Korean Circ J. 2024 Oct;54(10):603-615
https://doi.org/10.4070/kcj.2024.0017
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Original Research

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Impact of Complete Revascularization for Acute Myocardial Infarction In Multivessel Coronary Artery Disease Patients With Diabetes Mellitus

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OPEN ACCESS

Received: Jan 10, 2024
Revised: May 1, 2024
Accepted: May 1, 2024
Published online: Jun 4, 2024

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AUTHOR'S SUMMARY

This study investigated the clinical benefits of complete revascularization (CR) in acute myocardial infarction (AMI) patients with multivessel disease, particularly focusing on those with diabetes mellitus (DM). Analyzing 2,150 AMI patients over 3 years, CR significantly lowered patient-oriented composite outcomes (POCO) compared to incomplete revascularization. When stratified by DM, CR reduced 3-year clinical outcomes only in the non-DM group. Multivariate analysis demonstrated that CR significantly decreased 3-year POCO only in the non-DM group. Our results suggest that in AMI patients with multivessel disease, CR may be less beneficial in improving clinical outcomes for those with DM.

ABSTRACT

Background and Objectives: The clinical benefits of complete revascularization (CR) in acute myocardial infarction (AMI) patients are unclear. Moreover, the benefit of CR is unknown in AMI with diabetes mellitus (DM) patients. We sought to compare the prognosis of CR and incomplete revascularization (IR) in patients with AMI and multivessel disease, according to the presence of DM.
Methods: A total of 2,150 AMI patients with multivessel coronary artery disease were analyzed. CR was defined based on the angiographic image. The primary endpoint of this study was the patient-oriented composite outcome (POCO) defined as a composite of all-cause death, any myocardial infarction, and any revascularization within 3 years.
Results: Overall, 3-year POCO was significantly lower in patients receiving angiographic CR (985 patients, 45.8%) compared with IR (1,165 patients, 54.2%). When divided into subgroups according to the presence of DM, CR reduced 3-year clinical outcomes in the non-DM group but not in the DM group (POCO: 11.7% vs. 23.2%, p<0.001, any revascularization: 7.2% vs. 10.8%, p=0.024 in the non-DM group, POCO: 24.3% vs. 27.8%, p=0.295, any revascularization: 13.3% vs. 11.3%, p=0.448 in the DM group, for CR vs. IR). Multivariate analysis showed that CR significantly reduced 3-year POCO (hazard ratio, 0.52; 95% confidence interval, 0.36–0.75) only in the non-DM group.
Conclusions: In AMI patients with multivessel disease, CR may have less clinical benefit in DM patients than in non-DM patients.

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Korean Circulation Journal

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Funding
This study was supported by grants from the Patient-Centered Clinical Research Coordinating Center (grant number: HI19C0481, HC19C0305) and from Seoul National University Hospital (30-2023-0300).

Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Presentation
This abstract was presented at the ESC Congress 2020, The Digital Experience, 29 August–1 September, 2020.

Author Contributions
Conceptualization: Kang J, Park KW; Data curation: Han M; Formal analysis: Kang J, Park KW; Investigation and Methodology: Kang J; Resources: Han JK, Yang HM, Kang HJ, Koo BK; Supervision: Park KW, Kim HS; Writing - original draft: Kang J; Writing - review & editing: Kang J, Park S.

Keywords: Percutaneous coronary intervention; Myocardial infarction; Coronary vessels; Myocardial revascularization; Diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a well-known independent predictor of adverse clinical events in patients with coronary artery disease (CAD). Especially for the revascularization strategy, many trials have shown that diabetic patients have a higher risk of ischemic clinical events after coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).[1)2)] Also, patients with DM remain at high risk of adverse cardiovascular events after PCI compared with nondiabetic patients.[3)] Considering the expansion of the worldwide DM population[4)] and the higher mortality and cardiovascular disease prevalence in these patients, additional care should be focused on this population.[5)]

Meanwhile current guidelines support complete revascularization (CR) for multivessel CAD in acute myocardial infarction (AMI) patients. Various previous randomized controlled trials (RCTs) have demonstrated the superiority of CR compared to incomplete revascularization (IR) in ST-segment elevation myocardial infarction (STEMI) patients.[6-9)] Despite the paucity of RCTs dealing with this issue in non-STEMI patients with multivessel CAD, large-scale registry-based data have shown that CR appears to be superior to culprit-only PCI.[10)11)] Although the specific strategy of revascularization can be debated, the overall benefit of CR seems to be well accepted.

Regarding the treatment strategy in AMI patients with DM, no previous studies have given a clear answer for the benefit of CR. Therefore, we performed an analysis to evaluate the prognostic effects of CR on clinical outcomes in AMI patients with multivessel disease, according to the presence of DM.

METHODS

Ethical statement

The study protocol was approved by the ethics committee at each participating center and followed the principles of the Declaration of Helsinki 2013 and the study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (IRB No. H-1707-143-872). Informed consent was waived due to the retrospective nature of the study.

Study population

This study population was extracted from the 'Grand-DES' registry (NCT03507205), which is a Korean nationwide multicenter pooled registry of drug-eluting stents (**Supplementary Table 1**). The Grand-DES registry enrolled all-comers without any exclusion criteria except the patient's withdrawal of consent. A total of 17,286 patients were enrolled from January 1, 2004, to November 31, 2014, in 55 centers in Korea. After index PCI, clinical follow-ups were performed for up to 3 years.

Completeness of revascularization and calculation of the SYNTAX score

For evaluation of CR and calculation of the SYNTAX score (SS), quantitative coronary analysis (QCA) of baseline coronary angiographic images was performed at the Seoul National

https://doi.org/10.4070/kcj.2024.0017

University Hospital Cardiovascular Clinical Research Center Angiographic Core Laboratory by specialized QCA technicians, who were unaware of the purpose of this study. If there was a disagreement, a third blinded analyst reviewed the lesion and determined the final decision through consensus. The core laboratory has been verified by SS calculations, showing that the measurement correlation is more than 95%.[12]

Angiographic CR was defined as the treatment of any lesion with a diameter stenosis of more than 70% in vessels ≥2.5 mm as estimated on the diagnostic angiogram, leaving no residual significant lesions. Also, for additional analysis, we applied the SS system to quantify the degree of revascularization. The SS was calculated by visually assessing all coronary lesions with diameter stenosis ≥50% in vessels >1.5 mm diameter, using the SS algorithm on the official website (www.syntaxscore.com). Baseline SS was defined as the SS at initial coronary angiography, and 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.[13]

Endpoints and definitions

Clinical follow-up was performed up to 3 years (median: 1,123 days, interquartile range 1,078–1,137 days). The primary endpoint of the current study was the patient-oriented composite outcome (POCO) defined as a composite of all-cause death, any myocardial infarction (MI), and any revascularization within 3 years.

Statistical analyses

Data were presented as numbers and relative frequencies (percentages) for categorical variables and as mean ± standard deviation for continuous variables. Clinical and procedural characteristics were compared between patients according to the interventional strategy performed. For comparison among groups, χ^2 test for categorical variables and independent sample t-test or 1-way analysis of variance for continuous variables were applied. To evaluate the independent factors on endpoints, we used a multivariable Cox proportional hazards regression model. C-statistics with 95% confidence intervals (CIs) were calculated to validate the discriminant function of the model. In addition, the Cox proportional hazard regression in a propensity-score matched cohort and inverse probability treatment weighted (IPTW) Cox proportional hazard regression was also performed. Clinical and demographic factors such as age, previous hypertension, previous chronic kidney disease, dyslipidemia, previous peripheral vascular disease, left ventricle (LV) dysfunction, presence of anemia, prior history of MI, prior history of revascularization, family history of CAD, previously treated lesion, lesion characteristics (multiple lesions, bifurcation, left main vessel involvement), total stent number, total stent length, stent diameter, intravascular ultrasound (IVUS) usage, achievement of CR, angiographically severely calcified lesion, tortuosity, presence of thrombus, lesion success, device success, procedural success, usage of aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, statins and calcium channel blockers were used to estimate propensity score between the DM and non-DM groups. For the propensity score matching approach, a 1:1 greedy match was conducted with a caliper width of 0.05 of the standard deviation. Furthermore, we performed a multivariable analysis adjusting for variables with a standardized mean difference exceeding 20% in either the DM or non-DM group, as well as those with a standardized mean difference exceeding 10% in both groups. In order to address the issue of extreme weights, we performed IPTW trimming the lowest and highest 5.0 percentiles of the individuals.[14] Variables such as age, previous hypertension, previous DM, previous hypercholesterolemia, previous chronic kidney disease, presence of anemia, LV dysfunction, lesion characteristics

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(multiple lesions, bifurcation), total stent number, total stent length, stent diameter, IVUS usage and achievement of CR were added as covariates in the multivariate-adjusted Cox proportional hazard regression model. Event rates were calculated based on Kaplan-Meier censoring estimates, and the log-rank test was used to compare between CR and IR groups. For subgroup analysis, age, gender, body mass index, DM, LV dysfunction, clinical diagnosis, and culprit vessel were used to investigate. All probability values were 2-sided and p values <0.05 were considered statistically significant. Statistical tests were performed using SPSS, V23 (IBM Corp., Armonk, NY, USA) and R programming language, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The beneficial effect of complete revascularization in acute myocardial infarction patients

From the Grand-DES registry, a total of 2,150 AMI and multivessel disease patients were included in this study (**Figure 1**). Among these populations, CR was achieved in 985 patients

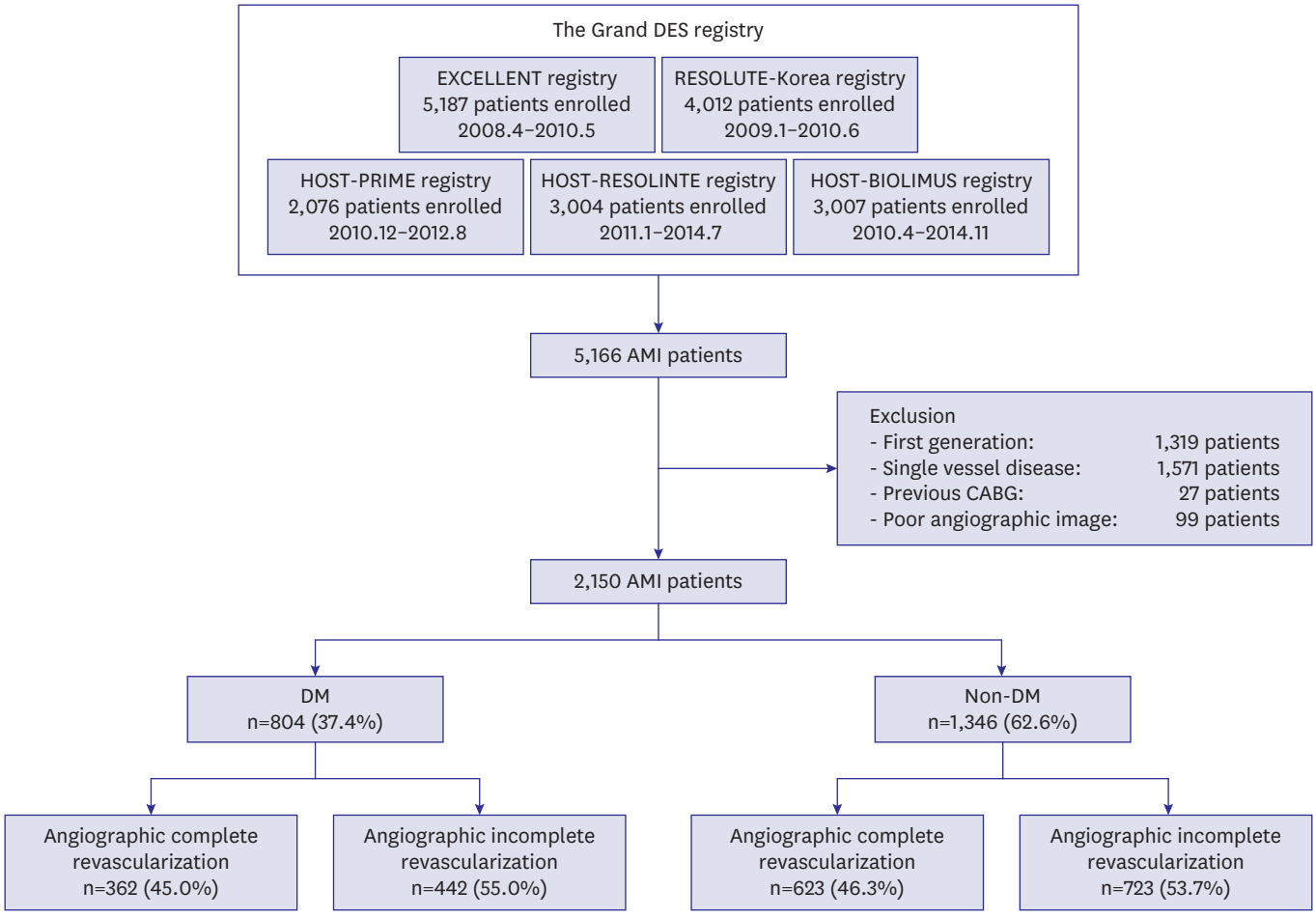

Figure 1. Study population.
The 'Grand DES registry' is a Korean Nationwide prospective registry, including the EXCELLENT registry, HOST-PRIME registry, HOST-RESOLINTE registry, RESOLUTE-Korea registry, and the HOST-BIOLIMUS registry. Out of the total 17,286 patients, 5,166 patients were AMI patients, and after excluding patients with a single vessel disease, patients with a previous CABG history, and those with a poor angiographic image, 2,150 patients were analyzed.
AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; DM = diabetes mellitus.

https://doi.org/10.4070/kcj.2024.0017

(45.8%), while 1,165 patients (54.2%) were performed IR. The baseline characteristics of the CR and IR groups are presented in **Table 1**. The IR group showed more risk factors, such as old age, hypertension, and chronic kidney disease, and showed a higher coronary complexity. In the CR group, the total stent length was longer (49.7±28.2 mm vs. 43.9±27.6 mm, p<0.001) and the minimal stent diameter was smaller (2.1±1.1 mm vs. 1.8±1.0 mm, p<0.001). The baseline SS was higher in the IR group (14.7±8.6 vs. 21.0±9.0, p<0.001, CR vs. IR). Of course, the delta SS was higher in the CR group (13.6±8.2 vs. 11.4±7.1, p<0.001, CR vs. IR). The medication pattern at discharge was similar between the CR and IR groups.

Table 1. Baseline characteristics according to completeness of revascularization

Variables	Total (n=2,150)	CR (n=985)	IR (n=1,165)	p value
Demographics				
Age (years)	64.6±12.0	63.7±12.1	65.4±11.9	0.001
Male	1,548 (72.0)	724 (73.5)	824 (70.7)	0.168
Body mass index (kg/m^2)	24.1±3.2	24.2±3.1	24.0±3.2	0.137
Diabetes mellitus	804 (37.4)	362 (36.8)	442 (37.9)	0.601
Hypertension	1,217 (56.6)	528 (53.6)	689 (59.1)	0.011
Dyslipidemia	1,160 (54.0)	540 (54.8)	620 (53.2)	0.484
Current smoking	863 (40.1)	404 (41.0)	459 (39.4)	0.473
Previous stroke	182 (8.5)	84 (8.5)	98 (8.4)	0.985
Congestive heart failure	63 (2.9)	23 (2.3)	40 (3.4)	0.169
Chronic kidney disease	884 (42.3)	368 (38.5)	516 (45.5)	0.002
Peripheral vascular disease	45 (2.1)	22 (2.2)	23 (2.0)	0.789
Prior MI	141 (6.6)	61 (6.2)	80 (6.9)	0.588
Prior PCI	220 (10.2)	104 (10.6)	116 (10.0)	0.699
STEMI	994 (43.9)	417 (42.3)	527 (45.2)	0.191
Family history of CAD	126 (5.9)	59 (6.0)	67 (5.8)	0.887
Angiographic findings				
Angiographic disease extent				<0.001
2 vessel disease	1,211 (56.3)	657 (66.7)	554 (47.6)	
3 vessel disease	939 (43.7)	328 (33.3)	611 (52.4)	
Left main disease	134 (6.2)	69 (7.0)	65 (5.6)	0.203
Bifurcation lesion	972 (45.2)	496 (50.4)	476 (40.9)	<0.001
Type B2/C lesion	1,902 (88.5)	882 (89.5)	1,020 (87.6)	0.170
Calcified lesion	220 (10.2)	93 (9.4)	127 (10.9)	0.298
Tortuous lesion	499 (23.2)	247 (25.1)	252 (21.6)	0.067
Thrombus in lesion	537 (25.0)	248 (25.2)	289 (24.8)	0.882
Previously treated lesion	171 (8.0)	71 (7.2)	100 (8.6)	0.274
Culprit lesion				0.502
LM	91 (4.2)	48 (4.9)	43 (3.7)	
LAD	898 (41.8)	422 (42.8)	476 (40.9)	
LCX	399 (18.6)	179 (18.2)	220 (18.9)	
RCA	760 (35.3)	335 (34.0)	425 (36.5)	
Stent diameter (mm)	3.0±0.4	3.0±0.4	3.0±0.4	0.716
Stent diameter <3 mm	952 (44.4)	424 (43.2)	528 (45.5)	0.316
Min. stent diameter (mm)	2.9±0.4	2.9±0.4	2.9±0.4	0.026
Min. stent diameter <3 mm	1,170 (54.6)	543 (55.4)	627 (54.0)	0.562
Total stent length (mm)	46.6±28.0	49.7±28.2	43.9±27.6	<0.001
Total stent length ≥30 mm	1,391 (64.8)	691 (70.3)	700 (60.1)	<0.001
Total stent number	1.9±1.0	2.1±1.1	1.8±1.0	<0.001
Staged PCI (among CR patients)	NA	89 (9.0)	NA	NA
Contrast volume (mL)	293±146	302±143	282±148	0.156
GP IIb/IIIa inhibitor usage	190 (8.8)	88 (8.9)	102 (8.8)	0.945
IVUS usage	789 (36.7)	399 (40.5)	390 (33.5)	0.001
Device success	2,108 (98.1)	967 (98.3)	1,141 (97.9)	0.687
Lesion success	2,100 (97.7)	962 (97.8)	1,138 (97.7)	1.000
Procedural success	2,095 (97.5)	960 (97.6)	1,135 (97.4)	0.950
SS at baseline	18.1±9.3	14.7±8.6	21.0±9.0	<0.001
SS after PCI (residual)	5.7±6.5	1.1±2.0	9.6±6.5	<0.001
Delta SS	12.4±7.7	13.6±8.2	11.4±7.1	<0.001

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https://doi.org/10.4070/kcj.2024.0017

Table 1. (Continued) Baseline characteristics according to completeness of revascularization

Variables	Total (n=2,150)	CR (n=985)	IR (n=1,165)	p value
Laboratory data				
LV ejection fraction (%)	51.8±11.5	53.4±10.8	50.4±11.9	<0.001
WBC (×10^3/μL)	9.83±3.74	9.73±3.65	9.92±3.82	0.244
Hemoglobin (g/dL)	13.4±2.2	13.6±2.1	13.3±2.3	0.006
Anemia (Hb<12 g/dL)	508 (24.1)	214 (22.4)	294 (25.6)	0.095
Creatinine (mg/dL)	1.2±1.2	1.2±1.0	1.2±1.3	0.083
Total cholesterol (mg/dL)	177±46	178±45	177±46	0.683
Triglyceride (mg/dL)	105±95	111±106	100±84	0.007
HDL-cholesterol (mg/dL)	35±19	35±19	35±19	0.825
LDL-cholesterol (mg/dL)	115±41	115±42	116±40	0.857
Discharge medication				
Aspirin	2,130 (99.1)	981 (99.6)	1,149 (98.6)	0.036
Clopidogrel	2,090 (97.2)	958 (97.3)	1,132 (97.2)	1.000
DAPT	2,083 (96.9)	956 (97.1)	1,127 (96.7)	0.766
Beta-blocker	1,692 (78.7)	789 (80.1)	903 (77.5)	0.159
ACE inhibitors or ARBs	1,638 (76.2)	752 (76.3)	886 (76.1)	0.914
Statin	1,926 (89.6)	899 (91.3)	1,027 (88.2)	0.022
Calcium channel blocker	235 (10.9)	106 (10.8)	129 (11.1)	0.872

Values are presented as mean±standard deviation or number (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CR = complete revascularization; DAPT = dual antiplatelet agent; GP = glycoprotein; HDL = high-density lipoprotein; IR = incomplete revascularization; IVUS = intravascular ultrasound; LAD = left anterior descending; LCX = left circumflex; LDL = low-density lipoprotein; LM = left main; LV = left ventricle; MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention; RCA = right coronary artery; SS = SYNTAX score; STEMI = ST-segment elevation myocardial infarction; WBC = white blood cell.

A comparison of clinical outcomes between the CR and IR groups is presented in **Supplementary Table 2**. CR group showed a lower rate of 3-year POCO compared to the IR group (16.3% [161/985] vs. 25.0% [291/1,165], p<0.001, CR vs. IR). Multivariable Cox regression analysis, propensity score-matched analysis, and inverse probability weighting adjusted analysis all consistently showed CR significantly reduced the risk of POCO compared with IR. The cumulative incidence of POCO according to completeness of revascularization is shown in **Figure 2**. As seen in the forest plot (**Supplementary Figure 1**), the effect of CR was not significantly different along various subgroups except the DM group.

Complete revascularization vs. incomplete revascularization according to the presence of diabetes mellitus

Upon multivariate analysis, DM was an independent predictor of 3-year POCO in AMI patients (hazard ratio [HR], 1.55; 95% CI, 1.25–1.91; p<0.001). As observed in the subgroup analysis (**Supplementary Figure 1**), the effect of CR did not show interaction with various subgroups, except for the DM subgroup (p-value for interaction=0.003). 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 804 patients (37.4%) in the DM group and 1,346 patients (62.6%) in the non-DM group. The baseline demographics, angiographic findings, laboratory findings, and discharge medication according to the presence of DM are summarized in **Supplementary Table 3**. Patients with DM seemed to have more clinical risk factors compared with those without (i.e. older in age, higher proportion of females, hypertension, dyslipidemia, history of stroke, chronic kidney disease, and anemia). Angiographic characteristics showed that the DM group had slightly more patients with 3-vessel disease and used smaller diameter stents.

The rates of POCO during the 3-year follow-up periods were significantly lower in the CR group compared with the IR group in the non-DM group (POCO rate: 73/623 [11.7%] vs. 168/723 [23.2%], p<0.001, in the CR and IR group, respectively). However, there were no significant

https://doi.org/10.4070/kcj.2024.0017

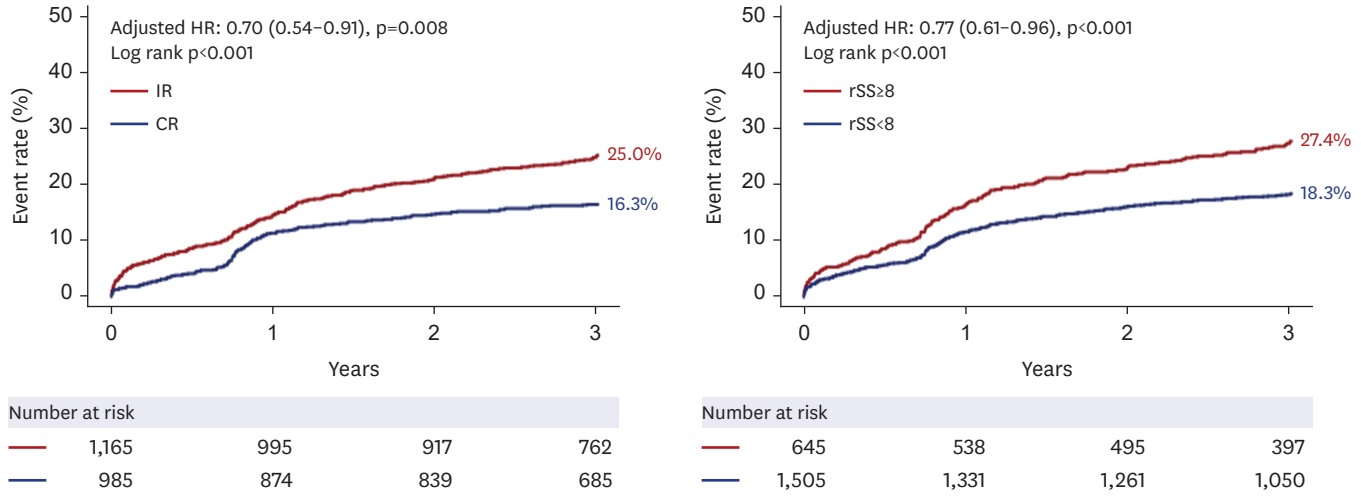

Figure 2. Cumulative Incidence of POCO during the 3-year follow-up period, according to the completeness of revascularization.
The survival curve of 3-year POCO according to CR. Overall, CR had a beneficial impact on 3-year POCO by an HR of 0.70 (95% CI, 0.54–0.91; p=0.008). Moreover, the 3-year POCO was significantly more common in those with an SS-based IR (POCO: 18.3% vs. 27.4%, p<0.001, in the SS-based CR vs. SS-based IR respectively).
CR = complete revascularization; HR = hazard ratio; IR = incomplete revascularization; POCO = patient-oriented composite outcome; rSS = residual SYNTAX score; SS = SYNTAX score.

differences in the DM group (POCO rate: 88/362 [24.3%] vs. 123/442 [27.8%], p=0.281 for CR vs. IR group). This trend was consistent for all components of 3-year POCO in the DM group. Upon multivariate analysis, IR was an independent predictor of 3-year POCO in only the non-DM group (**Table 2**, **Figure 3**). The cumulative incidence of POCO during the 3-year follow-up period following propensity score matching is shown in **Supplementary Figure 2**, and the histograms are plotted in **Supplementary Figure 3**. The propensity score-matched baseline characteristics of DM and non-DM are shown in **Supplementary Tables 4** and **5**. Especially for POCO, all-cause death, MI, and any revascularization, a significant interaction was observed between the revascularization strategy and the presence of DM (**Supplementary Figure 4**).

Subgroup analysis

Subgroup analysis was performed in those who received IVUS-guided PCI according to the severity of DM. In patients who received IVUS-guided PCI, the results were consistent with the total population; CR was favorable only in the non-DM population (**Supplementary Table 6**, **Supplementary Figure 5**). For the analysis according to the severity of DM, the DM group was divided into 2 groups by an HbA1c cut-off value of 7.0 (DM group 1 [HbA1c<7.0, n=337]; DM group 2 [HbA1c≥7.0, n=393]). The impact of CR was insignificant in both DM groups (DM group 1: 37/157 [23.6%] vs. 51/180 [28.3%], p=0.301, DM group 2: 44/182 [24.2%] vs. 60/221 [28.4%], p=0.307, for CR vs. IR group) (**Supplementary Figure 6**, **Supplementary Table 7**).

Corroboration using SYNTAX score-based complete revascularization

Due to the various 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 3-year POCO was significantly more common in those with an SS-based IR (POCO: 18.3% vs. 27.4%, p<0.001, in the SS-based CR vs. IR respectively). On multivariate analysis, SS-based IR was again an independent risk factor for 3-year clinical events (**Table 3**). When stratified into subgroups according to the presence of DM, SS-based CR, and IR showed distinct effects according to the presence of DM. SS-based CR was associated with a lower 3-year POCO, only in those without DM, while there were no significant differences in the 3-year clinical outcomes between SS-based CR and IR in the DM group (**Figure 3**).

https://doi.org/10.4070/kcj.2024.0017

Table 2. Three-year clinical outcomes according to the presence of DM in acute myocardial infarction

Event	Total	CR	IR	Unadjusted		Multivariable-adjusted		PSM*		IPTW	
				HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
DM	(n=804)	(n=362)	(n=442)								
POCO	211 (26.2)	88 (24.3)	123 (27.8)	0.85 (0.65–1.12)	0.245	0.86 (0.60–1.25)	0.429	0.94 (0.59–1.50)	0.789	0.88 (0.61–1.29)	0.518
All-cause death	126 (15.7)	47 (13.0)	79 (17.9)	0.53 (0.49–1.01)	0.056	0.71 (0.45–1.14)	0.157	0.86 (0.47–1.55)	0.605	0.73 (0.44–1.21)	0.221
MI	27 (3.4)	14 (3.9)	13 (2.9)	1.19 (0.55–2.58)	0.651	1.75 (0.52–5.89)	0.363	1.59 (0.43–5.89)	0.480	1.83 (0.61–5.53)	0.282
Any revascularization	98 (12.2)	48 (13.3)	50 (11.3)	1.15 (0.77–1.70)	0.498	1.38 (0.75–2.53)	0.298	1.36 (0.67–2.76)	0.393	1.04 (0.61–1.75)	0.887
TLF	118 (14.7)	47 (13.0)	71 (16.1)	0.79 (0.55–1.14)	0.207	0.88 (0.54–1.44)	0.614	1.26 (0.69–2.30)	0.447	0.81 (0.49–1.35)	0.428
Cardiac death	70 (8.7)	22 (6.1)	48 (10.9)	0.54 (0.33–0.90)	0.018	0.62 (0.33–1.14)	0.119	0.93 (0.43–2.01)	0.847	0.57 (0.29–1.12)	0.102
TVMI	16 (2.0)	10 (2.8)	6 (1.4)	2.00 (0.73–5.51)	0.179	3.48 (0.48–25.21)	0.216	5.38 (0.63–46.55)	0.126	3.62 (0.93–14.13)	0.064
TLR	55 (6.8)	30 (8.3)	25 (5.7)	1.43 (0.84–2.43)	0.185	2.14 (0.91–5.04)	0.083	2.45 (0.93–6.45)	0.069	1.29 (0.63–2.64)	0.495
Non-TLR	43 (5.3)	18 (5.0)	25 (5.7)	0.85 (0.46–1.55)	0.589	0.77 (0.32–1.87)	0.570	0.48 (0.14–1.65)	0.244	0.83 (0.39–1.79)	0.635
Stent thrombosis	12 (1.5)	8 (2.2)	4 (0.9)	2.40 (0.72–7.97)	0.153	1.30 (0.32–5.25)	0.709	1.59 (0.37–6.83)	0.528	12.22 (2.11–70.94)	0.005
Any bleeding	29 (3.6)	10 (2.8)	19 (4.3)	0.62 (0.29–1.34)	0.227	0.78 (0.27–2.22)	0.641	1.37 (0.42–4.41)	0.603	0.78 (0.29–2.08)	0.624
Non-DM	(n=1,346)	(n=623)	(n=723)								
POCO	241 (17.9)	73 (11.7)	168 (23.2)	0.48 (0.36–0.63)	<0.001	0.52 (0.36–0.75)	<0.001	0.47 (0.29–0.74)	0.001	0.35 (0.24–0.49)	<0.001
All-cause death	113 (8.4)	30 (4.8)	83 (11.5)	0.41 (0.27–0.62)	<0.001	0.53 (0.31–0.93)	0.028	0.54 (0.28–1.04)	0.065	0.26 (0.15–0.44)	<0.001
MI	36 (2.7)	8 (1.3)	28 (3.9)	0.29 (0.12–0.72)	0.007	0.18 (0.07–0.51)	0.001	0.18 (0.05–0.65)	0.008	0.38 (0.11–1.36)	0.140
Any revascularization	123 (9.1)	45 (7.2)	78 (10.8)	0.64 (0.44–0.92)	0.016	0.61 (0.37–0.99)	0.047	0.55 (0.29–1.03)	0.063	0.57 (0.34–0.94)	0.029
TLF	108 (8.0)	33 (5.3)	75 (10.4)	0.49 (0.33–0.74)	0.001	0.40 (0.23–0.70)	0.001	0.35 (0.16–0.74)	0.006	0.36 (0.21–0.64)	0.003
Cardiac death	70 (5.2)	15 (2.4)	55 (7.6)	0.31 (0.17–0.55)	<0.001	0.25 (0.11–0.55)	<0.001	0.25 (0.09–0.70)	0.007	0.19 (0.09–0.40)	<0.001
TVMI	20 (1.5)	7 (1.1)	13 (1.8)	0.61 (0.24–1.53)	0.294	0.25 (0.07–0.90)	0.035	0.35 (0.07–1.85)	0.217	3.04 (0.63–14.69)	0.165
TLR	40 (3.0)	20 (3.2)	20 (2.8)	1.13 (0.61–2.09)	0.710	0.80 (0.34–1.84)	0.584	0.85 (0.30–2.43)	0.764	1.06 (0.43–2.60)	0.903
Non-TLR	83 (6.2)	25 (4.0)	58 (8.0)	0.48 (0.30–0.76)	0.002	0.51 (0.28–0.96)	0.036	0.44 (0.20–0.97)	0.043	0.45 (0.24–0.84)	0.012
Stent thrombosis	18 (1.3)	6 (1.0)	12 (1.7)	0.57 (0.21–1.52)	0.261	0.43 (0.12–1.55)	0.197	0.55 (0.12–2.43)	0.430	0.48 (0.09–2.35)	0.366
Any bleeding	37 (2.7)	18 (2.9)	19 (2.6)	1.08 (0.57–2.06)	0.813	1.72 (0.67–4.40)	0.261	3.28 (1.03–10.42)	0.044	0.90 (0.36–2.29)	0.830

Values are presented as number (%).
CI = confidence interval; CR = complete revascularization; DM = diabetes mellitus; HR = hazard ratio; IPTW = inverse probability weighting analysis; IR = incomplete revascularization; MI = myocardial infarction; POCO = patient-oriented composite outcome; PSM = propensity score-matched analysis; SS = SYNTAX score; TLF = target lesion failure; TLR = target lesion revascularization; TVMI = target vessel myocardial infarction.
*Covariates included SS at baseline, minimum length of stent diameter, contrast volume for the DM group and presence of anemia, SS at baseline, minimum length of stent diameter, and contrast volume for the non-DM group.

DISCUSSION

In our current study, we analyzed the effect of CR on the 3-year outcomes of AMI patients with multivessel disease. Overall, our findings can be summarized as follows: 1) In AMI patients with multivessel CAD, CR was achieved in nearly half of the population and was associated with lower rates of POCO at 3 years follow-up. 2) DM was an independent predictor of 3-year POCO. 3) In subgroup analysis, a significant interaction was present between DM and CR. CR was associated with a lower rate of 3-year POCO only in the non-DM group, while this was not observed in the DM group. 4) SS-based CR also showed consistent results.

Our study was based on large-scale registry data, which enrolled all-comers without any exclusion criteria except for the patient's withdrawal of consent. Compared with previous RCTs that excluded high-risk patients, our study may be more representative of the real-world practice. Our analysis of real-world data showed that CR was associated with lower rates of clinical outcomes in patients with AMI and multivessel coronary disease. To confirm our findings using a more quantifiable definition of CR, we analyzed our data using an SS-based definition of CR.[12] We used the previously studied definition of reasonable IR of rSS<8,[15] to evaluate the effect of SS-based CR in our population. Similar to angiographic CR, SS-based CR was also beneficial in patients with AMI. Our findings were concordant using both an angiographic definition and an SS-based definition of CR.

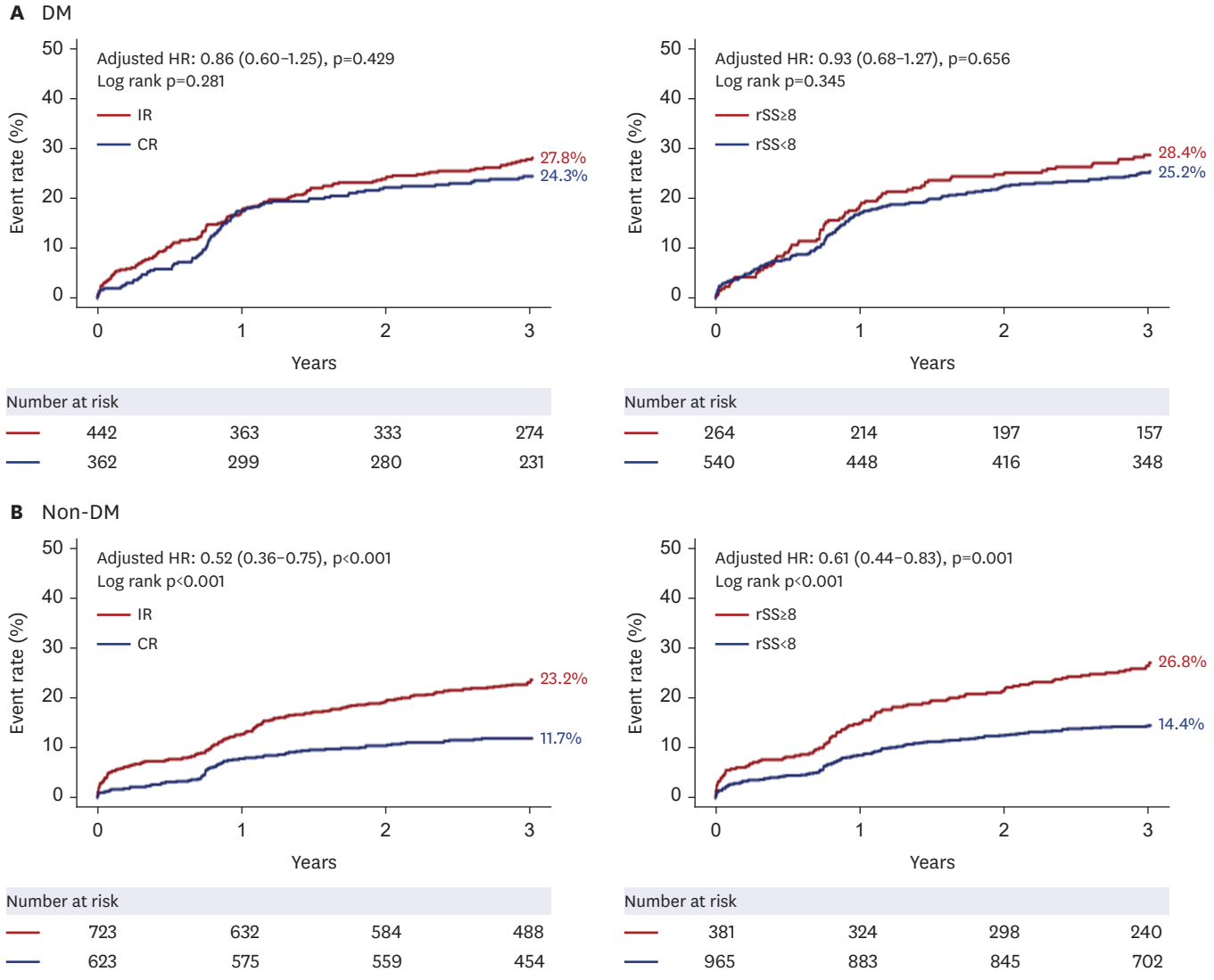

Figure 3. Cumulative Incidence of POCO during the 3-year follow-up period, according to the presence of DM and the completeness of revascularization. In the subgroup according to the presence of DM, CR reduced 3-year POCO only in the non-DM group (HR, 0.52; 95% CI, 0.36–0.75; p<0.001) The beneficial impact of SS-based CR was also only shown in the non-DM group (HR, 0.61; 95% CI, 0.45–0.83; p=0.001), while the effect was neutralized in the DM group.
CR = complete revascularization; DM = diabetes mellitus; HR = hazard ratio; IR = incomplete revascularization; POCO = patient-oriented composite outcome; rSS = residual SYNTAX score.

Table 3. Three-year POCO according to the residual SS

Three-year POCO	Residual SS <8	Residual SS ≥8	p value	Multivariable-adjusted*		p for interaction
				HR (95% CI)	p value	
Total population	275/1,505 (18.3)	177/645 (27.4)	<0.001	0.77 (0.62–0.96)	0.018	0.005
DM group	136/540 (25.2)	75/264 (28.4)	0.345	0.93 (0.68–1.27)	0.656	
Non-DM group	139/965 (14.4)	102/381 (26.8)	<0.001	0.61 (0.45–0.83)	0.009	

Values are presented as number (%).
CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; POCO = patient-oriented composite outcome; SS = SYNTAX score.
*The following patient risk factors were included in the multivariate-adjusted Cox proportional hazard regression model: age, hypertension, hypercholesterolemia, chronic kidney disease, anemia, left ventricular dysfunction, lesion characteristics (multiple lesions, bifurcation), total stent number, total stent length, stent diameter, intravascular ultrasound usage and achievement of complete revascularization.

Subgroup analysis showed that the effect of CR was significantly different only according to the presence of DM. Considering the clinical impact of DM on patients with CAD, this is an interesting finding that deserves in-depth analysis. Moreover, in the STEMI population of our

https://doi.org/10.4070/kcj.2024.0017

study, CR improved adverse clinical outcomes, which was consistent with the conclusions of previous RCTs.

DM is a well-recognized disease that is associated with worse outcomes after revascularization in patients with CAD. Some putative mechanisms, intimal hyperplasia, higher inflammatory response, higher coagulability, and endothelial dysfunction, have been considered to be probable causes of the high rate of adverse events in patients with DM after stent implantation.[16] Although it is acknowledged that CABG is recommended in diabetic patients with multivessel CAD, PCI is performed in the real-world process due to various reasons.[17] This study aimed to examine this patient population undergoing PCI. Also, a study focusing on the natural course of non-culprit coronary considered that DM was the only significant clinical factor to predict non-culprit ischemic-driven revascularization.[18] From the results of our study, we found that CR reduced the rates of 3-year POCO only in the non-DM group and not in those with DM. This is a finding that has been shown in previous studies.[19-21] A previous registry-based study showed that CR compared with IR did not improve mortality in CAD patients with DM.[20] Moreover, subgroup analysis of recent large-scale RCTs implied that CR cannot significantly reduce the adverse clinical events compared to the infarct-related artery (IRA)-only PCI in DM patients.[21] These studies can support our results that the beneficial effect of CR is not ideal in patients with DM. We also performed a subgroup analysis according to the severity of DM. We could find that the benefit of CR in terms of POCO risk gradually diminished along with the severity of DM. (HR, 0.52 vs. HR, 0.73 vs. HR, 0.89; in the non-DM vs. DM group 1 vs. DM group 2, respectively). Cui et al.'s study also suggested that staged PCI for non-culprit lesions had no effect in diabetic patients.[19] However, in this study, 1st generation DES and bare-metal stents account for 75%, and we exclusively included patients treated with 2nd generation DES. Therefore, our results could provide evidence for current clinical practice in 2nd generation DES era.

Our results showed that the reduction of POCO was driven by a significant reduction of its all components (death, MI, and revascularization). When comparing the effect of CR in those with and without DM, not only there was a statistical difference in incidence between CR and IR, but the impact of CR (numerical value of the HR) was less protective in the group with DM for all other secondary endpoints. As for CR, the beneficial effect of non-IRA strategy in AMI patients with multivessel disease is supported by various explanations. Multivessel PCI tends to improve blood flow to the ischemic myocardium and prevent the lesion progression of plaques. However, our results suggest that the theoretical benefit of CR did not improve the clinical outcomes in those with DM. As a practical explanation, this can be explained by the higher risk of revascularization in patients who received CR, due to the larger number of stents implanted and smaller stent diameters. Longer stenting and stenting in smaller vessels are well-known risk factors for target lesion revascularization (TLR) and target vessel MI (TVMI).[22] Those who end up with more metal are inevitably exposed to a higher risk of stent-related events. In our study, this was observed in patients with DM who received CR, in which the incidence of any revascularization, TVMI, TLR, and stent thrombosis was higher than that of those who received IR. Moreover, DM itself is a well-known risk factor for stent-related complications, which may have aggravated the event rate in the DM group.[23] Also, our findings can be interpreted that controlling DM as a risk factor may be more important than achieving CR, because the major determinant of clinical outcomes is DM itself, rather than the completeness of revascularization. However, these explanations are at best hypothesis-generating, while further studies are needed to concrete our findings.

https://doi.org/10.4070/kcj.2024.0017

Our study has several limitations. First, this study was an observational analysis of a prospective registry, therefore the PCI strategies (CR vs. IR) were not randomized. The non-randomized treatment strategy, which includes adjunctive post-PCI treatment is an inherent limitation, which leaves the possibility of selection bias and treatment bias. Although we used serial adjusted analyses to correct for possible biases and confounders, the possibility of unmeasurable factors, which were not compensated by statistical models, cannot be completely ruled out. Second, CR was evaluated only by angiography, without functional evaluations such as FFR. Third, the presence of DM was a binary value, and the diabetes control rate was not taken into account. Additional analysis should be done to evaluate the impact of CR according to the glycemic control rate. Fourth, current ACS guidelines recommend ticagrelor and prasugrel over clopidogrel. However, the enrollment period of the current study was from 2004 to 2014, during which the absolute majority of patients received clopidogrel as the P2Y12 inhibitor in Korea. Although this may be a limitation, this may also be interpreted as greater homogeneity within the study population. Fifth, it should be noted that a single center supervised data merging of multiple registries. This was an unblinded process and as such may be prone to unexpected confounding in the data analysis. Lastly, during the process of obtaining a propensity-score matched cohort, we were unable to achieve standardized mean differences below the successful cut-off value for all baseline characteristics. This requires careful attention in interpreting the results, as achieving balance between the 2 groups was challenging due to limitations in patient numbers. As to deal with this issue, we performed a multivariable analysis with the PSM population including the imbalanced variables as covariates.

The benefits of CR in AMI patients with multivessel disease were confirmed again in this large-scale prospective registry. However, when divided into subgroups by the presence of DM, there was less benefit of CR in patients with DM. Our results suggest that in patients with AMI and multivessel disease without DM, more positive consideration should be given to CR.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
List of investigators and participating centers of the Korean multicenter drug-eluting stent registry

Supplementary Table 2
Three-year clinical outcomes between CR and IR group

Supplementary Table 3
Baseline characteristics according to the presence of DM in acute myocardial infarction (n=2,150)

Supplementary Table 4
Baseline characteristics of the diabetes mellitus group in propensity score matching

Supplementary Table 5
Baseline characteristics of the non-diabetes mellitus group in propensity score matching

https://doi.org/10.4070/kcj.2024.0017

Supplementary Table 6
Impact of CR on POCO during the 3-year follow-up period in the IVUS subgroup

Supplementary Table 7
Impact of CR on POCO according to individual DM groups

Supplementary Figure 1
Subgroup analysis of the impact of CR and IR.

Supplementary Figure 2
Cumulative incidence of POCO during the 3-year follow-up period following propensity score matching.

Supplementary Figure 3
Histogram showing the density of propensity score distribution.

Supplementary Figure 4
The impact of CR according to the presence of DM in various outcomes.

Supplementary Figure 5
Cumulative incidence of POCO during the 3-year follow-up period in the IVUS subgroup.

Supplementary Figure 6
The impact of DM groups on the incidence of POCO.

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