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Impact of Ischemia-Guided Revascularization With Myocardial Perfusion Imaging for Patients With Multivessel Coronary Disease

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Objectives The aim of this study was to evaluate the impact of ischemia-guided (IG) revascularization.

Background The importance of IG revascularization has not been well-determined.

Methods The outcomes of IG revascularization, in which revascularization was performed in the matched coronary artery with the perfusion abnormality on myocardial perfusion image (MPI), were retrospectively compared with those of non-IG revascularization in a registry of 5,340 patients with multivessel coronary disease comprising 2,587 percutaneous coronary interventions (PCIs) with drug-eluting stents and 2,753 coronary artery bypass graft (CABG) surgeries after adjustment with inverse-probability-of-treatment weighting.

Results The MPI was performed in 42.3% of patients, and IG revascularization was performed in 17.3%, including 12.4% in PCI and 21.8% in CABG patients ($p < 0.001$). The incidence of major adverse cardiac and cerebrovascular events (MACCE) including death, myocardial infarction, stroke, or repeat revascularization was significantly lower in the IG than in the non-IG group (16.2% vs. 20.7%; adjusted hazard ratio [aHR]: 0.73; 95% confidence interval [CI]: 0.60 to 0.88; $p = 0.001$), primarily driven by the lower repeat revascularization rate (9.9% vs. 22.8%; aHR: 0.66; 95% CI: 0.49 to 0.90; $p = 0.009$). Subgroup analysis showed that IG reduced the risk of MACCE in PCI (17.4% vs. 22.8%; aHR: 0.59; 95% CI: 0.43 to 0.81; $p = 0.001$) but not in CABG (16.0% vs. 18.5%; aHR: 0.87; 95% CI: 0.67 to 1.14; $p = 0.31$) patients.

Conclusions Ischemia-guided revascularization with MPI, particularly in PCI-treated patients, seems to decrease the risk of repeat revascularization and MACCE for patients with multivessel disease. (J Am Coll Cardiol 2012;60: 181–90) © 2012 by the American College of Cardiology Foundation

The major purposes of stress testing are to identify high-risk patients who might require invasive angiography or revascularization and to objectively evaluate ischemia in patients with coronary artery disease (1). In the absence of disabling symptoms, evidence of ischemia has been recognized as critical in deciding whether to proceed with revascularization. Without objective determination of ischemia, complete angiographic revascularization might not be superior to reasonable incomplete revascularization (1,2). Myocardial perfusion imaging (MPI) with stress single-photon emission computed tomography (SPECT) has been used to diagnose inducible ischemia and to predict prognosis of patients with coronary artery disease, and SPECT results have shown fair concordance with the prevalence of significant ischemia (3).

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In addition to the diagnostic and prognostic utility of MPI, the area of perfusion abnormality can be used to

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Abbreviations and Acronyms

CABG = coronary artery bypass graft
DES = drug-eluting stent(s)
FFR = fractional flow reserve
IG = ischemia-guided
LAD = left anterior descending artery
MACCE = major adverse cardiac and cerebrovascular events
MI = myocardial infarction
MPI = myocardial perfusion imaging
MVD = multivessel disease
PCI = percutaneous coronary intervention
SPECT = single-photon emission computed tomography

delineate the ischemic myocardium and indicate the functional stenosis of the matched epicardial artery (4). The FAME (Flow Reserve versus Angiography for Multivessel Evaluation) study reported that ischemia-guided (IG) percutaneous coronary intervention (PCI) with fractional flow reserve (FFR) to localize ischemic area resulted in a lower 1-year incidence of death, myocardial infarction (MI), or repeat revascularization than conventional angiography-guided PCI for patients with multivessel disease (MVD) (5,6). To date, however, little is known about the clinical implications of MPI for IG revascularization in the treatment of MVD. Therefore, we evaluated the prognostic impact of IG revascularization with MPI in patients with MVD who underwent PCI with drug-eluting stents (DES) or coronary artery bypass graft (CABG) surgery.

Methods

Patients. The study population was a part of the Asan Multivessel Registry and included consecutive patients with MVD who underwent PCI with DES or CABG (Fig. 1) (2). Patients who presented with ST-segment elevation MI and/or cardiogenic shock or for whom no clinical follow-up information was available were excluded. The procedures and follow-up have been described previously (2). During the study period, DES was the default stent for PCI in patients with MVD. After DES implantation, dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least 1 year. The institutional review board of our institution approved the use of clinical data for this study, and all patients provided written informed consent for enrollment in our registry.

Stress SPECT protocol. IMAGING. Thallium-201 (Tl-201) SPECT was the default stress MPI during the study period. Images were acquired with a standardized protocol (7). Aden-

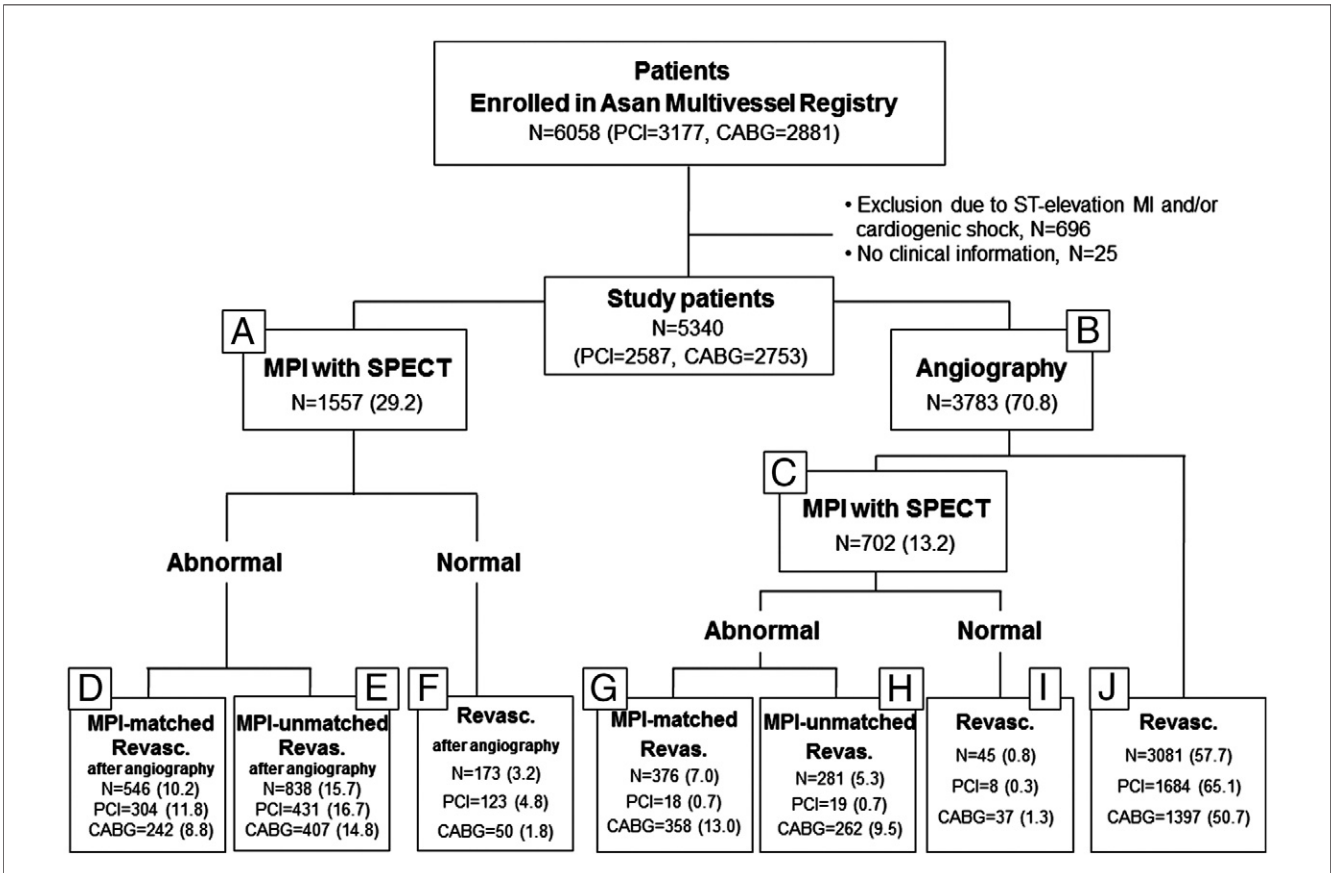

Figure 1 Study Flow Diagram

All values are presented as numbers and percentages. CABG = coronary artery bypass graft; MI = myocardial infarction; MPI = myocardial perfusion image; PCI = percutaneous coronary intervention; Revas(c) = revascularization; SPECT = single-photon emission computed tomography.

osine was intravenously administered at a rate of 0.14 $\mu g\ kg^{-1}min^{-1}$ for 6 min. Three minutes after the initiation of the adenosine infusion, a 92.5- to 148-MBq dose of Tl-201, depending on the body weight of each patient, was injected intravenously. Five minutes after adenosine infusion, post-stress MPI was acquired with a 2-head gamma camera (Ecam, Siemens, Munchen, Germany) equipped with low-energy, all-purpose collimators. Specific acquisition parameters were dependent on the camera. The images were evaluated by experienced nuclear medicine physicians.

INTERPRETATION. The MPI cohort included 2,259 (42.3%) patients, all of whom underwent Tl-SPECT within 1 year before index revascularization. Analysis of relative perfusion distribution was assessed in 17 myocardial segments (3). The SPECT study was considered to be abnormal if the summed stress score was 3 or greater. For the purpose of this study, the areas of perfusion abnormalities were classified into LAD and non-LAD territories. Patients with perfusion abnormalities in the anterior, anteroseptal, or anteroapical walls were regarded as having LAD ischemia, whereas patients with perfusion abnormalities in other segments were regarded as having non-LAD ischemia. When adjunctive markers of ischemia such as an increased stress–rest left ventricular cavity ratio or increased lung uptake were found, especially in the presence of abnormal MPI, the patient was assumed to have ischemia in both LAD and non-LAD territories.

MPI was undertaken before (A) or after (C) diagnostic angiography. After diagnostic angiography (B), patients underwent revascularization with (C) or without (J) MPI test. After diagnostic angiography and/or MPI examination, revascularization was performed in the vessel matched with abnormal MPI (D, G), in the vessel mismatched with abnormal MPI (E, H), and in the vessel with normal MPI (F, I). Ischemia-guided revascularization was defined as an attempted revascularization with PCI or CABG in all vessels matched with the perfusion abnormalities of MPI during the index hospital stay or within 30 days after the index procedure but before a new MI or urgent revascularization. Non-IG revascularization was defined as revascularization of non-ischemic vessel, non-revascularization of ischemic vessel, or revascularization without MPI (subgroup J). If any vessel was revascularized without ischemia guidance, the patient was categorized into the non-IG group.

Angiographic analysis. The angiographic cohort consisted of the 3,352 (62.8%) patients for whom we had available angiograms. Angiographic complexity was assessed with dedicated angiographic software (CAAS version 5, Pie Medical, Maastricht, the Netherlands) in the angiographic core laboratory of the CardioVascular Research Foundation, Seoul, Korea, according to the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) classification (8).

Clinical endpoints. The primary endpoint of this study was the rate of major adverse cardiac and cerebrovascular events (MACCE), consisting of death, MI, stroke, or repeat revascularization. Secondary endpoints included the individual endpoints of MACCE and the composite of death, MI, or stroke. Deaths were considered cardiac unless an unequivocal, noncardiac cause was established. Myocardial infarction as a complication was defined as either at index admission (defined as new Q-wave after index treatment) or at follow-up and requiring subsequent hospital stay (defined as new Q- or non–Q-wave), as described (9). Repeat revascularization included target vessel revascularization and non-target vessel revascularization. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist on the basis of imaging modalities. Procedural success was defined as the attainment of Thrombolysis In Myocardial Infarction (TIMI) flow grade of more than 1 without the occurrence of procedure-related in-hospital MACCE. In the PCI group, stent thrombosis was defined as the definite or probable occurrence of a thrombotic event, according to the Academic Research Consortium classification (10). All outcomes of endpoints were carefully verified and adjudicated by independent clinicians.

Clinical, angiographic, procedural or operative, and outcome data were prospectively recorded in the dedicated PCI and surgical databases by independent research personnel. Patients were clinically followed-up at 1, 6, and 12 months and annually thereafter, via office visit or telephone contact. To validate follow-up mortality, information about vital status was obtained through December 2009 from the National Population Registry of the Korea National Statistical Office with the unique personal identification number of each patient.

Statistical analysis. Differences in baseline clinical and angiographic characteristics and procedural findings were compared with the Wilcoxon rank sum test for continuous variables and the chi-square or Fisher exact test for categorical variables, as appropriate. Survival curves were constructed with the Kaplan-Meier method and compared with the log-rank test. Patients were censored at 5 years (1,800 days) or when events occurred.

Differences between the IG and non-IG groups in risk-adjusted, long-term rates of study outcomes were assessed with multivariable Cox proportional hazards regression analyses. The proportional hazards assumption was confirmed by examination of log (-log [survival]) curves and by testing of partial (Schoenfeld) residuals (11), and no relevant violations were identified. We also adjusted for differences in patient baseline characteristics with weighted Cox proportional hazards regression models with inverse-probability-of-treatment weighting (12). The primary adjustment was performed in all patients with the clinical covariates of age, sex, body mass index, diabetes mellitus, hypertension, current smoking, hyperlipidemia, left ventricular ejection fraction, atrial fibrillation, history of MI, cerebrovascular disease, chronic lung disease, peripheral vascular disease, congestive heart failure, prior coronary angioplasty, and acute coronary syndrome. This was followed by a second adjustment in the angiographic cohort

with the covariates of clinical factors, as in the preceding text, and angiographic factors including stenosis in the left main, LAD, left circumflex artery, and right coronary artery; 3-vessel disease; any total occlusion; and SYNTAX score. The subgroups of patients sorted according to various clinical and angiographic characteristics were analyzed after adjustment with the multivariable Cox model with clinical factors as covariates. Interactions between factors associated with IG and subgroups were tested by incorporation of formal interaction terms in the multivariable Cox model.

Matched propensity score analyses were used to ascertain the results of primary analysis (13), due to the possibility of biased effect estimates in observational studies. Patients between the 2 groups were matched in 1:1 on the logit of the propensity score with a caliper of width 0.2 of the SD of the logit of the propensity score. Matching was performed with %GMATCH SAS macro (Mayo Clinic, Rochester, Minnesota). Matching balance was assessed by standardized and absolute differences on each covariate (14). Cox proportional hazard models were used to calculate hazard ratios of outcomes comparing the matched groups. All reported p values are 2-sided, and p values <0.05 were considered statistically significant. The SAS software (version 9.1, SAS, Cary, North Carolina) and the R programming language were used for statistical analyses.

Results

Patient characteristics. From the registry, we enrolled 5,340 patients, including 2,587 who underwent PCI and 2,753 who underwent CABG (Table 1). Of these patients, 922 (17.3%) underwent IG revascularization, including 322 (12.4%) in the PCI and 600 (21.8%) in the CABG ($p < 0.001$) cohorts. The MPI was performed a median 15 days (interquartile range [IQR]: 6 to 44 days) before the index procedure. In the PCI group, IG patients presented with more stable coronary symptoms, underwent more treadmill tests, and received fewer DESs than non-IG patients. In the CABG group, IG patients were younger; had a higher rate of unstable symptoms; had lower rates of hypertension, smoking, and cerebrovascular disease; had lower left ventricular function; underwent more treadmill tests; and received a higher number of graft conduits.

The angiographic cohort consisted of 3,352 patients, including 2,023 (78.2%) PCI and 1,329 (48.3%) CABG patients, with angiograms available for retrospective analysis. In the PCI group, IG patients had a lower rate of LAD diseases and a higher rate of total occlusions than non-IG patients, whereas in the CABG group, IG patients had a higher rate of total occlusions than non-IG patients.

The characteristics of perfusion abnormalities in the MPI cohort are presented in Table 2. The IG patients had higher rates of perfusion abnormalities in the LAD and non-LAD territories, higher rates of reversible defects and larger perfusion defects in the both PCI and CABG groups. However, the 2 groups had a similar prevalence of patients with fixed defects.

Clinical outcomes. UNADJUSTED INCIDENCES. Procedural success was obtained in 5,258 (98.5%) patients comprising 905 (98.2%) in the IG and 4,353 (98.5%) in the non-IG groups ($p = 0.40$). In PCI (99.4% vs. 99.5%, $p = 0.69$) and CABG (97.5% vs. 97.5%, $p = 0.96$) patients, the procedural success rate did not differ between the IG and non-IG groups.

The median follow-up durations were 60 months (IQR: 48 to 60 months) in the IG group and 53 months (IQR: 37 to 60 months) in the non-IG group ($p < 0.001$). Figure 2 shows the Kaplan-Meier incidence curves of the primary and secondary endpoints in the IG and non-IG groups in the overall, PCI, and CABG cohorts. Table 3 presents the numbers and cumulative incidences of events in the IG and non-IG groups in the PCI and CABG patients. The primary endpoint of MACCE was significantly lower in the IG than in the non-IG group in overall and PCI patients. Of the individual endpoints of MACCE, the incidence of repeat revascularization was significantly lower in the IG than in the non-IG group in PCI patients. However, the incidence of death, MI, or stroke did not differ between the IG and non-IG groups in the overall, PCI, or CABG cohorts. In the CABG cohort, there was no difference between the IG and non-IG groups in the rate of any event.

ADJUSTED RISKS. Table 4 presents the adjusted hazard ratios and 95% confidence intervals of IG, as compared with non-IG, for MACCE; repeat revascularization; and the composite of death, MI, or stroke. After adjustments with the multivariate Cox model and inverse-probability-of-treatment weighting method, the hazard ratios for the primary endpoint of MACCE favored IG in overall and PCI patients. However, the risk of MACCE was not associated with IG in CABG patients. The risk of repeat revascularization was also lower with IG in overall and PCI but not in CABG patients. In both PCI and CABG patients, IG was not associated with the risk of the composite of death, MI, or stroke. There was no significant interaction between IG and treatment type (PCI or CABG) for the risks of MACCE and the composite of death, MI, or stroke. However, we observed a significant interaction for the risk of repeat revascularization. In the second adjustment for the angiographic cohort, the favorable pattern of hazard ratios was not changed in overall, PCI, and CABG patients.

In the propensity matching analyses, the IG group was associated with the reduction in risks of repeat revascularization and MACCE in 321 pairs of PCI patients, but not in 596 pairs of CABG patients (Table 5). When the patients were separated according to the subgroup classifications as in Figure 1, there was a tendency of a decreased risk of repeat revascularization and MACCE in patients receiving revascularization after MPI (groups D to I) compared with those undergoing angiography-guided revascularization without MPI (group J). In addition, IG revascularization (group D or G) was associated with a

Table 1 Baseline Patient Characteristics

Variable	PCI			CABG		
	IG	Non-IG	p Value	IG	Non-IG	p Value
Clinical characteristics	n = 322	n = 2,265		n = 600	n = 2,153	
Age, yrs	62 (55–69)	64 (56–70)	0.35	63 (56–68)	64.0 (57.0–69.0)	0.006
Male	226 (70.2)	1,550 (68.4)	0.53	456 (76.0)	1,571 (73.0)	0.04
Body mass index, kg/m^2	25.2 (23.6–27.0)	25.0 (23.1–26.8)	0.060	24.8 (23.1–26.5)	24.5 (22.7–26.4)	0.051
Diabetes mellitus	120 (37.3)	727 (32.1)	0.064	191 (31.8)	772 (35.9)	0.068
Hypertension	205 (63.7)	1,339 (59.1)	0.12	226 (37.7)	1,114 (51.7)	<0.001
Current smoker	116 (36.0)	848 (37.4)	0.62	87 (14.5)	487 (22.6)	<0.001
Hyperlipidemia	114 (35.4)	750 (33.1)	0.42	182 (30.3)	665 (30.9)	0.80
Prior MI	9 (2.8)	76 (3.4)	0.60	85 (14.2)	259 (12.0)	0.16
Previous PCI	70 (21.7)	395 (17.4)	0.060	59 (9.8)	273 (12.7)	0.058
Congestive heart failure	3 (0.9)	16 (0.7)	0.72	26 (4.3)	99 (4.6)	0.78
Obstructive pulmonary disease	4 (1.2)	10 (0.4)	0.086	13 (2.2)	44 (2.0)	0.85
Cerebrovascular disease	23 (7.1)	144 (6.4)	0.59	55 (9.2)	272 (12.6)	0.020
Peripheral vascular disease	2 (0.6)	40 (1.8)	0.13	30 (5.0)	120 (5.6)	0.58
Renal failure	9 (2.8)	67 (3.0)	0.87	33 (5.5)	139 (6.5)	0.39
Atrial fibrillation	10 (3.1)	49 (2.2)	0.29	20 (3.3)	89 (4.1)	0.37
Left ventricular ejection fraction, %	60 (56–64)	60 (55–64)	0.29	58 (47–63)	59 (51–64)	0.001
Clinical presentation			0.006			<0.001
Stable angina	207 (64.3)	1,244 (54.9)		302 (50.3)	1,495 (69.4)	
Unstable angina	114 (35.4)	1,004 (44.3)		298 (49.7)	655 (30.4)	
Acute NSTEMI	1 (0.3)	17 (0.8)		0	3 (0.1)	
Angiographic characteristics	n = 310	n = 1,713		n = 268	n = 1,061	
SYNTAX score	15.5 (11.0–22.0)	17.0 (11.0–22.0)	0.30	24.5 (14.0–35.4)	23.0 (13.0–31.5)	0.016
Angiographic stenosis						
LAD	260 (83.9)	1,555 (90.8)	<0.001	214 (79.9)	854 (80.5)	0.81
Left circumflex	202 (65.2)	1,106 (64.6)	0.84	160 (59.7)	679 (64.0)	0.19
Right coronary	229 (73.9)	1,252 (73.1)	0.78	190 (70.9)	746 (70.3)	0.85
Left main	34 (11.0)	261 (15.2)	0.050	95 (35.4)	327 (30.8)	0.15
3-vessel disease	127 (41.0)	714 (41.7)	0.82	147 (54.9)	604 (56.9)	0.54
Any total occlusion	61 (19.7)	247 (14.4)	0.018	98 (36.6)	283 (26.7)	0.001
Procedures	n = 322	n = 2,265		n = 600	n = 2,153	
Treadmill test*	113 (35.1)	431 (19.0)	<0.001	99 (16.5)	251 (11.7)	0.002
Treated vessel						
LAD or left main	205 (63.7)	1,768 (78.1)	<0.001	589 (98.2)	2,091 (97.1)	0.16
Left circumflex	113 (35.1)	940 (41.5)	0.029	477 (79.5)	1,680 (78.0)	0.44
Right coronary	138 (42.9)	1,172 (51.7)	0.003	439 (73.2)	1,427 (66.3)	0.001
CABG						
Number of conduits	—	—	—	3.0 (3.0–4.0)	3.0 (2.0–4.0)	<0.001
Number of arterial conduit	—	—	—	3.0 (2.0–3.0)	2.0 (1.0–3.0)	<0.001
Internal thoracic artery	—	—	—	510 (85.0)	1,867 (86.7)	0.28
Off-pump surgery	—	—	—	370 (61.7)	1,243 (57.7)	0.084
PCI						
Number of total stents	2.0 (1.0–3.0)	2.0 (2.0–3.0)	<0.001	—	—	—
Length of total stents, mm	51 (32–67)	56 (33–84)	<0.001	—	—	—
Mean stent size, mm	3.1 (3.0–3.5)	3.2 (3.0–3.5)	0.11	—	—	—

Values are median (interquartile range) and n (%). *Treadmill tests performed 1 year before the index revascularization.

CABG = coronary artery bypass graft; IG = ischemia-guided; LAD = left anterior descending artery; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

reduction in the risks of repeat revascularization, a composite of death, MI, or stroke, and MACCE compared with MPI-unmatched revascularization (group E or H) among patients receiving MPI.

Figure 3 presents the incidences and adjusted hazard ratios of IG for MACCE in various clinical and angiographic subgroups. A tendency of reduced risk of MACCE was observed in most subgroups. No subgroup had a significant interaction with regard to IG.

Discussion

The major findings of this study were: 1) fewer than one-half of patients with MVD who underwent revascularization received

Table 2 Myocardial Perfusion Abnormalities Among Patients Undertaking Myocardial Perfusion Imaging

Variable	PCI			CABG		
	IG (n = 322)	Non-IG (n = 581)	p Value	IG (n = 600)	Non-IG (n = 756)	p Value
Site of perfusion defects						
LAD	205 (63.7)	246 (42.3)	<0.001	589 (98.2)	299 (39.6)	<0.001
Non-LAD	199 (61.8)	236 (40.6)	<0.001	556 (92.7)	363 (48.0)	<0.001
Reversibility						
Any fixed defect	32 (9.9)	56 (9.6)	0.88	88 (14.7)	90 (11.9)	0.14
Any reversible defect	301 (93.5)	362 (62.3)	<0.001	572 (95.3)	564 (74.6)	<0.001
Area of perfusion defect ≥ medium	306 (95.0)	397 (68.3)	<0.001	600 (100)	625 (82.7)	<0.001

Values are n (%).
Abbreviations as in Table 1.

MPI with SPECT before the procedure; 2) fewer than one-half of patients undergoing MPI underwent IG revascularization on the basis of the perfusion abnormalities on MPI; 3) IG revascularization decreased the 5-year risk of MACCE, primarily driven by the reduction of repeat revascularization rate after PCI with DES but not after CABG; and 4) safety—as reflected by the risk of death, MI, or stroke—was comparable between IG and non-IG patients.

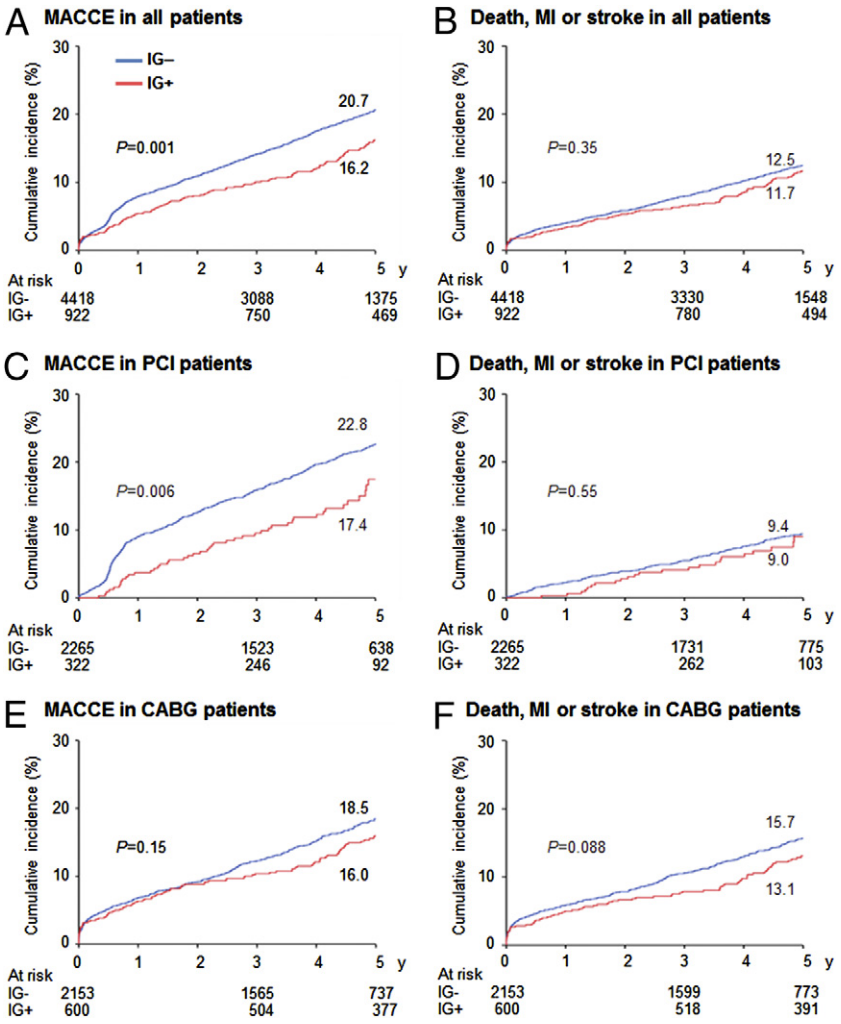

Figure 2 Kaplan-Meier Incidence Curves Over 5 Years

IG = ischemia-guided; MACCE = major adverse cardiac and cerebrovascular events; other abbreviations as in Figure 1.

Table 3 Incidences of Adverse Events Over 5 Years

Outcomes	PCI			CABG		
	IG (n = 322)	Non-IG (n = 2,265)	p Value*	IG (n = 600)	Non-IG (n = 2,153)	p Value*
Primary endpoint of MACCE	45 (17.4)	451 (22.8)	0.006	90 (16.0)	339 (18.5)	0.15
Composite of death, MI, or stroke	23 (9.0)	179 (9.4)	0.55	73 (13.1)	289 (15.7)	0.088
Death	17 (6.4)	140 (7.4)	0.46	54 (9.6)	226 (12.2)	0.072
Cardiac	4 (1.8)	67 (3.6)	0.072	29 (5.4)	123 (7.0)	0.14
Noncardiac	13 (4.7)	73 (3.9)	0.52	25 (4.5)	103 (5.6)	0.29
MI	3 (0.9)	23 (1.2)	0.86	5 (1.0)	22 (1.2)	0.54
STEMI	2 (0.6)	8 (0.4)	0.50	0	5 (0.3)	0.20
NSTEMI	1 (0.3)	15 (0.7)	0.44	5 (1.0)	17 (0.9)	0.95
Repeat revascularization	26 (9.9)	291 (14.8)	0.010	24 (4.3)	66 (3.9)	0.53
Target vessel	18 (7.2)	211 (10.8)	0.020	21 (3.8)	56 (3.4)	0.50
Non-target vessel	8 (2.7)	80 (3.9)	0.30	3 (0.5)	10 (0.6)	0.99
Stroke	5 (2.5)	35 (1.9)	0.96	22 (4.1)	70 (4.1)	>0.99
Hemorrhagic	1 (0.6)	7 (0.6)	0.98	3 (0.6)	15 (0.9)	0.44
Non-hemorrhagic	4 (1.9)	28 (1.5)	0.97	19 (3.5)	55 (3.2)	0.70
Stent thrombosis (definite or probable)	1 (0.3)	28 (1.3)	0.14	—	—	—
Definite	1 (0.3)	11 (0.5)	0.65	—	—	—
Probable	0	17 (0.8)	0.12	—	—	—

Values are n and Kaplan-Meier incidence of events. *p Values were analyzed with the log-rank test.
MACCE = major adverse cardiac and cerebrovascular event; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

In making decisions on revascularization, stress tests are strongly recommended to confirm inducible ischemia because recent clinical trials failed to show the benefits of routine rather than provisional revascularization for stable coronary disease (1,15). In real-world practice, however, stress tests are infrequently performed, and revascularization is potentially over- or under-used, due to a paucity of data with regard to its role in guiding optimal revascularization (16). We found that MPI assessments were performed in fewer than 50% of revascularized patients, even those with MVD.

In our large MVD registry, IG revascularization reduced the risk of MACCE by 27%, driven by a 34% reduction in

Table 4 Adjusted HRs of Ischemia-Guided Revascularization for Events

Population	Outcomes	Groups	Multivariate Adjustment				Inverse-Probability-of-Treatment Weighting Method			
			HR	95% CI	p Value	Interaction p Value	HR	95% CI	p Value	Interaction p Value
All patients										
	Death, MI, or stroke	All	0.86	0.69–1.07	0.18	0.77	0.84	0.66–1.06	0.13	0.96
		PCI	0.84	0.54–1.30	0.43		0.83	0.53–1.29	0.41	
		CABG	0.84	0.65–1.09	0.18		0.82	0.61–1.10	0.18	
	Repeat revascularization	All	0.76	0.57–1.03	0.072	0.015	0.66	0.49–0.90	0.009	0.044
		PCI	0.56	0.37–0.84	0.005		0.53	0.35–0.80	0.003	
		CABG	1.18	0.74–1.90	0.49		1.16	0.70–1.94	0.57	
	MACCE	All	0.77	0.64–0.93	0.007	0.12	0.73	0.60–0.88	0.001	0.18
		PCI	0.61	0.45–0.84	0.002		0.59	0.43–0.81	0.001	
		CABG	0.85	0.67–1.07	0.17		0.87	0.67–1.14	0.32	
Angiographic cohort										
	Death, MI, or stroke	All	0.79	0.58–1.07	0.13	0.87	0.77	0.56–1.06	0.11	0.52
		PCI	0.85	0.53–1.36	0.50		0.77	0.48–1.24	0.28	
		CABG	0.80	0.54–1.20	0.28		0.89	0.57–1.39	0.60	
	Repeat revascularization	All	0.71	0.50–1.00	0.047	0.015	0.71	0.50–1.01	0.054	0.006
		PCI	0.57	0.38–0.86	0.007		0.52	0.35–0.79	0.002	
		CABG	1.56	0.80–3.07	0.19		1.78	0.86–3.66	0.12	
	MACCE	All	0.70	0.55–0.89	0.003	0.18	0.70	0.55–0.90	0.005	0.044
		PCI	0.61	0.44–0.84	0.002		0.58	0.42–0.80	0.001	
		CABG	0.94	0.66–1.34	0.72		1.01	0.68–1.49	0.97	

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 3.

Table 5 Propensity Score Matching Analyses

Groups	No. of Matched Pairs	Repeat Revascularization		Death, MI, or Stroke		MACCE	
		HR (95% CI)	p Value	HR (95% CI)	p Value	HR	p Value
Ischemia-guidance							
Overall	919	0.72 (0.50–1.03)	0.075	0.98 (0.74–1.30)	0.90	0.82 (0.65–1.03)	0.085
PCI group	321	0.58 (0.36–0.91)	0.019	0.82 (0.48–1.41)	0.47	0.61 (0.44–0.84)	0.003
CABG group	596	1.16 (0.65–2.05)	0.62	0.99 (0.70–1.39)	0.94	1.02 (0.75–1.39)	0.91
Inter-groups							
(D, E, F, G, H, and I) vs. J	2,176	0.80 (0.65–0.99)	0.039	1.18 (0.98–1.41)	0.079	0.997 (0.87–1.15)	0.96
(D, E, and F) vs. J	1,543	0.94 (0.50–1.03)	0.61	1.27 (1.03–1.57)	0.026	1.12 (0.95–1.32)	0.17
(G, H, and I) vs. J	700	0.67 (0.43–1.02)	0.060	1.24 (0.91–1.69)	0.18	0.96 (0.74–1.23)	0.74
(D and G) vs. J	915	0.68 (0.47–0.99)	0.042	0.89 (0.67–1.19)	0.44	0.76 (0.60–0.96)	0.023
(D and G) vs. (E and H)	842	0.75 (0.52–1.09)	0.13	0.75 (0.57–0.99)	0.046	0.71 (0.57–0.90)	0.004

Abbreviations as in Tables 1, 3, and 4.

repeat revascularization after adjustment. In particular, the risk reductions in patients undergoing PCI were 47% for repeat revascularization and 41% for MACCE. Our findings were in line with those of the FAME study, which showed that FFR-guided stenting significantly reduced the risks of MACCE and repeat revascularization, compared

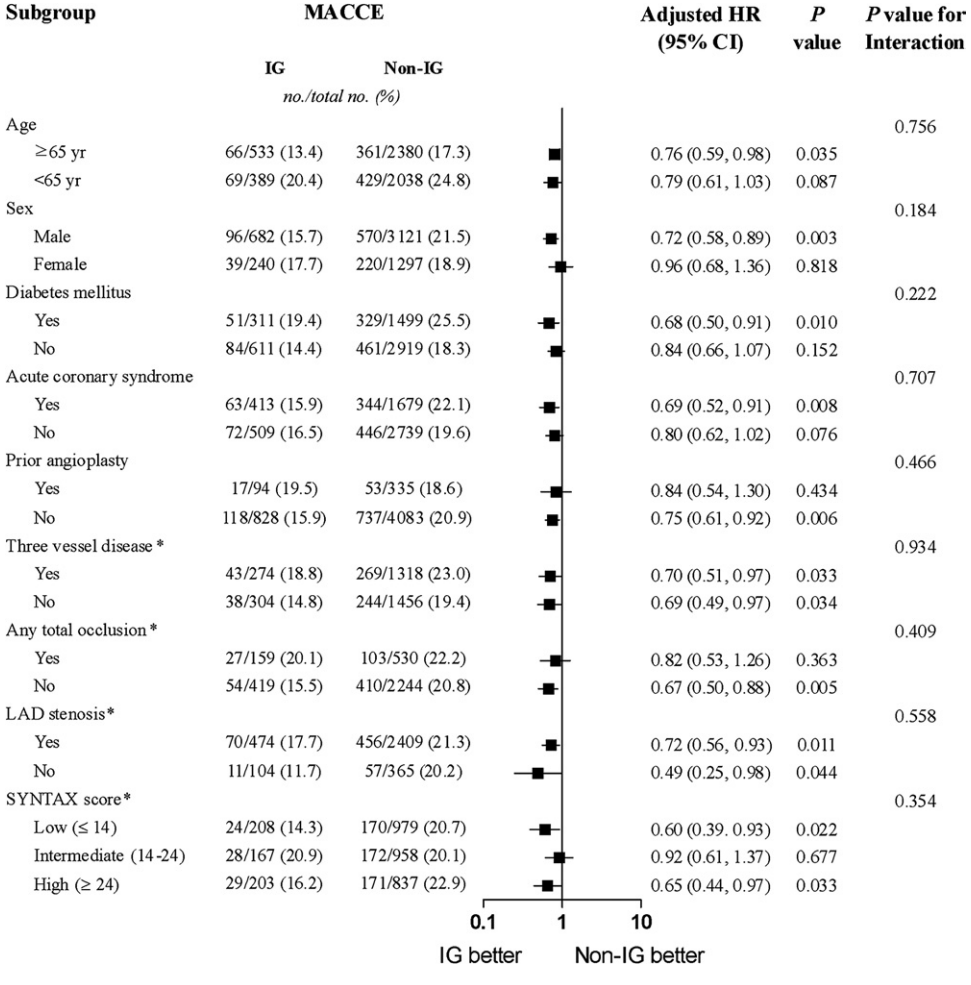

Figure 3 Adjusted HRs for MACCE in Subgroups

CI = confidence interval; HR = hazard ratio; LAD = left anterior descending artery; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; other abbreviations as in Figure 1.

with angiography-guided stenting for stable patients with MVD (5). The superiority of IG revascularization was primarily due to the weak correlation between morphological severity and functional ischemia (17–19). The IG stenting reduced the number of devices used as well as the subsequent risks of acute and chronic events by avoiding unnecessary procedures, both here and in the FAME study (5). The risks of adverse events of DES cannot be avoided when implanted into multiple lesions (20). Moreover, not performing revascularization for ischemic areas might have contributed to the unfavorable outcomes of non-IG revascularization (15,21).

Ischemia guidance did not affect the clinical outcomes after CABG, in contrast with PCI. Because anatomical complete revascularization was often attempted in CABG by anastomosing the bypass graft distal to the site of coronary disease (2), functional evaluation with MPI might have had a reduced influence on operational technique and resultant clinical outcomes. The safety of IG—as reflected by the endpoints of death, MI, or stroke—was comparable to that of non-IG after either PCI or CABG. This finding was in good agreement with previous studies, which showed very low incidences of death or MI in patients with nonischemic coronary lesions, as evidenced by MPI or FFR (5,17,22).

Although our study confirmed the observations of the FAME study, the clinical implications of these 2 studies should be independently addressed (5,23). First, the 2 studies had different study designs. In contrast with the randomized FAME study, our analysis was performed with data derived from a large registry. Because clinical trials include relatively healthy patients, the real benefits of IG can be diluted in a randomized study (24). Second, our study had a longer follow-up duration than the 2-year follow-up in the FAME study (23). We found that the curves for MACCE rate in the IG and non-IG groups progressively diverged through 5 years. Moreover, although the differences in MACCE rate were not statistically significant, the curves started to diverge after 2 years in the CABG group. Third, MPI and FFR each have unique advantages and disadvantages. For example, although MPI with SPECT has been reported to have a lower sensitivity than FFR for detecting ischemic myocardium in MVD patients, the practical sensitivity of SPECT might be clinically sufficient to identify "clinically culprit vessels" determining clinical outcomes (6,21). Moreover, MPI has technical advantages, including its noninvasiveness and universal applicability to all lesion subsets, including chronic total occlusion, calcified lesions, and severely tortuous lesions, in which FFR assessment is practically difficult.

Study limitations. First, a match between the perfusion abnormality and revascularized vessel for adjudication of IG was roughly divided into LAD and non-LAD territories. Further prospective studies with a pre-specified protocol to define the ischemic territory will confirm the clinical benefit of IG and clarify the mechanism of superiority. Second, we did not combine information on reversibility and abnormal perfusion area in our analysis. Myocardial viability or ischemic area might influence the results, regardless of the type of revascularization treatment (25). Because our study included all patients with or without MPI, further studies are required to investigate this issue. Third, our study was based on the experience of a large-volume center. Therefore, it might not be possible to generalize our utility pattern and findings on the clinical impact of MPI to other institutions. Nonetheless, the similar rate of stress testing in a large U.S. national registry indicates that our results might be widely applicable in daily practices (16). Fourth, unobserved confounders might have biased our results, due to the nonrandomized study design. In fact, high-risk patients who were expected not to tolerate stress imaging tests might have been included in the non-IG group. However, the concordant results after vigorous 2-stage adjustments support their reliability. Fifth, because of limited angiographic analysis, we might not have completely adjusted for angiographic factors. However, analyses in an independent angiographic core laboratory of a large patient cohort strengthened the objectivity of our findings and might overcome their limitations. Sixth, our study used Tl-201, which might be more susceptible to scatter or attenuation artifact than technetium. However, both Tl-201 and technetium are considered comparable to assess the extent and severity of reversible perfusion abnormalities (26). Finally, the 1-year time window of MPI before revascularization might have influenced the true incidence of abnormal tests and the impact of IG. This limitation warrants further studies with a well-designed protocol for pre-specified times of stress image tests, angiography, and revascularization.

Conclusions

IG revascularization with MPI with SPECT seems to reduce the risk of repeat revascularization and subsequent MACCE, particularly in patients with MVD who undergo PCI with DES. Our results might promote a better adherence to clinical practice guidelines in the treatment of patients with MVD.

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Key Words: bypass surgery ■ coronary disease ■ myocardial perfusion imaging ■ revascularization ■ stents.