Safety and Efficacy of Second-Generation Everolimus-Eluting Xience V Stents versus Zotarolimus-Eluting Resolute Stents in Real-World Practice: Patient-related and Stent-related Outcomes from The Multicenter Prospective EXCELLENT and RESOLUTE-Korea Registries

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MPH Thesis

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Brief Title: EES vs. ZES-R in Real-World Patients

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Abstract

Objectives

To compare everolimus-eluting (EES) versus zotarolimus-eluting Resolute stent (ZES-R) regarding patient- or stent-related clinical outcomes in an "all-comer" group of patients.

Background

Published head-to-head comparisons are limited to only two randomized controlled trials.

Methods

The EXCELLENT and RESOLUTE-Korea registries prospectively enrolled patients treated with EES (3056 patients with 4248 lesions) and ZES-R (1998 patients with 2836 lesions), respectively. There were no restrictions or exclusion criteria. Stent-related composite outcomes (target lesion failure) and patients-related composite outcomes were compared between two stent groups in both crude and propensity score matched analyses.

Results

Of 5054 patients, 3830 patients (75.8%) had off label indication (2217 treated with EES and 1613 treated with ZES-R). The stent-related outcome (82 [2.7%] vs. 58 [2.9%], p=0.662) and the patient-related outcome (225 [7.4%] vs. 153 [7.7%], p=0.702) did not differ between EES and ZES-R respectively at 1 year, which was corroborated by similar results from the propensity score-matched cohort. The rate of definite or probable stent thrombosis (18 [0.6%] vs. 7 [0.4%], p=0.306) was also similar. In multivariate analysis, off label indication was the most powerful predictor of target lesion failure (adjusted HR 2.882, 95% CI 1.226-6.779, p=0.015).

Conclusion

In this robust real world registry with unrestricted use of EES and ZES-R, both stents showed comparable safety and efficacy at 1 year follow-up. Overall incidences of target lesion failure and

definite stent thrombosis were low, even in the patients with off label indication, suggesting excellent safety and efficacy of both types of second generation drug-eluting stents.

Key Words

Resolute zotarolimus-eluting stent; Everolimus-eluting stent; Target lesion failure; Patient-oriented composite outcome; Clinical outcome; Stent thrombosis

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Condensed Abstract

Although the Xience-V/Promus everolimus-eluting stent (EES) and the Endeavor Resolute zotarolimus-eluting stents (ZES-R) are the most widely used 2nd generation DES, the published head-to-head comparisons between the two stents are limited to only two randomized controlled trials, suggesting the need for more data from everyday commercial use of these stents. We evaluated the safety and efficacy of the two 2nd generation DES in a total of 5,054 all-comers from two separate prospective registries. The stent-related outcome (82 [2.7%] vs. 58 [2.9%], p=0.662) and the patient-related outcome (225 [7.4%] vs. 153 [7.7%], p=0.702) did not differ between EES and ZES-R respectively at 1 year, which was corroborated by similar results from the propensity score-matched cohort. The rate of definite or probable stent thrombosis (18 [0.6%] vs. 7 [0.4%], p=0.306) was also similar. In multivariate analysis, off label indication was the most powerful predictor of target lesion failure (adjusted HR 2.882, 95% CI 1.226-6.779, p=0.015). In this robust real world registry with unrestricted use of EES and ZES-R, both stents showed comparable safety and efficacy at 1 year follow-up. Overall incidences of target lesion failure and definite stent thrombosis were low, even in the patients with off label indication, suggesting excellent safety and efficacy of both types of 2nd generation drug-eluting stents.

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Abbreviations

CI = confidence interval

DES = drug eluting stent

EES = everolimus-eluting stent(s)

MI = myocardial infarction

POCO = patient-oriented composite outcome

RCT = randomized controlled trial

ST = stent thrombosis

TLF = target lesion failure

TLR = target lesion revascularization

ZES-R = zotarolimus-eluting Resolute stent(s)

Introduction

Although first-generation DES substantially reduced angiographic and clinical measures of restenosis, safety issues including the risk of ST have remained problems to be solved by future developments.(1) Newer generation DES has incorporated a thinner cobalt-chromium stent platform with a durable but more biocompatible polymer. The most widely used second-generation DES is the Xience V/Promus everolimus-eluting stent (EES) (Abbott Vascular, CA, Illinois, USA) and the Endeavor Resolute zotarolimus-eluting stents (ZES-R) (Medtronic Cardiovascular, CA, Minnesota, USA). However, published head-to-head comparisons between the two stents are limited to only two RCTs,(2-4) suggesting the need for more data from everyday commercial use of these stents. In addition, long term surveillance studies of unrestricted registries may help elucidate mechanisms responsible for death, MI, and late ST risks not observed during the RCTs. The purpose of this study was to evaluate the safety and efficacy of the EES and ZES-R in everyday real-world use with a wide range of patient and lesion complexity.

Methods

Study design and patient population

This study evaluated 1 year clinical outcomes of EES and ZES-R from two separate prospectively-enrolled, multicenter registries: the EXCELLENT and RESOLUTE-Korea. Both registries enrolled all-comers who were treated with at least 1 EES or ZES-R (3056 patients from 29 participating centers or 1998 patients from 25 participating centers, respectively). There were no exclusion criteria or restrictions regarding lesion character or patient severity. The patients enrolled in the EXCELLENT registry were different from those enrolled in the previously reported EXCELLENT RCT which had strict inclusion and exclusion criteria, the main results of which have been published.(5) The flow of patients in the study is presented in Supplementary Figure 1.

Interventional Procedures

During the enrollment period of each registry, EES was available in diameters of 2.25, 2.50, 2.75, 3.00, 3.50, and 4.00 mm, with each available in lengths of 8, 12, 15, 18, 23, and 28 mm. On the other hand, the ZES-R was available in diameters of 2.25, 2.50, 2.75, 3.00, 3.50, 4.00 mm and in lengths of 8 mm and 14 mm for stents with a diameter ≤2.5 mm; 9, 15, and 38 mm for stents with a diameter of ≥3.00 mm; and 12, 14, 18, 24, and 30 mm for all available stent diameters. Coronary interventions were performed according to current standard techniques. The choice of the stent, predilatation, post-stenting adjunctive balloon inflation, and the use of intravascular ultrasound or glycoprotein IIb/IIIa inhibitors were all left to the operators' discretion. The aim of the procedure was to obtain full lesion coverage with one or more stents. Since enrollment to the registries was decided at the time of stenting according to the initially implanted stents, mixture of EES and ZES-R was not permitted for a given patient unless the operator was unable to insert same type of second stent. In the case of unplanned revascularization procedure requiring stent implantation, it was recommended that the operator use same type stent initially inserted. All patients received a loading dose of aspirin or were on chronic therapy before the procedure. A loading dose of 300 to 600 mg of clopidogrel was

administered to all patients who were not on clopidogrel prior to the procedure. Post-procedure, all patients were given aspirin (atleast 100 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 6 months after index procedure. Procedural anticoagulation was obtained with unfractionated heparin at a dose of 5000 IU or 70 to 100 IU per kilogram of body weight, according to the standard protocols.

Follow-up

Angiographic follow-up was allowed at 9 months post-PCI, but were not mandatory. Clinical follow-ups were performed 1, 3, 9 and 12 months after index PCI and will be continued annually for up to 3 years through outpatient clinic visits or, if not feasible, telephone interview. For any events, all medical records and relevant clinical information were sent to an external event committee for adjudication. If required, on-site review of the medical record was also performed. All of the clinical events were reviewed by a clinical event committee who were unaware of the purpose of this study. Because the Korean health system is a one payer (government) system with mandatory national health insurance, and all residents have a unique identification number which can be used to trace the vital status, the vital status of 100% of the patients were cross-checked with the national system. Therefore, even in those lost to follow-up, the occurrence of death was confirmed.

Definition and Outcome analysis

The primary clinical outcome was target lesion failure (TLF), defined as a composite of cardiac death, myocardial infarction (not clearly attributed to a nontarget vessel), or a clinically indicated target lesion revascularization by percutaneous or surgical methods at 12 months. All clinical outcomes were defined according to the Academic Research Consortium (ARC).(6,7) The key secondary outcome was the patient-oriented composite outcome (POCO) which included all-cause mortality, any myocardial infarction (including nontarget vessel territory), and any revascularization (including all target and nontarget vessels, regardless of percutaneous or surgical methods). Other secondary outcomes included individual components of the primary and key secondary clinical outcomes; target or non-target vessel myocardial infarction; any target lesion revascularization (TLR), defined as

repeat revascularization within the stented segment including 5 mm proximal and distal border zones; clinically-driven or angiographically-driven repeat revascularization including TLR or target vessel revascularization (TVR); any TVR; and stent thrombosis defined according to the ARC as definite, probable, or possible.(6,7) All deaths were considered cardiac unless an undisputed noncardiac cause was present. Myocardial infarction (MI) was defined according to the ARC definitions and an extended historical protocol definition.(6,7) A revascularization was considered clinically-driven if angiography during follow-up showed a diameter stenosis ≥50% with at least one of the following: 1) history of recurrent angina pectoris, presumably related to the target vessel; 2) objective signs of ischemia at rest or during exercise test by electrocardiogram, presumably related to target vessel; 3) abnormal test results of invasive functional diagnostic test (fractional flow reserve); or 4) a TLR with a diameter stenosis ≥70% even in the absence of the aforementioned ischemic signs or symptoms.(6,8) The indication of PCI was considered "off label" if any of the following features were present: serum creatinine concentration ≥140 umol/L (1.6 mg/dL); left ventricular ejection fraction (LVEF) < 30%; an acute MI within the previous 72 hours; more than one lesion per vessel; two or more vessels treated with a stent; a lesion length ≥ 28 mm; or a bifurcated lesion, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion.(2,3,8)

Statistical Analysis

The analysis was performed in two parts. First, analysis and comparison of primary and secondary clinical outcomes were conducted in the crude population. Second, a propensity score matched population was selected to adjust for uneven distribution of baseline characteristics. Subgroup analysis of primary clinical outcome, TLF, was conducted for clinically important risk factors in the crude population and propensity scored matched population. Categorical variables were presented as numbers and relative frequencies (percentages) and were compared using the χ^2 test or the Fisher exact test for independent groups and a two-tail p-value. Normally distributed continuous variables were expressed as means and standard deviations, and were analyzed using the independent sample t-test. Kaplan-Meier analysis was used to calculate cumulative incidence of primary and secondary clinical outcomes, and the Breslow test was used to compare between-group differences. Since

differences in baseline clinical and angiographic characteristics could impact the primary and secondary clinical outcomes, a 1:1 matched analysis without replacement was performed using propensity score. Logistic regression model was conducted to generate propensity score which was probability that a patient received a ZES-R. The adjusted covariates which were used to calculate the propensity score were as follows: age, sex, hypertension, diabetes mellitus, current smoking, dyslipidemia, chronic renal failure, peripheral vascular disease, family history of cardiovascular disease, LVEF, serum creatinine, previous PCI, previous coronary bypass surgery, previous MI, previous congestive heart failure, previous cerebrovascular accident, angiographic extent of disease (1 vessel disease [VD], 2VD, 3VD), clinical indication of PCI (stable angina, unstable angina, non ST segment elevation MI [NSTEMI], ST segment elevation MI [STEMI], silent ischemia), left main coronary artery stenting, bypass graft PCI, in-stent restenosis lesion, bifurcation, the presence of thrombus which was induced thrombosuction, long lesion (lesion length $\geq$ 28 mm), small vessel treatment(reference diameter $\leq$ 2.75 mm), off label indication, baseline medications including insulin, and multivessel procedure (2 or more vessel stenting) or not. For matching, a caliper width of 0.6 SDs was used because this value has been shown to eliminate almost 90% of the bias in the observed confounders.(9,10) Baseline clinical and angiographic characteristics were compared within the propensity score matched group. Success of the propensity score matching was assessed by calculating percentage standardized differences of the baseline characteristics. A less than 10% difference supports the assumption of a balance between matched groups.(11) A stratified Cox proportional hazard regression model was used to evaluate the adjusted hazard ratio (HR) of each clinical variable in a subgroup analysis and to identify independent predictors of primary clinical outcome, TLF. The covariates used in multivariate analysis were selected if they were significantly different between the two groups (p value < 0.1) or if they had predictive values. In addition, the individual components of off label indication (i.e. STEMI, NSTEMI, in-stent restenosis, bifurcation, thrombotic total occlusion, long lesion, multivessel PCI, severe left ventricular dysfunction [LVEF< 30%], and left main procedure) were not included individually to the final model due to significant correlation with off label indication itself (i.e. co-linearity between these co-variates). For the subgroup analysis of TLF, the logistic regression model was used to calculate the interaction p values

between treatment and each subgroup. In order to reduce possible confounding factors from the differences in baseline characteristics, multivariable adjusted stratified Cox proportional hazard regression and subgroup analysis were performed in propensity score matched cohorts. Additionally, we performed pooled analysis for stent thrombosis by gathering the data from the published RCT, the RESOLUTE All Comers trial(3) and TWENTE trial,(4) to enhance statistical power for this rare clinical events. Odds ratios (OR) with 95% confidence interval (CI) were presented as summary statistics. The pooled OR was calculated with the DerSimonian and Laird method for random effects.(12,13) Statistical heterogeneity was assessed with Cochran Q via a $\chi 2$ test and was quantified with the I^2 test.(14) All probability values were two-sided and p-values < 0.05 were considered statistically significant. The statistical package SPSS, version 18.0 (SPSS Inc., Chicago, IL, USA). R programming language, version 2.15.1 (R Foundation for Statistical Computing), and Review manager, version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) were used for statistical analyses.

Treatment of Missing Data and Sensitivity Analysis with Multiple Imputation Model

Basically, all of statistical analysis was performed with complete-case analysis.(15,16) In the baseline clinical and lesional characteristics, the exact numerators were presented for all variables with missing data in the Tables. In propensity score matching, random missing values in each covariates of propensity score model caused 20.5% of population (1038/5054 patients) with missing value of propensity score. The detailed proportion of missing data in the covariates of the propensity score model is presented in the Supplementary Table 4. 1:1 matched analysis without replacement was performed with the 79.5% of total population (4016/5054 patients). Given the concern for ascertainment bias in the propensity score matching in the observational studies due to missing data, we performed additional sensitivity analysis using multiple imputation model to estimate missing data of covariates which were used in the propensity score matching. The process of sensitivity analysis was as follows. Firstly, we compared the patients who incorporated to the matching process versus the others with missing value of propensity score (Supplementary Table 5). To be valid, complete-case analysis must assume that participants with missing data were intended to be observed, or at least that

the likelihood of exposure being missing is independent of the outcome given the exposures (Missing Completely At Random [MCAR]).(17) When data are MCAR, missing cases are no different than non-missing cases, in terms of the analysis being performed.(16) In the Supplementary Table 5, either groups with or without missing value of propensity score showed even distribution of the baseline clinical and lesion characteristics with the only exception of discharge medication (aspirin and clopidogrel). Secondly, in order to validate the results of propensity score matched group, we used multiple imputation model and estimated all of missing values in the covariates, presented in Supplementary Table 4. This method created 5 imputed dataset without any missing values. In each of imputed dataset, 1:1 matching without replacement was performed using same propensity score model. Lastly, the odds ratios of ZES-R for TLF or POCO were calculated with logistic regression model in each matched imputed dataset. The pooled estimates of imputed datasets were calculated from Rubin's rule.(16,18) As a result, the pooled estimate of odds ratio of ZES-R for TLF or POCO were remarkably similar with that of propensity score matched group with complete-case analysis (Supplementary Table 6). In the analysis of independent predictors of TLF with stratified Cox proportional hazard model (Table 5), the analysis was performed with propensity score matched population. 9 patients of the propensity matched population (9/2024 patients, 0.4%) was excluded from generating the multivariate model.

Institutional Review Board

The study protocol was approved by the ethics committee at each participating center and was conducted according to the principals of the Declaration of Helsinki. All patients provided written informed consent.

Results

Baseline Patient and Angiographic Characteristics

The main analyzed crude cohort was 5,054 patients with 7,084 lesions who were treated with EES (3056 patients with 4248 lesions) or ZES-R (1998 patients with 2836 lesion). A total of 55 patients (1.8%) in the EES group and 32 patients (1.6%) in the ZES-R group were lost to follow-up before the 12-month follow-up. All of lost to follow-up patients were confirmed to be alive with cross-checking of the national system. Baseline clinical and angiographic characteristics are presented in Tables 1 and 2 respectively. In the distribution of cardiac risk factors, both groups were mostly similar and comparable except for the proportion of dyslipidemia. Notably, the overall proportion of acute coronary syndrome was 63.3% (3186/5036 patients), those with diabetes was 36.9% (1855/5029 patients), those with multivessel disease was 56.2% (2830/5037 patients), and mean stent length was 38.97±26.01 mm per patients and 27.97±14.34 mm per lesion. PCI was "off label" in 75.8% of the cases and was more frequent in the ZES-R group. The large proportion of high-risk patients and lesions implies that our registries were an enriched PCI population, and well reflects real-world practice in Korea without any exclusion or restriction. In general, the lesion complexity was greater in the ZES-R group, except for use in left main disease treatment, which was higher in EES. A high percentage of lesions (38.0%) were treated under intravascular ultrasound (IVUS) guidance. The device, lesion, and procedure success rates were excellent for both stents and did not show between-group differences (Table 2).

Clinical Outcomes at 1 Year in Crude population

At 1 year, the incidence of primary clinical outcome, TLF, was 2.7% for EES and 2.9% for ZES-R, which was not significantly different (p=0.662). The rate of individual component of TLF (cardiac death, TLR, target vessel MI) was not statistically different between the two groups. POCO was also similar (7.4% vs. 7.7% for EES vs. ZES-R, p=0.702), as was the individual components (all cause death, any revascularization, any MI). About half of the target vessel related-MI was due to ST (10/19 events, 52.6%) (Table 3). In survival analysis, there were no differences between the two groups

regarding cumulative incidence of TLF (log rank p=0.641) or POCO (log rank p=0.717), as with its individual components (Figure 1A and 1B). Survival analysis of individual components of TLF or POCO was presented in Supplementary Figure 2.

Stent Thrombosis

Definite or probable ST was occurred in 25 patients (25/5054 patients, 0.5%) without between-group difference (18 patients in EES group [0.6%] vs. 7 patients in ZES-R group [0.4%], log rank p=0.240) (Table 4 and Figure 2). Only 2 patients in the EES group were off dual antiplatelet agent therapy at the time of ST occurrence due to bleeding (subarachnoid hemorrhage in one patient and upper gastrointestinal bleeding after PCI in another). More than half of the events were probable ST, which presented as sudden cardiac death or malignant arrhythmia. In the pooled analysis regarding definite or probable ST with the RESOLUTE All Comers trial and the TWENTE trial,(3,4) the incidence of definite or probable ST was 0.76% (37/4876 patients) in the EES group and 0.89% (34/3814 patients) in the ZES-R group, and did not differ between the two groups (odds ratio [OR], 1.00; 95% CI, 0.46 to 2.19; p=0.99) (Supplementary Figure 3).

Propensity Score Matched Group Analysis

Matching by propensity score yielded 1014 pairs of patients in both stent groups. Baseline clinical and angiographic characteristics of the matched groups are shown in Supplementary Table 1, and more balanced than crude population, confirmed with less than 10% of standardized difference of adjusted variables (Supplementary Figure 4). The cumulative incidence of TLF and POCO was comparable between the two groups (log rank p=0.675 and 0.708, respectively) (Figure 1C and 1D) as with its individual components and definite or probable ST (0.6% vs. 0.2%, p=0.288) (Supplementary Table 2 and 3). The results of sensitivity analysis are presented in Supplementary Table 4 to 6. In sensitivity analysis, the pooled OR of ZES-R for TLF in the multiple imputed propensity score matched group was 0.99 (95% CI 0.68-1.45, p=0.960), remarkably similar with the result of complete-case analysis (OR 0.890, 95% CI 0.515-1.537, p=0.781) (Supplementary Table 6).

Independent Predictors of Target Lesion Failure

In the univariate analysis, several underlying comorbidities and lesional characteristics were significantly different between those with and without events (Supplementary Table 7). In multivariate analysis to find independent predictors of TLF, PCI with off label indication was the most powerful predictor of target lesion failure (adjusted HR 2.882, 95% CI 1.226-6.779, p=0.015). In addition, other significant predictors of TLF included chronic renal failure, diabetes mellitus, and age (Table 5). Overall Harrell's c-index of the model was 0.777 (95% CI 0.716-0.838).

Subgroup Analysis of Propensity Score Matched Population

The results of subgroup analysis in the propensity score matched population are presented in Figure 3. Significant interaction was observed between stent type and multivessel PCI ($P_{interaction}$=0.032) and long lesion ($P_{interaction}$=0.016). In the other subgroups such as presence of off label indication, diabetes, or chronic renal failure, there were no significant interaction between stent type and subgroup and showed comparable rates of TLF.

Discussion

To date, this is the largest registry analysis comparing the safety and efficacy of everolimus-eluting Xience V/Promus stents versus zotarolimus-eluting Resolute stents. There were no exclusion criteria except those who refused to be enrolled. The finding from this comprehensive analysis showed that in both the crude population and the propensity score-matched population, EES and ZES-R showed comparable results regarding stent-related composite outcomes (TLF) and patients-related composite outcomes at 1 year. In addition, clinical events occurred more often after off label use of both DES, which was the strongest predictor of TLF. However within this subgroup, both stents showed similar clinical outcomes. Finally, the rates of ST were very low in both stents considering the complexity of the lesions treated, and in contrary to previous RCTs, the rates of definite and probable ST were comparable between EES and ZES-R.

Although the highest level of evidence for clinical practice is mostly generated from well-designed large scale RCTs, it is noteworthy that the subjects enrolled in RCTs do not fully represent the whole patient population in real world practice, and thus data from these trials have limitations regarding generalizability. Most RCTs have strict inclusion and exclusion criteria, and patients with higher-risk profiles and higher early in-hospital mortality tend to be excluded from participation in RCTs.(19) Even RCTs with an 'all-comers' design were not able to enroll all eligible patients, but included only 47% of the target population.(19) In this regard, prospective observational registries have the strength of including a broader patient population more reflective of every day practice. In this study, over 98% of the enrolled patients were strictly followed, and survival status of all patients was thoroughly investigated.

Although the patients in EES or ZES-R group showed several significant differences in the baseline clinical and angiographic characteristics, which is an inherent limitation of non-randomized study, these differences were balanced with propensity score matching and the clinical outcome including primary clinical outcome and the rest of secondary clinical outcomes showed comparable results between two stent groups.

Only 2 RCTs previously compared head-to-head, newer-generation DES – the RESOLUTE All Comers trials and the TWENTE trials.(2,4) The TLF rate of EES and ZES-R at 1 year were 8.3% versus 8.2% in the RESOLUTE ALL Comers trial (p=0.94), and 6.8% versus 7.9% in the TWENTE trial (p=0.42), respectively. In the present study, the TLF rate was lower (2.7% versus 2.9%, p=0.662) despite a more enriched PCI population where the rate of off label DES use was relatively higher (72.5% and 80.7%, respectively) than the RESOLUTE All Comers trial (65.6% and 67.0%, respectively). All three studies used the same definition of off label use. Although 77.4% of enrolled patients had off label indication in the TWENTE trial, the study excluded STEMI patients.

In line with the low rate of TLF, the incidence of definite or probable ST was also very low (18 patients [0.6%] vs. 7 patients [0.4%] for EES vs. ZES-R, respectively) without between-group difference. Recently, Palmerini et al. reported network meta-analysis which showed significantly lower rates of 1-year definite ST in cobalt-chromimum everolimus-eluting stent (CoCr-EES), compared with Resolute zotarolimus-eluting stent (ZES-R, OR 0.14, 95% CI 0.03-0.47), but not in 2-year definite ST (OR 0.35, 95% CI 0.10-1.07). Conversely, the rates of definite or probable ST in CoCr-EES did not significantly differ from ZES-R at 1 year (OR 0.65, 95% CI 0.31-1.40) and 2 year (OR 0.49, 95% CI 0.19-1.19).(20) Since most of pooled CoCr-EES data (16,584 patients of 13 trials; 81.8% of total 20,215 patients of 15 trials) were extracted from the studies which did not compare CoCr-EES directly with ZES-R, but rather those studies compared CoCr-EES with BMS, PES, or SES. Therefore, direct comparison of pooled CoCr-EES data with limited ZES-R data should be interpreted carefully. In contrast to the recent meta-analysis, we did not find any clustering of ST in either stent group in the pooled analysis of definite or probable ST from our study, the RESOLUTE All Comers Trial, and the TWENTE Trial. More data of head-to-head comparison between EES versus ZES-R regarding ST is needed to clarify this issue.

Notably, all ST cases occurred in those with off label use. Several trials with all-comers design and unrestricted use of DES have reported an overall rate of definite ST up to 18 months to range from 0% to 0.8% in EES (2,4,21-24) and 0.1 % to 1.2% in ZES-R.(2,4,25,26) In addition to these results, our results confirm the excellent safety and efficacy of both type of newer-generation even in an enriched PCI population with high numbers of off label use.

EES vs. ZES-R in Real-World Patients

In multivariate analysis, "off label" DES use was the most powerful predictor of TLF (adjusted HR 2.882, 95% CI 1.226-6.779, p=0.015), which is concordant with previous literature.(8) Even with the extremely low rates of events seen with second generation DES from other studies and from the current study, the risk of poor outcome still increases significantly with off label DES use. The TLF rate was 1.0% for EES and 1.1% for ZES-R in on label DES use, but increased to 3.5% for EES and 3.0% for ZES-R in off label DES use. It should be noted however, that even in off label indications the performance of both EES and ZES-R was excellent and comparable. Other independent predictors of TLF were chronic renal failure, diabetes mellitus, and increasing age. Chronic renal failure and diabetes mellitus have been well-recognized risk factors for major adverse cardiac events and angiographic restenosis (27-30) after stent implantation ever since the bare metal stent era and even in the 1st generation DES era. Increasing age has also been reported to be associated with adverse outcome in past studies.(31) In most RCTs, patients older than 75 years are often excluded and are underrepresented due to multiple comorbidities, more severe clinical presentation, and age itself.

In subgroup analysis, there were a couple of subgroups that had significant interaction with stent performance (subgroup of multivessel PCI and subgroup of lesions greater than or equal to 28mm). These subgroup results suggest that EES may have worse outcomes compared with ZES-R in multivessel PCI or long lesions. However, caution is warranted in interpreting these results. First, because EES with lengths greater than 28mm were not available during the study period, while those of 30 and 38mm were available for the ZES-R, it is inevitable that two EES were implanted for lesions where one ZES-R would have been enough in certain cases. Second, one major reason that the interaction p-value was significant for the two subgroups was the fact that TLF rates for ZES-R actually decreased with increased lesion complexity (TLF in ZES-R: 2.6% vs. 2.2% for single vessel vs. multivessel PCI and 3.0% vs. 1.5% for lesion length <28mm vs. ≥28mm) which is usually against our expectations. Third, it is well known that exploratory subgroup analysis has limited statistical power due to the problem of multiple testing and small sample size, therefore, there is a possibility that the results were a play of chance.

Study limitations.

EES vs. ZES-R in Real-World Patients

First, this was a non-randomized comparison of two different registries. Therefore, this study cannot be free from inherent limitations of observational registries such as allocation bias and uneven distribution of risk factors. Although we used propensity score matching to minimize the allocation bias and control for potential confounding variables, the possibilities of uncontrolled and unknown confounding factors need to be considered. However, because of the large of number of patients that were analyzed in this study, we believe the risk of play of chance findings especially regarding stent oriented composite outcomes and patient oriented composite outcomes can be minimized. We analyzed data from over 5000 patients and 7000 lesions in the crude analyses, and even after 1:1 propensity score matching we still had 1014 pairs (2028 patients), which is a quite large sample size. Second, because data were from observational registries, the clinical events may not have been captured with scrutiny and patient follow-up may not have been as tight as would be in RCTs. This may have been the reason for the low event rates. However, all patient data were collected by dedicated study nurses, and in order to minimize underreporting of events, we cross-checked the vital status of 100% of the study patients with the Korean national database using a citizen registration number that is unique to each individual. In addition, the national insurance reimbursement records were reviewed in patients without regular outpatient follow-ups. Nonetheless, we cannot exclude the possibility of under-reporting of clinical outcomes other than death, for example, MI or TLR, in the patients who were lost to follow-up but alive. Third, the data analyzed in the present study is only up to 1 year, which is relatively short to make any conclusions regarding ST and safety issues. Careful further follow-up is required to address this issue.

Conclusions

In this robust enriched PCI population with unrestricted use of EES and ZES-R, both stents showed comparable safety and efficacy at 1 year follow-up, with very low event rates. Overall incidences of stent and patient oriented composite outcomes along with rates of stent thrombosis were low, even with off label DES use, suggesting excellent safety and efficacy of both types of second generation drug-eluting stents.

Abstract (Korean)

2 세대 약물 방출 스텐트인 Xience V everolimus 방출 스텐트와 Resolute zotarolimus 방출 스텐트의 관상동맥 질환 치료 성적의 전향적 비교 분석: 다기관 전향적 레지스트리(EXCELLENT and RESOLUTE-Korea registry)의 비교 분석 연구

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학번 ; 2011 - 22114

연구 목적

전향적 다기관 레지스트리에 등재된 환자의 제한 기준 없이 삽입된 2 세대 약물방출스텐트간의 (Xience V everolimus 방출 스텐트와 Resolute zotarolimus 방출 스텐트) 임상적 예후에 대한 비교 연구

연구 배경

최근 중재적 심혈관 시술에서 2 세대 약물 방출 스텐트(Xience V everolimus 방출 스텐트와 Resolute zotarolimus 방출 스텐트)는 1 세대 약물방출 스텐트에 비하여 시술 후의 예후가 양호함이 밝혀졌다. 그러나 두종류의 2 세대 약물 방출 스텐트간의 비교 연구는 전세계적으로 2 건의 무작위 배정연구에 한정되어 있으며, 기존의 두 연구는 제한된 선정 기준으로 인하여 실제 진료 현장에서 시술을 받는 환자군을 모두 대변하지 못하며 이는 시술의 고위험군 환자들의 경우 무작위 배정 연구의 결과를 적용하기 어려운 제한점으로

작용하고 있다. 이에 본 연구는 제한 기준 없이 등재된 전향적 다기관 레지스트리에서 두 스텐트의 임상적 안전성 및 효능을 비교하고자 한다.

연구 방법

2008.04 월부터 2010.06 월까지 국내 29 및 25 개 기관에서 Everolimus 방출 스텐트(EES) 또는 Resolute zotarolimus 방출 스텐트 (ZES-R)를 삽입한 3056 명 및 1998 명의 환자들은 각각 EXCELLENT 와 RESOLUTE-Korea 레지스트리에 등재되었다. 환자 등재에 있어 임상적 또는 시술상의 제외기준은 없었다. 임상적 예후는 크게 스텐트 연관 사건인 심장사, 표적혈관 심근 경색, 표적혈관 재시술을 일차 종결점(Target lesion failure)으로, 환자 연관 사건인 사망, 심근 경색, 재시술을 주요 이차 종결점(Patient-oriented composite outcome)으로 설정하여 두 스텐트간의 사건 발생을 비교 분석하였다.

결과

전체 5,054 명의 환자중, 3,830 명 (75.8%)는 시술의 고위험군에 해당하였다 (off-label indication). 시술후 1 년 시점에서 일차 종결점인 스텐트 연관 사건은 EES 와 ZES-R 군에서 각각 82 명(2.7%) 및 58 명(2.9%)에서 발생하였으며, 두 군간의 차이를 보이지 않았다 (비교 위험도 1.08 (0.78-1.51), p=0.662). 환자 연관 사건 또한 225 명(7.4%) 및 153 (7.7%)에서 발생하였으며, 두 군간의 차이를 보이지 않았고 (비교 위험도 1.04 (0.85-1.27), p=0.702), 이러한 결과는 기저 특성의 차이를 보정한 propensity-score matched cohort 에서도 같은 결과를 보였다. Definite 또는 Probable 스텐트 혈전증의 빈도 역시 두 군간에 차이를 보이지 않았다 (18 [0.6%] vs. 7 [0.4%], p=0.306). 다변량 분석의 결과상 일차종결점인 target lesion failure 의 발생에 있어 스텐트의 종류 보다는 시술의 고위험도(off label indication)가 가장 사건 발생의 위험도가 높은 독립인자로 나타났다 (adjusted HR 2.882, 95% CI 1.226-6.779, p=0.015).

결론

본 연구는 현재까지 발표된 연구 중 가장 큰 규모의 전향적 레지스트리에서 제한 기준 없이 관상 동맥 중재 시술에 사용된 EES 와 ZES-R 의 임상적 안전성과 효능을 비교 하였으며, 그 결과상 두 2 세대 약물 방출 스텐트는 스텐트 연관 및 환자 연관 사건의 발생에서 1 년 시점까지 차이를 보이지 않았다. 시술 후 사건 발생률은 고 위험군 환자에서 조차 두 스텐트군 모두 매우 낮은 수준이었으며, 스텐트 혈전증의 빈도 역시 매우 낮은 양상을 보였다. 이는 2 세대 약물 방출 스텐트의 향상된 안전성을 반영하며, 스텐트 자체보다 환자의 위험인자에 대한 치료의 중요성을 시사한다.

주요어

약물방출 스텐트 (Drug-eluting stent)

관상동맥 중재술 (Percutaneous Coronary Intervention)

임상적 예후 (Clinical outcomes)

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References

1. Kirtane AJ, Gupta A, Iyengar S et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. Circulation 2009;119:3198-206.
2. Serruys PW, Silber S, Garg S et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. The New England journal of medicine 2010;363:136-46.
3. Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. Lancet 2011;377:1241-7.
4. von Birgelen C, Basalus MW, Tandjung K et al. A Randomized Controlled Trial in Second-Generation Zotarolimus-Eluting Resolute Stents Versus Everolimus-Eluting Xience V Stents in Real-World Patients: The TWENTE Trial. Journal of the American College of Cardiology 2012;59:1350-61.
5. Park KW, Chae IH, Lim DS et al. Everolimus-eluting versus sirolimus-eluting stents in patients undergoing percutaneous coronary intervention: the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) randomized trial. Journal of the American College of Cardiology 2011;58:1844-54.
6. Cutlip DE, Windecker S, Mehran R et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
7. Vranckx P, Cutlip DE, Mehran R et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871-4.
8. Stefanini GG, Serruys PW, Silber S et al. The impact of patient and lesion complexity on clinical and angiographic outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). Journal of the American College of Cardiology 2011;57:2221-32.

9. Gu XS, Rosenbaum PR. Comparison of Multivariate Matching Methods: Structures, Distances, and Algorithms. Journal of Computational and Graphical Statistics 1993;2:405-420.
10. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharmaceutical statistics 2011;10:150-61.
11. Cohen J. Statistical power analysis for the behavioral sciences (rev. ed.): Hillsdale, NJ, England: Lawrence Erlbaum Associates, Inc, 1977.
12. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 1959;22:719-48.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials 1986;7:177-88.
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
15. Karahalios A, Baglietto L, Carlin JB, English DR, Simpson JA. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures. BMC medical research methodology 2012;12:96.
16. Wayman JC. Multiple Imputation For Missing Data: What Is It And How Can I Use It? Annual Meeting of the American Educational Reserch Association. Chicago, IL, 2003.
17. White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. Statistics in medicine 2010;29:2920-31.
18. Rubin DB. Multiple imputation for non-response in surveys. New York: John Wiley & Sons, 1987.
19. de Boer SP, Lenzen MJ, Oemrawsingh RM et al. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. Eur Heart J 2011;32:2161-7.
20. Palmerini T, Biondi-Zoccai G, Della Riva D et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393-402.

21. Stone GW, Midei M, Newman W et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. JAMA 2008;299:1903-13.

22. Stone GW, Rizvi A, Newman W et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. The New England journal of medicine 2010;362:1663-74.

23. Jensen LO, Thayssen P, Hansen HS et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation 2012;125:1246-55.

24. Kedhi E, Joesoef KS, McFadden E et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-9.

25. Yeung AC, Leon MB, Jain A et al. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. Journal of the American College of Cardiology 2011;57:1778-83.

26. Massberg S, Byrne RA, Kastrati A et al. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. Circulation 2011;124:624-32.

27. Applegate RJ, Hermiller JB, Gordon PC et al. Predictors of early and late outcomes after everolimus and paclitaxel-eluting coronary stents. EuroIntervention 2012;7:1030-42.

28. Briguori C, Airoldi F, Visconti G et al. Novel approaches for preventing or limiting events in diabetic patients (Naples-diabetes) trial: a randomized comparison of 3 drug-eluting stents in diabetic patients. Circulation Cardiovascular interventions 2011;4:121-9.

29. Choi DH, Park KW, Yang HM et al. Renal dysfunction and high levels of hsCRP are additively associated with hard endpoints after percutaneous coronary intervention with drug eluting stents. International journal of cardiology 2011;149:174-81.

30. Saltzman AJ, Stone GW, Claessen BE et al. Long-term impact of chronic kidney disease in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. JACC Cardiovasc Interv 2011;4:1011-9.

31. Schroder J, Muller-Werdan U, Reuter S et al. Are the elderly different? : Factors influencing mortality after percutaneous coronary intervention with stent implantation. Zeitschrift fur Gerontologie und Geriatrie 2012.

Figure Legends

Figure 1. Kaplan-Meier Curves for Primary and Major Secondary Clinical Outcome

A) Target lesion failure in crude population **B)** Patient-oriented composite outcome in crude population **C)** Target lesion failure in propensity score matched population **D)** Patient-oriented composite outcome in propensity score matched population

Abbreviations: EES, everolimus-eluting stent; ZES-R, Resolute zotarolimus-eluting stent.

Figure 2. Cumulative Incidence of Definite or Probable Stent Thrombosis

Cumulative incidence and the worst hierarchical outcomes of all definite or probable stent thrombosis during 1 year period in both stent groups. Arrow indicates the patients not on dual-antiplatelet agent therapy at the time of stent thrombosis.

Abbreviations as in Figure 1.

Figure 3. Subgroup Analysis for Target Lesion Failure in Propensity Score Matched Population

Abbreviations: AMI, acute myocardial infarction; EES, everolimus-eluting stent; LM, left main vessel; PCI, percutaneous coronary intervention; STEMI, myocardial infarction with ST-segment elevation; ZES-R, Resolute zotarolimus-eluting stent

Tables

Table 1. Baseline Clinical Characteristics of Patients in Crude Population.*

	Total (N=5054)	EES (N=3056)	ZES-R (N=1998)	p value
Demographics				
Age, years	63.9 ± 10.8 (5054)	63.9 ± 10.8 (3056)	63.9 ± 10.9 (1998)	0.897
Male	3419/5054 (67.6%)	2053/3056 (67.2%)	1366/1998 (68.4%)	0.389
BMI (kg/m^2)	24.9 ± 9.32 (4892)	25.0 ± 11.8 (2935)	24.8 ± 3.1 (1957)	0.333
Coexisting Condition				
Diabetes mellitus	1855/5029 (36.9%)	1149/3031 (37.9%)	706/1998 (35.3%)	0.068
Hypertension	3251/5025 (64.7%)	1980/3027 (65.4%)	1271/1998 (63.6%)	0.195
Dyslipidemia	3268/5017 (65.1%)	1850/3019 (61.3%)	1418/1998 (71.0%)	<0.001
Peripheral artery disease	80/4989 (1.6%)	47/2991 (1.6%)	33/1998 (1.7%)	0.909
Chronic renal failure	186/5017 (3.7%)	105/3019 (3.5%)	81/1998 (4.1%)	0.321
Cardiac Risk Factors				
Current smoker	1506/4971 (29.8%)	893/2998 (29.8%)	613/1973 (31.1%)	0.344
Previous PCI	757/5035 (15.0%)	440/3041 (14.5%)	317/1998 (15.9%)	0.184
Previous CABG	87/5039 (1.7%)	56/3041 (1.8%)	31/1998 (1.6%)	0.507
Previous MI	326/5034 (6.5%)	212/3036 (7.0%)	114/1998 (5.7%)	0.079
Previous CHF	102/4992 (2.0%)	62/2994 (2.1%)	40/1998 (2.0%)	0.919
Previous CVA	395/4996 (7.9%)	250/2998 (8.3%)	145/1998 (7.3%)	0.181
Family history of CAD	263/4898 (5.4%)	171/2900 (5.9%)	92/1998 (4.6%)	0.053
LV ejection fraction	58.8 ± 11.4 (4453)	59.3 ± 11.4 (2714)	58.0 ± 11.4 (1739)	<0.001
LV dysfunction (LVEF < 30%)	75/4453 (1.7%)	41/2714 (1.5%)	34/1739 (2.0%)	0.283
Clinical Indication of PCI				**<0.001**
Stable angina	1696/5036 (33.7%)	1095/3038 (36.0%)	601/1998 (30.1%)	<0.001
Unstable angina	1856/5036 (36.9%)	1117/3038 (36.8%)	739/1998 (37.0%)	0.881
Acute myocardial infarction	1330/5036 (26.4%)	729/3038 (24.0%)	601/1998 (30.1%)	<0.001

NSTEMI	624/5036 (12.4%)	344/3038 (11.3%)	280/1998 (14.0%)	0.005
STEMI	706/5036 (14.0%)	385/3038 (12.7%)	321/1998 (16.1%)	0.001
Silent ischemia	154/5036 (3.1%)	97/3038 (3.2%)	57/1998 (2.9%)	0.505
Complexity of CAD				
Angiographic disease extent				<0.001
- 1VD	2207/5037 (43.8%)	1424/3046 (46.7%)	783/1991 (39.3%)	
- 2VD	1597/5037 (31.7%)	923/3046 (30.3%)	674/1991 (33.9%)	
- 3VD	1233/5037 (24.5%)	699/3046 (22.9%)	534/1991 (26.8%)	
No. of treated lesion/patients	1.49 ± 0.77 (5024)	1.47 ± 0.74 (3038)	1.53 ± 0.80 (1986)	0.009
At least 1 ISR	373/5054 (7.4%)	231/3056 (7.6%)	142/1998 (7.1%)	0.548
At least 1 Bifurcation	832/5054 (16.5%)	388/3056 (12.7%)	444/1998 (22.2%)	<0.001
At least 1 Thrombotic total	561/5054 (11.1%)	293/3056 (9.6%)	268/1998 (13.4%)	<0.001
At least 1 Small vessel[†]	1033/5054 (20.4%)	612/3056 (20.0%)	421/1998 (21.1%)	0.368
At least 1 Long lesion[‡]	2215/5054 (43.8%)	1240/3056 (40.6%)	975/1998 (48.8%)	<0.001
Multivessel PCI	1569/5054 (31.0%)	930/3056 (30.4%)	639/1998 (32.0%)	0.250
GP IIb/IIIa antagonist use	133/4759 (2.8%)	61/2763 (2.2%)	72/1996 (3.6%)	0.004
At least one off-label indication[§]	3830/5054 (75.8%)	2217/3056 (72.5%)	1613/1998 (80.7%)	<0.001
Medication at discharge				
Aspirin	4929/5018 (98.2%)	2969/3030 (98.0%)	1960/1988 (98.6%)	0.126
Clopidogrel	4937/5017 (98.4%)	2974/3027 (98.2%)	1963/1990 (98.6%)	0.301
Statin	4335/4998 (86.7%)	2613/3023 (86.4%)	1722/1975 (87.2%)	0.468
ACE inhibitor	1843/4966 (37.1%)	1113/3011 (37.0%)	730/1955 (37.3%)	0.810
Angiotensin-II receptor blocker	1562/4939 (31.6%)	939/3016 (31.1%)	623/1923 (32.4%)	0.363
Beta-blocker	3159/4970 (63.6%)	1853/3009 (61.6%)	1306/1961 (66.6%)	<0.001
Calcium-channel blocker	1343/4931 (27.2%)	830/3016 (27.5%)	513/1915 (26.8%)	0.577

[*] Data are number (%), unless otherwise indicated. Plus-minus values are means ± SD.

[†] Small vessel denotes lesion with reference diameter ≤ 2.75 mm.

‡ Long lesion denotes lesion with length ≥ 28 mm.

§ Off label indication: the indication of PCI was considered "off label" if any of the following features were present: serum creatinine concentration ≥140 umol/L (1.6 mg/dL); left ventricular ejection fraction (LVEF) < 30%; an acute MI within the previous 72 hours; more than one lesion per vessel; two or more vessels treated with a stent; a lesion length ≥ 28 mm; or a bifurcated lesion, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion.

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; GP, glycoprotein; ISR, in-stent restenosis; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, myocardial infarction with ST-segment elevation; VD, vessel disease.

Table 2. Baseline Angiographic Characteristics of Lesions in Crude Population.[*]

	Total (N=7084)	EES (N=4248)	ZES-R (N=2836)	p value
Target vessel location				0.001
- Left main artery	258/7084 (3.6%)	178/4248 (4.2%)	80/2836 (2.8%)	0.003
- LAD	3179/7084 (44.9%)	1907/4248 (44.9%)	1272/2836 (44.9%)	0.981
- LCX	1567/7084 (22.1%)	976/4248 (23.0%)	591/2836 (20.8%)	0.035
- RCA	2071/7084 (29.2%)	1182/4248 (27.8%)	889/2836 (31.3%)	0.002
- Bypass Graft	9/7084 (0.1%)	5/4248 (0.1%)	4/2836 (0.1%)	>0.999
ACC/AHA lesion class				<0.001
- A	564/7084 (8.0%)	247/4248 (5.8%)	317/2836 (11.2%)	
- B1	1705/7084 (24.1%)	1064/4248 (25.0%)	641/2836 (22.6%)	
- B2	1650/7084 (23.3%)	987/4248 (23.2%)	663/2836 (23.4%)	
- C	2285/7084 (32.3%)	1358/4248 (32.0%)	927/2836 (32.7%)	
Type B2 or C lesions[†]	3935/7084 (55.5%)	2345/4248 (55.2%)	1590/2836 (56.1%)	0.479
In-stent restenosis	424/7084 (6.0%)	257/4248 (6.0%)	167/2836 (5.9%)	0.798
Severe Calcification	623/7084 (8.8%)	388/4248 (9.1%)	235/2836 (8.3%)	0.231
Bifurcation[‡]	919/7084 (13.0%)	419/4248 (9.9%)	500/2836 (17.6%)	<0.001
- Bifurcation treatment	394/7084 (5.6%)	194/4248 (4.6%)	200/2836 (7.1%)	<0.001
Thrombus present	633/7084 (8.9%)	336/4248 (7.9%)	297/2836 (10.5%)	<0.001
Small vessel[§]	1200/7084 (16.9%)	704/4248 (16.6%)	496/2836 (17.5%)	0.316
Long lesion[¶]	2671/7084 (37.7%)	1504/4248 (35.4%)	1167/2836 (41.1%)	<0.001
Max Pressure deployment, atm	13.56 ± 4.63 (6487)	13.45 ± 4.79 (3790)	13.72 ± 4.40 (2697)	0.024
Mean stent diameter/lesion, mm	3.13 ± 3.39 (7084)	3.16 ± 4.31 (4248)	3.09 ± 0.85 (2836)	0.363
Total Stent Length, mm				
- Per patient	38.97 ± 26.01 (5054)	37.41 ± 25.50 (3056)	41.35 ± 26.58 (1998)	<0.001

- Per lesion	27.97 ± 14.34 (7084)	26.90 ± 14.06 (4248)	29.61 ± 14.61 (2836)	<0.001
Number of stents				
- Per patient	1.67 ± 0.97 (5054)	1.65 ± 0.97 (3056)	1.70 ± 0.98 (1998)	0.091
- Per lesion	1.19 ± 0.49 (7084)	1.19 ± 0.48 (4248)	1.19 ± .51 (2836)	0.467
IVUS guided stenting	2695/7084 (38.0%)	1601/4248 (37.7%)	1094/2836 (38.6%)	0.454
Device Success	6908/7084 (97.5%)	4147/4248 (98.2%)	2761/2836 (98.5%)	0.484
Lesion Success	6903/7084 (97.4%)	4145/4248 (98.1%)	2758/2836 (98.5%)	0.399
Procedure Success	6912/7084 (97.6%)	4140/4248 (98.1%)	2772/2836 (98.5%)	0.479

* Data are number (%), unless otherwise indicated. Plus-minus values are means ± SD.

† Type B2 or C lesions according to ACC/AHA classification.

‡ Bifurcation means bifurcated lesion that have been treated solely by drug-eluting stents.

§ Small vessel denotes lesion with reference diameter ≤ 2.75 mm.

¶ Long lesion denotes lesion with length ≥ 28 mm.

Abbreviations: IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 3. Clinical Outcomes in Crude Population at 1 year. *

	Total (N=5054)	EES (N=3056)	ZES-R (N=1998)	RR (95% CI)	p value
All cause death	108 (2.1%)	62 (2.0%)	46 (2.3%)	1.13 (0.78-1.65)	0.551
- Cardiac death	65 (1.3%)	37 (1.2%)	28 (1.4%)	1.16 (0.71-1.89)	0.610
Any myocardial infarction	25 (0.5%)	17 (0.6%)	8 (0.4%)	0.72 (0.31-1.66)	0.541
- Target vessel	19 (0.4%)	14 (0.5%)	5 (0.3%)	0.55 (0.20-1.51)	0.254
- Non Target vessel	6 (0.1%)	3 (0.1%)	3 (0.2%)	2.29 (0.38-13.72)	0.686
- MI due to ST	10 (0.2%)	7 (0.2%)	3 (0.2%)	0.66 (0.17-2.53)	0.749
Any revascularization	267 (5.3%)	161 (5.3%)	106 (5.3%)	1.00 (0.79-1.28)	0.954
Clinically driven revascularization	193 (3.8%)	120 (3.9%)	73 (3.7%)	0.93 (0.70-1.24)	0.653
Target lesion revascularization	68 (1.3%)	40 (1.3%)	28 (1.4%)	1.07 (0.66-1.73)	0.803
Target vessel revascularization	109 (2.2%)	60 (2.0%)	49 (2.5%)	1.25 (0.86-1.81)	0.276
Cerebrovascular accident	30 (0.6%)	18 (0.6%)	12 (0.6%)	1.02 (0.49-2.11)	0.958
Target lesion failure†	140 (2.8%)	82 (2.7%)	58 (2.9%)	1.08 (0.78-1.51)	0.662
Target vessel failure‡	182 (3.6%)	102 (3.3%)	80 (4.0%)	1.20 (0.90-1.60)	0.217
Patient-oriented composite outcomes*	378 (7.5%)	225 (7.4%)	153 (7.7%)	1.04 (0.85-1.27)	0.702

* Data are number (%), unless otherwise indicated.

† Target lesion failure defined as a composite of cardiac death, myocardial infarction (not clearly attributed to a nontarget vessel), or clinically indicated target lesion revascularization by percutaneous or surgical methods at 1 years.

‡ Target vessel failure defined as a composite of cardiac death, myocardial infarction (not clearly attributed to a nontarget vessel), or clinically indicated target vessel revascularization by percutaneous or surgical methods at 1 years.

* Patient-oriented composite outcomes included all-cause mortality, any myocardial infarction (includes nontarget vessel territory), and any revascularization (includes all target and nontarget vessel, regardless of percutaneous or surgical methods).

Abbreviations: CI, confidence interval; MI, myocardial infarction; MACE, major adverse cardiovascular events; RR, relative risk; ST, stent thrombosis.

Table 4. Stent Thrombosis in Crude Population at 1 Year. *

	Total (N=5054)	EES (N=3056)	ZES-R (N=1998)	p value
Definite	9 (0.2%)	6 (0.2%)	3 (0.2%)	0.751
- Acute (0-1 day)	4 (0.1%)	3 (0.1%)	1 (0.1%)	0.657
- Subacute (2-30 days)	3 (0.1%)	2 (0.1%)	1 (0.1%)	1.000
- Late (31-360 days)	2 (<0.1%)	1 (<0.1%)	1 (0.1%)	1.000
Probable	17 (0.3%)	12 (0.4%)	5 (0.3%)	0.464
- Acute (0-1 day)	4 (0.1%)	1 (<0.1%)	3 (0.2%)	0.307
- Subacute (2-30 days)	12 (0.2%)	10 (0.3%)	2 (0.1%)	0.142
- Late (31-360 days)	1 (<0.1%)	1 (<0.1%)	0 (0%)	1.000
Stent thrombosis				
- Definite or Probable	25 (0.5%)	18 (0.6%)	7 (0.4%)	0.306
Duration of Dual Anti-platelet agent				
- For 6 months	4271/4412 (96.8%)	2599/2684 (96.8%)	1672/1728 (96.8%)	0.930
- For 1 year	3740/4412 (84.8%)	2277/2684 (84.8%)	1463/1728 (84.7%)	0.898
- Mean duration of DAT	351.09 ± 62.62 (4412)	351.19 ± 62.94 (2684)	350.94 ± 62.15 (1728)	0.896

* Data are number (%), unless otherwise indicated.

Abbreviations: DAT, dual anti-platelet agent therapy

Table 5. Independent Predictors of Target lesion failure in Propensity Score Matched Group.*

	Hazard Ratio	95% CI	p value
Off Label Indication	2.882	1.226-6.779	0.015
Chronic Renal Failure	2.774	1.166-6.603	0.021
Diabetes Mellitus	1.957	1.128-3.396	0.043
Age	1.051	1.022-1.081	0.001

* Identification of independent predictors was done with stratified Cox proportional hazard regression model, and the variables were presented with multivariable adjusted hazard ratios, 95% confidence intervals, and p values. Included variables to the final model were presented in Supplementary Table 7. The individual components of off label indication (i.e. STEMI, NSTEMI, in-stent restenosis, bifurcation, thrombotic total occlusion, long lesion, multivessel PCI, severe left ventricular dysfunction [LVEF< 30%], and left main procedure) were not included individually to the final model due to significant correlation with off label indication itself (i.e. co-linearity between these co-variates).

Abbreviations: CI, confidence interval; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, myocardial infarction with ST-segment elevation; LVEF, left ventricular ejection fraction.

Figure 1.

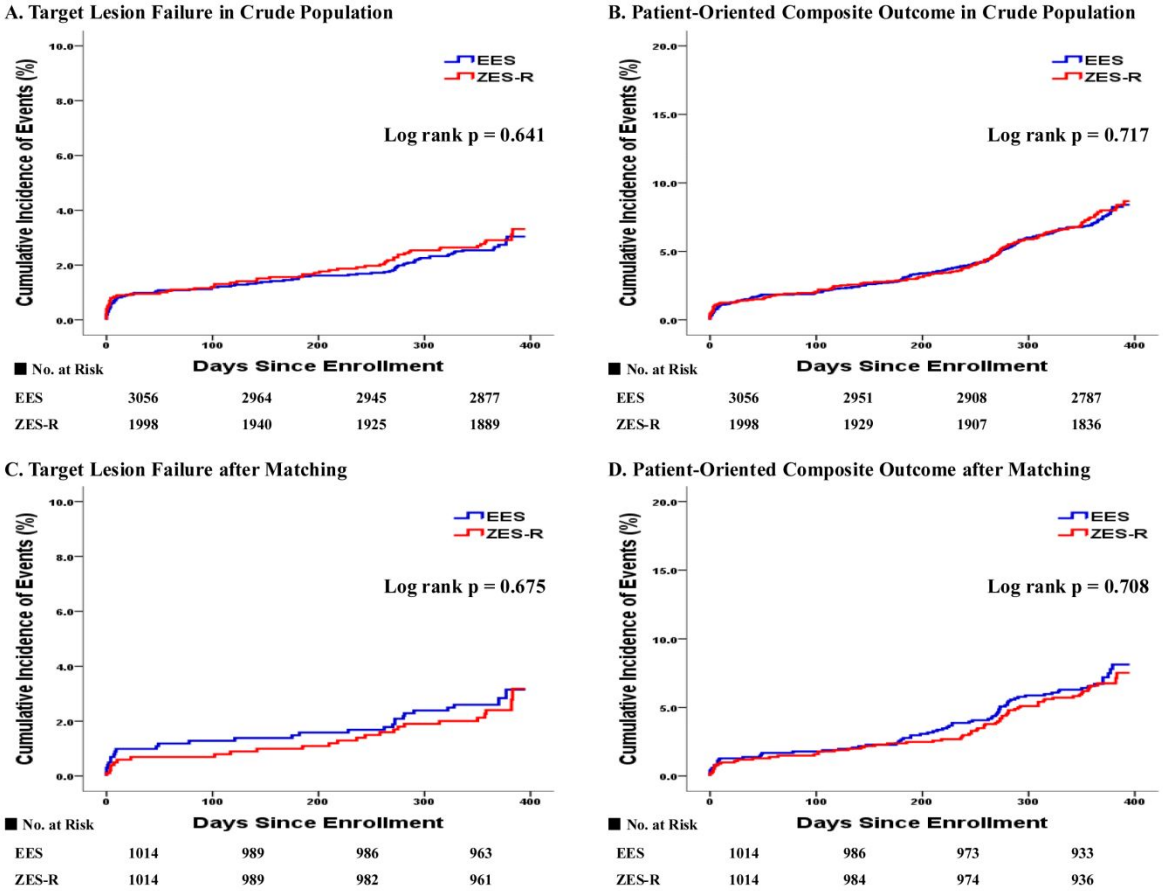

A. Target Lesion Failure in Crude Population
Cumulative Incidence of Events (%)
EES
ZES-R
Log rank p = 0.641
Days Since Enrollment
No. at Risk
EES 3056 2964 2945 2877
ZES-R 1998 1940 1925 1889
B. Patient-Oriented Composite Outcome in Crude Population
Cumulative Incidence of Events (%)
EES
ZES-R
Log rank p = 0.717
Days Since Enrollment
No. at Risk
EES 3056 2951 2908 2787
ZES-R 1998 1929 1907 1836
C. Target Lesion Failure after Matching
Cumulative Incidence of Events (%)
EES
ZES-R
Log rank p = 0.675
Days Since Enrollment
No. at Risk
EES 1014 989 986 963
ZES-R 1014 989 982 961
D. Patient-Oriented Composite Outcome after Matching
Cumulative Incidence of Events (%)
EES
ZES-R
Log rank p = 0.708
Days Since Enrollment
No. at Risk
EES 1014 986 973 933
ZES-R 1014 984 974 936

Figure 2.

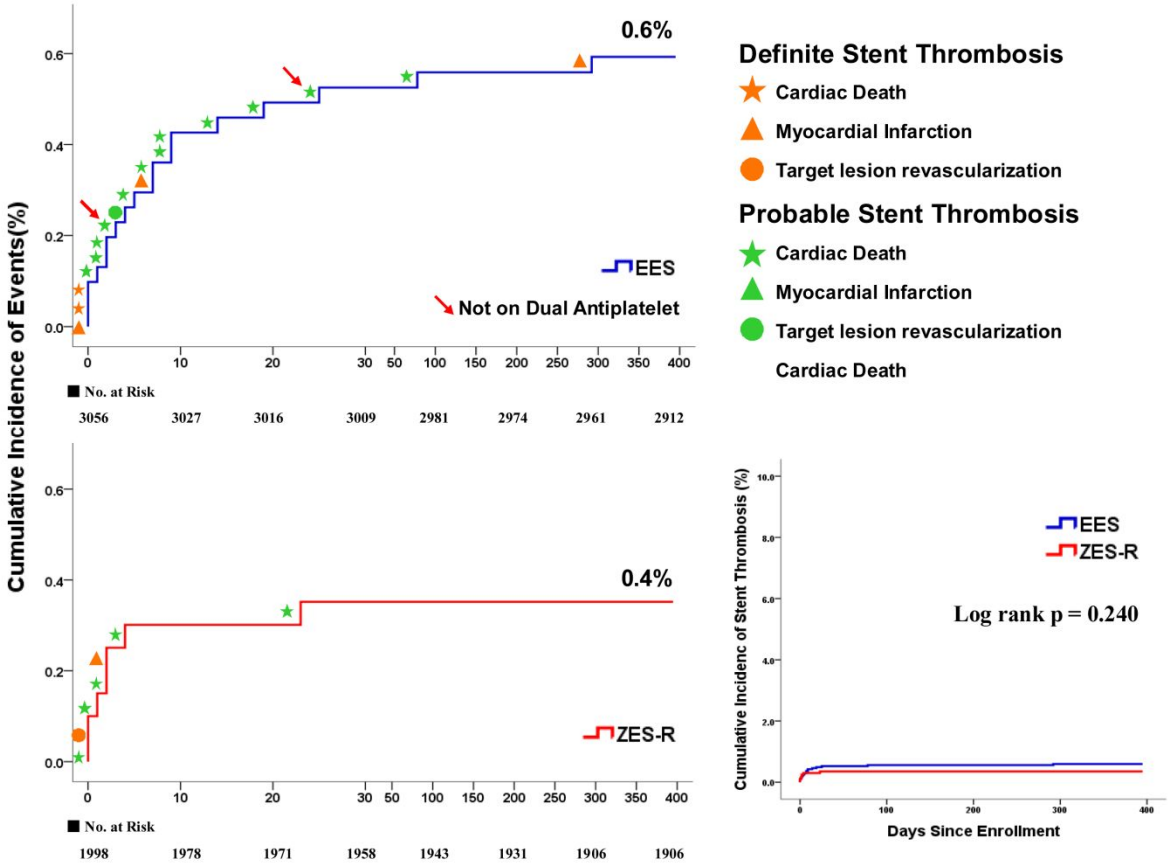
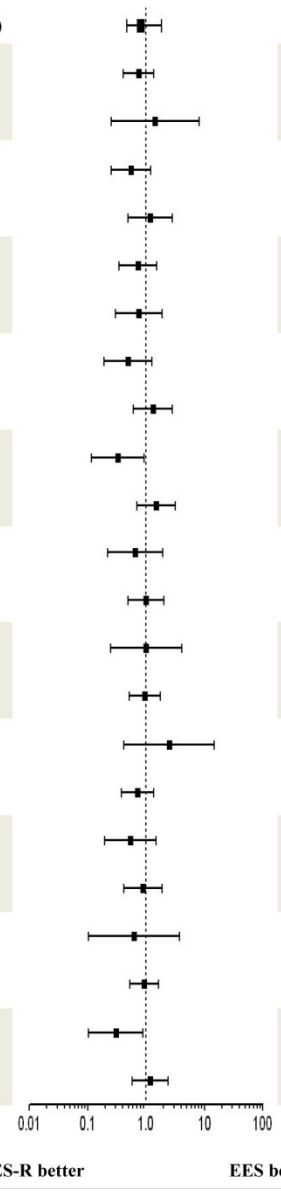

Cumulative Incidence of Events(%)
0.6%
EES
Not on Dual Antiplatelet
No. at Risk
3056 3027 3016 3009 2981 2974 2961 2912
0.4%
ZES-R
No. at Risk
1998 1978 1971 1958 1943 1931 1906 1906
Definite Stent Thrombosis
Cardiac Death
Myocardial Infarction
Target lesion revascularization
Probable Stent Thrombosis
Cardiac Death
Myocardial Infarction
Target lesion revascularization
Cardiac Death
Cumulative Incidenc of Stent Thrombosis (%)
EES
ZES-R
Log rank p = 0.240
Days Since Enrollment

Figure 3.

	EES N = 3056	ZES-R N = 1998	HR (95% C.I.)	Interaction P value
All patients	**2.8 (28/1014)**	**2.5 (25/1014)**	**0.813 (0.466-1.825)**	
Off label indication	3.5 (25/716)	3.0 (22/729)	0.745 (0.409-1.357)	0.798
On label indication	1.0 (3/298)	1.1 (3/285)	1.437 (0.255-8.090)	
Diabetes	4.7 (18/379)	3.2 (12/380)	0.553 (0.253-1.212)	0.224
No diabetes	1.6 (10/635)	2.1 (13/634)	1.178 (0.488-2.844)	
Dyslipidemia	2.7 (18/658)	1.8 (12/653)	0.727 (0.343-1.539)	0.241
No Dyslipidemia	2.8 (10/356)	3.6 (13/361)	0.748 (0.299-1.875)	
Multivessel PCI	5.0 (16/317)	2.2 (7/313)	0.492 (0.191-1.272)	0.032
Single vessel PCI	1.7 (12/697)	2.6 (18/701)	1.314 (0.605-2.851)	
Lesion length ≥28mm	4.1 (16/388)	1.5 (6/390)	0.327(0.116-0.921)	0.016
Lesion length <28mm	1.9 (12/626)	3.0 (19/624)	1.488 (0.701-3.160)	
Vessel diameter < 2.75mm	5.3 (11/209)	3.3 (7/212)	0.654 (0.221-1.931)	0.374
Vessel diameter ≥2.75mm	2.1 (17/805)	2.2 (18/802)	0.991 (0.489-2.005)	
Bifurcation	12.2 (6/49)	6.9 (4/58)	1.000 (0.246-4.072)	0.420
No Bifurcation	2.3 (22/965)	2.2 (21/956)	0.941 (0.510-1.747)	
STEMI	3.1 (4/130)	5.5 (7/127)	2.491 (0.417-14.87)	0.210
Other indication	2.7 (24/884)	2.0 (18/887)	0.710 (0.375-1.345)	
AMI (<72 hrs)	4.9 (12/246)	4.8 (11/231)	0.538 (0.194-1.492)	0.805
No AMI (72 hrs)	2.1 (16/768)	1.8 (14/783)	0.880 (0.413-1.873)	
LM	5.7 (3/53)	3.6 (2/55)	0.621 (0.104-3.725)	0.706
No LM	2.6 (25/961)	2.4 (23/959)	0.921 (0.523-1.623)	
Overlapping Stent	6.6 (13/197)	3.4 (7/207)	0.303 (0.103-0.887)	0.127
No Overlapping stent	1.8 (15/817)	2.2 (18/807)	1.168 (0.576-2.368)	



Supplementary Tables

Supplementary Table 1. Baseline Characteristics in Propensity Score Matched Group.*

	Everolimus-Eluting Stent (N=1014)	**Zotarolimus-Eluting Stent (N=1014)**	**Standardized Difference (%)**
Demographics			
Age, years	63.5 ± 10.8	63.7 ± 10.6	-2.24
Male	664 (65.5%)	691 (68.1%)	-5.52
Diabetes mellitus	379 (37.4%)	380 (37.5%)	-0.21
Hypertension	651 (64.2%)	647 (63.8%)	0.83
Dyslipidemia	658 (64.9%)	653 (64.4%)	1.05
Peripheral artery disease	10 (1.0%)	11 (1.1%)	-0.98
Chronic renal failure	34 (3.4%)	29 (2.9%)	2.86
Cardiac Risk Factors			
Current smoker	287 (28.3%)	318 (31.4%)	-6.78
Previous PCI	135 (13.3%)	133 (13.1%)	0.59
Previous CABG	17 (1.7%)	19 (1.9%)	-1.50
Previous MI	79 (7.8%)	76 (7.5%)	0.00
Previous CHF	18 (1.8%)	23 (2.3%)	-3.53
Previous CVA	80 (7.9%)	82 (8.1%)	-0.74
Family history of CAD	69 (6.8%)	55 (5.4%)	5.85
LV ejection fraction	60.0 ± 10.5	60.0 ± 10.4	-0.67
LV dysfunction (LVEF < 30%)	10 (1.0%)	11 (1.1%)	-0.98
Clinical Indication of PCI			
Stable angina	341 (33.6%)	364 (35.9%)	-4.83
Unstable angina	393 (38.8%)	387 (38.2%)	1.23
Acute myocardial infarction	246 (24.3%)	231 (22.8%)	3.54

NSTEMI	116 (11.4%)	104 (10.3%)	3.54
STEMI	130 (12.8%)	127 (12.5%)	0.90
Silent ischemia	34 (3.4%)	32 (3.2%)	1.12
Complexity of CAD			
Angiographic disease extent			
- 1VD	488 (48.1%)	502 (49.5%)	-2.80
- 2VD	304 (30.0%)	295 (29.1%)	1.97
- 3VD	222 (21.9%)	217 (21.4%)	1.21
No. of treated lesion/patients	1.45 ± 0.71	1.46 ± 0.73	-1.39
At least 1 ISR	69 (6.8%)	87 (8.6%)	-6.76
At least 1 Bifurcation	49 (4.8%)	58 (5.7%)	-4.04
At least 1 Thrombotic total	110 (10.8%)	102 (10.1%)	2.29
At least 1 Small vessel[†]	209 (20.6%)	212 (20.9%)	-0.74
At least 1 Long lesion[‡]	388 (38.3%)	390 (38.5%)	-0.41
Multivessel PCI	317 (31.3%)	313 (30.9%)	0.86
GP IIb/IIIa antagonist use	6 (0.6%)	11 (1.1%)	-5.45
At least one off-label use[§]	716 (70.6%)	729 (71.9%)	-2.87
Medication at discharge			
Aspirin	999 (98.5%)	998 (98.4%)	0.81
Clopidogrel	999 (98.5%)	1002 (98.8%)	-2.60
Statin	885 (87.3%)	881 (86.9%)	1.19
ACE inhibitor	404 (39.8%)	383 (37.8%)	4.10
Angiotensin-II receptor blocker	289 (28.5%)	290 (28.6%)	-0.22
Beta-blocker	617 (60.8%)	599 (59.1%)	3.47
Calcium-channel blocker	297 (29.3%)	303 (29.9%)	-1.31

[*] Data are number (%), unless otherwise indicated. Plus-minus values are means ± SD.

[†] Small vessel denotes lesion with reference diameter ≤ 2.75 mm.

‡ Long lesion denotes lesion with length ≥ 28 mm.

§ Off label indication: the indication of PCI was considered "off label" if any of the following features were present: serum creatinine concentration ≥140 umol/L (1.6 mg/dL); left ventricular ejection fraction (LVEF) < 30%; an acute MI within the previous 72 hours; more than one lesion per vessel; two or more vessels treated with a stent; a lesion length ≥ 28 mm; or a bifurcated lesion, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion.

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; GP, glycoprotein; ISR, in-stent restenosis; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, myocardial infarction with ST-segment elevation; VD, vessel disease.

Supplementary Table 2. Clinical Outcomes in Propensity Score Matched Group at 1 year. *

	Total (N=2028)	EES (N=1014)	ZES-R (N=1014)	RR (95% CI)	p value
All cause death	37 (1.8%)	17 (1.7%)	20 (2.0%)	1.18 (0.62-2.23)	0.741
- Cardiac death	21 (1.0%)	11 (1.1%)	10 (1.0%)	0.91 (0.39-2.13)	0.826
Any myocardial infarction	9 (0.4%)	6 (0.6%)	3 (0.3%)	0.50 (0.13-1.99)	0.507
- Target vessel	7 (0.3%)	6 (0.5%)	1 (0.3%)	0.17 (0.02-1.38)	0.124
- Non Target vessel	2 (0.1%)	0 (0.0%)	2 (0.2%)	NA	0.500
- MI due to ST	4 (0.2%)	3 (0.3%)	1 (0.1%)	0.33 (0.03-3.20)	0.375
Any revascularization	101 (5.0%)	54 (5.3%)	47 (4.6%)	0.87 (0.59-1.27)	0.540
Clinically driven revascularization	76 (3.7%)	41 (4.0%)	35 (3.5%)	0.85 (0.55-1.33)	0.559
Target lesion revascularization	30 (1.5%)	24 (2.4%)	23 (2.3%)	0.96 (0.54-1.69)	0.883
Target vessel revascularization	47 (2.3%)	60 (2.0%)	49 (2.5%)	0.82 (0.57-1.18)	0.276
Cerebrovascular accident	12 (0.6%)	6 (0.6%)	6 (0.6%)	1.00 (0.32-3.09)	1.000
Target lesion failure†	53 (2.6%)	28 (2.8%)	25 (2.5%)	0.89 (0.52-1.52)	0.781
Target vessel failure‡	70 (3.5%)	37 (3.6%)	33 (3.3%)	0.89 (0.56-1.41)	0.715
Patient-oriented composite outcomes§	138 (6.8%)	71 (7.0%)	67 (6.6%)	0.94 (0.68-1.30)	0.791

* Data are number (%), unless otherwise indicated.

† Target lesion failure defined as a composite of cardiac death, myocardial infarction (not clearly attributed to a nontarget vessel), or clinically indicated target lesion revascularization by percutaneous or surgical methods at 1 years.

‡ Target vessel failure defined as a composite of cardiac death, myocardial infarction (not clearly attributed to a nontarget vessel), or clinically indicated target vessel revascularization by percutaneous or surgical methods at 1 years.

§ Patient-oriented composite outcomes included all-cause mortality, any myocardial infarction (includes nontarget vessel territory), and any revascularization (includes all target and nontarget vessel, regardless of percutaneous or surgical methods).

Abbreviations: CI, confidence interval; MI, myocardial infarction; MACE, major adverse cardiovascular events; RR, relative risk; ST, stent thrombosis.

Supplementary Table 3. Stent Thrombosis in Propensity Score Matched Group at 1 year. *

	Total (N=2028)	EES (N=1014)	ZES-R (N=1014)	p value
Definite	4 (0.2%)	3 (0.3%)	1 (0.1%)	0.625
- Acute (0-1 day)	2 (0.1%)	2 (0.2%)	0 (0.0%)	0.500
- Subacute (2-30 days)	1 (<0.1%)	1 (0.1%)	0 (0.0%)	1.000
- Late (31-360 days)	2 (<0.1%)	0 (0.0%)	1 (0.1%)	1.000
Probable	5 (0.2%)	3 (0.3%)	2 (0.2%)	0.687
- Acute (0-1 day)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
- Subacute (2-30 days)	4 (0.2%)	2 (0.2%)	2 (0.2%)	1.000
- Late (31-360 days)	1 (<0.1%)	1 (0.1%)	0 (0%)	1.000
Stent thrombosis				
- Definite or Probable	8 (0.4%)	6 (0.6%)	2 (0.2%)	0.288
Duration of Dual Anti-platelet agent				
- For 6 months	1735 (85.6%)	876 (97.1%)	859 (97.1%)	1.000
- For 1 year	1509 (74.4%)	764 (84.7%)	745 (84.2%)	0.794
- Mean duration of DAT	351.02 ± 61.16	350.19 ± 61.82	351.87 ± 60.50	0.562

* Data are number (%), unless otherwise indicated.

Abbreviations: DAT, dual anti-platelet agent therapy

Supplementary Table 4. The Proportion of Missing values in Each Covariates of the Propensity

Variable	% of Missing	Variable	% of Missing
Age	0	In-stent restenosis	0 (0.0%)

Score Model*

LV ejection fraction	601 (11.9%)	Bifurcation	0 (0.0%)
Creatinine	44 (0.9%)	Thrombotic Total	0 (0.0%)
Male	0 (0.0%)	Long lesion†	0 (0.0%)
Prev. PCI	15 (0.3%)	Small vessel‡	0 (0.0%)
Prev. CABG	15 (0.3%)	Multivessel PCI	0 (0.0%)
Prev. MI	20 (0.4%)	Bypass graft lesion	0 (0.0%)
Prev. CHF	62 (1.2%)	Left main vessel lesion	0 (0.0%)
Prev. CVA	58 (1.1%)	Stable angina	18 (0.4%)
Diabetes mellitus	25 (0.5%)	Unstable angina	18 (0.4%)
Insulin treated DM	0 (0.0%)	NSTEMI	18 (0.4%)
Chronic renal failure	37 (0.7%)	STEMI	18 (0.4%)
Hypertension	29 (0.6%)	Silent ischemia	18 (0.4%)
Peripheral artery disease	65 (1.3%)	Off label use§	0 (0.0%)
Current smoker	83 (1.6%)	*Baseline Medications*	
Dyslipidemia	37 (0.7%)	Aspirin	36 (0.7%)
Family history of CAD	156 (3.1%)	Clopidogrel	37 (0.7%)
1VD	17 (0.3%)	Beta blocker	84 (1.7%)
2VD	17 (0.3%)	Statin	56 (1.1%)
3VD	17 (0.3%)	ACEI	88 (1.7%)

* Multiple imputation model was performed to estimate the missing values of abovementioned covariates with missing values.

† Long lesion denotes lesion with length ≥ 28 mm.

‡ Small vessel denotes lesion with reference diameter ≤ 2.75 mm.

§ Off label indication: the indication of PCI was considered "off label" if any of the following features were present: serum creatinine concentration ≥140 umol/L (1.6 mg/dL); left ventricular ejection fraction (LVEF) < 30%; an acute MI within the previous 72 hours; more than one lesion per vessel; two or more vessels treated with a stent; a lesion length ≥ 28 mm; or a bifurcated lesion, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; GP, glycoprotein; LV, left ventricle; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, myocardial infarction with ST-segment elevation; VD, vessel disease.

Supplementary Table 5. Baseline Clinical Characteristics of Group with or without Missing Value of Propensity Score in the Complete Case Analysis.*

	Total (N=5054)	Missing (-) (N=4016, 79.5%)	Missing (+) (N=1038, 20.5%)	p value
Demographics				
Age, years	63.9 ± 10.8	63.9 ± 10.9	63.9 ± 10.7	0.790
Male	3419 (67.6%)	2726 (67.9%)	693 (66.8%)	0.503
BMI (kg/m^2)	24.9 ± 9.32	24.8 ± 7.1	25.6 ± 15.2	0.103
Stent				<0.001
EES	3056 (60.5%)	2353 (58.6%)	703 (67.7%)	
ZES-R	1998 (39.5%)	1663 (41.4%)	335 (32.3%)	
Coexisting Condition				
Diabetes mellitus	1855 (36.7%)	1479 (36.8%)	376 (37.1%)	0.884
Hypertension	3251 (64.3%)	2578 (64.2%)	673 (66.7%)	0.141
Dyslipidemia	3268 (64.7%)	2641 (65.8%)	627 (62.6%)	0.064
Peripheral artery disease	80 (1.6%)	60 (1.5%)	20 (2.1%)	0.254
Chronic renal failure	186 (3.7%)	150 (3.7%)	36 (3.6%)	0.853
Cardiac Risk Factors				
Current smoker	1506 (29.8%)	1223 (30.5%)	283 (29.6%)	0.638
Previous PCI	757 (15.0%)	592 (14.7%)	165 (16.1%)	0.281
Previous CABG	87 (1.7%)	64 (1.6%)	23 (2.2%)	0.177
Previous MI	326 (6.5%)	264 (6.6%)	62 (6.1%)	0.618
Previous CHF	102 (2.0%)	85 (2.1%)	17 (1.7%)	0.529
Previous CVA	395 (7.8%)	306 (7.6%)	89 (9.1%)	0.129
Family history of CAD	263 (5.2%)	214 (5.3%)	49 (5.6%)	0.804
EF	58.8 ± 11.4	58.9 ± 11.3	57.9 ± 12.7	0.096
LV dysfunction (LVEF < 30%)	75 (1.5%)	64 (1.6%)	11 (2.5%)	0.167

Clinical Indication of PCI				0.116
Stable angina	1696 (33.6%)	1331 (33.1%)	365 (35.8%)	0.119
Unstable angina	1856 (36.7%)	1500 (37.4%)	356 (34.9%)	0.156
Acute myocardial infarction	1330 (26.3%)	1072 (26.7%)	258 (25.3%)	0.382
NSTEMI	624 (12.3%)	513 (12.8%)	111 (10.9%)	0.110
STEMI	706 (14.0%)	559 (13.9%)	147 (14.4%)	0.686
Silent ischemia	154 (3.0%)	113 (2.8%)	41 (4.0%)	0.053
Complexity of CAD				
Angiographic disease extent				0.863
- 1VD	2207 (43.7%)	1766 (44.0%)	441 (43.2%)	
- 2VD	1597 (31.6%)	1273 (31.7%)	324 (31.7%)	
- 3VD	1233 (24.4%)	977 (24.3%)	256 (25.1%)	
No. of treated lesion/patients	1.49 ± 0.77	1.50 ± 0.77	1.47 ± 0.75	0.278
At least 1 ISR	373 (7.4%)	297 (7.4%)	76 (7.3%)	0.947
At least 1 Bifurcation	832 (16.5%)	674 (16.8%)	158 (15.2%)	0.241
At least 1 Thrombotic total	561 (11.1%)	456 (11.4%)	105 (10.1%)	0.268
At least 1 Small vessel†	1033 (20.4%)	826 (20.6%)	207 (19.9%)	0.666
At least 1 Long lesion‡	2215 (43.8%)	1773 (44.1%)	442 (42.6%)	0.380
Multivessel PCI	1569 (31.0%)	1262 (31.4%)	307 (29.6%)	0.259
GP IIb/IIIa antagonist use	133 (2.6%)	115 (3.0%)	18 (1.9%)	0.095
Medication at discharge				
Aspirin	**4929 (97.5%)**	**3955 (98.5%)**	**974 (97.2%)**	**0.008**
Clopidogrel	**4937 (97.7%)**	**3960 (98.6%)**	**977 (97.6%)**	**0.025**
Statin	4335 (85.8%)	3480 (86.8%)	855 (86.4%)	0.714
ACEI/ARB	1620 (32.5%)	1316 (32.8%)	304 (31.0%)	0.287
Beta-blocker	3159 (62.5%)	2544 (63.3%)	615 (64.5%)	0.525
Calcium-channel blocker	1343 (26.6%)	1097 (27.4%)	246 (26.4%)	0.540

* Data are number (%), unless otherwise indicated. Plus-minus values are means ± SD.

† Small vessel denotes lesion with reference diameter ≤ 2.75 mm.

‡ Long lesion denotes lesion with length ≥ 28 mm.

§ Off label Use (=Complex patients): Patients with complex lesions were defined as having at least one of the following characteristics: serum creatinine concentration of 140 umol/L (1.6 mg/dL) or more; left ventricular ejection fraction < 30%; an acute myocardial infarction within the previous 72 hours; more than one lesion per vessel; two or more vessels treated with a stent; a lesion ≥ 28 mm; or bifurcated lesion, bypass graft, in-stent restenosis, unprotected left main coronary artery, presence of thrombus, or total occlusion.

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; EES, everolimus-eluting stent; GP, glycoprotein; ISR, in-stent restenosis; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, myocardial infarction with ST-segment elevation; VD, vessel disease; ZES-R, zotarolimus-eluting Resolute stent.

Supplementary Table 6. The Comparison of Clinical Outcomes Between Original Propensity Score Matched Group versus Imputed Propensity Score Matched Group.[*]

Outcomes	Original PS Matched Group			Multiple Imputed PS Matched Group		
	OR	95% CI	P value	Pooled OR	95% CI	P value
TLF[†]	0.890	0.515-1.537	0.781	0.99	0.68-1.45	0.960
POCO[‡]	0.940	0.665-1.328	0.791	0.96	0.75-1.23	0.768

[*] The pooled estimate of odds ratio of ZES-R for TLF or POCO were calculated from 5 imputed dataset.

[†] Target lesion failure (TLF) defined as a composite of cardiac death, myocardial infarction (not clearly attributed to a nontarget vessel), or clinically indicated target lesion revascularization by percutaneous or surgical methods at 1 years.

[‡] Patient-oriented composite outcomes (POCO) included all-cause mortality, any myocardial infarction (includes nontarget vessel territory), and any revascularization (includes all target and nontarget vessel, regardless of percutaneous or surgical methods).

Abbreviations: POCO, patient-oriented composite outcome; PS, propensity score; TLF, target lesion failure.

Supplementary Table 7. Univariate Analysis of Independent Predictors for Target lesion failure in Propensity Score Matched Group.*

Variables	HR (95% CI)	p value	Variables	HR (95% CI)	p value
Risk Factors			***Lesion characteristics***		
Age (*)	1.051 (1.023-1.081)	<0.001	Off Label Use (*)	3.220 (1.377-7.533)	0.007
Female (*)	1.682 (0.979-2.889)	0.060	Acute MI	2.558 (1.486-4.403)	0.001
Diabetes Mellitus (*)	2.215 (1.287-3.814)	0.004	ISR	0.976 (0.352-2.704)	0.963
Previous PCI (*)	1.710 (0.880-3.321)	0.113	Bifurcation	4.402 (2.212-8.763)	<0.001
Previous CABG (*)	3.448 (1.075-11.056)	0.037	Thrombotic total occlusion	2.343 (1.206-4.552)	0.012
Previous MI	1.825 (0.824-4.043)	0.138	Total No. of treated lesion	1.500 (1.136-1.982)	0.004
Previous CHF	4.263 (1.538-11.817)	0.005	Long lesion (≥ 28 mm)	1.143 (0.662-1.975)	0.631
CRF (*)	4.174 (1.784-9.764)	0.001	Small vessel (≤ 2.75 mm) (*)	1.964 (1.112-3.467)	0.020
Previous CVA (*)	2.141 (1.009-4.543)	0.047	Left main vessel PCI	1.909 (0.760-4.796)	0.169
Hypertension (*)	1.573 (0.854-2.896)	0.146	Overlapping stent (*)	2.468 (1.416-4.301)	0.001
PVD	1.799 (0.249-13.017)	0.561	LVEF < 30%	15.773 (6.739-36.92)	<0.001
Current Smoking (*)	0.419 (0.198-0.889)	0.023	GPI Use	8.236 (2.568-26.419)	<0.001
Dyslipidemia (*)	0.701 (0.407-1.207)	0.200			
Family History of CAD	0.587 (0.143-2.410)	0.459			

* Stratified Cox proportional hazard regression model was used to calculated unadjusted hazard ratio of covariates for target lesion failure. The variables were presented with unadjusted hazard ratios, 95% confidence intervals, and p values. (*) denotes co-variates which were included to final multivariable Cox proportional hazard model.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium-channel blocker; CHF, congestive heart failure; CRF, chronic renal failure; CVA, cerebrovascular accident; GPI, glycoprotein IIb/IIIa inhibitor; ISR, in-stent restenosis; LV, left ventricle; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, myocardial infarction with ST-segment elevation.

Supplementary Figure Legends

Supplementary Figure 1. Flow of Participants Diagram

Abbreviations: CVA, cerebrovascular accident; EES, everolimus-eluting stent; MI, myocardial infarction; SES, sirolimus-eluting stent; TLR, target lesion failure; ZES, zotarolimus-eluting stent; ZES-R, Resolute zotarolimus-eluting stent.

Supplementary Figure 2. Survival Analysis of the Individual Component of Primary and Major Secondary Composite Outcomes

[1] Individual components of target lesion failure; **A)** Clinically driven target lesion revascularization **B)** Cardiac death **C)** Target vessel myocardial infarction

[2] Individual components of patient-oriented composite outcome; **D)** Any revascularization **E)** All cause death **F)** Any myocardial infarction

Abbreviations: EES, everolimus-eluting stent; ZES-R, Resolute zotarolimus-eluting stent.

Supplementary Figure 3. Pooled Analysis of Definite or Probable Stent Thrombosis

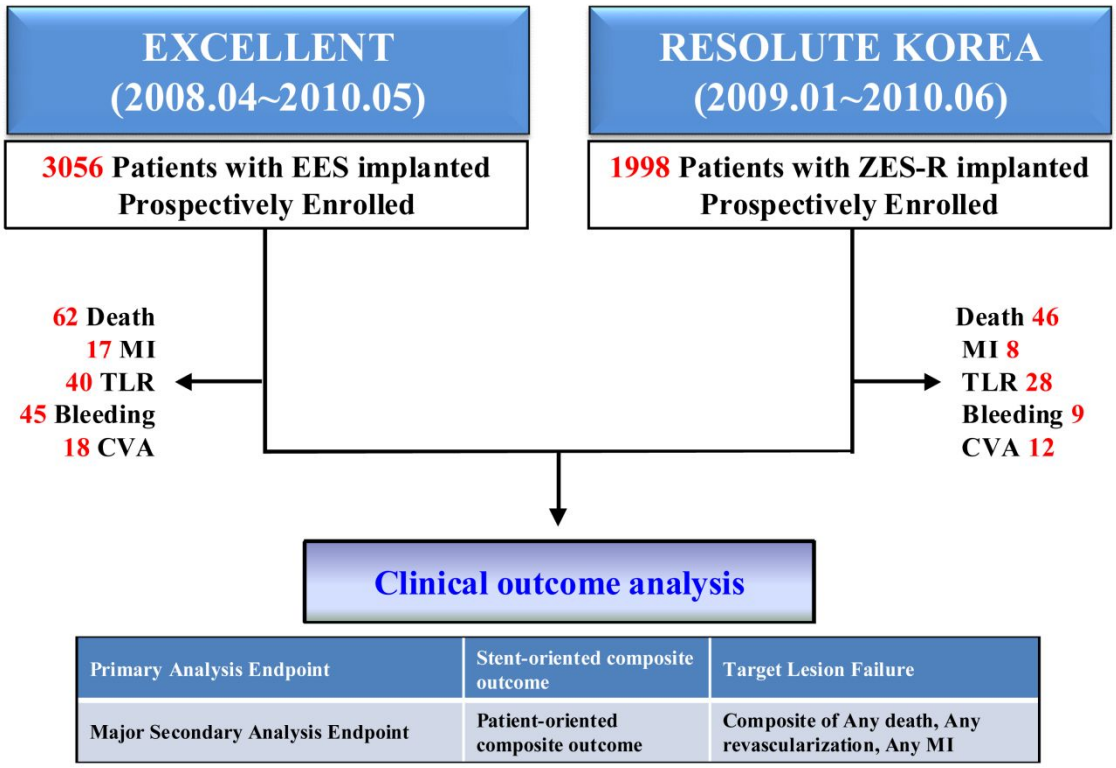
Forest plot with odds ratios for definite or probable stent thrombosis for individual studies and the pooled population. The squares and the horizontal lines indicate the odds ratios (OR) and the 95% confidence intervals (CI) for each study included; the size of each square is proportional to the statistical weight of a trial in the meta-analysis; diamond indicates the effect estimate derived from meta-analysis, with the center indicating the point estimate and the left and the right ends the 95% CI.

Abbreviations: EES, everolimus-eluting stent; ZES-R, Resolute zotarolimus-eluting stent.

Supplementary Figure 4. The Standardized Difference of Variables which were incorporated to Propensity Score Model

Open circle or solid square denotes standardized differences of variables before or after propensity score matching, respectively.

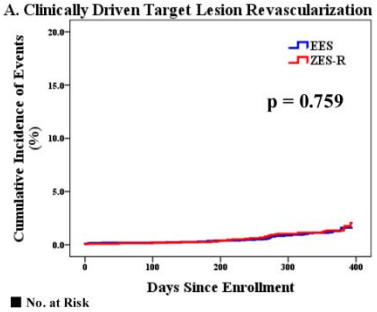
Supplementary Figure 1.



Supplementary Figure 2.

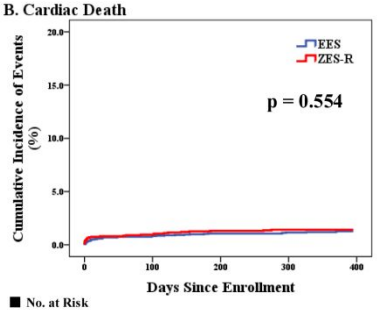
[1] Individual Components of Target Lesion Failure

A. Clinically Driven Target Lesion Revascularization



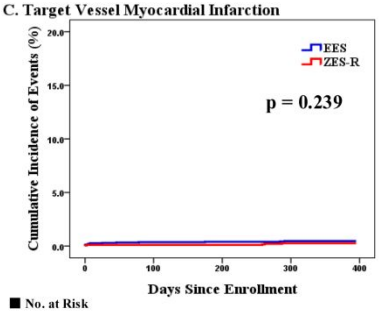
No. at Risk				
EES	3056	2978	2966	2892
ZES-R	1998	1941	1926	1890

B. Cardiac Death



No. at Risk				
EES	3056	2975	2962	2910
ZES-R	1998	1945	1933	1909

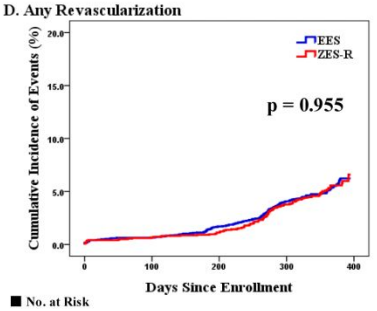
C. Target Vessel Myocardial Infarction



No. at Risk				
EES	3056	2966	2953	2900
ZES-R	1998	1943	1930	1904

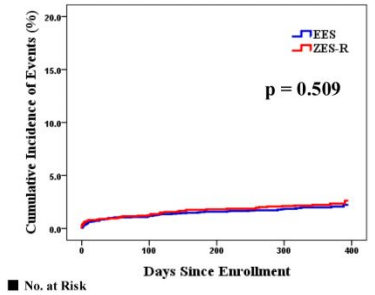
[2] Individual Components of Patient-Oriented Composite Outcome

D. Any Revascularization



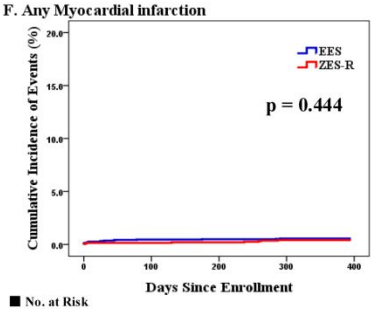
No. at Risk				
EES	3056	2961	2917	2801
ZES-R	1998	1932	1911	1838

E. All Cause Death



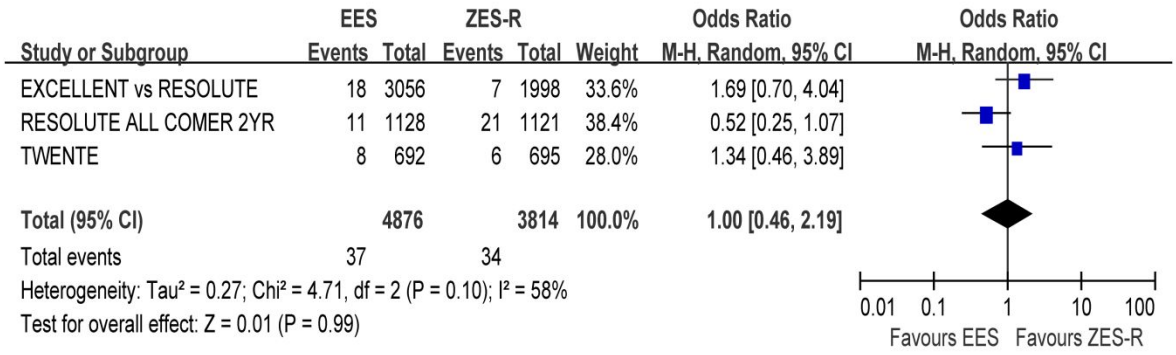
No. at Risk				
EES	3056	2975	2962	2910
ZES-R	1998	1945	1933	1909

F. Any Myocardial infarction



No. at Risk				
EES	3056	2975	2968	2909
ZES-R	1998	1942	1931	1905

Supplementary Figure 3.



Supplementary Figure 4.