

Prognosis of deferred non-culprit lesions according to fractional flow reserve in patients with acute coronary syndrome



Joo Myung Lee¹, MD, MPH, PhD; Ki Hong Choi¹, MD; Bon-Kwon Koo^{2,3*}, MD, PhD; Eun-Seok Shin^{4,5}, MD, PhD; Chang-Wook Nam⁶, MD, PhD; Joon-Hyung Doh⁷, MD, PhD; Doyeon Hwang², MD; Jonghanne Park², MD, PhD; Jinlong Zhang², MD; Hong-Seok Lim⁸, MD, PhD; Myeong-Ho Yoon⁸, MD, PhD; Seung-Jea Tahk⁸, MD, PhD

1. Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; 2. Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, South Korea; 3. Institute on Aging, Seoul National University, Seoul, South Korea; 4. Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea; 5. The 3rd Medical Department, Cardiology, Academic Teaching Hospital of University of Greifswald, Greifswald, Germany; 6. Department of Medicine, Keimyung University Dongsan Medical Center, Daegu, South Korea; 7. Department of Medicine, Inje University Ilsan Paik Hospital, Goyang, South Korea; 8. Department of Cardiology, Ajou University School of Medicine, Suwon, South Korea

J.M. Lee and K.H. Choi contributed equally to this work.

KEYWORDS

- ACS/NSTE-ACS
- drug-eluting stent
- fractional flow reserve

Abstract

Aims: There are limited data on the prognosis of deferred non-culprit lesions in patients with acute coronary syndrome (ACS) based on fractional flow reserve (FFR). We aimed to investigate the prognosis of deferred non-culprit lesions in ACS patients, compared with deferred lesions in patients with stable coronary artery disease (SCAD), on the basis of FFR.

Methods and results: The clinical outcomes of 449 non-culprit lesions (301 patients with ACS) were compared with 2,484 lesions (1,295 patients with SCAD) in which revascularisation was deferred on the basis of a high FFR (>0.80). The primary outcome was major adverse cardiac events (MACE), a composite of cardiac death, target vessel-related myocardial infarction (MI) and ischaemia-driven revascularisation. Among the ACS population, 65.8% presented with unstable angina and 34.2% with non-ST-segment elevation MI. Mean angiographic percent diameter stenosis and FFR of the deferred lesions were 39.3±15.0% and 0.92±0.06, respectively. During the median follow-up duration of 722.0 days, the deferred non-culprit lesions of ACS patients showed a significantly higher rate of MACE (3.8% vs. 1.6%, HR_{adj} 2.97, 95% CI: 1.23-7.17, p=0.016), mainly driven by the higher rate of ischaemia-driven revascularisation (2.8% vs. 1.1%, HR_{adj} 3.39, 95% CI: 1.29-8.92, p=0.013) than the deferred lesions in SCAD patients. Regardless of the range of FFR in the deferred lesions (0.81-0.85, 0.86-0.90, 0.91-0.95, and 0.95-1.00), non-culprit lesions of ACS showed a more than twofold higher rate of MACE than that of SCAD. In a multivariable marginal Cox model, ACS was the most powerful independent predictor of MACE (HR_{adj} 2.74, 95% CI: 1.13-6.64, p=0.026).

Conclusions: Compared to the deferred lesions of SCAD patients, deferred non-culprit lesions of ACS on the basis of FFR showed a higher rate of clinical events, regardless of FFR range.

*Corresponding author: Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101 Daehang-Ro, Chongno-Gu, Seoul, 110-744, South Korea. E-mail: bkkoo@snu.ac.kr

Abbreviations

ACS	acute coronary syndrome
CABG	coronary artery bypass graft surgery
CI	confidence interval(s)
FFR	fractional flow reserve
HR_{adj}	adjusted hazard ratio
MACE	major adverse cardiac events
MI	myocardial infarction
NSTEMI	non-ST-segment elevation myocardial infarction
SCAD	stable coronary artery disease
STEMI	ST-elevation myocardial infarction

Introduction

Fractional flow reserve (FFR)-guided decision making has been regarded as a standard invasive method to evaluate the functional significance of epicardial coronary artery stenosis. The clinical outcomes of an FFR-guided percutaneous coronary intervention (PCI) strategy were reported to be better than those of angiography-guided PCI or medical treatment¹. This study on the FFR-guided strategy was performed mainly in patients with stable coronary artery disease (SCAD).

In patients with acute coronary syndrome (ACS), individual variation and the unpredictable nature of microvascular function in the culprit vessels may preclude FFR for proper assessment of the functional significance of coronary stenosis². Although previous studies have shown the benefit of patient-level FFR-guided decision making in patients with ACS and multivessel disease^{3,4}, there have been debates regarding the clinical relevance of per-lesion decisions based on FFR, especially for the culprit lesion⁵⁻⁹. A recent study by Hakeem et al showed significantly worse clinical outcomes of deferred culprit lesions according to FFR compared with those of SCAD⁸ and proposed a cut-off value of FFR <0.84 in the culprit vessel of ACS patients.

Rather than the evaluation of culprit lesions, more common situations for FFR use in real-world practice would be the evaluation of non-culprit lesions in ACS patients. Although the reliability of FFR measurement for non-culprit lesions in ACS patients was reported from a previous study¹⁰, the clinical outcomes of deferred non-culprit lesions based on FFR and the comparative risk between deferred non-culprit lesions of ACS and deferred lesions in SCAD patients according to the FFR value have not yet been fully investigated.

Therefore, the current study investigated the clinical outcomes of deferred non-culprit lesions according to FFR in ACS patients and compared these with deferred lesions in SCAD patients.

Methods

STUDY DESIGN AND PATIENT POPULATION

The current study population was derived from the pooled population of the Korean 4-Centers registry and 3-vessel FFR FRIENDS study. The 4-Centers registry (NCT01409577) is a registry of patients who were treated using an FFR-guided strategy. From 2003 up to 2011, 1,294 consecutive patients (1,628 lesions) who underwent FFR measurement for at least one *de novo* lesion in a major epicardial vessel were enrolled from four major cardiovascular

centres in Korea¹¹. In ACS patients, the culprit lesions were revascularised without FFR measurement, followed by FFR measurement for the other non-culprit lesions. The 3-vessel FFR FRIENDS study (NCT01621438) is a prospective, multinational, multicentre study. From 2011 to 2014, 1,136 consecutive patients (3,298 lesions) who underwent FFR measurement for all three major epicardial vessels were enrolled from 11 centres in three countries¹². In the 3-vessel FFR FRIENDS study, ACS patients also underwent revascularisation for clinically indicated culprit lesions, followed by FFR measurement for non-culprit lesions. In both registries, patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-elevation myocardial infarction (STEMI) within 72 hours, previous coronary artery bypass graft surgery (CABG), abnormal epicardial coronary flow (TIMI flow <3) or planned CABG after diagnostic angiography were excluded.

Among the total population of the two studies, 335 ACS patients whose non-culprit lesions were deferred based on an FFR >0.80, and 1,295 non-ACS patients with 2,484 deferred lesions based on an FFR >0.80, were extracted for the current analysis. Among ACS patients, 34 patients with unclear culprit lesions were excluded from the analysis.

DEFINITIONS OF ACUTE CORONARY SYNDROME

In the current study, ACS patients included those with non-ST-segment elevation myocardial infarction (NSTEMI), which was defined as a combination of clinical presentation, positive biomarkers with or without electrocardiographic changes, and those with unstable angina who had recent onset angina or accelerating or rest angina with electrocardiographic changes, but without evidence of positive biomarkers.

ANGIOGRAPHIC ANALYSIS AND QUANTITATIVE CORONARY ANGIOGRAPHY

Coronary angiography was performed using standard techniques. All angiograms were analysed at a core laboratory in a blinded fashion. Quantitative coronary angiography was performed in optimal projections with validated software (CAAS II; Pie Medical Imaging BV, Maastricht, the Netherlands). Minimum lumen diameter, reference vessel size and lesion length were measured, and percent diameter stenosis was calculated.

CORONARY PHYSIOLOGIC MEASUREMENTS

All coronary physiologic measurements were performed after diagnostic angiography. A 5-7 Fr guide catheter was used to engage the coronary artery, and a pressure-temperature sensor guidewire (St. Jude Medical, St. Paul, MN, USA) was used for FFR measurement. The pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100 or 200 mg) was administered before each FFR measurement. Hyperaemia was induced with an intracoronary bolus administration (80 µg in the left coronary artery, 40 µg in the right coronary artery), or an intracoronary (240 µg/min) or intravenous continuous infusion (140 µg/kg/min) of adenosine. FFR was calculated as the lowest average

of hyperaemic proximal aortic pressure (Pa)/distal coronary arterial pressure (Pd) during three consecutive beats under stable hyperaemia. After FFR measurement, the guidewire was pulled back to the guide catheter, and the presence of pressure drift was checked.

PATIENT FOLLOW-UP, OUTCOME MEASUREMENTS AND ADJUDICATION OF CLINICAL EVENTS

Clinical data were obtained at outpatient clinic visits or by telephone contact when needed. An independent clinical events committee adjudicated all events. The primary outcome was major adverse cardiac events (MACE), including cardiac death, target vessel-related myocardial infarction (MI) and target vessel-related ischaemia-driven revascularisation. All clinical outcomes were defined according to the Academic Research Consortium criteria, including the addendum to the definition of MI. Ischaemia-driven revascularisation was defined as a revascularisation procedure with at least one of the following: (1) recurrence of angina; (2) positive non-invasive test; and (3) positive invasive physiologic test. Clinical outcome analysis was carried out during a median follow-up of 722.0 days (interquartile range 657.0-747.0).

STATISTICAL ANALYSIS

Data were analysed on a per-patient basis for clinical characteristics and on a per-lesion basis for the others. For per-lesion comparison of characteristics, a generalised estimating equation (GEE) was used to adjust intrasubject variability among deferred lesions from the same patient. The cumulative incidence of clinical events was presented as Kaplan-Meier estimates and compared using the log-rank test. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated using a marginal Cox proportional hazards regression model in order to adjust the clustering of multiple vessel measurements in the same patient. In comparison of clinical events between ACS and SCAD, the differences in patient and lesion profiles were adjusted using a multivariable adjusted marginal Cox proportional hazards regression model. As a sensitivity analysis, comparison of clinical outcomes was also performed on a per-patient basis between ACS patients with deferred non-culprit lesions and SCAD patients with deferred lesions. For this, the differences in baseline characteristics were adjusted using a multivariable adjusted Cox proportional hazards regression model.

A multivariable marginal Cox model was used to identify independent predictors of MACE. C-statistics with 95% CI were calculated to validate the discriminant function of the model. All probability values were two-sided, and p-values <0.05 were considered statistically significant.

Results

CHARACTERISTICS OF PATIENTS AND LESIONS

Table 1 presents baseline characteristics of the study population. Although distributions of cardiovascular risk factors were similar between SCAD and ACS patients, the SCAD population showed a higher proportion of hyperlipidaemia, previous MI, and previous revascularisation. Among the ACS population, 65.8% of patients

Table 1. Baseline clinical characteristics.

	Total (n=1,596)	SCAD (n=1,295)	ACS (n=301)	p-value
Age (years)	62.3±9.8	62.4±9.4	62.0±11.1	0.617
Male	1,112 (69.7%)	896 (69.2%)	216 (71.8%)	0.421
Hypertension	964 (60.4%)	790 (61.0%)	174 (57.8%)	0.339
Diabetes mellitus	479 (30.0%)	394 (30.4%)	85 (28.2%)	0.499
Hyperlipidaemia	777 (48.7%)	658 (50.8%)	119 (39.5%)	0.001
Previous myocardial infarction	127 (8.0%)	116 (9.0%)	11 (3.7%)	0.003
Previous revascularisation	431 (27.0%)	399 (30.8%)	32 (10.6%)	<0.001
Ejection fraction (%)	62.5±7.7	62.8±7.4	61.2±8.8	0.004
Clinical presentation				
Stable coronary artery disease	1,295 (81.1%)	1,295 (100%)	0 (0.0%)	<0.001
Unstable angina	198 (12.4%)	0 (0.0%)	198 (65.8%)	
Non-ST-elevation myocardial infarction	103 (6.5%)	0 (0.0%)	103 (34.2%)	
Discharge medications				
Aspirin	1,333 (83.5%)	1,032 (79.7%)	301 (100%)	<0.001
P2Y ₁₂ inhibitor	1,011 (63.3%)	710 (54.8%)	301 (100%)	<0.001
Dual antiplatelet agents	971 (60.8%)	670 (51.7%)	301 (100%)	<0.001
Statin	1,317 (82.5%)	1,035 (79.9%)	282 (93.7%)	<0.001
Beta-blocker	648 (40.6%)	488 (37.7%)	160 (53.2%)	<0.001
ACE inhibitor or ARB	567 (35.5%)	435 (33.6%)	132 (43.9%)	0.003
Values are mean±SD or n (%). ACS: acute coronary syndrome; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; SCAD: stable coronary artery disease				

presented with unstable angina and 34.2% with NSTEMI. In 2,933 deferred lesions, the mean percent diameter stenosis and FFR were 39.3±15.0% and 0.92±0.06, respectively. The deferred non-culprit lesions in ACS patients showed significantly higher stenosis severity and longer lesion length despite a similar FFR value to those in SCAD patients (**Table 2**). The distribution of FFR in deferred lesions was similar between SCAD and non-culprit vessels in ACS patients (**Figure 1**).

CLINICAL OUTCOMES OF DEFERRED LESIONS IN PATIENTS WITH ACS AND SCAD

Deferred lesions in ACS patients showed a significantly higher rate of MACE compared with those in SCAD patients (3.8% vs. 1.6%, log-rank p=0.001). The median time to event for two-year MACE was 265.0 days (Q1-Q3, 154.0-543.0) and 361.0 days (Q1-Q3, 220.0-618.0) for deferred non-culprit lesions in ACS patients and deferred lesions in SCAD patients, respectively. Even with adjustment of stenosis severity, lesion length, and different distribution of risk factors, deferred non-culprit lesions in ACS patients showed about a threefold higher risk of MACE than SCAD (HR_{adj} 2.97, 95% CI: 1.23-7.17, p=0.016) (**Figure 2A**). The higher risk of MACE in ACS patients was mainly driven by the higher rate of ischaemia-driven revascularisation (HR_{adj} 3.39, 95% CI: 1.29-8.92, p=0.013) (**Table 3**). The 56.7% of ischaemia-driven revascularisations were due to ACS, and the others were due to deferred lesion progression with objective evidence of ischaemia. When

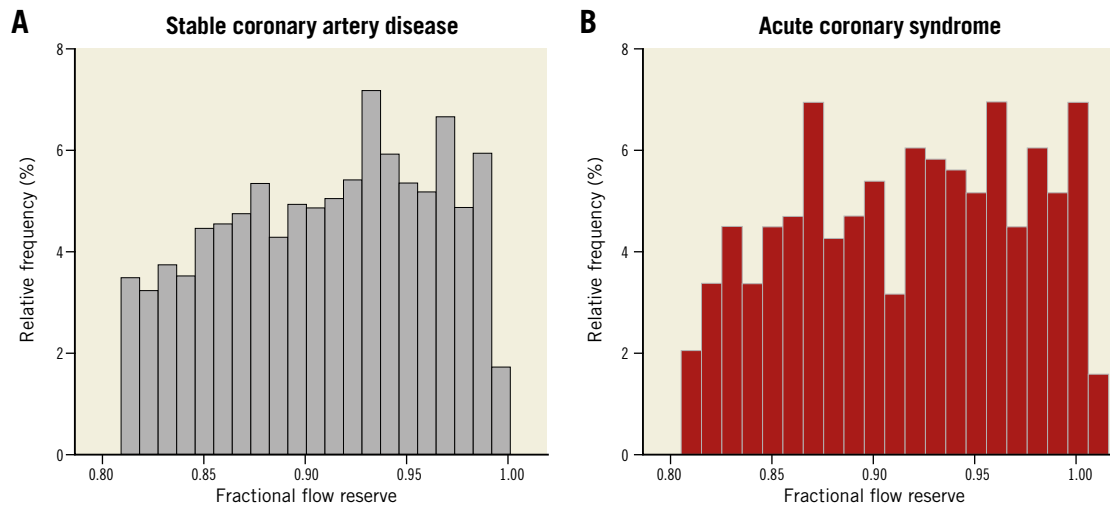


Figure 1. Distribution of fractional flow reserve in deferred lesions. Distribution of FFR values in (A) 2,484 deferred lesions in SCAD patients and (B) 449 deferred non-culprit lesions in ACS patients.

Table 2. Lesion characteristics according to clinical presentation.

	Total (n=2,933)	SCAD (n=2,484)	ACS (n=449)	p-value
Lesion location				
Left anterior descending	906 (30.9%)	785 (31.6%)	121 (26.9%)	0.133
Left circumflex	1,022 (34.8%)	860 (34.6%)	162 (36.1%)	
Right coronary artery	1,005 (34.3%)	839 (33.8%)	166 (37.0%)	
Quantitative coronary angiography				
Reference diameter (mm)	3.0±0.6	3.0±0.6	3.1±0.6	0.040
Minimum lumen diameter (mm)	1.9±0.6	1.9±0.6	1.8±0.6	0.550
Diameter stenosis (%)	39.3±15.0	38.9±15.0	41.2±15.1	0.021
Lesion length (mm)	10.5±7.7	10.3±7.4	11.8±8.9	0.002
Fractional flow reserve	0.92±0.06	0.92±0.06	0.92±0.06	0.890

Values are mean±SD or n (%). ACS: acute coronary syndrome; SCAD: stable coronary artery disease

stratifying ACS by unstable angina and NSTEMI, the risk of MACE was not different (**Figure 2B**).

The patient-level comparison of MACE risk between ACS patients with deferred non-culprit lesions and SCAD patients with

deferred lesions showed similar results to the lesion-level comparison (**Figure 3, Table 4**).

CLINICAL OUTCOMES OF DEFERRED LESIONS BETWEEN ACS AND SCAD ACCORDING TO FFR CATEGORIES AND IN SUBGROUPS

Figure 4 shows comparisons of the rates of MACE between the two groups according to FFR category. In all FFR categories, deferred lesions of ACS showed higher MACE rates than those of SCAD. The higher risk of MACE in deferred non-culprit lesions of ACS patients was similarly observed in various subgroups without significant interaction (**Figure 5**).

INDEPENDENT PREDICTORS OF MACE

In a multivariable marginal Cox proportional hazard model of the total population, ACS was the most powerful independent predictor of MACE (HR_{adj} 2.74, 95% CI: 1.13-6.64, p=0.026). Other independent predictors were diameter stenosis ≥50% and multi-vessel disease (**Table 5**). Among the deferred lesions with an FFR between 0.80 and 0.90, FFR value did not show significant association with the risk of MACE in both the ACS (HR of FFR per 0.1

Table 3. Cumulative rates of clinical events among deferred lesions according to clinical presentation.

	Event rates		Unadjusted*		Adjusted [†]	
	SCAD (n=2,484)	ACS (n=449)	HR (95% CI)	p-value	HR (95% CI)	p-value
Major adverse cardiac events	31 (1.6%)	15 (3.8%)	2.768 (1.320-5.790)	0.007	2.966 (1.226-7.172)	0.016
Cardiac death	12 (0.6%)	4 (1.0%)	1.911 (0.422-8.650)	0.400	2.040 (0.346-12.000)	0.432
Myocardial infarction	9 (0.4%)	2 (0.6%)	1.266 (0.242-6.620)	0.780	1.380 (0.263-7.250)	0.700
Ischaemia-driven revascularisation	19 (1.1%)	11 (2.8%)	3.303 (1.470-7.430)	0.004	3.390 (1.289-8.920)	0.013

Values are n (%). Cumulative incidence of events was presented as Kaplan-Meier estimates. *Marginal Cox model was utilised to adjust the repeated measures involving the same subject. [†]Adjusted variables included age, sex, previous revascularisation, left ventricular ejection fraction, quantitative coronary angiography-based diameter stenosis, and quantitative coronary angiography-based lesion length. ACS: acute coronary syndrome; CI: confidence interval; HR: hazard ratio; SCAD: stable coronary artery disease

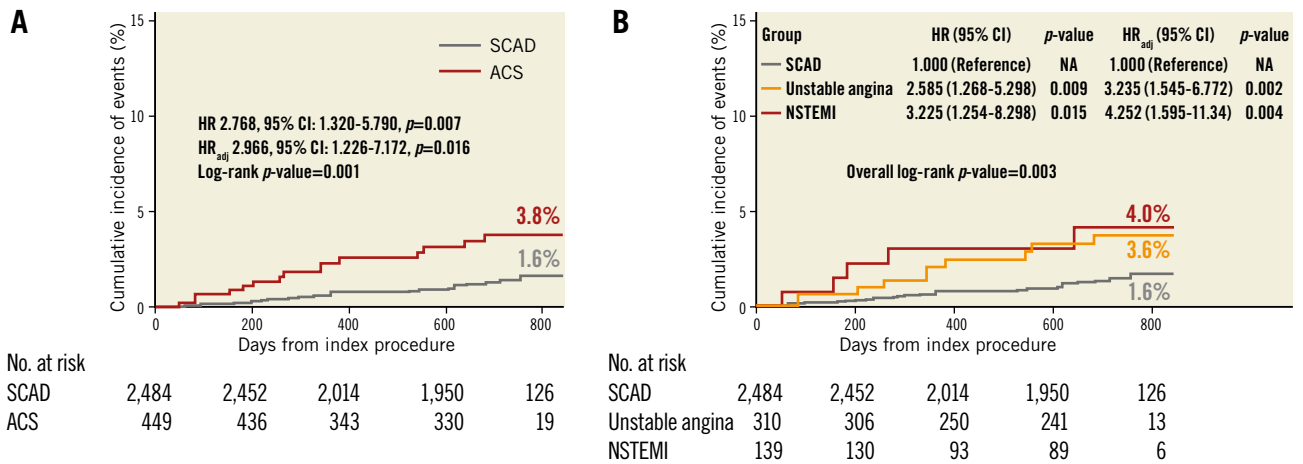


Figure 2. Comparison of MACE rates in deferred lesions between ACS and SCAD. Kaplan-Meier curves for the comparison of rates of MACE in deferred lesions according to (A) SCAD and ACS, (B) SCAD, unstable angina, and NSTEMI. ACS: acute coronary syndrome; CI: confidence interval; HR: hazard ratio; HR_{adj} : multivariable adjusted hazard ratio; NSTEMI: non-ST-segment elevation myocardial infarction; SCAD: stable coronary artery disease

increase 0.91, 95% CI: 0.09-9.56, $p=0.934$) and SCAD populations (HR of FFR per 0.1 increase 0.48, 95% CI: 0.09-2.59, $p=0.395$).

Discussion

The current study compared clinical outcomes between deferred non-culprit lesions in ACS patients and deferred lesions in SCAD patients based on FFR. Despite the similar FFR values in both groups, the rate of MACE was significantly higher in ACS patients than in SCAD patients. The higher risk of MACE in ACS patients compared to that in SCAD patients was consistently observed in all categories of non-ischæmic FFR values, as well as in various subgroups. Furthermore, in the multivariable predictive model, ACS was the most powerful independent predictor for MACE.

FFR-GUIDED STRATEGY IN ACS PATIENTS: PER-PATIENT LEVEL DECISION

The representative studies for per-patient level decision were the FAME ACS substudy³ and the FAMOUS-NSTEMI trial⁴. The FAME ACS substudy demonstrated the equivalent benefit of an FFR-guided strategy versus an angiography-guided strategy between ACS and SCAD populations. The FAMOUS-NSTEMI trial randomly allocated patients into an FFR-disclosure group versus an angiography-guided group and showed that the rate of revascularisation remained lower in the FFR-disclosure group with similar clinical outcomes and quality of life between the two groups⁴. Although these two studies showed clinical benefit of an FFR-guided strategy over an angiography-guided strategy in ACS patients, there has been no previous study which compared

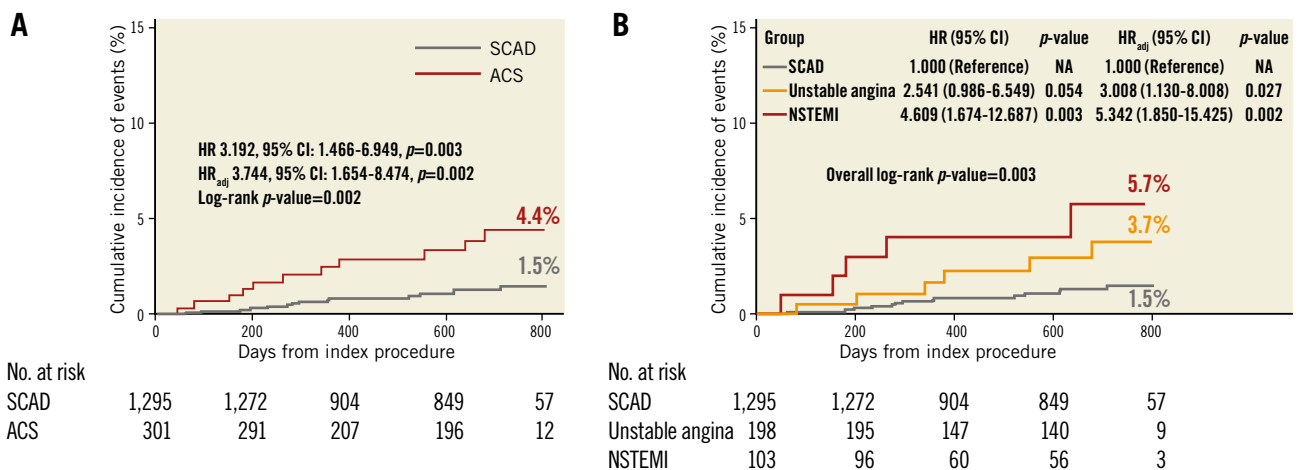


Figure 3. Patient-level comparison of MACE rates between ACS and SCAD. Kaplan-Meier curves for the comparison of rates of MACE (A) between ACS patients with deferred non-culprit lesions and SCAD patients with deferred lesions, and (B) according to clinical presentations (SCAD, unstable angina, and NSTEMI). ACS: acute coronary syndrome; CI: confidence interval; HR: hazard ratio; HR_{adj} : multivariable adjusted hazard ratio; NSTEMI: non-ST-segment elevation myocardial infarction; SCAD: stable coronary artery disease

Table 4. Cumulative rates of clinical events among the patients according to clinical presentation.

	Event rates		Unadjusted		Adjusted*	
	SCAD (n=1,295)	ACS (n=301)	HR (95% CI)	p-value	HR (95% CI)	p-value
Major adverse cardiac events [†]	15 (1.5%)	11 (4.4%)	3.192 (1.466-6.949)	0.003	3.744 (1.654-8.474)	0.002
Cardiac death	5 (0.5%)	3 (1.2%)	2.604 (0.622-10.890)	0.190	2.936 (0.665-12.973)	0.155
Myocardial infarction	4 (0.4%)	2 (0.9%)	2.161 (0.396-11.800)	0.373	2.662 (0.449-15.798)	0.281
Ischaemia-driven revascularisation	10 (0.9%)	8 (3.2%)	3.486 (1.376-8.833)	0.009	4.100 (1.549-10.849)	0.005

Values are n (%). Cumulative incidence of events was presented as Kaplan-Meier estimates. *Adjusted variables included age, sex, previous revascularisation, previous myocardial infarction, and presence of hypertension. [†]Major adverse cardiac events were defined as a composite of cardiac death, target vessel-related myocardial infarction and ischaemia-driven revascularisation. ACS: acute coronary syndrome; CI: confidence interval; HR: hazard ratio; SCAD: stable coronary artery disease

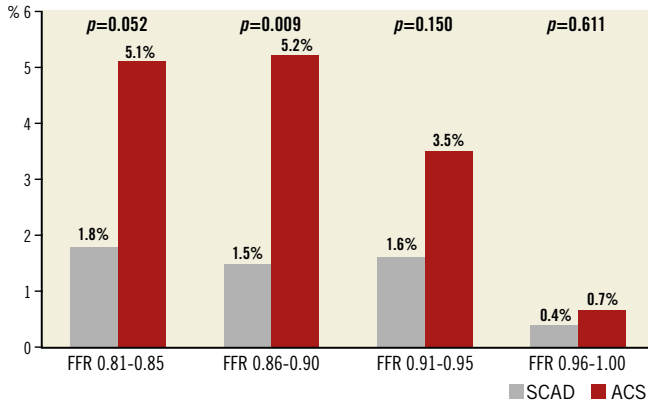


Figure 4. Comparison of MACE rates in deferred lesions between ACS and SCAD according to the range of FFR. The cumulative rates of MACE in deferred lesions were compared between SCAD and ACS, according to the range of FFR. ACS: acute coronary syndrome; SCAD: stable coronary artery disease

per-lesion-based clinical outcomes between ACS and SCAD patients, especially for deferred non-culprit lesions under the current FFR-guided strategy.

Table 5. Independent predictors of major adverse cardiac events in patients with deferred lesions.

Variable	Adjusted HR (95% CI)	p-value
Acute coronary syndrome	2.870 (1.473-5.595)	0.002
Diameter stenosis ≥50%	2.576 (1.398-4.748)	0.002
Multivessel disease	2.191 (1.140-4.212)	0.019
Previous revascularisation	2.165 (1.174-3.995)	0.013
Diabetes mellitus	1.614 (0.901-2.890)	0.108
Fractional flow reserve (per 0.1 increase)	0.599 (0.345-1.039)	0.068

*C-index of the marginal Cox regression model was 0.772 (95% CI: 0.690-0.853). CI: confidence interval; HR: hazard ratio

FFR-GUIDED STRATEGY IN ACS PATIENTS: PER-LESION LEVEL DECISION FOR CULPRIT LESIONS

Fischer et al presented comparable one-year clinical outcomes between 35 ACS patients and 76 SCAD patients whose revascularisation was deferred based on an FFR >0.75 (28.5% vs. 17.0%, p=0.21)⁵. Potvin et al also presented similar rates of cardiac events between 124 ACS patients and 77 SCAD patients whose revascularisation was deferred based on an FFR ≥0.75 at 24 months of

	SCAD	ACS		HR _{adj} (95% CI)	Interaction p-value
All population	1.6% (31/2,484)	3.8% (15/449)		2.966 (1.226-7.172)	
Diabetes	2.3% (17/743)	2.8% (4/143)		1.990 (0.628-6.309)	0.258
No diabetes	0.8% (14/1,741)	3.6% (11/306)		5.486 (2.404-12.52)	
Previous PCI	1.9% (16/863)	9.3% (5/54)		5.447 (1.987-14.93)	0.256
No previous PCI	0.9% (15/1,621)	2.5% (10/395)		2.657 (1.193-5.919)	
%DS ≥50%	2.6% (16/604)	6.3% (8/126)		2.934 (1.248-6.897)	0.882
%DS <50%	0.8% (15/1,853)	2.2% (7/313)		2.667 (1.086-6.555)	
FFR ≤0.95	1.6% (28/1,750)	4.5% (14/310)		3.082 (1.622-5.858)	0.055
FFR >0.95	0.4% (3/734)	0.7% (1/139)		1.555 (0.161-15.04)	
NSTEMI	1.6% (31/2,484)	3.6% (10/310)		4.252 (1.595-11.34)	0.619
Unstable angina	1.6% (31/2,484)	4.0% (5/139)		3.235 (1.545-6.772)	
Left main disease	1.4% (3/212)	4.2% (3/71)		2.883 (0.568-14.63)	0.619
Non-left main disease	1.2% (28/2,272)	3.2% (12/378)		2.642 (1.342-5.201)	

Figure 5. Comparison of MACE rates of deferred lesions between ACS and SCAD according to subgroup. The cumulative rates of MACE in deferred lesions were compared between SCAD and ACS, according to various subgroups. %DS: percent diameter stenosis; ACS: acute coronary syndrome; CI: confidence interval; HR: hazard ratio; HR_{adj}: multivariable adjusted hazard ratio; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease

follow-up (11% in ACS vs. 19% in SCAD, $p=0.47$)⁶. Although these relatively small studies reported comparable outcomes between culprit lesions in ACS patients and lesions in SCAD patients, recent studies have shown different results.

Mehta et al evaluated clinical outcomes of 334 ACS patients and 340 non-ACS patients whose revascularisation was deferred based on an FFR >0.80 (mean follow-up 4.5 years) and reported that deferred ACS patients had a higher risk of cardiac events (32% vs. 23%, $p=0.02$). In their study, a lower FFR value was associated with an increase in adverse cardiac events in the ACS group (HR 1.08 per 0.01 decrease in FFR, 95% CI: 1.03-1.12)⁷. In a study by Hakeem et al, 206 ACS patients with deferred culprit lesions based on an FFR >0.75 showed higher rates of MACE than 370 SCAD patients during a mean follow-up of 3.4 years (25% vs. 12%, $p<0.001$); the authors proposed a cut-off value of FFR <0.84 in the culprit vessel of ACS patients⁸. However, it is unclear whether these findings can be reproduced in deferred non-culprit lesions.

FFR-GUIDED STRATEGY IN ACS PATIENTS: PER-LESION LEVEL DECISION FOR NON-CULPRIT LESIONS

Previous studies focusing on the relevance of an FFR-guided per-patient level decision did not separately present the clinical outcomes according to culprit and non-culprit lesions. Furthermore, all the previous studies which evaluated the FFR-guided per-lesion level decision focused on the assessment of culprit lesions of ACS patients. The current study focused mainly on the clinical outcomes of deferred non-culprit lesions of ACS patients rather than the culprit lesion. In a comparison of lesion characteristics, deferred non-culprit lesions of ACS patients showed higher stenosis severity and longer lesion length than deferred lesions in SCAD. Nevertheless, the deferred non-culprit lesions in ACS patients showed a significantly higher risk of MACE than deferred lesions in SCAD patients, even after adjustment for baseline clinical and lesion differences. These results suggest that the plaque characteristics of non-culprit lesions in ACS patients might be a potential mechanism for the higher event rates.

The significant difference of two-year MACE rates between deferred non-culprit lesions in ACS patients and deferred lesions in SCAD patients was mainly driven by ischaemia-driven revascularisation. As the current study included deferred lesions with insignificant FFR values, the cumulative rate of death or MI was relatively low, as in previous studies with deferred lesions^{1,3}. The higher risk of MACE in deferred non-culprit lesions of ACS rather than SCAD patients might be partly explained by the results from intravascular imaging studies which consistently presented the higher prevalence of vulnerable features in non-culprit lesions of ACS patients compared with lesions of SCAD patients^{13,14}. The link between vulnerable plaque characteristics in non-culprit lesions of ACS patients and the risk of clinical events was also shown by those studies¹⁵.

In our study, the MACE rate was consistently higher in ACS patients than in SCAD patients in all FFR categories above 0.80 and in various subgroups. The absolute difference in MACE rate between ACS and SCAD in FFR ranges of 0.81-0.85 and 0.86-0.90 was similar (3.3% in FFR 0.81-0.85 vs. 3.7% in FFR 0.86-0.90). In

addition, among the deferred lesions with FFR between 0.80 and 0.90, FFR value did not show a significant association with the risk of MACE in both ACS and SCAD populations. This finding is different from the results of studies by Hakeem et al⁸ and Mehta et al⁷, which assessed the outcome of FFR-guided deferral in culprit lesions for ACS, and presented a higher risk of MACE in the lower range of FFR value and suggested a higher FFR cut-off value in the culprit lesion evaluation. Theoretically, microvascular injury in patients with ACS can underestimate lesion severity, especially in the myocardial territory of a culprit vessel². However, our study finding supports the use of the current cut-off value of FFR for non-culprit lesions in ACS patients. In addition, the recently published studies which investigated the outcomes of an FFR-guided strategy for non-culprit lesions also support the use of an FFR-guided revascularisation strategy for non-culprit lesions in patients with STEMI^{16,17}.

CLINICAL IMPLICATIONS

Our study showed that deferred non-culprit lesions in ACS patients showed a higher event rate than deferred lesions in a SCAD setting. This result may represent the systemic nature and plaque characteristics of ACS, which is associated with higher event rates, in both culprit and non-culprit vessels. Therefore, strict medical treatment and secondary prevention for comorbidities are required for ACS patients with deferred non-culprit lesions.

Limitations

This study has some limitations. First, the current study was not a randomised comparison of clinical outcomes following FFR-guided deferral or revascularisation for non-culprit lesions of ACS patients. Second, the intravascular imaging study was not systematically performed; therefore, the current study could not directly compare plaque characteristics and vulnerability between deferred non-culprit lesions in ACS patients and deferred lesions in SCAD patients. The difference in plaque characteristics may be one of the main mechanisms for the higher event rate in ACS patients than that in SCAD patients. Third, although FFR measurement was routinely performed in consecutive patients during the enrolment period of both registries, patients with acute STEMI or cardiogenic shock were excluded. In addition, as the current study focused on deferred non-culprit lesions of ACS patients rather than the culprit lesion, the lesions were mostly of mild to moderate severity. Fourth, although all the medications prescribed at discharge were mandatorily collected, the medications during follow-up were not systematically collected. Fifth, the ACS population was relatively small. Last, various methods for hyperaemia induction were used in this study. However, each centre applied the same method, for both ACS and SCAD patients included from that centre.

Conclusions

Deferred non-culprit lesions of ACS patients on the basis of non-ischaemic FFR showed significantly higher rates of clinical events, compared with deferred lesions of SCAD patients. This finding was consistent in various FFR categories and subgroups.

Impact on daily practice

The current study compared clinical outcomes between deferred non-culprit lesions in ACS patients and deferred lesions in SCAD patients based on FFR. Despite the similar FFR values in both groups, the rate of MACE was significantly higher in ACS patients than that in SCAD patients. The higher risk of MACE in ACS patients than that in SCAD patients was consistently observed in all categories of non-ischæmic FFR values, as well as in various subgroups. These results suggest a systemically increased risk of clinical events in the ACS population. Therefore, strict medical treatment and secondary prevention for comorbidities are required for ACS patients with deferred non-culprit lesions.

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Conflict of interest statement

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