AHA 2014 - Session LBCT.01 - Risk and Benefit of Dual Antiplatelet Therapy

November 16, 2014, 3:45 - 5:00 PM
North Hall B

Commentary

G. Montalescot

COI DISCLOSURE FOR DR. MONTALESCOT are available @ http://www.action-coeur.org
Duration of DAPT after DES

< 12 months
Is shorter better?

Similar early S.T.
Similar MI
Similar death
LESS BLEEDING

> 12 months
Is longer better?

LESS MI
Less late S.T.
Less death
MORE BLEEDING
Duration of DAPT after DES

< 12 months

EXCELLENT
OPTIMIZE
RESET
SECURITY

> 12 months

ARCTIC-INTERRUPTION
DES-LATE
Hu et al.
REAL/ZEST

PRODIGY

19,262 patients
Duration of DAPT after DES

< 12 months

ISAR-SAFE

ITALIC

> 12 months

DAPT

ITALIC

15,783 patients
• 1° EP (both studies looked at net clinical benefit)
• Wide margins for non inferiority (20%)
• Long enrolment periods (both started in 2008)
• Very low event rates (both ~1.5% for 1°EP)
• Premature study interruption (both ~65% of the size)
• Study treatment not followed (both ~14% of patients)
• Patients lost to FU (1.5-7%)

S. Schulz-Schüpke et al. AHA 2014

Studies difficult to conduct
No study in itself is conclusive

The 2 studies are aligned with the 5 previous studies

M. Gilard et al. AHA 2014
Is shorter better?
Meta-analysis (n=15,870)

Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
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</thead>
<tbody>
<tr>
<td>EXCELLENT</td>
<td>1.870</td>
<td>0.742</td>
<td>4.715</td>
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<tr>
<td>OPTIMIZE</td>
<td>1.167</td>
<td>0.768</td>
<td>1.773</td>
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<tr>
<td>RESET</td>
<td>0.499</td>
<td>0.091</td>
<td>2.728</td>
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<tr>
<td>SECURITY</td>
<td>1.167</td>
<td>0.622</td>
<td>2.191</td>
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<tr>
<td>PRODIGY</td>
<td>1.058</td>
<td>0.676</td>
<td>1.655</td>
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<tr>
<td>ISAR-safe</td>
<td>0.931</td>
<td>0.436</td>
<td>1.986</td>
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<tr>
<td>ITALIC</td>
<td>1.500</td>
<td>0.422</td>
<td>5.333</td>
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<tr>
<td><strong>ALL</strong></td>
<td><strong>1.135</strong></td>
<td><strong>0.891</strong></td>
<td><strong>1.446</strong></td>
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</table>

Major bleeding

<table>
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<tr>
<td>EXCELLENT</td>
<td>0.498</td>
<td>0.091</td>
<td>2.727</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>0.871</td>
<td>0.315</td>
<td>2.406</td>
</tr>
<tr>
<td>RESET</td>
<td>0.332</td>
<td>0.067</td>
<td>1.647</td>
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<tr>
<td>SECURITY</td>
<td>0.655</td>
<td>0.213</td>
<td>2.011</td>
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<tr>
<td>PRODIGY</td>
<td>0.373</td>
<td>0.145</td>
<td>0.956</td>
</tr>
<tr>
<td>ISAR-safe</td>
<td>0.802</td>
<td>0.215</td>
<td>2.991</td>
</tr>
<tr>
<td>ITALIC</td>
<td>0.142</td>
<td>0.007</td>
<td>2.754</td>
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<tr>
<td><strong>ALL</strong></td>
<td><strong>0.547</strong></td>
<td><strong>0.338</strong></td>
<td><strong>0.885</strong></td>
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</table>

EXCELLENT (Gwon et al. Circ 2014); OPTIMIZE (Feres et al. JAMA 2013); RESET (Kim et al. JACC 2013); SECURITY (Colombo et al. JACC 2014); PRODIGY (Valgimigli et al. Circ 2012); ISAR-safe (Schulz-Schüpke et al. AHA 2014); ITALIC (Gilard et al. AHA 2014).
Is longer better?

DAPT

12

30

Rd

PEP
30 mths

Powered for:
Stent Thrombosis
Major bleeding

DES
1st and 2nd
generation

Double blind

3-month extended FU
after interruption

Clopidogrel
Prasugrel
ACS and stable CAD

Eligible for Enrollment
- Age 18 years or above
- PCI with DES or BMS
- No contraindications to dual antiplatelet therapy (clopidogrel or prasugrel)
- Able and willing to provide written informed consent

Planned N: 15,615 DES, 5,400 BMS

22,866 DES

Not Eligible for Randomization
- Death
- MI or repeat PCI at > 6 weeks
- CABG
- Stroke
- Major bleed

56% excluded

9,961 DES

ARCTIC- Interruption: 47% excluded

12 month Observation Period
All subjects on aspirin + open label thienopyridine treatment

Eligible for Randomization
Planned N: 12,066 DES, 4,320 BMS

1:1

12 month DAPT Arm
Aspirin + blinded placebo

30 month DAPT Arm
Aspirin + blinded thienopyridine

Am Heart J 2010;160:1035-1041.e1
**ARCTIC-interruption**

**MACCE**

**DAPT**

**Bleeding**

Major or minor bleeding (STEEPLE definition)

1.9% vs. 0.5%,  p=0.03

Moderate or severe bleeding (GUSTO definition)

2.5% vs. 1.6%,  p=0.001


Mauri L et al. AHA Nov. 2014
Paclitaxel DES: Additional risk factor
ST: 2.9% vs. 0.8%
Off label use of prasugrel: >12 months / elective PCI
Prasugrel prevents MI, related or not to ST
Rebound effect at interruption of prasugrel

Garratt KN et al. AHA 2014
For Every 1000 Pts with continued DAPT up to 30 months

Events / 1000 Pts

-20

-10

-5

0

5

10

15

-20

-15

-10

-5

0

p<0.001

p<0.001

P=0.052

p<0.001

MI  Stent thrombosis  Death  Bleed
Severe/moderate
All-cause death in studies with 12 months vs. > 12 months after DES

<table>
<thead>
<tr>
<th>Study name</th>
<th>Event rates (%)</th>
<th>SHORT (12 mths)</th>
<th>PROLONGED</th>
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</thead>
<tbody>
<tr>
<td>DAPT (n=9961)</td>
<td></td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>DES-Late (n=5045)</td>
<td></td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>ARCTIC-Interruption (n=1259)</td>
<td></td>
<td>1.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT</td>
<td>0.800</td>
<td>0.599</td>
<td>1.068</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>0.696</td>
<td>0.442</td>
<td>1.097</td>
</tr>
<tr>
<td>ARCTIC-interruption</td>
<td>1.313</td>
<td>0.486</td>
<td>3.547</td>
</tr>
<tr>
<td>All</td>
<td>0.792</td>
<td>0.625</td>
<td>1.004</td>
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</table>

Odds ratio and 95% CI

- p=0.054

Death rates worse than 12 months vs. >12 months in DAPT (n=9961) 1.5 vs. 2.0, DES-Late (n=5045) 1.4 vs. 2.0, ARCTIC-Interruption (n=1259) 1.4 vs. 1.1.
Interpretation

**Reassuring**
- Small signal / small number of events / late appearance (>24mths)
- Asymmetrical split for cancer-related deaths
- No signal on death in PES-DAPT (n=2191)
- No signal on death in BMS-DAPT (n=1687)
- No significant effect on death in a large meta-analysis of dual antiplatelet therapy

**Disturbing**
- Asymmetrical split on bleeding related to non-CV deaths (21 vs. 5)
- Relation major bleeding – death well documented
- Similar trend on death in a small meta-analysis of similar DES-studies
BLEEDING RISK
- Prior bleeding
- Advanced age
- Need for surgery
- Nuisance bleedings
- Need for anticoagulation (e.g. AFib)
- Co-morbidities at risk (e.g. GI or stroke)
BLEEDING RISK
No

ISCHEMIC RISK
- Extended CAD/stenting;
- 1st generation DES (PES)
- Other diseased territories
- Prior stent thrombosis or MI

> 12 months
Conclusions and points for discussion

1. **Interruption of DAPT 6 months after DES implantation is possible**, including in ACS patients
2. Patients studied beyond 1-year were at lower risk
3. **There is an ischemic benefit with DAPT continuation beyond 1 year**
4. **There is more bleeding (more death?) with DAPT continuation**
5. **There is hazard (MI/ST) within 3 months of thienopyridine discontinuation**
6. Magnitude of benefit may be greater with prasugrel than clopidogrel
7. Difficult to identify the patients who may benefit more from continuation
8. **No common rule for duration of DAPT, only individualized decisions**