Primary Outcomes of a Pivotal Multicenter Randomized Trial Comparing the AGENT Paclitaxel-Coated Balloon with Conventional Balloon Angioplasty for In-Stent Restenosis

Robert W. Yeh, MD
Beth Israel Deaconess Medical Center, Boston, MA

Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a relevant financial relationships with ineligible companies listed below.

<table>
<thead>
<tr>
<th>Nature of Financial Relationship</th>
<th>Ineligible Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Abbott Vascular, BD Bard, Boston Scientific, Cook Medical, Philips Medical and Medtronic</td>
</tr>
<tr>
<td>Consulting</td>
<td>Abbott Vascular, Boston Scientific, CathWorks, Elixir Medical, Infraredx, Medtronic, Shockwave Medical and Zoll</td>
</tr>
</tbody>
</table>

All relevant financial relationships have been mitigated.
Faculty disclosure information can be found on the app.
Introduction

- Treatment of in-stent restenosis (ISR) is commonly encountered and clinically challenging.
- Drug coated balloons (DCBs) transfer a therapeutic dose of an anti-restenotic agent to the vessel wall without introducing another layer of metal.
- No coronary DCBs are currently approved in the United States.
- The AGENT DCB delivers a targeted low-dose formulation of paclitaxel (2 \( \mu g/mm^2 \)) to the treated vessel.
- AGENT IDE is a pivotal randomized trial comparing the safety and efficacy of the AGENT DCB to conventional balloon angioplasty in patients with ISR.
AGENT IDE Study Design

Prospective, randomized, multicenter, superiority trial across 40 US sites (N=480 patients*)

- Key Inclusion Criteria: Patients with ISR of a lesion previously treated with BMS or DES; lesion length <26 mm, RVD >2.0 - ≤4.0 mm, and %DS >70 - <100% (asymptomatic) or %DS >50 - <100% (symptomatic)
- Key Exclusion Criteria: Recent STEMI, bifurcation, LM, SVG or arterial graft, thrombus in target vessel

2:1 randomization after successful pre-dilation of target lesion

AGENT DCB

Balloon Angioplasty

Primary Endpoint: Target Lesion Failure at 1-year (composite of TLR, TV-MI, or cardiac death)

Clinical follow-up: In-hospital, 30 days, 6 months, 1-year and annually between 2 and 5 years

*Based on an adaptive trial design (interim analysis with pre-specified sample size readjustment plan); Yeh et al. Am Heart J. 2021;241:101-107
AGENT IDE Study Leadership Team

Principal Investigator
Robert W. Yeh
Beth Israel Deaconess Medical Center
Boston, MA

Study Chair
Ajay J. Kirtane
Columbia University/NewYork-Presbyterian Hospital
New York, NY

Steering Committee
J. Dawn Abbott  Cinthia Bateman  Wayne Batchelor
Suhail Dohad  J Aaron Grantham  William Bachinsky
Robert Stoler  Jennifer Tremmel

Angiographic Core Laboratory
Dr. Charles Michael Gibson
Baim Institute for Clinical Research, Inc
Boston, MA
### AGENT IDE Centers – Top Enrolling Sites

<table>
<thead>
<tr>
<th>Richard Shlofmitz (79)</th>
<th>Cinthia Tjan Bateman (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Francis Hospital</td>
<td>South Denver Cardiology Associates, PC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Jeffrey Moses (49)</th>
<th>Amar Krishnaswamy (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columbia University Medical Center</td>
<td>Cleveland Clinic Foundation</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>William Bachinsky (41)</th>
<th>J. Aaron Grantham (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinnacle Health Cardiovascular Institute</td>
<td>St. Luke's Hospital of Kansas City</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Suhail Dohad (34)</th>
<th>Francis J. Zidar (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cedars - Sinai Medical Center</td>
<td>Austin Heart</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Steven Rudick (31)</th>
<th>Rajendran Sabapathy (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindner Center at Christ Hospital</td>
<td>Overland Park Regional Medical Center</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Robert Stoler (30)</th>
<th>Jennifer Tremmel (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baylor Heart &amp; Vascular Hospital</td>
<td>Stanford University Medical Center</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brian Jefferson (30)</th>
<th>Cindy Grines (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centennial Medical Center</td>
<td>Northside Hospital</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>William Nicholson (28)</th>
<th>Mustafa Ahmed (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emory University Hospital</td>
<td>University of Alabama at Birmingham</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>John Altman (20)</th>
<th>Azeem Latib (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Anthony Hospital</td>
<td>Montefiore Medical Center</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Robert Yeh (16)</th>
<th>Behnam Tehrani (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beth Israel Deaconess Medical Center</td>
<td>Inova Fairfax Hospital</td>
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</tbody>
</table>
Sample Size Calculation

Hypothesis: AGENT DCB superior to balloon angioplasty (BA) in ISR lesions for the primary endpoint of 1-year TLF

Expected rates*: AGENT DCB = 10.6%; BA = 21.2%
Randomization ratio = 2 DCB: 1 BA
Test significance level ($\alpha$) = 0.025 (1-sided)
Power = 85%
Expected rate of attrition = 3%
Planned enrollment = 480 patients**

The study primary endpoint will be considered met if the P-value from the z-test is <0.025 and the TLF rate in the DCB arm is less than the BA arm

*Based on meta-analysis of historical trials and including an adjustment to account for the oculo-stenotic reflex; Yeh et al. Am Heart J. 2021;241:101-107;
**Based on an adaptive trial design; final sample size increased to 600 patients; primary endpoint analysis conducted on the first 480 patients enrolled
Patient Disposition

480 patients were eligible for randomization

321 randomized to DCB

305 patients (95.0%) had 1-year clinical follow-up or death
  0 Investigator discretion
  5 Withdrew consent
  11 Missed 1-year visit

159 randomized to BA

148 patients (93.1%) had 1-year clinical follow-up or death
  1 Investigator discretion
  2 Withdrew consent
  8 Missed 1-year visit

Allocation (2:1)
## Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AGENT DCB N=321</th>
<th>Balloon Angioplasty N=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.6±9.8</td>
<td>67.5±9.9</td>
</tr>
<tr>
<td>Female</td>
<td>26.8%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>73.8%</td>
<td>76.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50.5%</td>
<td>50.9%</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>32.1%</td>
<td>27.8%</td>
</tr>
<tr>
<td>Prior Myocardial Infarction</td>
<td>47.8%</td>
<td>48.7%</td>
</tr>
<tr>
<td>Previous Congestive Heart Failure</td>
<td>22.4%</td>
<td>20.3%</td>
</tr>
<tr>
<td>History of Renal Disease</td>
<td>18.2%</td>
<td>16.4%</td>
</tr>
<tr>
<td>History of Multivessel Disease</td>
<td>79.4%</td>
<td>77.1%</td>
</tr>
<tr>
<td>History of Left Main Disease</td>
<td>22.4%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Indication for Index Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>37.4%</td>
<td>39.6%</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>54.2%</td>
<td>52.8%</td>
</tr>
<tr>
<td>Silent Ischemia</td>
<td>1.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Other Indication</td>
<td>6.5%</td>
<td>6.3%</td>
</tr>
</tbody>
</table>
## Baseline Restenosis Pattern

|                      | AGENT DCB  
|----------------------|------------  
|                      | N=321       | Balloon Angioplasty  
|                      |            | N=159                 
| Single stent layer   | 56.4%       | 56.6%                
| Multiple stent layers| 43.6%       | 43.4%                
| Mehran ISR pattern*  |             |                       
| 0                    | 0.0%        | 0.0%                  
| 1A (articulation)    | 0.0%        | 0.0%                  
| 1B (margin)          | 1.3%        | 1.3%                  
| 1C (focal)           | 35.8%       | 44.2%                 
| 1D (multifocal)      | 0.3%        | 0.6%                 
| 2 (intrastent)       | 57.5%       | 48.1%               
| 3 (proliferative)    | 4.4%        | 5.2%                  
| 4 (total occlusion)  | 0.6%        | 0.6%                 

*Quantified by the angiographic core laboratory*
## Angiographic Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AGENT DCB N=322 Lesions†</th>
<th>Balloon Angioplasty N=159 Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Procedur</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target vessel treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>34.9%</td>
<td>35.2%</td>
</tr>
<tr>
<td>LCx</td>
<td>24.6%</td>
<td>26.4%</td>
</tr>
<tr>
<td>RCA</td>
<td>37.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td>LMCA</td>
<td>2.8%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Lesion Length, mm</td>
<td>12.97±6.33</td>
<td>11.88±6.51</td>
</tr>
<tr>
<td>&lt;10 mm</td>
<td>37.0%</td>
<td>46.5%</td>
</tr>
<tr>
<td>10 – 20 mm</td>
<td>48.0%</td>
<td>43.9%</td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>15.0%</td>
<td>9.7%</td>
</tr>
<tr>
<td>MLD*, mm</td>
<td>0.95±0.38</td>
<td>0.94±0.38</td>
</tr>
<tr>
<td>Diameter Stenosis*, %</td>
<td>64.86±12.63</td>
<td>65.52±12.19</td>
</tr>
<tr>
<td><strong>Post-Procedur</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD*, mm</td>
<td>2.13±0.45</td>
<td>2.15±0.51</td>
</tr>
<tr>
<td>Diameter Stenosis*, %</td>
<td>22.09±10.66</td>
<td>21.90±10.56</td>
</tr>
<tr>
<td>Acute Gain*, mm</td>
<td>1.17±0.47</td>
<td>1.21±0.52</td>
</tr>
</tbody>
</table>

*in-lesion values; †One patient in the AGENT arm had two target lesions treated with DCB that was counted as a protocol deviation
## Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AGENT DCB N=321</th>
<th>Balloon Angioplasty N=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical success</td>
<td>92.9%</td>
<td>89.3%</td>
</tr>
<tr>
<td>(Post-procedure diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stenosis of &lt;30% in 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>near-orthogonal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>projections with TIMI 3 flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical procedural</td>
<td>91.9%</td>
<td>88.7%</td>
</tr>
<tr>
<td>success</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Technical success with no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in-hospital MI, TVR, or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardiac death)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>56.9±31.0</td>
<td>52.7±27.3</td>
</tr>
<tr>
<td>Patients with only target</td>
<td>87.2%</td>
<td>87.4%</td>
</tr>
<tr>
<td>lesion treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with both target</td>
<td>12.8%</td>
<td>12.6%</td>
</tr>
<tr>
<td>&amp; non-target lesion treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravascular imaging</td>
<td>72.3%</td>
<td>76.7%</td>
</tr>
<tr>
<td>use during procedure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antiplatelet Medication Usage

- Aspirin: AGENT
- Aspirin: BA
- DAPT: AGENT
- DAPT: BA

DAPT required for at least a month; Antiplatelet monotherapy through the duration of the study
Primary Endpoint: TLF at 1-Year

Binary event rates; A z-test with unpooled variance for the difference of two proportions was used

AGENT DCB demonstrated superior outcomes compared to BA for 1-year TLF

Difference [95% CI] = -10.7% [-19.2 to -2.3]

\( P_{\text{superiority}} = 0.0063 \)
TLR and Target Vessel Related MI at 1-Year

Log-rank P values; Periprocedural MI occurring within 48 hours of the index procedure adjudicated by the SCAI definition, and spontaneous MI occurring 48 hours after the index procedure was adjudicated according to the 4th Universal MI definition
Definite/Probable ST at 1-Year

**AGENT 0.0% vs. BA 3.9%**
P = 0.001

KM Event Rate; Log-rank P values; All definite ST in the BA arm (6 patients)
Additional Endpoints at 1-Year

KM Event Rate; Log-rank P values
# Subgroup Analyses of the Primary Outcome

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>AGENT DCB</th>
<th>BA</th>
<th>Hazard Ratio [95% CI]</th>
<th>P-Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>17.4%</td>
<td>28.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (N=129)</td>
<td>10.6%</td>
<td>24.1%</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Male (N=351)</td>
<td>20.0%</td>
<td>29.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years (N=349)</td>
<td>19.2%</td>
<td>26.4%</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>≥75 years (N=131)</td>
<td>12.9%</td>
<td>32.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes* (N=213)</td>
<td>21.3%</td>
<td>23.4%</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>No† (N=265)</td>
<td>14.7%</td>
<td>32.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vessel size‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (RVD&lt; 2.75 mm) (N=259)</td>
<td>16.8%</td>
<td>25.5%</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Large (RVD≥2.75 mm) (N=218)</td>
<td>18.4%</td>
<td>31.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stent Layer§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single (N=270)</td>
<td>14.0%</td>
<td>19.7%</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Multiple (N=209)</td>
<td>21.9%</td>
<td>39.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Diabetic patients requiring medical treatment; †Diabetic patients treated with diet only or patients without diabetes; ‡RVD based on angiographic core lab data.
Discussion Points - Sample Size

- Sample Size
  - Interim analysis was planned after 90% of patients enrolled, expecting 40% achieving 1-year endpoint at that time.
  - Due to rapid enrollment, very limited 1-year follow-up available after 90% enrollment -> DMC recommended continuing enrollment to 600.
  - FDA recommended performing interim analysis when 40% had achieved 1-year follow up. Analysis demonstrated 480 to be adequately powered.
  - 600 patient full sample will be included in the final manuscript.
Discussion Points – Control Group

- Study designed for superiority over balloon angioplasty rather than non-inferiority vs. DES.
- Trial enrolled high number of patients with multiple-stent layers, for whom additional DES are often avoided.
- The design incorporated practical considerations necessary for conducting a successful trial to support regulatory approval.
Conclusions

- AGENT IDE is the first RCT conducted in the US examining the efficacy and safety of DCB in patients with coronary ISR

- AGENT DCB was superior to conventional balloon angioplasty for the primary endpoint of TLF at 1-year (17.9% vs. 28.7%; P=0.006)
  - These differences were driven by ~50% reductions in rates of TLR and TV-MI in the AGENT vs. BA arms

- No definite thrombosis in the AGENT arm (0.0% vs. 3.9%; P=0.001)

- These data support the use of AGENT DCB for the treatment ISR lesions
THANK YOU