Multivessel vs Single-Vessel Revascularization in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome and Multivessel Disease in the Drug-Eluting Stent Era

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ABSTRACT

Background: We sought to compare long-term outcomes for multivessel revascularization (MVR) vs single-vessel revascularization (SVR) with drug-eluting stents (DES) in patients with non–ST-segment elevation acute coronary syndrome (NSTEMI-ACS) and multivessel coronary artery disease (MVD).

Hypothesis: In DES era, MVR would improve long-term clinical outcomes in patients with NSTEMI-ACS.

Methods: We studied 179 patients undergoing MVR and 187 patients undergoing SVR for NSTEMI-ACS and MVD. Major adverse cardiac events (MACE) were defined as death, myocardial infarction, or any revascularization.

Results: During follow-up (median 36 months), MACE occurred in 96 patients (26.2%); 35 (19.6%) in the MVR group and 61 (32.6%) in the SVR group ($P = 0.003$). In multivariate analysis, MVR was associated with a lower incidence of MACE (hazard ratio [HR]: 0.50, 95% confidence interval [CI]: 0.30–0.85) and revascularization (HR: 0.43, 95% CI: 0.24–0.78), but not of death (HR: 0.69, 95% CI: 0.25–1.93) and myocardial infarction (HR: 0.39, 95% CI: 0.11–1.47). The incidence of periprocedural renal dysfunction was not significantly different between patients undergoing MVR vs SVR (3.4% vs 1.6%, $P = 0.33$). Definite or probable stent thrombosis occurred at a similar rate (2.2% in the MVR group and 2.7% in the SVR group, $P = 0.99$).

Conclusions: In patients with NSTEMI-ACS and MVD, MVR using drug-eluting stents may reduce MACE. Our findings should be confirmed by a prospective, randomized trial.

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Introduction

Multivessel disease (MVD) is noted in about half of patients with non–ST-segment elevation acute coronary syndrome (NSTEMI-ACS) at presentation^{1–3} and is associated with increased mortality after myocardial infarction (MI).^{4,5} In the Framingham and Fast Revascularization During Instability in Coronary Artery Disease (FRISC) II trial, one of the landmark studies that changed the NSTEMI strategy toward an early invasive strategy, revascularization was recommended in any artery with $\geq 70\%$ stenosis.⁶ However, it is not clear whether multivessel percutaneous coronary intervention (PCI) beyond the culprit lesion in patients with

NSTEMI-ACS and MVD can improve long-term prognosis. Few studies have compared long-term outcomes of multivessel revascularization (MVR) and single-vessel revascularization (SVR) in patients with NSTEMI-ACS and MVD undergoing PCI.^{7,8} Moreover, these studies were conducted in the era of bare-metal stents. Therefore, we sought to compare long-term outcomes for MVR vs SVR using drug-eluting stents (DES) in patients with NSTEMI-ACS and MVD.

Methods

Study Population

Between April 2003 and December 2006 at the Samsung Medical Center (Seoul, Republic of Korea), 532 consecutive patients with NSTEMI-ACS and MVD underwent PCI using DES. Multivessel disease was defined as coronary lesions with $\geq 50\%$ -diameter stenosis by quantitative coronary analysis in at least 2 of the 3 major epicardial coronary arteries or their major branches.⁷ Patients who had prior coronary bypass grafts, isolated left main coronary artery disease (CAD), or chronic total occlusions; who had experienced cardiogenic shock before intervention; and

This work was supported by Sungkyunkwan University Foundation for Corporate Collaboration (2008-1366-000) and the IN-SUNG Foundation for Medical Research, Republic of Korea (CA88161). The authors have no other funding, financial relationships, or conflicts of interest to disclose.

who underwent planned staged intervention after discharge from the index hospitalization were excluded. After the exclusions, the study population for the analysis included 366 patients. Baseline characteristics, angiographic and procedural data, medication use, and outcome data were recorded prospectively by research coordinators of the dedicated PCI registry. For validation, information about vital status was obtained from the National Population Registry of the Korea National Statistical Office using a unique personal identification number. The local institutional review board approved this study and waived the requirement for informed consent for access to the institutional PCI registry.

Percutaneous Coronary Intervention

All procedures were performed with standard interventional techniques.⁹ The decision to perform MVR was made by the operators. Type of DES, predilation, poststent adjunctive balloon inflation, use of intravascular ultrasound, and administration of glycoprotein IIb/IIIa receptor antagonists were all at the operator's discretion. After the procedure, aspirin (100 or 200 mg once daily) was continued indefinitely. The duration of clopidogrel use was at the operator's discretion.

Angiographic Analysis

The amount of myocardium at risk was assessed using the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) lesion score.¹⁰ In addition, the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score was calculated to further grade the CAD.¹¹ The total APPROACH lesion score and SYNTAX score were derived from the summation of the individual scorings for each separate lesion, respectively. To calculate these scores, all coronary angiograms were reviewed by 2 experienced technicians who were blinded to the study purpose.

Definitions and Outcome Variables

Multivessel revascularization was defined as PCI on ≥ 2 major epicardial coronary vessels during the index hospitalization.¹² The PCI of multiple lesions in 1 epicardial vessel was considered as SVR. Staged PCI during the index hospitalization was considered as 1 index procedure and subsequently included in MVR strategy. When a plan for staged intervention was identified in medical records during the index hospitalization but staged PCI was performed after discharge, patients were excluded to avoid confusion in classifying those events into staged intervention or ischemia-driven revascularization. The primary outcome was major adverse cardiac events (MACE), defined as the composite of death from any cause or MI, or any revascularization. Secondary outcomes were periprocedural renal dysfunction and stent thrombosis (ST) in addition to the components of the primary outcome. Periprocedural renal dysfunction was defined as an increase in creatinine >0.5 mg/dL or a $\geq 25\%$ increase in creatinine after the index procedure.¹³ Definite, probable, and possible ST was defined according to the Academic Research Consortium definitions.¹⁴

Statistical Analysis

Differences between groups of patients receiving MVR and SVR in baseline characteristics were compared using the *t* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables, as appropriate. Survival curves were constructed using Kaplan-Meier estimates and compared with the log-rank test. The effect of MVR on MACE, death or MI, and revascularization were determined using the Cox proportional hazard model. Unadjusted and risk-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) controlling for age, gender, diabetes mellitus, prior PCI, left ventricular ejection fraction, the APPROACH lesion score, the SYNTAX score, left main disease, use of intravascular ultrasound, and total stent length use were calculated. All *P* values are 2-tailed and *P* < 0.05 was considered significant. Prespecified subgroup analyses were performed according to the values of the APPROACH lesion and SYNTAX scores. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Multivessel revascularization was performed in 179 patients (48.9%) and SVR in 187 patients (51.1%). Baseline demographic, clinical, angiographic, and procedural characteristics of the 2 groups are shown in Tables 1 and 2. In general, the 2 groups were similar regarding demographic characteristics, risk factors for CAD, and medication at discharge. However, patients undergoing MVR had a lower experience of previous PCI. Left main disease was more common, and the APPROACH lesion score was significantly higher in the MVR group compared with the SVR group.

Clinical Outcomes

There was a total of 96 events during a median follow-up of 36 months (interquartile range [IQR], 30–43 mo). In unadjusted analysis, the incidence of MACE was significantly lower in patients with MVR vs SVR (Table 3 and Figure 1). Although both groups had comparable incidences of the composite of death or MI, the MVR group had a significantly lower incidence of any revascularization. Difference in revascularization was attributable to non-target-vessel revascularization (non-TVR) rather than target-vessel revascularization. In multivariate analysis, the MVR group still had a lower incidence of MACE compared with the SVR group. The rates of any revascularization and non-TVR were also lower in the MVR group than in the SVR group after adjusting for covariates (Table 3). The incidence of periprocedural renal dysfunction was not significantly different between patients undergoing MVR vs SVR (3.4% in the MVR group vs 1.6% in the SVR group, *P* = 0.33). During the follow-up period, definite, probable, and possible ST occurred in 6, 3, and 3 patients, respectively. The incidence of definite or probable ST was similar between the 2 groups (2.2% in the MVR group vs 2.7% in the SVR group, *P* = 0.99). Of patients who had definite or probable thrombosis, 1 patient was on dual antiplatelet therapy and 3 were on aspirin only in the MVR group, and 4 were on dual antiplatelet therapy and 1 was on aspirin only in the SVR

Table 1. Clinical Characteristics of the Study Subjects

	MVR (N = 179)	SVR (N = 187)	P Value
Demographic characteristics			
Age, y	64.5 ± 10.8	65.3 ± 11.6	0.488
Male sex	128 (71.5)	117 (62.6)	0.069
Coexisting conditions or risk factors			
DM	60 (33.5)	76 (40.6)	0.159
Hypertension	104 (58.1)	117 (62.6)	0.383
Current smoker	45 (25.1)	35 (18.7)	0.137
Dyslipidemia	57 (31.8)	47 (28.3)	0.465
Family history of CAD	13 (7.3)	12 (6.4)	0.749
PAOD	6 (3.4)	8 (4.3)	0.644
Prior MI	16 (8.9)	15 (8.0)	0.753
Prior CVA	16 (8.9)	14 (7.5)	0.613
Prior PCI	14 (7.8)	29 (15.5)	0.022
CHF	20 (11.2)	29 (15.5)	0.223
Chronic renal failure	10 (5.6)	11 (5.9)	0.903
LVEF, %	57.3 ± 11.6	56.6 ± 10.8	0.587
LVEF < 50%	36 (20.5)	40 (21.6)	0.786
Medication at discharge			
Aspirin	175 (97.8)	184 (98.4)	0.660
Clopidogrel	176 (98.3)	183 (97.9)	0.746
β-Blocker	121 (67.6)	117 (62.6)	0.313
Statin	137 (76.5)	145 (77.5)	0.819
ACEI or ARB	132 (73.7)	141 (75.4)	0.716
Duration of clopidogrel (mo)	14.4 ± 10.9	14.6 ± 11.4	0.873
Clopidogrel use > 12 mo	74 (41.3)	81 (43.3)	0.702
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVR, multivessel revascularization; PAOD, peripheral arterial occlusive disease; PCI, percutaneous coronary intervention; SVR, single-vessel revascularization. Data are presented as n (%) or mean ± SD.			

group. Most definite or probable ST occurred after 1 month (3 of 4 definite or probable ST cases in MVR group and 4 of 5 definite or probable ST cases in the SVR group).

Analysis According to APPROACH Lesion Score and SYNTAX Score

The median of the APPROACH lesion score was 61 (IQR, 47–69) and that of the SYNTAX score was 22 (IQR, 15–29), respectively. Patients with an APPROACH lesion score above the median had a tendency to undergo MVR more

Table 2. Angiographic and Procedural Characteristics of the Study Subjects

	MVR (n = 179)	SVR (n = 187)	P Value
APPROACH lesion score	60.0 ± 14.3	56.2 ± 15.4	0.016
SYNTAX score	23.1 ± 9.3	22.4 ± 10.7	0.47
Left main disease	41 (22.9)	17 (9.1)	<0.001
3-vessel disease	74 (41.3)	81 (43.3)	0.702
Proximal LAD disease	103 (57.5)	99 (52.9)	0.376
Use of glycoprotein IIb/IIIa inhibitor	3 (1.7)	4 (2.1)	0.746
Guidance of IVUS	63 (35.2)	26 (13.9)	<0.001
No. of stents	2.5 ± 0.9	1.4 ± 0.6	<0.001
Total stent length (mm)	59.2 ± 25.4	33.3 ± 17.7	<0.001
Type of stent used			0.01
SES only	101 (56.4)	112 (59.9)	NA
PES only	35 (19.6)	61 (32.6)	NA
ZES or mixed	43 (24.0)	14 (7.5)	NA
Abbreviations: APPROACH, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; IVUS, intravascular ultrasound; LAD, left anterior descending artery; MVR, multivessel revascularization; NA, not applicable; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; SVR, single-vessel revascularization; SYNTAX, Synergy Between PCI with Taxus and Cardiac Surgery; ZES, zotarolimus-eluting stent. Data are presented as n (%) or mean ± SD.			

frequently than those with an APPROACH lesion score below the median (53.8% vs 46.2%, $P = 0.06$). However, there was no significant difference in the rate of MVR between patients with a SYNTAX score above the median and those with a SYNTAX score below the median (50.8% vs 49.2%, $P = 0.47$). Although statistical significance was not found in patients with an APPROACH lesion score below the median and in those with a SYNTAX score above the median, the rate of MACE was substantially lower in the MVR group than in the SVR group across all subgroups. There was no significant interaction between the treatment strategy and the APPROACH lesion score or the SYNTAX score (Figure 2).

Discussion

In this study, we examined the efficacy and safety of MVR compared with SVR in patients with NSTEMI-ACS and MVD undergoing PCI using DES. Multivessel revascularization with DES was associated with a lower incidence of MACE, which was primarily driven by the significantly lower incidence of revascularization. However, there was no difference in death, MI, or ST between the 2 groups. The rate of periprocedural renal dysfunction was similar.

Because MVD was associated with a poor prognosis in patients with ACS,⁵ it is important to determine the

Table 3. Unadjusted and Adjusted HRs and 95% CI for Clinical Outcomes in the 2 Groups

	MVR (N = 179)	SVR (N = 187)	Unadjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value
Composite of death, MI, or revascularization	35 (19.6)	61 (32.6)	0.53 (0.35–0.80)	0.003	0.50 (0.30–0.85)	0.01
Composite of death or MI	16 (8.9)	19 (10.2)	0.85 (0.44–1.66)	0.64	0.56 (0.24–1.31)	0.18
Death	11 (6.1)	13 (7.0)	0.87 (0.39–1.94)	0.73	0.69 (0.25–1.93)	0.48
MI	6 (3.4)	9 (4.8)	0.68 (0.24–1.92)	0.47	0.39 (0.11–1.47)	0.17
Any revascularization	24 (13.4)	54 (28.9)	0.41 (0.25–0.66)	<0.001	0.43 (0.24–0.78)	0.01
TVR	20 (11.2)	30 (16.0)	0.67 (0.38–1.18)	0.17	0.65 (0.32–1.30)	0.22
Non-TVR	6 (3.4)	37 (19.8)	0.15 (0.07–0.36)	<0.001	0.17 (0.06–0.50)	0.001

Abbreviations: APPROACH, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVR, multivessel revascularization; PCI, percutaneous coronary intervention; SVR, single-vessel revascularization; SYNTAX, Synergy Between PCI with Taxus and Cardiac Surgery; TVR, target-vessel revascularization. Adjusted covariates included age, male sex, DM, previous history of PCI, LVEF, APPROACH lesion score, SYNTAX score, left main disease, use of IVUS, and total stent length.

Figure 1. Kaplan-Meier survival curves for the composite outcome of death, myocardial infarction, or any revascularization (A), death or myocardial infarction (B), any revascularization (C), and non-target-vessel revascularization (D) in all patients with MVR vs SVR. Abbreviations: MVR, multivessel revascularization; SVR, single-vessel revascularization.

Figure 2. Effects of MVR on the primary outcome, according to the APPROACH lesion score and the SYNTAX score. The dashed vertical line indicates the overall relative risk reduction for total study population. Abbreviations: APPROACH, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; MVR, multivessel revascularization; SVR, single-vessel revascularization; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

optimal treatment strategy in patients with NSTEMI-ACS and MVD. Since the FRISC II trial, complete revascularization is considered the best documented invasive treatment strategy.⁶ However, few studies have compared outcomes of MVR and SVR in these patients undergoing PCI.^{7,8,12} Results from previous studies are controversial. Moreover, these studies were conducted before the introduction of DES and cannot reflect current practice. Therefore, we compared long-term outcomes for MVR vs SVR using DES in patients with NSTEMI-ACS and MVD in the present study, and demonstrated that MVR reduced MACE, supporting the recommendation from the FRISC II trial.

Multivessel revascularization may afford advantages in greater myocardial salvage or reducing myocardial ischemia, whereas it can result in greater myocardial damage¹⁵ or higher exposure to radiocontrast agent compared with SVR.¹⁶ Multivessel revascularization was reported to be associated with increased risk of in-stent restenosis leading to revascularization.¹⁷ Considering that the risk of ST after DES implantation is related to stent length, MVR may increase the risk of ST.¹⁸ Percutaneous coronary intervention on the culprit lesion only with the optimal medical treatment may be safer than MVR in an ACS setting. However, our study demonstrated that MVR using DES improved clinical outcomes compared with SVR in patients with NSTEMI-ACS and MVD. With similar death, MI, or ST risk, MVR reduced repeat revascularization compared with SVR. Multivessel revascularization did not increase periprocedural renal dysfunction, either. These results were consistent with the results from previous studies with bare-metal stents on the same topic.^{7,8} Because selection of treatment strategy is apt to be strongly affected by jeopardized myocardial territory and lesion complexity, we investigated whether the benefit of MVR might differ according to the APPROACH lesion score and the SYNTAX score. Although the SYNTAX score did not affect treatment strategy, the APPROACH lesion score was associated with

the performance of MVR. Meanwhile, the benefit of MVR was observed regardless of both scores. Taken together, MVR should be considered as a preferred strategy in patients with large jeopardized myocardium even if lesions are quite complex.

Our study had several strengths compared with previous studies. First, we calculated the APPROACH lesion and SYNTAX score to assess the amount of myocardium at risk and grade the complexity of CAD, which are assumed as potential predictors of clinical outcomes. Second, the long-term follow-up results were available. The median follow-up was 3 years. Third, we evaluated periprocedural complications. And fourth, we investigated the incidence of ST and the duration of antiplatelet therapy, which have important implications for prognosis.

Our study had several limitations. First, this was a nonrandomized, observational design, which may have significantly affected the results because of confounding factors. The decision to perform MVR or SVR in each patient was at the operator's discretion. Although we performed multivariate analysis to adjust for these potential confounding factors, we were not able to correct for the unmeasured variables. The observed significant difference with regard to MACE may therefore reflect confounding by indication rather than a true observation. Second, this was a relatively small study and lacked power, especially in the assessment of rare events such as cardiac death, MI, and ST as well as renal dysfunction. Third, of 532 consecutive patients during the study period, only 366 patients met selection criteria and were included in our analysis. This may create selection bias and affect the external validity of the current study.

Conclusion

In the current observational, relatively small study, MVR strategy using DES was associated with better long-term clinical outcome without increase of adverse outcomes in patients with NSTEMI-ACS and MVD. The benefit of MVR was driven mainly by the lower incidence of revascularization rate with similar death, MI, or ST. Further large, prospective, randomized trials are warranted to confirm the benefit of MVR in this clinical setting.

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