Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation

A Pooled Analysis of the REAL-LATE and the ZEST-LATE Trial

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on behalf of the REAL-LATE and the ZEST-LATE trial
Disclosure Information

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No industry sponsorship relevant to this study
The use of drug-eluting stents (DES) is associated with significant reductions in restenosis and target-lesion revascularization compared with use of bare-metal stents (BMS).

Based on the pivotal trials, DES have been widely used for percutaneous coronary intervention (PCI) in clinical practice.

However, some longer-term studies have reported that DES are associated with increased rates of late stent thrombosis, mortality or myocardial infarction compared to BMS.
Early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis with drug-eluting stents.

Current PCI guidelines recommend that clopidogrel 75 mg daily should be given for at least 12 months after implantation of DES if patients are not at high risk of bleeding.

However, the optimal duration of dual antiplatelet therapy and the risk–benefit ratio of long-term dual antiplatelet therapy remain uncertain for patients receiving DES.
OBJECTIVE

• The findings of observational studies have been inconsistent, and no randomized trials have been performed to address this issue.

• Accordingly, we evaluated the effect of extended dual antiplatelet therapy beyond 12 months on long-term clinical outcomes in patients who underwent initial PCI with drug-eluting stents.
METHODS
The current analysis merged data from two concurrent randomized, clinical trials comparing continuation and discontinuation of clopidogrel in patients who were free of major adverse cardiac or cerebrovascular events and major bleeding for at least 12 month period after implantation of drug-eluting stents.
STUDY DESIGN

• The first trial was called **REAL-LATE** (Correlation of Clopidogrel Therapy Discontinuation in *REAL*-world Patients treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events; ClinicalTrials.gov number, NCT00484926)

• The second trial was called **ZEST-LATE** (Evaluation of the Long-term Safety After Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or PacliTaxel-Eluting Stent Implantation for Coronary Lesions - Late Coronary Arterial Thrombotic Events; ClinicalTrials.gov number, NCT00590174)
The study designs of the two trials were similar; the main difference was that the ZEST-LATE trial included only individuals who had participated in another randomized trial, the ZEST (Comparison of the Efficacy and the Safety of Zotarolimus-Eluting Stent versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions, NCT00418067).

The REAL-LATE trial enrolled a broader population of patients without limiting the clinical or lesion characteristics.
These two trials (the REAL-LATE and ZEST-LATE) were merged as the result of a decision of the executive committees, on the basis of the slower-than-anticipated enrollment in each of the trials and substantial similarities in their designs.

The data and safety monitoring board, which was the same for both trials, agreed to the merger.
STUDY DESIGN

REAL-LATE
Broader population of patients who had received any DES

ZEST-LATE
Patients who had participated in ZEST trial

Data Merged
Patients who were free of MACCE with dual therapy (clopidogrel plus aspirin) for 12 months

Clopidogrel + Aspirin

Aspirin Alone

1
2 year F/U
Inclusion Criteria

Patients were eligible to enroll in the REAL-LATE and ZEST-LATE trials if they had undergone implantation of a drug-eluting stents at least 12 months before enrollment, had not had a major adverse cardiovascular event (myocardial infarction, stroke, or repeat revascularization) or major bleeding since implantation, and were receiving dual antiplatelet therapy at the time of enrollment.
Exclusion Criteria

• Contraindications to use of antiplatelet drugs.
• Concomitant vascular disease requiring long-term use of clopidogrel or other established indications for clopidogrel therapy (e.g., a recent acute coronary syndrome)
• Non-cardiac co-morbid conditions with life expectancy <1 year
• Participants in another drug or coronary-device study.
Patients in both trials were randomly assigned either to clopidogrel (75 mg per day) plus low-dose aspirin (100 to 200 mg per day) or low-dose aspirin alone.

The treatment allocation was performed using a preestablished, computer-generated randomization scheme, stratified according to site and type of DES.

Both were open-label trials without blinding of either the study subjects or the investigators.

Follow-up evaluations were performed every 6 months. At these visits, data pertaining to patients’ clinical status, all interventions, outcome events, adverse events, and drug compliance were recorded.
END POINTS

The Primary End Points

The first occurrence of myocardial infarction or death from cardiac cause after treatment assignment.

The Principal Secondary End Points

- Each component of death, myocardial infarction, stroke (of any cause), definite stent thrombosis, or repeat revascularization
- Composite death or myocardial infarction
- Composite death, myocardial infarction or stroke
- Composite cardiac death, myocardial infarction, or stroke
- Major bleeding, according to the TIMI definition.
• Assuming an event rate of 5.0% at 2 years for the primary end point among patients who were assigned to the aspirin-alone group, we estimated that 1,812 patients (906 per group) would need to be enrolled for the detection of a 50% reduction in relative risk of the primary end point in the dual-therapy group as compared with aspirin-alone group, with a statistical power 80% power at a two-sided significance level of 0.05.

• The assumed rates of the primary end point and the assumed relative risk reduction were based on historical data (the BASEKET-LATE study and the Duke registry data).

• The planned sample size was increased by 10% to allow for noncompliance and loss to follow-up, for a total overall enrollment goal of 2000 patients for each trial.
• All enrolled patients from both trials were included in the analysis of primary and secondary clinical outcomes according to the intention-to-treat principle.
• Differences between treatment groups were evaluated by Student’s t-test for continuous variables and by the chi-square or Fisher’s exact test for categorical variables.
• Cumulative event curves were generated by means of the Kaplan-Meier method.
• We used a Cox proportional-hazards model to compare clinical outcomes between the groups.
• An additional stratified Cox regression analysis was performed to test whether merging of the data from the two trials would influence the primary outcome.
<table>
<thead>
<tr>
<th>Name</th>
<th>Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seung-Jung Park</td>
<td>Asan Medical Center, Seoul</td>
</tr>
<tr>
<td>Yangsoo Jang</td>
<td>Yonsei University Medical Center, Seoul</td>
</tr>
<tr>
<td>Ki Bae Seung</td>
<td>Catholic Medical Center, Seoul</td>
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<td>Hyo-Soo Kim</td>
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<td>In-Whan Seong</td>
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<td>Joo-Young Yang</td>
<td>NHIC Ilsan Hospital, Ilsan</td>
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<td>Seung-Ho Hur</td>
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<tr>
<td>Do-Sun Lim</td>
<td>Korea University Hospital, Seoul</td>
</tr>
</tbody>
</table>
CLINICAL TRIAL ORGANIZATION

**Principal Investigators**
Seung-Jung Park, MD, PhD
Asan Medical Center

**Clinical Events Committee**
Jae-Joong Kim, MD, PhD
Asan Medical Center

**Data Safety Monitoring Board**
Moo-Song Lee, MD, PhD
University of Ulsan Medical College

**Data Coordination/Site Management**
Clinical Research Center
Asan Medical Center

**Angiographic Core Lab**
CVRF in Korea
RESULTS
STUDY PATIENTS
From July 2007 through September 2008

REAL-LATE
N=1,625
Broader population of patients who had received any DES

ZEST-LATE
N=1,357
Patients who had participated in ZEST trial

Data Merged
N=2,701
Patients who were free of MACCE with dual therapy (clopidogrel plus aspirin) for 12 months

Data Merged
N=1,357
Clopidogrel + Aspirin

Data Merged
N=1,344
Aspirin Alone

From July 2007 through September 2008
## Baseline Patients Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel + Aspirin (n=1357)</th>
<th>Aspirin Alone (n=1344)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age (yr)</td>
<td>62.0±9.8</td>
<td>61.9±9.9</td>
<td>0.97</td>
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<tr>
<td>Male sex</td>
<td>950 (70.0)</td>
<td>933 (69.4)</td>
<td>0.74</td>
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<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>340 (25.1)</td>
<td>364 (27.1)</td>
<td>0.23</td>
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<tr>
<td>Hypertension</td>
<td>775 (57.1)</td>
<td>765 (56.9)</td>
<td>0.92</td>
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<td>Hyperlipidemia</td>
<td>586 (43.2)</td>
<td>584 (43.5)</td>
<td>0.89</td>
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<td>Current smoker</td>
<td>404 (29.8)</td>
<td>431 (32.1)</td>
<td>0.20</td>
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<tr>
<td>Previous coronary angioplasty</td>
<td>177 (13.0)</td>
<td>159 (11.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>51 (3.8)</td>
<td>45 (3.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>57 (4.2)</td>
<td>45 (3.3)</td>
<td>0.25</td>
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<tr>
<td>Characteristic</td>
<td>Clopidogrel + Aspirin (n=1357)</td>
<td>Aspirin alone (n=1344)</td>
<td>P Value</td>
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<tr>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>------------------------</td>
<td>---------</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>59.2±9.3</td>
<td>59.7±8.5</td>
<td>0.20</td>
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<tr>
<td>Multivessel disease</td>
<td>667 (49.2)</td>
<td>633 (47.1)</td>
<td>0.29</td>
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<tr>
<td>Clinical indication</td>
<td></td>
<td></td>
<td>0.79</td>
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<tr>
<td>Stable angina</td>
<td>514 (37.9)</td>
<td>500 (37.2)</td>
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<tr>
<td>Unstable angina</td>
<td>543 (40.0)</td>
<td>559 (41.6)</td>
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<tr>
<td>NSTEMI</td>
<td>145 (10.7)</td>
<td>144 (10.7)</td>
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<tr>
<td>STEMI</td>
<td>155 (11.4)</td>
<td>141 (10.5)</td>
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<td>Discharge medications</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>1353 (99.7)</td>
<td>1399 (99.6)</td>
<td>0.73</td>
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<tr>
<td>Clopidogrel</td>
<td>1353 (99.7)</td>
<td>1343 (99.9)</td>
<td>0.38</td>
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<tr>
<td>ACE inhibitor</td>
<td>633 (46.6)</td>
<td>603 (44.9)</td>
<td>0.35</td>
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<tr>
<td>ß-blockers</td>
<td>917 (67.6)</td>
<td>869 (64.7)</td>
<td>0.11</td>
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<tr>
<td>Calcium channel blocker</td>
<td>730 (53.8)</td>
<td>739 (55.0)</td>
<td>0.54</td>
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<tr>
<td>Statin</td>
<td>1081 (79.7)</td>
<td>1058 (78.7)</td>
<td>0.55</td>
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## Baseline Lesions Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel + Aspirin (n=1357)</th>
<th>Aspirin Alone (n=1344)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Lesions stented, No</td>
<td>1872</td>
<td>1847</td>
<td>0.35</td>
</tr>
<tr>
<td>Vessel treated</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left anterior descending artery</td>
<td>912 (48.7)</td>
<td>921 (49.9)</td>
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<tr>
<td>Left circumflex artery</td>
<td>372 (19.9)</td>
<td>334 (18.1)</td>
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<tr>
<td>Right coronary artery</td>
<td>533 (28.5)</td>
<td>546 (29.6)</td>
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<tr>
<td>Left main disease</td>
<td>55 (2.9)</td>
<td>44 (2.4)</td>
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<tr>
<td>Bifurcation</td>
<td>226 (12.1)</td>
<td>231 (12.5)</td>
<td>0.69</td>
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<tr>
<td>Ostial location</td>
<td>125 (6.7)</td>
<td>128 (6.9)</td>
<td>0.76</td>
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<tr>
<td>B2 or C type</td>
<td>1494 (79.8)</td>
<td>1461 (79.1)</td>
<td>0.59</td>
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<tr>
<td>Calcification</td>
<td>80 (4.3)</td>
<td>91 (4.9)</td>
<td>0.34</td>
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<tr>
<td>Total occlusion</td>
<td>219 (11.7)</td>
<td>190 (10.3)</td>
<td>0.17</td>
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## Baseline Procedural Characteristics

<table>
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<tr>
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<th>Clopidogrel + Aspirin (n=1357)</th>
<th>Aspirin Alone (n=1344)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions stented, No</td>
<td>1872</td>
<td>1847</td>
<td></td>
</tr>
<tr>
<td>Stents per lesion, No.</td>
<td>1.3±0.5</td>
<td>1.2±0.5</td>
<td>0.13</td>
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<tr>
<td>Stent length per lesion, mm</td>
<td>31.8±16.4</td>
<td>30.9±15.4</td>
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<tr>
<td>Type of drug-eluting stents</td>
<td></td>
<td></td>
<td>0.98</td>
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<tr>
<td>Sirolimus-eluting stents</td>
<td>1057 (56.6)</td>
<td>1052 (57.0)</td>
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<tr>
<td>Paclitaxel-eluting stents</td>
<td>456 (24.4)</td>
<td>439 (23.8)</td>
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<tr>
<td>Zotarolimus-eluting stents</td>
<td>350 (18.7)</td>
<td>347 (18.8)</td>
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<tr>
<td>Others</td>
<td>9 (0.5)</td>
<td>9 (0.5)</td>
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### Timing of Randomization after the Index PCI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel + Aspirin (n=1357)</th>
<th>Aspirin Alone (n=1344)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Time to randomization</td>
<td>1189 (87.6)</td>
<td>1187 (88.3)</td>
<td>0.86</td>
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<tr>
<td>12 Mo – 18 Mo after procedure</td>
<td>167 (12.3)</td>
<td>156 (11.6)</td>
<td></td>
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<tr>
<td>18 Mo – 24 Mo after procedure</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
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<tr>
<td>&gt;24 Mo after procedure</td>
<td>12.8 (12.2–14.6)</td>
<td>12.8 (12.2–14.8)</td>
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## Status of Antiplatelet Therapy during Follow up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel + Aspirin (n=1357)</th>
<th>Aspirin Alone (n=1344)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At randomization</td>
<td>1348/1357 (99.3)</td>
<td>1338/1344 (99.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>6 Mo after randomization</td>
<td>1338/1349 (99.2)</td>
<td>1328/1333 (99.6)</td>
<td>0.14</td>
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<tr>
<td>12 Mo after randomization</td>
<td>1129/1143 (98.8)</td>
<td>1103/1117 (98.7)</td>
<td>0.95</td>
</tr>
<tr>
<td>18 Mo after randomization</td>
<td>752/759 (99.1)</td>
<td>722/730 (98.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>24 Mo after randomization</td>
<td>327/333 (98.2)</td>
<td>313/318 (98.4)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At randomization</td>
<td>1335/1357 (98.4)</td>
<td>59/1344 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 Mo after randomization</td>
<td>1297/1349 (96.1)</td>
<td>78/1332 (5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 Mo after randomization</td>
<td>1011/1143 (88.5)</td>
<td>72/1117 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18 Mo after randomization</td>
<td>654/758 (86.3)</td>
<td>46/730 (6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 Mo after randomization</td>
<td>276/333 (82.9)</td>
<td>14/318 (4.4)</td>
<td>&lt;0.001</td>
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</tbody>
</table>
Primary End Point: 
Cardiac Death or Myocardial Infarction

Log-rank, P=0.17

No. at Risk
Continuation group  1357                                    1122                                       299
Discontinuation group  1344                                     1100                                       301

Primary End Point:
Cardiac Death or Myocardial Infarction

Aspirin Alone

Clopidogrel + Aspirin

0.5
0.7
1.8
1.2

Days after Randomization
Cumulative Incidence (%)
0 0 0
0 365 730
0 0 0
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total Events</th>
<th>Hazard Ratio</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Dual Therapy</td>
<td>Aspirin Only</td>
<td>(95% CI)</td>
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<tr>
<td><strong>Primary End Point</strong></td>
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<tr>
<td>Cardiac death or MI</td>
<td>20</td>
<td>12</td>
<td>1.65 (0.80-3.36)</td>
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<td></td>
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<tr>
<td><strong>Secondary End Points</strong></td>
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<tr>
<td>Death</td>
<td>20</td>
<td>13</td>
<td>1.52 (0.75-3.5)</td>
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<tr>
<td>MI</td>
<td>10</td>
<td>7</td>
<td>1.41 (0.54-3.71)</td>
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<tr>
<td>Stroke</td>
<td>9</td>
<td>4</td>
<td>2.22 (0.68-7.20)</td>
</tr>
<tr>
<td>Stent thrombosis, definite</td>
<td>5</td>
<td>4</td>
<td>1.23 (0.33-4.58)</td>
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<tr>
<td>Repeat revascularization</td>
<td>36</td>
<td>26</td>
<td>1.37 (0.83-2.27)</td>
</tr>
<tr>
<td>Death or MI</td>
<td>27</td>
<td>17</td>
<td>1.57 (0.85-2.88)</td>
</tr>
<tr>
<td>Death, MI, or stroke</td>
<td>35</td>
<td>20</td>
<td>1.73 (0.99-3.0)</td>
</tr>
<tr>
<td>Cardiac death, MI, or stroke</td>
<td>28</td>
<td>15</td>
<td>1.84 (0.99-3.45)</td>
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<tr>
<td>Major bleeding, TIMI criteria‡</td>
<td>3</td>
<td>1</td>
<td>2.96 (0.31-28.46)</td>
</tr>
</tbody>
</table>
Days after Randomization

Cumulative Incidence (%)

No. at Risk
Continuation group 1357
Discontinuation group 1344

Log-rank, P=0.24

Death from Any Cause

Clopidogrel + Aspirin

Aspirin Alone

0.5 0.5 1.4 1.6

0 0 365 730

Days after Randomization

No. at Risk
Continuation group 1357 1125 302
Discontinuation group 1344 1103 303
Days after Randomization

Cumulative Incidence (%)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Continuation group</th>
<th>Discontinuation group</th>
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<td>1357</td>
<td>1344</td>
</tr>
<tr>
<td>At Risk</td>
<td>1124</td>
<td>1102</td>
</tr>
<tr>
<td></td>
<td>301</td>
<td>303</td>
</tr>
</tbody>
</table>

Log-rank, P=0.76

Definite Stent Thrombosis

Clopidogrel + Aspirin

Aspirin Alone

0.1

0.2

0.4

0.4

0.4
Days after Randomization

Cumulative Incidence (%)

No. at Risk

Continuation group 1357                                    1119                                        295
Discontinuation group  1344                                     1097                                        300

Log-rank, P=0.048

Death, Myocardial Infarction, or Stroke

Clopidogrel + Aspirin

Aspirin Alone

1.1

3.2

1.8
In this combined analysis of two randomized multi-center trials, we found no significant benefit associated with clopidogrel continuation as compared with clopidogrel discontinuation after 12 months in reducing the incidence of cardiac death or myocardial infarction for patients who had received drug-eluting coronary stents.
The rate of composite outcomes (all-cause or cardiac death, myocardial infarction, or stroke) was greater with clopidogrel continuation than with clopidogrel discontinuation, but this difference was not statistically significant.

However, the study had insufficient statistical power to allow a firm conclusion regarding the safety of clopidogrel discontinuation after 12 months. Larger clinical trials will be necessary to resolve this issue.
Thank You !!

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