Executive Summary

1. Objectives

We aim to provide objective evidence to healthcare providers to efficiently manage patients with acute myocardial infarction with ST-elevation (STEMI) by following detailed objectives.

1) Evaluate the clinical efficacy and safety of drug-eluting stents (DES) versus bare-metal stents (BMS) in patients with acute myocardial infarction through a systematic review and meta-analyses.
2) Perform an economic assessment comparing DES and BMS in patients with acute myocardial infarction through a cost-minimization analysis.

2. Methods

1) Systematic Review

We searched the Cochrane Library, TRIP database, SUM search database, and seven Korean databases to identify review articles comparing outcomes between DES and BMS in patients with acute myocardial infarction. Each review article was assessed and evaluated by two independent reviewers using AMSTAR, a measurement tool for the assessment of multiple systematic reviews.

In addition, Ovid-Medline, EMBASE, the Cochrane Library, and seven Korean databases were searched for primary research articles comparing outcomes between DES and BMS in patients with STEMI, and presented or published through September 2009. Major conference proceeding databases were also searched and included the

Scientific Sessions of the American College of Cardiology, the American Heart Association, the Transcatheter Cardiovascular Therapeutics, and the European Society of Cardiology. Finally, websites including cardiosource.com and TCTMD.com were also searched for relevant studies. The references of prior review articles and meta-analyses were reviewed for additional possible studies and authors were contacted if needed. Randomized controlled trials (RCTs) and observational studies (non-RCTs) were included.

Two independent reviewers extracted variables of clinical endpoints (death, recurrent myocardial infarction, target vessel revascularization [TVR], target lesion revascularization [TLR], and stent thrombosis), and examined study types (RCTs and non-RCTs). The relative risk (RR) was calculated using the inverse variance method to pool the outcomes of each clinical endpoints. The average effects of eachoutcome and 95% confidence intervals (CI) were obtained using a random-effects model since this model provided wider, more conservative confidence intervals than would the fixed-effects model. It also allowed for generalization despite some degree of heterogeneity among patient samples included in the meta-analyses. A funnel plot, Begg test and Egger test were used to assess the presence of publication bias. If publication bias was suspected, the non-parametric trim and fill method were used to examine the impact of hypothetically imputed studies on the pooled estimates. The Cochrane Q statistic and the I2 statistic were also used to assess the heterogeneity of RRs. Subgroup analyses, sensitivity analyses, and meta-regression were also performed. Two independent reviewers assessed the quality of included articles by using the Cochrane's risk of bias for RCTs, and the methodological index for non-randomized studies (MINORS). To determine the quality of evidence, GRADEpro was used.

2) Economic Assessment

The patient population for the economic assessment was stent-naive patients with STEMI. A cost-minimization analysis was performed because there was no significant difference between DES and BMS in the occurrence of death, which was the major clinical endpoint. The cost difference caused by the difference in the rate of revascularization between DES and BMS was reflected in this analysis. A decision analytic model with a societal perspective was developed to estimate the cost difference between DES and BMS. The time horizon used was one year because STEMI is an acute disease requiring emergency treatments and revascularization usually occurs within one year.

The National Insurance Claims Database obtained from the Health Insurance Review and Assessment Service (HIRA) was utilized to obtain transition probabilities and cost estimates reflecting the local situation. The patient population was defined as subjects with acute myocardial infarction who underwent stent procedures through emergency department visits between January 1st, 2006 and December 31st, 2007.

The transition probabilities of DES, BMS, CABG, and balloons were obtained from the results of the systematic review and the analysis results of HIRA data. Costs in 2009 were obtained from the analysis results of HIRA data and the micro-costing method. Univariate sensitivity analyses were performed by presenting a Tornado diagram and probabilistic sensitivity analyses were performed.

3. Results

1) Systematic Review

Nine reviews and meta-analyses were identified. After assessing the quality of reviews, the systematic review performed by Brar, et al was chosen. Including the clinical studies considered in the review of Brar, et al and those identified through a new search, fifty studies were identified (N=52,503). Among them, fifteen studies were RCTs and 35 studies were non-RCTs.

A meta-analysis using data from 7,654 patients in RCTs showed that when comparing DES and BMS, there were no detectable differences in mortality (RR=0.88, 95%CI 0.70-1.11, p=0.28) or stent thrombosis (RR=0.93, 95%CI 0.72-1.21, p=0.59). On the other hand, a significant reduction was observed from the DES group in terms of the recurrence of myocardial infarction (RR=0.76, 95%CI 0.60-0.96, p=0.02), TVR (RR=0.48, 95%CI 0.41-0.56, p<0.00001), and TLR (RR=0.42, 95%CI 0.33-0.54, p<0.0001). There was no evidence of statistical heterogeneity or publication bias among these studies.

In non-RCTs with 44,894 patients, the use of DES was associated with significant reductions in mortality (RR=0.82, 95%CI 0.73-0.91), TVR (RR=0.61, 95%CI 0.48-0.77), and TLR (RR=0.44, 95%CI 0.32-0.60) compared with BMS. However, there was no significant difference between DES and BMS in the recurrence of myocardial infarction (RR=0.94, 95%CI 0.85-1.03) or stent thrombosis (RR=0.88, 95%CI 0.64-1.23). Since there was significant heterogeneity in the pooled data, a meta-analyses was performed by follow-up period (within one/two year(s) of the index stenting). The use of DES was still associated with significant reductions in mortality, TVR, and TLR. However, even though DES was associated with significant reductions in the recurrent myocardial infarction and stent thrombosis within one year of the index stenting, there were no differences between DES and BMS at two years of follow-up. Among six observational studies (N=6,646) with over two years' of follow-up,

the use of DES was associated with a significant elevation of stent thrombosis compared with BMS. When studies were categorized by follow-up period and performed analyses, we found no evidence of statistical heterogeneity and publication bias.

The quality of the evidence derived from the RCTs was evaluated as "moderate" for mortality and myocardial infarction, "high" for TVR and TLR, and "low" for stent thrombosis. The quality of the evidence from non-RCTs was "very low" or "low" for all clinical endpoints.

2) Economic Assessment

Based on HIRA data, the average one-year cost per patient in the perspective of insurer was estimated to be 9,085,047 KRW and 8,040,351 for DES and BMS, respectively. The use of DES resulted in the higher costs of 1,017,696 KRW per person a year compared with BMS. From a societal perspective, the average costs of using DES and BMS in 2009 was 10,939,786 KRW per person a year and 9,710,672 KRW per person a year respectively. The use of DES was associated with the higher costs of 1,229,114 KRW per person a year compared with BMS. Using micro-costing method, the average costs of using DES and BMS were 5,570,288 KRW per person a year and 5,305,411 KRW per person a year respectively from a societal perspective. The use of DES was associated with the higher costs of 264,877 KRW per person a year compared with BMS. The cost difference between the use of DES and BMS was highly sensitive to incurred costs and the proportion of patients without revascularization.

4. Limitations

This study is subject to a number of limitations. First, most of articles included in this meta-analysis were based outside of Korea.

Secondly, an economic assessment considering various lesions that underwent procedures (single vessel, small vessel, long lesion, and multi-vessel) was no performed. DES are used more often in long lesions or multi-vessels which often result in worse outcomes and higher costs compared with BMS. Thus, an economic assessment that does not consider procedure lesions might produce results against DES. the effect that differing procedures have is not a true picture. Since HIRA data does not include data presenting lesions or the diameter of vessels, this limitation is hard to overcome without specific chart reviews.

Thirdly, the disease severity or comorbidity condition of patients was not factored in when using HIRA data for economic assessments. Since DES are used more often in severe patients who may also have a comorbid disease, the estimated costs incurred in patients from DES group may be overestimated than from BMS group if disease severity and comorbidity are not considered.

5. Conclusions

In this meta-analysis of 52,503 patients with STEMI from forty nine studies including RCTs and observational studies, the use of DES compared with BMS was associated with a significant reduction in TVR and TLR. DES and BMS did not show any differences in adverse effect outcomes such as death or stent thrombosis in RCTs. The use of DES in RCTs was associated with statistically significant reduction in the recurrence of myocardial infarction, but the significance level was in the margin. In observational studies, the use of DES was associated with a significant reduction in mortality compared with BMS. However, there were no differences between DES and BMS in recurrent myocardial infarction and stent thrombosis overall. The use of DES was related with a significant increase in stent thrombosis compared with BMS in observational studies with over two years of

follow-up. However, caution is needed to interpret this result because it is derived from observational studies and the evidence level was evaluated as "very low quality".

The use of DES appears to cost more than BMS. However, since this was very sensitive to the costs and proportions of patients without revascularization, additional studies are required to obtain more accurate estimates of costs and proportions of patients without revascularization after initial stenting. Large-scale, long term local RCTs or prospective studies with high quality are required to ascertain the clinical efficacy, safety, and economic effects of DES compared with BMS.

급성 심근경색증 환자에서 약물방출 스텐트와 금속 스텐트의 비교

Drug-eluting stents versus bare-metal stents in acute myocardial infarction
(Quality of the evidence of meta-analyses' results of RCTs)

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk BMS (in RCT)	Corresponding risk DES	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Death	Study population		RR 0.88 (0.70 to 1.11)	7654 (14 studies)	⊕⊕⊕⊖ moderate[1,2,3]
	45 per 1000	40 per 1000 (31 to 50)			
	Medium risk population				
	42 per 1000	37 per 1000 (29 to 47)			
MI	Study population		RR 0.76 (0.6 to 0.96)	7645 (14 studies)	⊕⊕⊕⊖ moderate[1,2,3]
	43 per 1000	33 per 1000 (26 to 41)			
	Medium risk population				
	41 per 1000	31 per 1000 (25 to 39)			
TVR	Study population		RR 0.48 (0.41 to 0.56)	7645 (14 studies)	⊕⊕⊕⊕ high[1,2,3,4]
	118 per 1000	57 per 1000 (48 to 66)			
	Medium risk population				
	133 per 1000	64 per 1000 (55 to 74)			
TLR	Study population		RR 0.42 (0.33 to 0.54)	5694 (9 studies)	⊕⊕⊕⊕ high[1,2,3,4]
	106 per 1000	45 per 1000 (35 to 57)			
	Medium risk population				
	131 per 1000	55 per 1000 (43 to 71)			
ST	Study population		RR 0.93 (0.72 to 1.21)	7262 (12 studies)	⊕⊕⊖⊖ low[1,2,3,5]
	35 per 1000	33 per 1000 (25 to 42)			
	Medium risk population				
	35 per 1000	33 per 1000 (25 to 42)			

1:In most of studies, sequence generation and allocation concealment were uncertain
2:In stenting, single blind does not affect the performance.
3:Inconsistency is not an issue since NSTEMI patients are not included.
4:RR<0.5
5.95% confidence interval includes 1 and 1.2.