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Outcomes of Deferring Percutaneous Coronary Intervention Without Physiologic Assessment for Intermediate Coronary Lesions

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AUTHOR'S SUMMARY

Although long-term outcomes after deferring percutaneous coronary intervention (PCI) in functionally non-significant lesion are known to be favorable, the outcomes of deferring PCI for intermediate coronary lesions without physiologic assessment remain uncertain. In this post hoc analysis of a randomized trial comparing deferring PCI versus performing PCI based on angiography alone, it was found that deferring PCI was associated with a higher risk of major adverse cardiac events at 3 years. Therefore, the decision to pursue medical therapy alone for intermediate coronary lesions should not be based solely on angiography.

ABSTRACT

Background and Objectives: Outcomes of deferring percutaneous coronary intervention (PCI) without invasive physiologic assessment for intermediate coronary lesions is uncertain. We sought to compare long-term outcomes between medical treatment and PCI of intermediate lesions without invasive physiologic assessment.

Methods: A total of 899 patients with intermediate coronary lesions between 50% and 70% diameter-stenosis were randomized to the conservative group (n=449) or the aggressive group (n=450). For intermediate lesions, PCI was performed in the aggressive group, but was deferred in the conservative group. The primary endpoint was major adverse cardiac events

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Trial Registration

ClinicalTrials.gov Identifier: [NCT00743899](https://clinicaltrials.gov/ct2/show/study/NCT00743899)

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Conflict of Interest

The authors have no financial conflicts of interest.

(MACE, a composite of all-cause death, myocardial infarction [MI], or ischemia-driven any revascularization) at 3 years.

Results: The number of treated lesions per patient was 0.8 ± 0.9 in the conservative group and 1.7 ± 0.9 in the aggressive group ($p=0.001$). At 3 years, the conservative group had a significantly higher incidence of MACE than the aggressive group (13.8% vs. 9.3%; hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.00–2.21; $p=0.049$), mainly driven by revascularization of target intermediate lesion (6.5% vs. 1.1%; HR, 5.69; 95% CI, 2.20–14.73; $p<0.001$). Between 1 and 3 years after the index procedure, compared to the aggressive group, the conservative group had significantly higher incidence of cardiac death or MI (3.2% vs. 0.7%; HR, 4.34; 95% CI, 1.24–15.22; $p=0.022$) and ischemia-driven any revascularization.

Conclusions: For intermediate lesions, medical therapy alone, guided only by angiography, was associated with a higher risk of MACE at 3 years compared with performing PCI, mainly due to increased revascularization.

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Keywords: Coronary artery disease; Percutaneous coronary intervention; Coronary angiography

INTRODUCTION

Several randomized and observational studies consistently demonstrated that patients without functionally significant coronary stenosis by invasive physiologic assessment have a favorable outcome with medical therapy alone and percutaneous coronary intervention (PCI) can be safely deferred in these patients.¹⁻⁵ Therefore, the current major guidelines recommend fractional flow reserve (FFR) or instantaneous wave-free ratio to assess hemodynamic relevance of intermediate-grade stenosis.^{6,7} However, only a minority of patients undergoes physiology-guided PCI in routine clinical practice. In the second report from the Korean PCI registry, the proportion of FFR-guided PCI is only 4.1% in spite of medical reimbursement for FFR measurement.⁸ Currently, the most widely used modality for decision on whether to perform PCI or not is invasive coronary angiography and a large number of intermediate lesions are deferred without functional assessment.^{9,10}

In the Conservative Revascularization versus Aggressive Revascularization Strategy for Coronary Artery Disease with Everolimus-Eluting Stents (SMART-CASE) trial, a conservative revascularization strategy of deferring PCI with angiographic guidance alone was noninferior to an aggressive revascularization strategy of performing PCI for intermediate coronary lesions during 1 year of follow-up.¹¹ However, long-term outcomes of deferring PCI without invasive physiologic assessment for intermediate coronary lesions is uncertain. The aim of this study was to investigate whether noninferior outcomes of deferring PCI for intermediate coronary lesions, compared with performing PCI, would be maintained over 3 years of follow-up in the SMART-CASE trial.

METHODS

Ethical statement

The Institutional Review Board at each participating center approved the trial protocol (2008-06-027-027). All patients provided written informed consent. An independent data safety

Data Sharing Statement

The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions

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monitoring board reviewed the data periodically. The independent clinical event adjudication committee, whose members were masked to the study-group assignments, assessed all of the clinical end points.

Study design and patients

This was a post hoc analysis from the SMART-CASE trial. The study design and main results of the SMART-CASE trial was previously reported.¹¹⁾ This study was a multicenter, randomized, noninferiority trial that was conducted at 16 centers in Republic of Korea. Patients were eligible for the trial if they had 1 or more intermediate coronary lesion(s) defined as diameter stenosis between 50% and 70% by quantitative coronary analysis. Target lesion(s) had to be located in a native coronary artery with diameter ≥ 2.25 mm and ≤ 4.25 mm. Major exclusion criteria included: 1) cardiogenic shock; 2) myocardial infarction (MI) within 48 hours; 3) left main lesion; 4) drug-eluting stent implantation in the target vessel prior to enrollment; 5) ≥ 2 chronic total occlusions in major coronary territories; 6) history of bleeding diathesis or known coagulopathy; 7) recent major bleeding or major surgery; 8) planned elective surgical procedure requiring interruption of dual antiplatelet therapy during the first 6 months after enrollment; and 9) non-cardiac co-morbid conditions that may result in protocol non-compliance.

Randomization and study procedures

Patients were randomly assigned to the conservative group or the aggressive group in a 1:1 ratio after diagnostic angiography. On-line quantitative coronary analysis was performed at each center before randomization to determine eligibility. Randomization was performed using a web-based response system and was stratified by the site of enrollment and diabetes. In the conservative group, stenting was performed only in lesions with diameter stenosis $>70\%$ and reference diameter (RD) ≥ 2.25 mm. In the aggressive group, stents were implanted in lesions with diameter stenosis $>50\%$ and RD ≥ 2.25 mm and balloon angioplasty was performed in lesions with diameter stenosis $>50\%$ and RD ≥ 2.0 mm and <2.25 mm. If patients had lesions with diameter stenosis $>70\%$ that were amenable to PCI, lesions were treated in both groups. The stents used were limited to cobalt-chromium everolimus-eluting stents (Xience V or Xience Prime, Abbott Vascular) for all lesions. However, other stents were allowed in case of device failure or situations in which the operators decided otherwise, considering the best interests of patients. PCI was conducted according to standard techniques. There was no restriction in terms of the number or total length of stents used. Use of intravascular imaging was at the operators' discretion.

Follow-up and angiographic analysis

After the procedure, dual antiplatelet therapy (aspirin 100 mg/day plus clopidogrel 75 mg/day) was recommended for at least 12 months after implantation of drug-eluting stents. Other P2Y₁₂ receptor inhibitors were not available in Korea during the study period. All patients were recommended to receive optimal pharmacologic therapy including statins, beta-blockers, or renin-angiotensin system blockade following the current guidelines. Prescription of antianginal medication was at the duty physicians' discretion. Clinical follow-up was done at 1, 3, and 12 months after the index PCI and annually thereafter. Although this study was a post hoc analysis of the SMART-CASE trial, which was initially planned for a 1-year follow-up, physicians were encouraged to follow-up with their patients for 3 years through hospital visits or telephone calls.

Routine follow-up coronary angiography was prohibited, and revascularization was performed clinically indicated. Definition of clinically indicated revascularization was based on the Academic Research Consortium criteria: a percent diameter stenosis $\geq 50\%$ (core laboratory quantitative coronary angiography assessment) and if one of the following occurs: 1) a positive history of recurrent angina pectoris, presumably related to the target vessel; 2) objective signs of ischemia at rest (electrocardiogram changes) or during exercise test (or equivalent), presumably related to the target vessel; 3) abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve, FFR); 4) A target lesion or target vessel revascularization with a diameter stenosis $\geq 70\%$ even in the absence of the above-mentioned ischemic signs or symptoms. Preprocedural and postprocedural coronary angiographies were analyzed in a blind fashion at the angiographic core laboratory (Heart Vascular Stroke Institute, Samsung Medical Center, Seoul, Korea) with an automated edge-detection system (Centricity CA 1000 system; GE Healthcare, Waukesha, WI, USA). The minimum luminal diameter (MLD) and RD were measured. Diameter stenosis was calculated by $100 \times (\text{RD} - \text{MLD}) / \text{RD}$. Lesion severity was assessed by the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score, which was derived from the summation of the individual scores for each separate lesion with $\geq 50\%$ diameter stenosis in vessels ≥ 1.5 mm as previously described.¹²⁾

End points and definitions

The primary end point was major adverse cardiac events (MACE, a composite of all-cause death, MI, or ischemia-driven any revascularization) at 3 years after the index procedure. Secondary end points included individual component of the primary end point, cardiac death, death or MI, cardiac death or MI, ischemia-driven revascularization of the target intermediate lesion, revascularization of the target vessel in which the target intermediate lesion is located, target vessel failure, and stent thrombosis.

All deaths were considered cardiac unless a definite noncardiac cause could be established. MI was defined as an elevation in creatine kinase MB fraction or troponin-T/troponin-I greater than the upper limit of normal with concomitant ischemic symptoms or electrocardiography findings indicative of ischemia.¹³⁾ Periprocedural MI, defined as an elevation of cardiac troponin or creatine kinase MB fraction to more than 3 times the upper normal limit, was considered a clinical end point. In patients with elevated baseline levels of cardiac enzyme before the index procedure, reinfarction was defined as stable or decreasing values on 2 samples and 20% increase 3 to 6 hours after the second sample.¹³⁾ Target vessel failure was defined as a composite of cardiac death, MI not clearly attributable to a non-target vessel, or target vessel revascularization of the target intermediate lesion. Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium classification.

Statistical analysis

The trial was originally powered to test a noninferiority of the conservative revascularization strategy versus the aggressive revascularization strategy for the primary end point at 1 year. A sample size calculation was described previously.¹¹⁾ The 3-year analysis was post hoc and was not explicitly powered or adjusted for multiple comparisons. The principal analysis was done according to the intention-to-treat principle. Patients who were lost to follow-up were censored at the time of the last known contact. Cumulative event rates were estimated using the Kaplan-Meier method. Survival curves were compared with the log-rank test. The Cox proportional hazard model was used to compare the risks of adverse cardiac events between

the conservative group and the aggressive group. Categorical variables were compared using the χ^2 test. Continuous variables were compared using the Student's t-test or Mann-Whitney U test, as appropriate. All tests were 2-sided, and a p value <0.05 was considered statistically significant. Statistical analysis was performed using R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Between January 2009 and June 2012, a total of 899 patients with intermediate coronary lesion were enrolled in the SMART-CASE trial (**Figure 1**). After 1:1 randomization to either the conservative group (n=449) or the aggressive group (n=450), there were no significant differences in demographic and clinical characteristics (**Table 1**). At discharge, the prescription rate of antiplatelet agents, particularly clopidogrel, were lower in the conservative group than the aggressive group.

The extent of coronary artery disease, and the location, lesion length, and diameter stenosis of the target intermediate lesion were similar between the groups (**Table 2**). After the assigned procedure, the mean number of treated lesions was 0.8 ± 0.9 in the conservative group and 1.7 ± 0.9 in the aggressive group ($p < 0.001$). Total length of stent implanted was significantly shorter in the conservative group than the aggressive group (16.1 ± 21.8 vs. 40.0 ± 24.3 mm, $p < 0.001$). The residual SYNTAX score was significantly higher in the conservative group than the aggressive group (8.9 ± 6.7 vs. 4.4 ± 5.5 , $p < 0.001$).

Clinical outcomes at 3 years

A median follow-up duration was 1,096 days in the conservative group and 1,097 days in the aggressive group ($p = 0.448$), and 853 (94.9%) completed the 3-year follow-up. At 3 years after the index procedure, MACE frequently occurred in the conservative group compared to the aggressive group (14.8% vs. 9.8%; hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.03–2.23; $p = 0.036$; **Table 3** and **Figure 2**). The difference in MACE between the groups was mainly driven by revascularization of target intermediate lesion (7.7% vs. 1.6%; HR, 4.79;

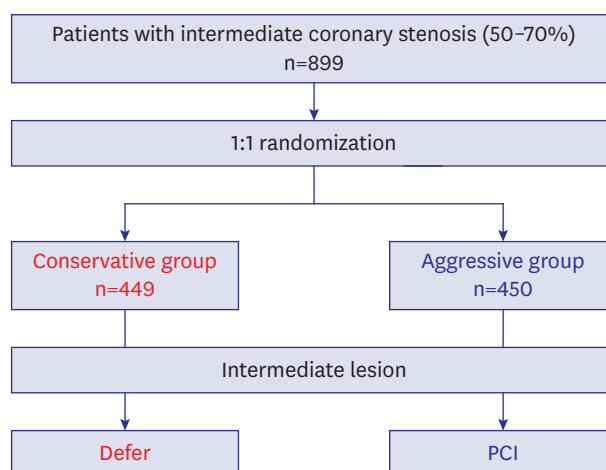


Figure 1. Study population.
PCI = percutaneous coronary intervention.

Table 1. Baseline characteristics

Variables	Conservative group (n=449)	Aggressive group (n=450)	p value
Age (years)	64.1±9.4	65.3±9.9	0.066
Male sex	289 (64.4)	305 (67.8)	0.280
Body mass index (m ²)	24.7±2.9	24.5±3.0	0.425
Diabetes mellitus	145 (32.3)	151 (33.6)	0.687
Hypertension	293 (65.3)	295 (65.7)	0.925
Dyslipidemia	114 (25.4)	125 (27.8)	0.418
Cerebrovascular accident	34 (7.6)	30 (6.7)	0.697
Chronic kidney disease	5 (1.1)	6 (1.3)	0.673
Current smoker	93 (20.7)	116 (25.8)	0.073
Previous MI	25 (5.6)	16 (3.6)	0.148
Previous revascularization	56 (12.5)	46 (10.2)	0.288
Clinical presentation			0.461
Stable ischemic heart disease	298 (66.4)	282 (62.7)	
Unstable angina	112 (27.2)	139 (30.9)	
MI	29 (6.5)	29 (6.4)	
Left ventricular ejection fraction (%)	62.1±9.3	62.4±9.5	0.642
Discharge medication			
Aspirin	432 (96.2)	444 (98.7)	0.020
Clopidogrel	313 (69.7)	444 (98.7)	<0.001
Statin	381 (84.9)	378 (84.0)	0.724
ACE inhibitor or ARB	246 (54.8)	262 (58.2)	0.299
Beta-blocker	258 (57.5)	247 (54.9)	0.437
Calcium channel blocker	154 (34.3)	146 (32.4)	0.556
Other anti-anginal medication	180 (40.1)	151 (33.6)	0.042

Data are presented as number (%) or mean ± standard deviation.

ACE = angiotensin-converting enzyme; ARB = angiotensin II-receptor blocker; MI = myocardial infarction.

Table 2. Angiographic and procedural characteristics

Variables	Conservative group (n=449)	Aggressive group (n=450)	p value
Extent of coronary artery disease			
Multivessel disease	253 (56.3)	237 (52.7)	0.268
SYNTAX score	13.3±7.9	13.0±7.3	0.507
Target intermediate lesion			
Location			0.254
Left anterior descending artery	197 (43.9)	218 (48.4)	
Left circumflex artery	106 (23.6)	88 (19.6)	
Right coronary artery	146 (32.5)	144 (32.0)	
Proximal lesion	127 (28.3)	134 (29.8)	0.675
Quantitative coronary analysis*			
Lesion length (mm)	13.4±5.1	13.1±4.4	0.390
Minimum lumen diameter (mm)	1.4±0.3	1.3±0.3	0.745
Reference diameter (mm)	3.1±0.6	3.0±0.5	0.680
Diameter stenosis	55.6±6.3	55.6±6.0	0.967
<50%	29 (6.5)	35 (7.8)	
50–60%	321 (72.5)	322 (72.2)	
60–70%	91 (20.5)	85 (19.0)	
>70%	2 (0.5)	5 (1.1)	
Treatment of coronary artery disease			
Residual SYNTAX score	8.9±6.7	4.4±5.5	<0.001
Number of treated lesions	0.8±0.9	1.7±0.9	<0.001
Total stent length per patients (mm)	16.1±21.8	40.0±24.3	<0.001
Average stent diameter per patient (mm)	3.1±0.7	3.1±0.6	0.690

Data are presented as number (%) or mean ± standard deviation.

SYNTAX = Synergy between PCI with Taxus and Cardiac Surgery.

*Available in 443 patients (98.7%) in the conservative group and 447 patients (99.3%) in the aggressive group.

Table 3. Clinical outcomes at 3-year follow-up

Variables	Conservative group (n=449)	Aggressive group (n=450)	HR (95% CI)	p value
Major adverse cardiac event	60 (13.8)	41 (9.3)	1.49 (1.00–2.21)	0.049
All cause-death	13 (3.0)	19 (4.3)	0.68 (0.34–1.37)	0.281
Cardiac death	8 (1.9)	7 (1.6)	1.13 (0.41–3.13)	0.808
MI	11 (2.6)	6 (1.4)	1.83 (0.68–4.95)	0.234
Death or MI	24 (5.6)	23 (5.2)	1.04 (0.59–1.84)	0.893
Cardiac death or MI	19 (4.5)	11 (2.5)	1.72 (0.82–3.62)	0.152
Ischemia-driven any revascularization*	46 (10.6)	23 (5.3)	2.03 (1.23–3.35)	0.006
Ischemia-driven target intermediate lesion revascularization	28 (6.5)	5 (1.1)	5.69 (2.20–14.73)	<0.001
Stent thrombosis	1 (0.2)	2 (0.4)	0.50 (0.05–5.48)	0.568

Data are presented as number (%). The percentages shown are Kaplan-Meier estimates. Major adverse cardiac event is a composite of all-cause death, MI, or any revascularization.

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

*Ischemia driven revascularization because of acute coronary syndrome or recurrent chest pain during optimal medical therapy.

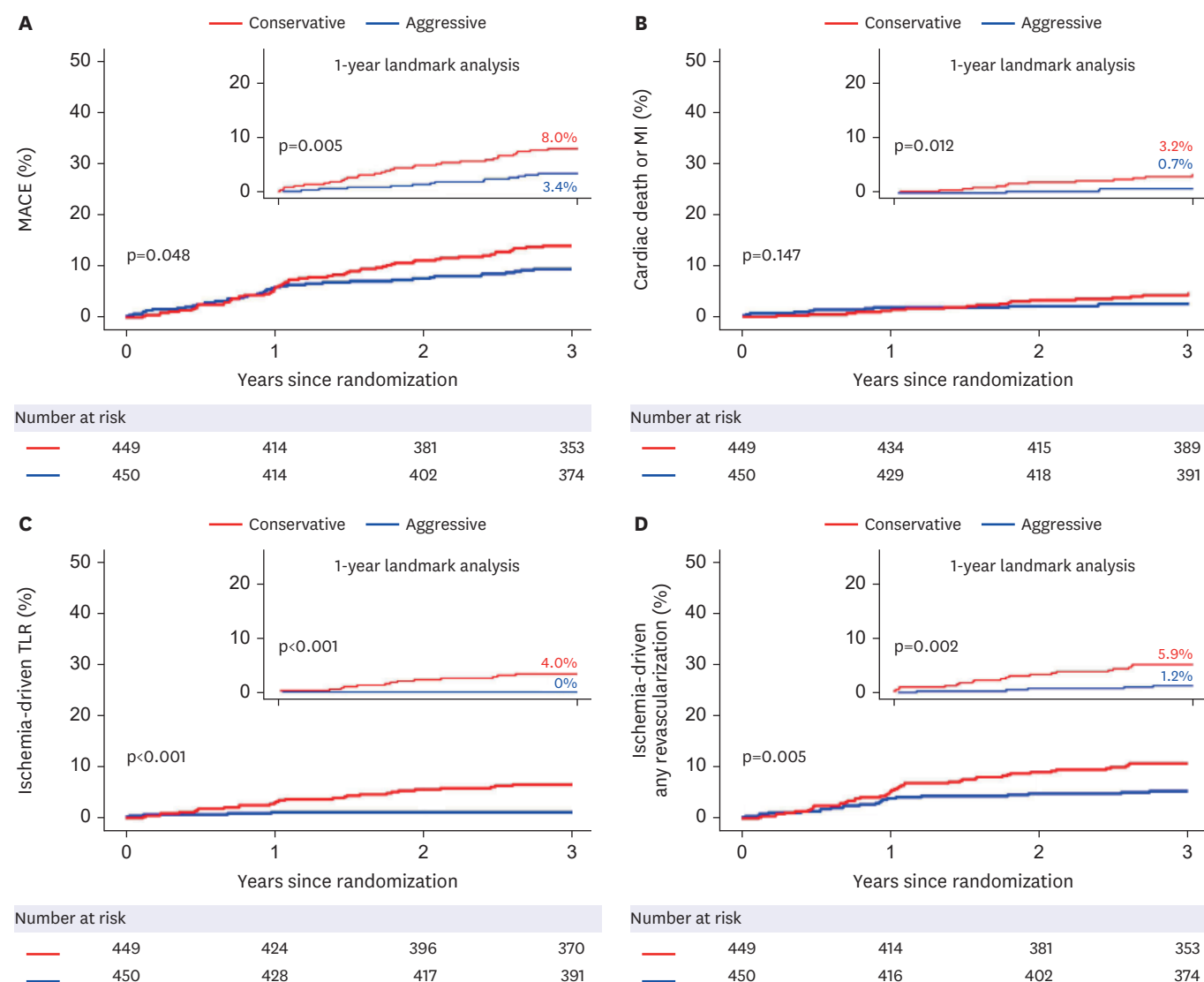


Figure 2. Clinical outcomes at 3 years after the index procedure. MACE (A), cardiac death or MI (B), ischemia-driven revascularization of target intermediate lesion (C), ischemia-driven any revascularization (D).

MACE = major adverse cardiac events; MI = myocardial infarction, TLR = target lesion revascularization.

95% CI, 2.12–10.83; $p < 0.001$), particularly due to acute coronary syndrome or recurrent chest pain despite optimal medical therapy (6.5% vs. 1.1%; HR, 5.69; 95% CI, 2.20–14.43; $p < 0.001$). The rate of target vessel failure was also significantly higher in the conservative group than in the aggressive group (11.1% vs. 5.2%; HR, 2.11; 95% CI, 1.29–3.48; $p = 0.003$).

Subgroup analysis of primary end point

The results of comparison between the conservative and aggressive group were consistent across various subgroups (Figure 3).

Landmark analysis at 1 year from index procedure

Between 1 year and 3 years after the index procedure, the conservative group had significantly higher rate of MACE (8.5% vs. 3.4%; HR, 2.53; 95% CI, 1.36–4.71; $p = 0.004$), any revascularization (5.9% vs. 1.2%; HR, 4.79; 95% CI, 1.82–12.59; $p = 0.002$), and target vessel failure (6.0% vs. 1.0%; HR, 6.20; 95% CI, 2.15–17.86; $p < 0.001$) than the aggressive group (Supplementary Table 1 and Figure 2). In addition, the rate of cardiac death or MI was also significantly higher in the conservative group than in the aggressive group (3.2% vs. 0.7%; HR, 4.34; 95% CI, 1.24–15.22; $p = 0.022$).

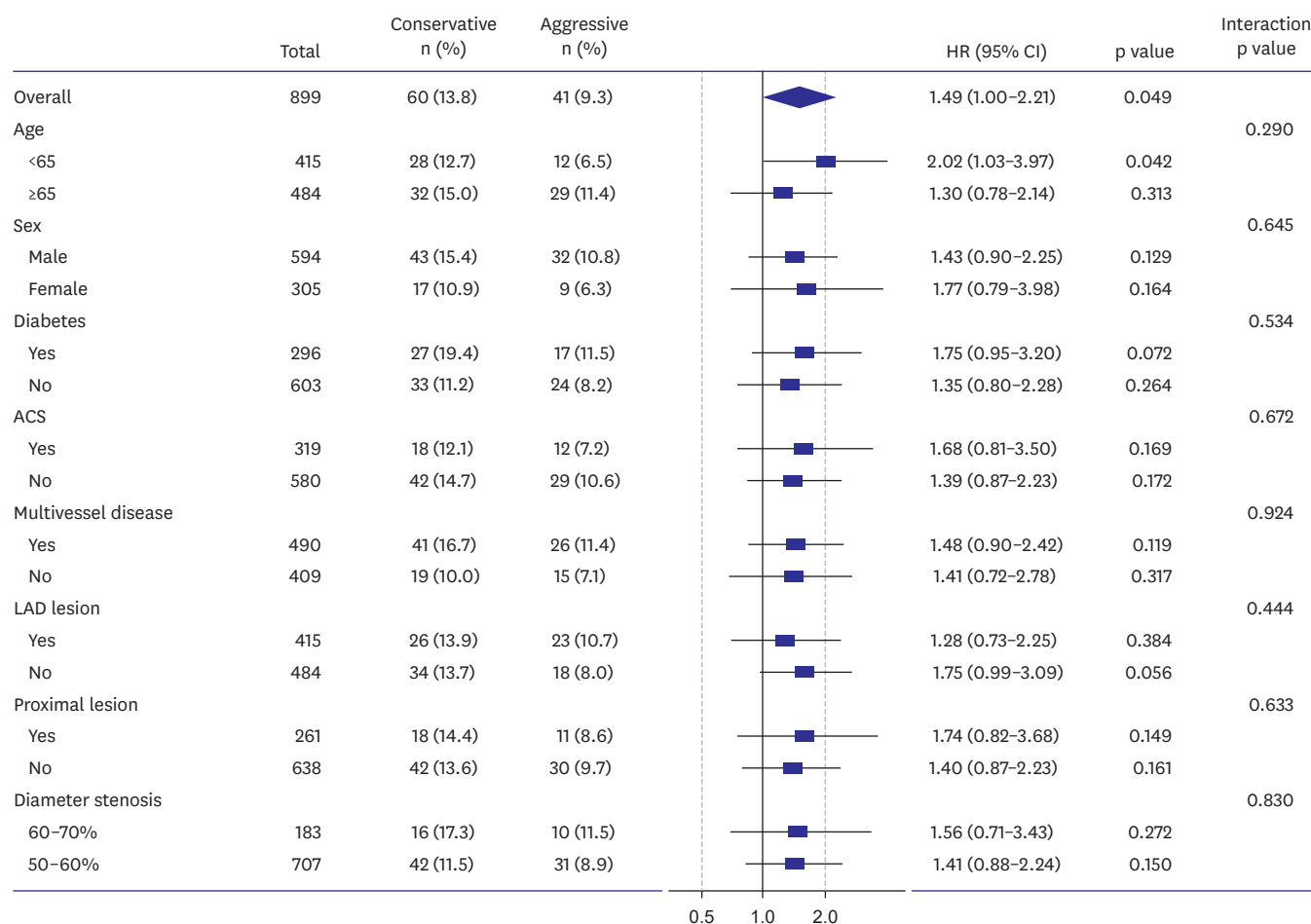


Figure 3. Subgroup analysis for primary end point.

ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; LAD = left anterior descending artery.

DISCUSSION

In this 3-year follow-up results of the SMART-CASE trial, deferring PCI without invasive physiologic test was associated with a higher risk of a composite of all-cause death, MI, or any compared to performing PCI. The main contributor to the difference in the composite primary end point between the 2 treatment strategies was the revascularization of target intermediate lesion. Furthermore, beyond 1 year after the index procedure, deferring PCI was significantly associated with an increased risk of cardiac death or MI compared to performing PCI.

Current guidelines strongly recommended documentation of myocardial ischemia prior to treatment decision.^{6,7)} When guided by functional assessment, PCI improves clinical outcome compared with angiography-guided PCI or medical therapy alone.^{2-4,14)} In real-world practice, however, the majority of patients undergoes elective PCI based on angiographic guidance alone.^{8-10,15)} Treatment decisions based solely on coronary angiography often lead to misleading results due to overestimation or underestimation of lesions, interobserver variability, and discrepancies between anatomical and functional severity, particularly in cases of intermediate coronary stenoses.¹⁶⁻¹⁹⁾ Although many studies have assessed an efficacy of PCI compared to medical therapy in stable ischemic heart disease, there is a lack of data specifically focusing on intermediate coronary stenoses without information on functional significance.

In the present study, deferring PCI and medical therapy alone for intermediate lesions with a diameter stenosis between 50% and 70% based on angiography guidance alone resulted in a significantly higher risk of revascularization during the 3-year follow-up compared to performing PCI. Although long-term outcomes after deferring PCI in functionally non-significant lesion are generally favorable,⁵⁾ Park et al.¹⁹⁾ reported that over 40% of lesions with a diameter stenosis 50% or greater had a FFR value below 0.8. This finding supports the higher rate of ischemia-driven revascularization observed in our study for deferred intermediate lesions. On the contrary, recent advances in drug-eluting stents, interventional techniques, and medical therapy would contribute to a relatively lower risk of complications and repeat revascularization of stented intermediate lesions.²⁰⁾

In the landmark analysis, the risk of cardiac death or MI beyond 1 year after index procedure was higher for patients who deferred PCI compared to those who underwent PCI. The question of whether PCI can decrease cardiac death or MI in stable ischemic heart disease has long been a topic of controversy. However, this late catch-up in the incidence of cardiac death or MI was also observed in large clinical trials. In the recent International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial,²¹⁾ the risk of cardiovascular death or MI tended to be higher in medical treatment arm than in PCI arm beyond 1 year after procedure. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 2 trial, medical arm had a strong trend towards a higher risk of cardiac death or MI compared to PCI arm. Additionally, the medical arm experienced a significantly higher frequency of MIs beyond the initial period of follow-up.⁴⁾ However, it is important to note that there are differences in the inclusion criteria and patient populations between the studies mentioned and SMART-CASE trial. The ISCHEMIA and FAME 2 trial included patients with functionally significant coronary lesions, and the proportion of intermediate coronary lesions with a diameter stenosis between 50% and 70% was relatively small, around 38% in the FAME 2 trial. Other studies have indicated that vulnerable plaques are prone to causing future cardiovascular events even in non-significant lesions and that PCI for these lesions could reduce such events.^{22,23)} The SMART-CASE trial specifically enrolled

patients with intermediate coronary lesions,¹¹⁾ not considering the flow-limiting status. Given that MI can frequently develop in lesion with diameter stenosis <70%, it is understandable that there may be different risks of cardiac death or MI between treatment strategies in the SMART-CASE trial.

The present study had several limitations. First, it was not a double-blinded study, which may have introduced bias into the study outcomes, particularly in terms of target vessel revascularization. Although clinical events were adjudicated by an independent committee, the lack of blinding could have influenced the decision-making process for revascularization. Operators might have been more inclined to adhere to medical treatment and delay revascularization in patients assigned to the conservative group. Conversely, patients themselves may have had concerns about their coronary intermediate lesions and preferred to undergo PCI. Therefore, we defined ischemia-driven revascularization as a part of clinical outcomes. Second, there were no physiologic data. Since only a minority of patients undergoes PCI with physiologic assessment in routine clinical practice,⁹⁾¹⁰⁾¹⁵⁾ the findings of this study have important clinical implications for treatment decisions regarding intermediate coronary stenoses. However, physiologic assessment, such as FFR or noninvasive stress tests, might aid in interpreting our results. Additionally, plaque characteristics in target lesion, which might have been related to the risk of cardiac death or MI, were not systematically assessed. The findings of present study should be applied with caution to angiography-guidance decision-making. Third, the inclusion criteria were not confined to patients with single vessel disease with 50 to 70% of stenosis. However, the result was consistent in the subgroup analysis based on the presence of multivessel disease, and the primary end point was mainly driven by revascularization of target intermediate lesion. Given that almost half of the patients undergoing PCI have multivessel disease,²⁴⁾ our study may reflect real-world patients and provide evidence for the revascularization strategy for patients having intermediate coronary lesions. Lastly, the medication profile was only presented at the time of hospital discharge. Medications used during follow-up, such as dual antiplatelet therapy and the intensity of statin, might affect long-term clinical outcomes. Especially, bleeding-associated outcomes might be different between the groups.

For intermediate coronary lesions, medical therapy alone, guided only by angiography, was associated with a higher risk of MACE compared with performing PCI at 3 years, mainly due to increased revascularization.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Clinical outcomes at 1-year and between 1- and 3-year after randomization

REFERENCES

1. Ahn JM, Park DW, Shin ES, et al. Fractional flow reserve and cardiac events in coronary artery disease: data from a prospective IRIS-FFR registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation* 2017;135:2241-51. [PUBMED](#) | [CROSSREF](#)
2. Berger A, Botman KJ, MacCarthy PA, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *J Am Coll Cardiol* 2005;46:438-42. [PUBMED](#) | [CROSSREF](#)

3. van Nunen LX, Zimmermann FM, Tonino PA, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet* 2015;386:1853-60. [PUBMED](#) | [CROSSREF](#)
4. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med* 2018;379:250-9. [PUBMED](#) | [CROSSREF](#)
5. Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J* 2015;36:3182-8. [PUBMED](#) | [CROSSREF](#)
6. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;60:e44-164. [PUBMED](#) | [CROSSREF](#)
7. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87-165. [PUBMED](#) | [CROSSREF](#)
8. Shin DH, Kang HJ, Jang JS, et al. The current status of percutaneous coronary intervention in Korea: based on year 2014 & 2016 cohort of Korean Percutaneous Coronary Intervention (K-PCI) registry. *Korean Circ J* 2019;49:1136-51. [PUBMED](#) | [CROSSREF](#)
9. Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2012;60:2337-9. [PUBMED](#) | [CROSSREF](#)
10. Toth GG, Toth B, Johnson NP, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. *Circ Cardiovasc Interv* 2014;7:751-9. [PUBMED](#) | [CROSSREF](#)
11. Hahn JY, Choi SH, Jeong JO, et al. Conservative versus aggressive treatment strategy with angiographic guidance alone in patients with intermediate coronary lesions: the SMART-CASE randomized, non-inferiority trial. *Int J Cardiol* 2017;240:114-9. [PUBMED](#) | [CROSSREF](#)
12. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72. [PUBMED](#) | [CROSSREF](#)
13. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-51. [PUBMED](#) | [CROSSREF](#)
14. Li J, Elrashidi MY, Flammer AJ, et al. Long-term outcomes of fractional flow reserve-guided vs. angiography-guided percutaneous coronary intervention in contemporary practice. *Eur Heart J* 2013;34:1375-83. [PUBMED](#) | [CROSSREF](#)
15. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA* 2008;300:1765-73. [PUBMED](#) | [CROSSREF](#)
16. Arnett EN, Isner JM, Redwood DR, et al. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. *Ann Intern Med* 1979;91:350-6. [PUBMED](#) | [CROSSREF](#)
17. Zir LM, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. *Circulation* 1976;53:627-32. [PUBMED](#) | [CROSSREF](#)
18. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med* 1984;310:819-24. [PUBMED](#) | [CROSSREF](#)
19. Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv* 2012;5:1029-36. [PUBMED](#) | [CROSSREF](#)
20. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. *Eur Heart J* 2015;36:3320-31. [PUBMED](#) | [CROSSREF](#)
21. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;382:1395-407. [PUBMED](#) | [CROSSREF](#)
22. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226-35. [PUBMED](#) | [CROSSREF](#)
23. Park SJ, Ahn JM, Kang DY, et al. Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicentre, open-label, randomised controlled trial. *Lancet* 2024;403:1753-65. [PUBMED](#) | [CROSSREF](#)
24. Baumann AAW, Tavella R, Air TM, et al. Prevalence and real-world management of NSTEMI with multivessel disease. *Cardiovasc Diagn Ther* 2022;12:1-11. [PUBMED](#) | [CROSSREF](#)