One-Month Dual Antiplatelet Therapy Followed by Clopidogrel Monotherapy versus Standard 12-Month Dual Antiplatelet Therapy with Clopidogrel After Drug-Eluting Stent Implantation:

STOPDAPT-2

Hirotoshi Watanabe

Takenori Domei, Takeshi Morimoto, Hiroki Shiomi, Masahiro Natsuaki, Toshiaki Toyota, Kensuke Takagi, Yoshiki Hata, Satoru Suwa, Mamoru Nanasato, Masanobu Ohya, Masahiro Yagi, Takafumi Yokomatsu, Mitsuru Abe, Kenji Ando, Kazushige Kadota, Ken Kozuma, Yoshihiro Morino, Yuji Ikari, Kengo Tanabe, Koichi Nakao, Kazuya Kawai, Yoshihisa Nakagawa, and Takeshi Kimura, on behalf of STOPDAPT-2 investigators
• Mandatory 1-month DAPT had been the standard care after BMS implantation.
• DAPT duration was prolonged after introduction of DES without firm scientific evidence.
• New generation DES has substantially reduced stent thrombosis.
• Prolonged DAPT is inevitably associated with increase in bleeding.
• Bleeding is associated with subsequent mortality risk at least comparable to that of MI.
• Therefore, very short mandatory DAPT duration after DES might be an attractive option, if not associated with increase in ischemic events disproportionate to the reduction in bleeding events.
STOPDAPT

Prospective multicenter open-label single arm trial evaluating 3-month DAPT after CoCr-EES implantation

Primary Endpoint
Cardiovascular death, MI, Stroke, Definite ST, and Bleeding

Adjusted HR 0.64 (0.42-0.95)
P=0.03

The objective of the STOPDAPT-2 trial is to explore the safety and efficacy of the experimental regimen of 1-month DAPT followed by clopidogrel monotherapy as compared with the standard 12-month DAPT with aspirin and clopidogrel after implantation of cobalt-chromium everolimus-eluting stents (CoCr-EES).
STOPDAPT-2:
Prospective multicenter open-label randomized trial comparing 1-month versus 12-month DAPT after CoCr-EES implantation with limited exclusion criteria.

Primary analysis for Non-inferiority

1-month DAPT group
- ASA
- P2Y12i
- Clopidogrel 75mg/d

12-month DAPT group
- ASA
- P2Y12i
- Clopidogrel 75mg/day or Prasugrel 3.75 mg/day

1Y (335-394d)
5Y

STOPDAPT-2: Prospective multicenter open-label randomized trial comparing 1-month versus 12-month DAPT after CoCr-EES implantation with limited exclusion criteria.
Study Organization

**Steering Committee**

Takeshi Kimura (PI)
Kazushige Kadota
Ken Kozuma
Yoshihiro Morino
Keiichi Igarashi-Hanaoka
Yuji Ikari
Kengo Tanabe
Kenji Ando
Koichi Nakao
Kazuya Kawai
Mitsuru Abe

**Clinical Event Committee**

Yoshihisa Nakagawa
Yutaka Furukawa
Masahiro Natsuaki
Hiroki Shiomi
Toshiaki Toyota

**Safety Evaluation Committee**

Shunichi Miyazaki
Ryuji Nohara

**Coordinating Center**

Research Institute for Production Development, Kyoto, Japan
Saori Tezuka
Yumika Fujino

**Angiography Core Laboratory**

Cardio Core Japan, Tokyo, Japan

**Study administrative staff**

Masahiro Natsuaki
Hirotoshi Watanabe
Toshiaki Toyota
Toshikazu Jinnai

**Funded by**

Abbott Vascular Japan, Co., Ltd.
90 Participating Centers

Teine Keijinkai Hospital
Hokko Memorial Hospital
Hirosaki University Hospital
Iwate Medical University Hospital
Sendai Kousei Hospital
Sendai Cardiovascular Center
Tohoku Medical and Pharmaceutical University Hospital
Nakadori General Hospital
Nihonkai General Hospital
Hoshi General Hospital
Jichi Medical University Hospital
Mashiko Hospital
Mitsui Memorial Hospital
Juntendo University Hospital
The Fraternity Memorial Hospital
Edogawa Hospital
Showa University Koto Toyosu Hospital
Tokyo Women’s Medical University Hospital
Tokyo General Hospital
Juntendo University Nerima Hospital
Kawakita General Hospital
Sakakibara Heart Institute
Tokyo Metropolitan Tama Medical Center
Minamino Cardiovascular Hospital
Higashiyama Hospital
St.Marianna University School of Medicine Hospital
Yokohama Rosai Hospital
Showa University Fujigaoka Hospital
Saiseikai Yokohamashi Tobu Hospital
Yokohama City University Medical Center
Kitasato University Hospital
Hiratsuka Kyosai Hospital
Tokai University Hospital
Kimitsu Chuo Hospital
Kanazawa Cardiovascular Hospital
University of Fukui Hospital
Municipal Tsuruga Hospital
University of Yamanshi Hospital
Gifu Prefectural General Medical Center
Ogaki Municipal Hospital
Juntendo University Shizuoka Hospital
Shizuoka General Hospital
Japanese Red Cross Nagoya Daini Hospital
Handa City Hospital
Tosei General Hospital
Ichinomiyanishi Hospital
Yokkaichi Hazu Medical Center
Matsusaka Central General Hospital
Nabari City Hospital
Otsu Red Cross Hospital
Hikone Municipal Hospital
Kyoto University Hospital
Kyoto Medical Center
Mitsubishi Kyotou Hospital
Kitano Hospital
Osaka Red Cross Hospital
National Cerebral and Cardiovascular Center
Kindai University Hospital
Mimihara General Hospital
Bell Land General Hospital
Kobe City Medical Center General Hospital
Kindai University Nara Hospital
Tenri Hospital
Japanese Red Cross Wakayama Medical Center
Wakayama Medical University Hospital
Shimane University Hospital
Japanese Red Cross Okayama Hospital
Kurashiki Central Hospital
Hiroshima University Hospital
Iwakuni Medical Center
Tokuyama Central Hospital
Shimonoseki City Hospital
Tokushima University Hospital
Tokushima Red Cross Hospital
Kagawa Prefectural Central Hospital
Ehime Prefectural Central Hospital
Matsuyama Red Cross Hospital
Chikamori Hospital
Kokura Memorial Hospital
Hospital of University of Occupational and Environmental Health Japan
Saiseikai Fukuoka General Hospital
Fukuoka Tokushukai Hospital
Kumamoto University Hospital
Saiseikai Kumamoto Hospital
Japanese Red Cross Kumamoto Hospital
Miyazaki Prefectural Noeoka Hospital
Ibusuki Medical Center
Izumi Regional Medical Center
Urasoe General Hospital
Nakagami Hospital
Inclusion Criteria

• PCI with exclusive use of CoCr-EES (Xience™ series)
• No major complications during hospitalization for index PCI
• No plan for staged PCI
• Patients who could take DAPT with aspirin and P2Y$_{12}$ inhibitors

Key Exclusion Criteria

• Needs for oral anticoagulants
• History of intracranial hemorrhage
Endpoints

- **Primary endpoint:**
  
  Net adverse cardiovascular events (NACE: Ischemia and Bleeding)
  
  - A composite of cardiovascular death, MI, Definite ST, Stroke, or TIMI major/minor bleeding

- **Major secondary endpoints:**
  
  Ischemic composite endpoint
  
  - A composite of cardiovascular death, MI, Definite ST, or Stroke

  Bleeding endpoint
  
  - TIMI major/minor bleeding
Sample Size Calculation

- Hypothesis: Non-inferiority of 1-month DAPT to 12-month DAPT for the primary endpoint at 1-year
- Assumption: Event rate at 1-year: 4.6% (Based on RESET study).
- Non-inferiority margin; 50% on the hazard ratio scale
- Randomization ratio: 1:1
- One-sided alpha: 0.025
- Power: 85%
- Sample size: 3000 patients (1500 in each arm)
Study Flow

Eligible patients
PCI exclusively with CoCr-EES/No scheduled staged PCI
Dec. 2015-Dec. 2017
N=6504

Enrolled and randomized
N=3045

3459 did not participate
1731 Physicians' judgement
1280 Patients' refusal
362 Logistic reasons
47 Ethical reasons
39 Unknown

Participants
N=3009

36 withdrawal

Non-Participants with demographic data
N=3287

172 Data missing
<table>
<thead>
<tr>
<th></th>
<th>Participants N=3009</th>
<th>Non-participants N=3287</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.6±10.7</td>
<td>70.0±11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACS</td>
<td>38%</td>
<td>39%</td>
<td>0.61</td>
</tr>
<tr>
<td>STEMI</td>
<td>19%</td>
<td>22%</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior MI</td>
<td>14%</td>
<td>23%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior 1st-generation DES implantation</td>
<td>4%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39%</td>
<td>39%</td>
<td>0.47</td>
</tr>
<tr>
<td>Severe CKD</td>
<td>6%</td>
<td>9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>3%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Target of LMCA</td>
<td>3%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Two or more target vessels</td>
<td>7%</td>
<td>9%</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Study Flow

Eligible patients
Dec. 2015-Dec. 2017
N=6504

Enrolled and randomized
N=3045

Stratified by Center

1-month DAPT arm
N=1523
23 withdrew consent
ITT population
N=1500
Complete 1-Year FU
N=1478 (98.5%)

12-month DAPT arm
N=1522
13 withdrew consent
ITT population
N=1509
Complete 1-Year FU
N=1496 (99.1%)

3459 did not participate
1731 Physicians’ judgment
1280 Patients’ refusal
362 Logistic reasons
47 Ethical reasons
39 Unknown

Eligible patients
Dec. 2015-Dec. 2017
N=6504

1-month DAPT arm
N=1523
ITT population
N=1500
Complete 1-Year FU
N=1478 (98.5%)

12-month DAPT arm
N=1522
ITT population
N=1509
Complete 1-Year FU
N=1496 (99.1%)

3459 did not participate
1731 Physicians’ judgment
1280 Patients’ refusal
362 Logistic reasons
47 Ethical reasons
39 Unknown
## Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>1-month DAPT N=1500</th>
<th>12-month DAPT N=1509</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>68.1 ± 10.9</td>
<td>69.1 ± 10.4</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>79%</td>
<td>77%</td>
</tr>
<tr>
<td><strong>ACS</strong></td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>STEMI</strong></td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Stable CAD</strong></td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Severe CKD (eGFR&lt;30ml/min/m²)</strong></td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>CREDO-Kyoto thrombotic risk score</strong></td>
<td>8%; 21%; 71%</td>
<td>8%; 24%; 68%</td>
</tr>
<tr>
<td><strong>High; Intermediate; Low</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CREDO-Kyoto bleeding risk score</strong></td>
<td>7%; 27%; 66%</td>
<td>7%; 27%; 66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Procedural Characteristics and Medications

<table>
<thead>
<tr>
<th></th>
<th>1-month DAPT (N=1500)</th>
<th>12-month DAPT (N=1509)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transradial approach</strong></td>
<td>82%</td>
<td>84%</td>
</tr>
<tr>
<td>N of target lesions</td>
<td>1.12 ± 0.35</td>
<td>1.14 ± 0.39</td>
</tr>
<tr>
<td>Minimal stent diameter, mm</td>
<td>2.98 ± 0.49</td>
<td>2.96 ± 0.48</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>30.3 ± 16.7</td>
<td>30.5 ± 16.8</td>
</tr>
<tr>
<td><strong>SYNTAX Score</strong></td>
<td>8 (5-14)</td>
<td>9 (6-15)</td>
</tr>
<tr>
<td>Target of LMCA</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>CTO</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>IVUS or OCT</strong></td>
<td>97%</td>
<td>98%</td>
</tr>
<tr>
<td><strong>ASA</strong></td>
<td>99.8%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></td>
<td>60%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Prasugrel (3.75mg/day)</strong></td>
<td>40%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>88%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>PPI</strong></td>
<td>79%</td>
<td>79%</td>
</tr>
</tbody>
</table>
Persistent DAPT discontinuation rate

Cumulative incidence

Days after index PCI

Number of patients on DAPT
- 1-month DAPT: 1500, 1346, 67, 38, 32, 28, 25, 23, 9
- 12-month DAPT: 1509, 1499, 1467, 1442, 1412, 1387, 1352, 1314, 178
Primary Endpoint: Net clinical benefit
CV death/MI/ST/Stroke/TIMI major/minor bleeding

HR 0.64, 95%CI (0.42-0.98)
P non-inferiority <0.001
P superiority =0.04

Log rank P=0.037

No. at risk
12-month DAPT: 1509, 1501, 1486, 1481, 1469, 1458, 1442, 1159
1-month DAPT: 1500, 1494, 1479, 1475, 1468, 1453, 1441, 1151
Major secondary ischemic endpoint
CV death/MI/ST/Stroke

HR 0.79, 95%CI (0.49-1.29)
P non-inferiority =0.005
P superiority =0.34

Log rank P=0.34

Cumulative Incidence

No. at risk
12-month DAPT 1509 1504 1490 1488 1479 1473 1458 1172
1-month DAPT 1500 1495 1480 1476 1471 1458 1446 1157
Major secondary bleeding endpoint
TIMI major/minor bleeding

HR 0.26, 95%CI (0.11-0.64)
P superiority = 0.004

Log rank P = 0.002

Cumulative Incidence

Days after index PCI

No. at risk
12-month DAPT 1509 1504 1491 1487 1480 1471 1462 1180
1-month DAPT 1500 1495 1483 1481 1477 1467 1457 1166
Clinical Outcomes at 1 year

<table>
<thead>
<tr>
<th>Event</th>
<th>1-month DAPT</th>
<th>12-month DAPT</th>
<th>P value for superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.4</td>
<td>1.2</td>
<td>P=0.61</td>
</tr>
<tr>
<td>MI</td>
<td>0.9</td>
<td>0.8</td>
<td>P=0.66</td>
</tr>
<tr>
<td>Definite ST</td>
<td>0.13</td>
<td>0.07</td>
<td>P=0.57</td>
</tr>
<tr>
<td>Probable ST</td>
<td>0.13</td>
<td>0.0</td>
<td>*</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.5</td>
<td>1.1</td>
<td>P=0.11</td>
</tr>
<tr>
<td>TIMI major/minor</td>
<td>0.4</td>
<td>1.5</td>
<td>P=0.004</td>
</tr>
<tr>
<td>Bleeding BARC 3 or 5</td>
<td>0.5</td>
<td>1.8</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>

* 2 cases of probable ST (undefined death) in the 1-month DAPT group occurred before discontinuing DAPT at 1-month.
Subgroup analysis for the primary endpoint (1)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>1-month DAPT (N=1500)</th>
<th>12-month DAPT (N=1509)</th>
<th>HR (95%CI)</th>
<th>P_simplicity</th>
<th>P_interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=75 years</td>
<td>10/448 (2.26%)</td>
<td>25/499 (5.08%)</td>
<td>0.44 (0.21-0.92)</td>
<td>0.03</td>
<td>0.20</td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>25/1052 (2.41%)</td>
<td>30/1010 (3.02%)</td>
<td>0.80 (0.47-1.36)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td><strong>ACS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16/565 (2.88%)</td>
<td>23/583 (4.02%)</td>
<td>0.72 (0.38-1.36)</td>
<td>0.44</td>
<td>0.64</td>
</tr>
<tr>
<td>No</td>
<td>19/935 (2.05%)</td>
<td>32/926 (3.49%)</td>
<td>0.59 (0.33-1.03)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td><strong>STEMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9/291 (3.15%)</td>
<td>14/270 (5.26%)</td>
<td>0.60 (0.26-1.38)</td>
<td>0.23</td>
<td>0.87</td>
</tr>
<tr>
<td>No</td>
<td>26/1209 (2.18%)</td>
<td>41/1239 (3.36%)</td>
<td>0.65 (0.40-1.06)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td><strong>Severe CKD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9/82 (11.22%)</td>
<td>5/84 (5.97%)</td>
<td>1.93 (0.65-5.75)</td>
<td>0.24</td>
<td>0.03</td>
</tr>
<tr>
<td>No</td>
<td>26/1418 (1.86%)</td>
<td>50/1425 (3.57%)</td>
<td>0.52 (0.32-0.84)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18/585 (3.12%)</td>
<td>25/574 (4.45%)</td>
<td>0.70 (0.38-1.29)</td>
<td>0.26</td>
<td>0.65</td>
</tr>
<tr>
<td>No</td>
<td>17/915 (1.88%)</td>
<td>30/935 (3.24%)</td>
<td>0.58 (0.32-1.05)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td><strong>Total stent length &gt;=28mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19/742 (2.60%)</td>
<td>33/787 (4.23%)</td>
<td>0.61 (0.35-1.07)</td>
<td>0.08</td>
<td>0.76</td>
</tr>
<tr>
<td>No</td>
<td>16/758 (2.14%)</td>
<td>22/722 (3.12%)</td>
<td>0.69 (0.36-1.32)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td><strong>Two or more target vessels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4/100 (4.14%)</td>
<td>8/116 (6.94%)</td>
<td>0.58 (0.17-1.92)</td>
<td>0.37</td>
<td>0.85</td>
</tr>
<tr>
<td>No</td>
<td>31/1400 (2.24%)</td>
<td>47/1393 (3.43%)</td>
<td>0.66 (0.42-1.03)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>35/1500 (2.36%)</td>
<td>55/1509 (3.70%)</td>
<td>0.64 (0.42-0.98)</td>
<td>0.038</td>
<td></td>
</tr>
</tbody>
</table>

1-month DAPT better 12-month DAPT better
## Subgroup analysis for the primary endpoint (2)

### PARIS thrombotic risk score

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>1-month DAPT (N=1500)</th>
<th>12-month DAPT (N=1509)</th>
<th>HR (95%CI)</th>
<th>P superiority</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate/High</td>
<td>26/771 (3.43%)</td>
<td>37/751 (5.00%)</td>
<td>0.68 (0.41-1.13)</td>
<td>0.14</td>
<td>0.56</td>
</tr>
<tr>
<td>Low</td>
<td>9/729 (1.24%)</td>
<td>18/758 (2.40%)</td>
<td>0.52 (0.23-1.15)</td>
<td>0.11</td>
<td>0.56</td>
</tr>
</tbody>
</table>

### CREDO-Kyoto thrombotic risk score

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>1-month DAPT (N=1500)</th>
<th>12-month DAPT (N=1509)</th>
<th>HR (95%CI)</th>
<th>P superiority</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate/High</td>
<td>15/431 (3.55%)</td>
<td>30/480 (6.31%)</td>
<td>0.55 (0.30-1.03)</td>
<td>0.06</td>
<td>0.45</td>
</tr>
<tr>
<td>Low</td>
<td>20/1069 (1.89%)</td>
<td>25/1029 (2.47%)</td>
<td>0.77 (0.43-1.39)</td>
<td>0.38</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Overall**

<table>
<thead>
<tr>
<th>1-month DAPT (N=1500)</th>
<th>12-month DAPT (N=1509)</th>
<th>HR (95%CI)</th>
<th>P superiority</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>35/1500 (2.36%)</td>
<td>55/1509 (3.70%)</td>
<td>0.64 (0.42-0.98)</td>
<td>0.038</td>
<td></td>
</tr>
</tbody>
</table>

1-month DAPT better

12-month DAPT better
Limitations

- Lack of consensus on the use of the NACE as primary endpoint
- Open label design with its inherent limitations
- Limited enrollment of high ischemic risk patients
- Lower ischemic risk of Japanese versus US/European CAD patients
- Ticagrelor / Prasugrel (standard dose) not available in Japan
- No assessment of aspirin monotherapy after 1-month DAPT
Conclusions

One-month DAPT followed by clopidogrel monotherapy provided a net clinical benefit for ischemic and bleeding events over 12-month DAPT with aspirin and clopidogrel after CoCr-EES implantation.

The benefit was driven by significant reduction in bleeding events without increase in ischemic events.