

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Park S-J, Park D-W, Kim Y-H, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med* 2010;362:1374-82. DOI: 10.1056/NEJMoa1001266.

Supplementary Appendix

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I. Detailed Description of Each of the Trials (REAL-LATE Trial and ZEST-LATE Trial) and the Decision to Merge Them

Our trial is a merged analysis of two trials (REAL-LATE; NCT00484926 and ZEST-LATE; NCT00590174) that were originally independent of one another. The REAL-LATE trial was initiated on July 1, 2007, with a planned sample size of 2000 patients. The ZEST-LATE trial was initiated on January 4, 2008, also with a planned sample size of 2000 patients. Detailed information about each of the trials is presented in **Appendix Table 1**.

The decision to terminate enrollment and perform a merged analysis of the two trials was made by the Executive Committee of each study, and the Data and Safety Monitoring Board (which was the same for both trials) agreed to the merger. The decision was made on September 30, 2008, at which time the REAL-LATE trial had enrolled 1625 patients and the ZEST-LATE trial had enrolled 1076 patients. This decision took into account several factors. First, the patient recruitment for each trial was much slower than anticipated, and it was proving very hard to achieve the recruitment target for each trial. Second, each trial had the same study purpose and followed the same protocol. Third the number of enrolled patients after merger of the two trials was 2701 patients – more than the 2,000 patients initially planned to test each primary study hypothesis. Fourth, all members of the two executive committees and the Data and Safety Monitoring Board fully agreed with the description of the situation and accepted the decision regarding the merging of the trials. None of the data from either trial was analyzed, nor was the randomization code for either trial broken, before the decision was made to merge the trials.

Trial follow-up continued until September 30, 2009 for the purposes of data collection for the analyses described in this report.

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II. Detailed Description of the ZEST trial

The Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent with Sirolimus-Eluting and PacliTaxel-Eluting Stent for Coronary Lesions (ZEST trial; NCT00418067) was a prospective, randomized, single-blind, controlled study conducted at 19 centers in Korea between October 2006 and January 2008. The study purpose was to evaluate the relative efficacy and safety of zotarolimus-eluting stents in comparison to the established and widely used sirolimus- and paclitaxel-eluting stents in patients undergoing percutaneous coronary intervention (PCI).¹

The study had an “*all-comers*” design involving the consecutive enrollment of eligible patients aged 18 years or older with either stable angina or an acute coronary syndrome who had at least one coronary lesion (defined as stenosis of more than 50%) suitable for stent implantation. There were no limitations on the number of lesions or vessels or on the length of the lesions, reflecting routine clinical practice. Exclusion criteria were ST-segment elevation myocardial infarction necessitating primary PCI; severely compromised ventricular function (ejection fraction less than 25%) or cardiogenic shock; allergy to antiplatelet drugs, heparin, stainless steel, contrast agents, zotarolimus, sirolimus, or paclitaxel; left main coronary artery disease (defined as stenosis of more than 50%); in-stent restenosis of drug-eluting stents; terminal illness; and participation in another coronary-device study.

Between October 2006 and January 2008, a total of 2,645 patients (3613 lesions) were enrolled in the study and randomly assigned to receive zotarolimus (883 patients; 1,190 lesions),

sirolimus (878 patients; 1,218 lesions) or paclitaxel (884 patients; 1,205 lesions) stents. After the procedure, all patients received 100 mg/day of aspirin indefinitely, as well as 75 mg/day clopidogrel for at least 12 months. Use of standard postintervention care was recommended. Patients who completed the ZEST trial without experiencing a major adverse cardiovascular event or major bleeding were eligible to enroll in the ZEST-LATE trial as described above.

III. The Details of Sample Size Estimation

At the time that the REAL-LATE and ZEST-LATE trials were being designed, only two clinical studies (the Basel Stent Kosten-Effektivitats Trial-Late Thrombotic Events [BASKET-LATE; ISRCTN75663024] study² and a report from a large single-center registry at Duke University³) were available for sample size assumption.

In the BASKET-LATE trial, the 18-month rate of cardiac death or myocardial infarction was 4.9% in the aspirin monotherapy group after drug-eluting stent implantation and 1.3% after bare-metal stent implantation (used as a proxy for the event rate in the dual antiplatelet therapy group after drug-eluting stent implantation) (73% relative risk reduction). In the Duke registry, the adjusted 24-month rate of death or myocardial infarction was 4.5% in the aspirin monotherapy group and 0% in the dual antiplatelet therapy group among patients with drug-eluting stents who were event-free at 12 months (hazard ratios were not reported as there were no events for patients in the dual antiplatelet group). The expected cumulative rate of the primary end point in the aspirin monotherapy group (5% at two years) and the assumed relative risk reduction with dual antiplatelet therapy (50%) were thus based on the results seen in the BASKET-LATE trial and the Duke registry. Sample size was calculated with use of the PASS software (NCSS, Kaysville, UT, USA).

IV. Cox Model Stratified by Trial (REAL-LATE Trial and ZEST-LATE Trial)

Because our trial is a merged analysis of two trials (REAL-LATE and ZEST-LATE) that were originally independent of one another, we performed a stratified Cox regression analysis to test whether merging of the data from the two trials would influence the primary outcome. The treatment effect was estimated separately for each trial, and the estimates from each were combined to provide an overall estimate of the treatment effect. A likelihood ratio test for homogeneity was performed, indicating that the assumption of homogeneity was not violated (P=0.61). In the stratified Cox regression analysis, the overall hazard ratio for the primary end point was essentially unchanged (hazard ratio for clopidogrel continuation relative to discontinuation, 1.66; 95% CI, 0.81 to 3.39; P = 0.16), suggesting that there was no differential treatment effect between the two trials.

Appendix Table 1. Detailed Description of Each of the Trials (REAL-LATE Trial and ZEST-LATE Trial)

	REAL-LATE Trial	ZEST-LATE Trial
Study purpose	To assess the relationship between clopidogrel use and long-term clinical events after drug-eluting stent implantation in real-world practice and to estimate the optimal duration of dual antiplatelet therapy for preventing late thrombotic events.	To assess the relationship between long-term clopidogrel use beyond 1 year and long-term clinical events after drug-eluting stent implantation and to estimate the optimal duration of dual antiplatelet therapy for preventing late thrombotic events.
Study design	Randomized, open-label, parallel-group, multicenter trial	Randomized, open-label, parallel-group, multicenter trial
Study eligibility criteria	<p><u>Inclusion criteria:</u></p> <p>1. Among consecutive patients treated with drug-eluting stents, patients who survived at least the first 12 months without a major adverse cardiac or cerebrovascular event (death, myocardial infarction, stroke, or repeat revascularization) or major bleeding and were on dual antiplatelet therapy at the time of enrollment.</p> <p>2. Patient or guardian agrees to the study protocol and the schedule of clinical follow-</p>	<p><u>Inclusion criteria:</u></p> <p>1. Among the participants in the ZEST trial, patients who survived at least the first 12 months without a major adverse cardiac or cerebrovascular event (death, myocardial infarction, stroke, or repeat revascularization) or major bleeding and were on dual antiplatelet therapy at the time of enrollment.</p> <p>2. Patient or guardian agrees to the study protocol and the schedule of clinical follow-</p>

up, and provides informed, written consent, as approved by the appropriate Institutional Review Board/Ethical Committee of the respective clinical site.

Exclusion criteria:

1. Contraindication to antiplatelet therapy
2. Non-cardiac co-morbid conditions with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment).
3. Patients who are actively participating in another drug or device investigational study, which has not completed the primary end point follow-up period.
4. Concurrent bleeding diathesis or major bleeding history requiring discontinuation of antiplatelet drugs.
5. Concomitant vascular disease requiring long-term use of clopidogrel or established indication for clopidogrel therapy (such as recent acute coronary syndromes).

2,000 patients

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Exclusion criteria:

1. Contraindication to antiplatelet therapy
2. Non-cardiac co-morbid conditions with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment).
3. Patients who are actively participating in another drug or device investigational study, which has not completed the primary end point follow-up period.
4. Bleeding diathesis.
5. Concurrent organ damage
6. Left main stem stenosis

2,000 patients

Planned sample size

Trial monitoring	Academic coordinating center (<i>Clinical Research Center, Asan Medical Center, Seoul, Korea</i>)	Academic coordinating center (<i>Clinical Research Center, Asan Medical Center, Seoul, Korea</i>)
Study initiation time	July 1, 2007	January 4, 2008.
Number of patients enrolled in final analysis	1,625 patients	1,076 patients
Follow-up duration after randomization in months, median (interquartile range)	19.6 (12.3-25.5)	18.6 (14.2-21.9)
Executive Committee members	<p><u>Chairman:</u> Seung-Jung Park (Asan Medical Center, Seoul, Korea)</p> <p><u>Members:</u> Duk-Woo Park (Asan Medical Center, Seoul, Korea) Seung-Whan Lee (Asan Medical Center, Seoul, Korea) Cheol-Whan Lee (Asan Medical Center, Seoul, Korea) Seong-Wook Park (Asan Medical Center, Seoul, Korea)</p>	<p><u>Chairman:</u> Seung-Jung Park (Asan Medical Center, Seoul, Korea)</p> <p><u>Members:</u> Duk-Woo Park (Asan Medical Center, Seoul, Korea) Young-Hak Kim (Asan Medical Center, Seoul, Korea) Seung-Whan Lee (Asan Medical Center, Seoul, Korea) Cheol-Whan Lee (Asan Medical Center, Seoul, Korea) Seong-Wook Park (Asan Medical Center, Seoul, Korea)</p>

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