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2 세대 약물용출스텐트 삽입후 자연경과와 심근경색환자에서의 사용성적에 관한 연구

Natural Course of Contemporary Drug Eluting Stent and Its Performance in Patients with Myocardial Infarction

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Chengbin Zheng

A thesis of the Doctor of Philosophy degree

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Natural Course of Contemporary Drug Eluting Stent and Its Performance in Patients with Myocardial Infarction

by

Chengbin Zheng

A thesis submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Medicine (Internal Medicine) in Seoul National University College of Medicine

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Abstract

Objectives

We investigated the course of in-stent restenosis and evaluated the revascularization strategy in patients with ST-segment elevation myocardial infarction (STEMI) in a large scale registry.

Background

The progression of restenosis has not been fully evaluated in 2nd-generation drug eluting stents era. Moreover, the completeness of revascularization in STEMI patients with high risk factors is uncertain.

Methods

We investigated and analyzed the restenosis course of 944 stented lesions from 394 patients who had at least two serial follow-up angiograms, using quantitative coronary angiography analysis. A total of 1,311 STEMI patients with multivessel coronary artery disease were analyzed. Complete revascularization (CR) was defined by angiography and by a residual SYNTAX score <8. The primary study endpoints were patient oriented composite outcome (POCO) and cardiac death during 3-year follow-

up. We also evaluated the effects of CR in patients with diabetes mellitus patients and those with reduced left ventricle (LV) function.

Results

The restenosis progression velocity of diameter stenosis was 12.1±21.0%/year and 3.7±10.1%/year during the first and second follow-up periods, respectively, which showed no significant difference ($p>0.05$) between contemporary stents. Overall, patients who underwent angiographic CR (579 patients, 44.2%) had significantly fewer 3-year clinical events than those of patients who underwent incomplete revascularization (IR). (POCO: 14.9% and 24.0%, $p<0.001$, cardiac death: 3.5% and 8.9%, $p<0.001$, for CR vs. IR). Multivariate analysis showed that CR significantly reduced 3-year POCO (adjusted HR 0.63, 95% CI 0.48-0.83) and cardiac death (adjusted hazard ratio [HR] 0.51, 95% CI 0.29-0.89). The results were corroborated using SS-based CR definition. When divided into subgroups according to the presence of diabetes, CR significantly reduced 3-year POCO (adjusted HR 0.52, 95% CI 0.35-0.76) only in the non-diabetes group. When the patients were divided into subgroups according to baseline left ventricular (LV) function, CR significantly reduced 3-year POCO (adjusted HR 0.58, 95% CI 0.43-0.82) only in the preserved LV function group.

Conclusions

The progression rate of in-stent restenosis differed at different time intervals. Contemporary stents had similar rates of restenosis progression. CR could improve clinical outcomes in STEMI patients with multivessel disease. However, the beneficial effect of CR neutralized in those with diabetes mellitus or reduced LV function.

Keywords: In-stent restenosis; Quantitative Coronary Angiography; Percutaneous coronary intervention; ST-segment elevation myocardial infarction; Complete revascularization; SYNTAX score; Diabetes mellitus; Left ventricular dysfunction

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LIST OF ABBREVIATIONS

ISR: In-stent restenosis

DS: Diameter stenosis

MLD: Minimal luminal diameter

DES: Drug-eluting stent

STEMI: ST-segment elevation myocardial infarction

CR: Complete revascularization

IR: Incomplete revascularization

POCO: Patient-oriented composite outcomes

SS: SYNTAX score

DM: Diabetes mellitus

LV: Left ventricle

General Introduction

According to the report of World Health Organization, 17.9 million individuals die every year from coronary artery disease, which accounts for an estimated 31% of all deaths worldwide, and this number is increasing every year.[1] Percutaneous coronary intervention (PCI) is a non-surgical procedure used to treat stenosis of the coronary arteries. Coronary angiography and PCI are the most common invasive cardiovascular procedures performed worldwide. From the first percutaneous transluminal coronary angioplasty performed by Andreas Gruntzig in 1977 to the 2nd-generation drug eluting stents (DES) era, devices and procedural techniques have witnessed tremendous growth.[2] However, these developments have been accompanied by various problems and challenges.

Although, the rate of in-stent restenosis (ISR) has significantly reduced with the development of devices and techniques, its incidence is still about 10%.[3-5] However, its prevalence is not negligible, because it can lead to poor clinical prognosis. The progression of ISR has not been fully evaluated in 2nd-generation DES era. Recent randomized clinical trials (RCT) have confirmed the beneficial effect of complete revascularization (CR) in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease.[6-9] However, these RCTs had strict inclusion

criteria; they only included patients who were hemodynamically stable, and those with few clinical risk factors. In real world practice, however, we often encounter patients with various clinical problems and risk factors, and whether we can extrapolate the beneficial effects of CR to these patients is uncertain.

In the present study, the first chapter describes the progression of ISR in stented coronary arteries, and the second chapter describes the strategy of coronary stent therapy.

CHAPTER 1

Progression of restenosis in stented coronary

Introduction

In-stent restenosis, which is thought to be mostly caused by neointimal hyperplasia (NIH), was an important medical concern in the era of bare-metal stents (BMS).[10] Subsequent intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) studies further strengthened the view that the main mechanism of restenosis after BMS implantation was intra-stent NIH[11,12] with a biphasic change of lumen loss in the first 6 months and regression of NIH between 6 months and 1–3 years after BMS implantation.[13,14] Therefore, late target lesion revascularization (TLR) after BMS implantation was not a common phenomenon. Compared with BMS, DES significantly reduced the rates of in-stent restenosis (ISR).[15,16] However, some studies mentioned a “late catch-up” phenomenon after the implantation of first-generation DES.[17-23] The “late catch-up” phenomenon suggests that the mechanism and rate of neointimal formation may vary at different time intervals.

In this study, we analyzed stented lesions treated using 2nd-generation DESs, using longitudinal QCA analysis. We observed the progression of stented lesions and compared the restenosis progression rates between contemporary DESs.

Methods

Study design and population

Patients who underwent PCI in our institute we enrolled from serial stent registries. These registries included four types of 2nd-generation DESs: cobalt chromium everolimus-eluting stent (CoCr-EES), platinum chromium everolimus-eluting stent (PtCr-EES), zotarolimus-eluting stent (ZES), and biolimus-eluting stent (BES). Follow-up coronary angiography was recommended at 9 to 12 months after PCI according to the protocol of the individual registries (not mandatory). In the patients who consented to and underwent the first follow-up angiogram, the second follow-up angiogram was recommended at 24 months. During the study period (July 2008 to March 2013), 3,365 patients were enrolled in various stent registries in Seoul National University Hospital. Among these, 3170 patients (94.2%) were treated using 2nd-generation DESs and, 1545 patients (45.9%) underwent at least two serial angiographic follow-ups. In total, 944 lesions from 394 patients (11.7%) were subjected to longitudinal QCA analysis. We performed a sensitivity analysis to check the possibility of selection bias, which showed that the baseline demographics were similar between the entire parent population and our study population (**Table 1**). From July 2008 to March 2013, a total of 394 patients with 944 lesions were enrolled in the

study. The mean follow-up durations from baseline to the first and second angiography were 325 ± 90 days and 772 ± 133 days, respectively. The study flowchart is shown in **Figure 1**. In total, 58 lesions performed TLR at the first angiographic follow-up (early TLR: 6.1%), whereas 23 lesions that did not require TLR at first follow-up performed TLR at the second angiographic follow-up (late TLR: 2.4%) (**Figure 2**). The study was approved by the ethics committee and the institutional review board, and it was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent for participation in the registry.

Procedure and data collection

Interventional procedures were performed according to current standard techniques. All patients undergoing PCI were pre-administered with a loading dose of aspirin (300 mg) and clopidogrel (300-600 mg). Unfractionated heparin was administered to achieve an activated clotting time of ≥250 seconds. Either the radial or femoral artery was used for vascular access. The use of glycoprotein IIb/IIIa inhibitors, predilation devices, type of DES, stenting techniques, and IVUS guidance were at the operators' discretions. After the index procedure, all patients were recommended to receive dual antiplatelet therapy for at least 6 months and life-long aspirin.

Clinical, angiographic, and procedural data were collected by dedicated database managers and independent research nurses who were not aware of the purpose of the study and had not participated in the management and care of the study patients. Angiography at baseline and first and second angiographic follow-up was recorded in DICOM format. We filmed all routine views and other additional views as needed using identical projections that were taken for quantitative angiographic measurements at baseline. All angiographic recordings were preceded by an intracoronary injection of nitrates.

Quantitative coronary angiography and definition of measured parameters

Quantitative analysis of coronary angiographic images was performed at the Seoul National University Hospital Cardiovascular Clinical Research Center Angiographic Core Lab by specialized QCA technicians unaware of the purpose of this study and the type of stent used for treatment. The CAAS II QCA system (Pie Medical, Maastricht, the Netherlands) was used for automated contour detection and quantification. Projections, where foreshortening of the analysis segment could be minimized and where the severity of the stenosis could be maximized, were used in the analysis. Same views with identical projections for baseline and first and second angiographic follow-up were used. Using the guiding catheter for calibration, we measured the minimal luminal diameter (MLD) and reference vessel diameter and

lesion length before and after the index procedure and at first and second angiographic follow-up.[17]

Study endpoints and definitions

The study endpoints were the velocity of diameter stenosis (DS) progression during the follow-up periods. DS% was defined as 100% minus the ratio of minimal lumen diameter (MLD) and diameter of the reference segment. Early delta DS% indicated the difference in DS% between the angiogram performed immediately after the index procedure and the first follow-up angiogram, and delayed delta DS% denoted the changes of DS% between the first and second follow-up. Depending on the time interval, we converted early and delayed delta DS% into rates (early DS%/year & delayed DS%/year).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. The Student t test or one-way analysis of variance was used for comparison of continuous variables, and we analyzed categorical variables using the chi-square test (or the Fisher exact test when any expected count was <5 for a 2×2 table) test. Statistical analysis was

performed with SPSS (version 23.0), and a value of P values less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The mean age of our study population (73.4% male) was 65.5±10.4 years; 69.8% of them had hypertension and 33.8% had diabetes mellitus (DM). The mean reference vessel diameter of the lesions was 2.92 ±0.52 mm and the mean length of the lesions was 27.7 ±17.3 mm. Baseline patient and lesion characteristics are summarized in **Table 2**. Laboratory findings at the follow-up periods are shown in **Table 3**.

Incidence of target lesion revascularization

The cumulative incidence of TLR is shown in **Figure 2.** TLR was performed for 58 lesions (6.1%) during the first angiographic follow-up period, and for 23 lesions (2.4%) during the second follow-up period. TLR in this cohort included ischemic driven TLR and TLR during routine angiographic follow-up.

Angiographic outcome

In our study, 944 lesions were treated using four types of 2nd generation DES, namely CoCr-EES, ZES, BES, and PtCr-EES, which accounted for 25.8%, 32.8%, 17.6%, and 23.7%, respectively. There were no significant differences in both reference vessel diameter (p=0.054 using ANOVA) and lesion length (p=0.247 using ANOVA) between the four types of DES. The QCA analysis of 944 lesions showed that the mean angiographic DS% before the procedure was 74.8% ±15.7%; it decreased to 11.8% ±8.5% after the procedure **(Table 2)**. The mean MLD also showed no significant difference between the four DES groups at all the different time points (initial state, post-procedure, at the first angiographic follow-up, and at the second angiographic follow-up) (**Table 4**). The MLD cumulative probability curves of the four groups are shown in **Figure 3**. Both initial delta DS% and delayed delta DS% were also similar between the four DESs (Initial delta DS%: 9.5 ± 16.0%, 10.3 ± 15.2%, 9.5 ± 14.4%, 11.7 ± 17.6%, p = 0.204 using ANOVA, delayed delta DS%: 4.8 ± 14.1%, 3.7 ± 9.9%, 5.3 ± 11.5%, 5.1 ± 11.1%, p = 0.486 using ANOVA, for CoCr-EES, ZES, BES, and PtCr-EES respectively.)

With regard to the progression of ISR, the early delta DS%/year was 12.12% ± 20.97%/year, and delayed delta DS% /year was 3.68% ± 10.10%/year, showing that the delayed ISR progression rate was about 30% of the early progression rate. Between the four types of DES, both the early ISR progression rate and delayed ISR progression rate showed no significant difference (initial restenosis progression rate: 12.2% ± 20.9%/year, 12.2% ± 18.6%/year, 14.3% ± 29.8%/year, 10.4% ± 15.7%/year,

p = 0.525; delayed restenosis progression rate: 4.1% ± 12.8%/year, 2.4% ± 8.1% /year, 4.0% ± 8.3%/year, 4.8% ± 10.5%/year, p = 0.205) (**Table 4).**

Discussion

In this study, the cumulative incidence rates for early and late TLR were 6.1%, and 2.4% respectively, in stented lesions, during the overall median follow-up period of 772 days. The rates of early and late ISR progression were 12.1 ± 21.0 %/year and 3.7 ± 10.1%/year, respectively. Our results showed that the rates of initial DS%/year and delayed DS%/year were all similar ($p > 0.05$) in the four types of DES.

Mechanism of restenosis after implantation of DES

Restenosis is a progressive phenomenon and the specific mechanisms at different time intervals of ISR are unclear. Since the era of support, the two mechanisms recoil and vascular remodeling had almost been cancelled with the advent of stents compared with simple balloon angioplasty, and NIH became the primary cause of restenosis.[24] ISR is primarily a non-specific inflammatory response to vessel wall injury, and the injured tissue reacts via an inflammatory process that leads to NIH, eventually leading to lumen narrowing. Regardless of the exact pathophysiology, ISR is the end result of endothelial injury caused by stent deployment and foreign materials left at the deployment site.[25-28] Goto et al. retrospectively analyzed 298 ISR lesions using IVUS data. The main finding of this study was that NIH was an important mechanism

of ISR, even in the 2nd-generation DES era.[29] Compared with BMS, although the drug and polymer of DES counteract the excessive NIH, greatly reducing the incidence of ISR, a late catch-up phenomenon is observed.[30] Owing to drugs and polymers, compare to BMS, DES prolong the healing time of endothelials. This may account for the different incidences of early and late events. This is also the main reason behind the prolonged duration of dual antiplatelet therapy duration required after entering the DES era. However, the exact mechanism of ISR associated with DES remains unclear. The possible mechanisms of restenosis after implantation of DES are biological factors (drug resistance, hypersensitivity); mechanical factors (stent underexpansion, nonuniform stent strut distribution, stent fracture, nonuniform drug elution/deposition, polymer peeling) and technical factors (barotrauma outside stented segment, stent gap, residual uncovered atherosclerotic plaques).[30] Although DES are constantly improving, ISR is still a challenge that has to be overcome.

Restenosis progression in 2nd generation DES

According to our results, the early delta DS%/year was 3.3-fold larger than the delayed delta DS%/year, implying that ISR progression is more rapid in the early phase. Interestingly, a previous study by Kang et al. analyzed the natural progression of atherosclerotic plaques.[31] This study showed that the natural progression rate of non-stented lesions was 2.19%/year, which was lower than that of stented lesions.

From these results, we can conclude that compared with natural atherosclerotic lesions, stented lesions are more susceptible to restenosis.

Limitations

This study has some limitations. First, its retrospective nature may have caused a bias in patient selection. We compared the baseline clinical characteristics of the patients with those of the total parent population that underwent PCI during the study period, and we found minimal difference between the two populations. However, we cannot complete deny the possibility of other selection biases within our study population. Second, we did not perform imaging analysis using IVUS, which may enable to assess the cause of restenosis. Lastly, the data used in the analysis in this study were based on a relatively small sample and were collected from a single center.

Conclusion

Our data suggested that, the progression rate of ISR in the early phase was 3.3-fold greater than that in the late phase in 2nd generation DES era. There was no difference in the rate of DS progression in stented lesions between four types of contemporary DESs.[32]

Statement

The first chapter of this thesis is part of a paper [32] in which I am the first author. With the consent of the co-authors, part of the following paper is included in my thesis.

32. Zheng, C.; Kang, J.; Park, K.W.; Han, J.K.; Yang, H.M.; Kang, H.J.; Koo, B.K.; Kim, H.S. The predictors of target lesion revascularization and rate of in-stent restenosis in the second-generation drug-eluting stent era. *J Interv Cardiol* **2019**, *2019*, 3270132.

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Quantitative analysis of coronary angiographic images was performed at the Seoul National University Hospital Cardiovascular Clinical Research Center Angiographic Core Lab by specialized QCA technicians. The authors would like to thank QCA technicians and clinical research coordinators for their assistance in data measurement and coordination.

CHAPTER 2

Comparative analysis of coronary stent therapy in patients with myocardial infarction

Introduction

Current guidelines advocate PCI for non-culprit arteries in STEMI patients who are hemodynamically stable.[33-35] The recommendation is supported by four recent RCTs that confirmed the beneficial effect of CR in multivessel STEMI patients.[6-9] In these studies, CR which was achieved through either a one-step or staged procedure, improved clinical outcomes compared with IR by 44%–65% at follow-up ranging from 1 to 3 years, although the primary endpoints slightly varied among studies.

Previous RCTs had strict inclusion criteria, and they excluding high-risk patients, such as those with cardiogenic shock or renal impairment, those who had undergone previous coronary artery bypass graft, and those with a life expectancy less than the duration of the trial. These RCTs only included patients who were hemodynamically stable, and patients with few clinical risk factors. In particular, the proportion of patients with DM in these RCTS was less than 15%. It is well known that the rate of DM exceeds 15% in real world clinical data. Whether CR is still effective for these patients is unclear. Compared with patients without DM, those with DM remain at high risk of adverse cardiovascular events after PCI.[36] In addition, CR may not have profound beneficial effects in this subgroup; patients with DM show higher coagulability, higher inflammatory response, endothelial dysfunction, and more

aggressive intimal hyperplasia. In fact, a previous registry-based study showed that compared with IR, CR did not improve mortality in coronary artery disease patients with DM.[37] To the best of our knowledge, no studies have yet investigated the effectiveness of CR in patients with STEMI according to the presence of DM. The CULPRIT-SHOCK trial showed that CR could not reduce mortality in STEMI patients with cardiogenic shock,[38] stressing that additional evidence is required to ascertain the benefits of CR in high-risk STEMI patients. Reduced LV function is associated with increased mortality in STEMI patients,[39,40] and CR may not have profound beneficial effects in this subgroup, as these patients are at increased risk for sudden cardiac death, ventricular arrhythmia, and death from progression of heart failure. The CULPRIT-SHOCK trial showed that CR could not reduce mortality in STEMI patients with cardiogenic shock.[41] In fact, a previous registry-based study showed that compared with IR, CR did not improve clinical outcomes in coronary artery disease patients with left ventricular ejection fraction (LVEF) <40%.[37]

In real world practice, however, we often encounter patients with various clinical problems and risk factors, and whether the beneficial effects of CR can be extrapolated to these real-world patients is unclear.

Therefore, in our study, we compared the clinical outcomes between CR and IR in STEMI patients**,** through a large-scale prospective registry. In addition, we evaluated

the clinical outcomes in these patients according to the presence of DM and baseline LV function.

Methods

Study Population

This study was based on the 'Grand-DES' (NCT03507205), which is a Korean nationwide multicenter pooled registry of drug-eluting stents, from January 1, 2004, to November 31, 2014 in 55 centers in Korea. The Grand-DES registry incorporated five different multicenter registry, HOST-BIOLIMUS-Korea-3000 (Biomatrix; Biomatrix Flex; Nobori), EXCELLENT-PRIME (Xience Prime), HOST-RESOLINTE (Resolute Integrity), EXCELLENT Prospective cohort (Xience V/Promus; Cypher), and the RESOLUTE-Korea (Endeavor; Resolute), which together included 17,286 patients. After index PCI, clinical follow-ups were performed up to 3 years. The median follow-up duration was 1123 days (IQR 1078, 1137 days). All registries enrolled all-comers without any exclusion criteria except patient's withdrawal of consent. From the GRAND-DES registry, 1,311 STEMI patients with multivessel disease were analyzed in the current study. Among the total population, CR was achieved in 579 patients (44.2%), while IR was achieved in 732 patients (55.8%) (**Figure 4**). The study complied with the provisions of the Declaration of Helsinki, and the study was approved by the institutional review board at each center.

Completeness of revascularization and Calculation of the SYNTAX Score

To evaluate the angiographic completeness of revascularization, angiographic images were retrospectively evaluated. Angiographic CR was defined as the treatment of any lesion with more than 70% diameter stenosis in vessels ≥2.5 mm as estimated on the diagnostic angiogram, leaving no residual significant angiographic stenosis. Also, due to the various definitions of CR, and due to the fact that it is not always feasible to completely revascularize multivessel diseases, we calculated the SYNTAX score (SS) system to quantify the degree of revascularization. The SS was calculated by visually assessing all coronary lesions with a diameter stenosis ≥50% in vessels >1.5 mm diameter, using the SS algorithm, which is available on the SYNTAX score website (www.syntaxscore.com). For evaluation of CR and calculation of the SYNTAX score, quantitative analysis of baseline coronary angiographic images was performed by 3 specialized QCA technicians at the Seoul National University Hospital Cardiovascular Clinical Research Center Angiographic Core Laboratory, who were blinded to all clinical data, presentation, implanted stents and outcomes. In the event of disagreement, the lesion was reviewed and a final decision was established by consensus. The core lab has been validated with SS calculation, showing measurement correlation above 95%.[42] Baseline SS was defined as the SS at initial coronary angiography, while the residual SS (rSS) was calculated as the SS after index PCI. SS-

based CR was defined as the rSS of less than 8, which was the definition used in previous studies.[43]

End Points

Clinical follow-up was performed up to three years (median: 1123 days, interquartile range 1078-1137 days). The primary endpoint of current study was patient-oriented composite outcome (POCO) defined as a composite of all cause death, any myocardial infarction, and any revascularization within 3 years. And the key secondary analysis endpoint was cardiac death which was component of POCO during the follow-up periods. Myocardial infarction and stent thrombosis were defined according to the Academic Research Consortium definitions.[44]

Echocardiographic study

For each patient, echocardiography was performed during admission, mostly after the acute phase when the patient was clinically stable. The LV systolic and diastolic function, dimensions were assessed according to international guidelines.[45] Specifically, the LV volume and LVEF were calculated by Simpson's biplane method, or by the 2-dimensional method or visual estimation when the Simpson's biplane method was not available. All measurements were obtained from the mean of 3 beats

(patients in sinus rhythm) or 5 beats (patients in atrial fibrillation). Reduced LV function was defined as LVEF less than 40%, while those with LVEF ≥ 40% were classified as the preserved LV function group.

Statistical Analyses

Data are presented as numbers and frequencies for categorical variables and as mean±SD for continuous variables. Clinical and procedural characteristics were compared between patients experiencing clinical events, defined as endpoints. For comparison among groups, $\chi 2$ (or the Fisher exact test when any expected count was <5 for a 2×2 table) test for categorical variables and unpaired Student t test or one-way analysis of variance for continuous variables were applied. To estimate the independent factors on endpoints, a multivariable Cox proportional hazards regression model using a backward elimination algorithm and 0.05 as the significance level was performed. Variables such as age, gender, body mass index, previous hypertension, previous diabetes mellitus, previous dyslipidemia, previous PCI, previous peripheral vascular disease, current smoking, previous chronic renal failure, presence of anemia, presence of significant left ventricular (LV) dysfunction, baseline SYNTAX score and achievement of complete revascularization were added as covariates. The Cox proportional hazard regression in a propensity-score matched cohort and inverse probability of treatment weighted Cox proportional hazard regression were performed.

Event rates were calculated based on Kaplan-Meier censoring estimates, and the log-rank test or the Breslow test was used to compare between CR and IR groups. All probability values were two-sided and p-values <0.05 were considered statistically significant. Statistical tests were performed using SPSS, V23 (SPSS Inc.) and R programming language, version 3.4.1 (R Foundation for Statistical Computing).

Results

Beneficial effect of CR in STEMI patients

The baseline characteristics of patients in the CR and IR groups are shown in **Table 5**. The IR group had more risk factors, such as old age, hypertension, and chronic renal failure, and showed a higher coronary complexity. During revascularization, more DES with a greater total length and a smaller minimal stent diameter were used in the CR group. The baseline SYNTAX score was higher in the IR group (20.2 ± 8.7 and 15.6 ± 8.0, respectively; $p < 0.001$), whereas the delta SYNTAX score was higher in the CR group than in the IR group (13.8 ± 7.8 and 11.5 ± 7.2, respectively; $p < 0.001$). The pattern of discharge medication was similar between the CR and IR groups.

In terms of the 3-year clinical outcomes, CR was associated with a significantly lower rate of 3-year POCO than IR was (14.9% [86/579] and 24.0% [176/732], respectively; $p < 0.001$), which was mainly driven by a decrease in cardiac death (3.5% [20/579] and 8.9% [65/732], respectively; $p < 0.001$). Multivariable Cox regression analysis, propensity score matched analysis, and inverse probability of treatment weighting adjusted analysis all consistently showed that compared with IR, CR significantly reduced the risk of POCO and cardiac death (**Table 6**). The survival curve of POCO and cardiac death according to CR is shown in **Figures 5** and **6**. No statistical

difference in in-hospital events was observed between the CR and IR groups (**Table 7**). Landmark analysis from 30 days showed that CR reduced POCO and cardiac death in the late phase (≥30days to 3 years) (**Figure 7**).

Corroboration using SS-based CR

Owing to the heterogeneity in the definitions of CR, we calculated the rSS and analyzed the clinical impact of SS-based CR (rSS < 8) vs SS-based IR (rSS ≥ 8). The baseline characteristics of the rSS < 8 and rSS ≥ 8 groups are shown in **Table 8**. The 3-year POCO and cardiac death were significantly more common in those with a SS-based IR (POCO: 17.3% and 27.2%, p < 0.001; cardiac death: 4.4% and 12.0%, p < 0.001, in SS-based CR and IR groups respectively). On multivariate analysis, SS-based IR was again an independent risk factor for 3-year clinical events (**Table 9**), **(Figure 8)**.

CR vs. IR in subgroup analysis

As observed in the forest plot (**Figure 9)**, the effect of CR was not significantly different along various subgroups, except for the DM group (P-value for interaction = 0.043). However, the beneficial effect of CR is relatively weak in the high risk groups. With regard to the strategy of CR, there was no statistical difference in the rates of

POCO and cardiac death between the two CR strategies (one-time CR vs. staged CR) (**Table 10**, **Figure 10**).

CR vs. IR according to the presence of DM

As observed in the forest plot (**Figure 9)**, there was a significant interaction for POCO according to the presence of DM (P for interaction = 0.043). Thus, to evaluate whether the beneficial effect of CR was preserved in patients with DM, we analyzed the effect of CR according to the presence of DM. There were 425 patients (32.4%) in the DM (+) group and 886 patients (67.6%) in the DM (-) group. The baseline demographics, angiographic findings, laboratory findings, and discharge medication according to the presence of DM are summarized in **Table 11**. Compared with patients without DM, those with DM seemed to have more clinical risk factors (i.e. older in age, higher proportion of female patients, hypertension, dyslipidemia, history of stroke, chronic renal failure, and anemia). Angiographic characteristics showed that the DM (+) group had slightly more patients with 3 vessel disease, and stent with smaller-diameter, and greater length-stents.

The rates of POCO during the 3 year follow-up period were significantly lower in the CR group than in the IR group in the non-DM group (POCO rate: 45/384 [11.7%] and 117/502 [23.3%], respectively; $p < 0.001$). However, there were no significant differences in the DM group (POCO rate: 41/195 [21.0%] and 59/230 [25.7%] for CR

and IR group, respectively; p = 0.302). This trend was consistent for 3-year all components of POCO, with significantly lower event rates with CR observed only in the non-DM group. Upon multivariate analysis, IR was an independent predictor of 3-year POCO and its components in only the DM (-) group (**Table 12, Figure 11**). Especially for POCO, myocardial infarction, and target vessel myocardial infarction, significant interaction was observed between the revascularization strategy and the presence of DM (**Figure 12**).

CR vs. IR according to baseline LV function

To evaluate whether the beneficial effect of CR was preserved regardless of the baseline LV function, we analyzed the effect of CR according to the presence of baseline LV dysfunction. There were 233 patients (17.8%) in the reduced LV function group and 1078 patients (82.2%) in the preserved LV function group. The baseline demographics, angiographic findings, and laboratory findings according to LV function are summarized in **Table 13**. Compared with patients without reduced LV function, those with reduced LV function tended to be sicker, with a greater number of risk factors (i.e. older in age, higher proportion of congestive heart failure, chronic renal failure, and anemia). Angiographic characteristics showed that the reduced LV function group had more patients with 3 vessel disease, had more calcified lesions, used smaller-diameter stents, and had higher baseline SS and rSS. Meanwhile CR was

more frequently achieved in the preserved LV function group than in the group without preserved LV function (rate of CR: 506/1078 [46.9%] and 73/233 [31.3%], respectively; $p < 0.001$).

At the 3-year follow-up, POCO rates were significantly lower in the CR group than in IR group in the preserved LV function group (POCO rate: 67/506 [13.2%] and 125/572 [21.9%], respectively; $p < 0.001$). However, the difference was attenuated in the reduced LV function group resulting in no significant differences between the groups (POCO rate: 19/73 [26.0%] and 51/160 [31.9%] in the CR and IR groups, respectively; $p = 0.442$). This trend was consistent for 3-year cardiac death, with significantly lower cardiac death rates with CR observed only in the preserved LV function group. Upon multivariate analysis, IR was an independent predictor of 3-year POCO and cardiac death in only the preserved LV function group (**Table 14, Figure 13**). There was a significant interaction for cardiac death between the effect of CR and the presence of LV dysfunction (P for interaction = 0.023, **Figure 14**). Landmark analysis from 30 days showed that CR reduced POCO in the late phase (≥30days to 3 years) only in the preserved LV function group (**Figure 15**).

Discussion

In our current study, we analyzed the effect of CR on the 3-year outcomes of STEMI patients with multivessel disease. We observed that overall, in STEMI patients with multivessel coronary artery disease, CR was associated with lower rates of POCO and cardiac death at 3 years. Multivariable analysis confirmed that CR was an independent protective factor of POCO and cardiac death at 3 years. Our results showed that the significant difference seen in 3-year any revascularization between CR and IR groups was from non-TLR revascularization and not from TLR. In other words, the IR group performed more revascularization for the residual lesion than the CR group. The ratio of TLR and non-TLR in the CR group was 1: 1, but 1: 3 in the IR group. Our findings were concordant using both an angiographic definition and a SS-based definition of CR.

CR in STEMI patients

Thus far, four RCTs have compared CR and IR in STEMI patients with multivessel coronary disease. Two RCTs used angiography-guided revascularization, and reported lower rates of major adverse cardiac events in the CR group, in which routine revascularization of the non–infarct-related coronary arteries was performed.[6,8]

Two other studies involved fractional flow reserve-guided treatment of non–infarct-related coronary arteries and also reported a significant reduction in major adverse cardiac events, supporting the beneficial effect of CR.[7,9] Taken together, these studies consistently showed that additional PCI for non-culprit arteries could reduce adverse clinical outcomes by up to 44%–65%. In the present study, concurrent with previous observations, CR improved both POCO and cardiac death in the overall population with STEMI and multivessel coronary disease. However, the major caveat of the previous RCTs was that they excluded high-risk patients, such as those with cardiogenic shock, those with renal impairment, those who had undergone previous coronary artery bypass graft, and those with a life expectancy less than the duration of the trial. This limits the generalizability of the results of these studies. As much of the dilemma in clinical decision making occurs with regard to the decision on whether to perform CR in these patients, more studies that address the effect of CR in these patients are required. One of the key studies that addressed such a population was the CULPRIT-SHOCK trial, where the effect of CR was studied in patients with STEMI with cardiogenic shock. The trial showed that CR failed to reduce 1-year mortality in this high-risk population,[41] suggesting that whether CR actually improves outcome in other high-risk populations should be evaluated in future studies. In our study, we also compared the one-time CR and staged CR. As with previous studies,[46] staged CR was not proven to be better. Future large RCT are needed to assess the optimal timing of CR

Confirmation of the effect of CR using a SYNTAX score-based definition of CR

To confirm out findings using a more quantifiable definition of CR, we analyzed our data using a SS-based definition of CR.[42] We calculated the rSS post-PCI by quantifying the residual disease, summing the points of each coronary lesion with ≥50% stenosis in vessels ≥1.5 mm in diameter.[47] We used the previously studied definition of reasonable incomplete revascularization of rSS <8,[43] to evaluate the effect if SS-based CR in our population. Similar to angiographic CR, SS-based CR was also beneficial in patients with STEMI.

CR in STEMI patients with DM

A previous registry-based study showed that CR compared with IR did not improve mortality in coronary artery disease patients with DM.[37] Our results are in line with those of this study. Although CR can improve myocardial salvage by revascularization of the hibernating myocardium and increase of blood flow to watershed areas, our results suggest that the theoretical benefit of CR did not lead to improve the clinical outcomes in patients with DM. To the best of our knowledge, DM is a well-recognized disease that is associated with worse outcome after surgical or percutaneous

revascularization in patients with coronary artery disease. From the results of our study, we found that CR reduces the rates of 3-year POCO only in patients without DM and not in those with DM. Our results showed that the reduction of POCO was driven by significant reduction of all its components. When he effect of CR was compared between patients with and without DM, not only was there a statistical difference in the incidence between CR and IR, but the numerical spot hazard ratio (HR) of CR (vs. IR) was also less protective in the group of patients with DM. This trend was reflected not only in POCO, but also in other components (i.e. all-cause death, cardiac death, MI, and any revascularization), suggesting that the value of CR in patients with DM was neutral. Although it is difficult to explain the exact mechanism, this may be explained by the relevant mechanisms of DM, such as higher coagulability, higher inflammatory response, endothelial dysfunction, and more aggressive intimal hyperplasia, leading to more revascularization. A study on the natural course of non-culprit coronary arteries even considered that DM was the only significant clinical factor to predict non-culprit ischemic-driven revascularization.[31] Moreover, the increased thrombotic risk in patients with DM may lead to a higher risk of stent-related ischemic events such as myocardial infarction and stent thrombosis.

CR in STEMI patients with reduced LV function (moderate to severe LV dysfunction)

Regarding baseline LVEF, previous trials have reported that up to 20% of STEMI patients have LV dysfunction,[48] while these patients are at higher risk for future event after treatment of STEMI. This is due to increases in risk of fatal arrhythmic events, thrombotic events, and aggravation of heart failure.[49,50] In fact, cardioverter-defibrillator implantation has been shown to reduce mortality in STEMI patients with reduced LVEF, and therefore is recommended by the guidelines for primary prevention of sudden cardiac death.[51] Moreover, a previous study showed that PCI is superior to CABG in patients with lower LVEF.[52] This may be related to higher surgical risk in patients with lower LVEF and loss of major advantages of CABG. Regarding this analysis, we can stress the clinical importance of PCI in STEMI patients with lower LV dysfunction. However, those with significant LV dysfunction were excluded in the previous RCTs. Moreover, a previous study based on the New York State's PCI reporting system analyzed that there were no significant difference in 18-month mortality between CR and iCR in patients with LVEF<40%.[37] Therefore, we wanted to evaluate whether the beneficial effect of CR in multivessel STEMI patients would be sustained in those with reduced LVEF.

With regard to CR, many mechanisms can explain the beneficial effect of additional non-culprit intervention. This includes improvement in myocardial salvage by revascularization of the hibernating myocardium and increase of blood flow to watershed areas. However, our study showed that in patients with reduced baseline LV function, the theoretical benefits of CR did not lead to improved clinical outcomes.

Interestingly, a previous meta-analysis suggested that revascularization was superior to medical treatment only in the presence of a viable myocardium in patients with coronary artery disease and significant LV dysfunction.[53] Our results are in line with this study, because CR was performed without any evaluation of myocardial viability. Although some studies have evaluated the association of fractional flow reserve and myocardial viability, fractional flow reserve values alone have limitations in assessing viability, and other non-invasive methods such as cardiac magnetic resonance imaging and positron emission tomography scanning are necessary to accurately assess myocardial viability.

In the present study, we found that CR reduced 3-year POCO by 42%, which is consistent with the result of previous RCTs. However, this was observed only in patients with preserved LV function and not in those with reduced LV function. The reduction in clinical events was mainly driven by a significant reduction in cardiac death, whereas any myocardial infarction and any revascularization events were also numerically lower in the CR group. When the effect of CR was compared between patients in those with and without significant LV dysfunction, not only was the statistical difference between CR and IR not significant in those with reduced LV function, but the numerical spot HR of CR (vs. IR) was also less protective in the group with reduced LV function. This trend was found in not only POCO but also other components such as all-cause death, cardiac death, and target lesion failure, suggesting that the effect of CR was not as prominent in these patients. This may be

explained by the increased risk of arrhythmia in STEMI patients with significant LV dysfunction, leading to more cardiac death events.[50,54] In addition, the increased thrombotic risk in LV dysfunction patients leads to a higher risk of stent-related ischemic events such as myocardial infarction and stent thrombosis.[49,55,56] Through landmark analysis, we showed that the lack of benefit of CR in patients with reduced LV function was consistent both within the initial 30 days after PCI, and from 30 days to 3 years. A recent trial showed that CR was superior to culprit-only PCI in STEMI patients with LVEF<45%.[57] Although the results seem to be inconsistent with our analysis, a few points should be noted before comparison. Compared to this study, our study population included patients presenting as cardiogenic shock, included patients with more clinical risk factors (i.e. hypertension, diabetes, chronic renal failure, etc.) and had a higher baseline SYNTAX score. Also, the randomization point was after the index PCI within 72 hours, implying that very high-risk patients were not enrolled in the study. Collectively, our study was based on real-world patients, including patients with a higher risk profile. The markedly different study population, along with the intrinsic difference between RCTs and registry-based studies, could have contributed to the different results from our study.

Limitations

Our study has several limitations. First, this study was an observational analysis of a prospective registry; therefore, treatment (CR vs. IR) was not randomized and was decided by the treating physician. Second, adjunctive therapy after PCI was also determined by the treating physician. These limitations are associated with a possibility of selection bias and treatment bias. Although we used multiple statistical models to correct for possible biases and confounders, the possibility of unforeseen confounders affecting the outcome cannot be completely ruled out. Third, LVEF assessment at baseline may not reliably predict chronic LV dysfunction, especially in STEMI patients.[58] To minimize this risk, echocardiography was performed after the patients were stabilized, which may clinically be assumed as the point of recovery of myocardial stunning. Fourth, the follow-up was limited to three years. In the subgroup analysis, although there was no statistical difference between CR and IR in the DM group and reduced LV function group, CR did not improve the 3-year clinical outcome. However, the effect of CR may be presented with extended follow-up, therefore, evaluation during extended follow-up is required. Finally, CR was evaluated by angiography, without functional studies such as fractional flow reserve.

Conclusion

The benefit of overall CR among patients with STEMI and multivessel coronary artery disease, was confirmed in a large-scale prospective registry. When divided into subgroups by the presence of DM, less benefit of CR was observed in patients with DM. When the patients were divided into those with and without significant LV dysfunction, the beneficial effect of CR was not observed in those with reduced LV function. Our results suggest that CR of multivessel disease in STEMI patients should be attempted more actively in these low-risk patients.

Reference

1. Organization, W.H. Cardiovascular diseases (cvds) fact sheet. *World Health Organization* **2017**.

2. Grüntzig, A.R.; Senning, Å.; Siegenthaler, W.E. Nonoperative dilatation of coronary-artery stenosis: Percutaneous transluminal coronary angioplasty. *New England Journal of Medicine* **1979**, *301*, 61-68.

3. Zahn, R.; Hamm, C.W.; Schneider, S.; Zeymer, U.; Nienaber, C.A.; Richardt, G.; Kelm, M.; Levenson, B.; Bonzel, T.; Tebbe, U. Incidence and predictors of target vessel revascularization and clinical event rates of the sirolimus-eluting coronary stent (results from the prospective multicenter german cypher stent registry). *The American journal of cardiology* **2005**, *95*, 1302-1308.

4. Mauri. Long-term clinical outcomes after drug-eluting and bare metal stenting in massachusetts (vol 118, pg 1817, 2008). *CIRCULATION* **2010**, *122*, E398-E398.

5. Lemos, P.A.; Serruys, P.W.; van Domburg, R.T.; Saia, F.; Arampatzis, C.A.; Hoye, A.; Degertekin, M.; Tanabe, K.; Daemen, J.; Liu, T.K. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the “real world” the r apamycin-e luting s tent e valuated a t r

otterdam c ardiology h ospital (research) registry. *Circulation* **2004**, *109*, 190-195.

6. Wald, D.S.; Morris, J.K.; Wald, N.J.; Chase, A.J.; Edwards, R.J.; Hughes, L.O.; Berry, C.; Oldroyd, K.G. Randomized trial of preventive angioplasty in myocardial infarction. *New England Journal of Medicine* **2013**, *369*, 1115-1123.

7. Engstrom, T.; Kelbaek, H.; Helqvist, S.; Hofsten, D.E.; Klovgaard, L.; Holmvang, L.; Jorgensen, E.; Pedersen, F.; Saunamaki, K.; Clemmensen, P., *et al.* Complete revascularisation versus treatment of the culprit lesion only in patients with st-segment elevation myocardial infarction and multivessel disease (danami-3-primulti): An open-label, randomised controlled trial. *Lancet* **2015**, *386*, 665-671.

8. Gershlick, A.H.; Khan, J.N.; Kelly, D.J.; Greenwood, J.P.; Sasikaran, T.; Curzen, N.; Blackman, D.J.; Dalby, M.; Fairbrother, K.L.; Banya, W., *et al.* Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for stemi and multivessel disease: The cvlprit trial. *Journal of the American College of Cardiology* **2015**, *65*, 963-972.

9. Smits, P.C.; Abdel-Wahab, M.; Neumann, F.J.; Boxma-de Klerk, B.M.; Lunde, K.; Schotborgh, C.E.; Piroth, Z.; Horak, D.; Wlodarczak, A.; Ong, P.J., *et al.*

Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med* **2017**, *376*, 1234-1244.

10. Komatsu, R.; Ueda, M.; Naruko, T.; Kojima, A.; Becker, A.E. Neointimal tissue response at sites of coronary stenting in humans: Macroscopic, histological, and immunohistochemical analyses. *Circulation* **1998**, *98*, 224-233.

11. Hoffmann, R.; Mintz, G.S.; Dussaillant, G.R.; Popma, J.J.; Pichard, A.D.; Satler, L.F.; Kent, K.M.; Griffin, J.; Leon, M.B. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation* **1996**, *94*, 1247-1254.

12. Mudra, H.; Regar, E.; Klauss, V.; Werner, F.; Henneke, K.-H.; Sbarouni, E.; Theisen, K. Serial follow-up after optimized ultrasound-guided deployment of palmaz-schatz stents: In-stent neointimal proliferation without significant reference segment response. *Circulation* **1997**, *95*, 363-370.

13. Kuroda, N.; Kobayashi, Y.; Nameki, M.; Kuriyama, N.; Kinoshita, T.; Okuno, T.; Yamamoto, Y.; Komiyama, N.; Masuda, Y. Intimal hyperplasia regression from 6 to 12 months after stenting. *American Journal of Cardiology* **2002**, *89*, 869-872.

14. Kimura, T.; Yokoi, H.; Nakagawa, Y.; Tamura, T.; Kaburagi, S.; Sawada, Y.; Sato, Y.; Yokoi, H.; Hamasaki, N.; Nosaka, H. Three-year follow-up after

implantation of metallic coronary-artery stents. *New England Journal of Medicine* **1996**, *334*, 561-567.

15. Stone, G.W.; Ellis, S.G.; Cox, D.A.; Hermiller, J.; O'Shaughnessy, C.; Mann, J.T.; Turco, M.; Caputo, R.; Bergin, P.; Greenberg, J., *et al.* A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* **2004**, *350*, 221-231.

16. Moses, J.W.; Leon, M.B.; Popma, J.J.; Fitzgerald, P.J.; Holmes, D.R.; O'Shaughnessy, C.; Caputo, R.P.; Kereiakes, D.J.; Williams, D.O.; Teirstein, P.S., *et al.* Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* **2003**, *349*, 1315-1323.

17. Park, K.W.; Kim, C.H.; Lee, H.Y.; Kang, H.J.; Koo, B.K.; Oh, B.H.; Park, Y.B.; Kim, H.S. Does "late catch-up" exist in drug-eluting stents: Insights from a serial quantitative coronary angiography analysis of sirolimus versus paclitaxel-eluting stents. *American heart journal* **2010**, *159*, 446-453.e443.

18. Byrne, R.A.; Iijima, R.; Mehilli, J.; Pinieck, S.; Bruskina, O.; Schomig, A.; Kastrati, A. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc Interv* **2009**, *2*, 291-299.

19. Wessely, R.; Kastrati, A.; Schomig, A. Late restenosis in patients receiving a polymer-coated sirolimus-eluting stent. *Annals of internal medicine* **2005**, *143*, 392-394.

20. Valgimigli, M.; Malagutti, P.; van Mieghem, C.A.; Vaina, S.; Ligthart, J.M.; Sianos, G.; Serruys, P.W. Persistence of neointimal growth 12 months after intervention and occurrence of delayed restenosis in patients with left main coronary artery disease treated with drug-eluting stents. *Journal of the American College of Cardiology* **2006**, *47*, 1491-1494.

21. Sheiban, I.; Chiribiri, A.; Galli, S.; Biondi-Zoccai, G.; Montorsi, P.; Beninati, S.; Fabbiocchi, F.; Moretti, C.; Omede, P.; Trabattoni, D., *et al.* Sirolimus-eluting stent implantation for bare-metal in-stent restenosis: Is there any evidence for a late catch-up phenomenon? *Journal of cardiovascular medicine (Hagerstown, Md.)* **2008**, *9*, 783-788.

22. Park, D.W.; Hong, M.K.; Mintz, G.S.; Lee, C.W.; Song, J.M.; Han, K.H.; Kang, D.H.; Cheong, S.S.; Song, J.K.; Kim, J.J., *et al.* Two-year follow-up of the quantitative angiographic and volumetric intravascular ultrasound analysis after nonpolymeric paclitaxel-eluting stent implantation: Late "catch-up" phenomenon from aspect study. *Journal of the American College of Cardiology* **2006**, *48*, 2432-2439.

23. Finn, A.V.; Nakazawa, G.; Joner, M.; Kolodgie, F.D.; Mont, E.K.; Gold, H.K.; Virmani, R. Vascular responses to drug eluting stents: Importance of delayed healing. *Arteriosclerosis, thrombosis, and vascular biology* **2007**, *27*, 1500-1510.

24. Buccheri, D.; Piraino, D.; Andolina, G.; Cortese, B. Understanding and managing in-stent restenosis: A review of clinical data, from pathogenesis to treatment. *J Thorac Dis* **2016**, *8*, E1150-E1162.

25. Choi, I.J.; Park, H.J.; Seo, S.M.; Koh, Y.S.; Lee, J.M.; Chang, K.; Chung, W.S.; Seung, K.B.; Kim, P.J. Predictors of early and late target lesion revascularization after drug-eluting stent implantation. *J Interv Cardiol* **2013**, *26*, 137-144.

26. Virmani, R.; Liistro, F.; Stankovic, G.; Di Mario, C.; Montorfano, M.; Farb, A.; Kolodgie, F.D.; Colombo, A. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. *Circulation* **2002**, *106*, 2649-2651.

27. Goto, I.; Itoh, T.; Kimura, T.; Fusazaki, T.; Matsui, H.; Sugawara, S.; Komuro, K.; Nakamura, M. Morphological and quantitative analysis of vascular wall and neointimal hyperplasia after coronary stenting: Comparison of bare-metal and sirolimus-eluting stents using optical coherence tomography. *Circ J* **2011**, *75*, 1633-1640.

28. Nicholls, S.J.; Tuzcu, E.M.; Sipahi, I.; Grasso, A.W.; Schoenhagen, P.; Hu, T.; Wolski, K.; Crowe, T.; Desai, M.Y.; Hazen, S.L., *et al.* Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* **2007**, *297*, 499-508.

29. Goto, K.; Zhao, Z.; Matsumura, M.; Dohi, T.; Kobayashi, N.; Kirtane, A.J.; Rabbani, L.E.; Collins, M.B.; Parikh, M.A.; Kodali, S.K. Mechanisms and patterns of intravascular ultrasound in-stent restenosis among bare metal stents and first-and second-generation drug-eluting stents. *The American journal of cardiology* **2015**, *116*, 1351-1357.

30. Lee, M.S.; Banka, G. In-stent restenosis. *Interv Cardiol Clin* **2016**, *5*, 211-220.

31. Kang, J.; Park, K.W.; Lee, M.S.; Zheng, C.; Han, J.K.; Yang, H.M.; Kang, H.J.; Koo, B.K.; Kim, H.S. The natural course of nonculprit coronary artery lesions; analysis by serial quantitative coronary angiography. *BMC Cardiovasc Disord* **2018**, *18*, 130.

32. Zheng, C.; Kang, J.; Park, K.W.; Han, J.K.; Yang, H.M.; Kang, H.J.; Koo, B.K.; Kim, H.S. The predictors of target lesion revascularization and rate of in-stent restenosis in the second-generation drug-eluting stent era. *J Interv Cardiol* **2019**, *2019*, 3270132.

33. Ibánez, B.; James, S.; Agewall, S.; Antunes, M.J.; Bucciarelli-Ducci, C.; Bueno, H.; Caforio, A.L.; Crea, F.; Goudevenos, J.A.; Halvorsen, S. 2017 esc guidelines for the management of acute myocardial infarction in patients presenting with st-segment elevation. *Revista espanola de cardiologia (English ed.)* **2017**, *70*, 1082.

34. Levine, G.N.; Bates, E.R.; Blankenship, J.C.; Bailey, S.R.; Bittl, J.A.; Cercek, B.; Chambers, C.E.; Ellis, S.G.; Guyton, R.A.; Hollenberg, S.M., *et al.* 2015 acc/aha/scai focused update on primary percutaneous coronary intervention for patients with st-elevation myocardial infarction: An update of the 2011 accf/aha/scai guideline for percutaneous coronary intervention and the 2013 accf/aha guideline for the management of st-elevation myocardial infarction. *Journal of the American College of Cardiology* **2016**, *67*, 1235-1250.

35. Ibanez, B.; James, S.; Agewall, S.; Antunes, M.J.; Bucciarelli-Ducci, C.; Bueno, H.; Caforio, A.L.P.; Crea, F.; Goudevenos, J.A.; Halvorsen, S., *et al.* 2017 esc guidelines for the management of acute myocardial infarction in patients presenting with st-segment elevation: The task force for the management of acute myocardial infarction in patients presenting with st-segment elevation of the european society of cardiology (esc). *Eur Heart J* **2018**, *39*, 119-177.

36. Smith, S.C., Jr.; Faxon, D.; Cascio, W.; Schaff, H.; Gardner, T.; Jacobs, A.; Nissen, S.; Stouffer, R. Prevention conference vi: Diabetes and cardiovascular disease: Writing group vi: Revascularization in diabetic patients. *Circulation* **2002**, *105*, e165-169.

37. Hannan, E.L.; Wu, C.; Walford, G.; Holmes, D.R.; Jones, R.H.; Sharma, S.; King, S.B., 3rd. Incomplete revascularization in the era of drug-eluting stents: Impact on adverse outcomes. *JACC Cardiovasc Interv* **2009**, *2*, 17-25.

38. Thiele, H.; Akin, I.; Sandri, M.; de Waha-Thiele, S.; Meyer-Saraei, R.; Fuernau, G.; Eitel, I.; Nordbeck, P.; Geisler, T.; Landmesser, U., *et al.* One-year outcomes after pci strategies in cardiogenic shock. *N Engl J Med* **2018**.

39. Burns, R.J.; Gibbons, R.J.; Yi, Q.; Roberts, R.S.; Miller, T.D.; Schaer, G.L.; Anderson, J.L.; Yusuf, S.; Investigators, C.S. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. *Journal of the American College of Cardiology* **2002**, *39*, 30-36.

40. Ng, V.G.; Lansky, A.J.; Meller, S.; Witzenbichler, B.; Guagliumi, G.; Peruga, J.Z.; Brodie, B.; Shah, R.; Mehran, R.; Stone, G.W. The prognostic importance of left ventricular function in patients with st-segment elevation myocardial infarction: The horizons-ami trial. *Eur Heart J Acute Cardiovasc Care* **2014**, *3*, 67-77.

41. Thiele, H.; Akin, I.; Sandri, M.; de Waha-Thiele, S.; Meyer-Saraei, R.; Fuernau, G.; Eitel, I.; Nordbeck, P.; Geisler, T.; Landmesser, U., *et al.* One-

year outcomes after pci strategies in cardiogenic shock. *N Engl J Med* **2018**, *379*, 1699-1710.

42. Kang, J.; Park, K.W.; Han, J.-K.; Yang, H.-M.; Kang, H.-J.; Koo, B.-K.; Kim, H.-S. Usefulness of the baseline syntax score to predict 3-year outcome after complete revascularization by percutaneous coronary intervention. *The American journal of cardiology* **2016**, *118*, 641-646.

43. Farooq, V.; Serruys, P.W.; Bourantas, C.V.; Zhang, Y.; Muramatsu, T.; Feldman, T.; Holmes, D.R.; Mack, M.; Morice, M.C.; Ståhle, E. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (syntax) trial validation of the residual syntax score. *Circulation* **2013**, *128*, 141-151.

44. Cutlip, D.E.; Windecker, S.; Mehran, R.; Boam, A.; Cohen, D.J.; van Es, G.A.; Steg, P.G.; Morel, M.A.; Mauri, L.; Vranckx, P., *et al.* Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* **2007**, *115*, 2344-2351.

45. Lang, R.M.; Badano, L.P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Flachskampf, F.A.; Foster, E.; Goldstein, S.A.; Kuznetsova, T., *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the american society of echocardiography and the

european association of cardiovascular imaging. *J Am Soc Echocardiogr* **2015**, *28*, 1-39 e14.

46. Gaffar, R.; Habib, B.; Filion, K.B.; Reynier, P.; Eisenberg, M.J. Optimal timing of complete revascularization in acute coronary syndrome: A systematic review and meta-analysis. *J Am Heart Assoc* **2017**, *6*.

47. Park, K.W.; Kang, J.; Kang, S.H.; Ahn, H.S.; Kang, H.J.; Koo, B.K.; Chae, I.H.; Youn, T.J.; Oh, B.H.; Park, Y.B., *et al.* The impact of residual coronary lesions on clinical outcomes after percutaneous coronary intervention: Residual syntax score after percutaneous coronary intervention in patients from the efficacy of xience/promus versus cypher in reducing late loss after stenting (excellent) registry. *American heart journal* **2014**, *167*, 384-392 e385.

48. Sutton, N.R.; Li, S.; Thomas, L.; Wang, T.Y.; de Lemos, J.A.; Enriquez, J.R.; Shah, R.U.; Fonarow, G.C. The association of left ventricular ejection fraction with clinical outcomes after myocardial infarction: Findings from the acute coronary treatment and intervention outcomes network (action) registry-get with the guidelines (gwtg) medicare-linked database. *American heart journal* **2016**, *178*, 65-73.

49. Delewi, R.; Zijlstra, F.; Piek, J.J. Left ventricular thrombus formation after acute myocardial infarction. *Heart* **2012**, *98*, 1743-1749.

50. Henkel, D.M.; Witt, B.J.; Gersh, B.J.; Jacobsen, S.J.; Weston, S.A.; Meverden, R.A.; Roger, V.L. Ventricular arrhythmias after acute myocardial infarction: A 20-year community study. *American heart journal* **2006**, *151*, 806-812.

51. Russo, A.M.; Stainback, R.F.; Bailey, S.R.; Epstein, A.E.; Heidenreich, P.A.; Jessup, M.; Kapa, S.; Kremers, M.S.; Lindsay, B.D.; Stevenson, L.W. Accf/hrs/aha/ase/hfsa/scai/scct/scmr 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: A report of the american college of cardiology foundation appropriate use criteria task force, heart rhythm society, american heart association, american society of echocardiography, heart failure society of america, society for cardiovascular angiography and interventions, society of cardiovascular computed tomography, and society for cardiovascular magnetic resonance. *Journal of the American College of Cardiology* **2013**, *61*, 1318-1368.

52. De Rosa, S.; Polimeni, A.; Sabatino, J.; Indolfi, C. Long-term outcomes of coronary artery bypass grafting versus stent-pci for unprotected left main disease: A meta-analysis. *BMC Cardiovasc Disord* **2017**, *17*, 240.

53. Allman, K.C.; Shaw, L.J.; Hachamovitch, R.; Udelson, J.E. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: A meta-analysis. *Journal of the American College of Cardiology* **2002**, *39*, 1151-1158.

54. Russo, A.M.; Stainback, R.F.; Bailey, S.R.; Epstein, A.E.; Heidenreich, P.A.; Jessup, M.; Kapa, S.; Kremers, M.S.; Lindsay, B.D.; Stevenson, L.W. Accf/hrs/aha/ase/hfsa/scai/scct/scmr 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: A report of the american college of cardiology foundation appropriate use criteria task force, heart rhythm society, american heart association, american society of echocardiography, heart failure society of america, society for cardiovascular angiography and interventions, society of cardiovascular computed tomography, and society for cardiovascular magnetic resonance. *Journal of the American College of Cardiology* **2013**, *61*, 1318-1368.

55. Shantsila, E.; Lip, G.Y. The risk of thromboembolism in heart failure: Does it merit anticoagulation therapy? *American Journal of Cardiology* **2011**, *107*, 558-560.

56. Shantsila, E.; Lip, G.Y. The risk of thromboembolism in heart failure: Does it merit anticoagulation therapy? *Am J Cardiol* **2011**, *107*, 558-560.

57. Mehta, S.R.; Wood, D.A.; Storey, R.F.; Mehran, R.; Bainey, K.R.; Nguyen, H.; Meeks, B.; Di Pasquale, G.; Lopez-Sendon, J.; Faxon, D.P., *et al.* Complete revascularization with multivessel pci for myocardial infarction. *N Engl J Med* **2019**, *381*, 1411-1421.

58. Stolfo, D.; Cinquetti, M.; Merlo, M.; Santangelo, S.; Barbati, G.; Alonge, M.; Vitrella, G.; Rakar, S.; Salvi, A.; Perkan, A. St-elevation myocardial infarction with reduced left ventricular ejection fraction: Insights into persisting left ventricular dysfunction. A ppci-registry analysis. *International journal of cardiology* **2016**, *215*, 340-345.

Table 1. Baseline demographic and clinical characteristics of the current study population and total patent population.

	Current study population (n=394)	Total parent population (n=3365)	P value
Age (years)	65.5±10.4	65.5±10.4	1.000
BMI (kg/m^2)	24.7±2.9	24.5±3.1	0.223
Male, n (%)	289 (73.4)	2383 (70.8)	0.668
Previous PCI, n (%)	48 (12.2)	612 (18.2)	0.011
Diabetes Mellitus, n (%)	133 (33.8)	1322 (39.3)	0.150
Hypertension, n (%)	275 (69.8)	2217 (65.9)	0.488
Dyslipidemia, n (%)	248 (62.9)	2294 (68.2)	0.350
CRF, n (%)	162 (41.1)	1323 (39.3)	0.651
Current Smoking, n (%)	104 (26.4)	778 (23.1)	0.258
FHx of CAD, n (%)	52 (13.2)	398 (11.8)	0.484
LV ejection fraction, (%)	60.0±8.6	57.4±10.4	<0.001
Clinical diagnosis			0.002
- Silent ischemia, n (%)	21 (5.3)	169 (5.0)	
- Stable angina, n (%)	232 (58.9)	1630 (48.4)	

- Unstable angina, n (%)	78 (19.8)	809 (24.0)	
- STEMI, n (%)	24 (6.1)	362 (10.8)	
- NSTEMI, n (%)	39 (9.9)	391 (11.6)	
Vessel disease			0.363
- 1 Vessel disease, n (%)	108 (27.4)	1051 (31.2)	
- 2 Vessel disease, n (%)	149 (37.8)	1143 (34.0)	
- 3 Vessel disease, n (%)	137 (34.8)	1171 (34.8)	

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CRF, chronic renal failure; FHx, family history; CAD, coronary artery disease; LV, left ventricle; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction.

Table 2. Baseline patients and lesions characteristics

Patient character (N=394)	Value
Age (years)	65.5±10.4
BMI (kg/m^2)	24.7±2.9
Male, n (%)	289 (73.4)
Previous PCI, n (%)	48 (12.2)
Previous CABG, n (%)	7 (1.8)
Previous MI, n (%)	29 (7.4)
Previous CHF, n (%)	3 (0.8)
Diabetes Mellitus, n (%)	133 (33.8)
- No control, n (%)	16 (4.1)
- Dietary, n (%)	6 (1.5)
- Oral, n (%)	102 (25.9)
- Insulin, n (%)	20 (5.1)
Hypertension, n (%)	275 (69.8)
CRF, n (%)	162 (41.1)
Dyslipidemia, n (%)	248 (62.9)
Smoking, (%)[*]	44.7 / 26.4 / 27.9
FHx of CAD, n (%)	52 (13.2)
LV Ejection fraction, (%)	60.0±8.6
Clinical diagnosis, (%)[†]	5.3 / 58.9 / 19.8 / 6.1 / 9.9
Number of Vessel disease, (%)[‡]	27.4 / 37.8 / 34.8
Laboratory tests	
WBC (10^9/L)	6.9±2.3

Hemoglobin (g/dl)	13.5±1.8
Creatinine(mg/dl)	1.08±0.66
GFR (ml/min)	69.3±24.8
CrCl (ml/min)	67.6±23.1
HbA1c (%)	6.79±1.21
Total cholesterol (mg/dl)	158±39
Triglyceride (mg/dl)	138±84
LDL (mg/dl)	97±36
HDL (mg/dl)	42±11
CRP(mg/dl)	0.40±1.13
Medication at discharge	
- Aspirin, n (%)	393 (99.7)
- Clopidogrel, n (%)	393 (99.7)
- DAPT, n (%)[#]	392 (99.5)
- Beta blocker, n (%)	279 (70.8)
- Statin, n (%)	368 (93.4)
- CCB, n (%)	86 (21.8)
- ACEI, n (%)	101 (25.6)
- ARB, n (%)	153 (38.8)
Medication at first follow-up	
- Aspirin, n (%)	391 (99.2)
- Clopidogrel, n (%)	385 (97.7)
- DAPT, n (%)[#]	382 (97.0)
- Beta blocker, n (%)	294 (74.6)
- Statin, n (%)	392 (99.5)
- CCB, n (%)	87 (22.1)

- ACEI, n (%)	44 (11.2)
- ARB, n (%)	158 (40.1)
Medication at second follow-up	
- Aspirin, n (%)	362 (91.9)
- Clopidogrel, n (%)	337 (85.5)
- DAPT, n (%)[#]	307 (77.9)
- Beta blocker, n (%)	281 (71.3)
- Statin, n (%)	388 (98.5)
- CCB, n (%)	77 (19.5)
- ACEI, n (%)	35 (8.9)
- ARB, n (%)	150 (38.1)
Lesion character (N=944)	
Stent/person (n)	2.4±1.6
Second generation DES (%)	100
Stent type	
- CoCr-EES (%)	25.8
- ZES (%)	32.8
- BES (%)	17.6
- PtCr-EES (%)	23.7
Lesion type	100
- A (%)	10.6
- B1 (%)	23.5
- B2 (%)	6.3
- C (%)	56.5
Type B2/C lesion (%)	62.7
Treated coronary location	
- LM (%)	8.8
- LAD (%)	37.7
- Proximal LAD (%)	22.7

- Mid LAD (%)	8.7
- Distal LAD (%)	1.9
- Diagonal 1 (%)	3.7
- Diagonal 2 (%)	0.7
- LCX (%)	24.8
- Proximal LCX (%)	11.2
- Distal LCX (%)	8.6
- Ramus (%)	2.0
- OM1 (%)	2.6
- OM2 (%)	0.3
- RCA (%)	28.5
- Proximal RCA (%)	17.4
- Mid RCA (%)	5.0
- Distal RCA (%)	4.7
- PDA (%)	0.7
- PL branch (%)	0.7
- SVG (%)	0.2
Bifurcation lesion (%)	35.3
Calcified lesion (moderate & severe) (%)	32.1
Tortuous lesion (%)	6.9
Angulation lesion (%)	6.4
Thrombus in lesion (%)	3.1
Ostial lesion (%)	19.4
Ulceration (%)	0.5
Aneurysm (%)	1.1
Previously treated lesion (%)	1.7
Stent diameter (mm)	3.03±0.44
Stent length (mm)	25.4±6.0
Pre-procedure MLD (mm)	0.73±0.50

Pre-procedure DS (%)	74.8±15.7
Reference Vessel Diameter (mm)	2.92±0.52
Lesion length (mm)	27.7±17.3
Post-procedure MLD (in-stent) (mm)	2.48±0.44
Post-procedure MLD (in-segment) (mm)	2.11±0.52
Post-procedure DS (in-stent) (%)	11.8±8.5
Post-procedure DS (in-segment) (%)	21.5±11.6
Restenosis pattern at first angiographic follow-up	
- 0-No Restenosis (%)	89.1
- 1-Focal articulation or Gap (%)	0.3
- 2-Focal in stent (stent body) (%)	3.1
- 3-Focal in stent (stent proximal edge) (%)	2.5
- 4-Focal in stent (stent distal edge) (%)	0.4
- 5-Multiple focal in segment (<5mm from edge) (%)	0.8
- 6-Diffuse in stent (%)	1.3
- 7-Diffuse proliferative (%)	0.1
- 8-Complete stent occlusion (%)	0.8
Restenosis pattern at second angiographic follow-up	
- 0-No Restenosis (%)	83.2
- 1-Focal articulation or Gap (%)	0.0
- 2-Focal in stent (stent body) (%)	1.6
- 3-Focal in stent (stent proximal edge) (%)	2.0
- 4-Focal in stent (stent distal edge) (%)	1.3
- 5-Multiple focal in segment (<5mm from edge) (%)	0.3
- 6-Diffuse in stent (%)	1.1
- 7-Diffuse proliferative (%)	0.2
- 8-Complete stent occlusion (%)	0.4

Abbreviations: BMI, body mass index; kg, kilogram; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; MI, Myocardial infarction; CHF, Congestive heart failure; CRF, chronic renal failure; FHx, family history; CAD, coronary artery disease; LV, left ventricle; WBC, white blood cell; GFR, glomerular filtration rate; CrCl, creatinine clearance; HbA1c, hemoglobin A1c; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; CRP, C-reactive protein; DAPT, dual antiplatelet therapy; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; DES, drug eluting stent; CoCr-EES, cobalt chromium everolimus-eluting stent; ZES, zotarolimus-eluting stent; BES, Biolimus- eluting stent: PtCr-EES, platinum chromium everolimus-eluting stent; LM, left main; LAD, left anterior descending; LCX, left circumflex; OM, obtuse marginal; RCA, right coronary artery; PDA, posterior descending artery; PL, posterolateral; SVG, saphenous vein graft; MLD, minimal lumen diameter; DS, diameter stenosis.

* Smoking: Never smoker / Current smoker / Ex-smoker

† Clinical diagnosis: Silent ischemia / Stable angina / Unstable angina / non ST-segment elevation myocardial infarction / ST-segment elevation myocardial infarction

‡ Vessel disease: 1 Vessel disease / 2 Vessel disease / 3 Vessel disease

DAPT: Combination of aspirin and Clopidogrel.

Table 3. Laboratory findings at the follow-up periods

	Baseline	1st follow-up	2nd follow-up
WBC (10^9/L)	6.9±2.3	6.0±1.5	5.9±1.5
Hemoglobin (g/dl)	13.5±1.8	13.2±1.8	13.4±1.6
Creatinine(mg/dl)	1.08±0.66	1.02±0.70	1.07±0.97
Total cholesterol (mg/dl)	158±39	129±27	129±25
Triglyceride (mg/dl)	138±84	115±51	113±54
LDL (mg/dl)	97±36	66±22	65±20
HDL (mg/dl)	42±11	44±12	47±12
CRP(mg/L)	0.40±1.13	0.14±0.43	0.23±0.85

Abbreviations: WBC, white blood cell; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; CRP, C-reactive protein

Table 4. Lesion characteristics and DS% progression rate according to types of DESs.

Clinical Factors	Overall (N=944)	CoCr-EES (N=244)	ZES (N=310)	BES (N=166)	PtCr-EES (N=224)	P
Reference vessel diameter (mm)	2.92±0.52	2.97±0.56	2.91±0.52	2.96±0.49	2.85±0.48	0.054
Lesion length (mm)	27.73±17.25	26.04±16.45	28.97±17.98	26.56±15.96	28.93±18.05	0.247
Pre-procedure MLD (mm)	0.73±0.50	0.76±0.53	0.65±0.51	0.87±0.44	0.71±0.46	0.755
Pre-procedure DS (%)	74.8±15.7	74.4±16.0	77.0±16.6	70.6±13.7	75.1±14.9	0.431
Acute gain (mm)	1.74±0.54	1.73±0.53	1.81±0.58	1.61±0.47	1.75±0.51	0.395
MLD (mm)						
- Post-procedure	2.48±0.44	2.49±0.47	2.47±0.43	2.47±0.42	2.48±0.44	0.852
- 1st follow-up	2.19±0.60	2.19±0.62	2.20±0.59	2.21±0.59	2.15±0.60	0.782

- 2nd follow-up	2.13±0.55	2.16±0.61	2.12±0.54	2.17±0.50	2.09±0.54	0.480
DS%						
- Post-procedure	11.8±8.5	13.0±8.4	10.5±8.8	12.6±9.0	11.7±7.4	0.460
- 1st follow-up	22.0±17.5	22.4±17.9	20.8±16.4	21.8±18.3	23.3±17.9	0.454
- 2nd follow-up	23.7±15.5	24.0±17.8	22.8±15.3	22.9±12.3	25.3±15.5	0.346
Initial ΔDS (%)	10.28±15.89	9.52±16.02	10.27±15.15	9.46±14.43	11.72±17.63	0.204
Delayed ΔDS (%)	4.59±11.60	4.81±14.08	3.73±9.87	5.27±11.49	5.10±11.11	0.486
Initial DS%/year	12.12±20.97	12.23±20.92	12.15±18.60	14.34±29.76	10.36±15.74	0.525
Delayed DS%/year	3.68±10.10	4.11±12.83	2.39±8.13	4.02±8.30	4.77±10.46	0.205

Abbreviations: CoCr-EES, cobalt chromium everolimus-eluting stent; ZES, zotarolimus-eluting stent; BES, Biolimus- eluting stent: PtCr-EES, platinum chromium everolimus-eluting stent; MLD, minimal lumen diameter; DS, diameter stenosis.

Table 5. Baseline characteristics according to the completeness of revascularization

	Total (N=1311)	CR (N=579)	IR (N=732)	P Value
Demographics				
Age (years)	63.3 ± 12.1	62.1 ± 11.8	64.2 ± 12.3	0.002
Male, n (%)	994 (75.8)	452 (78.1)	542 (74.0)	0.104
Body mass index (kg/m^2)	23.9 ± 3.0	24.0 ± 3.0	23.9 ± 3.0	0.568
Diabetes mellitus, n (%)	425 (32.4)	195 (33.7)	230 (31.4)	0.419
Hypertension, n (%)	686 (52.3)	281 (48.5)	405 (55.3)	0.017
Dyslipidemia, n (%)	607 (46.3)	263 (45.4)	344 (47.0)	0.609
Current smoking, n (%)	631 (48.1)	286 (49.4)	345 (47.1)	0.448
Previous Stroke, n (%)	87 (6.6)	36 (6.2)	51 (7.0)	0.667
Congestive heart failure, n (%)	20 (1.5)	8 (1.4)	12 (1.6)	0.880
Chronic renal failure, n (%)	484 (38.5)	194 (34.5)	290 (41.8)	0.009
Peripheral vascular disease, n (%)	14 (1.1)	9 (1.6)	5 (0.7)	0.210
Prior MI, n (%)	92 (7.0)	41 (7.1)	51 (7.0)	1.000
Prior PCI, n (%)	129 (9.8)	63 (10.9)	66 (9.0)	0.302
Family history of CAD, n (%)	74 (5.6)	30 (5.2)	44 (6.0)	0.599
Angiographic findings				
Angiographic disease extent				<0.001
- 2 vessel disease, n (%)	794 (60.6)	407 (70.3)	387 (52.9)	
- 3 vessel disease, n (%)	517 (39.4)	172 (29.7)	345 (47.1)	
Left main disease, n (%)	49 (3.7)	24 (4.1)	25 (3.4)	0.586
Bifurcation lesion, n (%)	489 (37.3)	246 (42.5)	243 (33.2)	0.001
Type B2/C lesion, n (%)	1114 (85.0)	499 (86.2)	615 (84.0)	0.311
Calcified lesion, n (%)	109 (8.3)	48 (8.3)	61 (8.3)	1.000

Tortuous lesion, n (%)	279 (21.3)	136 (23.5)	143 (19.5)	0.095
Thrombus in lesion, n (%)	454 (34.6)	206 (35.6)	248 (33.9)	0.560
Previously treated lesion, n (%)	106 (8.1)	46 (7.9)	60 (8.2)	0.949
Culprit lesion				0.782
- LM, n (%)	35 (2.7)	15 (2.6)	20 (2.7)	
- LAD, n (%)	618 (47.1)	281 (48.5)	337 (46.0)	
- LCX, n (%)	151 (11.5)	70 (12.1)	81 (11.1)	
- RCA, n (%)	505 (38.5)	212 (36.6)	293 (40.0)	
Stent diameter, mm	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	0.840
- Stent diameter <3mm, n (%)	505 (38.6)	223 (38.6)	282 (38.6)	1.000
Min. stent diameter, mm	3.0 ± 0.4	2.9 ± 0.4	3.0 ± 0.4	<0.001
- Min. stent diameter <3mm, n (%)	619 (47.4)	294 (51.0)	325 (44.6)	0.024
Total stent length, mm	43.5 ± 25.9	49.9 ± 28.8	38.5 ± 22.2	<0.001
-Total stent length ≥30mm, n (%)	801 (61.1)	398 (68.9)	403 (55.1)	<0.001
Total stent number	1.8 ± 1.0	2.1 ± 1.1	1.5 ± 0.8	<0.001
Staged PCI *(Among CR patients)***, n (%)**	NA	97 (16.8)	NA	NA
Contrast Volume, ml	273 ± 112	283 ± 108	264 ± 115	0.208
GP IIb/IIIa inhibitor usage, n (%)	143 (10.9)	59 (10.2)	84 (11.5)	0.514
IVUS usage, n (%)	396 (30.2)	201 (34.7)	195 (26.6)	0.002
SYNTAX score at baseline	18.2 ± 8.7	15.6 ± 8.0	20.2 ± 8.7	<0.001
SYNTAX score after PCI (residual)	5.6 ± 6.2	1.7 ± 2.4	8.7 ± 6.5	<0.001
Delta SYNTAX score	12.5 ± 7.5	13.8 ± 7.8	11.5 ± 7.2	<0.001
Laboratory data				
LV ejection fraction (%)	50.2 ± 11.5	52.1 ± 11.4	48.8 ± 11.4	<0.001
WBC (/ul)	10867± 3934	10715±4075	10984±3819	0.224
Hemoglobin (g/dL)	13.8 ± 2.1	13.9 ± 2.0	13.7 ± 2.2	0.083
Anemia (Hb<12g/dL) , n (%)	234 (18.0)	93 (16.3)	141 (19.4)	0.174
Creatinine (mg/dL)	1.1 ± 0.7	1.0 ± 0.5	1.1 ± 0.9	0.066

Total Cholesterol (mg/dL)	181.6 ± 45.4	181.2 ± 45.1	181.8 ± 45.6	0.808
Triglyceride (mg/dL)	129.8 ± 87.8	133.1 ± 87.3	127.2 ± 88.2	0.274
HDL-cholesterol (mg/dL)	42.0 ± 12.2	41.9 ± 12.0	42.2 ± 12.2	0.685
LDL-cholesterol (mg/dL)	115.9 ± 38.0	116.3 ± 39.5	115.5 ± 36.9	0.710
Discharge medication				
Aspirin, n (%)	1303 (99.4)	576 (99.5)	727 (99.3)	0.981
Clopidogrel, n (%)	1282 (97.8)	569 (98.3)	713 (97.4)	0.383
DAPT, n (%)	1280 (97.6)	568 (98.1)	712 (97.3)	0.423
Beta blocker, n (%)	1028 (78.4)	460 (79.4)	568 (77.6)	0.458
ACE inhibitor or ARBs, n (%)	1049 (80.0)	457 (78.9)	592 (80.9)	0.421
Statin, n (%)	1147 (87.5)	512 (88.4)	635 (86.7)	0.407
Calcium channel blocker, n (%)	106 (8.1)	51 (8.8)	55 (7.5)	0.452

Abbreviations: CR, complete revascularization; IR, incomplete revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention; CAD, coronary artery disease; LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; GP, glycoprotein; IVUS, intravascular ultrasound; LV, left ventricle; WBC, white blood cell; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; DAPT, dual antiplatelet agent; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

Table 6. 3-year Clinical Outcomes according to the completeness of revascularization

	Total	CR	IR	Unadjusted		Multivariable adjusted		PSM		IPTW	
	N=1311	N=579	N=732	HR (95%CI)	P Value	HR (95%CI)	P Value	HR (95%CI)	P Value	HR (95%CI)	P Value
POCO	262 (20.0%)	86 (14.9 %)	176 (24.0 %)	0.59 (0.46-0.77)	<0.001	0.63 (0.48-0.83)	0.001	0.61 (0.46-0.82)	0.001	0.63 (0.52-0.76)	<0.001
All cause death	130 (9.9%)	39 (6.7%)	91 (12.4 %)	0.53 (0.36-0.77)	0.001	0.65 (0.43-0.99)	0.042	0.62 (0.40-0.96)	0.031	0.65 (0.49-0.86)	0.003
Cardiac death	85 (6.5%)	20 (3.5%)	65 (8.9%)	0.38 (0.23-0.63)	<0.001	0.51 (0.29-0.89)	0.019	0.52 (0.28-0.94)	0.030	0.52 (0.36-0.75)	0.001
Non- Cardiac death	45 (3.4%)	19 (3.3%)	26 (3.6%)	0.90 (0.50-1.62)	0.899	0.89 (0.47-1.71)	0.729	0.77 (0.40-1.49)	0.771	0.87 (0.56-1.36)	0.548
MI	45 (3.4%)	13 (2.2%)	32 (4.4%)	0.50 (0.26-0.96)	0.037	0.59 (0.29-1.17)	0.130	0.51 (0.25-1.04)	0.062	0.58 (0.36-0.92)	0.022
TV MI	27 (2.1%)	10 (1.7%)	17 (2.3%)	0.74 (0.34-1.61)	0.445	1.01 (0.40-2.55)	0.990	0.87 (0.33-2.24)	0.765	0.95 (0.51-1.79)	0.878
Stent thrombosis	18 (1.4%)	8 (1.4%)	10 (1.4%)	1.00 (0.40-2.53)	0.999	1.63 (0.53-5.00)	0.391	1.29 (0.42-3.95)	0.655	1.49 (0.68-3.22)	0.317
Any revascularization	131 (10.0%)	49 (8.5%)	82 (11.2 %)	0.73 (0.51-1.04)	0.083	0.69 (0.48-0.99)	0.046	0.68 (0.46-1.00)	0.049	0.69 (0.54-0.89)	0.004
TLR	44 (3.4%)	24 (4.1%)	20 (2.7%)	1.50 (0.83-2.71)	0.183	1.52 (0.80-2.90)	0.206	1.53 (0.77-3.01)	0.223	1.53 (0.98-2.40)	0.062
Non-TLR	87 (6.6%)	25 (4.3%)	62 (8.5%)	0.49 (0.31-0.79)	0.003	0.46 (0.29-0.74)	0.001	0.45 (0.28-0.74)	0.001	0.46 (0.33-0.64)	<0.001

TLF	127 (9.7%)	42 (7.3%)	85 (11.6 %)	0.61 (0.42-0.89)	0.010	0.75 (0.50-1.12)	0.158	0.77 (0.50-1.19)	0.243	0.75 (0.56-0.99)	0.039
Any Bleeding	30 (2.3%)	10 (1.7%)	20 (2.7%)	0.62 (0.29-1.32)	0.217	0.65 (0.28-1.49)	0.304	0.53 (0.23-1.21)	0.132	0.65 (0.36-1.16)	0.141

Abbreviations: CR, complete revascularization; IR, incomplete revascularization; HR, hazard ratio; CI, confidence interval; PSM, propensity score matched analysis; IPTW, inverse probability weighting analysis; POCO, patient oriented composite outcome; MI, myocardial infarction; TVMI, target vessel myocardial infarction; TLR, target lesion revascularization; TLF, target lesion failure

Table 7. In-hospital events according to the completeness of revascularization

	Total N=1311	**CR N=579**	**IR N=732**	**P Value**
POCO-in hospital	41 (3.1%)	15 (2.6%)	26 (3.6%)	0.342
All cause death-in hospital	34 (2.6%)	12 (2.1%)	22 (3.0%)	0.382
Cardiac death-in hospital	28 (2.1%)	9 (1.6%)	19 (2.6%)	0.249
MI-in hospital	11 (0.8%)	6 (1.0%)	5 (0.7%)	0.551
TV MI-in hospital	8 (0.6%)	5 (0.9%)	3 (0.4%)	0.313
Any revascularization-in hospital	5 (0.4%)	3 (0.5%)	2 (0.3%)	0.660
TLR-in hospital	3 (0.2%)	3 (0.5%)	0 (0.0%)	0.086
TLF-in hospital	32 (2.4%)	12 (2.1%)	20 (2.7%)	0.476

Abbreviations: CR, complete revascularization; IR, incomplete revascularization; POCO, patient oriented composite outcome; MI, myocardial infarction; TVMI, target vessel myocardial infarction; TLR, target lesion revascularization; TLF, target lesion failure

Table 8. Baseline characteristics according to the residual SYNTAX score

	Total (N=1311)	rSS<8 (N=954)	rSS≥8 (N=357)	P Value
Demographics				
Age (years)	63.3 ± 12.1	62.2 ± 12.0	66.2 ± 12.1	<0.001
Male, n (%)	994 (75.8)	735 (77.0)	259 (72.5)	0.105
Body mass index (kg/m^2)	23.9 ± 3.0	24.0 ± 3.0	23.6 ± 3.0	0.048
Diabetes mellitus, n (%)	425 (32.4)	301 (31.6)	124 (34.7)	0.303
Hypertension, n (%)	686 (52.3)	468 (49.1)	218 (61.1)	<0.001
Dyslipidemia, n (%)	607 (46.3)	440 (46.1)	167 (46.8)	0.881
Current smoking, n (%)	631 (48.1)	488 (51.2)	143 (40.1)	<0.001
Previous Stroke, n (%)	87 (6.6)	61 (6.4)	26 (7.3)	0.652
Congestive heart failure, n (%)	20 (1.5)	12 (1.3)	8 (2.2)	0.299
Chronic renal failure, n (%)	484 (38.5)	318 (34.5)	166 (49.6)	<0.001
Peripheral vascular disease, n (%)	14 (1.1)	11 (1.2)	3 (0.8)	0.850
Prior MI, n (%)	92 (7.0)	57 (6.0)	35 (9.8)	0.022
Prior PCI, n (%)	129 (9.8)	90 (9.4)	39 (10.9)	0.482
Family history of CAD, n (%)	74 (5.6)	57 (6.0)	17 (4.8)	0.476
Angiographic findings				
Angiographic disease extent				<0.001
- 2 vessel disease, n (%)	794 (60.6)	668 (70.0)	126 (35.3)	
- 3 vessel disease, n (%)	517 (39.4)	286 (30.0)	231 (64.7)	
Left main disease, n (%)	49 (3.7)	32 (3.4)	17 (4.8)	0.302
Bifurcation lesion, n (%)	489 (37.3)	376 (39.4)	113 (31.7)	0.012
Type B2/C lesion, n (%)	1114 (85.0)	817 (85.6)	297 (83.2)	0.309
Calcified lesion, n (%)	109 (8.3)	81 (8.5)	28 (7.8)	0.791
Tortuous lesion, n (%)	279 (21.3)	205 (21.5)	74 (20.7)	0.823
Thrombus in lesion, n (%)	454 (34.6)	345 (36.2)	109 (30.5)	0.065

Previously treated lesion, n (%)	106 (8.1)	76 (8.0)	30 (8.4)	0.885
Culprit lesion				<0.001
- LM, n (%)	35 (2.7)	22 (2.3)	13 (3.6)	
- LAD, n (%)	618 (47.1)	493 (51.7)	125 (35.0)	
- LCX, n (%)	151 (11.5)	111 (11.6)	40 (11.2)	
- RCA, n (%)	505 (38.5)	326 (34.2)	179 (50.1)	
Stent diameter, mm	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	0.650
-Stent diameter <3mm, n (%)	505 (38.6)	364 (38.3)	141 (39.5)	0.734
Min. stent diameter, mm	3.0 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	0.620
- Min. stent diameter <3mm, n (%)	619 (47.4)	455 (47.9)	164 (46.1)	0.587
Total stent length, mm	43.5 ± 25.9	45.0 ± 26.4	39.6 ± 24.3	0.001
-Total stent length ≥30mm, n (%)	801 (61.1)	605 (63.5)	196 (54.9)	0.006
Total stent number	1.8 ± 1.0	1.8 ± 1.0	1.6 ± 0.8	<0.001
Contrast Volume, ml	273 ± 112	274 ± 110	270 ± 116	0.787
GP IIb/IIIa inhibitor usage, n (%)	143 (10.9)	109 (11.4)	34 (9.5)	0.377
IVUS usage, n (%)	396 (30.2)	302 (31.7)	94 (26.3)	0.072
SYNTAX score at baseline	18.2 ± 8.7	15.8 ± 7.4	24.5 ± 8.7	<0.001
SYNTAX score after PCI (residual)	5.6 ± 6.2	2.6 ± 2.4	13.7 ± 6.0	<0.001
Delta SYNTAX score	12.5 ± 7.5	13.2 ± 7.5	10.8 ± 7.4	<0.001
Laboratory data				
LV ejection fraction (%)	50.2 ± 11.5	51.1 ± 11.2	47.9 ± 12.0	<0.001
WBC (/ul)	10867±3934	10852±3990	10907±3783	0.824
Hemoglobin (g/dL)	13.8 ± 2.1	14.0 ± 2.1	13.4 ± 2.3	<0.001
Anemia (Hb<12g/dL), n (%)	234 (18.0)	146 (15.5)	88 (24.8)	<0.001
Creatinine (mg/dL)	1.1 ± 0.7	1.1 ± 0.8	1.1 ± 0.6	0.037
Total Cholesterol (mg/dL)	181.6 ± 45.4	183.3 ± 45.7	176.7 ± 44.2	0.021
Triglyceride (mg/dL)	129.8 ± 87.8	132.2 ± 90.7	123.0 ± 78.8	0.101
HDL-cholesterol (mg/dL)	42.0 ± 12.2	42.1 ± 11.7	41.9 ± 13.3	0.827

LDL-cholesterol (mg/dL)	115.9 ± 38.0	116.9 ± 38.2	112.9 ± 37.6	0.131
Discharge medication				
Aspirin, n (%)	1303 (99.4)	951 (99.7)	352 (98.6)	0.064
Clopidogrel, n (%)	1282 (97.8)	934 (97.9)	348 (97.5)	0.799
DAPT, n (%)	1280 (97.6)	933 (97.8)	347 (97.2)	0.666
Beta blocker, n (%)	1028 (78.4)	761 (79.8)	267 (74.8)	0.061
ACE inhibitor or ARBs, n (%)	1049 (80.0)	761 (79.8)	288 (80.7)	0.775
Statin, n (%)	1147 (87.5)	853 (89.4)	294 (82.4)	0.001
Calcium channel blocker, n (%)	106 (8.1)	76 (8.0)	30 (8.4)	0.885

Abbreviations: rSS, residual SYNTAX score; MI, myocardial infarction; PCI, percutaneous coronary intervention; CAD, coronary artery disease; LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; GP, glycoprotein; IVUS, intravascular ultrasound; LV, left ventricle; WBC, white blood cell; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; DAPT, dual antiplatelet agent; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

Table 9. 3-year Clinical Outcomes according to the residual SYNTAX score

	Total	rSS<8	rSS≥8	Unadjusted		Multivariable-adjusted	
	N=1311	N=954	N=357	HR (95%CI)	P Value	HR (95%CI)	P Value
POCO	262 (20.0%)	165 (17.3%)	97 (27.2%)	0.60 (0.46-0.77)	<0.001	0.72 (0.55-0.95)	0.020
All cause death	130 (9.9%)	70 (7.3%)	60 (16.8%)	0.42 (0.30-0.59)	<0.001	0.62 (0.41-0.92)	0.017
Cardiac death	85 (6.5%)	42 (4.4%)	43 (12.0%)	0.35 (0.23-0.54)	<0.001	0.58 (0.35-0.96)	0.034
MI	45 (3.4%)	33 (3.5%)	12 (3.4%)	1.00 (0.52-1.93)	0.994	1.41 (0.65-3.03)	0.386
TV MI	27 (2.1%)	20 (2.1%)	7 (2.0%)	1.06 (0.45-2.49)	0.904	1.89 (0.61-5.89)	0.273
Stent thrombosis	18 (1.4%)	13 (1.4%)	5 (1.4%)	0.95 (0.34-2.67)	0.923	1.80 (0.47-6.83)	0.390
Any revascularization	131 (10.0%)	93 (9.7%)	38 (10.6%)	0.86 (0.59-1.25)	0.431	0.82 (0.55-1.22)	0.336
TLR	44 (3.4%)	32 (3.4%)	12 (3.4%)	0.96 (0.49-1.86)	0.898	0.91 (0.45-1.86)	0.801
TLF	127 (9.7%)	74 (7.8%)	53 (14.8%)	0.50 (0.35-0.71)	<0.001	0.69 (0.46-1.04)	0.075
Any Bleeding	30 (2.3%)	15 (1.6%)	15 (4.2%)	0.36 (0.18-0.73)	0.005	0.41 (0.18-0.94)	0.034

Abbreviations: rSS, residual SYNTAX score; HR, hazard ratio; CI, confidence interval; PSM, propensity score matched analysis; IPTW, inverse probability weighting analysis; POCO, patient oriented composite outcome; MI, myocardial infarction; TVMI, target vessel myocardial infarction; TLR, target lesion revascularization; TLF, target lesion failure

Table 10. 3-year POCO and cardiac death according to the strategy of complete revascularization

	CR	One-time CR	Staged CR	Unadjusted		Multivariable adjusted	
	N=579	N=482	N=97	HR (95%CI)	P Value	HR (95%CI)	P Value
POCO	86 (14.9%)	75 (15.6%)	11 (11.3%)	0.70 (0.37-1.33)	0.277	0.63 (0.32-1.24)	0.180
Cardiac death	20 (3.5%)	18 (3.7%)	2 (2.1%)	0.54 (0.13-2.35)	0.414	0.19 (0.03-1.59)	0.124

Abbreviations: CR, complete revascularization; HR, hazard ratio; CI, confidence interval; POCO, patient oriented composite outcome

Table 11. Baseline characteristics according to the presence of DM

Total (N=1311)	DM group				Non-DM group				P Value‡
	Total(N=425)	CR(N=195)	IR(N=230)	P Value*	Total(N=886)	CR(N=384)	IR(N=502)	P Value†	
Demographics									
Age (years)	64.5± 10.9	62.8 ± 10.6	65.9 ± 11.0	0.004	62.7 ± 12.6	61.7 ± 12.4	63.4 ± 12.8	0.042	0.008
Male, n (%)	286 (67.3)	132 (67.7)	154 (67.0)	0.954	708 (79.9)	320 (83.3)	388 (77.3)	0.032	<0.001
Body mass index (kg/m^2)	24.0 ± 3.1	24.0 ± 3.3	24.0 ± 3.0	0.994	23.9 ± 2.9	23.9 ± 2.8	23.8 ± 3.0	0.494	0.401
Hypertension, n (%)	301 (70.8)	139 (71.3)	162 (70.4)	0.933	385 (43.5)	142 (37.0)	243 (48.4)	0.001	<0.001
Dyslipidemia, n (%)	215 (50.6)	96 (49.2)	119 (51.7)	0.676	392 (44.2)	167 (43.5)	225 (44.8)	0.744	0.036
Current smoking, n (%)	179 (42.1)	77 (39.5)	102 (44.3)	0.361	452 (51.0)	209 (54.4)	243 (48.4)	0.088	0.003
Previous Stroke, n (%)	10 (2.4)	5 (2.6)	5 (2.2)	1.000	10 (1.1)	3 (0.8)	7 (1.4)	0.592	0.146
Congestive heart failure, n (%)	200 (48.8)	86 (45.0)	114 (52.1)	0.186	284 (33.6)	108 (29.0)	176 (37.1)	0.016	<0.001
Chronic renal failure, n (%)	88 (20.7)	33 (16.9)	55 (23.9)	0.099	145 (16.4)	40 (10.4)	105 (20.9)	<0.001	0.065
LV ejection fraction<40%, n (%)	113 (26.8)	44 (22.9)	69 (30.0)	0.127	121 (13.8)	49 (13.0)	72 (14.5)	0.584	<0.001
Anemia (Hb<12g/dL), n (%)	7 (1.6)	5 (2.6)	2 (0.9)	0.324	7 (0.8)	4 (1.0)	3 (0.6)	0.721	0.260
Peripheral vascular disease, n (%)	46 (10.8)	20 (10.3)	26 (11.3)	0.849	41 (4.6)	16 (4.2)	25 (5.0)	0.682	<0.001
Prior MI, n (%)	35 (8.2)	14 (7.2)	21 (9.1)	0.581	57 (6.4)	27 (7.0)	30 (6.0)	0.620	0.280
Prior PCI, n (%)	49 (11.5)	30 (15.4)	19 (8.3)	0.032	80 (9.0)	33 (8.6)	47 (9.4)	0.781	0.186
Family history of CAD, n (%)	23 (5.4)	11 (5.6)	12 (5.2)	1.000	51 (5.8)	19 (4.9)	32 (6.4)	0.449	0.900
Angiographic findings									
Angiographic disease extent				0.001				<0.001	0.041

- **2 vessel disease, n (%)**	240 (56.5)	127 (65.1)	113 (49.1)		554 (62.5)	280 (72.9)	274 (54.6)		
- **3 vessel disease, n (%)**	185 (43.5)	68 (34.9)	117 (50.9)		332 (37.5)	104 (27.1)	228 (45.4)		
Left main disease, n (%)	16 (3.8)	6 (3.1)	10 (4.3)	0.667	33 (3.7)	18 (4.7)	15 (3.0)	0.252	1.000
Bifurcation lesion, n (%)	162 (38.1)	83 (42.6)	79 (34.3)	0.101	327 (36.9)	163 (42.4)	164 (32.7)	0.004	0.717
Type B2/C lesion, n (%)	363 (85.4)	169 (86.7)	194 (84.3)	0.591	751 (84.8)	330 (85.9)	421 (83.9)	0.449	0.822
Calcified lesion, n (%)	41 (9.6)	19 (9.7)	22 (9.6)	1.000	68 (7.7)	29 (7.6)	39 (7.8)	1.000	0.270
Tortuous lesion, n (%)	144 (33.9)	77 (39.5)	67 (29.1)	0.032	310 (35.0)	129 (33.6)	181 (36.1)	0.490	0.740
Thrombus in lesion, n (%)	94 (22.1)	51 (26.2)	43 (18.7)	0.084	185 (20.9)	85 (22.1)	100 (19.9)	0.471	0.660
Previously treated lesion, n (%)	36 (8.5)	17 (8.7)	19 (8.3)	1.000	70 (7.9)	29 (7.6)	41 (8.2)	0.833	0.806
Culprit lesion				0.474				0.282	0.192
- **LM, n (%)**	12 (2.8)	3 (1.5)	9 (3.9)		23 (2.6)	12 (3.1)	11 (2.2)		
- **LAD, n (%)**	187 (44.0)	86 (44.1)	101 (43.9)		431 (48.6)	195 (50.8)	236 (47.0)		
- **LCX, n (%)**	44 (10.4)	19 (9.7)	25 (10.9)		107 (12.1)	51 (13.3)	56 (11.2)		
- **RCA, n (%)**	182 (42.8)	87 (44.6)	95 (41.3)		323 (36.5)	125 (32.6)	198 (39.4)		
Stent diameter, mm	3.0 ± 0.4	3.0 ± 0.3	3.0 ± 0.4	0.869	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	0.036	<0.001
Stent diameter <3mm, n (%)	187 (44.3)	81 (42.0)	106 (46.3)	0.429	318 (35.9)	142 (37.0)	176 (35.1)	0.603	0.004
Min. stent diameter, mm	2.9 ± 0.4	2.9 ± 0.4	2.9 ± 0.4	0.049	3.0 ± 0.4	2.9 ± 0.4	3.0 ± 0.4	<0.001	<0.001
Min. stent diameter <3mm, n (%)	228 (54.2)	110 (57.0)	118 (51.8)	0.329	391 (44.2)	184 (48.0)	207 (41.3)	0.054	0.001
Total stent length, mm	45.4 ± 25.8	50.4 ± 27.5	41.2 ± 23.6	<0.001	42.6 ± 26.0	49.6 ± 29.5	37.3 ± 21.4	<0.001	0.069
Total stent length ≥30mm, n (%)	281 (66.3)	141 (72.7)	140 (60.9)	0.014	520 (58.7)	257 (66.9)	263 (52.4)	<0.001	0.010
Total stent number	1.8 ± 0.9	2.1 ± 1.0	1.6 ± 0.8	<0.001	1.7 ± 1.0	2.0 ± 1.1	1.5 ± 0.8	<0.001	0.202
Staged PCI *(Among CR patients)***, n (%)**	NA	31 (15.9)	NA	NA	NA	66 (17.2)	NA	NA	0.590

Second generation DES usage, n (%)	314 (73.9)	140 (71.8)	174 (75.7)	0.429	630 (71.1)	277 (72.1)	353 (70.3)	0.606	0.326
Contrast Volume, ml	265±118	269 ± 97	261 ± 138	0.735	278 ± 107	291 ± 114	266 ± 100	0.160	0.395
GP IIb/IIIa inhibitor usage, n (%)	42 (9.9)	22 (11.3)	20 (8.7)	0.467	101 (11.4)	37 (9.6)	64 (12.7)	0.181	0.465
IVUS usage, n (%)	123 (28.9)	60 (30.8)	63 (27.4)	0.511	273 (30.8)	141 (36.7)	132 (26.3)	0.001	0.531
Device success, n (%)	416 (97.9)	190 (97.4)	226 (98.3)	0.802	871 (98.3)	379 (98.7)	492 (98.0)	0.599	0.751
Lesion success, n (%)	413 (97.2)	187 (95.9)	226 (98.3)	0.241	868 (98.0)	377 (98.2)	491 (97.8)	0.885	0.484
Procedural success, n (%)	412 (96.9)	186 (95.4)	226 (98.3)	0.152	866 (97.7)	376 (97.9)	490 (97.6)	0.939	0.497
SYNTAX score at baseline	18.3 ± 8.9	15.9 ± 8.3	20.4 ± 8.9	<0.001	18.1 ± 8.6	15.4 ± 7.9	20.1 ± 8.6	<0.001	0.582
SYNTAX score after PCI (residual)	5.7 ± 5.9	1.9 ± 2.7	8.9 ± 6.0	<0.001	5.6 ± 6.3	1.7 ± 2.3	8.6 ± 6.7	<0.001	0.893
Delta SYNTAX score	12.7 ± 7.6	14.0 ± 7.6	11.6 ± 7.4	0.001	12.4 ± 7.5	13.7 ± 7.9	11.5 ± 7.0	<0.001	0.599
Laboratory data									
LV ejection fraction (%)	49.6 ± 11.9	51.0 ± 12.3	48.4 ± 11.5	0.036	50.5 ± 11.3	52.7 ± 10.9	49.0 ± 11.4	<0.001	0.200
WBC (/ul)	10779±4069	10772±4415	10785±3766	0.974	10909±3869	10686±3896	11076±3843	0.142	0.579
Hemoglobin (g/dL)	13.3 ± 2.3	13.4 ± 2.0	13.2 ± 2.5	0.356	14.1 ± 2.0	14.2 ± 2.0	14.0 ± 2.1	0.091	<0.001
Creatinine (mg/dL)	1.2 ± 0.9	1.1 ± 0.7	1.2 ± 1.0	0.254	1.0 ± 0.6	1.0 ± 0.4	1.1 ± 0.8	0.113	0.002
Total Cholesterol (mg/dL)	170.4 ± 44.7	167.5 ± 44.1	172.9 ± 45.1	0.225	186.9 ± 44.7	188.2 ± 44.0	185.9 ± 45.3	0.464	<0.001
Triglyceride (mg/dL)	131.1 ± 87.3	135.3 ± 80.6	127.6 ± 92.4	0.410	129.3 ± 88.1	132.0 ± 90.4	127.1 ± 86.3	0.448	0.750
HDL-cholesterol (mg/dL)	40.7 ± 11.2	40.4 ± 11.5	41.0 ± 11.1	0.624	42.7 ± 12.5	42.6 ± 12.3	42.7 ± 12.7	0.875	0.009
LDL-cholesterol (mg/dL)	107.0 ± 36.7	105.1 ± 36.8	108.5 ± 36.7	0.394	120.1 ± 38.0	121.7 ± 39.6	118.8 ± 36.6	0.312	<0.001
Discharge medication									

Aspirin, n (%)	423 (99.5)	195(100.0)	228 (99.1)	0.552	880 (99.3)	381 (99.2)	499 (99.4)	1.000	0.944
Clopidogrel, n (%)	416 (97.9)	192 (98.5)	224 (97.4)	0.670	866 (97.7)	377 (98.2)	489 (97.4)	0.594	1.000
DAPT, n (%)	416 (97.9)	192 (98.5)	224 (97.4)	0.670	864 (97.5)	376 (97.9)	488 (97.2)	0.652	0.831
Beta blocker, n (%)	336 (79.1)	152 (77.9)	184 (80.0)	0.690	692 (78.1)	308 (80.2)	384 (76.5)	0.214	0.748
ACE inhibitor or ARBs, n (%)	345 (81.2)	155 (79.5)	190 (82.6)	0.487	704 (79.5)	302 (78.6)	402 (80.1)	0.660	0.513
Statin, n (%)	370 (87.1)	174 (89.2)	196 (85.2)	0.279	777 (87.7)	338 (88.0)	439 (87.5)	0.878	0.812
Calcium channel blocker, n (%)	38 (8.9)	21 (10.8)	17 (7.4)	0.296	68 (7.7)	30 (7.8)	38 (7.6)	0.994	0.497

Abbreviations: CR, complete revascularization; IR, incomplete revascularization; DM, diabetes mellitus; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; CAD, coronary artery disease; LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; DES, drug-eluting stent; GP, glycoprotein; IVUS, intravascular ultrasound; WBC, white blood cell; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; DAPT, dual antiplatelet agent; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

Table 12. 3-year Clinical Outcomes according to the presence of DM

	Total	CR	IR	Unadjusted		Multivariable-adjusted	
				HR (95%CI)	P Value	HR (95%CI)	P Value
DM	*N=425*	*N=195*	*N=230*				
POCO	100 (23.5%)	41 (21.0%)	59 (25.7%)	0.82 (0.55-1.22)	0.322	0.86 (0.55-1.35)	0.519
All cause death	55 (12.9%)	21 (10.8%)	34 (14.8%)	0.72 (0.42-1.24)	0.237	0.77 (0.40-1.46)	0.419
Cardiac death	35 (8.2%)	11 (5.6%)	24 (10.4%)	0.54 (0.26-1.10)	0.087	0.52 (0.21-1.27)	0.151
MI	16 (3.8%)	9 (4.6%)	7 (3.0%)	1.52 (0.57-4.09)	0.405	1.69 (0.56-5.09)	0.351
TV MI	9 (2.1%)	6 (3.1%)	3 (1.3%)	2.36 (0.59-9.44)	0.224	3.02 (0.56-16.40)	0.201
Stent thrombosis	7 (1.6%)	5 (2.6%)	2 (0.9%)	2.94 (0.57-15.16)	0.197	2.30 (0.39-13.52)	0.357
Any revascularization	49 (11.5%)	22 (11.3%)	27 (11.7%)	0.97 (0.55-1.70)	0.902	0.99 (0.54-1.82)	0.981
TLR	23 (5.4%)	12 (6.2%)	11 (4.8%)	1.30 (0.57-2.94)	0.535	1.78 (0.73-4.36)	0.205
TLF	54 (12.7%)	22 (11.3%)	32 (13.9%)	0.81 (0.47-1.40)	0.453	1.00 (0.54-1.87)	0.994

Any Bleeding	7 (1.6%)	1 (0.5%)	6 (2.6%)	0.19 (0.02-1.60)	0.127	0.45 (0.04-4.93)	0.515
Non-DM	*N=886*	*N=384*	*N=502*				
POCO	162 (18.3%)	45 (11.7%)	117 (23.3%)	0.47 (0.34-0.67)	<0.001	0.52 (0.35-0.76)	0.001
All cause death	75 (8.5%)	18 (4.7%)	57 (11.4%)	0.40 (0.24-0.68)	0.001	0.54 (0.29-0.99)	0.048
Cardiac death	50 (5.6%)	9 (2.3%)	41 (8.2%)	0.28 (0.14-0.58)	0.001	0.45 (0.20-1.02)	0.056
MI	29 (3.3%)	4 (1.0%)	25 (5.0%)	0.20 (0.07-0.58)	0.003	0.20 (0.06-0.69)	0.011
TV MI	18 (2.0%)	4 (1.0%)	14 (2.8%)	0.37 (0.12-1.12)	0.078	0.37 (0.08-1.83)	0.224
Stent thrombosis	11 (1.2%)	3 (0.8%)	8 (1.6%)	0.48 (0.13-1.82)	0.281	1.00 (0.16-6.13)	0.999
Any revascularization	82 (9.3%)	27 (7.0%)	55 (11.0%)	0.61 (0.38-0.96)	0.034	0.55 (0.34-0.91)	0.019
TLR	21 (2.4%)	12 (3.1%)	9 (1.8%)	1.70 (0.72-4.03)	0.229	2.43 (0.84-7.03)	0.101
TLF	73 (8.2%)	20 (5.2%)	53 (10.6%)	0.48 (0.29-0.80)	0.005	0.71 (0.39-1.30)	0.266
Any Bleeding	23 (2.6%)	9 (2.3%)	14 (2.8%)	0.83 (0.36-1.91)	0.656	0.83 (0.33-2.12)	0.699

Abbreviations: CR, complete revascularization; IR, incomplete revascularization; HR, hazard ratio; CI, confidence interval; PSM, propensity score matched analysis; IPTW, inverse probability weighting analysis; DM, diabetes mellitus; POCO, patient oriented composite outcome; MI, myocardial infarction; TVMI, target vessel myocardial infarction; TLR, target lesion revascularization; TLF, target lesion failure

Table 13. Baseline characteristics according to the baseline LV function

Total (N=1311)	Reduced LV function group				Preserved LV function group				P Value‡
	Total (N=233)	CR (N=73)	IR (N=160)	P Value*	Total (N=1078)	CR (N=506)	IR (N=572)	P Value†	
Demographics									
Age (years)	66.6 ± 11.8	65.3 ± 11.4	67.2 ± 11.9	0.251	62.5 ± 12.1	61.6 ± 11.8	63.3 ± 12.3	0.018	<0.001
Male, n (%)	178 (76.4)	60 (82.2)	118 (73.8)	0.215	816 (75.7)	392 (77.5)	424 (74.1)	0.228	0.887
Body mass index (kg/m^2)	23.1 ± 3.4	23.1 ± 3.8	23.2 ± 3.2	0.942	24.1 ± 2.9	24.1 ± 2.9	24.1 ± 2.9	0.898	<0.001
Diabetes mellitus, n (%)	88 (37.8)	33 (45.2)	55 (34.4)	0.151	337 (31.3)	162 (32.0)	175 (30.6)	0.662	0.065
Hypertension, n (%)	134 (57.5)	41 (56.2)	93 (58.1)	0.890	552 (51.2)	240 (47.4)	312 (54.5)	0.023	0.094
Dyslipidemia, n (%)	105 (45.1)	30 (41.1)	75 (46.9)	0.496	502 (46.6)	233 (46.0)	269 (47.0)	0.794	0.730
Current smoking, n (%)	111 (47.6)	39 (53.4)	72 (45.0)	0.292	520 (48.2)	247 (48.8)	273 (47.7)	0.768	0.926
Previous Stroke, n (%)	14 (6.0)	6 (8.2)	8 (5.0)	0.508	6 (0.6)	2 (0.4)	4 (0.7)	0.795	<0.001
Congestive heart failure, n (%)	124 (56.9)	38 (52.8)	86 (58.9)	0.475	360 (34.7)	156 (31.8)	204 (37.3)	0.072	<0.001
Chronic renal failure, n (%)	62 (27.0)	19 (26.4)	43 (27.2)	1.000	172 (16.1)	74 (14.9)	98 (17.2)	0.335	<0.001
Anemia (Hb<12g/dL), n (%)	4 (1.7)	3 (4.1)	1 (0.6)	0.175	10 (0.9)	6 (1.2)	4 (0.7)	0.608	0.477
Peripheral vascular disease, n (%)	17 (7.3)	5 (6.8)	12 (7.5)	1.000	70 (6.5)	31 (6.1)	39 (6.8)	0.737	0.763
Prior MI, n (%)	17 (7.3)	5 (6.8)	12 (7.5)	1.000	75 (7.0)	36 (7.1)	39 (6.8)	0.943	0.966
Prior PCI, n (%)	28 (12.0)	14 (19.2)	14 (8.8)	0.040	101 (9.4)	49 (9.7)	52 (9.1)	0.819	0.267
Family history of CAD, n (%)	9 (3.9)	1 (1.4)	8 (5.0)	0.333	65 (6.0)	29 (5.7)	36 (6.3)	0.796	0.253
Angiographic findings									
Angiographic disease extent				0.003				<0.001	<0.001

- **2 vessel disease, n (%)**	109 (46.8)	45 (61.6)	64 (40.0)		685 (63.5)	362 (71.5)	323 (56.5)		
- **3 vessel disease, n (%)**	124 (53.2)	28 (38.4)	96 (60.0)		393 (36.5)	144 (28.5)	249 (43.5)		
Left main disease, n (%)	13 (5.6)	3 (4.1)	10 (6.2)	0.724	36 (3.3)	21 (4.2)	15 (2.6)	0.221	0.149
Bifurcation lesion, n (%)	93 (39.9)	32 (43.8)	61 (38.1)	0.496	396 (36.7)	214 (42.3)	182 (31.8)	<0.001	0.404
Type B2/C lesion, n (%)	196 (84.1)	60 (82.2)	136 (85.0)	0.726	918 (85.2)	439 (86.8)	479 (83.7)	0.192	0.764
Calcified lesion, n (%)	33 (14.2)	9 (12.3)	24 (15.0)	0.734	76 (7.1)	39 (7.7)	37 (6.5)	0.500	0.001
Tortuous lesion, n (%)	74 (31.8)	23 (31.5)	51 (31.9)	1.000	380 (35.3)	183 (36.2)	197 (34.4)	0.598	0.347
Thrombus in lesion, n (%)	56 (24.0)	17 (23.3)	39 (24.4)	0.988	223 (20.7)	119 (23.5)	104 (18.2)	0.037	0.297
Previously treated lesion, n (%)	24 (10.3)	8 (11.0)	16 (10.0)	1.000	82 (7.6)	38 (7.5)	44 (7.7)	1.000	0.217
Culprit lesion, n (%)				0.850				0.500	0.001
- **LM, n (%)**	10 (4.3)	2 (2.7)	8 (5.0)		25 (2.3)	13 (2.6)	12 (2.1)		
- **LAD, n (%)**	134 (57.5)	44 (60.3)	90 (56.2)		484 (44.9)	237 (46.8)	247 (43.2)		
- **LCX, n (%)**	24 (10.3)	7 (9.6)	17 (10.6)		127 (11.8)	63 (12.5)	64 (11.2)		
- **RCA, n (%)**	65 (27.9)	20 (27.4)	45 (28.1)		440 (40.8)	192 (37.9)	248 (43.4)		
Stent diameter, mm	3.0 ± 0.4	3.0 ± 0.3	3.0 ± 0.4	0.371	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	0.048	0.001
Stent diameter <3mm, n (%)	107 (45.9)	34 (46.6)	73 (45.6)	1.000	398 (37.0)	189 (37.5)	209 (36.6)	0.810	0.014
Min. stent diameter, mm	2.9 ± 0.4	2.8 ± 0.3	2.9 ± 0.4	0.009	3.0 ± 0.4	2.9 ± 0.4	3.0 ± 0.4	<0.001	0.012
Min. stent diameter <3mm, n (%)	119 (51.3)	43 (58.9)	76 (47.8)	0.153	500 (46.6)	251 (49.9)	249 (43.7)	0.048	0.220
Total stent length, mm	45.1 ± 28.0	52.6 ± 30.4	41.7 ± 26.3	0.006	43.2 ± 25.5	49.5 ± 28.6	37.6 ± 20.8	<0.001	0.296
Total stent length ≥30mm, n (%)	153 (65.7)	54 (74.0)	99 (61.9)	0.098	648 (60.2)	344 (68.1)	304 (53.1)	<0.001	0.137
Total stent number	1.8 ± 1.0	2.2 ± 1.1	1.6 ± 0.9	<0.001	1.8 ± 0.9	2.0 ± 1.1	1.5 ± 0.7	<0.001	0.508

Staged PCI *(Among CR patients)***, n (%)**		11 (15.1%)	NA	NA		86 (17.0)	NA	NA	0.725
Second generation DES usage, n (%)	166 (71.2)	51 (69.9)	115 (71.9)	0.874	778 (72.2)	366 (72.3)	412 (72.0)	0.966	0.838
Contrast Volume, ml	284.2 ± 113.0	298.3 ± 103.7	276.2 ± 118.9	0.513	269.9 ± 111.2	279.5 ± 108.6	259.0 ± 113.6	0.223	0.424
GP IIb/IIIa inhibitor usage, n (%)	25 (10.7)	7 (9.6)	18 (11.2)	0.879	118 (10.9)	52 (10.3)	66 (11.5)	0.572	1.000
IVUS usage, n (%)	69 (29.6)	21 (28.8)	48 (30.0)	0.971	327 (30.3)	180 (35.6)	147 (25.7)	0.001	0.890
Device success, n (%)	226 (97.0)	71 (97.3)	155 (96.9)	1.000	1061 (98.4)	498 (98.4)	563 (98.4)	1.000	0.228
Lesion success, n (%)	224 (96.1)	69 (94.5)	155 (96.9)	0.618	1057 (98.1)	495 (97.8)	562 (98.3)	0.777	0.126
Procedural success, n (%)	223 (95.7)	68 (93.2)	155 (96.9)	0.341	1055 (97.9)	494 (97.6)	561 (98.1)	0.766	0.094
SYNTAX score at baseline	22.3 ± 9.5	19.1 ± 9.7	23.7 ± 9.1	0.001	17.3 ± 8.3	15.1 ± 7.6	19.2 ± 8.3	<0.001	<0.001
SYNTAX score after PCI (residual)	8.0 ± 7.6	2.3 ± 3.0	10.6 ± 7.6	<0.001	5.1 ± 5.7	1.7 ± 2.3	8.2 ± 6.0	<0.001	<0.001
Delta SYNTAX score	14.3 ± 7.9	16.8 ± 8.8	13.1 ± 7.2	0.002	12.1 ± 7.4	13.4 ± 7.5	11.0 ± 7.1	<0.001	<0.001
Laboratory data									
LV ejection fraction (%)	31.8 ± 5.6	31.9 ± 5.5	31.7 ± 5.7	0.827	53.8 ± 8.6	55.0 ± 8.8	52.8 ± 8.3	<0.001	<0.001
WBC (/ul)	11002 ± 4125	10984 ± 4614	11010 ± 3896	0.965	10837 ± 3893	10676 ± 3994	10977 ± 3801	0.210	0.565
Hemoglobin (g/dL)	13.2 ± 2.3	13.2 ± 2.1	13.3 ± 2.3	0.815	13.9 ± 2.1	14.0 ± 2.0	13.8 ± 2.2	0.144	<0.001
Creatinine (mg/dL)	1.3 ± 1.1	1.3 ± 1.0	1.3 ± 1.1	0.971	1.1 ± 0.6	1.0 ± 0.4	1.1 ± 0.8	0.091	0.004
Total Cholesterol (mg/dL)	172.9 ± 45.0	169.3 ± 44.5	174.4 ± 45.2	0.440	183.4 ± 45.3	182.8 ± 45.0	183.8 ± 45.5	0.722	0.002
Triglyceride (mg/dL)	111.0 ± 70.8	116.9 ± 79.9	108.5 ± 66.7	0.475	133.4 ± 90.2	135.0 ± 88.0	131.9 ± 92.2	0.600	<0.001
HDL-cholesterol (mg/dL)	41.2 ± 10.9	39.7 ± 10.5	41.9 ± 11.1	0.221	42.2 ± 12.4	42.1 ± 12.2	42.2 ± 12.5	0.900	0.305
LDL-cholesterol (mg/dL)	111.5 ± 38.9	113.1 ± 36.0	110.8 ± 40.3	0.731	116.7 ± 37.8	116.7 ± 39.9	116.6 ± 36.0	0.963	0.107

Discharge medication									
Aspirin, n (%)	231 (99.1)	72 (98.6)	159 (99.4)	1.000	1072 (99.4)	504 (99.6)	568 (99.3)	0.795	0.942
Clopidogrel, n (%)	224 (96.1)	70 (95.9)	154 (96.2)	1.000	1058 (98.1)	499 (98.6)	559 (97.7)	0.393	0.100
DAPT, n (%)	224 (96.1)	70 (95.9)	154 (96.2)	1.000	1056 (98.0)	498 (98.4)	558 (97.6)	0.430	0.155
Beta blocker, n (%)	147 (63.1)	48 (65.8)	99 (61.9)	0.673	881 (81.7)	412 (81.4)	469 (82.0)	0.871	<0.001
ACE inhibitor or ARBs, n (%)	176 (75.5)	52 (71.2)	124 (77.5)	0.385	873 (81.0)	405 (80.0)	468 (81.8)	0.506	0.073
Statin, n (%)	185 (79.4)	59 (80.8)	126 (78.8)	0.851	962 (89.2)	453 (89.5)	509 (89.0)	0.852	<0.001
Calcium channel blocker, n (%)	15 (6.4)	5 (6.8)	10 (6.2)	1.000	91 (8.4)	46 (9.1)	45 (7.9)	0.541	0.376

Abbreviations: CR, complete revascularization; IR, incomplete revascularization; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; CAD, coronary artery disease; LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; DES, drug-eluting stent; GP, glycoprotein; IVUS, intravascular ultrasound; WBC, white blood cell; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; DAPT, dual antiplatelet agent; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker

Table 14. 3-year Clinical Outcomes according to the LV function

	Total	CR	IR	Unadjusted		Multivariable-adjusted	
				HR (95%CI)	P Value	HR (95%CI)	P Value
Reduced LV function	*N=233*	*N=73*	*N=160*				
POCO	70 (30.0%)	19 (26.0%)	51 (31.9%)	0.82 (0.49-1.39)	0.464	0.80 (0.43-1.46)	0.461
All cause death	48 (20.6%)	15 (20.5%)	33 (20.6%)	1.01 (0.55-1.86)	0.968	1.04 (0.50-2.14)	0.916
Cardiac death	39 (16.7%)	11 (15.1%)	28 (17.5%)	0.87 (0.43-1.75)	0.702	0.79 (0.35-1.82)	0.583
MI	13 (5.6%)	3 (4.1%)	10 (6.3%)	0.66 (0.18-2.39)	0.526	1.04 (0.24-4.51)	0.954
TV MI	10 (4.3%)	3 (4.1%)	7 (4.4%)	0.94 (0.24-3.62)	0.924	2.27 (0.38-13.79)	0.372
Stent thrombosis	6 (2.6%)	3 (4.1%)	3 (1.9%)	2.18 (0.44-10.81)	0.340	3.93 (0.49-31.63)	0.199
Any revascularization	23 (9.9%)	6 (8.2%)	17 (10.6%)	0.79 (0.31-2.00)	0.613	0.60 (0.21-1.76)	0.354
TLR	8 (3.4%)	4 (5.5%)	4 (2.5%)	2.26 (0.57-9.04)	0.249	3.06 (0.61-15.45)	0.176
TLF	47 (20.2%)	14 (19.2%)	33 (20.6%)	0.94 (0.50-1.76)	0.847	1.02 (0.49-2.09)	0.968

Any Bleeding	3 (1.3%)	0 (0.0%)	3 (1.9%)	-	0.497	-	0.977
Preserved LV function	*N=1078*	*N=506*	*N=572*				
POCO	192 (17.8%)	67 (13.2%)	125 (21.9%)	0.58 (0.43-0.78)	<0.001	0.59 (0.43-0.82)	0.002
All cause death	82 (7.6%)	24 (4.7%)	58 (10.1%)	0.46 (0.29-0.74)	0.001	0.52 (0.30-0.89)	0.017
Cardiac death	46 (4.3%)	9 (1.8%)	37 (6.5%)	0.27 (0.13-0.56)	<0.001	0.34 (0.14-0.80)	0.013
MI	32 (3.0%)	10 (2.0%)	22 (3.8%)	0.50 (0.24-1.06)	0.072	0.53 (0.23-1.20)	0.128
TV MI	17 (1.6%)	7 (1.4%)	10 (1.7%)	0.79 (0.30-2.07)	0.629	0.85 (0.25-2.91)	0.801
Stent thrombosis	12 (1.1%)	5 (1.0%)	7 (1.2%)	0.80 (0.25-2.52)	0.701	1.26 (0.26-6.08)	0.770
Any revascularization	108 (10.0%)	43 (8.5%)	65 (11.4%)	0.73 (0.49-1.07)	0.102	0.69 (0.45-1.03)	0.071
TLR	36 (3.3%)	20 (4.0%)	16 (2.8%)	1.40 (0.72-2.70)	0.318	1.68 (0.79-3.55)	0.176
TLF	80 (7.4%)	28 (5.5%)	52 (9.1%)	0.60 (0.38-0.95)	0.029	0.75 (0.45-1.28)	0.296
Any Bleeding	27 (2.5%)	10 (2.0%)	17 (3.0%)	0.65 (0.30-1.43)	0.286	0.86 (0.35-2.09)	0.735

Abbreviations: CR, complete revascularization; IR, incomplete revascularization; HR, hazard ratio; CI, confidence interval; PSM, propensity score matched analysis; IPTW, inverse probability weighting analysis; LV, left ventricle; POCO, patient oriented composite outcome; MI, myocardial infarction; TVMI, target vessel myocardial infarction; TLR, target lesion revascularization; TLF, target lesion failure

Figure 1. Flowchart of the study

From July 2008 to March 2013, a total of 394 patients with 944 lesions were enrolled in the study. The mean follow-up duration from baseline to the first and second angiography were 325±90 days and 772 ±133 days, respectively.

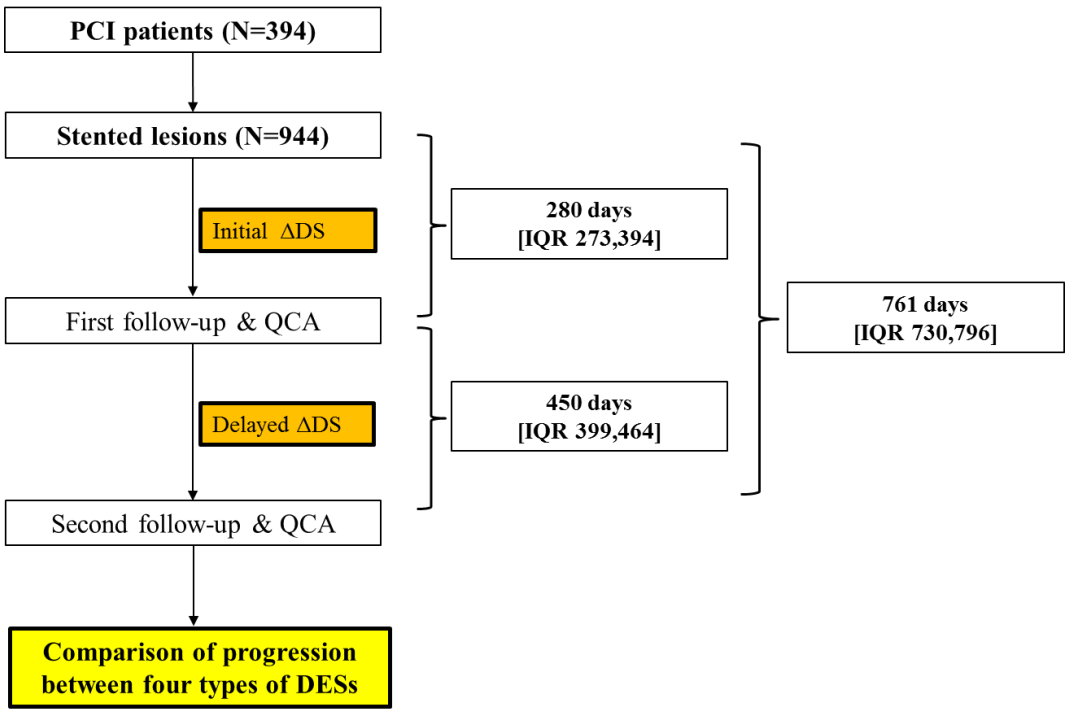


Figure 2. Incidence of target lesion revascularization

TLR was performed for 58 lesions (6.1%) in 40 patients (10.2%) at the first angiographic follow-up period, and for 23 lesions (2.4%) in 19 patients (4.8%) at the second follow-up period.

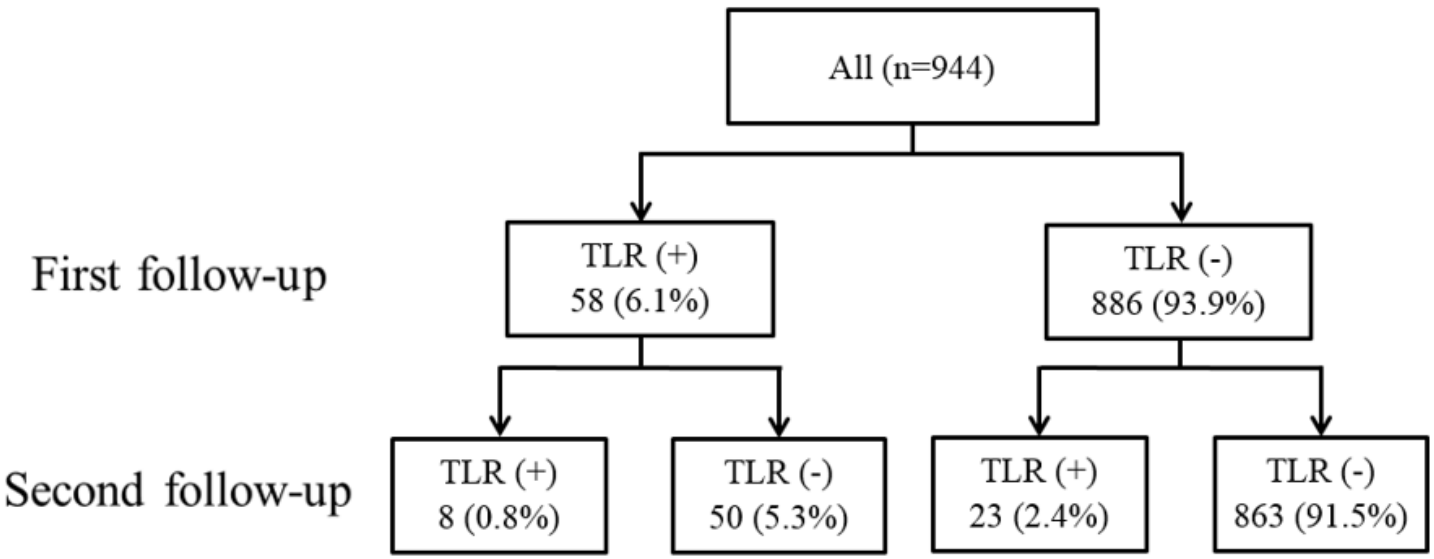


Figure 3. Cumulative probability curve of MLD (post procedure, first angiographic follow-up, second angiographic follow-up)

The MLD showed no significant difference between the four DES groups at all the different points in time.

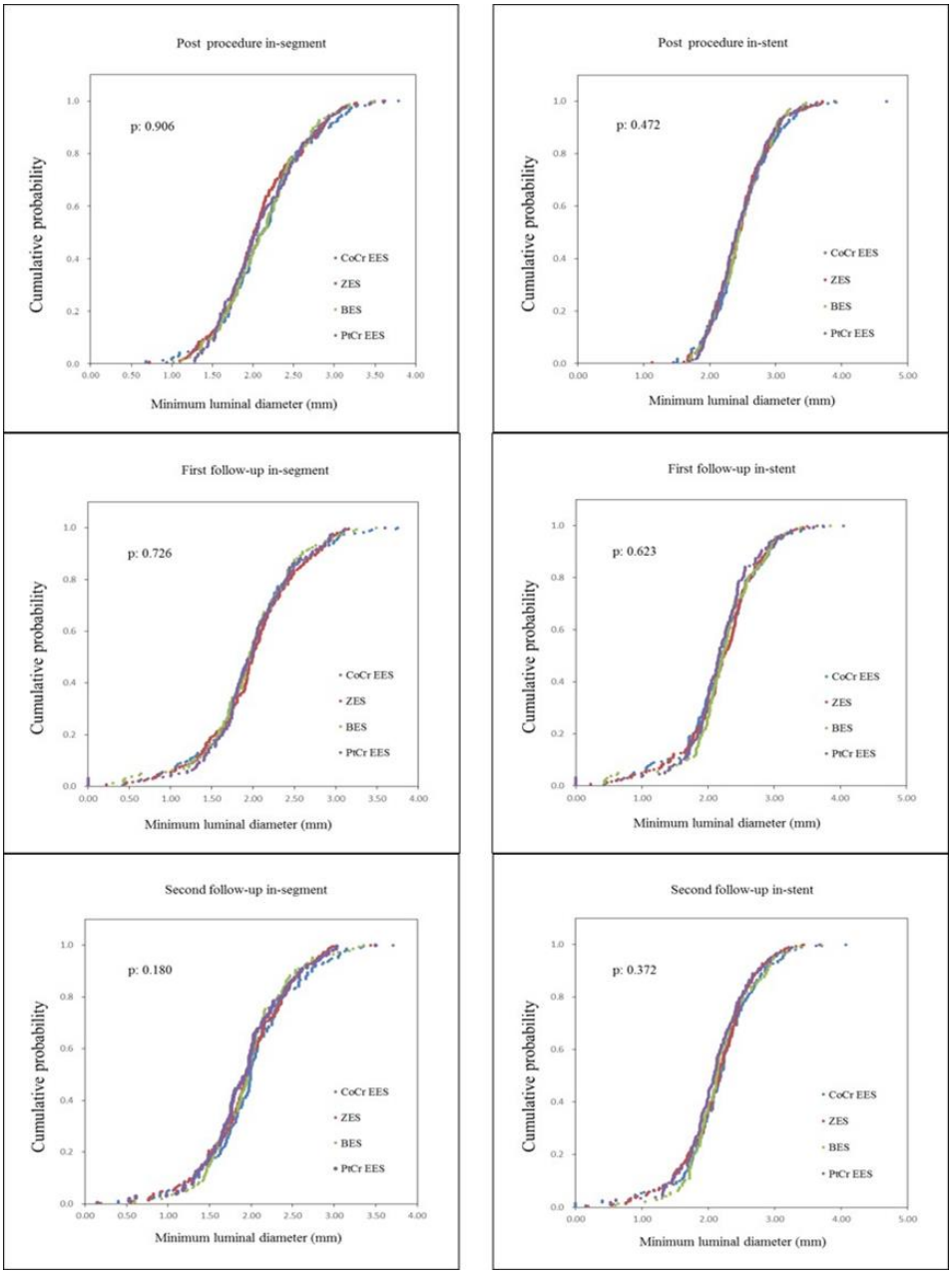


Figure 4. Study population

The ‘Grand DES registry’ is a Korean Nation-wide prospective registry, including the EXCELLENT registry, HOST-PRIME registry, HOST-RESOLINTE registry, RESOLUTE-Korea registry, and the HOST-BIOLIMUS registry. Out of the total 17,286 patients, 2,729 patients were STEMI patients, and after excluding patients with a single vessel disease, patients with a previous coronary artery bypass graft history, with a poor angiographic image, and those with procedure failure, 1,311 patients were analyzed.

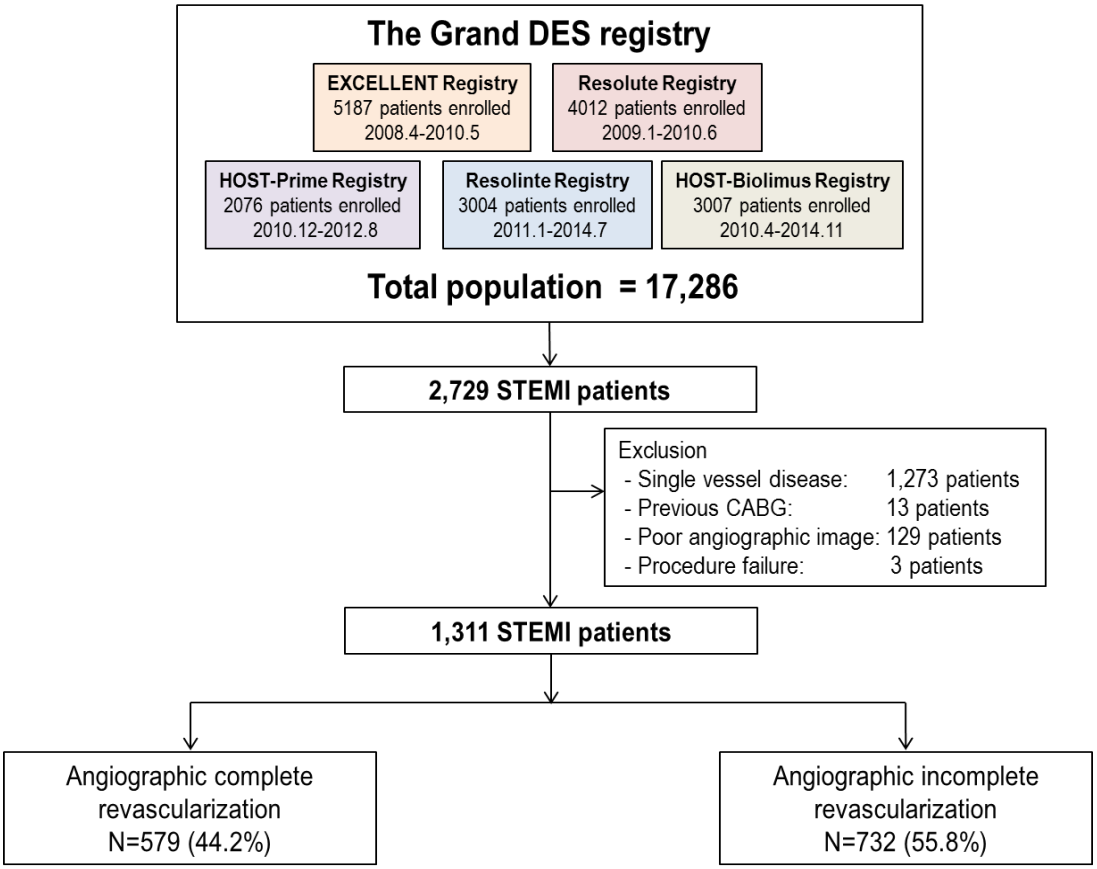
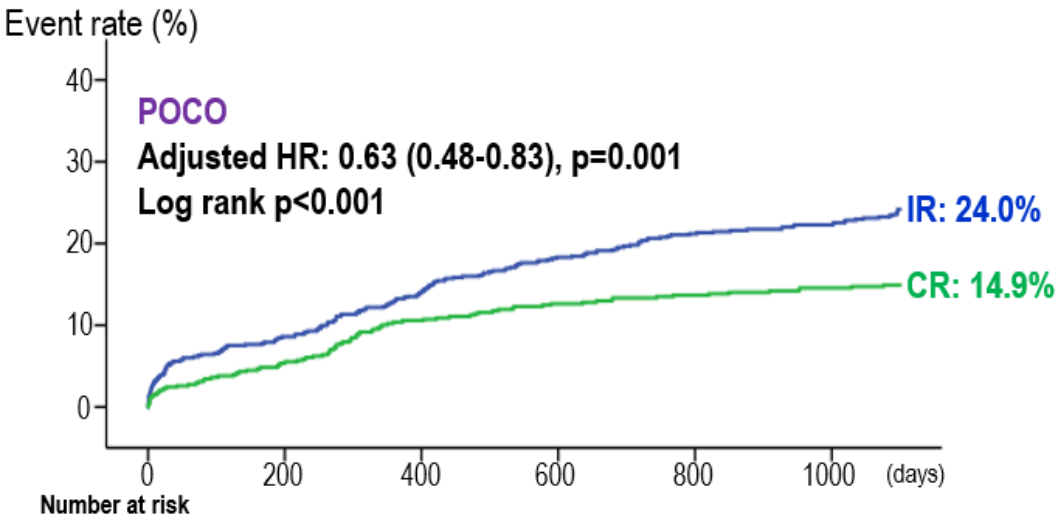


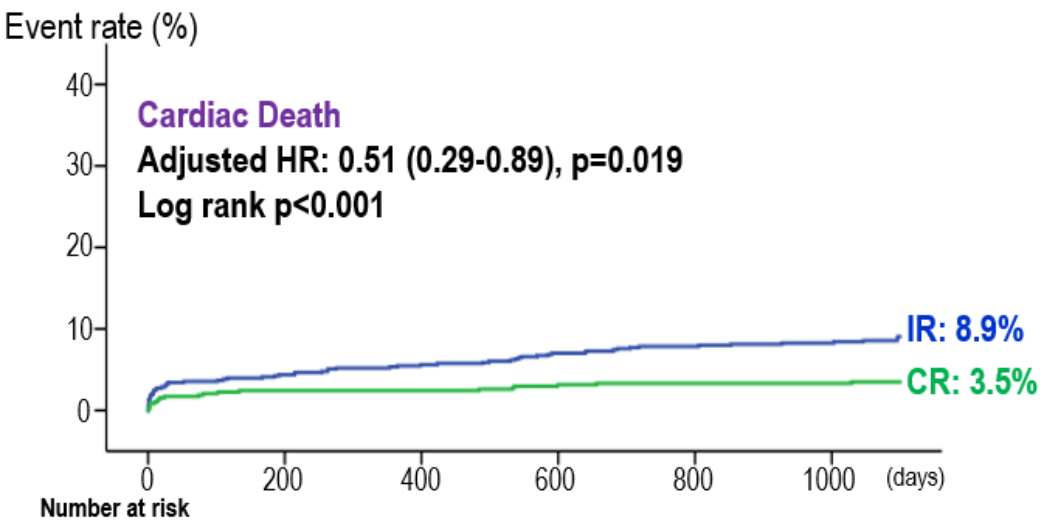
Figure 5. Survival curves during the 3-year follow up period

The survival curve of 3-year POCO and 3-year cardiac death according to CR. Overall, CR had a beneficial impact for 3-year POCO by a HR of 0.63 (95% CI 0.48-0.83, p=0.001), and for 3-year cardiac death by a HR of 0.51 (95% CI 0.29-0.89, p=0.019).



Number at risk

IR	732	669	629	598	575	564
CR	579	547	517	503	494	482

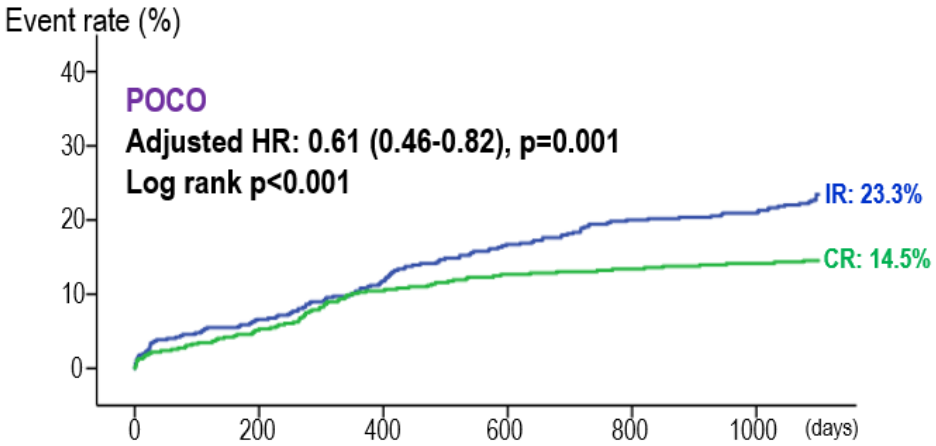


Number at risk

IR	732	693	682	667	652	642
CR	579	556	553	546	540	529

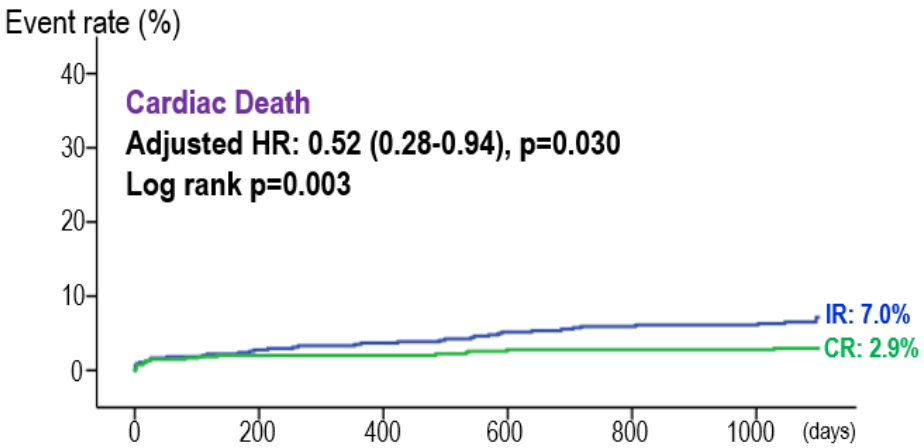
Figure 6. Survival curves during the 3-year follow up periods following propensity matching with 1,090 patients

The survival curve of 3-year POCO and 3-year cardiac death according to CR following propensity matching with 1,090 patients. Overall, CR had a beneficial impact for 3-year POCO by a HR of 0.61 (95% CI 0.46-0.82, p=0.001), and for 3-year cardiac death by a HR of 0.52 (95% CI 0.28-0.94, p=0.030).



Number at risk

IR	545	509	481	454	435	428
CR	545	517	488	474	467	456

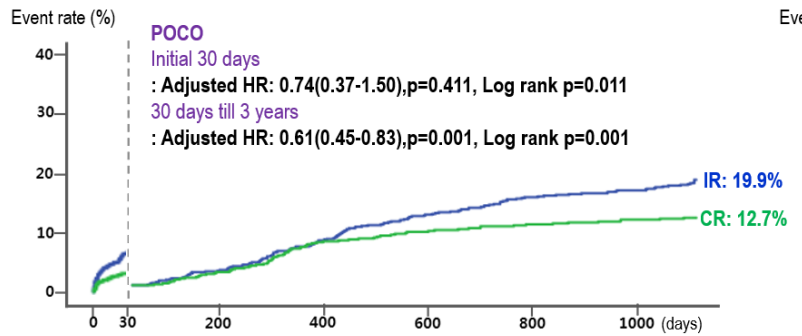


Number at risk

IR	545	527	520	507	495	490
CR	545	526	523	516	511	501

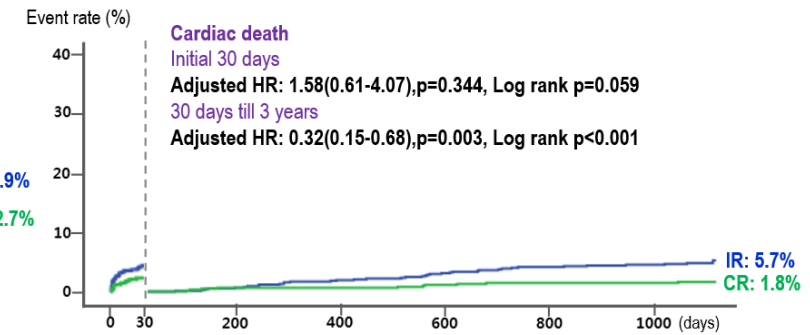
Figure 7. Landmark analysis of 3-year POCO and cardiac death

Landmark analysis at 30 days showed that CR had a beneficial effect in the and late phase (≥30days to 3 years).



Number at risk

IR	732 695	669	629	598	575	564
CR	579 565	547	517	503	494	482

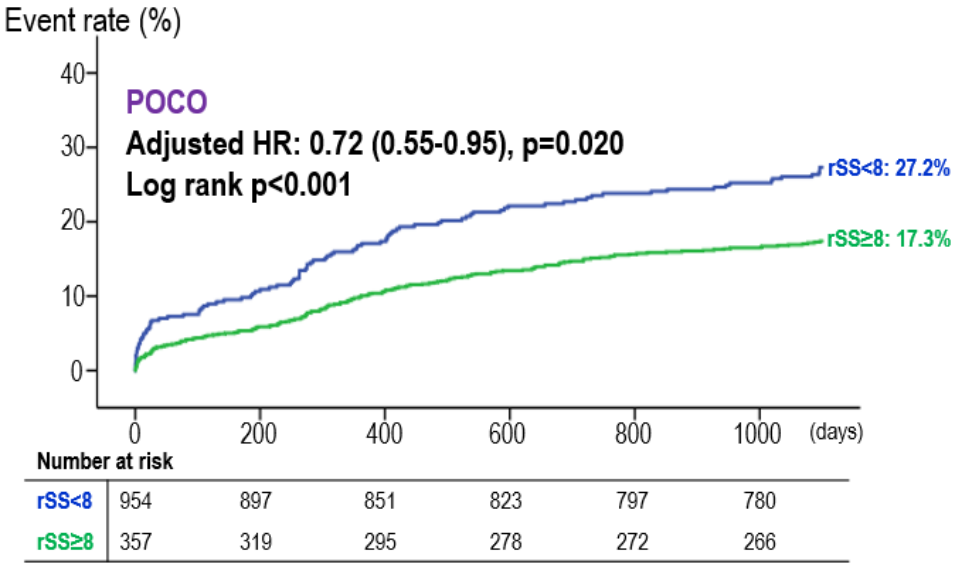


Number at risk

IR	732 708	693	682	667	652	642
CR	579 569	556	553	546	540	529

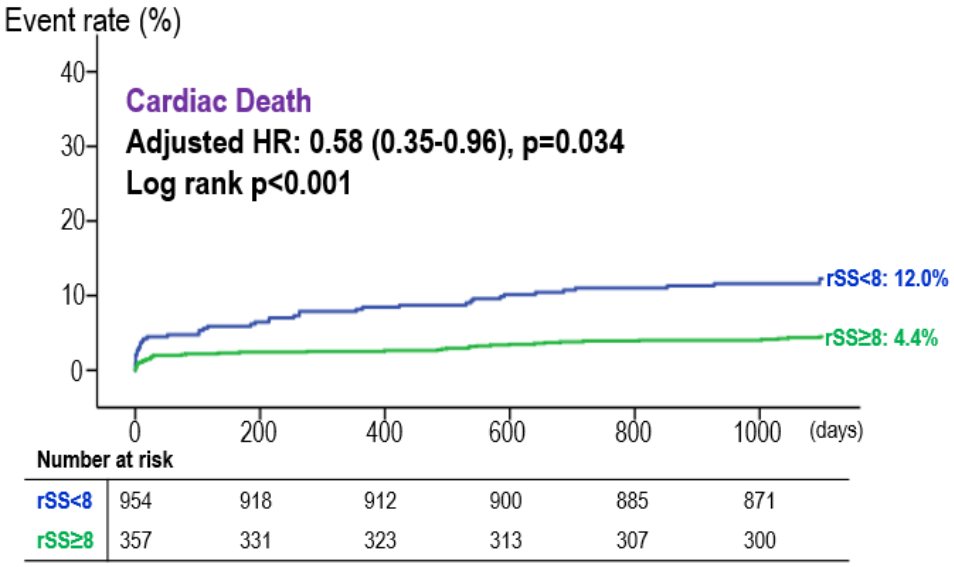
Figure 8. Survival curves during the 3-year follow up period, according to the residual SYNTAX score

The survival curve of 3-year POCO and 3-year cardiac death, according to the SS based CR. Overall, SS based CR also had a beneficial impact for 3-year POCO by a HR of 0.72 (95% CI 0.55-0.95, p=0.020), and for 3-year cardiac death by a HR of 0.58 (95% CI 0.35-0.96, p=0.034).



Number at risk

rSS<8	954	897	851	823	797	780
rSS≥8	357	319	295	278	272	266



Number at risk

rSS<8	954	918	912	900	885	871
rSS≥8	357	331	323	313	307	300

Figure 9. CR vs. IR in subgroup analysis

The effect of CR was not significantly different along various subgroups except diabetes mellitus group (P value for interaction = 0.043). However, the beneficial effect of CR is relatively weak in the high risk groups.

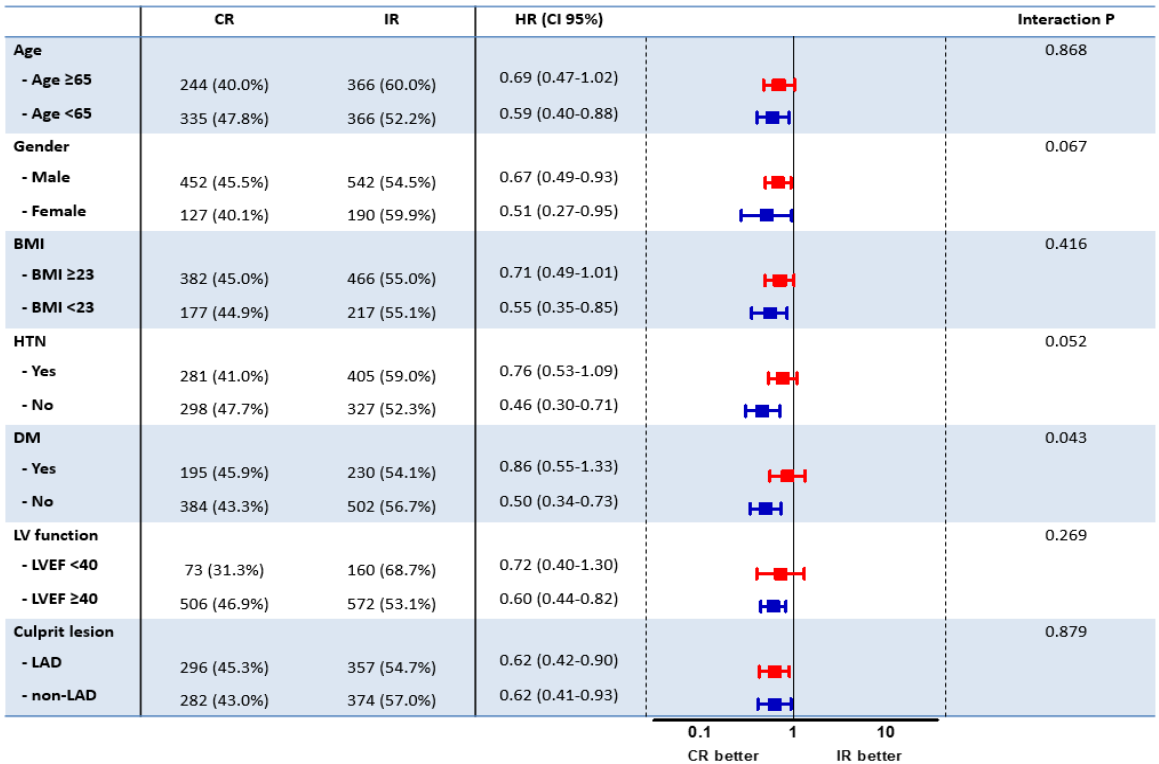


Figure 10. Survival curves during the 3-year follow up period, according to the strategy of complete revascularization

The survival curve of 3-year POCO and 3-year cardiac death according to the stage of CR. There is no statistical difference between the one-time CR and staged CR.

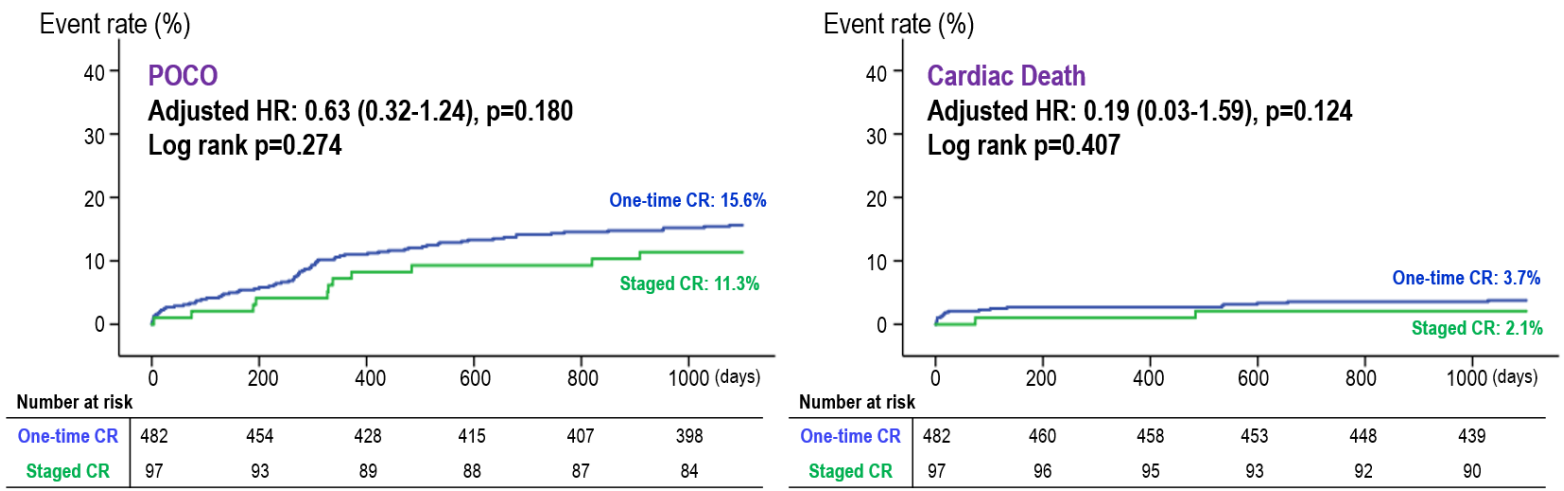


Figure 11. Survival curves during the 3-year follow up period, according to the presence of DM

The survival curve of 3-year POCO and 3-year cardiac death in the DM group and non-DM group, according to the CR and IR. In the subgroups according to the presence of DM, CR reduced 3-year POCO only in the non-DM group (HR 0.52, 95% CI 0.35-0.76, p=0.001)

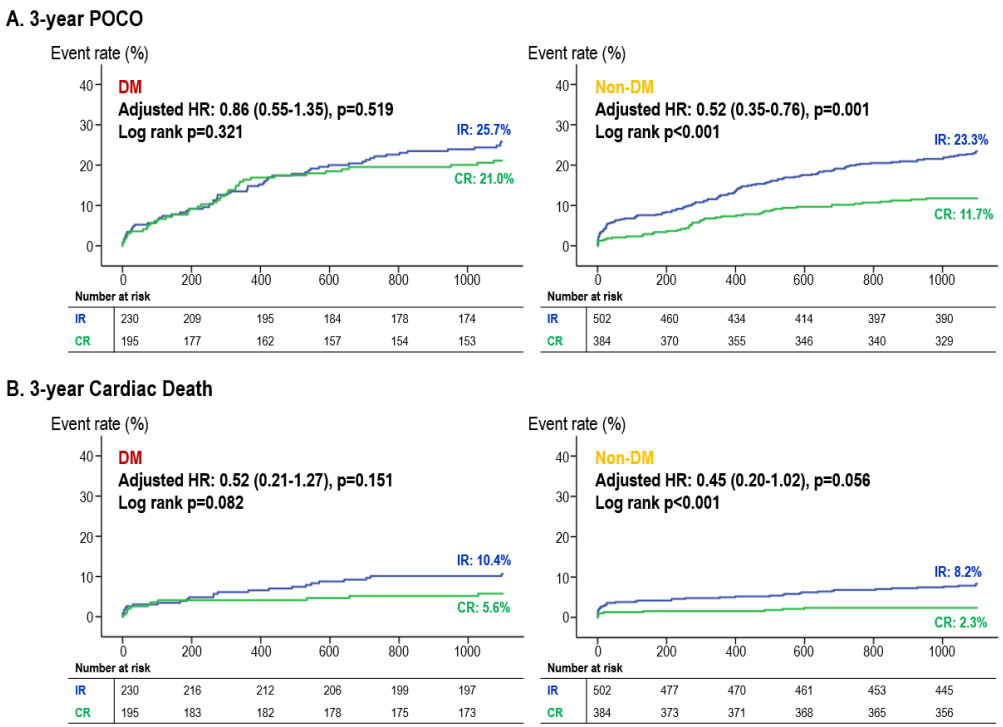


Figure 12. The impact of CR according to the presence of DM in various outcomes

The effect of CR was left-shifted (proving the beneficial effect of CR) in the non-DM group compared to the DM group in all endpoints except TLR. Especially for POCO, MI, TVMI, a significant interaction were observed between the revascularization strategy and the presence of DM (Interaction p=0.043, Interaction p=0.006, Interaction p=0.041, respectively).

		CR	IR	HR(CI 95%)	Interaction P value
POCO	DM	41 (21.0%)	59 (25.7%)	0.86(0.55-1.35)	0.043
	Non-DM	45 (11.7%)	117 (23.3%)	0.52(0.35-0.76)	
All cause death	DM	21 (10.8%)	34 (14.8%)	0.77(0.40-1.46)	0.131
	Non-DM	18 (4.7%)	57 (11.4%)	0.54(0.29-0.99)	
Cardiac death	DM	11 (5.6%)	24 (10.4%)	0.52(0.21-1.27)	0.210
	Non-DM	9 (2.3%)	41 (8.2%)	0.45(0.20-1.02)	
MI	DM	9 (4.6%)	7 (3.0%)	1.69(0.56-5.09)	0.006
	Non-DM	4 (1.0%)	25 (5.0%)	0.20 (0.06-0.69)	
TVMI	DM	6 (3.1%)	3 (1.3%)	3.02(0.56-16.40)	0.041
	Non-DM	4 (1.0%)	14 (2.8%)	0.37(0.08-1.83)	
ST	DM	5 (2.6%)	2 (0.9%)	2.30 (0.39-13.52)	0.093
	Non-DM	3 (0.8%)	9 (1.8%)	1.00 (0.16-6.13)	
Any revascularization	DM	22 (11.3%)	27 (11.7%)	0.99(0.54-1.82)	0.218
	Non-DM	27 (7.0%)	55 (11.0%)	0.55(0.34-0.91)	
TLR	DM	12 (6.2%)	11 (4.8%)	1.78(0.73-4.36)	0.650
	Non-DM	12 (3.1%)	9 (1.8%)	2.43(0.84-7.03)	
TLF	DM	22 (11.3%)	32 (13.9%)	1.00(0.54-1.87)	0.167
	Non-DM	20 (5.2%)	53 (10.6%)	0.71(0.39-1.30)	

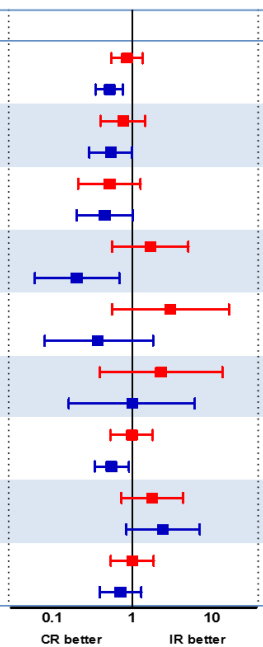


Figure 13. Survival curves during the 3-year follow up period, according to the presence of reduced LV function

The survival curve of 3-year POCO and 3-year cardiac death in the reduced LV function group and preserved LV function group, according to the CR and IR. The beneficial impact of CR was only shown in the preserved LV function group, while the effect was neutralized in the reduced LV function group.

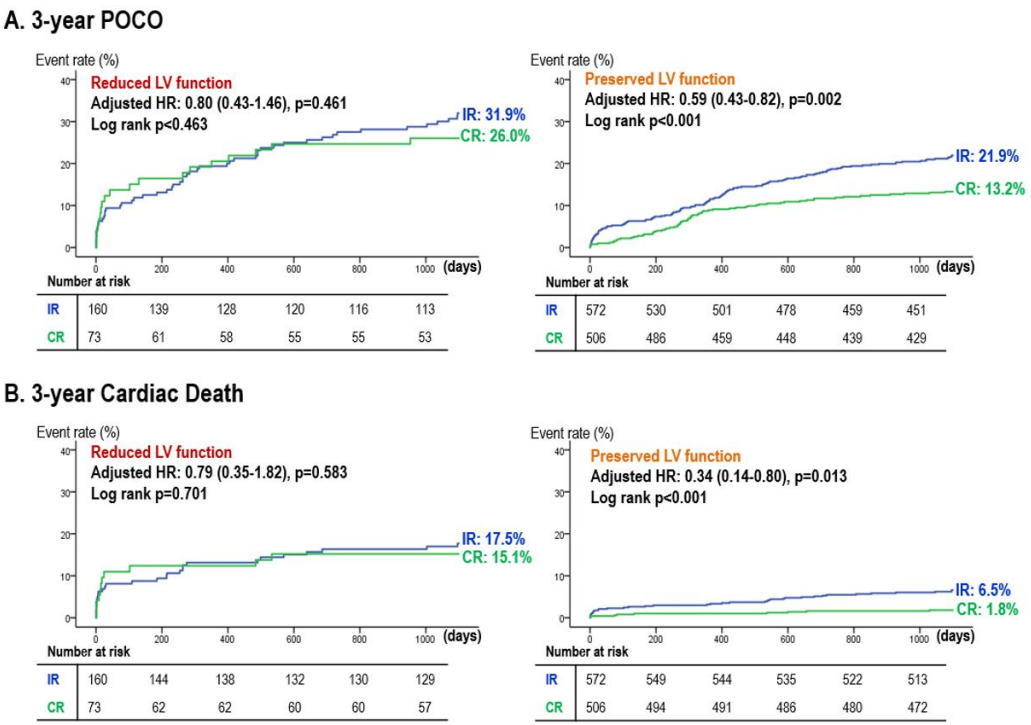


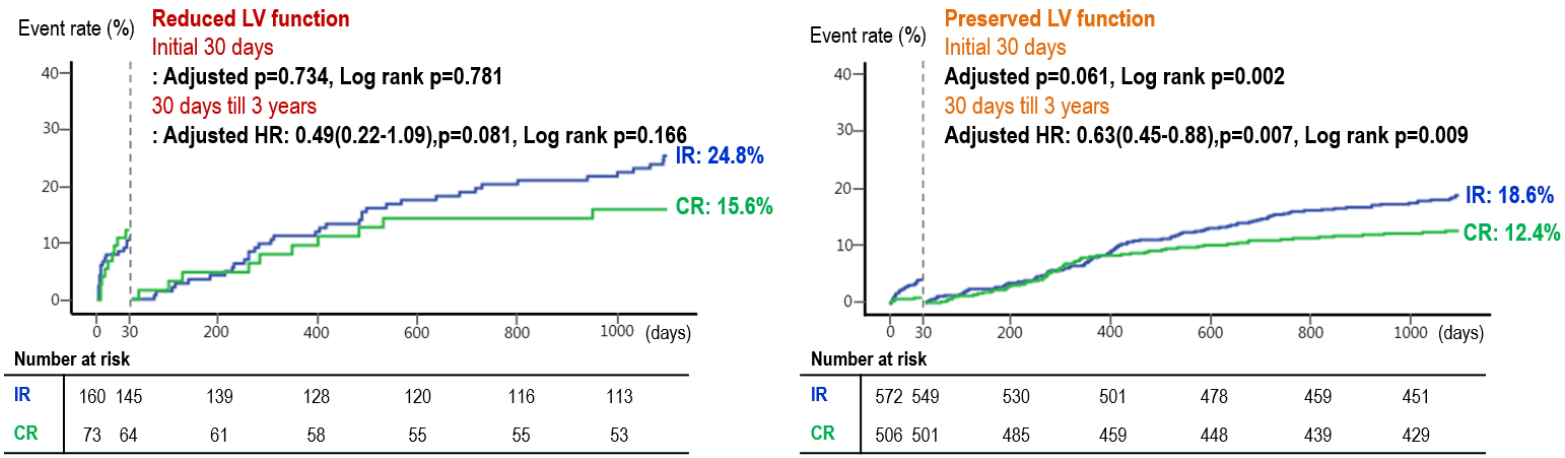
Figure 14. The impact of CR according to LV function in various outcomes

The effect of CR was left-shifted (proving the beneficial effect of CR) in the non-DM group compared to the DM group in all endpoints except TLR. Especially for all death, cardiac death, a significant interaction were observed between the revascularization strategy and the presence of DM (Interaction p=0.045, Interaction p=0.023, respectively).

		CR	IR	HR(CI 95%)	Interaction P value
POCO	Significant LV dysfunction (+)	19 (26.0%)	51 (31.9%)	0.80(0.43-1.46)	0.269
	Significant LV dysfunction (-)	67 (13.2%)	125 (21.9%)	0.59(0.43-0.82)	
All cause death	Significant LV dysfunction (+)	15 (20.5%)	33 (20.6%)	1.04(0.50-2.14)	0.045
	Significant LV dysfunction (-)	24 (4.7%)	58 (10.1%)	0.52(0.30-0.89)	
Cardiac death	Significant LV dysfunction (+)	11 (15.1%)	28 (17.5%)	0.79(0.35-1.82)	0.023
	Significant LV dysfunction (-)	9 (1.8%)	37 (6.5%)	0.34(0.14-0.80)	
MI	Significant LV dysfunction (+)	3 (4.1%)	10 (6.3%)	1.04(0.24-4.51)	0.732
	Significant LV dysfunction (-)	10 (2.0%)	22 (3.8%)	0.53 (0.23-1.20)	
TVMI	Significant LV dysfunction (+)	3 (4.1%)	(4.4%)	2.27(0.38-13.79)	0.846
	Significant LV dysfunction (-)	7 (1.4%)	10 (1.7%)	0.85(0.25-2.91)	
ST	Significant LV dysfunction (+)	3 (4.1%)	3 (1.9%)	3.93 (0.49-31.63)	0.316
	Significant LV dysfunction (-)	5 (1.0%)	7 (1.2%)	1.26 (0.26-6.08)	
Any revascularization	Significant LV dysfunction (+)	6 (8.2%)	17 (10.6%)	0.60(0.21-1.76)	0.871
	Significant LV dysfunction (-)	43 (8.5%)	65 (11.4%)	0.69(0.45-1.03)	
TLR	Significant LV dysfunction (+)	4 (5.5%)	4 (2.5%)	3.06(0.61-15.45)	0.537
	Significant LV dysfunction (-)	20 (4.0%)	16 (2.8%)	1.68(0.79-3.55)	
TLF	Significant LV dysfunction (+)	14 (19.2%)	33 (20.6%)	1.02(0.49-2.09)	0.253
	Significant LV dysfunction (-)	28 (5.5%)	52 (9.1%)	0.75(0.45-1.28)	

Figure 15. Landmark analysis of 3-year POCO, by baseline LV function

Landmark analysis at 30 days showed that CR had a beneficial effect in the and late phase (≥30days to 3 years) in the preserved LV function group. Meanwhile, in the reduced LV function group, the beneficial effect CR was not observed in both phases.



초록

연구목적

본 연구는 대규모 다기관 레지스트리를 통하여 ST 분절 상승 급성 심근경색환자에서 완전 재관류술과 비완전 재관류술의 3 년 임상결과를 비교하고자 한다. 또한 스텐트내재협착의 진행률에 대해 조사해보려고 한다.

본 연구는 스텐트내재협착의 진행경과에 대해 조사하였다. 또한 대규모 다기관 레지스트리를 통하여 ST 분절 상승 급성 심근경색환자에서 관상동맥 스텐트 치료방식에 따른 3 년 임상결과를 비교하고자 한다.

연구배경

2 세대 약물용출스텐트의 재협착의 진행률에 대하여 완전히 평가되지 않았다. 위험인소를 동반한 ST 분절 상승 급성 심근경색환자들에서 완전 재관류술의 치료 효과는 확실하지 않다.

연구방법

스텐트 시술후 두 차례의 병원 방문으로 조영술을 시행하고 정량적 관상동맥조영술 분석을 진행한 394 명 환자의 944 개의 관상동맥 병변의 진행경과에 대해 조사 및 분석을 진행하였다. 또한 총 1311 명의 ST 분절 상승 급성 심근경색 다혈관 질환 환자들에서 분석을 진행하였다. 완전 재관류술은 혈관조영술상의 판독과 잔여 SYNTAX 점수<8 점, 두 가지 방법으로 정의를 하였다. 임상예후는 환자 연관 사건인 사망, 심근경색, 재시술(Patient oriented composite outcome)과 심장사를 주요 종결점으로 설정하였다. ST 분절 상승 급성 심근경색환자들에서 당뇨병과 좌심실기능저하의 동반여부에 따라 완전 재관류술의 효과를 평가하였다.

결과

재협착의 진행경과에 대한 분석결과를 보았을 때 스텐트 삽입후 재협착의 진행률은 9 개월 전과 9 개월후에 다르게 보여졌으며 각각 12.1±21.0%/년, 3.7±10.1%/년 이였다. 또한 현시대의 약물용출스텐트들간 재협착의 진행정도와 진행속도은 유의한 차이를 보이지 않았다($p>0.05$).

완전 재관류술을 받은 환자는(579 명, 44.2%) 비완전 재관류술을 받은 환자에 비해 3 년 임상사건의 발생률이 유의하게 낮았다. (환자 연관 사건: 14.9% vs. 24.0%, $p<0.001$; 심장사: 3.5% vs. 8.9%, $p<0.001$). 다변량 분석에서도 완전 재관류술이 3 년 환자 연관 사건과 심장사를 유의가게 줄였음을 보여 준다. [환자 연관 사건: 보정 위험비 0.63(0.48−0.83); 심장사: 보정 위험비 0.51(0.29−0.89)]. 또한 잔여 SYNTAX 점수에 근거하여 정의한 완전 재관류술의 평가에서도 완전 재관류술의 효과가 보여졌다. 당뇨병의 동반 여부에 따라 분석을 진행해 보았을 때, 완전 재관류술은 당뇨병을 동반하지 않은 환자그룹에서만 3 년 환자 연관 사건을 유의하게 줄였다 [보정 위험비 0.52(0.35−0.76)]. 또한 좌심실기능저하의 동반 여부에 따라 분석을 진행해 보았을 때, 완전 재관류술은 좌심실 기능저하를 동반하지 않은 환자그룹에서만 3 년 환자 연관 사건을 유의하게 줄였다 [보정 위험비 0.58(0.43−0.82)].

결론

스텐트내재협착의 진행률은 초기와 후기에 다르게 진행 되었고 현시대의 약물용출스텐트들은 비슷한 재협착 진행률을 보였다. 완전 재관류술은 ST 분절 상승 급성 심근경색 다혈관 질환 환자의 임상 결과를 개선 할 수 있다. 하지만 완전 재관류술은 당뇨병 혹은 좌심실기능저하를 동반한 환자에서는 효과를 보이지 않았다.

주요어: 스텐트내재협착; 정량적 관상동맥 조영술 경피적관상동맥시술; ST 분절 상승 급성 심근경색; 완전 재관류술; SYNTAX 점수; 당뇨병; 좌심실기능저하

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