

Effect of intermediate lesions on the 10-years clinical outcomes in patients with significant coronary artery disease

Yong Kyun Kim

Konyang University Hospital

Dong Ju Yang

Eulji University Hospital

Chae Won Jang

Konyang University Hospital

Soon Ho Kwon

Konyang University Hospital

Jae Kwang Lee

Konyang University Hospital

Seong Soo Park

Konyang University Hospital

Young Hoon Seo

Konyang University Hospital

Ki Hong Kim

Konyang University Hospital

Taek Geun Kwon

Konyang University Hospital

Moo-Sik Lee

Konyang University Hospital

Jang-Ho Bae (✉ janghobae@yahoo.co.kr)

Konyang University Hospital

Research Article

Keywords: Intermediate coronary lesion, Coronary artery stenosis, Prognosis

Posted Date: April 13th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1496165/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Intermediate lesions (ILs) are challenging to treat. This study aimed to assess the impact of ILs on long-term clinical outcomes in patients with significant coronary lesions (SLs).

Methods: This was a non-randomized, retrospective, single-center study. The study subjects were patients with SL (n=403, Men=249), followed up for 10 years (118.5±5.5 months), and divided into 2 groups according to the presence of IL (IL (-) and IL (+) groups with 192 and 211 patients, respectively). The primary outcome was the occurrence of major adverse cardiovascular events (MACE), which included all-cause death, myocardial infarction (MI), stroke, and revascularization (RVSC).

Results: There were no significant differences in MACEs between the IL (-) and IL (+) groups (death, 7.8% vs. 12.3%; MI, 0.0% vs. 2.4%; stroke, 5.7% vs. 6.6%; and RVSC, 19.8% vs. 24.6%). However, the RVSC rate related to IL was lower (5.2% vs. 13.2%) than that related to stented lesions in all subjects. The important predictors for total MACEs in all subjects were the number of ILs and ejection fraction. The predictors of total RVSC events were IL location (right coronary artery [RCA]) and hypertension. The predictor of IL-related RVSC was the number of ILs.

Conclusion: Ten-year clinical outcomes of IL were excellent and better than those of stented lesions in patients with SL. Thus, ILs can be managed with optimal medical treatment with acceptable clinical outcomes in patients with SL. The increased risk of MACE in patients with multiple ILs and ILS in the RCA should be carefully managed.

1. Background

Acute coronary syndrome can occur in patients with significant and nonsignificant (minimal or intermediate) stenotic coronary lesions. (1–3) The decision to treat stenosis in non-culprit vessels is always challenging, especially in patients with multivessel disease and intermediate coronary lesions (ILs), which are common findings of coronary angiography. The prevalence of ILs is relatively high, ranging from 39.4–79.3% in patients with coronary artery disease (CAD). (1, 2, 4) The recommended diagnostic approach for ILs involves fractional flow reserve (FFR) or instantaneous wave-free ratio to identify the functional significance of coronary lesions or intravascular ultrasound to determine the morphologic significance of coronary lesions. (5–11) Despite the availability of additional invasive functional or morphologic technology, coronary angiography alone is still the usual practical technique for guiding percutaneous coronary intervention (PCI) due to equipment availability, reimbursement policies, and other financial considerations. (12–14)

Many studies have shown that treatment of ILs with conservative medical treatment might be safe and justified; therefore, performing PCI may not lead to a better outcome in patients with this lesion. (15–17) We had previously reported that the 10-year clinical outcomes of patients with ILs, especially with no combined culprit lesion, were favorable compared to those of patients with significantly stenosed culprit

lesions treated with stenting. (18, 19) However, the long-term outcomes of deferred ILs based on angiography alone in patients with significant coronary artery disease remain unclear.

The objectives of this study were to determine the real-world long-term (10 years) clinical outcomes of angiographically determined ILs and to identify predictors of major adverse clinical effects (MACE) in a relatively large number of patients with significant CAD.

2. Methods

2.1. Study population

This was a nonrandomized, retrospective, single-center study. Details of these methods have been previously published. (This study uses the method of Kim et al. and the method description partly reproduces their wording.) (18) We analyzed the records of 1,096 patients who underwent coronary angiography for ischemic heart disease or cardiovascular disease between January 2008 and December 2008 at Konyang University Hospital, Daejeon, South Korea. We reviewed the patients' demographics and laboratory and angiographic findings. Significant lesion (SL) was defined as angiographic stenosis of more than 70%, and IL was defined as angiographic stenosis between 30% and 70% by visual estimation. (20, 21) Two cardiologists (KYK and JCW) reviewed and determined the extent of angiographic stenosis. Another senior cardiologist (BJH) determined whether the evaluations of the two cardiologists were consistent. We excluded 693 patients who did not have SL. In total, 403 patients were enrolled in this study. The enrolled patients were followed up for a pre-defined period of 10 years. The study subjects were divided into IL (+) and IL (-) groups based on whether ILs were present or not, respectively, in other major epicardial coronary arteries. Lipid profiles and serum creatinine, glucose, and high-sensitivity C-reactive protein levels at baseline were collected.

The study was approved by the Institutional Review Board of Konyang University Hospital (2020-07-003) and performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Study endpoint

The primary outcome of this study was the occurrence of MACE during the follow up period. A composite of MACEs included all-cause death, myocardial infarction (MI), stroke, and revascularization (RVSC; defined as PCI or coronary artery bypass grafting involving the target lesion). Adverse events were reviewed and adjudicated by at least 2 independent investigators blinded to the study group. MI was defined as a new or recurrent acute ischemic syndrome with or without change of electrocardiogram, combined with elevation of cardiac enzymes to at least three times the upper limit of the normal range. Stroke was an episode of neurological dysfunction caused by brain injury associated with abnormal radiological findings on computed tomography or magnetic resonance imaging. If a patient experienced two or more MACEs simultaneously or sequentially, it was counted as one incidence of MACE, and time-to-event duration was defined as the duration from enrollment to the first event.

2.3. Statistical analysis

This study uses the method of Kim et al. and the method description partly reproduces their wording.) (18) Continuous variables are presented as mean \pm standard deviation and categorical variables as numbers and percentages. Patient demographics and lesion characteristics were compared according to the ILs. In univariate analysis, the chi-square test or Fisher's exact test was performed to examine the differences between groups in categorical variables, and an independent *t*-test was performed to compare means between groups in continuous variables. The Kaplan–Meier method with the log-rank test was used to assess cumulative event rates and statistically compare the two groups. Multivariable Cox proportional hazard analysis was performed to investigate the independent predictors of all MACEs, RVSC, and IL-related RVSC. Clinically relevant CAD risk factors and angiographic finding variables that showed significant relationships with MACE and RVSC in univariate analysis (*p*-value < 0.10) were entered into the multivariate analysis.

Statistical data were processed using SPSS (version 18.0, USA), and a *p*-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient demographics

Demographic details of all patients are presented in Table 1. The mean age was 64.1 ± 11.8 years old (range, 28–92 years old), and 249 of the 403 patients with SL (61.8%) were men (Table 1). During the 10-year follow-up period, the loss rate was 28.3%, and there was no significant difference between the IL (-) and IL (+) groups (29.7% vs. 27.0%, *p* = 0.552). The follow-up duration was 118.6 ± 5.2 months and 118.5 ± 5.8 months (*p* = 0.865) in IL (-) and IL (+) groups, respectively. The IL (+) group were significantly older (65.5 ± 11.7 years vs. 62.7 ± 11.7 years, *p* = 0.018) and had higher triglyceride levels (193.0 ± 195.6 mg/dL vs. 154.1 ± 97.5 mg/dL, *p* = 0.012) than the IL (-) group (Table 1). There were no significant differences in other demographic and laboratory findings between the IL (-) and IL (+) groups.

Table 1
Demographic and lesion characteristics in patients with significant lesion stenosis

Variables	IL (-) N = 192 (47.6)	IL (+) N = 211 (52.4)	Total N = 403 (100)	p-value
FU loss, n (%)	57 (29.7)	57 (27.0)	114 (28.3)	0.552
FU duration, month				
Total subjects	93.8 ± 40.1	97.0 ± 37.7	95.48 ± 38.9	0.410
Those with FU	118.6 ± 5.2	118.5 ± 5.8	118.5 ± 5.5	0.865
Those with FU loss	35.1 ± 20.8	39.0 ± 23.6	37.0 ± 22.2	0.354
Age, years	62.7 ± 11.7	65.5 ± 11.7	64.1 ± 11.8	0.018
Men, n (%)	123 (64.1)	126 (59.7)	249 (61.8)	0.370
Hypertension, n (%)	102 (53.4)	117 (56.8)	219 (55.2)	0.497
Diabetes mellitus, n (%)	72 (37.7)	60 (29.1)	132 (33.2)	0.070
Smoking, n (%)	61 (31.9)	55 (26.7)	116 (29.2)	0.221
Diagnosis, n (%)	192 (100)	211 (100)	404 (100)	0.758
Stable angina	119 (62.0)	134 (63.5)	254 (62.9)	
ACS	73 (38.0)	77 (36.5)	150 (37.1)	
Lipid profile				
Total cholesterol, mg/dL	186.4 ± 52.2	194.2 ± 58.2	190.5 ± 55.5	0.164
Triglyceride, mg/dL	154.1 ± 97.5	193.0 ± 195.6	174.6 ± 158.1	0.012
HDL cholesterol, mg/dL	45.6 ± 12.1	48.8 ± 36.1	47.3 ± 27.6	0.218
LDL cholesterol, mg/dL	117.1 ± 37.7	121.5 ± 35.5	119.4 ± 36.6	0.232

IL, intermediate lesion; SL, significant lesion; FU, follow-up ACS, acute coronary syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hs C-reactive protein, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Variables	IL (-) N = 192 (47.6)	IL (+) N = 211 (52.4)	Total N = 403 (100)	p-value
Creatinine, mg/dL	1.21 ± 0.88	1.28 ± 1.47	1.25 ± 1.23	0.584
Glucose, mg/dL	162.5 ± 87.8	157.3 ± 80.1	159.8 ± 83.8	0.538
Hs C-reactive protein, mg/L	1.44 ± 7.40	4.54 ± 21.46	3.05 ± 16.36	0.056
Ejection fraction, %	64.0 ± 12.6	65.2 ± 11.6	64.6 ± 12.1	0.356
Previous PCI, n (%)	40 (20.8)	31 (14.7)	71 (17.6)	0.266
Previous CABG, n (%)	3 (1.6)	4 (1.9)	7 (1.7)	0.266
Significant lesion, n (%)	282 (49.0)	293 (51.0)	575 (100)	0.225
Numbers of SL/patient	282/192	293/211	575/403	
Multivessel disease	64 (33.3)	71 (33.6)	135 (33.5)	0.946
Location				
LAD, n (%)	125 (44.4)	122 (41.6)	247 (43.0)	0.134
LCX, n (%)	85 (30.1)	86 (29.4)	171 (29.7)	0.476
RCA, n (%)	72 (25.5)	85 (29.0)	157 (27.3)	0.567
Percent diameter stenosis (%)	92.1 ± 8.0	91.3 ± 7.9	91.7 ± 7.9	0.288
Intermediate lesion, n (%)	NA	291 (100)	291 (100)	NA
Numbers of IL/patient	NA	291/211	291/211	NA
Location				
LAD, n (%)	NA	119 (40.9)	NA	NA
LCX, n (%)	NA	66 (22.7)	NA	NA
RCA, n (%)	NA	106 (36.4)	NA	NA
Percent diameter stenosis (%)	NA	54.4 ± 13.2	NA	NA
Treatment for significant lesion (Patient level)	192 (100)	211 (100)	404(100)	0.496
IL, intermediate lesion; SL, significant lesion; FU, follow-up ACS, acute coronary syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hs C-reactive protein, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.				

Variables	IL (-) N = 192 (47.6)	IL (+) N = 211 (52.4)	Total N = 403 (100)	p-value
PCI + optimal medication	163 (84.9)	174 (82.5)	338 (83.7)	
Optimal medication only	29 (15.1)	37 (17.5)	66 (16.3)	

IL, intermediate lesion; SL, significant lesion; FU, follow-up ACS, acute coronary syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Hs C-reactive protein, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

3.2. Angiographic findings

There were 575 SLs in 403 patients in this study. The IL (-) group had 282 SLs in 192 patients, and the IL (+) group had 293 SLs and 291 combined ILs (1.38 ILs/patient) in 211 patients (Table 1). There were 135 patients with significant multivessel disease in the study population, and there was no significant difference between the IL (-) and IL (+) groups (n = 64, 33.3% vs. n = 71, 33.6%, p = 0.946) (Table 1). SL was most frequently located in the left anterior descending artery (LAD, n = 247, 43.0%), followed by left circumflex artery (LCX, n = 171, 29.7%) and right coronary artery (RCA, n = 157, 27.3%). There was no significant difference in angiographic percent diameter stenosis of SL ($92.1 \pm 8.0\%$ vs. $91.3 \pm 7.9\%$, p = 0.288) between the IL (-) and IL (+) groups. In IL (+) group, IL was most frequently located in the LAD (n = 119, 40.9%), followed by RCA (n = 106, 36.4%) and LCX (n = 66, 22.7%). The mean angiographic percent diameter stenosis of IL was $54.4 \pm 13.2\%$.

Most patients with SLs (IL [-] = 163 patients and IL [+] = 174 patients, p = 0.496) underwent PCI along with optimal medication in all subjects (Table 1). The remaining patients (n = 66) were treated with optimal medication only for various reasons, including old age, chronic total occlusion, and significant comorbidities.

3.3. Clinical outcomes

During a mean follow-up period of 118.5 ± 5.5 months, 135 MACEs occurred, with 56 and 79 events occurring in the IL (-) and IL (+) groups, respectively (Table 2). There was no significant difference in the occurrence of MACEs (death, 7.8% vs. 12.3%, p = 0.135; MI, 0.0% vs. 2.4%, p = 0.062; stroke, 5.7% vs. 6.6%, P = 0.707; and any RVSC, 19.8% vs. 4.6%, p = 0.243) between the IL (-) and IL (+) groups (Table 2).

Table 2
Comparison of MACE between 2 groups

Variables	IL (-) N = 192 (47.6)	IL (+) N = 211 (52.4)	All events N = 403 (100)	p-value
SL, n (%)	282 (49.0)	293 (51.0)	575 (100)	0.225
IL, n (%)	NA	291 (100)	291 (100)	NA
MACE, n (%)	56 (29.2)	79 (37.4)	135 (33.5)	0.079
Death, n (%)	15 (7.8)	26 (12.3)	41 (10.2)	0.135
MI, n (%)	0 (0.0)	5 (2.4)	5 (1.2)	0.062
New lesion, n (%) [†]	NA	3 (1.4)	3 (0.7)	NA
Stented lesion, n (%) ^{‡,¶}	NA	2 (0.9)	2 (0.5)	NA
Stroke, n (%)	11 (5.7)	14 (6.6)	25 (6.2)	0.707
Revascularization, n (%)	38 (19.8)	52 (24.6)	90 (22.3)	0.243
New lesion, n (%) [†]	7 (3.6)	12 (5.7)	19 (4.7)	0.334
SL, n (%) [§]	7 (3.6)	3 (1.4)	10 (2.5)	0.204
IL, n (%)	NA	11 (5.2)	11 (2.7)	0.001
Stented lesion, n (%) [‡]	26 (13.5)	27 (12.8)	53 (13.2)	0.825
MACE, major adverse cardiovascular event; SL, significant lesion; IL, intermediate lesion; MI, myocardial infarction; NA, not applicable				
[†] De novo coronary artery stenosis lesion, which initially looked normal or stenosed less than 30% at the baseline angiogram				
[‡] Lesions related to previously inserted stents, such as stent thrombosis or in-stent restenosis				
[§] Lesions initially treated with optimal medication only.				
[¶] Follow-up coronary angiogram revealed that 1 patient had MI due to very late stent thrombosis (aspirin stopped for polypectomy), and 1 patient had MI due to in-stent restenosis.				

The most common RVSC lesion was a previously stented lesion (13.2% during 10 years follow-up period), found in 26 and 27 patients in the IL (-) and IL (+) groups, respectively (p = 0.825). There was no significant difference in the occurrence of new lesions, i.e., which looked normal or was stenosed less than 30%, RVSC rate between the IL (-) and IL (+) groups (n = 7, 3.6% vs. n = 12, 5.7%, p = 0.334) during the 10-year follow-up period. RVSC rate of SLs, which were initially treated with optimal medication, was 2.5%

in all subjects during the follow-up period, while the IL-related RVSC rate was 5.2%, which was similar to that of new lesion RVSC (5.7%) (Table 2).

3.4. Predictors for MACE and RVSC

Adjusted multivariate Cox proportional hazard analysis identified two variables as predictors of total MACE rate: number of ILs (hazard ratio (HR) 1.366, 95% confidence interval (CI) 1.114–1.675, $p = 0.003$) and ejection fraction (HR 0.986, 95% CI 0.972–0.999, $p = 0.041$, Table 3). The predictors of total RVSC events were IL location (RCA, HR 1.665, 95% CI 1.078–2.571, $p = 0.021$) and hypertension (HR 1.713, 95% CI 1.093–2.683, $p = 0.019$, Table 3). The predictor of IL-related RVSC events was the number of ILs (HR 3.356, 95% CI 1.730–6.510, $p \leq 0.001$, Table 3).

Table 3
Multivariable Cox proportional hazard analysis for MACE

Total MACE						
	Unadjusted model			Adjusted model		
Variables	HR	95% CI	p-value	HR	95% CI	p-value
ACS	1.167	0.823–1.656	0.387			
Group(Presence of IL)	1.395	0.990–1.965	0.057			
Multi-vessel disease	1.418	1.000–2.012	0.050	1.396	0.971–2.008	0.072
Number of IL	1.318	1.081–1.607	0.006	1.366	1.114–1.675	0.003
IL in the LCX	1.714	1.148–2.561	0.008			
IL in the RCA	1.463	1.023–2.093	0.037			
SL in the LAD	1.405	0.984–2.007	0.061			
Age	1.018	1.002–1.034	0.025	1.014	0.998–1.031	0.082
EF	0.985	0.971–0.998	0.025	0.986	0.972–0.999	0.041
Total RVSC						
	Unadjusted model			Adjusted model		
Variables	HR	95% CI	p-value	HR	95% CI	p-value
ACS	1.330	0.875–2.022	0.181			
Number of IL	1.362	1.071–1.732	0.012			
IL in the RCA	1.693	1.103–2.600	0.016	1.665	1.078–2.571	0.021
Previous PCI	1.581	0.989–2.527	0.056			
HTN	1.725	1.101–2.701	0.017	1.713	1.093–2.683	0.019
IL related RVSC						
	Unadjusted model			Adjusted model		
Variables	HR	95% CI	p-value	HR	95% CI	p-value
ACS	1.652	0.504–5.422	0.408			
Number of IL	3.356	1.730–6.510	≤ 0.001	3.356	1.730–6.510	≤ 0.001

MACE, major adverse cardiovascular event; RVSC, revascularization; ACS, acute coronary syndrome; SL, significant lesion; IL, intermediate lesion; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; EF, ejection fraction; HTN, hypertension; PCI, percutaneous coronary intervention; HR, hazard ratio; CI, confidence interval

Total MACE			
IL in the LAD	4.383	1.282–14.980	0.018
IL in the RCA	5.090	1.490–17.392	0.009
MACE, major adverse cardiovascular event; RVSC, revascularization; ACS, acute coronary syndrome; SL, significant lesion; IL, intermediate lesion; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; EF, ejection fraction; HTN, hypertension; PCI, percutaneous coronary intervention; HR, hazard ratio; CI, confidence interval			

The Kaplan–Meier curves for the primary endpoint during the 10-year follow-up period are shown in Fig. 1. The 10-year cumulative total MACE-free survival rate significantly decreased (70.8% vs. 67.9% vs. 52.7%, $p = 0.014$) as the number of ILs increased (Fig. 1A). The 10-year, cumulative total RVSC-free survival rate was significantly lower (68.9% vs. 80.8%, $p = 0.015$) in patients with ILs in the RCA than those with ILs not in the RCA (Fig. 1B). The 10-year cumulative IL-related RVSC-free survival rate was significantly decreased (100% vs. 97.1% vs. 90.5%, $p \leq 0.001$) as the number of ILs increased (Fig. 1C).

4. Discussion

The main findings of this study were that the 10 years clinical outcomes for patients with IL were excellent; specifically, they were better than the outcomes of patients with SL who had stented lesions, especially in terms of RVSC rate (5.2% vs. 13.2%). Further, the number of ILs, IL location (RCA), ejection fraction, and hypertension were significantly associated with the occurrence of MACEs during the 10-year follow-up period in patients with SL.

The treatment decisions for ILs are undertaken based on their functional assessment. (5, 8, 22, 23) However, almost 2/3 of the ILs were FFR-negative ($FFR > 0.8$), and there are no data on the long-term results of stented IL in FFR-positive patients. (24) We expect that stented ILs will have a similar result to the stented culprit lesions. Furthermore, there are insufficient data on the long-term clinical outcomes of ILs that were not stented in patients with SL, and whether risks related to stent placement, such as periprocedural complications, longer-term bleeding, stent thrombosis, the incidence of restenosis, and the cost related to FFR and stenting, are present even in patients with ILs. (25–27)

To the best of our knowledge, this is the first study to examine the impact of ILs that were treated only with optimal medical treatment on the long-term clinical outcomes in patients with SL. MACE and IL-related RVSC rates in patients with SL were associated with the number of ILs but not with ILs themselves. Two important points regarding these results should be considered. First, a single IL did not affect MACE in patients with SL. This suggests that a single IL can be managed using optimal medical treatment alone. Second, the IL-related RVSC rate was only 5.2%, which was considerably lower than that of stented lesions of SL (13.2%) during the 10-year follow up. This result suggests that the total IL-related RVSC rate was acceptably low, especially compared to the rate in patients with stented lesions due to SL, although multiple ILs were a significant predictor of IL-related RVSC rates in this study.

In our study, the number of ILs was an important long-term predictor of MACE and IL-related RVSC rates in patients with SL. We believe that multiple ILs could indicate a type of multivessel disease that represents a systemic atherosclerotic burden resulting from diffuse and pathologic inflammatory processes or endothelial dysfunction. Thus, it is known to be an important predictor of MACE in patients with CAD, (28, 29) as was also observed in our study.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial showed that the addition of PCI to optimal medical therapy did not reduce the cardiovascular event risk in patients with stable CAD. (15) The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial also showed that invasive intervention was not better than medical therapy alone in patients with stable CAD. (16) The results of these studies showed that routine additional RVSC with stenting strategy did not lead to better outcomes compared to conservative medical treatment in patients with stable CAD. Our study population was different from the two aforementioned studies; that is, we had an all-comer study population, and most culprit lesions were already treated with stenting. Despite these differences, our results showing that the presence of ILs did not affect MACEs in patients with SL who did not receive invasive treatment are consistent with the findings of the previous studies.

An IL occurring in the RCA was a significant predictor of the total RVSC rate and was related to the IL-related RVSC rate and total MACEs in the study subjects. Patients with IL in the RCA had a higher IL-related RVSC rate, although this was not statistically significant in the multivariate analysis. The possible mechanism was unclear, but this result was consistent with previous observational studies showing that CAD in the RCA progresses more rapidly, so stenosis in the RCA may make the patients more likely to develop MACEs than stenosis in other epicardial coronary arteries. (18, 30, 31)

Our study has some limitations. First, due to the single-center, retrospective nature of the study, selection bias could not be excluded. Second, our study analyzed lesion stenosis severity, not lesion length or irregularity, which are also important geometric parameters that affect coronary hemodynamics and resistance. Most ILs analyzed in our study were short; therefore, the lesion length and irregularities did not significantly differ. Third, given that the study lasted for almost ten years, we could not quantify the effects of medications (and changes in medications throughout the study) on the clinical outcomes. Future, large scale, prospectively designed studies can address these limitations and help confirm our results.

5. Conclusion

Our study suggests that IL can be managed with optimal medical treatment, with acceptable clinical outcomes in patients with SL. Patients with multiple ILs and/or ILs in the RCA were at higher risk of developing MACEs, although, their outcomes were still favorable compared to those of patients with a stented lesion. Thus, optimal medical treatment can be regarded as an alternative to routine FFR measurements in treating ILs in patients with SL.

Abbreviations

IL

Intermediate coronary lesion

CAD

Coroanary artery disease

FFR

Fractional flow reserve

PCI

Percutaneous coronary intervention

MACE

Major adverse clinical effects

SL

Significant coronary lesion

MI

Myocardial infarction

RVSC

Revascularizaiton

LAD

Left anterior descending artery

LCX

Left circumflex artery

RCA

Right coronary artery

HR

Hazard ratio

CI

Confidence interval

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Konyang University Hospital (IRB number: 2020-07-003). Institutional Review Board of Konyang University Hospital (IRB number: 2020-07-003) waived the informed consent owing to restrospective, observational nature of study. (Full name of committee; Son Ji Woong, Park Chang kyo, Kim Yung Jin, Lee Tae Hee, Cheun En Jung, Sung Tae Yoon, Shin Jae Ha, Kim Kwang Whan, Kong Sam Geun, Lee Dong Cheol, Ryoo Keung Seock, Oh Chang Hyeun, Lee Sung Hee)

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

Funding

Not applicable.

Authors' contribution

BJH, KYK and YDJ were responsible for the study concept and design. KYK and YDJ drafted and revised the manuscript. KYK, JCW and KSH were responsible for the acquisition and analysis of data. All authors contributed to the interpretation of the data. LJK, PSS, SYH, KKH and KWG reviewed the study and edited the manuscript. LMS supervised all statistical analysis. The corresponding author attests that all listed authors meet authorship criteria. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation*. 1988;78(5):1157–66.
2. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *Journal of the American College of Cardiology*. 1988;12(1):56–62.
3. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From Vulnerable Plaque to Vulnerable Patient. *Circulation*. 2003;108(14):1664–72.
4. Pijls NHJ, Schaardenburgh Pv, Manoharan G, Boersma E, Bech J-W, Veer Mvt, et al. Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis. *Journal of the American College of Cardiology*. 2007;49(21):2105–11.
5. van Nunen LX, Zimmermann FM, Tonino PAL, Barbato E, Baumbach A, Engstrøm T, 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. *The Lancet*. 2015;386(10006):1853–60.
6. Pijls NHJ, Fearon WF, Tonino PAL, Siebert U, Ikeno F, Bornschein B, et al. Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Intervention in Patients With Multivessel Coronary Artery Disease. *Journal of the American College of Cardiology*. 2010;56(3):177–84.
 7. Schuurman A-S, Vroegindewey Maxime M, Kardys I, Oemrawsingh Rohit M, Garcia-Garcia Hector M, van Geuns R-J, et al. Prognostic Value of Intravascular Ultrasound in Patients With Coronary Artery Disease. *Journal of the American College of Cardiology*. 2018;72(17):2003–11.
 8. Kushner FG, Hand M, Smith SC, King SB, Anderson JL, Antman EM, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update). *Journal of the American College of Cardiology*. 2009;54(23):2205-41.
 9. Petraco R, Escaned J, Sen S, Nijjer S, Asrress KN, Echavarria-Pinto M, et al. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. *EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2013;9(1):91–101.
 10. Petraco R, Park JJ, Sen S, Nijjer S, Malik I, Pinto ME, et al. Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularization. *American Journal of Cardiology*. 2013;111(7):54B.
 11. Fernandes MR, Silva GV, Caixeta A, Rati M, de Sousa e Silva NA, Perin EC. Assessing intermediate coronary lesions: angiographic prediction of lesion severity on intravascular ultrasound. *J Invasive Cardiol*. 2007;19(10):412–6.
 12. Samady H, Gogas BD. Does flow during rest and relaxation suffice?: American College of Cardiology Foundation Washington, DC; 2013.
 13. Lakhter V, Zack CJ, Bove AA, Bashir R. Abstract 18105: National Utilization Rates of Fractional Flow Reserve in Guiding Coronary Revascularization. *Circulation*. 2012;126(suppl_21):A18105-A.
 14. Dattilo Philip B, Prasad A, Honeycutt E, Wang Tracy Y, Messenger John C. Contemporary Patterns of Fractional Flow Reserve and Intravascular Ultrasound Use Among Patients Undergoing Percutaneous Coronary Intervention in the United States. *Journal of the American College of Cardiology*. 2012;60(22):2337–9.
 15. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. *New England journal of medicine*. 2007;356(15):1503–16.
 16. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial invasive or conservative strategy for stable coronary disease. *New England Journal of Medicine*. 2020;382(15):1395–407.

17. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation*. 2005;111(22):2906–12.
18. Kim YK, Jang CW, Kwon SH, Kim JH, Lerman A, Bae J-H. Ten-year clinical outcomes in patients with intermediate coronary stenosis according to the combined culprit lesion. *Clinical Cardiology*. 2021;44(8):1161–8.
19. Bae J-H, Corban MT, Seo Y-H, Kim T, Lee G, Kwon T-G, et al. Ten-year clinical outcomes of an intermediate coronary lesion; prognosis and predictors of major adverse cardiovascular events. *International Journal of Cardiology*. 2020;299:26–30.
20. Miller DD, Donohue TJ, Younis LT, Bach RG, Aguirre FV, Wittry MD, et al. Correlation of pharmacological 99mTc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. *Circulation*. 1994;89(5):2150–60.
21. Christou MAC, Siontis GCM, Katritsis DG, Ioannidis JPA. Meta-Analysis of Fractional Flow Reserve Versus Quantitative Coronary Angiography and Noninvasive Imaging for Evaluation of Myocardial Ischemia. *The American Journal of Cardiology*. 2007;99(4):450–6.
22. Pijls NHJ, Fearon WF, Tonino PAL, Siebert U, Ikeno F, Bornschein B, et al. Fractional Flow Reserve Versus Angiography for Guiding Percutaneous Coronary Intervention in Patients With Multivessel Coronary Artery Disease: 2-Year Follow-Up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) Study. *Journal of the American College of Cardiology*. 2010;56(3):177–84.
23. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van 't Veer M, et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. *New England Journal of Medicine*. 2009;360(3):213–24.
24. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study: fractional flow reserve versus angiography in multivessel evaluation. *Journal of the American College of Cardiology*. 2010;55(25):2816–21.
25. Hannan EL, Wu C, Walford G, Holmes DR, Jones RH, Sharma S, et al. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC: Cardiovascular Interventions*. 2009;2(1):17–25.
26. Teirstein PS. The Dueling Hazards of Incomplete Revascularization and Incomplete Data. *Circulation*. 2006;113(20):2380–2.
27. Moses JW, Stone GW, Nikolsky E, Mintz GS, Dangas G, Grube E, et al. Drug-Eluting Stents in the Treatment of Intermediate Lesions. *Journal of the American College of Cardiology*. 2006;47(11):2164–71.
28. van der Schaaf RJ, Timmer JR, Ottervanger JP, Hoorntje JCA, de Boer MJ, Suryapranata H, et al. Long-term impact of multivessel disease on cause-specific mortality after ST elevation myocardial infarction treated with reperfusion therapy. *Heart*. 2006;92(12):1760–3.

29. Bauters C, Deneve M, Tricot O, Meurice T, Lamblin N. Prognosis of Patients With Stable Coronary Artery Disease (from the CORONOR Study). *The American Journal of Cardiology*. 2014;113(7):1142–5.
30. Rafflenbeul W, Urthaler F, Lichtlen P, James T. Quantitative difference in "critical" stenosis between right and left coronary artery in man. *Circulation*. 1980;62(6):1188–96.
31. Cosby RS, Giddings JA, See JR, Mayo M. Clinicoarteriographic correlations in angina pectoris with and without myocardial infarction. *The American journal of cardiology*. 1972;30(5):472–5.

Figures

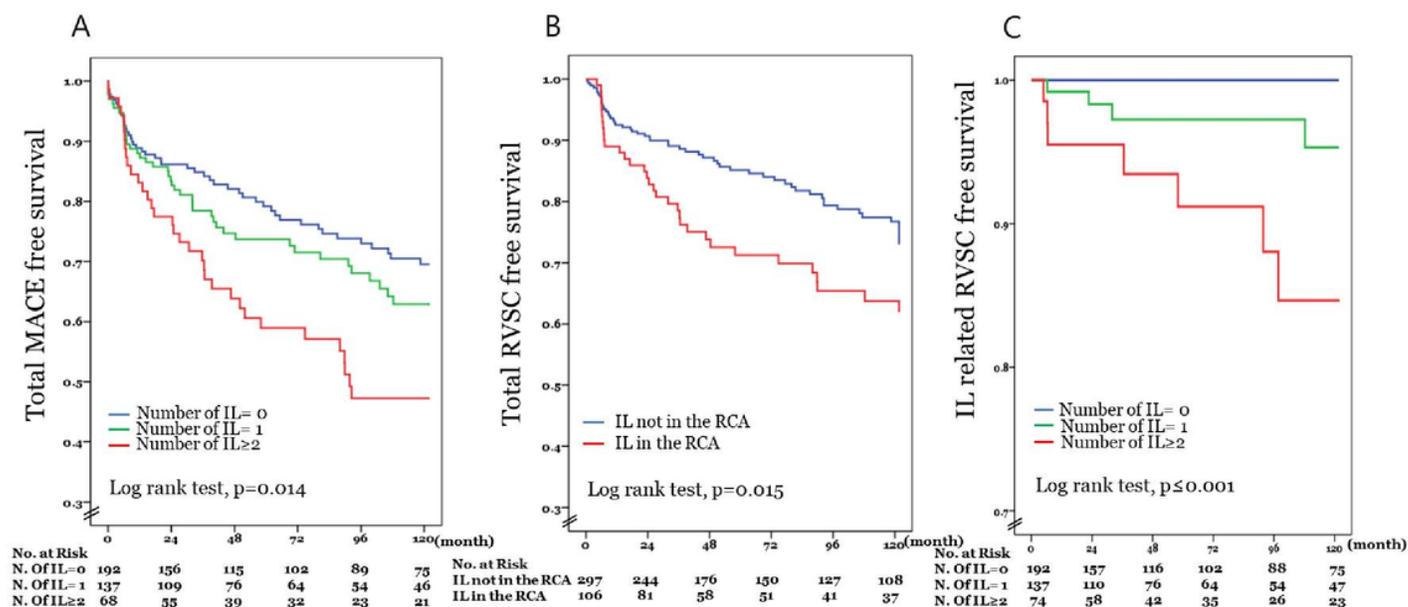


Figure 1

A: Kaplan–Meier curves for total MACE free survival rate according to the number of ILs, B: Kaplan–Meier curves for total RVSC free survival rate according to the presence of IL in the RCA, C: Kaplan–Meier curves for IL related RVSC free survival rate according to the number of ILs in total study subjects during the 10-year follow-up period.

MACE, major adverse cardiovascular event; RVSC, revascularization; IL, intermediate lesion; RCA, right coronary artery