</td>
<td>Yes: 46 (10.5)</td>
<td>0.44</td>
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<td></td>
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<tr>
<td>Crusade score &gt; median (35)</td>
<td>No: 33 (6.4)</td>
<td>Yes: 63 (13.6)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anemia, transfusion or bleeding leading to hospitalization</td>
<td>No: 84 (8.5)</td>
<td>Yes: 28 (13.6)</td>
<td>0.63</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Planned major surgery in following year</td>
<td>No: 93 (9.4)</td>
<td>Yes: 16 (8.4)</td>
<td>0.74</td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cancer in last 3 years*</td>
<td>No: 101 (9.3)</td>
<td>Yes: 11 (9.6)</td>
<td>0.87</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Multi-vessel disease at admission</td>
<td>No: 24 (5.4)</td>
<td>Yes: 84 (11.4)</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Total stent length &gt; 30 mm</td>
<td>No: 54 (8.0)</td>
<td>Yes: 56 (10.9)</td>
<td>0.19</td>
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<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Minimal stent diameter &lt; 3 mm</td>
<td>No: 49 (8.3)</td>
<td>Yes: 61 (10.2)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

**Note:** Hazard Ratio (95% CI)
Subgroups (continued)

Efficacy endpoint (clinically driven TLR)

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>DCS: Events (%)</th>
<th>BMS: Events (%)</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80</td>
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</tr>
<tr>
<td>No</td>
<td>1602</td>
<td>31 (4.0)</td>
<td>72 (9.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Yes</td>
<td>830</td>
<td>28 (7.1)</td>
<td>41 (10.6)</td>
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</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>738</td>
<td>17 (5.0)</td>
<td>33 (9.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>Yes</td>
<td>1694</td>
<td>42 (5.1)</td>
<td>80 (10.0)</td>
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<tr>
<td>ACS at admission</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1773</td>
<td>47 (5.5)</td>
<td>86 (10.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Yes</td>
<td>659</td>
<td>12 (3.9)</td>
<td>27 (9.0)</td>
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<td>Diabetes</td>
<td></td>
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<tr>
<td>No</td>
<td>1622</td>
<td>40 (5.3)</td>
<td>74 (9.4)</td>
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<tr>
<td>Yes</td>
<td>805</td>
<td>19 (4.7)</td>
<td>39 (10.7)</td>
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<tr>
<td>Renal failure at admission</td>
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</tr>
<tr>
<td>No</td>
<td>1754</td>
<td>42 (4.9)</td>
<td>88 (10.6)</td>
<td>0.02</td>
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<td>Yes</td>
<td>466</td>
<td>16 (7.9)</td>
<td>15 (6.7)</td>
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<td>Planned OAC at randomization</td>
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<tr>
<td>No</td>
<td>1553</td>
<td>39 (5.3)</td>
<td>80 (10.7)</td>
<td>0.61</td>
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<tr>
<td>Yes</td>
<td>879</td>
<td>20 (4.7)</td>
<td>33 (8.2)</td>
<td></td>
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<tr>
<td>Crusade score &gt; median (35)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1061</td>
<td>21 (4.1)</td>
<td>58 (10.7)</td>
<td>0.02</td>
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<tr>
<td>Yes</td>
<td>962</td>
<td>33 (7.5)</td>
<td>39 (8.7)</td>
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<td>Anemia, transfusion or bleeding leading to hospitalization</td>
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<tr>
<td>No</td>
<td>2007</td>
<td>41 (4.2)</td>
<td>95 (9.9)</td>
<td>0.03</td>
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<tr>
<td>Yes</td>
<td>425</td>
<td>18 (9.2)</td>
<td>18 (9.6)</td>
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</tr>
<tr>
<td>Planned major surgery in follow-up</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No</td>
<td>2002</td>
<td>49 (5.1)</td>
<td>89 (9.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>Yes</td>
<td>1845</td>
<td>55 (5.1)</td>
<td>101 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>

Were these potentially paradoxical findings driven by competing risk scenario with respect to mortality? Were mortality actually higher in these patients which explained why TVR risk was lower??

| Minimal stent diameter < 3 mm                  |       |                 |                 |                         |
| No                                            | 1195  | 26 (4.5)        | 41 (7.2)        | 0.26                    |
| Yes                                           | 1213  | 33 (5.7)        | 71 (12.4)       |                         |
Unanswered questions

• Is 1 month DAPT the optimal DAPT duration in this selected patient population?
• Can we transfer these data to other DES?
  – Is the polymer the real reason for prolonging DAPT after DES?
  – Or is it the drug-elution over time?
  – If so, how important are the drug release kinetics?
• Both E-ZES and DCS elute close to 100% of the drug within 1 month
BioFreedom™
Drug Coated Stent (DCS)

Potential Advantages:

✓ Avoid any possible polymer-related adverse effects
✓ Rapid drug transfer to vessel wall (98% within one month\(^1\))
✓ Safe to shorten DAPT?

1. Tada et al., Circ Cardiovasc Interv 2010;3;174-183
LEADERS FREE
Trial Design

Prospective, double-blind randomized (1:1) trial
2466 High bleeding risk (HBR) PCI patients

BioFreedom™ DCS

VS.

Gazelle™ BMS

DAPT mandated for 1 month only, followed by long-term SAPT

- **Primary safety endpoint:**
  Composite of cardiac death, MI, definite / probable stent thrombosis at 1 year (non-inferiority then superiority)

- **Primary efficacy endpoint:**
  Clinically-driven TLR at 1 year (superiority)

LEADERS FREE
Primary Endpoints

**Efficacy (cd-TLR)**

- DCS
- BMS

**Safety (cardiac death, MI, ST)**

- DCS
- BMS

For the first time in HBR patients, the current pre-specified analysis focuses on:

1. The location and consequences of major bleeding

2. The incidence and associated mortality of major thrombotic (stent thrombosis and/or MI) and bleeding (BARC 3-5) events.

3. The identification of predictors for both types of events in this population
Location of Major Bleeding

170 first major bleeding events

- **GI**: 76
- **access**: 24
- **intracranial**: 12
- **GU**: 10
- **diffuse**: 8
- **epistaxis**: 7
- **surgical**: 7
- **retroperit.**: 6
- **pulmonary**: 6
- **ocular**: 3
- **pericardial**: 1
- **other**: 2
- **unknown**: 8

PPI at discharge
- 51.9% of all trial patients
- 64.5% of patients with subsequent GI bleed
### Major Bleeding and Thrombotic Events by Main Inclusion Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>BARC 3-5</th>
<th>MI and/or ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected poor compliance (88)</td>
<td>4.7%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Age &gt; 75 (1564)</td>
<td>7.7%</td>
<td>8.1%</td>
</tr>
<tr>
<td>Planned surgery (398)</td>
<td>6.5%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Planned OAC use post-PCI (879)</td>
<td>6.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Cancer (239)</td>
<td>6.2%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Renal insufficiency (464)</td>
<td>11.3%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Bleeding in prior 12 months (79)</td>
<td>8.1%</td>
<td>13%</td>
</tr>
<tr>
<td>Hb&lt;11g/dl or recent transfusion (379)</td>
<td>11%</td>
<td>17.6%</td>
</tr>
</tbody>
</table>
Major Bleeding and Thrombotic Events in the DCS and BMS Arms

- **BMS - Bleeding**
  - Days since procedure:
    - 0: 8.6%
    - 90: 7.3%
    - 180: 7.2%
    - 270: 5.7%
    - 360: 5.7%

- **DCS - Bleeding**
  - Days since procedure:
    - 0: 8.6%
    - 90: 7.3%
    - 180: 7.2%
    - 270: 5.7%
    - 360: 5.7%

- **BMS - Thrombotic Events**
  - Days since procedure:
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- **DCS - Thrombotic Events**
  - Days since procedure:
    - 0: 8.6%
    - 90: 7.3%
    - 180: 7.2%
    - 270: 5.7%
    - 360: 5.7%

*p = 0.006*
BARC 3-5 Bleeding

Cumulative Percentage with Event

%

DAYS

0 90 180 270 390

DCS

BMS

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>1220</th>
<th>1129</th>
<th>1098</th>
<th>1078</th>
<th>1044</th>
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<tr>
<td>DCS</td>
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</tr>
<tr>
<td>BMS</td>
<td>1211</td>
<td>1116</td>
<td>1085</td>
<td>1058</td>
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</table>

p = 0.957
Mortality Following Bleeding and Thrombotic Events

Mortality during FU for patients with neither BARC 3-5 or MI/ST was 6.2%
Prediction of Major Bleeding and Thrombotic Events

- Development of 2 separate prediction models
  → Major bleeding
  → Major thrombotic events (MI/ST)

- Common set of 33 candidate predictors
  → Baseline or procedural characteristics

- Cox-regression
  → Forward selection of candidate predictors
  → P-value of 0.05 for inclusion
Candidate Predictors (n=33)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Procedural characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Type of trial stent</td>
</tr>
<tr>
<td>Gender</td>
<td>Femoral access</td>
</tr>
<tr>
<td>BMI</td>
<td>SVG target lesion (1 or more)</td>
</tr>
<tr>
<td>Hypertension (SBP &gt;=140 or DBP&gt;=100)</td>
<td>Bifurcation target lesion (1 or more)</td>
</tr>
<tr>
<td>Hypotension (≤100 mmHg at baseline)</td>
<td>Total stent length</td>
</tr>
<tr>
<td>Measured systolic BP at baseline</td>
<td>Maximum stent diameter</td>
</tr>
<tr>
<td>Active smoker</td>
<td>Overlapping stents implanted</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Number of stents implanted</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>Multivessel procedure</td>
</tr>
<tr>
<td>Prior CABG or PCI</td>
<td>Residual stenosis reported &gt; 50% or final TIMI flow &lt; 3</td>
</tr>
<tr>
<td>Prior MI</td>
<td>GP IIb-IIIa blockers used during procedure</td>
</tr>
<tr>
<td>Prior stroke</td>
<td></td>
</tr>
<tr>
<td>Planned use of OAC post-PCI</td>
<td></td>
</tr>
<tr>
<td>Non-skin cancer in last 3 years</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance &lt; 40 ml/min</td>
<td></td>
</tr>
<tr>
<td>Plasma creatinine</td>
<td></td>
</tr>
<tr>
<td>Hb &lt; 11 g/dl or recent TF or admission for bleeding &lt; 1 year</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td></td>
</tr>
<tr>
<td>Surgery planned in next year</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>ACS presentation (NSTEMI or STEMI)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td></td>
</tr>
</tbody>
</table>
Independent Predictors of Bleeding and Thrombosis
(Hazard Ratio % 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Thrombotic Events</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine &gt; 150 umol/l</td>
<td>1.80 (1.19-2.72) p=0.005</td>
<td>-</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.70 (1.14-2.54) p=0.010</td>
<td>-</td>
</tr>
<tr>
<td>Bifurcation target lesion (1 or more)</td>
<td>1.50 (1.03-2.19) p=0.036</td>
<td>-</td>
</tr>
<tr>
<td>BMS (vs. DCS)</td>
<td>1.43 (1.04-1.98) p=0.029</td>
<td>-</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>1.53 (1.08-2.16) p=0.017</td>
<td>1.50 (1.08-2.08) p=0.021</td>
</tr>
<tr>
<td>Number of stents/patient (per stent)</td>
<td>1.16 (1.02-1.31) p=0.018</td>
<td>1.14 (1.02-1.27) p=0.025</td>
</tr>
<tr>
<td>Haemoglobin (per 1 mmol/l lower)*</td>
<td>1.21 (1.04-1.40) p=0.014</td>
<td>1.74 (1.53-1.99) p&lt;0.001</td>
</tr>
<tr>
<td>Femoral access</td>
<td>-</td>
<td>1.66 (1.22-2.27) p=0.001</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>-</td>
<td>1.83 (1.34-2.50) p&gt;0.001</td>
</tr>
</tbody>
</table>

Model C-statistic
- Thrombotic Events: 0.66
- Major Bleeding: 0.71

* Below 9 mmol/l (145 g/l)
Baseline Haemoglobin: A **Very** Powerful Predictor of Bleeding

MI and/or ST

BARC 3-5
Predicted Individual Patient Risks of Major Bleeding & Thrombotic Events

Thrombotic risk ≥ 2x bleeding risk
n=286 (13.1%)

Predicted 1-year MI/ST risk (%) vs. Predicted 1-year bleeding risk (%)

DCS
BMS
Conclusions (I)

These data represent the first attempt to define the balance of bleeding and thrombosis in a population defined by a high bleeding risk and followed for 390 days after PCI with 1 month DAPT only:

- Major bleeding (BARC 3-5) was frequent (7.2%)
- Mortality rates during follow-up after major bleeding (25.4%) or thrombotic events (24.4%) were high and comparable
- Patients at the highest risk for bleeding were generally also those at the highest risk of thrombosis
- Thrombotic risk (ST and/or MI) was significantly lower with DCS (5.7%) than BMS (8.6%)
Conclusions (II)

9 predictors for thrombosis and/or bleeding were identified for HBR patients. It is a good model for bleeding, but has more limited discrimination for thrombosis

- **Predictors of bleeding:** low hemoglobin levels, planned use of OAC at discharge and femoral access

- **Predictors of thrombosis:** renal insufficiency, multivessel disease, bifurcation target lesion, and use of a BMS

- **Predictors of both:** advanced age and use of multiple stents

With the goal of aiding to define individual priorities, a simplified bleeding vs. thrombosis trade-off score is under development, and should be available soon.
LEADERS FREE – Impact on Practice

Conclusions

• LEADERS FREE is an important study:
  (1) raised awareness of HBR patients who represent a frequent clinical dilemma and have been excluded in most previous clinical trials;
  (2) introduced an alternative to BMS, assessed using rigorous study methodology

• Study demonstrated superiority of Biofreedom cw BMS: both safety and efficacy endpoints (as defined)

• Study outcomes raise many qualifying considerations: broad definition of HBR, control BMS ↑ ST at 1 year (2.2%), safety endpoint driven by ↑ MI 2rv ISR, no cw with best-in-class “current” generation DES
LEADERS FREE – Impact on Practice

Conclusions

(my thinking opinion)

• Is the 1 month DAPT regimen after PCI safe for HBR patients?
  • Definitely No!
    • The 1 week and 1yr mortalities due to bleeding and thrombotic events are too high (as high as 7.1% and 13.7%, and 25.4% and 24.4%!) with DCS!
    • The 1 yr rates of cardiac death and ST (5.3% and 2.2%) is also too high in the BMS arm

• Is the 1 month DAPT regimen after PCI Problematic in ethics for those patients with low thrombotic events
  • Yes, sure!

• What is the right strategy for those HBR patients?
  • Medical therapy in most cases
  • PTCA is of choice in some patients if needed

• What can we learn from the LEADERS FREE trial?
  • Negative example for lesson!
  • Forget the 1 month DAPT regimen for PCI patients no matter the bleeding risk is!
Thank you for your attention!