Multiple percutaneous coronary interventions worsen outcomes for subsequent surgical correction of chronic ischemic mitral regurgitation

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Satoshi Kainuma, MD, PhD,[a] Koichi Toda, MD, PhD,[a] Shigeru Miyagawa, MD, PhD,[a]
Daisuke Yoshioka, MD, PhD,[a] Takuji Kawamura, MD, PhD,[a] Ai Kawamura, MD, PhD,[a]
Noriyuki Kashiyama, MD, PhD,[a] Toru Kuratani, MD, PhD,[a] Kensuke Yokoi, MD, PhD,[b]
Seiko Ide, MD, PhD,[b] Isamu Mizote, MD, PhD,[b] Hidetaka Kioka, MD, PhD,[b] Tomohito Ohtani, MD, PhD,[b]
Shungo Hikoso, MD, PhD,[b] Haruhiko Kondoh, MD, PhD,[c] Arudo Hiraoka, MD, PhD,[d]
Taichi Sakaguchi, MD, PhD,[d] Hidenori Yoshitaka, MD, PhD,[d] Tetsuhisa Kitamura, MD, DPH, MS,[e]
Sho Komukai, PhD,[f] Atsushi Hirayama, MD, MPH,[g] Kazuhiro Taniguchi, MD, PhD,[c]
Yasushi Sakata, MD, PhD,[b] and Yoshiki Sawa, MD, PhD,[a] for the Osaka Cardiovascular Surgery
Research Group*

ABSTRACT

Objective: We investigated whether or not a history of multiple percutaneous coronary interventions (PCIs) is associated with clinical outcomes after surgery for ischemic mitral regurgitation.

Methods: A total of 309 patients with chronic ischemic mitral regurgitation and left ventricular ejection fraction ≤40% who underwent restrictive mitral annuloplasty were classified as follows: patients with no or 1 previous PCI (nonmultiple PCI group [n = 211]) and patients with 2 or more previous PCIs (multiple PCIs group [n = 98]). Mean follow-up duration was 53 ± 40 months.

Results: Before surgery, there were no intergroup differences in patient demographic characteristics except for lower estimated glomerular filtration rate in patients with multiple PCIs. These patients underwent concomitant coronary artery bypass grafting less frequently with a lower number of distal anastomoses ($P < .05$ for both). The 30-day mortality was 3.3% and 2.0% in the nonmultiple and multiple PCIs group, respectively ($P = .72$). During follow-up, there were 157 deaths. Patients with multiple PCIs showed lower 5-year survival rate (44% vs 64%; $P = .002$). After adjustments with inverse-probability-of-treatment weighting, multiple PCIs history was an independent risk factor for mortality (adjusted hazard ratio, 1.4; 95% confidential interval, 1.1-1.7; $P = .002$). Patients with multiple PCIs showed less improvement in left ventricular ejection fraction (interaction effect $P < .001$).

Conclusions: In patients with ischemic mitral regurgitation, a history of previous multiple PCIs was associated with increased risk of long-term postoperative mortality, with less improvement in left ventricular ejection fraction. (JTCVS Open 2021;7:195-206)
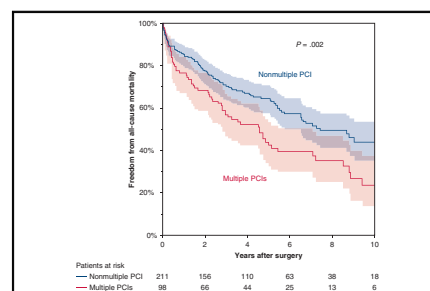
Outcomes following RMA for ischemic MR in patients with and without multiple PCIs history.

CENTRAL MESSAGE

In patients with chronic ischemic MR, a history of multiple PCIs was associated with increased risk of mortality and composite adverse events after RMA, and poorer LV reverse remodeling.

PERSPECTIVE

We demonstrated the negative influence of a history of multiple PCIs on postoperative survival and LV reverse remodeling in patients with ischemic MR and ischemic cardiomyopathy. These results are particularly relevant for physicians attempting to devise a revascularization strategy for these patients and highlight the importance of early referral for surgical intervention to improve outcomes.

See Commentaries on pages 207 and 209.

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
IPTW = inverse-probability-of-treatment
weighting
LV = left ventricular
MR = mitral regurgitation
PCI = percutaneous coronary intervention
RMA = restrictive mitral annuloplasty
SMDs = standardized mean differences

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Ischemic mitral regurgitation (MR) occurs frequently in the acute and chronic phases of myocardial infarction and adds volume overload to a decompensated left ventricle.[1,2] Multivessel coronary artery disease is also frequently documented in patients with acute myocardial infarction who undergo primary percutaneous coronary intervention (PCI) and can be treated with subsequent surgical revascularization or multiple/repeated percutaneous revascularizations plus medical treatment.[3,4] The choice of percutaneous or surgical revascularization should be determined on an individual basis, according to the patient's comorbidities, cardiac function, number and location of coronary vessels involved, and degree of MR. MacHaalany and colleagues[5] demonstrated that the severity of ischemic MR can worsen over time in patients presenting with no or mild ischemic MR that was documented after the primary PCI for acute myocardial infarction and that MR will generally not regress in patients with moderate to severe ischemic MR. An important feature is that patients with a history of primary PCI complicated with moderate to severe ischemic MR experienced a higher incidence of adverse cardiac events, primarily driven by higher rates of surgical revascularization and mitral valve correction. Therefore, the presence of significant ischemic MR after the primary PCI may be an indication for subsequent mitral valve surgery. However, a recent survey unfortunately revealed that one-quarter of more than 1000 cardiovascular specialists practicing in the United States and other countries did not evaluate patients for the presence of ischemic MR at the time of a PCI.[6]

A history of multiple PCIs negatively influences clinical outcomes after subsequent coronary artery bypass grafting (CABG) with a higher rate of adverse events soon after surgery and an unfavorable improvement in postoperative left ventricular (LV) function.[7] Furthermore, multiple PCIs can delay the timing of referral for surgical intervention and deprive patients of the opportunity to undergo CABG during subsequent mitral surgery, potentially affecting surgical outcomes. Therefore, a reasonable hypothesis is that patients with a history of multiple PCIs undergoing subsequent surgical correction of chronic secondary MR have a worse prognosis than patients without this history. The purpose of this study was to elucidate the clinical outcomes of patients with ischemic MR who undergo restrictive mitral annuloplasty (RMA) with a focus on a history of multiple PCIs and to clarify the clinical influence of previous multiple PCIs in patients with these conditions.

METHODS

Patients

Five hundred ninety-eight patients with chronic secondary MR who underwent RMA between 1999 and 2015 were identified. Patients with MR with nonischemic etiology (n = 131) and patients with a low level of LV remodeling with an ejection fraction >40% (n = 158) were excluded from this study. Finally, 309 patients with chronic MR secondary to ischemic cardiomyopathy—defined as severely impaired LV systolic function with an ejection fraction ≤40%—were included. Patients were classified into the nonmultiple PCI group (ie, 0-1 previous PCI [n = 211]) or the multiple PCIs group (ie, 2 or more previous PCIs [n = 98]). The flow diagram in Figure E1 depicts the selection of the patient population. Before the surgical referral, all patients were treated according to an optimized medical regimen for heart failure, including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretic agents. The final study protocol was approved by the ethics committees of all institutions involved in the study.

Surgical Procedures

Surgical procedures were performed using a standard cardiopulmonary bypass machine. All patients underwent stringent RMA, after careful assessment of the intercommissural distance and height of the anterior leaflet. No other adjunct procedures were performed on the mitral valve. The indication for CABG was influenced by cardiac and coronary anatomy, myocardial viability, and previous history of PCI or CABG. However, the final decision was at the discretion of the attending surgeon. For patients with indications for concomitant CABG, the in situ right or left internal thoracic artery was utilized, when possible, to bypass the left anterior descending artery. The decision to perform concomitant procedures, such as surgical ventricular restoration, papillary muscle approximation, or aortic valve replacement, was at the discretion of the attending surgeon.

Outcomes, Definitions, and Clinical Follow-up

The primary end point was all-cause mortality during follow-up. The secondary end point was the composite of mortality and readmission for heart failure. The diagnosis of postoperative recurrent heart failure was based on clinical symptoms, physical signs, or radiological evidence of pulmonary congestion. We also evaluated longitudinal changes in LV function parameters and MR severity by using serial echocardiography. All (100%) patients completed clinical follow-up with a mean follow-up duration of 72 ± 37 months (range, 5.6-179 months) among the survivors. The overall cumulative follow-up period was 1371 patient-years.

Statistical Analysis

All continuous variables were checked for normality using the Shapiro-Wilk test and normal probability plot and were presented as either mean ± standard deviation or medians with interquartile ranges, as appropriate. For the continuous variables, comparisons between the 2 study groups (ie, nonmultiple PCI and multiple PCIs groups) were made using a Student t test or Mann-Whitney U test, where appropriate. Categorical

variables were similarly summarized as frequencies with proportions and were compared by using the χ^2 test or Fisher exact test, as appropriate. The echocardiographic variables over time were analyzed using a mixed-effects model for repeated measures such as factors for group, time, and the group and time interaction. Each time and patient were treated as a random effect, whereas the assessment time points were treated as categorical factors. The variance–covariance matrix in the linear mixed-effects model was assumed to be unstructured.

Survival analysis was conducted using the Kaplan–Meier method for the estimation and the log-rank test for comparing the patient groups. To reduce the influence of treatment bias and potential confounding in the direct comparisons between patients with and without previous multiple PCIs, we estimated the average treatment effect by using weighted Cox proportional-hazards regression models with inverse-probability-of-treatment weighting (IPTW), owing to the observational nature of this study.[8,9] Based on this technique, the weights for patients with previous multiple PCIs were the inverse of the propensity score, and the weights for patients without it were the inverse of the 1 − propensity score. The probability of a history of multiple PCIs (ie, propensity score) for each patient was calculated by using multivariate logistic regression analysis, based on the clinically relevant covariates listed in Table 1 (ie, age, sex, body surface area, logistic European System for Cardiac Operative Risk Evaluation II, emergency operation, preoperative intra-aortic balloon pump implantation, redo operation, diabetes, estimated glomerular filtration rate <30 mL/min/1.73 m^2, peripheral vascular disease, LV end-systolic dimension, LV ejection fraction, and MR grade moderate or greater). To measure the covariate balance, we evaluated the standardized mean differences (SMDs) before and after adjustments with IPTW. We considered an SMD <0.25 (25%) as a negligible imbalance between the 2 groups.[10] After adjusting by using IPTW, the associations of a history of multiple PCIs with all-cause mortality and composite adverse events were examined with Cox proportional hazards models. The results are summarized as hazards ratios (HRs) and 95% confident intervals (CIs).

The results are summarized as the HR and 95% CIs. Statistical analyses were conducted using JMP version 7.0 (SAS Institute, Cary, NC) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Demographic Characteristics and Surgical Data

Before surgery, about two-thirds of patients with a history of nonmultiple PCI (n = 147 [67%]) did not receive any previous PCI, whereas the remaining 69 (33%) received 1 previous PCI. The mean number of PCIs history was 0.3 ± 0.5 in the nonmultiple PCI and 3.2 ± 1.5 in the multiple PCIs group ($P < .001$). At baseline, there were no intergroup differences in patient demographic characteristics, comorbidities, LV function parameters, and MR severity, except for a higher prevalence of male patients and chronic kidney disease among patients with previous multiple PCIs (Table 1). There were also no intergroup differences in the type (ie, partial or complete ring) and size of prosthetic ring implanted during RMA procedure. Patients with previous multiple PCIs were less likely to undergo concomitant CABG (47% vs 85%), with a smaller number of distal anastomoses (2.3 ± 1.1 vs 3.0 ± 1.2; $P = .002$). However, these patients tended to undergo concomitant papillary muscle approximation more frequently. After adjusting for the clinically relevant baseline profiles by using IPTW, no intergroup differences were found for these covariates. The SMD for each covariate was <0.25 (25%) (Table 1).

Clinical Outcomes

The 30-day mortality was 3.3% in the nonmultiple PCI group and 3.6% in the multiple PCIs group ($P = .72$). During follow-up, 157 deaths and 105 readmissions for heart failure occurred, and the overall 1- and 5-year survival rates were $83\% \pm 2\%$ and $58\% \pm 3\%$, respectively. The unadjusted comparisons between the study groups revealed that patients with previous multiple PCIs had a significantly lower 5-year survival rate ($44\% \pm 5\%$ vs $64\% \pm 3\%$; $P = .002$) and freedom from composite adverse events, defined as mortality and/or unscheduled heart failure admission ($24\% \pm 5\%$ vs $42\% \pm 4\%$; $P = .001$) (Figure 1). The main cause of mortality in both groups was heart failure, which accounted for 16% and 34% of deaths in patients with a history of nonmultiple and multiple PCIs, respectively ($P < .001$) (Figure 2). This finding indicated that the latter group were more likely to die from heart failure.

After adjusting by using IPTW, patients with a history of multiple PCIs showed a higher risk of all-cause mortality (HR, 1.4; 95% CI, 1.1-1.7; $P = .002$) and composite adverse events (HR, 1.4; 95% CI, 1.1-1.6; $P = .002$) compared with patients with a history of nonmultiple PCIs.

When comparing outcomes among patients without a history of PCI, those with single PCI and those with multiple PCIs, the 5-year survival rate and freedom from composite adverse events of patients with a history of a single PCI were comparable to that of patients without a history of PCI and were better than that of patients with previous multiple PCIs (Figure 3).

LV Reverse Remodeling After RMA

In the original cohort, serial echocardiography of patients in both study groups revealed significant improvements in LV end-systolic dimension and LV ejection fraction (time effect, $P < .001$ for both), with greater improvements in these values for patients in the nonmultiple PCIs group (interaction effect $P = .045$ and .004, respectively) (Figure 4). Consistently, compared with patients with a history of multiple PCIs, patients with a history of nonmultiple PCIs had a greater percent reduction in the LV end-systolic dimension from baseline to 24 months after surgery ($9.4\% \pm 14\%$ vs $16\% \pm 15\%$; $P = .006$) and in the absolute change in the LV ejection fraction ($5.9\% \pm 12\%$ vs $12\% \pm 13\%$; $P = .005$) (Table 2).

When we restricted our analysis to patients who underwent concomitant CABG with RMA, patients in the nonmultiple PCI group achieved sustainable improvements in these parameters, whereas patients in the multiple PCIs group tended to have a gradual re-enlargement in the LV end-systolic dimension over time and less improvement in LV ejection fraction (interaction effect, $P = .013$ and .049, respectively) (Figure 4). Patients with a history of nonmultiple PCI had a greater percent reduction in the LV end-systolic dimension from baseline to 24 months after surgery ($8.7\% \pm 12\%$ vs $17\% \pm 16\%$; $P = .002$) and in the

TABLE 1. Patient demographic characteristics before and after adjustments with inverse-probability-of-treatment weighting (IPTW)

| Variables | Original cohort (crude) | | | | IPTW | | |
	Nonmultiple PCI (n = 211)	Multiple PCI (n = 98)	P value	SMD	Nonmultiple PCI (n = 309)	Multiple PCI (n = 311)	SMD
Clinical variables							
Age (y)	66 ± 10	68 ± 9	.217	0.155	67 ± 10	67 ± 9	0.002
Male	165 (78)	87 (89)	.038	0.288	252 (82)	249 (80)	0.035
Body surface area (m²)	1.62 ± 0.18	1.64 ± 0.17	.458	0.092	1.63 ± 0.18	1.62 ± 0.19	0.057
IABP implantation	22 (10)	15 (15)	.298	0.146	39 (13)	42 (13)	0.028
Emergency operation	31 (15)	14 (14)	1.000	0.012	46 (15)	44 (14)	0.015
Redo operation	18 (8.5)	11 (11)	.585	0.090	30 (9.6)	30 (9.7)	0.004
Logistic EuroScore II	15 ± 15	16 ± 15	.410	0.101	15 ± 16	15 ± 15	0.009
Comorbidities							
Diabetes	116 (55)	53 (54)	.981	0.018	169 (55)	170 (55)	0.005
eGFR <30 (mL/min/1.73 m²)	54 (26)	39 (40)	.016	0.306	94 (30)	96 (31)	0.008
PVD	31 (15)	12 (12)	.688	0.072	44 (14)	53 (17)	0.080
Echocardiographic data							
LVESD (mm)	54 ± 8	56 ± 9	.136	0.065	55 ± 7	54 ± 9	0.068
LVEF (%)	29 ± 8	28 ± 8	.595	0.178	29 ± 8	29 ± 7	0.057
MR grade ≥moderate	177 (84)	85 (87)	.632	0.081	262 (85)	269 (87)	0.051
Prior PCI							
None	142 (67)	0 (0)	–				
Single	69 (33)	0 (0)					
Multiple	0 (0)	98 (100)					
No. of PCI history	0.3 ± 0.5	3.2 ± 1.5	<.001				
Surgical data							
Mitral annuloplasty ring							
Partial ring	7 (3.3)	5 (5.1)	.450				
Complete ring	204 (97)	93 (95)					
Ring size (mm)							
24	63 (30)	43 (44)	.059				
26	93 (44)	42 (43)					
28	48 (23)	12 (12)					
30	6 (2.8)	1 (1.0)					
32	1 (0.5)	0 (0)					
Concomitant procedures							
CABG	179 (85)	46 (47)	<.001				
Distal anastomoses	3.0 ± 1.2	2.3 ± 1.1	.002				
SVR	61 (29)	35 (36)	.229				
PM approximation	25 (12)	27 (28)	.001				
Aortic valve replacement	13 (6.2)	13 (13)	.036				

Values are presented as mean ± standard deviation or n (%). *PCI*, Percutaneous coronary intervention; *SMD*, standardized mean difference; *IABP*, Intra-aortic balloon pump; *EuroScore II*, European System for Cardiac Operative Risk Evaluation; *eGFR*, estimated glomerular filtration rate; *PVD*, peripheral vascular disease; *LVESD*, left ventricular end-systolic dimension; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation; *CABG*, coronary artery bypass grafting; *SVR*, surgical ventricular reconstruction; *PM*, papillary muscle.

absolute change in the LV ejection fraction (6.7% ± 12% vs 13% ± 13%; P = .017) (Table 2).

The MR grade significantly improved by 1 month after surgery, irrespective of the study group (time effect, P < .001). The prevalence of MR classified as moderate grade or higher did not change substantially thereafter during follow-up until 2 years after surgery. No intergroup differences existed at any follow-up time point (interaction effect, P = .252; group effect, P = .472) (Figure 5).

DISCUSSION

The novel findings of this study were as follows: patients with chronic MR secondary to ischemic cardiomyopathy can undergo surgery with acceptable operative mortality, irrespective of a history of multiple PCIs; patients with a history of multiple PCIs had a higher prevalence of chronic kidney disease before surgery and were less likely to undergo concomitant CABG with a smaller number of distal anastomoses; a history of multiple PCIs was independently and significantly
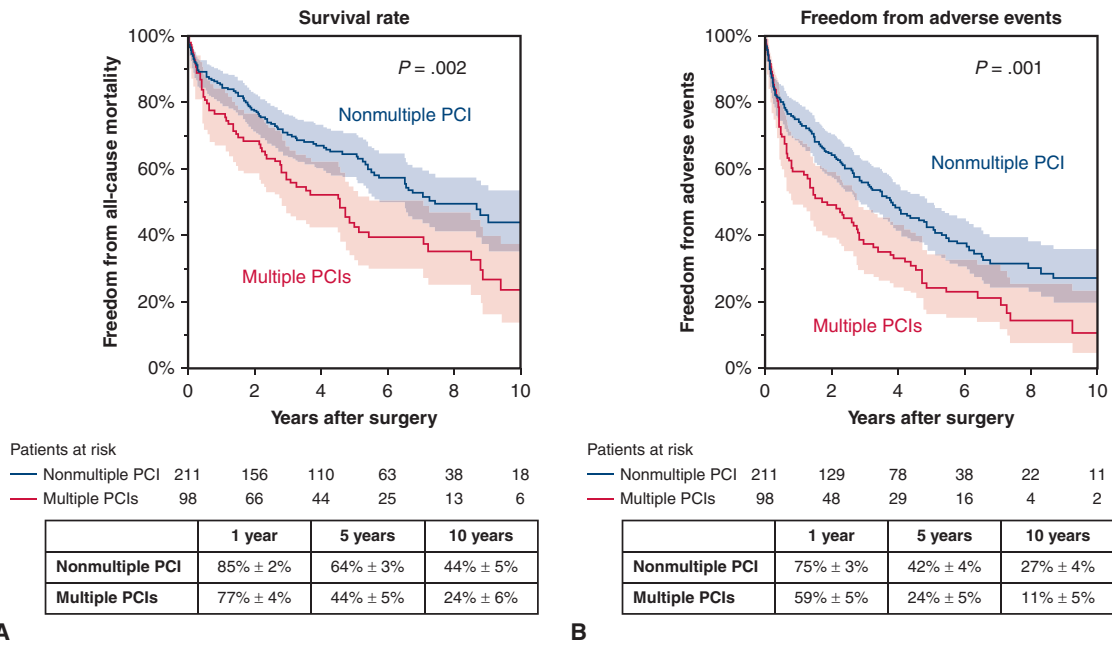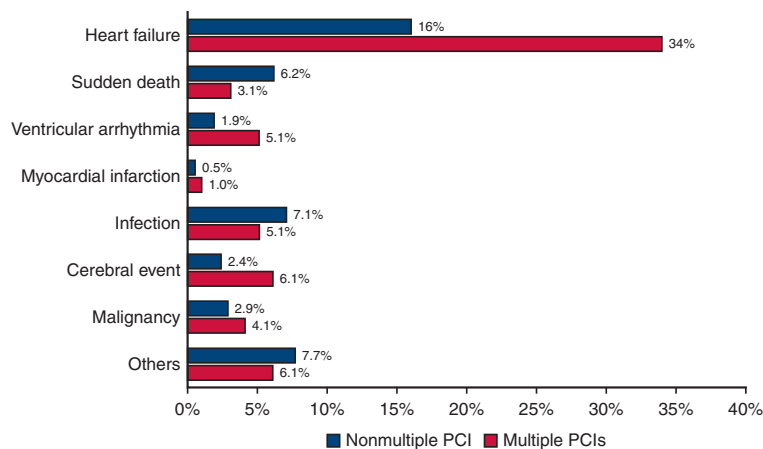
FIGURE 1. The unadjusted comparisons between the study groups. A, Freedom from all-cause mortality. B, Composite adverse events. Patients with a history of multiple percutaneous coronary interventions (PCIs) have a significantly lower 5-year survival rate and freedom from composite adverse events, defined as mortality and/or unscheduled heart failure admission.

associated with a lower 5-year survival rate and freedom from composite adverse events after surgery, accompanied by less improvement in LV function parameters (Figure 6); and the independent associations of a history of multiple PCIs with increased risks of mortality and composite adverse events were further confirmed, after adjusting for clinically relevant covariates by using the IPTW method (Video 1).

To the best of our knowledge, this study is the first to demonstrate the detrimental effect of previous multiple PCIs on the long-term outcomes of patients with chronic MR secondary to ischemic cardiomyopathy who undergo subsequent mitral valve surgery. In general, multiple stenting can cause coronary side-branch obstruction or occlusion, which may compromise collateral blood flow and cause myocardial

injury.[11] It may worsen LV systolic function in patients with previous multiple PCIs, compared with patients without this history. Contrary to this assumption, we did not find a statistical difference in LV function parameters between the 2 study groups before surgery. This finding suggested that impaired LV function may be associated more with ischemic insult secondary to myocardial infarction than with multiple PCI procedures. However, the most important finding was that the amount of improvement in LV function parameters after surgery was greater in patients without a history of multiple PCIs than in patients with a history of multiple PCIs.

Unfavorable myocardial recovery in patients with a history of multiple PCIs may have occurred for several reasons. First, patients with a history of multiple PCIs less frequently

FIGURE 2. Cause of death according to the study groups. The main cause of mortality in both groups was heart failure, which accounted for 16% and 34% of deaths in patients with a history of nonmultiple and multiple PCIs, respectively (*P* < .001). This finding indicated that those the latter group were more likely to die from heart failure. *PCI*, Percutaneous coronary intervention.
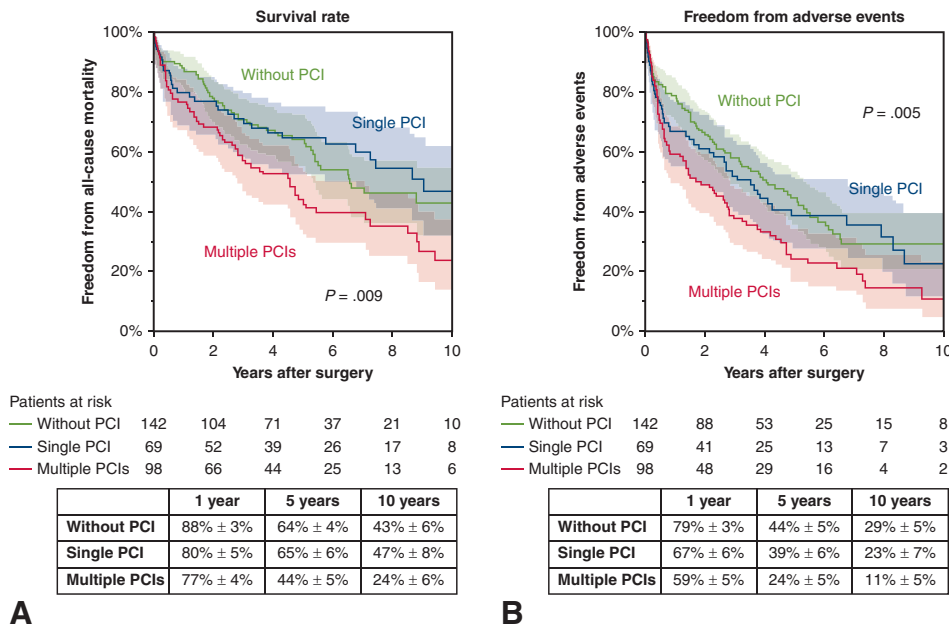
FIGURE 3. Comparisons of the survival rate and adverse events of patients who had 0, 1, or multiple percutaneous coronary interventions (*PCIs*). The graphs show (A) freedom from all-cause mortality and (B) composite adverse events. The survival of patients with a single PCI is comparable to that of patients without PCI history, and is better than that of patients with multiple PCIs.

underwent concomitant CABG with RMA. This finding may be due to the fact that coronary arteries treated with PCI sessions were not compromised with in-stent stenosis so no diseased vessels had to be bypassed or target vessels disease were too diffuse to be bypassed and there was associated insufficient myocardial viability. Second, PCI initiates a sequence of inflammatory reactions that cause endothelial hyperplasia at the site of stenting, and this inflammatory reaction may spread beyond the stent sites and promote diffuse lesions of the coronary artery, and thereby make bypass grafting more difficult and less effective.[12] In practice, patients with a history of multiple PCIs had fewer bypass grafts than did patients without multiple PCIs. This finding may account for less improvement in LV function parameters in patients with a history of multiple PCIs, even after we restricted our analysis to patients who underwent concomitant CABG with RMA. Third, local secondary inflammatory responses were activated by the coronary stents, aggregating platelets or neutrophils in coronary stents, and in vessels distal to the coronary stents where bypass grafts may be later anastomosed.[13] The graft must consequently be limited or forced to anastomose with areas where less viable myocardium exists and the vessels are smaller and are poor runoffs.[14] Fourth, renal dysfunction, which occurs more frequently in patients with a history of multiple PCIs, may be associated with unfavorable myocardial recovery after surgery, owing to suboptimal volume management during follow-up and residual elevated LV filling pressure (ie, cardiorenal syndrome).[15] The finding of a higher prevalence of death due to heart failure in patients with a history of multiple PCIs may support this hypothesis.

In this study, the rate of moderate or severe recurrent MR after surgery was not significantly different between the study groups at any follow-up time point and was substantially lower than the rates of 32.6% (1-year follow-up) and 58.8% (2-year follow-up) reported in a recent prospective randomized clinical study.[16] The difference in the MR recurrence rate could be explained by differences in the baseline LV function, MR severity, degree of leaflet tethering, and size of the mitral ring implanted during the repair. Of note, the average ring size utilized in the randomized clinical study was 27.9 mm, which is larger than the size (25.8 mm) used in our study.[16] The finding that the LV end-systolic dimension significantly decreased after surgery and the improvement was sustained during follow-up may have contributed to the lower rate of recurrent MR in the present study.

Patients with a history of multiple PCIs experienced lower rates of survival and freedom from composite adverse events than did patients without multiple PCIs, despite a comparable improvement in MR during follow-up. Therefore, correcting MR may not always modify the underlying pathophysiology and prevent patient readmission for heart failure. These findings may emphasize the importance of a treatment strategy aimed at reversing LV remodeling, along with or followed by an improvement in MR rather than a strategy aimed at eliminating MR simply by correcting mitral valve annular dilatation with an RMA procedure to improve the outcomes of patients with chronic secondary MR.

We found that the survival of patients with a history of a single PCI was comparable to that of patients without a history of PCI and was better than the survival of patients with previous multiple PCIs. Therefore, our data are consistent with the policy that a primary PCI is the treatment of choice for patients presenting with ST-segment elevation myocardial infarction. However, in nonacute settings, we speculate
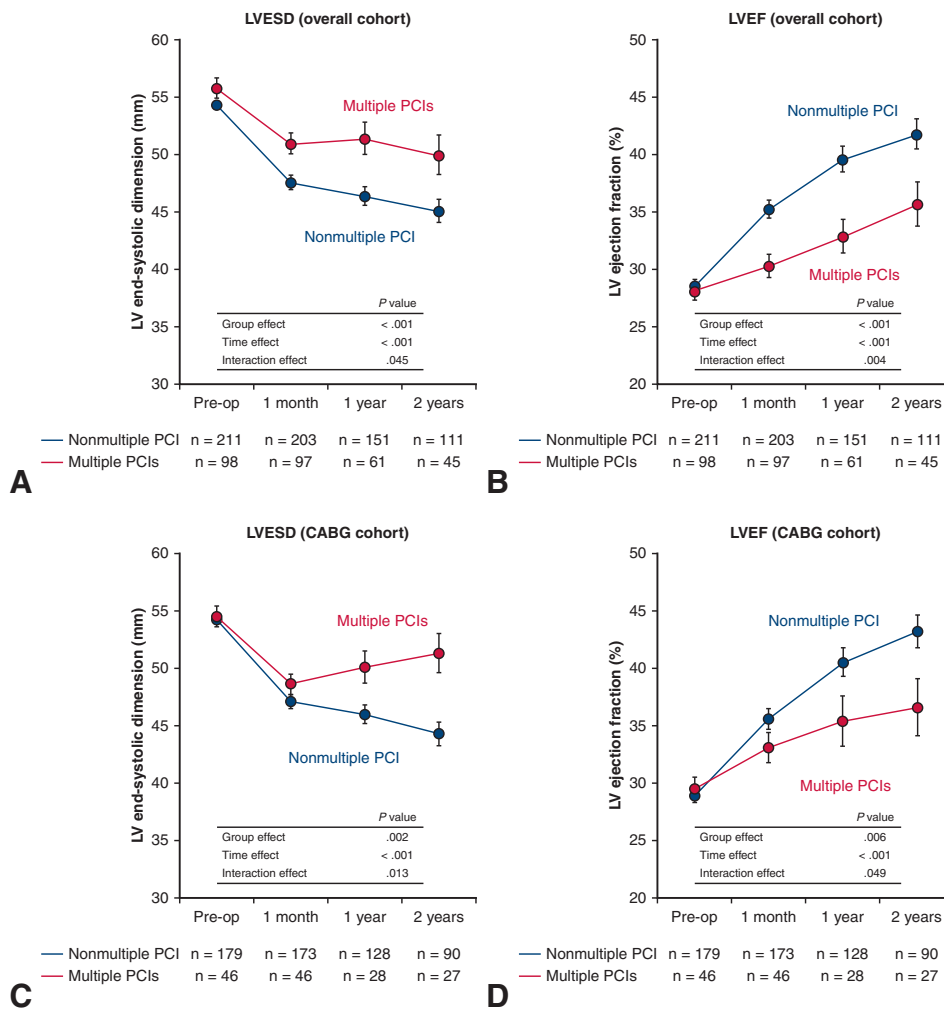
FIGURE 4. Serial echocardiography findings according to the study groups. Longitudinal changes among the entire cohort in (A) LV end-systolic dimension and (B) LVEF, based on the study group. Longitudinal changes among patients who received concomitant CABG in (C) LV end-systolic dimension and (D) LVEF, based on a history of multiple PCIs. *CABG*, Coronary artery bypass grafting; *LVEF*, left ventricular ejection fraction; *LVESD*, left ventricular end-systolic dimension; *PCI*, percutaneous coronary intervention.

that CABG may be the preferred treatment for patients with chronic MR and severely impaired LV function. Our hypothesis is supported by the finding by Kang and colleagues,[17] who first demonstrated that, compared with PCI, surgical revascularization is associated with improved long-term event-free survival for patients with ischemic MR. Furthermore, Castleberry and colleagues[18] reviewed the clinical outcomes of patients diagnosed with significant coronary artery disease and moderate or severe ischemic MR over 20 years. The patients were treated with medical treatment alone, PCI, CABG, or CABG plus mitral valve surgery. The investigators found that CABG with or without mitral valve surgery was associated with lower mortality than was PCI or medical treatment alone.[18]

Clinical Implications

Recent randomized controlled trials and large-scale real-world registries of PCI versus CABG performed in the current stent era support CABG as the treatment of choice for patients with severe coronary artery disease and/or LV dysfunction.[19,20] However, inconsistent with the recommendations, PCI is increasingly used to treat complex coronary artery disease that may be a candidate for CABG as the initial treatment. Aggressive repeated PCI with multiple stenting has become more common in the stent era. This situation may be more evident in Japan where the number of PCI procedures is disproportionately large, compared with the number of CABG procedures. In 2017, the ratio of the number of PCI procedures (273,516) to CABG procedures (18,293) was approximately 15:1, which is much greater than the ratio of 1.7:1 reported in the United States.[21,22]

A drawback of PCI overuse is that it can deprive patients with ischemic cardiomyopathy of the option of undergoing CABG, which improves patient survival.[23] The overuse of PCI can also affect the indications for subsequent mitral valve surgery, which are directly influenced by the indications for CABG. Current guidelines state that mitral valve surgery is reasonable when CABG is indicated (Class IIa

TABLE 2. Changes in left ventricular function

Variable	Nonmultiple PCI	Multiple PCIs	P value
Overall cohort			
Baseline to 1 mo	n = 203	n = 97	
% Reduction in LVEDD	−11 ± 8.8	−8.2 ± 8.1	.022
% Reduction in LVESD	−12 ± 12	−8.4 ± 10	.003
Change in LVEF	6.7 ± 10	2.2 ± 8.6	<.0001
Baseline to 12 mo	n = 150	n = 61	
% Reduction in LVEDD	−10 ± 9.5	−6.9 ± 10	.032
% Reduction in LVESD	−15 ± 14	−7.6 ± 15	.002
Change in LVEF	11 ± 13	4.0 ± 11	<.0001
Baseline to 24 mo	n = 111	n = 45	
% Reduction in LVEDD	−10 ± 10	−7.4 ± 11	.136
% Reduction in LVESD	−16 ± 15	−9.4 ± 14	.006
Change in LVEF	12 ± 13	5.9 ± 12	.005
Patients with concomitant CABG			
Baseline to 1 mo	n = 173	n = 46	
% Reduction in LVEDD	−11 ± 8.8	−9.5 ± 7.2	.207
% Reduction in LVESD	−13 ± 13	−11 ± 8.7	.163
Change in LVEF	6.7 ± 10	3.6 ± 8.5	.036
Baseline to 12 mo	n = 128	n = 28	
% Reduction in LVEDD	−10 ± 10	−7.3 ± 9.1	.108
% Reduction in LVESD	−16 ± 15	−11 ± 14	.073
Change in LVEF	12 ± 13	6.4 ± 10	.025
Baseline to 24 mo	n = 90	n = 27	
% Reduction in LVEDD	−11 ± 10	−6.0 ± 6.6	.008
% Reduction in LVESD	−17 ± 16	−8.7 ± 12	.002
Change in LVEF	13 ± 13	6.7 ± 12	.017

Values are presented as mean ± standard deviation. *PCI*, Percutaneous coronary intervention; *LVEDD*, left ventricular end-diastolic dimension; *LVESD*, left ventricular end-systolic dimension; *LVEF*, left ventricular ejection fraction; *CABG*, coronary artery bypass grafting.

recommendation) or can be considered as an isolated procedure (Class IIb recommendation); therefore, the strength of recommendation for mitral valve surgery is weakened when CABG is not indicated.[24] Accordingly, multiple PCIs performed with the aim of complete coronary revascularization would delay the timing of referral for subsequent mitral surgery and deprive patients of the opportunity to undergo concomitant CABG during subsequent mitral valve surgery, and would potentially negatively influence surgical outcomes. Therefore, our view is that the strategy of myocardial revascularization for patients who have undergone a primary PCI is extremely important, particularly in the presence of ischemic MR.

Our study highlighted the importance of careful discussion among members of the cardiac team (ie, cardiologists, interventionists, and surgeons) regarding the optimal revascularization strategy for nonculprit lesions in patients with ischemic MR who are likely to require subsequent surgical intervention for severe heart failure that is refractory to maximum medical treatment.

Limitations

The main limitations of this study are its nonrandomized retrospective nature and the small number of participants. To minimize potential bias related to patient selection, we excluded patients with a low degree of LV remodeling and ischemic MR secondary to nonischemic cardiomyopathy. We also restricted our analysis to patients with advanced cardiomyopathy secondary to ischemic etiology. An operation such as CABG is a major predictor of survival and secondary end points such as LV ejection fraction in patients with LV dysfunction. Therefore, the difference in the prevalence of concomitant CABG between the study groups may have led to differences in the outcomes measured and may be the primary reason for the poorer outcomes observed in the multiple PCIs group. Moreover, each additional procedure (eg, surgical ventricular reconstruction, papillary muscle approximation, and aortic valve replacement) is likely have a significant influence on the
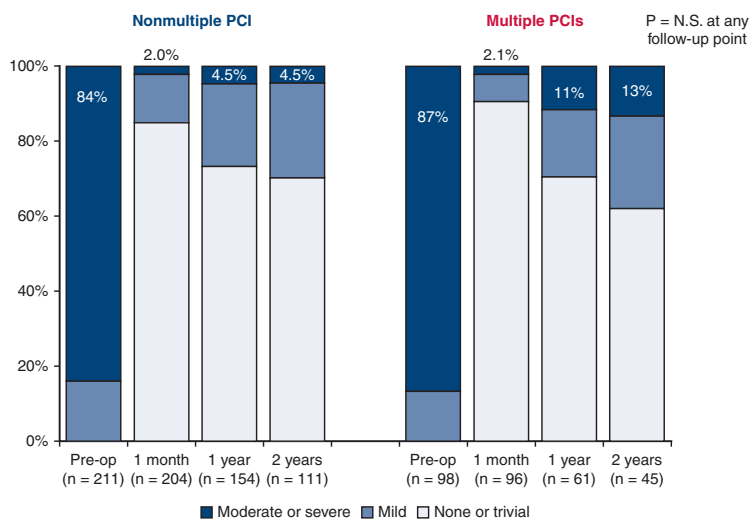
FIGURE 5. Longitudinal changes in mitral regurgitation (MR) grade, based on study group. In both groups, MR grade was significantly improved at 1 month after surgery. Thereafter, the prevalence of MR of moderate grade or higher did not substantially change for up to 24 months after surgery. *PCI*, Percutaneous coronary intervention; *N.S.*, not significant; *Pre-op*, preoperation.
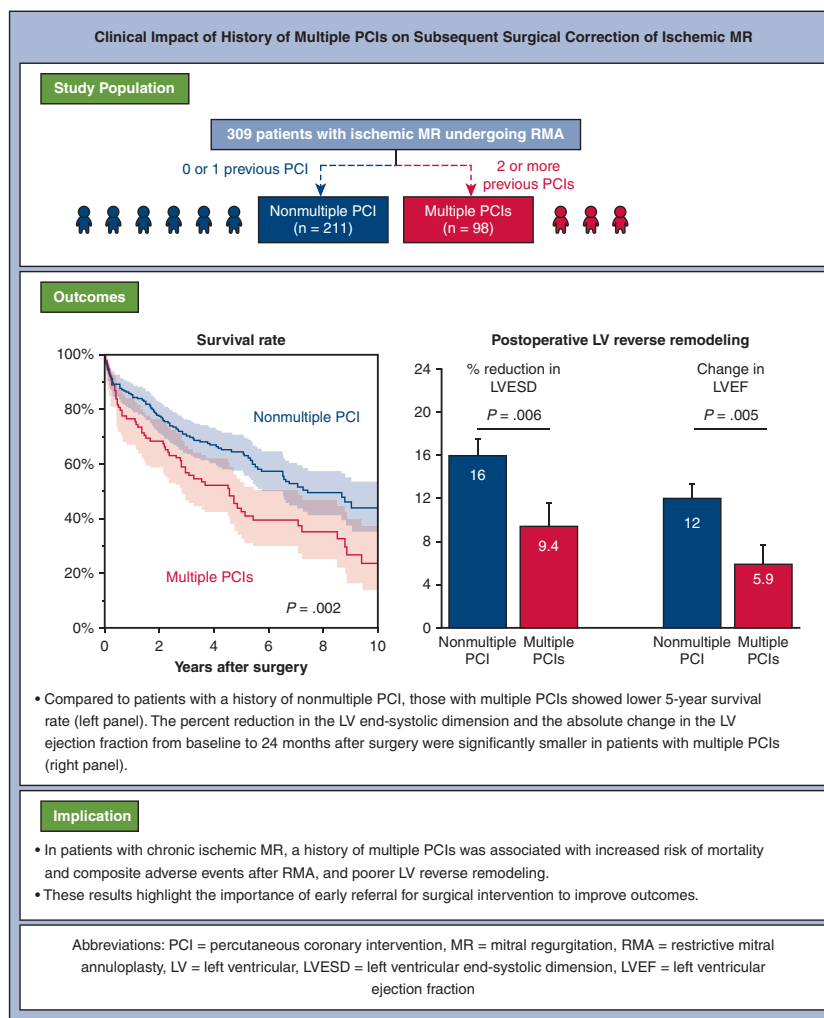
FIGURE 6. Three hundred nine patients with chronic mitral regurgitation (*MR*) secondary to ischemic cardiomyopathy—defined as severely impaired left ventricular (*LV*) systolic function with an ejection fraction ≤40%—were classified into the nonmultiple percutaneous coronary intervention (*PCI*) group (ie, zero to 1 previous PCI [n = 211]) or the multiple PCIs group (ie, 2 or more previous PCIs [n = 98]). Compared with patients in the nonmultiple PCI group, those in the multiple PCIs group had a significantly lower 5-year survival rate (44% vs 64%; *P* = .002) and a smaller percent reduction in the LV end-systolic dimension (*LVESD*) from baseline to 24 months after surgery (9.4% ± 14% vs 16% ± 15%; *P* = .006) and in the absolute change in the LV ejection fraction (*LVEF*) (5.9% ± 12% vs 12% ± 13%; *P* = .005). These results are particularly relevant for physicians attempting to devise a revascularization strategy for these patients and highlight the importance of early referral for surgical intervention to improve outcomes. *RMA*, Restrictive mitral annuloplasty.

outcomes. The number of patients in the multiple PCIs group was approximately 50% of the number of patients in the non-multiple PCI group. Therefore, these additional procedures may have negatively influenced this group. However, when the adjustment was further made for concomitant surgery, a history of multiple PCIs remained independently associated with a higher risk of mortality after surgery in the matched cohort (HR, 1.4; 95% CI, 1.1-1.7; *P* = .013).

The inclusion of patients with ischemic MR who underwent surgery between 1999 and 2015 may have influenced the results of this study because PCI and CABG techniques and technology developed and changed substantially over this time. When we compared the outcomes between the study groups, based on the tertile of the study period (ie, 1999-2007, 2007-2010, and 2010-2015), patients with non-multiple PCI had a significantly higher survival rate in the

second and third tertiles of the period (*P* = .019 and *P* = .042, respectively), but not in the first tertile (*P* = .276). This finding can be explained by a trend toward earlier referral for surgery during the study period over time, as evidenced by the gradual increase in the prevalence of patients without a history of PCI (40%, 44%, and 56% in the first, second, and third tertile, respectively; *P* = .059).

Viability assessment, which is associated with survival and postoperative LV function recovery following CABG, was not always performed. However, findings from a recent randomized clinical trial do not support the concept that myocardial viability assessment determines the likelihood of long-term benefit from surgical revascularization in patients with ischemic cardiomyopathy.[25] In patients with a history of multiple PCIs before surgery, an incomplete evaluation for the presence or severity of ischemic MR and coronary severity

VIDEO 1. Introduction and brief overview of the present study. Video available at: https://www.jtcvs.org/article/S2666-2736(21)00230-8/fulltext.

(ie, the Synergy Between PCI With Taxus and Cardiac Surgery [SYNTAX] score[26]) at the time of each PCI did not allow us to precisely elucidate the process of how interventionists determined to pursue PCI rather than CABG. In addition, due to the lack of data regarding coronary arterial dominance (ie, right or left dominant), its association with the presence of MR at the time of PCI or recurrent MR following primary PCI were not evaluated. Finally, quantitative grading of MR severity (eg, effective regurgitation orifice area and regurgitant volume) rather than the traditional semiquantitative measurement is a more objective evaluation.

CONCLUSIONS

Surgery in patients with ischemic mitral regurgitation had acceptable operative mortality, irrespective of a history of multiple PCIs. A history of previous multiple PCIs was independently associated with an increased risk of mortality and event-free survival after surgery, accompanied by less improvement in LV systolic function. These findings are particularly relevant for physicians attempting to devise a revascularization strategy for patients with ischemic MR because there is a lack of consensus on the optimal management of untreated residual coronary artery disease in patients with a history of myocardial infarction. Our data may also indicate the importance of early referral for surgical intervention to improve outcomes.

Webcast 🎦

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Tuesday_May7/205AC/205AC/S107%20-%20Cardiac%20surgery%20in%202019/S107_7_webcast_111026753.mp4.
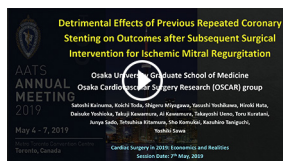
Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Discussion
Presenter: Dr Satoshi Kainuma

**Dr Robert E. Michler** (*New York, NY*). Dr Kainuma, the American Association for Thoracic Surgery selection committee made an excellent decision in selecting your abstract for oral presentation. The topic is provocative in answering the question of whether multiple percutaneous coronary intervention (PCI) negatively influences clinical outcomes for ischemic mitral regurgitation, and your work could change clinical practice. Now, with the opportunity to carefully review your manuscript, it appears that an answer is close, but not yet definitive.

The unifying aspect of the 2 comparison populations that you studied is that they both underwent restrictive annuloplasty for ischemic mitral regurgitation. Apart from this fact, the 2 groups were in fact very different. An operation such as coronary artery bypass grafting (CABG) is a major predictor of survival as is left ventricular ejection fraction.

CABG was performed in significantly different numbers in each comparison group, 85% of 211 in the group with one or fewer PCIs, versus 47% of the 98 patients in the group with multiple PCIs. This fact alone may have led to differences in the outcomes measured and served as the primary driver of why the multiple PCI group did less well, in comparison to the single or no PCI group. Moreover, each additional operation performed would likely have influenced the outcomes measured. Because the multiple PCI group included 50% fewer total patients, the influence of these additional procedures may have negatively influenced the results for the group. And, another cofounding variable such as surgical ventricular reconstruction, which is a highly technical and demanding operation, with its own morbidity and mortality, was performed in 61 of the 211 patients with no or 1 PCI and 35 of the 98 patients with multiple PCIs.

Was CABG required less frequently in the multiple PCI group because PCI was so successful in reperfusion of the at-risk territory or because the coronary anatomy was inherently bad? Or worse yet, perhaps the PCI—the prior PCI—had inflamed, sclerosed, and narrowed the distal vessel, making it ungraftable in the eyes of the surgeon?
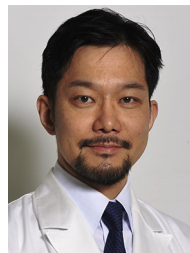
Dr Satoshi Kainuma (*Suita, Osaka, Japan*). Thank you, Professor Michler, for your great comments and important question. I think both are the reasons why patients with multiple PCI groups were not amenable to CABG. I mean that they were more likely to have more severe disease of the vessel, so bypass surgery was difficult. In addition to that, the result of the PCI was excellent for some patients, whereas not in others. So, I guess both factors were the reasons to explain the infrequent rates of concomitant bypass surgery for patients with multiple PCIs.

Dr Michler. Was ischemic mitral regurgitation present at the time of the original PCI? And if it was, was the decision to perform a restrictive annuloplasty made because the desire was to avoid bypass surgery or was the belief that it might in and of itself reduce the grade of ischemic mitral regurgitation?

Dr Kainuma. Thank you for your great question. Unfortunately, every patient was not evaluated in terms of ischemic mitral regurgitation at the time of the PCI. This is a problem. And secondly, interventionists in Japan are quite aggressive and prefer to do PCI whenever they see the ischemic mitral regurgitation. Probably because they do not consider that CABG is the best coronary revascularization therapy for patients with ischemic mitral regurgitation and myocardial dysfunction. So, Japanese cardiologists and interventionists are well trained in terms of the procedural aspect, but not with patient selection or indication for the PCI, especially for patients with stable coronary artery disease.
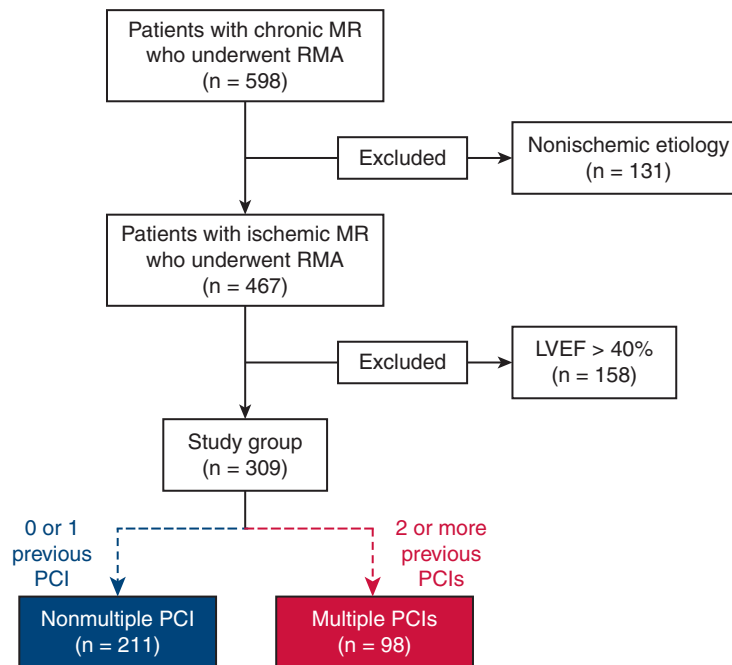
FIGURE E1. Consolidated Standards of Reporting Trials diagram of patients with ischemic cardiomyopathy who underwent restrictive mitral annulo-plasty (*RMA*) during the study period. *MR*, Mitral regurgitation; *LVEF*, left ventricular ejection fraction; *PCI*, percutaneous coronary intervention.