BASKET PROVE II
EVOLVE II
Discussant Review

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below. These relationships may lead to bias in my presentation.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tbody>
<tr>
<td>• Grant/Research Support (Institutional)</td>
<td>• The Medicines Co., BMS/Sanofi, Lilly/Daiichi Sankyo</td>
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<td>• Advisory Board</td>
<td>• Covidien, Janssen (J+J), Sanofi-Aventis</td>
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<td>• Consulting Fees/Honoraria</td>
<td>• Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, CSL Behring, Janssen (J+J), Maya Medical, Merck, Regado Biosciences, Sanofi-Aventis</td>
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</table>
Why reabsorb the polymer?

• Because polymer has no function after drug is released!

• Moreover:
  - Delayed endothelial healing and increased risk of late and very late ST
  - Require long-term DAPT
  - Chronic hypersensitivity and neoatherosclerosis development

BASKET PROVE II Trial
Phase 4, randomized, controlled, multicenter, 3 arms Trial (≥3mm stents)
N = 2400 patients
Randomization 2:1 to DES or BMS, and 1:1 to either DES subgroups (1:1:1)

- Centers in Austria, Denmark, Germany and Switzerland
- Open-label trial
- Follow-up: 24, 36 and 60 months.

Primary Endpoint:
Efficacy Endpoint: MACE at 24 Months [Composite endpoint including cardiac death, MI and TVR]

- Non-Inferiority of Nobori Vs. Xience
- Superiority of Nobori Vs. ProKinetic

Safety Endpoint [Composite of definite/probable ST, MI, cardiac death] at 12 and 24 months

ASA and Prasugrel for all patients 12 months after DES or ACS, 4 weeks after elective BMS
BASKET PROVE II Trial

Key Inclusion Criteria:
- Need for large (≥3.0 mm stents only) native vessel stenting.

Key Clinical and Angiographic Exclusion Criteria:
- In-Stent Restenosis or In-Stent Thrombosis
- Target lesion located within a bypass graft or left main coronary artery
- Cardiogenic shock
- Planned surgery in the next 12 months
- Oral anticoagulation needed
- Active bleeding disorders
- Index PCI = planned PCI of additional lesions
- Contraindications to Prasugrel (history of stroke, TIA, severe hypersensitivity to Prasugrel, ecc.)

Broad population Highly Inclusive
The Nobori Stent was non-inferior to Xience for the efficacy endpoint.

No significant differences in the safety endpoint among groups.

Nobori and Xience were superior to BMS for the efficacy endpoint.

Kaiser et al. Circulation 2014
Non-Inferiority Analysis

BP-DES versus DP-DES

**Intention to treat:** absolute risk difference 0.75% (95%CI -1.93% to 3.50%, p for non-inferiority: 0.04)

**Per protocol:** absolute risk difference 1.41% (95%CI 1.33% to 4.15%, p for non-inferiority: 0.09)

_Difference due to exclusion of 6 events in patients with protocol violations:_
4 due to DAPT violations, 2 no stent
No Late safety events with SAPT

No difference in late safety
BASKET PROVE II Trial

**Strengths**

- Evaluation of new-generation stent technology in a real-world all-comer population compared to bare stents and current DES with durable polymer
- Evaluation of more potent P2Y12 inhibitor in a real-world all-comer population (stable and unstable pts)
- Follow up out to two years

**Limitations**

- Inconsistent findings for non-inferiority in ITT versus PP analysis
- Duration of DAPT different for BMS (one mo), and DES (6-12 m)
- Underpowered to detect differences in safety between DP-DES, BP-DES and BMS
- Bleeding data not reported, especially important with more potent P2Y12 inhibitor
EVOLVE II Trial

Phase 3, multicenter, randomized, controlled trial

1,684 patients with atherosclerotic native coronary lesions ≤ 34 mm in length, RVD ≥ 2.25 mm to ≤ 4.0
Up to 3 lesions in 2 vessels
(excludes LM disease, CTO, ISR, STEMI)

PROMUS Element (EES) [n = 842]

SYNERGY (Biodegradable EES) [n = 842]

Single-blind, 1:1 randomization

Primary Endpoint:
Target Lesion Failure (TLF) at 12 months
[composite endpoint of ischemia-driven revascularization of the target lesion, myocardial infarction (Q-wave and non-Q-wave) related to the target vessel, or cardiac death].
Non-Inferiority of Synergy Vs. Promus Element

- Up to 160 global sites in 19 countries
- Follow-up: 30d, 6m, 12m, 18m and annual 2-5 years
• Key Inclusion Criteria:
  - Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia
  - Subject is eligible for percutaneous coronary intervention (PCI)

• Key Clinical Exclusion Criteria:
  - STEMI or cardiogenic shock
  - Planned PCI (including staged procedures) or CABG after the index procedure
  - Chronic (≥72 hours) anticoagulation therapy (i.e., heparin, Coumadin)
  - Severe chronic kidney disease, liver disease, bleeding diathesis or coagulopathy

• Key Angiographic Exclusion Criteria:
  - Planned treatment of more than 3 lesions,
  - Planned treatment of lesions in more than 2 major epicardial vessels
  - Planned treatment of a single lesion with more than 1 stent
  - Subject has 2 target lesions in the same vessel that are separated by less than 15 mm
  - Left Main and Ostial LAD / Cx Lesions
  - Totally Occluded Arteries (TIMI = 0)
  - SVG, ISR, CTO

Broad population
Highly Inclusive
**EVOLVE II Trial**

**Primary Endpoint Met!**
The Synergy Stent was non-inferior to the Promus Element Plus stent for TLF at 1 year.

**KEY FINDINGS**

- Higher technical success with Synergy.
- Low rates of ST at 1 year (0.2% with both stents):
  1. 2 cases in the Synergy group ≤ 1 day (Acute ST)
  2. 2 cases in the Promus Element group between 2 and 30 days (Subacute ST)

### Per Patient and Per Lesion

<table>
<thead>
<tr>
<th></th>
<th>PROMUS Element Plus</th>
<th>SYNERGY</th>
<th>P value</th>
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<tbody>
<tr>
<td>n=1043 lesions</td>
<td>n=1059 lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=838 patients</td>
<td>n=846 patients</td>
<td></td>
<td></td>
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<tr>
<td>Technical success</td>
<td>96.9%</td>
<td>98.3%</td>
<td>0.04</td>
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### ARC Stent Thrombosis

<table>
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<tr>
<th></th>
<th>PROMUS Element Plus</th>
<th>SYNERGY</th>
<th>P value</th>
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<tbody>
<tr>
<td>ARC Stent Thrombosis</td>
<td></td>
<td></td>
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<tr>
<td>Definite/Probable</td>
<td>0.6%</td>
<td>0.4%</td>
<td>0.50</td>
</tr>
<tr>
<td>Definite</td>
<td>0.2%</td>
<td>0.2%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Probable</td>
<td>0.4%</td>
<td>0.1%</td>
<td>0.37</td>
</tr>
<tr>
<td>Possible</td>
<td>0.1%</td>
<td>0.2%</td>
<td>&gt;0.99</td>
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**Difference [97.5% UCB]**

- Non-inferiority Margin: 4.4%
- 2.68% 1-sided UCB
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<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
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<td>• Large sample size, well designed</td>
<td>• Event rates lower than expected, but still within the non-inferiority margin.</td>
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<td>• Evaluation of new-generation stent technology in a real-world all-comer population- few exclusions</td>
<td>• Not powered for safety endpoints. Longer follow-up in larger sample size is needed to establish the safety of Bioresorbable Polymer DES compared to 2nd-generation DES.</td>
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<td>• The clinical and angiographic complexity make these results generalizable</td>
<td>• The duration of DAPT is still not clear even with this new technology (most pts received 12 months), with observed low event rates- ? can be shortened, simplified- This was not explored!</td>
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<td>• Encouraging results for the efficacy and safety of SYNERGY Stent in real-world PCI population</td>
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Conclusions

• Event rates are low after DES even in broader, more inclusive population

• New-generation Bioresorbable Polymer DES are similarly effective compared to 2nd-generation DES

• Potential improvement in safety through a more consistent and improved endothelial healing will still need to be determined:
  - Larger sample
  - Longer follow-up
  - Potential reduction in DAPT duration!
…..Thank You for Your Attention!