Meta-Analysis of Long-Term Clinical Outcomes of Everolimus-Eluting Stents

Toshiaki Toyota, MD[a], Hiroki Shiomi, MD[a], Takeshi Morimoto, MD, MPH[b], and Takeshi Kimura, MD[a,*]

The superiority of everolimus-eluting stents (EES) over sirolimus-eluting stents (SES) for long-term clinical outcomes has not been yet firmly established. We conducted a systematic review and a meta-analysis of randomized controlled trials (RCTs) comparing EES directly with SES using the longest available follow-up data. We searched PubMed, the Cochrane database, and *ClinicalTrials.gov* for RCTs comparing outcomes between EES and SES and identified 13,434 randomly assigned patients from 14 RCTs. EES was associated with significantly lower risks than SES for definite stent thrombosis (ST), definite/probable ST, target-lesion revascularization (TLR), and major adverse cardiac events (MACE). The risks for all-cause death and myocardial infarction were similar between EES and SES. By the stratified analysis according to the timing after stent implantation, the favorable trend of EES relative to SES for ST, TLR, and MACE was consistently observed both within and beyond 1 year. The lower risk of EES relative to SES for MACE beyond 1 year was statistically significant (pooled odds ratio 0.77, 95% confidence interval 0.61 to 0.96, $p = 0.02$). In conclusion, the current meta-analysis of 14 RCTs directly comparing EES with SES suggested that EES provided improvement in both safety and efficacy; EES compared with SES was associated with significantly lower risk for definite ST, definite/probable ST, TLR, and MACE. The direction and magnitude of the effect beyond 1 year were comparable with those observed within 1 year. **(Am J Cardiol 2015;116:187−194)**

The superiority of everolimus-eluting stent (EES; Xience V [Abbott Vascular, Santa Clara, California]/PROMUS [Boston Scientific, Natick, Massachusetts]) over sirolimus-eluting stent (SES; Cypher/Cypher select/Cypher select plus [Cordis Corporation, Johnson and Johnson, Warren, New Jersey]) is still unclear. There have been 3 reports of meta-analysis comparing EES directly with SES.[1−3] The latest report including 11 randomized controlled trials (RCTs) with 12,869 patients demonstrated superiority of EES over SES in terms of definite stent thrombosis (ST) and repeat revascularization (defined as target-lesion revascularization [TLR] or target-vessel revascularization varying among trials) but failed to show the differences in major adverse cardiac events (MACE) and definite or probable ST between EES and SES.[3] Since the publication of the last meta-analysis, a few new RCTs were reported and several RCTs included in the previous meta-analyses extended the follow-up duration, and beyond 1 year, outcomes became evaluable. In addition, the continuous hazards of SES have been postulated, and further analysis comparing EES and SES beyond 1 year is warranted.[4] Therefore, we conducted a systematic review and a meta-analysis of 14 RCTs comparing EES directly with SES using the longest available follow-up data.

Methods

We searched all reported trials comparing EES with SES in patients with coronary artery disease, using the term "everolimus eluting stent," "Xience," "Promus," "everolimus-eluting stent," "sirolimus eluting stent," "Cypher," and "sirolimus-eluting stent." We searched the US National Library of Medicine (Pubmed at *http://www.pubmed.gov*), the US National Institutes of Health clinical trials registry (*http://www.clinicaltrials.gov*), and the Cochrane Central Register of Controlled trials (*http://www.mrw.interscience.weiley.com/cochrane/cochrane_clcentral_articles_fs.html*). From the gathered studies, RCT comparing EES and SES were extracted, and if there were several reports from the same RCTs, we selected the report providing the longest follow-up data for the trial. The last search was performed in May 2014. Each trial was evaluated by referring to the Cochrane Collaboration's tool (recommendation for the qualification of RCT) for the adequacy of allocation concealment, performance of the analysis according to the intention-to-treat principle, and blind assessment of the outcomes of interest.[5] Because this study used only published reports without individual patient information, the procedure of informed consent and institutional review board approval was not applicable.

The end points analyzed in this study included ST (definite and definite/probable), repeat revascularization (TLR, TLR equivalent, and target-vessel revascularization equivalent), all-cause death, myocardial infarction, and MACE. ST was defined according to the Academic Research Consortium definition.[6] Academic Research Consortium definition was adopted in all trials except for one, which reported no event of ST.[7] ST was further analyzed according

[a]Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan and [b]Division of General Medicine, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan. Manuscript received January 24, 2015; revised manuscript received and accepted March 31, 2015.

See page 193 for disclosure information.

*Corresponding author: Tel: +81-75-751-4254; fax: +81-75-751-3289.
E-mail address: taketaka@kuhp.kyoto-u.ac.jp (T. Kimura).

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Table 1
Characteristics of the included studies

Study	Studies with follow-up >1-year						Studies with follow-up <=1-year					
	BASKET -PROVE	ISAR -TEST-4	SORT OUT IV	RESET	SEA -CORP †	XAMI/ APPENDIX -AMI †	EXCELLENT	LONG-DES III	ESSENCE -DIABETES	Song.HG et al.	Sakakibara.T et al.	CIBELES
Number of Patients	1549	1304	2774	3196	443	1602	1443	450	300	66	100	207
EES: Number of Patients	774	652	1390	1596	223	902	1079	224	149	34	50	106
SES: Number of Patients	775	652	1384	1600	220	700	364	226	151	32	50	101
Age (years)	66	67	64	69	64	63	63	63	63	-*	66	64
Male	75%	77%	76%	77%	80%	73%	65%	70%	59%	52%	70%	83%
Diabetes	17%	29%	14%	45%	31%	14%	38%	30%	100%	30%	70%	36%
Hypertension	61%	68%	55%	80%	68%	39%	73%	59%	71%	56%	70%	68%
Dyslipidemia	63%	65%	71%	75%	54%	42%	76%	57%	38%	79%	32%	71%
Smoker	32%	16%	30%	21%	21%	36%	27%	22%	24%	12%	24%	56%
Acute Coronary Syndrome	65%	40%	42%	18%	76%	67%	52%	42%	42%	N/A	N/A	44%
Acute Myocardial Infarction	33%‡	11%	10%‡	6%	N/A	44%	10%	N/A	5%	N/A	N/A	N/A
Multivessel Disease	43%	86%	N/A	47%	45%	52%	52%	56%	55%	30%	N/A	N/A
Bifurcation	8%	29%	12%	40%	100%	19%	11%	41%	N/A	14%	31%	25%
Chronic Total Occlusion	4%	7%	6%	6%	N/A	N/A	4%	N/A	N/A	N/A	N/A	100%
Follow-up Period (months)	24	36	24	36	36	24	12	12	12	12	12	12
Clopidogrel Duration	12	≥6	12	Not mandated	12	12	6 or 12	≥12	≥12	≥6	N/A	≥9
Follow-up Angiography	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Definition of Major Adverse Cardiac Events	Death, MI, TVR	Cardiac death, Target-vessel MI, TLR	Cardiac death, MI, Definite ST, TVR	Cardiac death, MI, Ischemia-driven TLR	Death, AMI, TVR	Cardiac death, MI, TVR	Cardiac death, Target-vessel related MI, Clinically indicated TLR	All-cause death, MI, Ischemia-driven TVR	Death, MI, Ischemia-driven TLR	Death, MI, TLR	All-cause death, Nonfatal MI, TLR	Death, MI, New target-vessel revascularization

Details of the 14 randomized control trials and 2 cooperative studies were shown in Supplementary Table 1.

EES = everolimus-eluting stent; MI = myocardial infarction; N/A = not available; SES = sirolimus-eluting stent; ST = stent thrombosis; TLR = target-lesion revascularization; TVR = target-vessel revascularization.

* Song HG et al reported median age of each groups (EES; 65 years, SES; 61 years) instead of mean age.

† Results of cooperative studies; SEA-CORP: the SEA-SIDE and CORpal trials, XAMI/APPENDIX-AMI: the XAMI and APPENDIX-AMI trials.

‡ Studies counted STEMI only.