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Deferred vs. performed revascularization for coronary stenosis with grey-zone fractional flow reserve values: data from the IRIS-FFR registry

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Aims The optimal fractional flow reserve (FFR) cut-off value for revascularization is debated. We evaluated the prognosis for deferred and performed revascularization in coronary stenosis with FFR values in the grey zone (0.75–0.80).

Methods and results This study included 1334 native coronary stenosis with grey-zone FFR values in 1334 patients from the prospective multicentre Interventional Cardiology Research In-cooperation Society Fractional Flow Reserve registry. Revascularization was deferred for 683 patients (deferred group) and performed for 651 (performed group). The primary outcome, a composite of death, target-vessel myocardial infarction (MI), and target vessel revascularization (TVR) occurred in 55 (8.1%) patients in the deferred group and 55 (8.4%) in the performed group [adjusted hazard ratio (aHR) 1.05, 95% confidence interval (CI) 0.67–1.66; $P = 0.79$] during a median follow-up of 2.9 years (interquartile range 1.5–4.1 years). Overall mortality and spontaneous MI did not differ between the groups (mortality 2.5% vs. 2.0%; aHR 0.82, 95% CI 0.34–2.00; $P = 0.66$; spontaneous MI 0.7% vs. 0.5%; aHR 1.85, 95% CI 0.35–9.75; $P = 0.47$). Myocardial infarction was significantly higher in the performed group (0.7% vs. 3.2%; aHR 0.27, 95% CI 0.09–0.80; $P = 0.02$) mainly because of a higher risk of periprocedural MI. Target vessel revascularization was significantly higher in the deferred group (5.7% vs. 3.7%; aHR 2.17, 95% CI 1.17–4.02; $P = 0.01$).

Conclusion For coronary stenosis with grey-zone FFR, revascularization was not associated with better clinical outcomes. The higher likelihood of periprocedural MI with revascularization was offset by the higher likelihood of TVR with deferral.

Trial registration Clinicaltrials.gov identifier: NCT01366404.

Keywords Fractional flow reserve • Coronary artery disease • Grey zone

Introduction

Fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) has shown better clinical outcomes than conventional angiography-guided PCI.[1–8] The optimal FFR cut-off value for revascularization is debated. With FFR ≤0.80, revascularization for coronary stenosis is associated with improved clinical outcomes, whereas with FFR ≥0.75, medical treatment has been shown to result in favourable long-term outcomes.[2,3] However, there has been controversy over revascularization decision-making for coronary stenosis with FFR between 0.75 and 0.80, the so-called grey zone.

Several studies have reported the outcomes of revascularization vs. deferral for coronary stenosis with grey-zone FFR values, with conflicting results.[9–15] However, these studies were hampered by

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limited numbers of patients and short follow-up periods. Clinically relevant information regarding the appropriate management for this uncertain subset requires a large multicentre cohort study with long-term follow-up. In this study, we compared long-term outcomes of deferral vs. revascularization for 1334 coronary stenosis with grey-zone FFR values included in a multicentre, prospective registry.

Methods

The Interventional Cardiology Research In-cooperation Society Fractional Flow Reserve (IRIS-FFR) registry is a prospective, multicentre registry designed for investigating the prognosis of coronary stenosis assessed using FFR in routine clinical practice. The inclusion and exclusion criteria of the registry have been previously described.[16] In brief, the registry consecutively enrolled all patients who underwent FFR measurement for at least one coronary lesion. The main exclusion criteria were thrombolysis in myocardial infarction (MI) flow < three, bypass graft, overt heart failure, technical unsuitability for FFR evaluation, and short life expectancy (<2 years).

For this substudy, we enrolled patients with a *de novo* native coronary artery stenosis with an FFR value in the grey zone (0.75–0.80). To eliminate the clustering effects of lesions within the same patient, we selected one lesion per patient, preferentially choosing those with lower FFR values, or left anterior descending arterial lesions when the FFR values were equal for two or more lesions. The study protocol was approved by the institutional review board or ethics committee of each participating centre, and all patients provided written informed consent.

Fractional flow reserve measurement and revascularization

Fractional flow reserve was measured after coronary angiography with a commercially available coronary pressure (*Pd*) wire, as previously described.[16] After the administration of intracoronary nitroglycerin (100 or 200 μg), the pressure wire was positioned in the distal segment of the target vessel. It was recommended that hyperaemia should be induced by intravenous adenosine infusion (140 or 200 μg/kg/min) via a central or large antecubital vein. The proximal aortic pressure (*Pa*) and distal *Pd* were measured during sustained hyperaemia, and FFR was calculated as the mean value of *Pd*/*Pa*. For FFR values between 0.75 and 0.80, the decision regarding revascularization was at the operator's discretion. All the revascularization procedures for PCI or bypass surgery were performed using standard techniques.[7,8] Second-generation drug-eluting stents were routinely used. Routine follow-up angiography after the index procedure was highly discouraged.

Quantitative coronary angiography and intravascular ultrasound

Quantitative coronary angiography was performed using standard techniques and automated edge-detection algorithms (CAAS-5, Pie Medical, Maastricht, Netherlands). Diameter stenosis, minimal lumen diameter,

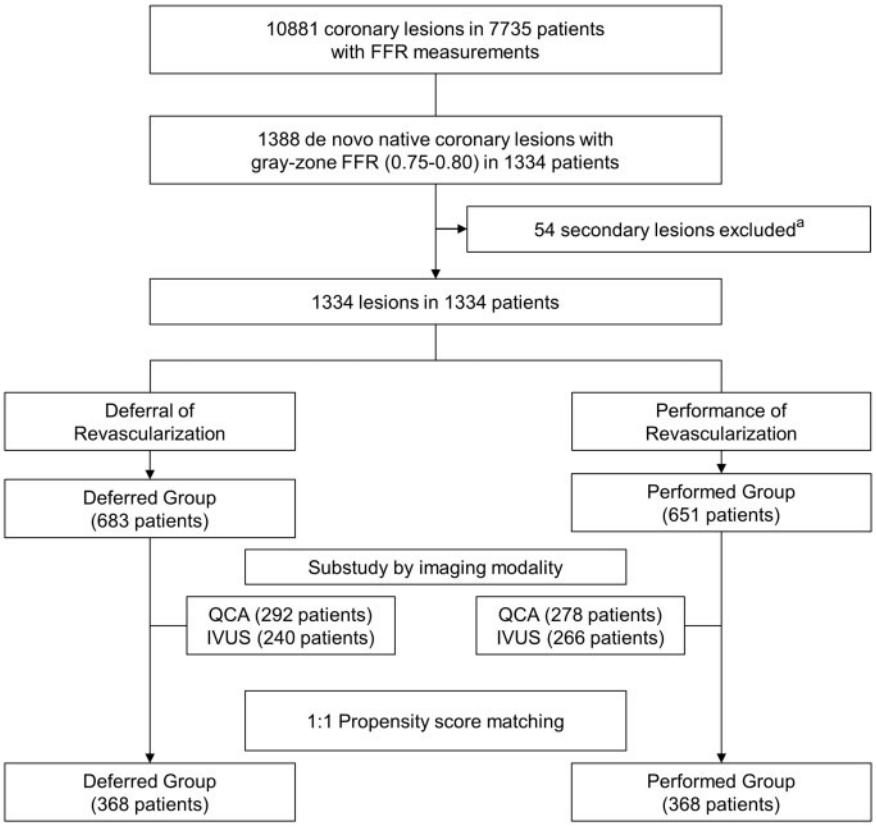

Figure 1 Study flowchart. [a]One lesion per patient was selected, preferentially choosing lesions with a lower fractional flow reserve value and those in the left anterior descending artery. IVUS, intravascular ultrasound; QCA, quantitative coronary angiography.

lesion length, and reference lumen diameter were measured.[17] The decision to conduct an intravascular ultrasound (IVUS) measurement was at the discretion of the operator. Intravascular ultrasound images obtained at the index procedure was analysed in accordance with standard methods.[18] Minimal lumen area (MLA) and external elastic membrane (EEM) area at the MLA site were measured. The plaque burden was calculated as (plaque + media area)/EEM area × 100 (%).Quantitative coronary angiography analysis and IVUS analysis were conducted at the Core Laboratory of the CardioVascular Research Foundation (Seoul, Korea).

Outcomes and definitions

The primary outcome was a major adverse cardiac event [MACE, a composite of death from any cause, target vessel MI and target vessel revascularization (TVR)]. Target vessel MI was defined as follows: (i) within the first 48 h of the index revascularization procedure, ischaemic symptoms and signs, with the creatinine kinase MB (CK-MB) fraction concentration elevated to more than five times the upper normal limit; or (ii) ≥48 h after the procedure, any elevation of CK-MB level above the upper normal limit related to the FFR-measured vessels, accompanied by ischaemic symptoms.[19] In the *post hoc* analysis, periprocedural MI was defined as an

Table 1 Patient and lesion characteristics in the overall and matched populations

	Overall population			Matched population		
	Deferred group (*n* = 683)	Performed group (*n* = 651)	*P*-value	Deferred group (*n* = 368)	Performed group (*n* = 368)	*P*-value
Age (years), mean ± SD	64.2 ± 9.8	63.8 ± 9.9	0.52	64.5 ± 9.9	64.2 ± 9.9	0.73
Male gender, *n* (%)	535 (78.3)	478 (73.4)	0.042	285 (77.4)	275 (74.7)	0.44
Body mass index (kg/m^2), mean ± SD	24.9 ± 3.1	25.1 ± 3.0	0.18	24.9 ± 3.2	24.9 ± 2.8	0.95
Acute coronary syndrome presentation, *n* (%)	125 (18.3)	163 (25.0)	0.003	71 (19.3)	73 (19.8)	0.85
Hypertension, *n* (%)	441 (64.6)	418 (64.2)	0.94	232 (63.0)	234 (63.6)	0.94
Diabetes, *n* (%)	220 (32.2)	203 (31.2)	0.73	112 (30.4)	119 (32.3)	0.63
Current smoking, *n* (%)	164 (24.0)	130 (20.0)	0.09	97 (26.4)	81 (22.0)	0.20
Hyperlipidaemia, *n* (%)	388 (56.8)	363 (55.8)	0.74	205 (55.7)	207 (56.2)	0.94
Previous percutaneous coronary intervention, *n* (%)	153 (22.4)	102 (15.7)	0.002	80 (21.7)	68 (18.5)	0.31
Previous stroke, *n* (%)	57 (8.3)	43 (6.6)	0.27	30 (8.2)	29 (7.9)	1.00
Chronic renal failure, *n* (%)	19 (2.8)	15 (2.3)	0.70	13 (3.5)	8 (2.2)	0.38
Left ventricular ejection fraction (%), mean ± SD	60.5 ± 11.4	60.8 ± 11.0	0.67	61.7 ± 6.9	61.5 ± 7.8	0.82
Discharge medication, *n* (%)						
Aspirin	573 (84.0)	636 (98.3)	<0.001	319 (86.9)	357 (97.3)	<0.001
P2Y12 inhibitor	443 (65.0)	631 (97.5)	<0.001	252 (68.7)	353 (96.2)	<0.001
Statin	623 (91.2)	618 (95.4)	0.003	339 (92.1)	352 (95.9)	0.039
Beta-blocker	339 (49.6)	386 (59.6)	0.001	194 (52.7)	219 (59.7)	0.11
Calcium-channel blocker	372 (54.5)	362 (55.9)	0.78	204 (55.4)	198 (54.0)	0.92
Multi-vessel coronary artery disease	375 (54.9)	413 (63.4)	0.002	223 (60.6)	228 (62.0)	0.76
Lesion characteristics						
Fractional flow reserve, mean ± SD	0.78 ± 0.02	0.77 ± 0.02	<0.001	0.78 ± 0.02	0.78 ± 0.02	0.14
Lesion territory, *n* (%)			0.001			0.98
Left main	20 (2.9)	48 (7.4)		15 (4.1)	17 (4.6)	
Left anterior descending artery	513 (75.1)	448 (68.8)		258 (70.1)	262 (71.2)	
Right coronary artery	72 (10.5)	86 (13.2)		49 (13.3)	47 (12.8)	
Left circumflex artery	54 (7.9)	56 (8.6)		34 (9.2)	32 (8.7)	
Others	24 (3.5)	13 (2.0)		12 (3.3)	10 (2.7)	
Lesion location, *n* (%)			0.002			0.80
Proximal	315 (46.1)	362 (55.6)		193 (52.4)	191 (51.9)	
Mid	264 (38.7)	215 (33.0)		125 (34.0)	132 (35.9)	
Distal	81 (11.9)	65 (10.0)		38 (10.3)	37 (10.1)	
Diameter stenosis, *n* (%)			<0.001			0.20
≥70%	88 (12.9)	349 (53.6)		83 (22.6)	90 (24.5)	
50–69%	446 (65.3)	295 (45.3)		270 (73.4)	271 (73.6)	
30–49%	149 (21.8)	7 (1.1)		15 (4.1)	7 (1.9)	
AHA/ACC B2C lesion	444 (65.0)	484 (74.3)	<0.001	249 (67.7)	262 (71.2)	0.34
Long lesion (>20 mm)	320 (46.9)	384 (59.0)	<0.001	180 (48.9)	199 (54.1)	0.18

ACC/AHA, American College of Cardiology/American Heart Association.

elevation of the CK-MB fraction to more than 10 times the upper normal limit. Target vessel revascularization was defined as any PCI or bypass surgery of the index vessel with FFR measurement. All outcomes of interest were confirmed by source documentation collected at each hospital, and were centrally adjudicated by an independent clinical events committee.

Data and follow-up

The data were collected using a web-based dedicated case report form. Members of the academic co-ordinating centre (Clinical Research Center, Asan Medical Center, Seoul, South Korea) monitored and verified the data in the participating hospitals. Clinical follow-ups were conducted during hospitalization, at 30 days, 6 months, and 12 months after the index procedure and subsequently at 6 month intervals. The patients' clinical status, interventions, and adverse events were recorded at each visit.

Statistical analysis

Baseline characteristics are presented as a number (%) for categorical variables and mean ± standard deviation for continuous variables. Differences between groups were analysed using the Student's *t*-test or the Mann–Whitney *U*-test for continuous variables and the χ^2 test or the Fisher's exact test for categorical variables, as appropriate. Survival curves were constructed using Kaplan–Meier estimates and compared with the log-rank test. Multivariable Cox proportional hazard regression models were used to adjust for the differences in the baseline characteristics between the groups.[20] Additional adjustments were made with propensity score matching and weighted Cox proportional hazards regression models with inverse probability of treatment weighting (IPTW). The propensity score was computed by a logistic regression model, and the matching was performed using the nearest neighbour method, with a calliper width of 0.2 standard deviation.[21–23] In the matched cohorts, survival curves were constructed using Kaplan–Meier estimates and compared using a Cox proportional hazard regression model. The statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). *P*-values <0.05 were considered statistically significant.

Results

Between August 2009 and October 2016, 10 881 lesions from 7735 patients were prospectively enrolled in the IRIS-FFR registry, of which 1388 *de novo* native coronary lesions in 1334 patients were with an FFR value in the grey zone (0.75–0.80). Among these, 1334 lesions were selected (one per patient) for the patient-level analysis (*Figure 1*). After FFR assessment, revascularization was deferred for 683 lesions (deferred group) and performed in 651 lesions (performed group).

The mean age of the patients was 64 years; 76% were men, 78% had stable angina, 32% were diabetic, and 59% had multi-vessel coronary artery disease. The deferred group patients were more likely to be men, and have a history of previous PCI and were associated with higher FFR values, less multi-vessel disease, less frequent left main or proximal diseases, and less complex coronary artery disease (*Table 1* and Supplementary material online, *Table S1*).

Quantitative coronary angiography showed larger minimal lumen diameters and smaller diameter stenosis in the deferred group, whereas IVUS showed that the deferred group patients had fewer plaque ruptures, larger MLA, and smaller plaque burden than the performed group patients (*Table 2*).

Outcomes for the overall population

During a median follow-up of 2.9 (interquartile range 1.5–4.1) years, MACE occurred in 55 (8.1%) patients in the deferred group and 55 (8.4%) in the performed group [adjusted hazard ratio (aHR) 1.05,

Table 2 Lesion characteristics at the index procedure by imaging analysis

Lesion characteristics	Overall population			Matched population		
	Deferred group	Performed group	*P*-value	Deferred group	Performed group	*P*-value
Quantitative coronary angiography, mean ± SD	*n* = 292	*n* = 278		*n* = 163	*n* = 172	
Lesion length (mm)	21.9 ± 12.7	21.8 ± 11.2	0.89	22.9 ± 14.0	20.8 ± 10.1	0.12
Reference lumen diameter (mm)	3.1 ± 0.5	3.1 ± 0.5	0.36	3.1 ± 0.5	3.1 ± 0.5	0.69
Minimal lumen diameter (mm)	1.5 ± 0.4	1.4 ± 0.4	0.004	1.5 ± 0.4	1.4 ± 0.4	0.03
Diameter stenosis (%)	50.9 ± 10.0	55.4 ± 10.0	<0.001	52.1 ± 10.7	55.8 ± 10.2	0.001
Intravascular ultrasound	*n* = 240	*n* = 266		*n* = 134	*n* = 167	
Lesion length (mm), mean ± SD	35.6 ± 14.2	26.4 ± 11.3	<0.001	36.6 ± 13.6	25.8 ± 11.6	<0.001
Qualitative analysis, *n* (%)						
Plaque rupture	27 (11.2)	59 (22.2)	<0.001	27 (11.2)	59 (22.2)	
Thrombus	38 (15.8)	35 (13.2)	0.39	38 (15.8)	35 (13.2)	
Severe calcification with calcium arc >180°	30 (12.5)	40 (15.0)	0.41	30 (12.5)	40 (15.0)	
Single-plane analysis at MLA site, mean ± SD						
External elastic membrane area (mm^2)	11.1 ± 4.4	12.1 ± 5.0	0.015	11.6 ± 4.8	12.1 ± 5.1	0.35
Plaque plus media area (mm^2)	8.3 ± 4.0	9.8 ± 4.6	<0.001	8.8 ± 4.3	9.8 ± 4.6	0.07
MLA (mm^2)	2.8 ± 1.1	2.3 ± 0.9	<0.001	2.8 ± 1.1	2.3 ± 0.9	0.001
Plaque burden (%)	74.2 ± 10.7	79.1 ± 7.6	<0.001	75.8 ± 10.5	79.1 ± 7.3	0.002

MLA, minimal lumen area.

Table 3 Clinical outcomes in the deferred and performed groups

	Total number of events (%)		Crude HR (95% CI)	*P*-value	Adjusted HR (95% CI)					
	Deferred group [*n* = 683; *n* (%)]	Performed group [*n* = 651; *n* (%)]			Multivariable[b]	*P*-value	Propensity matching	*P*-value	IPTW	*P*-value
Primary outcome										
MACE[a]	55 (8.1)	55 (8.4)	0.81 (0.55–1.17)	0.26	1.05 (0.67–1.66)	0.79	0.95 (0.57–1.57)	0.83	0.97 (0.67–1.40)	0.86
FFR 0.75 (*n* = 216)	6 (9.1)	10 (6.7)	1.27 (0.46–3.49)	0.65						
FFR 0.76 (*n* = 193)	5 (6.1)	11 (9.9)	0.53 (0.18–1.52)	0.23						
FFR 0.77 (*n* = 215)	5 (5.4)	10 (8.1)	0.61 (0.21–1.79)	0.37						
FFR 0.78 (*n* = 206)	10 (10.2)	10 (9.3)	0.99 (0.41–2.39)	0.99						
FFR 0.79 (*n* = 221)	10 (8.1)	9 (9.3)	0.71 (0.29–1.76)	0.46						
FFR 0.80 (*n* = 283)	19 (8.6)	5 (8.1)	0.96 (0.36–2.58)	0.94						
Secondary outcome										
Death from any cause	17 (2.5)	13 (2.0)	1.06 (0.52–2.19)	0.87	0.82 (0.34–2.00)	0.66	0.61 (0.23–1.60)	0.31	0.99 (0.51–1.91)	0.97
Cardiac death	9 (1.3)	4 (0.6)	1.82 (0.56–5.93)	0.32	1.09 (0.23–5.09)	0.91	0.84 (0.17–4.19)	0.84	1.15 (0.38–3.52)	0.81
MI	5 (0.7)	21 (3.2)	0.21 (0.08–0.55)	0.002	0.27 (0.09–0.80)	0.019	0.34 (0.11–1.07)	0.06	0.36 (0.16–0.82)	0.015
Periprocedural MI	0 (0.0)	18 (2.8)	NA	NA	NA	NA	NA	NA	NA	NA
Spontaneous MI	5 (0.7)	3 (0.5)	1.31 (0.31–5.50)	0.71	1.85 (0.35–9.75)	0.47	3.49 (0.39–31.24)	0.26	2.10 (0.51–8.59)	0.30
Death or MI	20 (2.9)	33 (5.1)	0.51 (0.29–0.88)	0.017	0.48 (0.25–0.95)	0.034	0.40 (0.18–0.89)	0.024	0.60 (0.36–1.01)	0.05
Death or spontaneous MI	20 (2.9)	16 (2.5)	1.02 (0.53–1.97)	0.96	0.90 (0.41–1.99)	0.80	0.72 (0.30–1.73)	0.46	1.09 (0.60–1.98)	0.78
Cardiac death or spontaneous MI	7 (1.0)	5 (0.8)	1.13 (0.36-3.56)	0.84	0.93 (0.21-4.12)	0.92	1.09 (0.29-4.06)	0.90	1.14 (0.40-3.23)	0.81
TVR	39 (5.7)	24 (3.7)	1.30 (0.78–2.16)	0.31	2.17 (1.17–4.02)	0.013	2.49 (1.16–5.34)	0.019	1.79 (1.05–3.04)	0.031

CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; IPTW, inverse probability-of-treatment weighting; MACE, major adverse cardiac events; MI, myocardial infarction; NA, not applicable; TVR, target vessel revascularization.

[a]Major adverse cardiac events comprised death, target vessel myocardial infarction, and target vessel revascularization.

[b]Adjusted by age, gender, clinical presentation, hypertension, diabetes, current smoking, hyperlipidaemia, history of percutaneous coronary intervention, chronic renal failure, lesion territory, lesion location, FFR value, diameter stenosis, lesion complexity, lesion length, and number of diseased vessels.

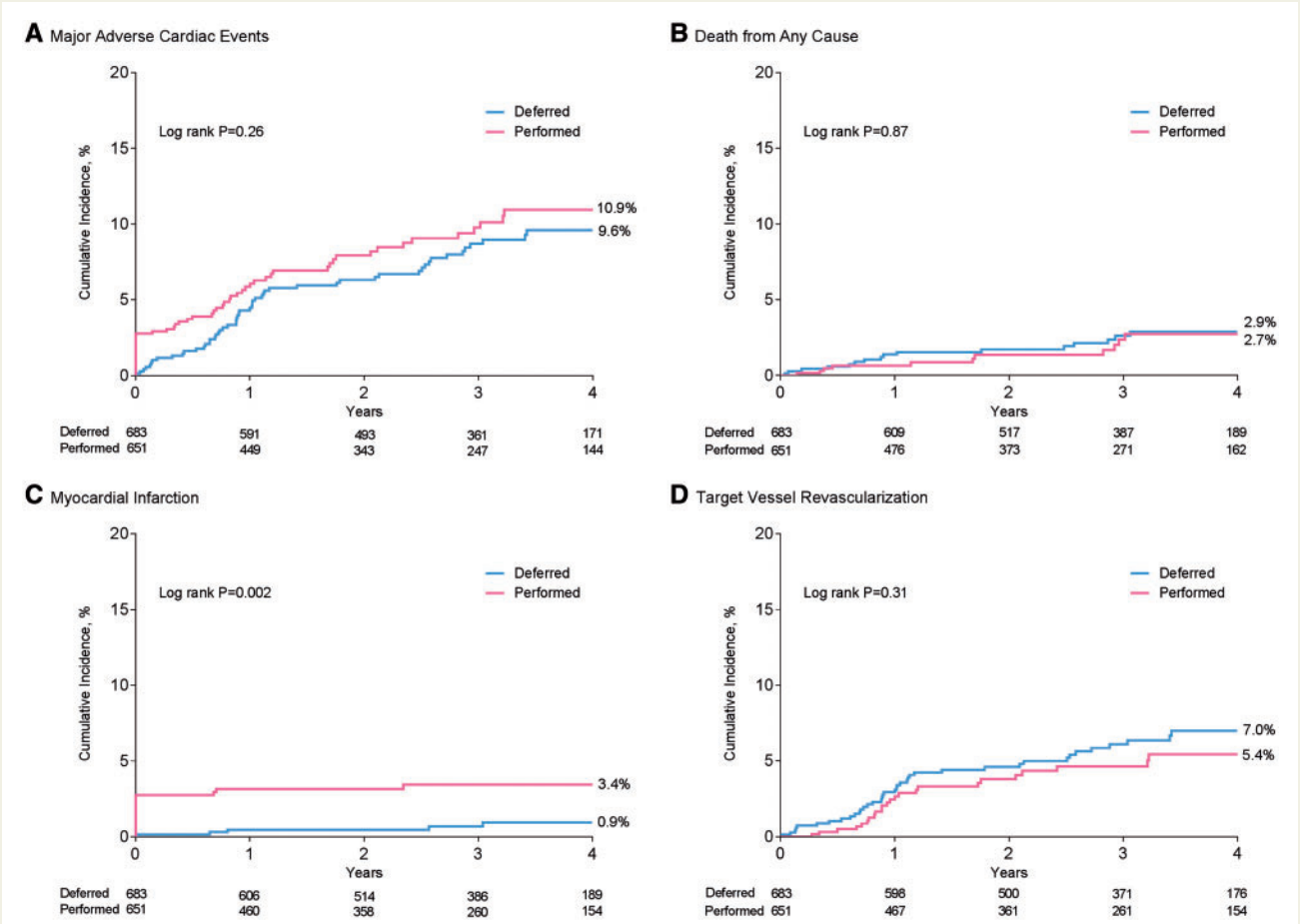

Figure 2 Kaplan–Meier curves for clinical outcomes in the overall population. (A) Major adverse cardiac events. (B) Death from any cause. (C) Myocardial infarction. (D) Target vessel revascularization.

95% confidence interval (CI) 0.67–1.66; $P = 0.79$]. Overall mortality did not differ between the groups (2.5% in deferred group vs. 2.0% in performed group; aHR 0.82, 95% CI 0.34–2.00; $P = 0.66$). The performed group showed a significantly higher risk of target vessel MI (0.7% vs. 3.2%; aHR 0.27, 95% CI 0.09–0.80; $P = 0.02$), mainly because of a higher risk of periprocedural MI but the incidence of spontaneous MI did not differ between the groups (0.7% vs. 0.5%; aHR 1.85, 95% CI 0.35–9.75; $P = 0.47$). Definite stent thrombosis did not occur. The risk of TVR was higher in the deferred group (5.9% vs. 3.7%; aHR 2.17, 95% CI 1.17–4.02; $P = 0.01$) (*Table 3*). Indications for target lesion revascularization are summarized in Supplementary material online, *Table S2*. *Figure 2* shows the Kaplan–Meier curves for the outcomes in the two groups. Independent predictors of MACE in the deferred and performed groups are shown in Supplementary material online, *Tables S3* and *S4*.

Outcomes for the propensity score-matched groups

Propensity score matching to adjust for the differences in the baseline characteristics created 368 matched pairs of patients. The two groups were well balanced with no significant differences in baseline characteristics, except for the more frequent post-procedural use of antiplatelet agents and statin in the performed group (*Table 1*). The clinical outcomes showed a similar trend to those for the overall population. The risk of MACE, death, cardiac death, and spontaneous MI did not differ between the groups (*Table 3*, *Figure 3*). The results after adjustment by IPTW were consistent (*Table 3*). The clinical outcomes of the patients not included in the propensity score matching showed a similar trend (see Supplementary material online, *Tables S5* and *S6*).

Subgroup analyses

In the subgroup analyses, the only difference in the effect on MACE between deferred and performed revascularization was with respect to MLA on IVUS ($\leq$2.5 mm^2 and >2.5 mm^2), in which a trend towards a treatment by subgroup interaction was observed ($P = 0.045$ for the interaction; *Figure 4*). Even when a stricter definition of periprocedural MI was applied, the overall findings remained consistent (see Supplementary material online, *Table S7*).

Discussion

Data from this large, prospective, multicentre registry showed that the risk of a composite of death, target vessel MI and TVR for patients

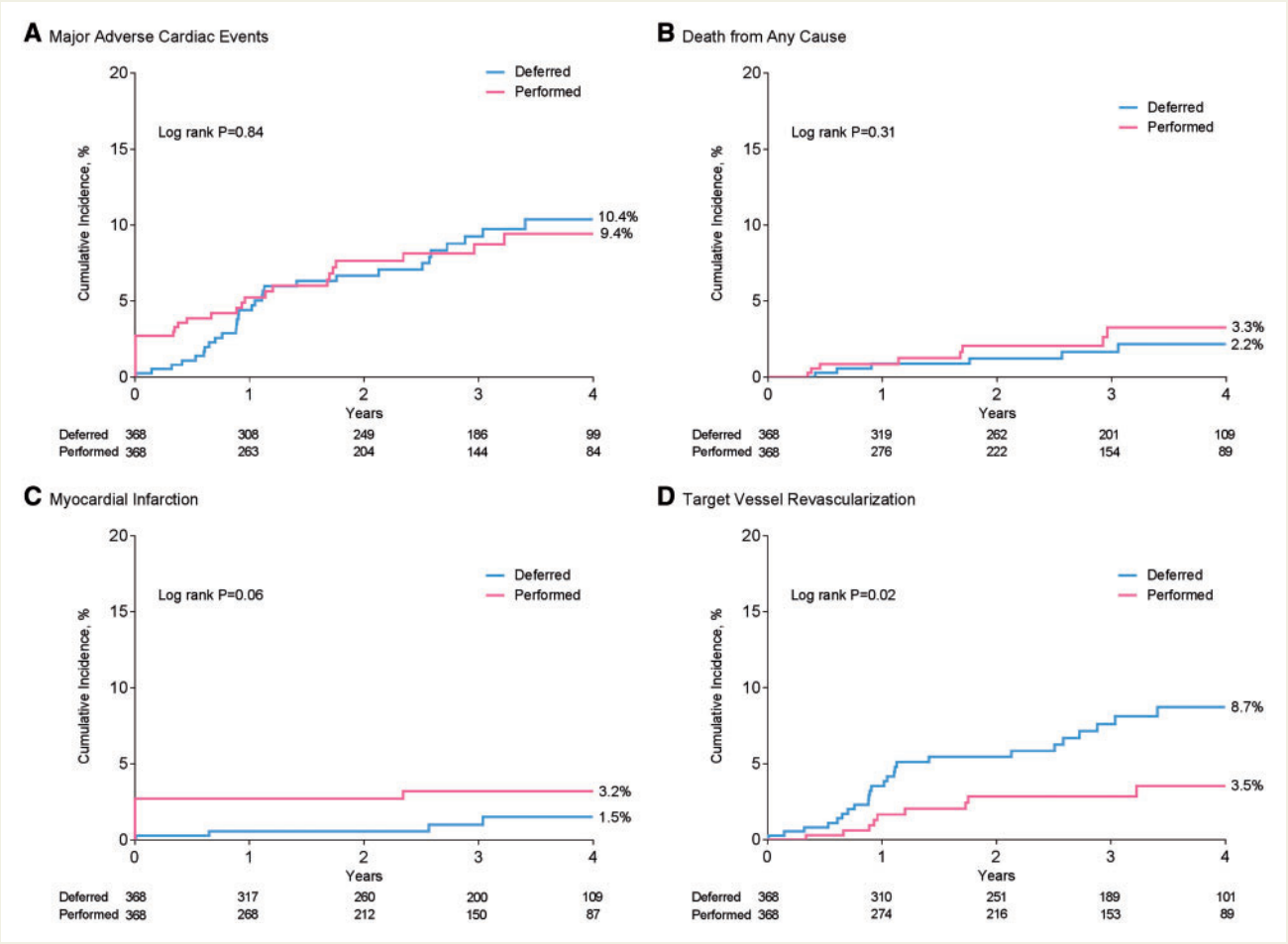

Figure 3 Kaplan–Meier curves for clinical outcomes in the matched population. (A) Major adverse cardiac events. (B) Death from any cause. (C) Myocardial infarction. (D) Target vessel revascularization.

with grey-zone FFR values did not significantly differ between the patients whose revascularization was deferred and those for whom it was performed. The incidence of death and spontaneous MI did not differ between the groups. Although the risk of TVR tended to be higher for the deferred group, this was offset by a higher risk of periprocedural MI for the performed group. This trend remained consistent even after adjustment by propensity score matching and IPTW. This suggests that the medical treatment of lesions with grey-zone FFR values would be a reasonable and safe strategy. Revascularization may be considered in patients with medically refractory angina.

Initially, the FFR cut-off value for revascularization was 0.75, with FFR values <0.75 having >99% positive predictive value for inducible myocardial ischaemia. Subsequent studies have reported that in a minority of patients, FFR between 0.75 and 0.80 was associated with flow-limiting stenosis.[24,25] Currently, FFR of 0.80 is used in revascularization threshold to avoid a few significant stenosis being left untreated.[1,2] Nevertheless, FFR values between 0.75 and 0.80 are still considered as being in the grey zone in revascularization decision-making.[9–15] Therefore, for the treatment of those lesions, careful clinical judgement considering typicality of complaints, other test results, and the lesion characteristics was suggested.[26]

Revascularization for stenosis with grey-zone FFR values has been investigated in only three small retrospective observational studies (see Supplementary material online, *Table S8*). Courtis *et al.*[9] reported that coronary revascularization was associated with a lower rate of MACE, mainly because of the reduction in target lesion revascularization. Conversely, Lindstaedt *et al.*[10] showed that deferral of revascularization was associated with lower rates of MACE and the composite of cardiac death and MI. Recently, Adjedj *et al.*[11] demonstrated that revascularization of stenosis with grey-zone FFR values tended to have a lower risk of overall mortality, and Agarwal *et al.*[12] reported that revascularization was associated with lower rates of MACE and spontaneous MI.

The IRIS-FFR registry includes the largest current cohort of prospectively enrolled coronary stenosis patients treated using contemporary medicine and interventional technology, with clinical events adjudicated by an independent committee. Furthermore, we controlled for selection bias between the groups in the present study using various statistical adjustments. This study could therefore provide valuable insights for daily catheterization laboratory practice.

The results suggested that deferred revascularization could be the preferred initial treatment strategy for stenosis with grey-zone FFR values. In the deferred group, the annual death and target vessel MI

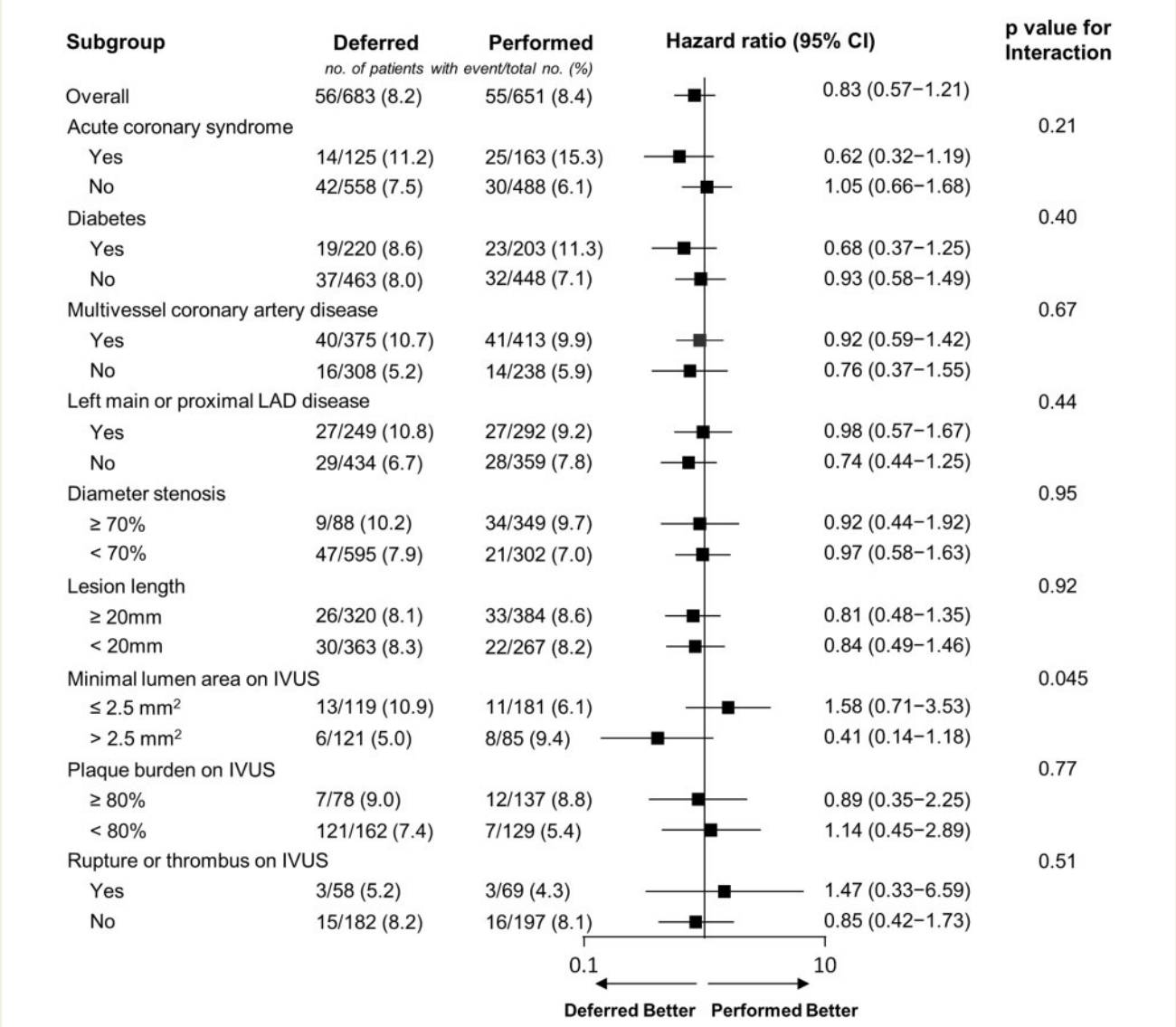

Figure 4 Subgroup analysis for major adverse cardiac events in the overall population. IVUS, intravascular ultrasound; LAD, left anterior descending artery.

rate was less than 1%. The annual incidence of TVR was less than 2%, which must be lower than that of contemporary PCI-related complications.[27,28] Late TVR after index procedure was more frequent in the deferred group. However, it is noteworthy that in performed group, all patients already received PCI and 3.7% experienced late TVR. Therefore, more patients actually received stent implantation in performed group than deferred group between index procedure and follow-up. Although we exclusively used second-generation drug-eluting stents, the risk of periprocedural MI and repeated TVR was not negligible in the performed group, and performing revascularization was not observed to be superior to medical treatment for stenosis with grey-zone FFR values. These overall findings remained consistent even when we applied a stricter definition of periprocedural MI in a supplementary analysis. A recent meta-analysis showed that the outcome-derived FFR threshold for revascularization was located within the grey zone[29] that was consistent with our findings.

The morphological characteristics of the stenosis and the patient's clinical context can affect clinical outcomes in coronary artery disease.[15,30,31] Thus, for stenosis with grey-zone FFR values, some operators favour revascularization for high-risk patients and lesion characteristics, such as patients with diabetes or acute coronary syndrome. However, our subgroup analysis showed no differences in effect between deferred and performed revascularization on the risk of MACE across the subgroups including acute coronary syndrome. This would be due to that unfavourable clinical and lesion characteristics affected outcomes of both revascularized and deferred lesions. Interestingly, MLA showed a marginally significant interaction. However, these results had insufficient statistical power and should be interpreted with caution. A further large study is needed to test whether MLA measured using IVUS could guide revascularization decisions for stenosis with grey-zone FFR values.

Limitation

This study has several limitations. First, there was the inherent limitation of this being an observational study. Second, the clinical and lesion characteristics differed between the groups. These differences were adjusted through propensity score matching; nevertheless, some differences remained, particularly with regard to the use of post-procedural medications. Third, we selected one lesion per patient to eliminate clustering effects. Additional analysis with the all 1388 lesions showed similar trends (Supplementary *Tables S9* and *S10*). Finally, the power of this study could be limited to detect small differences. Our findings warrant substantiation in larger studies with greater power. Although underpowered, this study is the largest cohort of prospectively enrolled patients with the longest follow-up duration that could give clinically relevant information for the debating issue.

Conclusion

In conclusion, this study based on a large, prospective, and multicentre registry demonstrated that revascularization was not associated with better clinical outcomes for coronary stenosis with grey-zone FFR values. A high risk of periprocedural MI in patients who underwent revascularization was offset by the high risk of TVR in the deferred group.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Corrigendum

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