



Complete versus incomplete revascularization in patients with multivessel coronary artery disease treated with drug-eluting stents

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Background The clinical impact of completeness of revascularization on adverse cardiovascular events remains unclear among patients with multivessel coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI).

Methods This analysis included consecutive patients with multivessel CAD, who underwent PCI with drug-eluting stents (DES) during the period from January 1, 2003, through to December 31, 2013. We compared the outcomes in patients, who achieved complete (CR) versus incomplete revascularization (IR) at the time of PCI. The primary outcome was death from any cause. Secondary outcomes were the rates of myocardial infarction (MI), stroke, and repeat revascularization. Propensity-score matching was used to assemble a cohort of patients with similar baseline characteristics.

Results Among 3901 patients with multivessel CAD treated with DES, 1402 pairs of similar propensity scores in each group of CR and IR were identified. At a median follow-up of 4.9 years (interquartile range, 2.4-7.5), IR was associated with a similar risk of death (hazard ratio [HR], 1.03; 95% CI, 0.80-1.32; $P = .83$) as compared with CR. IR was also associated with similar risks of stroke (HR, 1.26; 95% CI, 0.76-2.09; $P = .37$) and repeat revascularization (HR, 1.15; 95% CI, 0.93-1.41; $P = .19$), but associated with a higher risk of MI (HR, 1.86; 95% CI, 1.08-3.19; $P = .024$) compared to CR.

Conclusions Among patients with multivessel CAD treated with DES, as compared with CR, IR was associated with similar risk of death. However, IR was associated with a higher risk of MI during follow-up. (*Am Heart J* 2016;179:157-65.)

Although technical and pharmacologic advancements of percutaneous coronary intervention (PCI) have been achieved over the past several decades, PCI with stenting for complex multivessel coronary artery disease (CAD) is still challenging and requires thoughtful considerations for optimal revascularization. Previous several randomized and observational studies showed that PCI with stents for multivessel CAD was associated with higher rates of death and myocardial infarction (MI) as compared with coronary-artery bypass grafting (CABG).¹⁻³ Among several potential explanations which were postulated, the higher incidence of incomplete revascularization (IR) after PCI was suggested as one of the important factors of

less favorable outcomes of PCI relative to CABG.⁴ However, in the real-world PCI practice, achievement of complete revascularization (CR) for all-comer patients could be technically and clinically not feasible. CR for multivessel CAD would result in more and longer stents than IR, which could be a potential risk of stent-related clinical events.⁵⁻⁷ In addition, a previous landmark clinical trial showed that optimal medical management would provide equivalent clinical outcomes of death or MI as compared to PCI.⁸ With respect to the completeness of PCI, previous several studies have yielded conflicting results on mortality,^{5-7,9-11} but these are limited by a lack of long-term follow-up and small number of population. Using large-sized, prospective cohort of multivessel CAD, we evaluated the long-term clinical impact of angiographic CR versus IR on mortality and adverse cardiovascular events among patients who received PCI with drug-eluting stents (DES).

Method

Patients and definitions

The Asan Medical Center Multivessel Registry (ClinicalTrials.gov number, NCT02039752) is a

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single-center, prospective cohort study, which was designed to evaluate the comparative effectiveness of treatment modalities for multivessel CAD in the unselected, real-world population.¹² This analysis included consecutive patients with multivessel CAD, who underwent PCI with DES during the period from January 1, 2003, through to December 31, 2013. Patients who had prior CABG or concomitant valvular or aortic surgery and those who had an acute ST-segment elevation MI within 24 hours or presented with cardiogenic shock were excluded. In addition, patients underwent isolated balloon angioplasty, or bare-metal stents were all excluded. This study was approved by the local institutional review board, and all patients provided a written informed consent for enrollment in this registry.

Eligible patients were divided into 2 groups according to the angiographic completeness of revascularization; CR group versus IR group. In the current study, angiographic CR was defined as the absence of diameter stenosis $\geq 50\%$ in major epicardial coronary arteries or their side branches with a diameter ≥ 2.5 mm after successful stent implantation during index hospitalization irrespective of the function or viability of relevant myocardium.⁴ If CR criteria were not met for multivessel CAD, those were defined as the IR group.

Procedures

The decision to perform CR or IR was at the discretion of the interventional cardiologists. The PCI was performed according to current practice guidelines. The choice of stent type and the use of intravascular ultrasound, glycoprotein IIb/IIIa inhibitor, or other devices to facilitate optimal stenting were left to the operator's discretion. Antiplatelet therapy and peri-procedural anticoagulation followed standard regimens. After PCI, patients were prescribed standard dual antiplatelet therapy, consisting of 100 mg/d aspirin and 75 mg/d clopidogrel or 90 mg twice-a-day ticagrelor, for at least 6 months in the early period or at least 12 months in the late period.

Study outcomes and follow-up

The primary outcome was death from any cause. Secondary outcomes included the rates of MI, stroke, repeat revascularization, and a composite of death, MI, or stroke. Due to the differential clinical impact of periprocedural and follow-up MI,¹³ MI in this study was confined to clinically relevant, follow-up MI, which requiring subsequent hospitalization (defined as an emergency admission with a principal diagnosis of MI). Periprocedural MI was defined as any elevation of troponin >3 times upper range limit (URL) or CK-MB >3 times URL in relation to intervention and was analyzed separately.¹⁴ In addition, as sensitivity analysis, we compared the incidence of periprocedural MI using a higher threshold diagnosis for periprocedural MI on the

basis of the recommendation from the Society for Cardiovascular Angiography and Interventions (SCAI).¹⁵ Stroke, as indicated by neurological deficits, was confirmed by a neurologist on the basis of imaging modalities. Repeat revascularization included percutaneous or surgical revascularization of the target vessel or non-target vessel, regardless of whether the procedure was clinically or angiographically driven. All outcomes of interest were carefully verified and adjudicated by independent clinicians blinded to the completeness of revascularization.

Clinical, angiographic, procedural characteristics and outcome data were prospectively recorded in the dedicated PCI database by independent research personnel. Patients were clinically followed up at 1, 6, and 12 months and annually thereafter, via office visit or telephone contact. For the validation of complete follow-up data, the information on censored survival data (death or survival) was obtained from the National Health Insurance Service.

Statistical analysis

Differences in baseline clinical and angiographic characteristics and procedural findings were compared with the *t*-test for continuous variables and the χ^2 test for categorical variables. Given the differences in the baseline clinical characteristics between CR and IR groups, propensity-score matching was used to identify a cohort of patients with similar baseline characteristics. The propensity score is a conditional probability of having a particular exposure (CR versus IR) given a set of baseline measured clinical covariates.¹⁶ The propensity score was estimated without regarding outcomes, using a nonparsimonious multivariable logistic-regression model,¹⁷ with IR as the dependent variable and all the baseline characteristics outlined in Table I as covariates. Matching was performed with the use of a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. The absolute standardized differences were estimated for all the baseline covariates before and after matching to assess pre-match imbalance and post-match balance. Absolute standardized of less than 10.0% for a given covariate indicate a relatively small imbalance.¹⁸

Prespecified subgroup analyses were performed on the basis of key clinical and anatomical characteristics. Clinical subgroups were based on the status of age (<65 years vs ≥ 65 years), gender, diabetes, clinical presentation, and chronic renal failure. Anatomical subgroups were based on 3-vessel versus 2-vessel disease and with or without the involvement of the territory of the proximal left anterior descending coronary artery. In each subgroup, to maintain the baseline balance between the CR group and the IR group, only the corresponding matched pairs in a subgroup were chosen. For example, in the

Table I. Baseline clinical and anatomical characteristics before and after the propensity-score matching.

Characteristics	Before matching			Standardized difference	After matching		
	IR N = 2396	CR N = 1505	P		IR N = 1402	CR N = 1402	Standardized difference
Age	63.3 ± 9.6	62.1 ± 10.0	<.001	0.114	62.3 ± 9.6	62.4 ± 9.8	0.008
Male	1740 (72.6%)	1040 (69.1%)	.018	0.076	991 (70.68%)	994 (70.9%)	0.005
Body mass index	25.1 ± 3.0	25.1 ± 3.0	.584	0.018	25.1 ± 2.9	25.1 ± 2.9	0.011
Hypertension	1545 (64.5%)	931 (61.9%)	.098	0.054	874 (62.3%)	870 (62.1%)	0.006
Diabetes	859 (35.9%)	488 (32.4%)	.029	0.073	471 (33.6%)	459 (32.7%)	0.018
Cerebrovascular disease	197 (8.2%)	110 (7.3%)	.303	0.035	104 (7.4%)	100 (7.1%)	0.011
Dyslipidemia	895 (37.4%)	549 (36.5%)	.581	0.018	512 (36.5%)	505 (36.0%)	0.010
Prior PCI	412 (17.2%)	225 (15.0%)	.065	0.063	202 (14.4%)	206 (14.7%)	0.008
Current smoking	598 (25.0%)	387 (25.7%)	.730	0.017	368 (26.3%)	364 (26.0%)	0.007
Data missing	605 (25.3%)	367 (24.4%)		0.020	361 (25.8%)	355 (25.3%)	0.010
Presentation			.110	0.024			0.011
Stable angina	1099 (45.9%)	689 (45.8%)			662 (47.2%)	640 (45.6%)	
Unstable angina	717 (29.9%)	489 (32.5%)			422 (30.1%)	452 (32.2%)	
NSTEMI	580 (24.2%)	327 (21.7%)			318 (22.7%)	310 (22.1%)	
Chronic renal failure	409 (17.1%)	187 (12.4%)	<.001	0.141	189 (13.5%)	180 (12.8%)	0.019
Ejection fraction			.405	0.035			0.012
<35%	45 (1.9%)	22 (1.5%)			19 (1.4%)	17 (1.2%)	
≥35%	1510 (63.0%)	919 (61.1%)			871 (62.1%)	866 (61.8%)	
Data missing	841 (35.1%)	564 (37.5%)		0.040	512 (36.5%)	519 (37.0%)	0.007
No. of diseased vessels (%)							
Three vessel disease	1072 (44.7%)	320 (21.3%)	<.001	0.574	325 (23.2%)	318 (22.7%)	0.012
Two vessel disease	1324 (55.3%)	1185 (78.7%)			1077 (76.8%)	1084 (77.9%)	
CTO	146 (6.1%)	97 (6.5%)	.658	0.014	81 (5.8%)	81 (5.8%)	<0.001
Proximal LAD	1248 (52.1%)	808 (53.7%)	.330	0.032	748 (53.4%)	743 (53.0%)	0.007

Abbreviations: NSTEMI, Non-ST-segment-elevation myocardial infarction; CTO, chronic total occlusion; LAD, left anterior descending artery. Chronic renal failure was defined as GFR less than 60 mL/min/1.73 m². Chronic total occlusion was defined as the complete interruption of antegrade blood flow on coronary angiography, present for and duration of ≥3 months.¹⁹

subgroup of patients with diabetes, only the matched pairs of patients with diabetes in the CR group and the IR group were included in the analysis. Tests for interaction were performed to assess for heterogeneity of treatment effect among the subgroups.

In the matched cohort, paired comparisons were performed with the use of McNemar's test for binary variables and a paired Student *t*-test or paired-sample test for continuous variables. The comparative risks of primary and secondary outcomes were further adjusted for in the matched cohort with the use of a Cox proportional-hazards regression model that was stratified on the matched pair to preserve the benefit of matching. All reported p-values are 2-sided and have not been adjusted for multiple testing. All the analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

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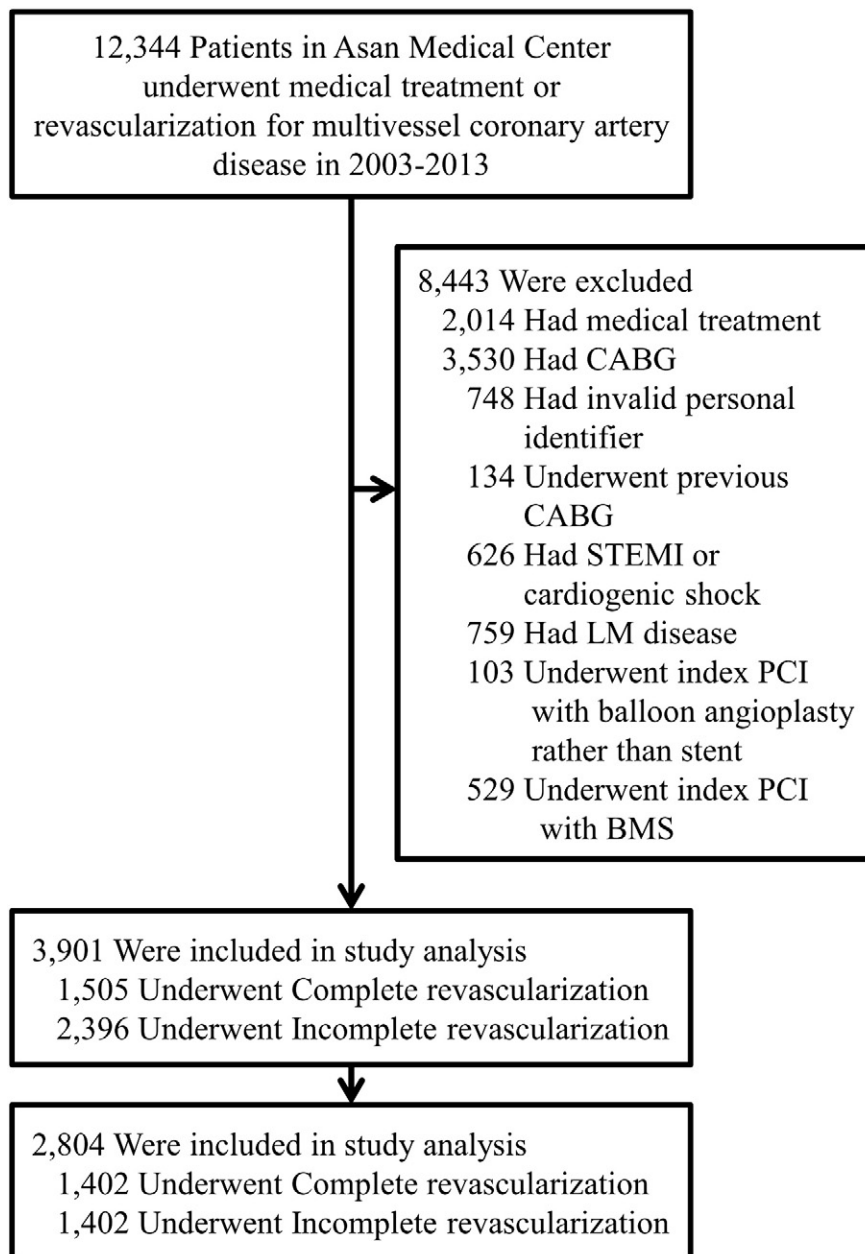
authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Patients characteristics

A total of 3901 patients with multivessel CAD underwent PCI with DES were included in the current analysis (Figure 1). Among them, 1505 patients were classified to CR group, and 2396 patients were classified IR group. Baseline clinical and anatomic characteristics are shown in Table I. Before the propensity-score matching, patients with IR were generally older and were more likely to be male gender. The IR group had a higher incidence of diabetes, chronic renal failure, and 3-vessel disease, as compared with the CR group. After the propensity-score matching, there were 1402 matched pairs of patients and no significant differences were present between the 2 groups for any of the covariates.

The procedural characteristics of the patients with selected features in the propensity-matched cohort are summarized in Table II. Use of first or second-generation DES was similar among the groups, whereas the CR group had a higher number of stents implanted compared to the IR group (2.78 ± 1.19/per patient vs. 1.98 ± 1.06/per

Figure 1

Study population. STEMI, ST-segment elevation myocardial infarction; LM, left main; BMS, bare-metal stent.

patient, $P < .001$); the numbers of stent used per patients was expressed in Supplementary Figure 1. There were significant differences in treated lesions between groups; the proximal major epicardial arteries were accounted for 48.6% of the CR group, and 55.5% of the IR group ($P < .001$). The CR group had a higher incidence of treated lesions confined to mid to distal major epicardial arteries and branch lesions as compared to the IR group;

therefore, among the IR group, the majority of untreated lesions were mid to distal major epicardial arteries or branches of major epicardial arteries, which accounted for 70.4% of untreated lesions.

Patients were well treated with standard medications in both groups, and there was no difference in use of dual anti-platelet therapy between groups during follow-up (Supplementary Table 1).

Table II. Procedural difference of patients with complete revascularization and incomplete revascularization in the propensity-matched cohort.

Variable	IR (N = 1402)	CR (N = 1402)	P
Stent number/per patient	1.98 ± 1.06	2.78 ± 1.19	<.001†
Type of stent			.613‡
1st generation DES (%)	859 (61.3%)	872 (62.2%)	
2nd generation DES (%)	543 (38.7%)	530 (37.8%)	
Diseased vessel			
LAD	1199 (85.5%)	1212 (86.4%)	.471*
LCX	933 (66.5%)	918 (65.5%)	.527*
RCA	988 (70.5%)	983 (70.1%)	.825*
RI	50 (3.6%)	34 (2.4%)	.077*
Lesion number/per patients	2.61 ± 0.82	2.43 ± 0.72	<.001†
Treated lesion	1969	3401	
Proximal major epicardial arteries	1092 (55.5%)	1653 (48.6%)	<.001†
Mid to distal major epicardial arteries	765 (38.9%)	1423 (41.8%)	<.001†
Branches of major epicardial arteries	112 (5.7%)	325 (9.6%)	<.001†
Untreated lesion	1807		
Proximal major epicardial arteries	534 (29.6%)	.	
Mid to distal major epicardial arteries	723 (40.0%)	.	
Branches of major epicardial arteries	550 (30.4%)	.	

Abbreviations: LAD, Left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; RI, ramus intermedius coronary artery. Major epicardial arteries indicates LAD, LCX and RCA; Branches of major epicardial arteries includes ramus intermedius, diagonal, obtuse marginal, right ventricular, posterior descending and posterolateral coronary artery.

* Marginal homogeneity test,

† Paired t test.

Study outcomes

The median follow-up period was 4.9 years (interquartile range, 2.4-7.5). During the entire follow-up period, 365 patients (9.4%) died from any cause, 85 patients (2.1%) experienced clinically relevant, follow-up MI, 86 patients (2.2%) experienced a stroke, and 516 (13.2%) had a repeat revascularization. During the in-hospital period, 433 (11.1%) of patients experienced periprocedural MI; among them, 137 (3.5%) had periprocedural MI by the SCAI definition.

Before the propensity score matching, the risk of all-cause death was similar between groups (Table III). The rate of stroke was also similar, but the rates of MI, repeat revascularization, and a composite of death, MI, and stroke were significantly higher in patients with IR than those with CR. After the propensity-score matching, the primary outcome of all-cause mortality had occurred in 126 (9.0%) in the IR group and 120 patients (8.6%) in the CR group (HR, 1.03; 95% CI, 0.80 to 1.32; $P = .834$) (Figure 2). In addition, the risk of stroke and repeat revascularization was similar between groups. However, the risk of follow-up MI was significantly higher in the IR group than in the CR group (HR, 1.86; 95% CI, 1.08-3.19; $P = .024$). With regard to periprocedural MI, the risk was similar between the groups (HR 0.87; 95% CI, 0.69-1.08; $P = .203$). When we assessed the periprocedural MI using more stringent SCAI recommendation, a similar pattern was observed between the groups (HR, 0.78; CI, 0.53-1.17; $P = .231$). There was no significant difference in the rate of a composite of death, MI and stroke between 2 groups.

If we performed a multivariable, Cox regression analysis utilizing all patients, incomplete revascularization was not a significant predictor of the primary outcome (all-cause mortality) in the whole study population (Supplementary Table 2).

Subgroup analysis

The effects of CR versus IR on mortality were similar across several clinical and anatomic subgroups, except group without proximal LAD disease suggesting better survival with CR (Figure 3). There was no significant interaction between completeness of revascularization and such characteristics on mortality after PCI. Likewise, there was no significant interaction between completeness of revascularization and subgroups with respect to any secondary outcomes (data not shown).

Discussion

In this large real-world registry involving multivessel CAD treated with DES, we found that IR was associated with a similar risk of long-term mortality as compared with CR. There was also no significant difference with regard to stroke or repeat revascularization. Clinically relevant, follow-up MI occurred more frequently in the IR group than in the CR group, but this difference was not translated into increased risk of mortality.

There are several distinctive features in our study. First, as the completeness of revascularization is frequently associated with clinical conditions affecting long-term outcomes, we used the propensity-score matching to

Table III. The risk of clinical outcomes in patients with complete revascularization and incomplete revascularization before and after the propensity-score matching.

Outcome	No. of patients with event	Event rate %/ year	Hazard ratio (95% CI)	P
Before matching (N = 3901)			Unadjusted HR	
Death				
IR	237	2.02	1.17 (0.95–1.45)	.150
CR	128	1.71	Reference	
MI*				
IR	64	0.56	1.30 (1.09–1.57)	.008
CR	21	0.28	Reference	
Stroke				
IR	56	0.48	1.19 (0.76–1.85)	.449
CR	30	0.40	Reference	
Repeat revascularization				
IR	343	3.33	1.30 (1.09–1.57)	.005
CR	173	2.55	Reference	
Composite of death, MI and stroke				
IR	322	2.83	1.22 (1.01–1.47)	.037
CR	169	2.30	Reference	
After matching (N = 2804)				
Death				
IR	126	1.77	1.03 (0.80–1.32)	.834
CR	120	1.70	Reference	
MI*				
IR	35	0.52	1.86 (1.08–3.19)	.024
CR	19	0.27	Reference	
Stroke				
IRs	35	0.52	1.26 (0.76–2.09)	.372
CR	28	0.41	Reference	
Repeat revascularization				
IR	182	2.98	1.15 (0.93–1.41)	.192
CR	165	2.62	Reference	
Composite of death, MI and stroke				
IR	174	2.60	1.12 (0.90–1.39)	.296
CR	157	2.29	Reference	

Abbreviations: IR, Indicates incomplete revascularization; CR, complete revascularization; MI, myocardial infarction.

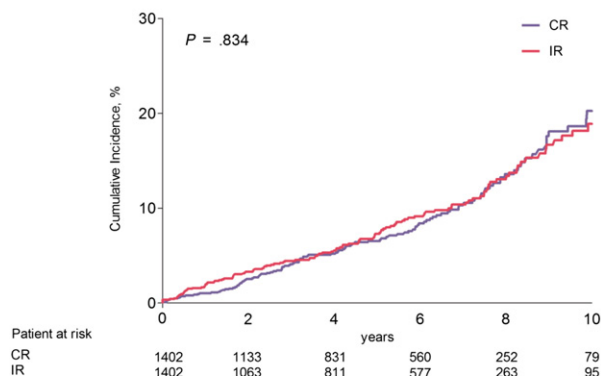
*MI was defined as clinically relevant, follow-up MI requiring re-hospitalization.

assemble a cohort of patients with similar clinical characteristics. Second, our study thoroughly identified the characteristics of the treated and untreated lesions in the IR and CR group. Interestingly, the major difference in treated and untreated lesions among the IR group was based on the lesion with the branches of major epicardial arteries; in the IR group, approximately 70% of untreated lesions were mid to distal lesions or side-branches of major epicardial arteries. Those findings in the real-world practice suggest that physicians might have a suitable reason for leaving angiographic lesions to be not treated (ie, a relatively small vessel or minor clinical importance). Lastly, in clinical viewpoint, untreated lesions might present as future, follow-up MI event, but was not manifested as a higher risk of repeat revascularization, which implies that the untreated, initial lesions might have a little importance of the revascularization during follow-up. However, because our study showed relatively lower event rates in all aspects than other multivessel registries, it might be possible that this discrepancy led to attenuate the potential benefit of CR.^{10,11}

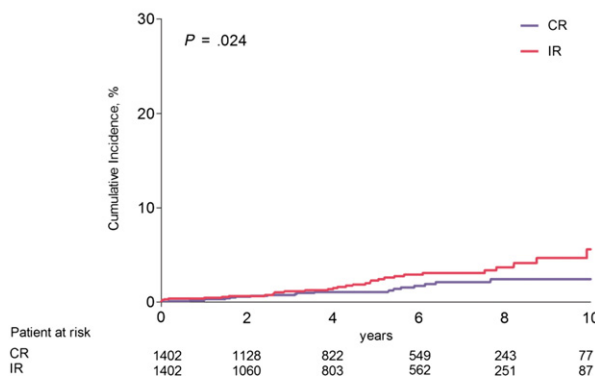
The completeness of PCI on the basis of coronary angiographic findings had been questioned for many aspects. In the COURAGE trial, although study participants had angiographically significant (at least 70%) stenosis of the proximal epicardial coronary artery and objective evidence of myocardial ischemia, PCI did not reduce the risk of death, MI, or stroke as compared with optimal medical treatment.⁸ Even for salvaging the infarct-related coronary artery, PCI failed to reduce the occurrence of death, reinfarction, or heart failure in OAT trial.¹⁹ In the subsequent FAME trial, fractional flow reserve (FFR)-based PCI improved clinical outcomes of death, MI, and repeat revascularization compared to angiography-based PCI.²⁰ Still, the impact of the angiographic completeness on clinical outcomes has not been sufficiently evaluated in the unselected, real-world PCI practice, and previous several observational studies showed conflicting results due to their various definitions of CR and IR.^{9–11} Because of the advances in procedural techniques and concepts, the relative proportion and clinical impact of CR in PCI requires further evaluation,²¹

Figure 2

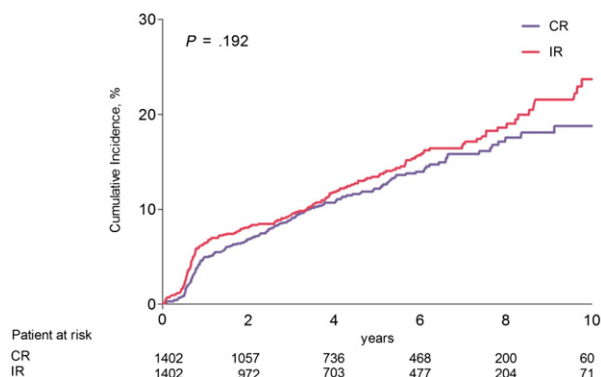
A) Death



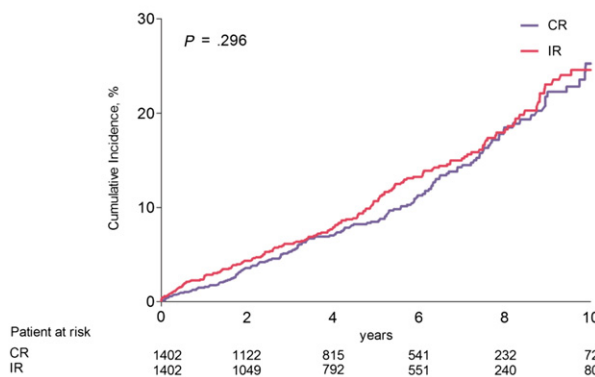
B) Myocardial Infarction



C) Revascularization



D) Death, Myocardial Infarction or Stroke



Kaplan-Meier Curve of Clinical Outcomes in the Propensity-Score Matched Cohort. The cumulative incidences of the primary outcome of death from any cause (A), myocardial infarction (B), repeat revascularization (C) and a composite of death, myocardial infarction or stroke (D) are shown. The p-values were calculated using the log-rank test.

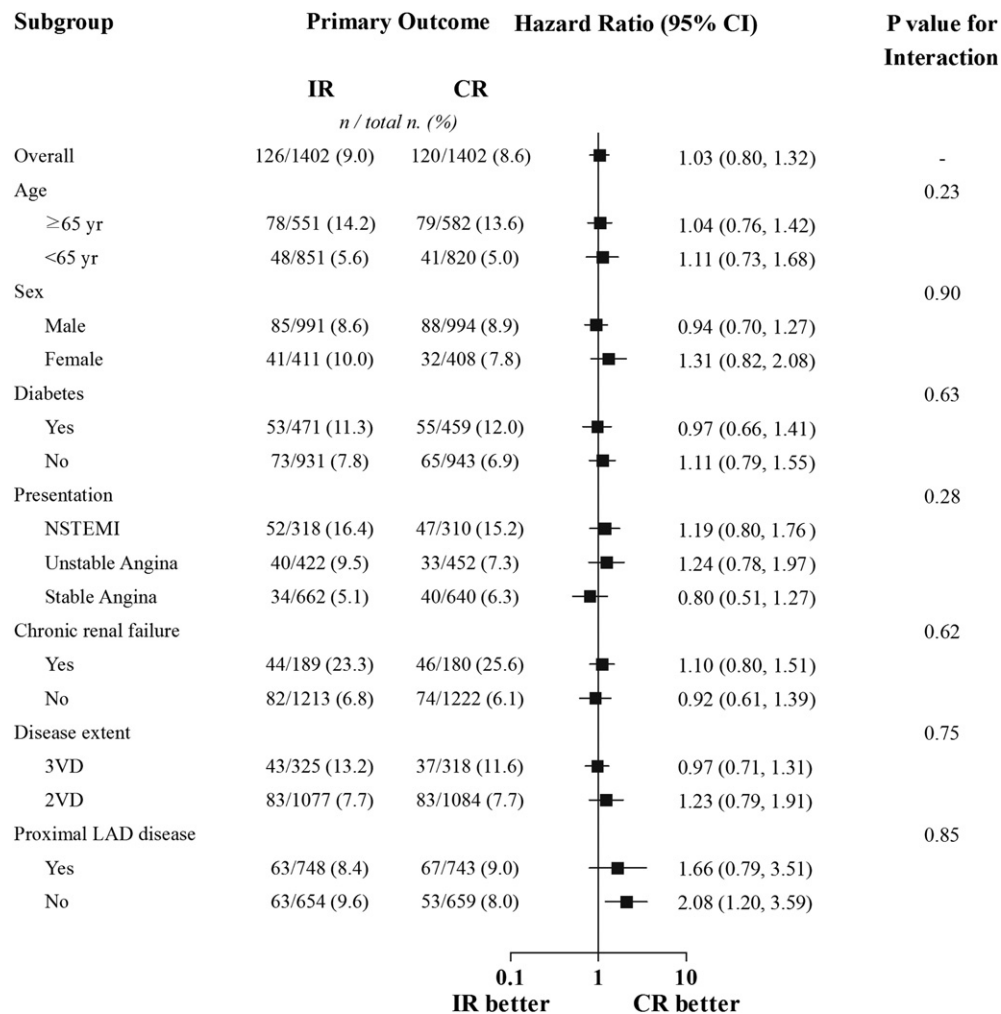
and therefore our study provides the valuable clinical insights with regards to the long-term clinical impact of CR or IR among real-world patients treated with DES.

Although there have been several definitions of CR or IR, the anatomical definition might be the most widely used criteria.⁴ As the benefit of revascularization depends on the presence and extent of myocardial ischemia, CR for a larger burden of myocardial ischemia would definitely confer a long-term clinical benefit compared to IR. In the routine PCI practice, the possible reasons to perform IR instead of CR might include non-viable myocardium of target vessels, chronic total occlusions, small vessel disease, anatomically not-eligible for technical reasons, or physician's choice after consideration of several factors (i.e., anatomically significant, but functionally not significant lesions); still, it is unclear whether treating such lesions with PCI potentially provide the clinical benefits. In a myocardial perfusion scan, retrospective study, selection for revascularization was asso-

ciated with greater survival compared to medical therapy alone in patients with moderate to large amounts of inducible ischemia.²² By contrast, a substudy of COURAGE trial showed that there was no gradient increase in clinical events between PCI and medical therapy according to the extent of ischemia by stress myocardial perfusion imaging.²³ In the FAME study, only 35% of angiographically significant stenosis were functionally ischemic by FFR, reflecting that angiographic CR might have a limited prognostic value.²⁰ Further clinical trials are required to provide the answer the question whether there are differences in mortality and hard clinical endpoints between CR and IR according to anatomic or functional criteria.

This study has several limitations. First, it was observational and nonrandomized in design. Despite rigorous statistical adjustments, undetermined potential biases exist due to unmeasured confounders. Therefore, overall findings are explorative and

Figure 3



Subgroup analysis of the primary outcome. Subgroup analyses were performed using Cox proportional-hazards regression. IR, incomplete revascularization; CR, complete revascularization; NSTEMI, non-ST-segment elevation myocardial infarction; 3VD, 3-vessel disease; 2VD, 2-vessel disease; LAD, left anterior descending coronary artery.

hypothesis-generating. Second, the definition of CR in our study was determined by anatomic criteria instead of functional criteria such as FFR measurements or myocardial perfusion scan; at present, definition of CR or IR based on % luminal stenosis is not the prevalent diagnosis of an angiographically significant stenosis, and many of these lesions were not significant after FFR testing. On the other hand, this is commonly the way cardiac surgeons still view significant lesions, so in a way, it might be a fair, real-world comparison. Third, our study did not assess the detailed angiographic information like lesion length, complexity and vessel size. Finally, the exact reasons for CR or IR during PCI were not captured in our study; it also might be usual limitations of PCI database analysis.

In conclusion, based on the angiographic definition, patients with IR showed a similar risk of mortality as

compared with those with CR. However, IR was associated with higher incidence of MI during the follow-up. Further clinical studies are needed to show the completeness of revascularization on the basis of functional criteria beyond anatomic criteria affects the future cardiovascular events.

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Disclosure statement

The other authors declare that they have no conflicts of interest.

Appendix. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ahj.2016.06.020>.

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