International Journal of Cardiology 277 (2019) 47–53

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Comparison of long-term clinical outcomes between revascularization versus medical treatment in patients with silent myocardial ischemia

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ARTICLE INFO

Article history:
Received 1 May 2018
Received in revised form 9 June 2018
Accepted 2 August 2018
Available online 3 August 2018

Keywords:
Percutaneous coronary intervention
Coronary artery bypass graft surgery
Silent myocardial ischemia
Coronary artery disease
Outcomes

ABSTRACT

Background: There have been limited and conflicting results regarding the prognostic impact of revascularization treatment on the long-term clinical outcomes of silent ischemia. The current study aimed to determine whether revascularization treatment compared with medical treatment (MT) alone reduces long-term risk of cardiac death of asymptomatic patients with objective evidence of inducible myocardial ischemia.
Methods: A total of 1473 consecutive asymptomatic patients with evidence of inducible myocardial ischemia were selected from a prospective institutional registry. All patients showed at least 1 epicardial coronary stenosis with ≥50% diameter stenosis in coronary angiography. Patients were classified according to their treatment strategies. The primary outcome was cardiac death up to 10 years.
Results: Among the total population, 709 patients (48.1%) received revascularization treatment including percutaneous coronary intervention (PCI, $n = 558$) or coronary artery bypass graft surgery (CABG, $n = 151$), with the remaining patients (764 patients, 51.9%) receiving MT alone. During the follow-up period, the revascularization treatment group showed a significantly lower risk of cardiac death compared with the MT alone group (25.4% vs. 33.7%, HR 0.624, 95%CI 0.498–0.781, $p < 0.001$). Among revascularized patients, patients with negative non-invasive stress test results after revascularization showed significantly lower risk of cardiac death compared to those with residual myocardial ischemia (8.9% vs. 18.7%, HR 0.406, 95% CI 0.175–0.942, $p = 0.036$).
Conclusions: In patients with silent myocardial ischemia, revascularization treatment was associated with significantly lower long-term risk of cardiac death compared with the MT alone group. The current results support contemporary practice of ischemia-directed revascularization, even in patients with silent myocardial ischemia.

1. Introduction

Although mortality from coronary artery disease (CAD) has substantially declined in the past 3 decades, CAD still remains a main cause of death worldwide [1]. Currently, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) are used as a revascularization treatment for CAD. However, survival benefit of revascularization treatment is uncertain in patients with stable CAD unlike in those with acute coronary syndrome [2–4]. Therefore, in addition to

Abbreviations: CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CI, confidence intervals; DES, drug-eluting stent; HR, hazard ratio; IPW, inverse-probability-weighted; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MT, medical treatment; PCI, percutaneous coronary intervention; SPECT, single-photon emission computed tomography.

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https://doi.org/10.1016/j.ijcard.2018.08.006
0167-5273/

optimal medical treatment (MT), revascularization treatment should be carefully determined in patients with silent myocardial ischemia, which is defined as asymptomatic patients with the presence of objective findings of inducible myocardial ischemia and significant angiographic stenosis.

Silent myocardial ischemia is not uncommon and previous studies demonstrated worse clinical outcomes in patients with silent myocardial ischemia after acute myocardial infarction (MI) or after revascularization [5–9]. In addition, the presence of silent myocardial ischemia is also associated with an increased risk of adverse clinical outcomes in a general population without history of CAD [10,11]. Nevertheless, among the limited studies which evaluated the prognostic impact of revascularization treatment in patients with silent myocardial ischemia, the results were conflicting [12–14]. It should be noted that, in these studies, the profile of MT was different from contemporary practice, revascularization treatment did not include drug-eluting stents (DES), study sample sizes were limited, and limited follow-up periods precluded any clear conclusion for the role of revascularization treatment in patients with silent myocardial ischemia and significant angiographic stenosis.

Therefore, the current study sought to compare the long-term clinical outcomes between revascularization treatment (CABG or PCI) and MT alone in asymptomatic patients with objective evidence of inducible myocardial ischemia based on non-invasive stress tests and treatment with contemporary practice.

2. Methods

2.1. Study population

From March 2003 through December 2015, 1473 consecutive patients with silent myocardial ischemia were selected from a prospective institutional registry in Samsung Medical Center. Silent myocardial ischemia was defined as asymptomatic patients who had objective findings of inducible myocardial ischemia on non-invasive stress tests, including exercise-stress electrocardiography, exercise or pharmacologic-stress echocardiography, or single-photon emission computed tomography (SPECT), and had significant angiographic stenosis (percent diameter stenosis ≥50%) of at least 1 epicardial coronary artery on coronary angiography. Thus, asymptomatic patients with objective evidence of inducible myocardial ischemia and significant angiographic CAD were included in the current analysis (Supplementary Fig. 1).

For this study, enrolled subjects were classified into those undergoing revascularization treatment ($n = 709$) and those undergoing MT alone ($n = 764$). In cases of planned revascularization by PCI or CABG being determined at the time of diagnostic coronary angiography, all these patients were classified into the revascularization group. The study protocol was approved by the institutional review board of Samsung Medical Center and was conducted according to the principals of the Declaration of Helsinki. All patients provided written informed consent prior to enrollment in the institutional registry.

2.2. Non-invasive stress test

All patients underwent at least 1 non-invasive stress test, such as exercise-stress electrocardiography, exercise or pharmacologic-stress echocardiography, or SPECT before coronary angiography. The selection of non-invasive stress test was at the discretion of the physician.

Exercise-stress electrocardiography testing was performed according to standard Bruce protocol [15]. Exercise target was according to 85% of predicted value of heart rate ([220 − age] × 0.85). Standard 12-lead electrocardiographic changes after exercise were considered positive if there was ≥1 mm of horizontal or down-sloping ST depression for ≥0.08 s after the J point in 2 or more contiguous leads compared with the resting electrocardiogram. Duke treadmill score was calculated as: Exercise time – (5 × Max ST) – (4 × Angina Index). The interpretation of exercise-stress electrocardiography was performed by physicians blinded to clinical information of patients.

Stress echocardiography testing was performed using either an exercise with standard Bruce protocol or pharmacologic stress with continuous titrated intravenous infusion of dobutamine [16]. Two-dimensional echocardiography was performed using harmonic imaging after exercise or pharmacologic stress. The left ventricle was visualized in the apical (4 chamber, 2-chamber, and 3-chamber) and in the parasternal (long and short axes) views. Post-exercise echocardiographic images were obtained within 30–60 s after termination of the treadmill exercise. For dobutamine stress echocardiography, the images were acquired at rest, low-dose, peak, and recovery phases. Target heart rates were determined as 85% of predicted value of heart rate per patient's age. All images were analyzed quantitatively by dedicated cardiologists specialized in cardiac imaging. Inducible myocardial ischemia was defined as newly developed regional wall-motion abnormality during stress in 2 or more contiguous left ventricular segments.

Thallium-201 SPECT was used to evaluate myocardial perfusion during pharmacologic stress [17]. Adenosine was administered intravenously (140 μg/kg/min via peripheral vein) to induce a stress condition. Relative perfusion defect was assessed in a 17-segment left ventricular model by experienced nuclear medicine physicians. Each segment was scored by a 5-point scoring system, and the scores were considered abnormal if the summed stress score was 3 or greater. All images were analyzed by experienced physicians in nuclear medicine who were blinded to clinical information of patients.

2.3. Treatment strategy

Optimal MT included antiplatelet agents, beta-blockers, renin angiotensin system blockers, and lipid lowering agents, including statins. The dosages of all medications were maximized as allowed by patient's heart rate, blood pressure, and clinical condition in the absence of justifiable contraindications, according to physician's discretion and guidelines [18,19]. Revascularization treatment was performed with either CABG or PCI, according to physician's discretion and guidelines [20,21]. For CABG cases, off-pump coronary bypass grafting utilizing the bilateral internal thoracic artery was the preferred technique as an institutional strategy [22]. PCI was performed according to current standard procedure guidelines [20,21]. During the study period, DES was the 1st line treatment modality used for revascularization treatment. The choice of stent, post-stenting adjunctive balloon inflation, and the use of intravascular ultrasound or glycoprotein IIb/IIIa inhibitors were all left to the operators' discretion. All patients received a loading dose of aspirin or were on chronic therapy before the procedure. A loading dose of P2Y12 inhibitors was administered to all patients who were not receiving a P2Y12 inhibitor prior to the procedure. Unless there was an undisputed reason for discontinuing dual antiplatelet therapy, all patients were recommended to take aspirin (at least 100 mg/day) indefinitely and a P2Y12 inhibitor for at least 6 months after their index procedure.

2.4. Data collection and outcome measurement

Baseline clinical, angiographic, and procedural data were prospectively recorded at the index procedure using a web-based reporting system by trained research coordinators. Follow-up outcomes were obtained from medical records and telephone contact, if necessary. The mortality data for patients lost to follow-up were ascertained by National Insurance data or National Death Records. All baseline and procedural coronary angiograms were reviewed and analyzed quantitatively by an independent core laboratory at Samsung Medical Center with validated software (Centricity CA 1000, GE, Waukesha, Wisconsin, USA). The SYNTAX score was calculated by a blinded investigator as previously reported [23]. Among patients who underwent PCI, those without residual angiographically significant stenosis were defined to have angiographically complete revascularization.

The primary endpoint of this study was cardiac death during follow-up. All deaths were considered cardiac unless a definite non-cardiac cause was established. The secondary endpoint was all-cause death, any spontaneous myocardial infarction (MI), or any revascularization. Spontaneous MI was defined as elevated cardiac enzyme levels, such as troponin I or myocardial band fraction of creatine kinase, greater than the upper limit of the normal range with either ischemic symptoms or electrocardiography changes indicating ischemia after index procedure [24]. Periprocedural MI was not included as a clinical event. Ischemia-driven revascularization included all target and non-target revascularization with either PCI or coronary artery bypass graft surgery. Any revascularization was adjudicated as ischemia-driven revascularization, which was defined as a revascularization procedure with at least one of the following: (1) Recurrence of angina; (2) Positive non-invasive test; and (3) Positive invasive physiologic test.

2.5. Statistical analysis

Continuous variables were tested using the Welch's *t*-test and presented as mean ± standard deviation. Categorical data were compared using the Chi-squared test and presented as numbers and relative frequencies. The cumulative incidence of clinical events was presented as Kaplan-Meier estimates and compared using a log-rank test. The hazard ratio (HR) and 95% confidence intervals (CI) was calculated by Cox proportional hazards model to compare the risk of mortality between the revascularization treatment group and the MT alone group. Multiple sensitivity analyses, including multivariable adjusted Cox proportional hazard regression, inverse-probability-weighted (IPW), and propensity-score matched analysis, were performed to reduce the possibility of biased effect estimates in observational studies.

We included in the multivariable models those covariates that were significant on univariate analysis or those that were clinically relevant, to identify independent predictors of clinical events. The adjusted HRs and 95% CIs on outcomes between revascularization treatment and MT alone group were obtained by the final Cox regression that included age, sex, presence of diabetes mellitus, dyslipidemia, left ventricular systolic dysfunction (ejection fraction <40%), history of PCI, multi-vessel disease, baseline regional wall motion abnormality, left main involvement, and chronic total occlusion. For propensity-score matching and IPW analysis, propensity score for all variables which showed an uneven distribution between the 2 groups was calculated, using a logistic regression model. Balance between the 2 groups after propensity-score matching or IPW adjustment was assessed by calculating percent standardized mean differences. Percent standardized mean differences after propensity-score matching or IPW adjustment were within ±10% across all matched covariates, demonstrating successful balance achievement between comparative groups (Supplementary Table 1). Stratified and IPW

adjusted Cox proportional hazard models were used to compare the outcomes of matched groups.

All probability values were two-sided and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using R Statistical Software (version 3.4.0; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Among patients with silent myocardial ischemia, 709 patients (48.1%) were treated with revascularization strategy including PCI ($n = 558$) or CABG ($n = 151$). The remaining 51.9% of patients ($n = 764$) were treated with MT alone. Baseline clinical and lesion characteristics according to treatment strategy are presented in Table 1. Compared with the revascularization treatment group, patients in the MT alone group were more likely to be older, a higher proportion of females, previous history of PCI, lower proportion of diabetes mellitus, and hyperlipidemia. Conversely, patients in the revascularization treatment group showed more complex lesion profiles, which were assessed by presence of multivessel disease, chronic total occlusion, left main disease, and SYNTAX score compared with the MT alone group. Although left ventricular ejection fraction (LVEF) did not differ between the 2 groups, baseline regional wall motion abnormality was more frequently observed in the revascularization treatment group than in the MT alone group (Table 1). However, there were no significant differences in total exercise duration and regional wall motion score index between the 2 groups (Table 1).

Supplementary Table 2 shows the procedural characteristics of revascularized patients with silent myocardial ischemia using PCI. Among the population who underwent PCI, 95.7% of patients were revascularized using DES (39.8% with 1st generation DES, 55.9% with 2nd generation DES) and 4.3% were treated with bare metal stent. Multi-vessel PCI was performed for 22.1% of patients and the mean number of treated lesions was 1.4 ± 0.9. Among revascularized patients,

Table 1
Baseline clinical and lesion characteristics in patients with silent myocardial ischemia according to treatment strategy.

Variables	Total ($n = 1473$)	Medical treatment ($n = 764$)	Revascularization treatment ($n = 709$)	p Value
Demographics				
Age (years)	64.5 ± 10.4	65.3 ± 10.3	63.7 ± 10.5	0.005
Male	1208 (82.0%)	604 (79.1%)	604 (85.2%)	0.003
Cardiovascular risk factors				
Hypertension	913 (62.0%)	485 (63.5%)	428 (60.4%)	0.239
Diabetes mellitus	798 (54.2%)	385 (50.4%)	413 (58.3%)	0.003
Chronic kidney disease	216 (14.7%)	108 (14.1%)	108 (15.2%)	0.603
Hyperlipidemia	1299 (88.2%)	638 (83.5%)	661 (93.2%)	<0.001
Previous percutaneous coronary intervention	530 (36.0%)	360 (47.1%)	170 (24.0%)	<0.001
Previous myocardial infarction	410 (27.8%)	226 (29.6%)	184 (26.0%)	0.135
Previous cerebrovascular accident	178 (12.1%)	84 (11.0%)	94 (13.3%)	0.211
Peripheral artery disease	88 (6.0%)	49 (6.4%)	39 (5.5%)	0.530
Complexity of CAD				
Multi-vessel disease	826 (56.1%)	346 (45.3%)	480 (67.7%)	<0.001
SYNTAX score	15.4 ± 10.4	13.7 ± 9.5	16.6 ± 10.8	0.021
Presence of chronic total occlusion	520 (35.3%)	222 (29.1%)	298 (42.0%)	<0.001
Left main involvement	65 (4.4%)	15 (2.0%)	50 (7.1%)	<0.001
Lesion location				
LAD	978 (66.4%)	446 (58.4%)	532 (75.0%)	<0.001
LCX	808 (54.9%)	387 (50.7%)	421 (59.4%)	0.001
RCA	807 (54.8%)	372 (48.7%)	435 (61.4%)	<0.001
Non-invasive test results				
Test modality				<0.001
Treadmill test	770 (52.3%)	440 (57.6%)	330 (46.5%)	
Stress echocardiography	612 (41.5%)	289 (37.8%)	323 (45.6%)	
SPECT	91 (6.2%)	35 (4.6%)	56 (7.9%)	
LVEF (%)	50.9 ± 13.9	51.4 ± 14.1	50.4 ± 13.8	0.215
LV dysfunction (EF <40%)	237 (20.9%)	100 (19.3%)	137 (22.3%)	0.249
Baseline regional wall motion abnormality	993 (67.4%)	461 (60.3%)	532 (75.0%)	<0.001
Total exercise duration (min)	8.3 ± 2.5	8.3 ± 2.4	8.3 ± 2.6	0.988
Duke score	−1.4 ± 5.0	−1.9 ± 5.2	−0.6 ± 4.5	0.012
Regional wall motion abnormality score index				
Resting	1.22 ± 0.28	1.20 ± 0.28	1.24 ± 0.28	0.477
Post-stress	1.37 ± 0.34	1.35 ± 0.35	1.39 ± 0.33	0.608
Revascularization strategy				<0.001
Medical therapy	764 (51.9%)	764 (100%)	–	
Percutaneous coronary intervention	558 (37.9%)	–	558 (78.7%)	
Coronary artery bypass graft surgery	151 (10.3%)	–	151 (21.3%)	
Laboratory findings at index admission				
Low-density lipoprotein (mg/dL)	99.1 ± 36.1	96.5 ± 35.4	101.4 ± 36.5	0.044
High-density lipoprotein (mg/dL)	42.3 ± 12.0	41.8 ± 11.5	42.7 ± 12.3	0.259
Triglyceride (mg/dL)	142.2 ± 98.5	139.2 ± 102.4	144.9 ± 94.9	0.391
Hemoglobin A1c (%)	7.3 ± 2.6	7.4 ± 3.3	7.2 ± 1.7	0.244
Discharge medication				
Aspirin	1382 (93.8%)	695 (91.0%)	687 (96.9%)	<0.001
P2Y12 inhibitor	1242 (84.3%)	596 (78.0%)	646 (91.1%)	<0.001
Beta-blocker	1067 (72.4%)	534 (69.9%)	533 (75.2%)	0.027
ACE inhibitor or ARB	1130 (76.7%)	579 (75.8%)	551 (77.7%)	0.416
Statin	1234 (83.8%)	606 (79.3%)	628 (88.6%)	<0.001

Data are presented as mean ± standard deviation, or n (%).
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; LAD, left anterior descending artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery.

59.5% of patients showed angiographically complete revascularization (Supplementary Table 2).

3.2. Clinical outcomes between revascularization treatment versus medical treatment among patients with silent myocardial ischemia

Among the total population, 92.5% (1362 patients) continued follow-up and 7.5% (111 patients) were lost follow-up. However, even among those lost to follow-up, vital status could be evaluated using the National Insurance data and National Death Records. The patients were followed up to 10 years with the median follow-up duration of 66 months (interquartile range: 29–111). Compared with the MT alone group, the revascularization treatment group showed significantly lower risk of cardiac death (revascularization vs. MT alone, 25.4% vs. 33.7%, HR 0.624, 95% CI 0.498–0.781, p < 0.001) (Table 2, Fig. 1A). Similarly, the risk of all-cause death (33.6% vs. 38.2%, HR 0.784, 95% CI 0.646–0.952, p = 0.014), MI (5.4% vs. 12.8%, HR 0.500, 95% CI 0.327–0.765, p = 0.001), and any revascularization (17.3% vs. 26.6%, HR 0.702, 95% CI 0.541–0.912, p = 0.008) was also significantly lower in the revascularization treatment group than in the MT alone group (Table 2, Fig. 1B, C, and D). Among the 764 patients with MT alone, 146 patients (19.1%) underwent PCI during follow-up for ischemia-driven revascularization and the median time point of revascularization was 38 months (interquartile range: 16–68). Multiple sensitivity analyses, including multivariate Cox proportional hazard model, IPW analysis, and propensity-score matched analysis consistently showed a significantly lower risk of cardiac death or all-cause mortality in the revascularization treatment group than in the MT alone group (Table 2).

Supplementary Table 3 shows the comparison of baseline characteristics among revascularized patients according to their revascularization strategies (CABG vs. PCI). Among these patients, the risk of cardiac death (25.2% vs. 25.5%, HR 0.952, 95% CI 0.608–1.490, p = 0.830) or all-cause death (38.0% vs. 32.4%, HR 1.210, 95% CI 0.860–1.711, p = 0.272) were comparable between the CABG and PCI groups (Supplementary Fig. 2). Sensitivity analysis using multivariable adjustment also showed similar results (Supplementary Table 4).

3.3. Independent predictors of cardiac death among patients with silent myocardial ischemia

On the multivariable adjusted Cox regression model, the MT alone group was independently associated with higher risk of cardiac death among patients with silent myocardial ischemia (adjusted HR 2.020, 95% CI 1.593–2.562, p < 0.001). Other independent predictors of cardiac death included baseline regional wall motion abnormality, left ventricular systolic dysfunction, age, and diabetes mellitus (Table 3).

3.4. Subgroup analysis

In the revascularization treatment group, 39.8% of patients (282/709) underwent follow-up non-invasive stress tests after revascularization with a median time of 275.5 days (Q1-Q3 34.0–525.3). Patients without follow-up stress tests showed significantly higher risk of cardiac (HR 3.317, 95% CI 2.129–5.169, p ≤ 0.001) and all-cause mortality (HR 4.068, 95% CI 2.754–6.009, p ≤ 0.001) compared to those with follow-up stress tests (Supplementary Fig. 3). Among patients with follow-up stress tests, those with negative results showed a significantly lower risk of cardiac death as well as all-cause death compared to those with positive results, suggesting residual myocardial ischemia (Supplementary Fig. 3).

In an exploratory subgroup analysis to evaluate the possible interaction between treatment strategy (revascularization treatment versus MT alone) and patient or lesion characteristics, the significantly lower risk of cardiac death in the revascularization treatment group than MT alone was consistently observed across various subgroups without significant interaction p value (Supplementary Fig. 4).

4. Discussion

The current study compared long-term clinical outcomes of patients with silent myocardial ischemia according to their treatment strategies. The main findings are as follows. First, among the patients with silent myocardial ischemia, those who were treated by revascularization showed significantly lower risk of cardiac death or all-cause mortality compared with MT alone. In addition, the results were consistent in multiple sensitivity analyses, adjusting for baseline differences between the 2 groups. Second, the MT alone group was independently associated with the occurrence of cardiac death, along with other independent predictors for cardiac death, including baseline regional wall motion abnormality, left ventricular systolic dysfunction, age, and diabetes mellitus. Third, among revascularized patients, those with resolution of myocardial ischemia showed significantly lower risk of cardiac death than those with residual myocardial ischemia.

4.1. Evidence of revascularization versus MT alone in patients with stable CAD

Studies in the early period of coronary revascularization consistently showed that the presence of myocardial ischemia, regardless of patient symptoms, was the most important prognostic factor [25–27]. Therefore, the presence of inducible myocardial ischemia is the prerequisite for revascularization treatment. However, the survival benefits of revascularization treatment using PCI or CABG have been uncertain as compared with MT alone. Although earlier RCTs comparing prognosis

Table 2
Comparison of clinical outcomes between medical treatment and revascularization among patients with silent myocardial ischemia.

	Cumulative incidence (%)	Univariate analysis			Multivariable analysis[a]			IPW analysis			PS matched analysis		
		HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Cardiac death													
Medical treatment	199 (33.7%)	1.000	Reference	NA	1.000	Reference	NA	1.000	Reference	NA	1.000	Reference	NA
Revascularization	112 (25.4%)	0.624	0.498–0.781	<0.001	0.495	0.390–0.628	<0.001	0.581	0.497–0.678	<0.001	0.554	0.414–0.743	<0.001
All-cause death													
Medical treatment	230 (38.2%)	1.000	Reference	NA	1.000	Reference	NA	1.000	Reference	NA	1.000	Reference	NA
Revascularization	167 (33.6%)	0.784	0.646–0.952	0.014	0.621	0.506–0.762	<0.001	0.722	0.631–0.826	<0.001	0.724	0.565–0.929	0.011
Myocardial infarction													
Medical treatment	68 (12.8%)	1.000	Reference	NA	1.000	Reference	NA	1.000	Reference	NA	1.000	Reference	NA
Revascularization	31 (5.4%)	0.500	0.327–0.765	0.001	0.413	0.263–0.649	<0.001	0.542	0.417–0.705	<0.001	0.427	0.256–0.713	0.001
Any revascularization													
Medical treatment	146 (26.6%)	1.000	Reference	NA	1.000	Reference	NA	1.000	Reference	NA	1.000	Reference	NA
Revascularization	92 (17.3%)	0.702	0.541–0.912	0.008	0.699	0.527–0.927	0.013	0.629	0.525–0.754	<0.001	0.565	0.409–0.779	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; PS, propensity score.

[a] Adjusted variables included age, sex, presence of diabetes mellitus, dyslipidemia, left ventricular systolic dysfunction (ejection fraction <40%), history of percutaneous coronary intervention, multi-vessel disease, baseline regional wall motion abnormality, left main involvement, and chronic total occlusion.

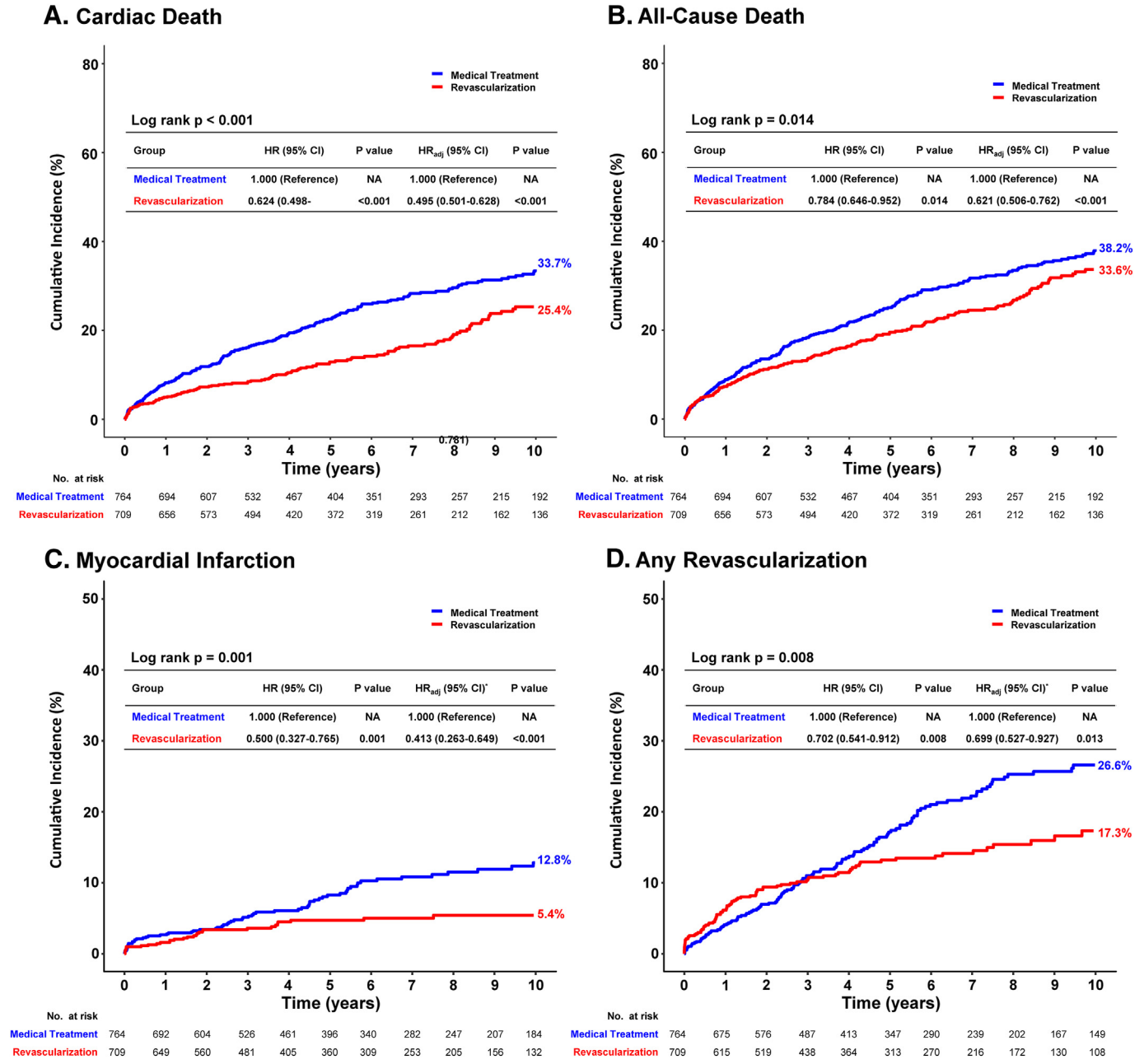

Fig. 1. Comparison of clinical outcomes between medical treatment and revascularization among patients with silent myocardial ischemia Kaplan-Meier curves are shown for comparison of: rates of cardiac death (A), all-cause death (B), myocardial infarction (C), and any revascularization (D) according to treatment strategy. Abbreviations: CI, confidence interval; HR, hazard ratio; HR$_{adj}$, multivariable adjusted hazard ratio.

between CABG versus MT alone showed significant survival benefit for the CABG group, especially in patients with depressed LV systolic function and extensive angiographic disease [28–32], the more recent BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial did not show a significant difference in mortality between CABG strata and MT alone group [3]. With regard to PCI, the survival benefit has been less clear than CABG. In the PCI strata of the BARI-2D trial, there was also no significant difference in mortality between the PCI and MT alone groups [3]. Similarly, the more recent COURAGE (Clinical Outcomes Utilizing Revascularization Aggressive Drug Evaluation) trial also demonstrated no significant difference in mortality between PCI and MT alone group during 15 years of follow-up [2,33]. However, the nuclear sub-study of the COURAGE trial presented that the addition of PCI to MT resulted in more effective reduction of myocardial ischemia than MT alone, and residual ischemic burden was significantly associated with mortality [34]. Moreover, post-hoc analysis of BARI-2D trial identified that amount of myocardial scar, and residual extent of ischemia assessed by myocardial perfusion imaging was significantly correlated

Table 3
Independent predictors of cardiac death.

	Adjusted HR (95% CI)[a]	p Value
Medical treatment alone	2.020 (1.593–2.562)	<0.001
Baseline regional wall motion abnormality	2.071 (1.549–2.770)	<0.001
LV systolic dysfunction (EF <40%)	1.983 (1.526–2.578)	<0.001
Age (per year)	1.042 (1.030–1.054)	<0.001
Diabetes mellitus	1.315 (1.047–1.651)	0.018

Abbreviations: EF, ejection fraction; LV, left ventricle; other abbreviations as listed in Table 2.
[a] Harrell's C-index of the Cox regression model for cardiac death was 0.733 (95% CI 0.700–0.766).

with the risk of cardiac death or MI [35]. The clinical relevance of ischemia-directed revascularization was recently further supported by landmark RCTs using fractional flow reserve (FFR), such as the FAME (Fractional Flow Reserve Versus Angiography for Multi-vessel Evaluation) trial, which presented significantly lower risk of death or myocardial infarction in the FFR-guided revascularization group than angiography-only guided group, or FAME 2 trial which demonstrated significantly lower risk of major adverse cardiac events after FFR-guided revascularization than MT alone in patients with functionally significant stenosis (FFR ≤ 0.80) [36,37]. These results imply that revascularization in addition to MT can provide greater reduction of burden of inducible myocardial ischemia, and clinical benefit of revascularization would be evident only for patients with proven inducible myocardial ischemia.

4.2. Role of revascularization treatment in patients with silent myocardial ischemia

Since current guidelines recommend PCI for patients with refractory anginal symptoms despite guideline-directed medical therapy, the role of revascularization, especially PCI, might be uncertain in patients with silent myocardial ischemia, even with the objective evidence of inducible myocardial ischemia [18,19]. However, previous studies reported that patients with silent myocardial ischemia were found to experience worse clinical outcomes than patients with stable angina [5–9], and previous studies consistently reported the presence of myocardial ischemia, regardless of patient symptoms, was the most important predictor of hard clinical outcome, such as death or non-fatal MI [25–27]. Nevertheless, there have only been 3 previous studies comparing clinical outcomes between revascularization and MT alone in patients with silent myocardial ischemia [12–14].

The ACIP (Asymptomatic Cardiac Ischemia Pilot) trial presented that revascularization improved survival in patients with asymptomatic stable CAD with objective evidence of inducible myocardial ischemia assessed by non-invasive stress tests or ambulatory 48-h ECG monitoring [12]. Similarly, the SWISSI II trial identified survival benefits of revascularization in patients with silent myocardial ischemia after MI [13]. Conversely, propensity score-matched analysis by Aldweib et al. presented comparable clinical outcomes between repeat revascularization and MT alone among asymptomatic patients with previous revascularization and inducible myocardial ischemia [14]. However, the overall number of the analyzed population in Aldweib et al. was only 230 patients and the proportion of ischemic cardiomyopathy (1.7%) or patients with severe LV dysfunction (0.8%) was very limited [14].

In contrast, the current analysis included an unrestricted asymptomatic population with inducible myocardial ischemia from a real-world registry. The relatively higher proportion of patients with multi-vessel disease, LV dysfunction, or baseline regional wall motion abnormality suggesting ischemic cardiomyopathy imply that the current population was a more enriched population of silent myocardial ischemia patients than in the study by Aldweib et al. [14] Although the current study was non-randomized, the study population is larger than in previous studies, and the significantly lower risk of cardiac death in the revascularization treatment group than the MT alone group was consistently observed, even with rigorous adjustment for baseline differences, up to 10 years of follow-up. Unlike the COURAGE or BARI-2D trials, in which DES was used only in 3% of the population, DES was the first-line treatment option for PCI during the current study period, with 95.7% of PCI patients being revascularized using DES, reflective of contemporary practice.

Of note, the risk of cardiac death was significantly lower in patients with resolution of inducible myocardial ischemia compared to those with residual myocardial ischemia, even after revascularization treatment. These results support the importance of ischemia-directed revascularization in patients with silent myocardial ischemia, and further trials are warranted to clarify this issue. The currently ongoing ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial (Clinicaltrials.gov, NCT 01471522) will be helpful to further clarify the benefit of revascularization treatment among patients with stable CAD and objective evidence of myocardial ischemia.

5. Limitations

This study had several limitations. First, the non-randomized nature of registry data could have resulted in selection bias and the selection of treatment strategy might reflect individual physician's preference. Although various sensitivity analyses including multivariate, IPW, and propensity-score matched analysis were performed, unmeasured confounding factors could not be adjusted. In particular, we did not have information on why revascularization was deferred in the MT alone group. Furthermore, discharge medical treatment including antiplatelet therapy, beta-blocker, or statins, was more intensively prescribed in the revascularization group than in the MT alone group. Intensive medical therapy for patients treated with revascularization may lead to better outcomes. Second, the types of non-invasive tests varied. However, each of the non-invasive stress tests were performed with standardized protocols and verified by experts. In addition, recent meta-analysis showed that the diagnostic accuracy among non-invasive stress tests other than cardiac magnetic resonance imaging or CT-derived FFR were not different to detect functionally significant epicardial coronary stenosis [38]. Although the current study could not present data of per-vessel FFR, which is the reference in contemporary practice to define inducible myocardial ischemia, the role of additional invasive physiologic assessments in patients with both significant angiographic stenosis and objective findings of inducible myocardial ischemia in non-invasive stress tests have not been clarified [20,21]. Third, follow-up non-invasive stress tests were not performed in all revascularized patients. Fourth, follow-up medications or laboratory findings in either group could not be assessed due to limited availability of data. Finally, although the entire study population showed objective signs of inducible myocardial ischemia and angiographically significant epicardial coronary stenosis, the possibility of accompanied microvascular disease or diffuse atherosclerotic narrowing without focal stenosis could not be fully explored. However, there has been no clear consensus or methodology for defining accompanied microvascular disease in patients with significant epicardial coronary stenosis. In addition, there is no clearly defined treatment method for patients with diffuse atherosclerotic narrowing without focal stenosis.

6. Conclusions

Among asymptomatic patients with objective signs of inducible myocardial ischemia, revascularization treatment showed significantly lower long-term risk of cardiac death compared with the MT alone group. The current results support contemporary practice of ischemia-directed revascularization, even in patients with silent myocardial ischemia.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.08.006.

Conflict of interest statement

Dr. Joo Myung Lee received a Research Grant from St. Jude Medical (Abbott Vascular) and Philips Volcano. All other authors declare that there is no conflict of interest relevant to the submitted work.

Acknowledgments and funding sources

None.

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