

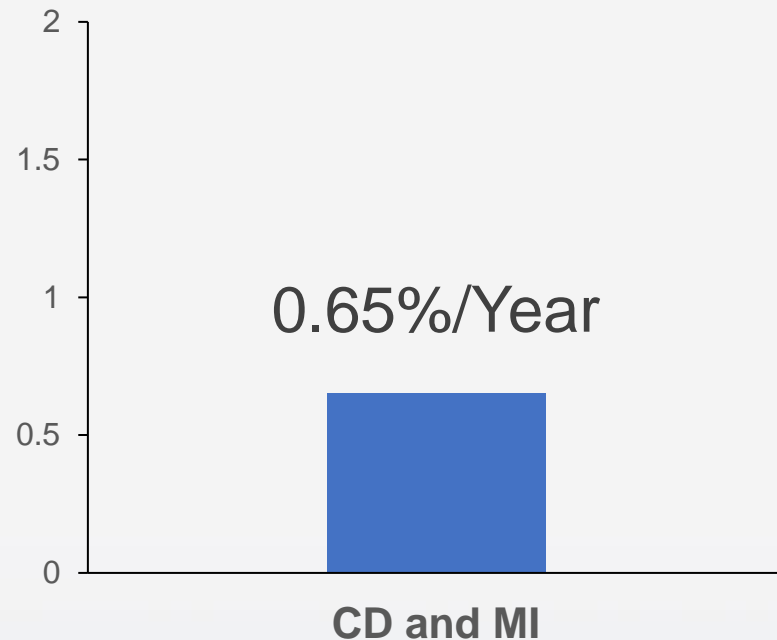
The Fate of Deferred Lesions; Insight From the IRIS-FFR Registry

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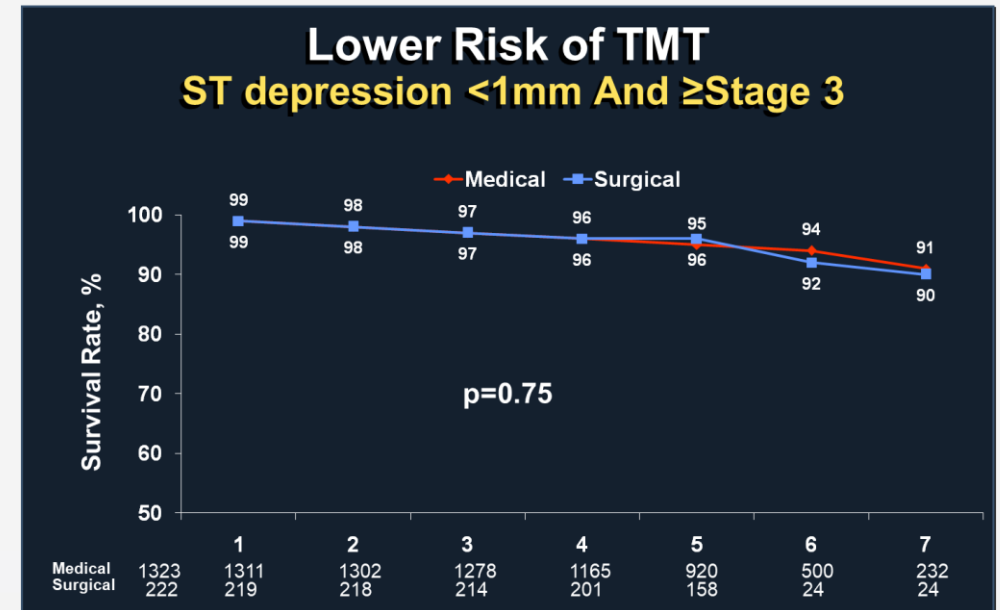
Premise (1) No Ischemia, Excellent Prognosis

Negative Exercise Myocardial Perfusion



Journal of Nuclear Cardiology, 11(5), 551-561

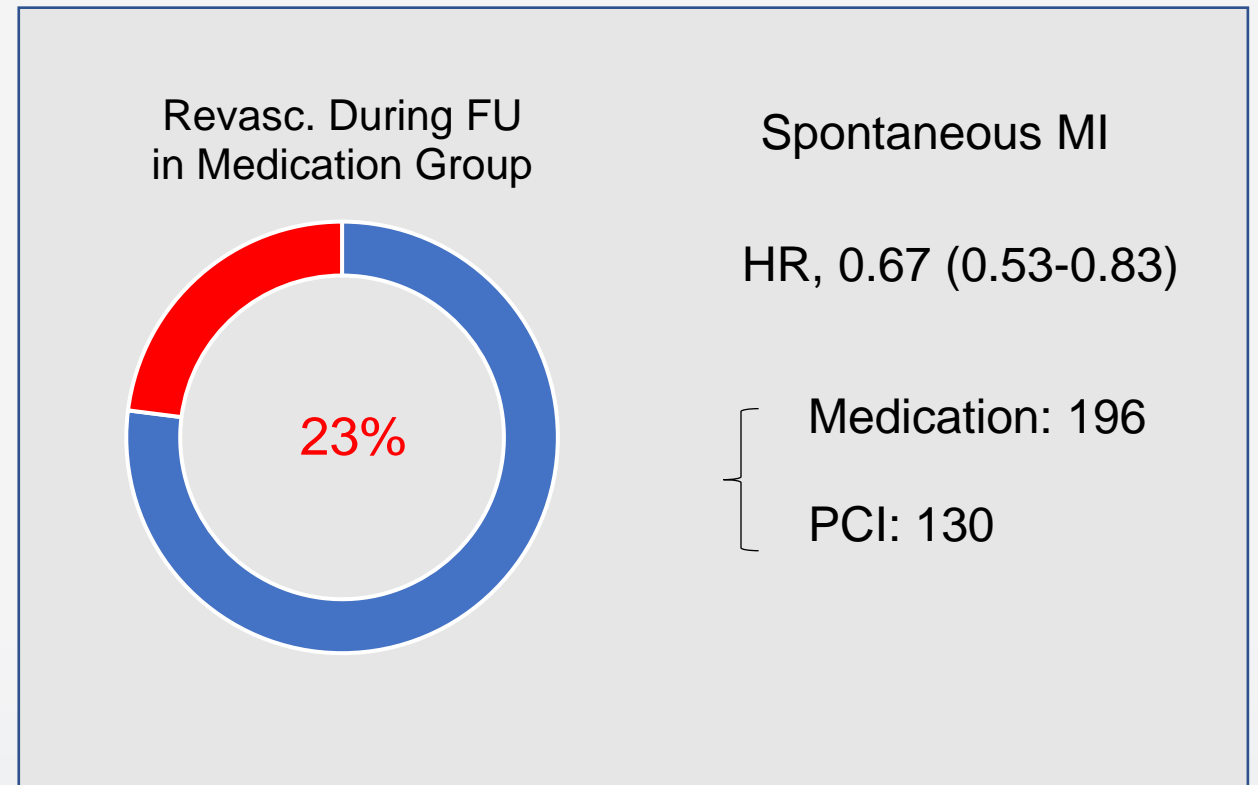
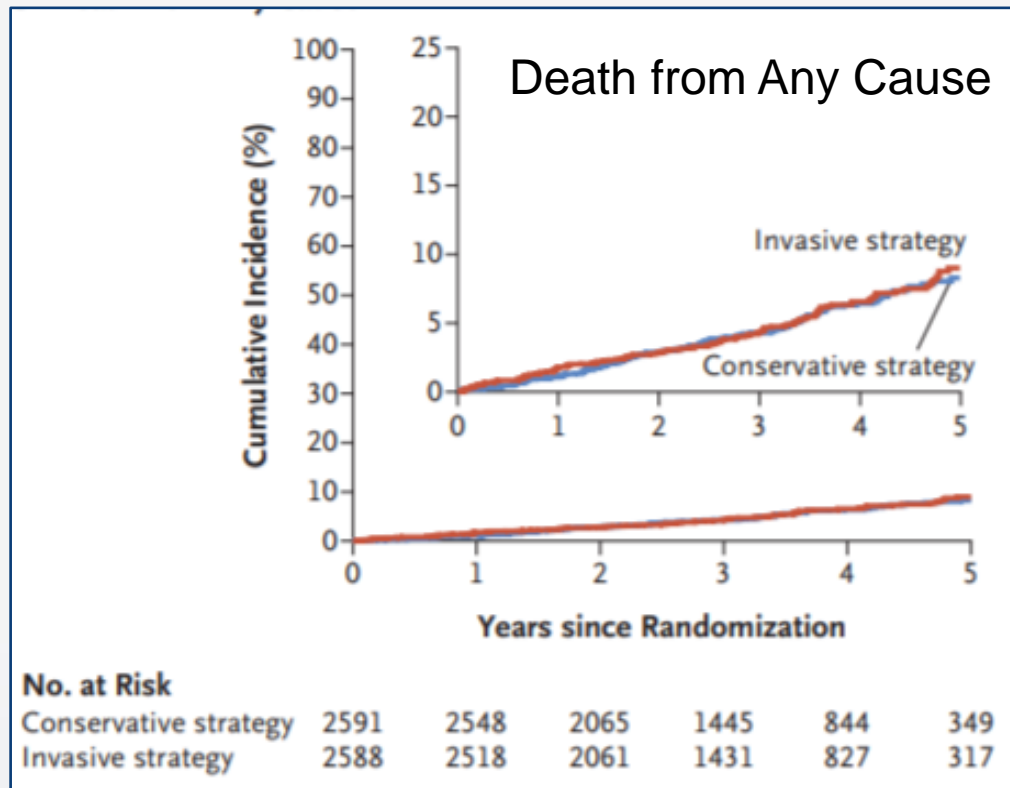
Survival Benefit of CABG Over Med.



DONALD AW et al. J Am Coll Cardiol 1986;8:741-8

Premise (2) ISCHEMIA Trial:

At Least Moderate Ischemia in SAP



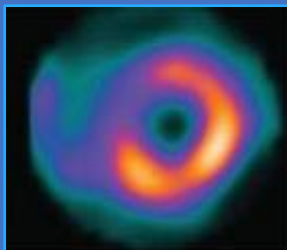
Boden et al. New Engl J Med 2007;356:1503-16.

Non-Invasive Functional Study In Cath Lab

Comparison with 3 Non-Invasive Functional Studies



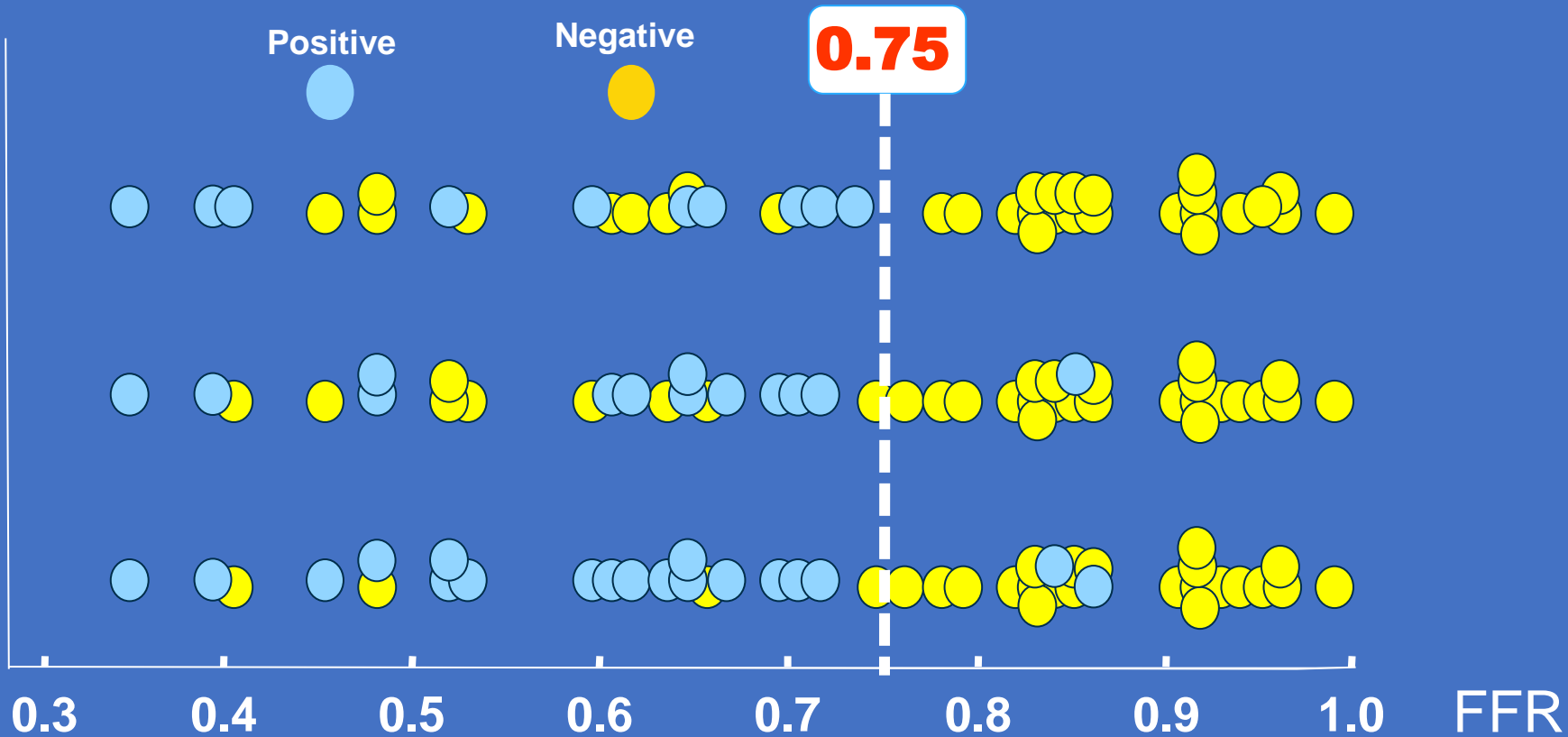
Stress Echo



SPECT



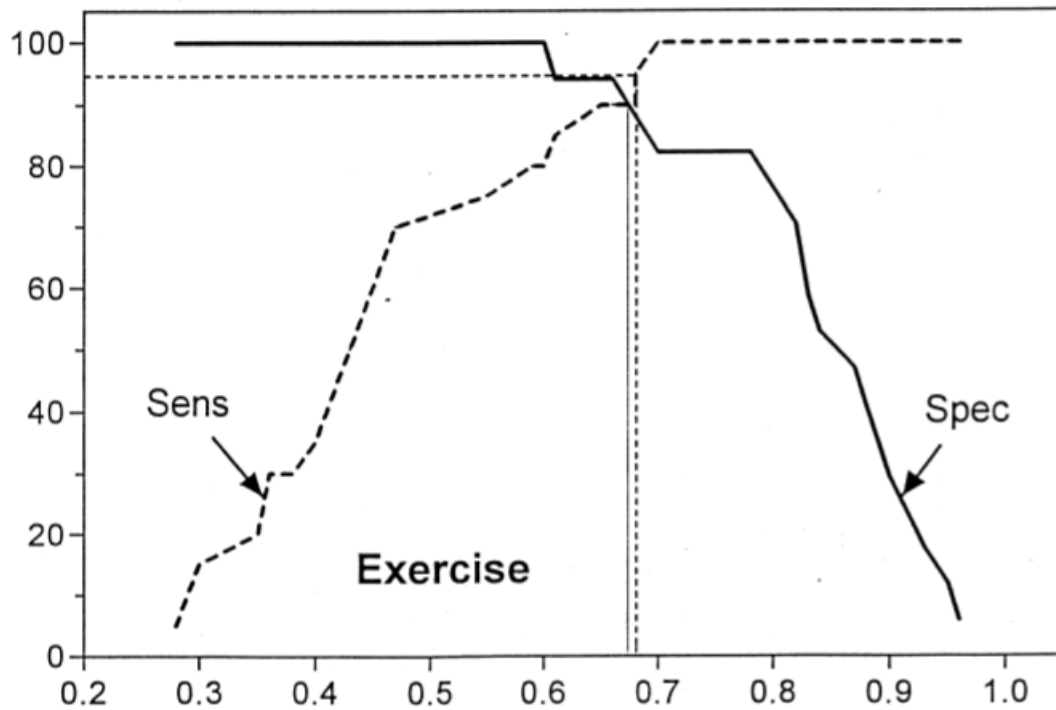
Exercise Test



- N = 45 patients
- Sensitivity 88%, Specificity 100%, PPV 100%, NPV 88%

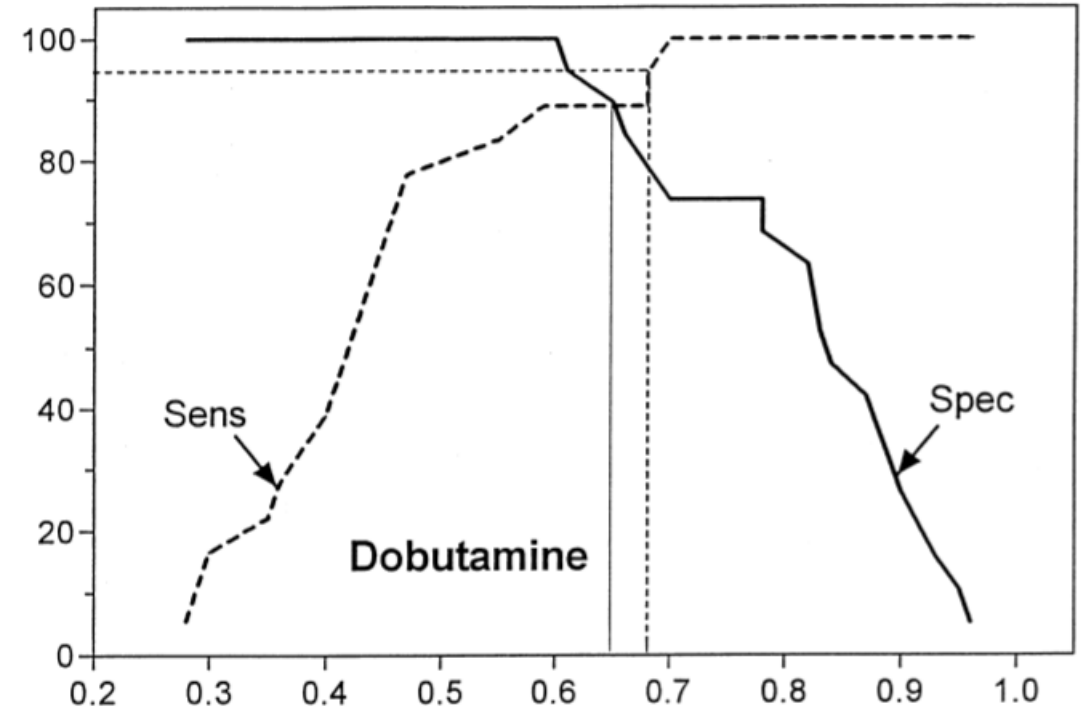
FFR Cutoff Value from Bicycle Exercise Test and Dobutamine Echo

ST Depression



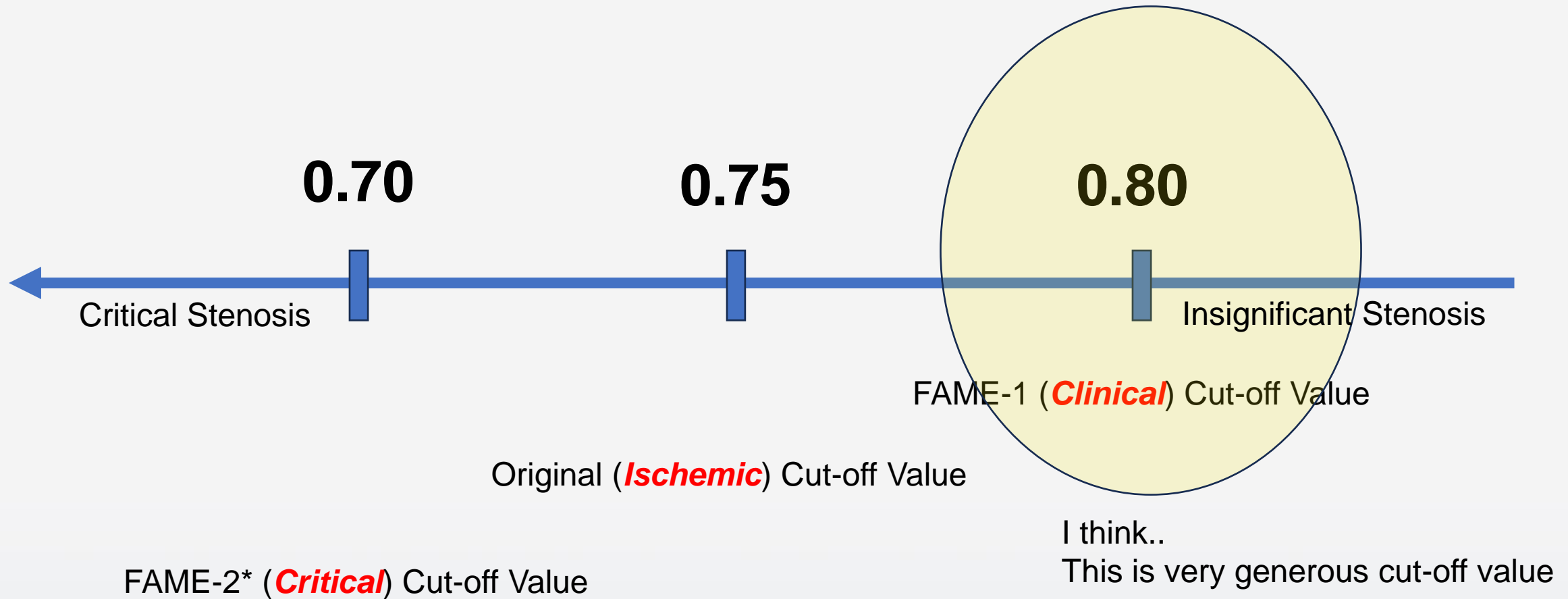
FFR 0.67

Wall Motion Abnormality



FFR 0.65

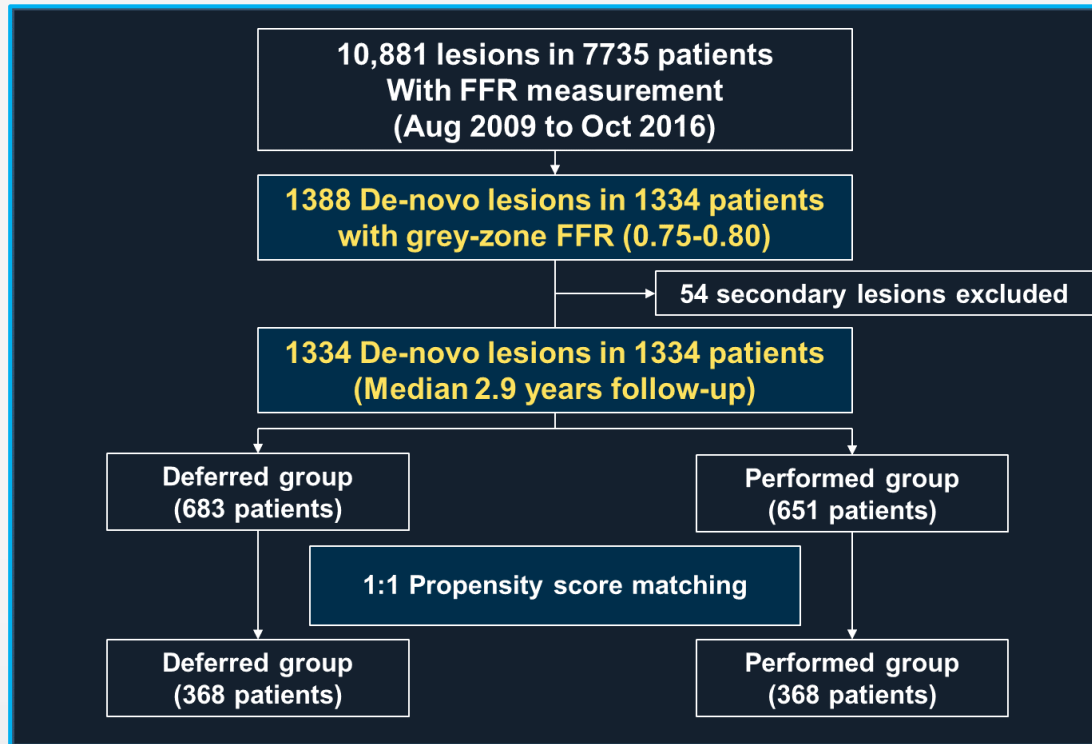
Continuum of FFR Cut-off Value



* Mean FFR value was 0.68

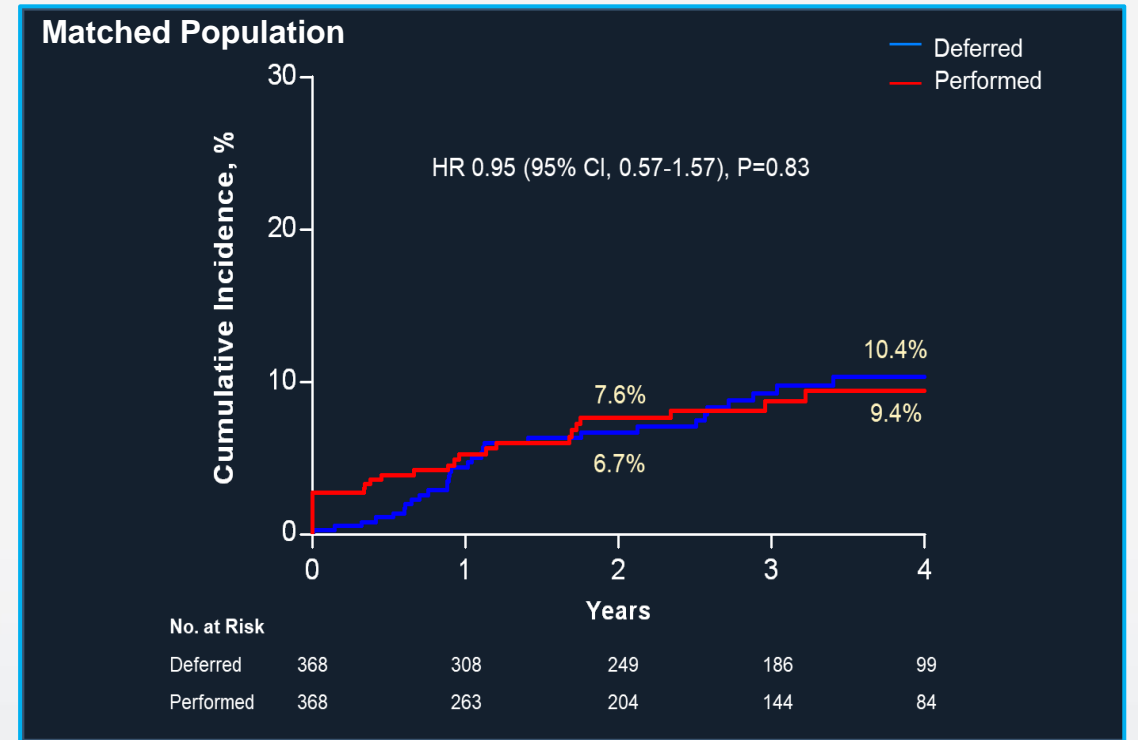
Decision Making in the Grey-Zone FFR

Grey Zone FFR From IRIS-FFR Registry



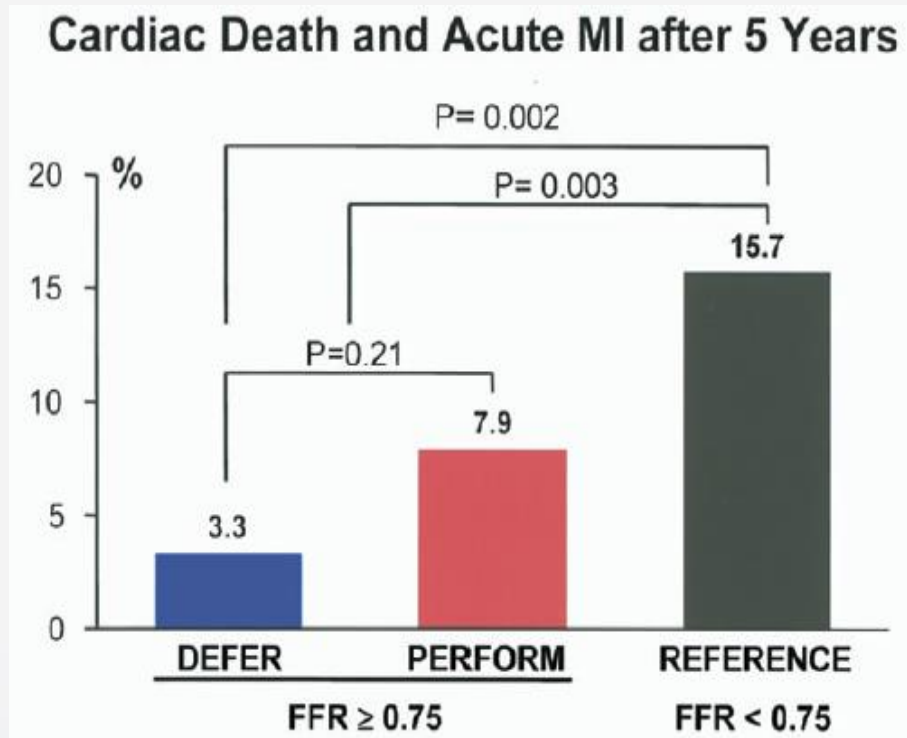
Primary End Point

(Death, TV-MI, Target Vessel Revascularization)

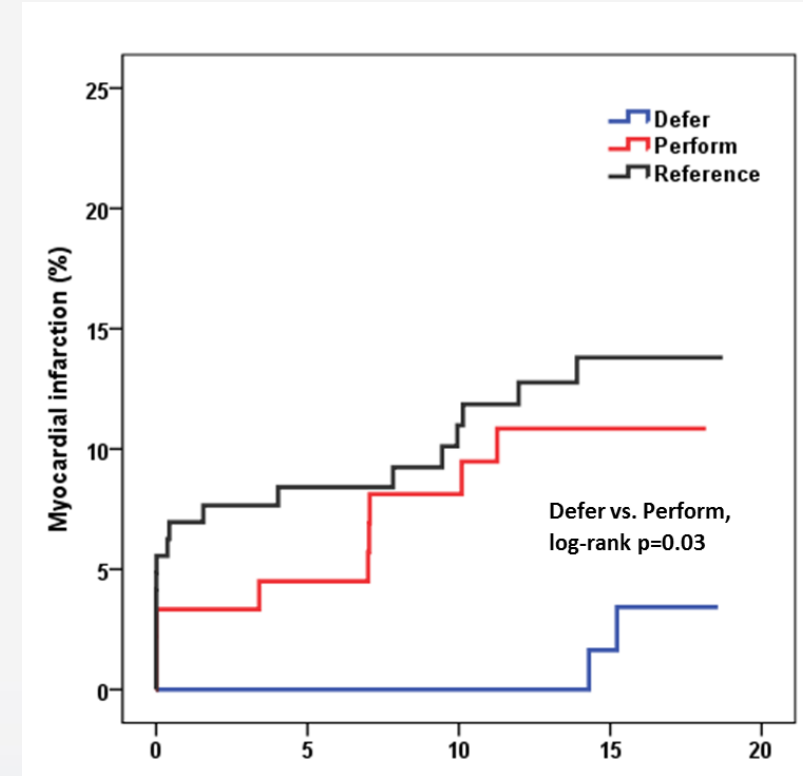


Kang DY et al. Eur Heart J. 2018 May 7;39(18):1610-1619

Deferred Lesion Outcome: DEFER Study



J Am Coll Cardiol 2007;49:2105–11



Eur Heart J. 2015 Dec 1;36(45):3182-8

Deferred Lesion Outcome: FAME-1 Trial

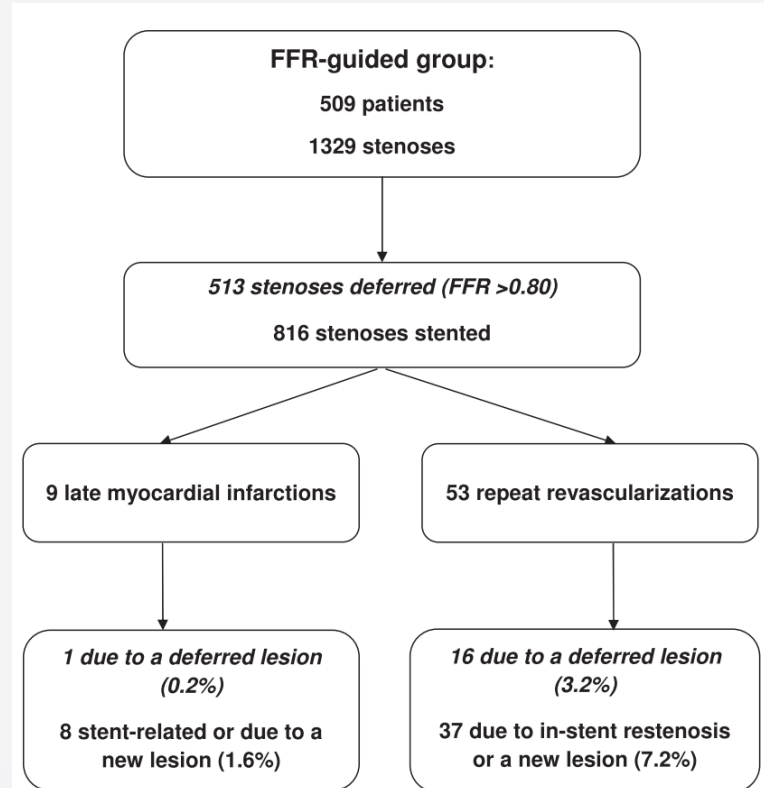


Figure 4 2-Year Outcome of Stenoses in FFR Group Initially Deferred on Basis of FFR >0.80

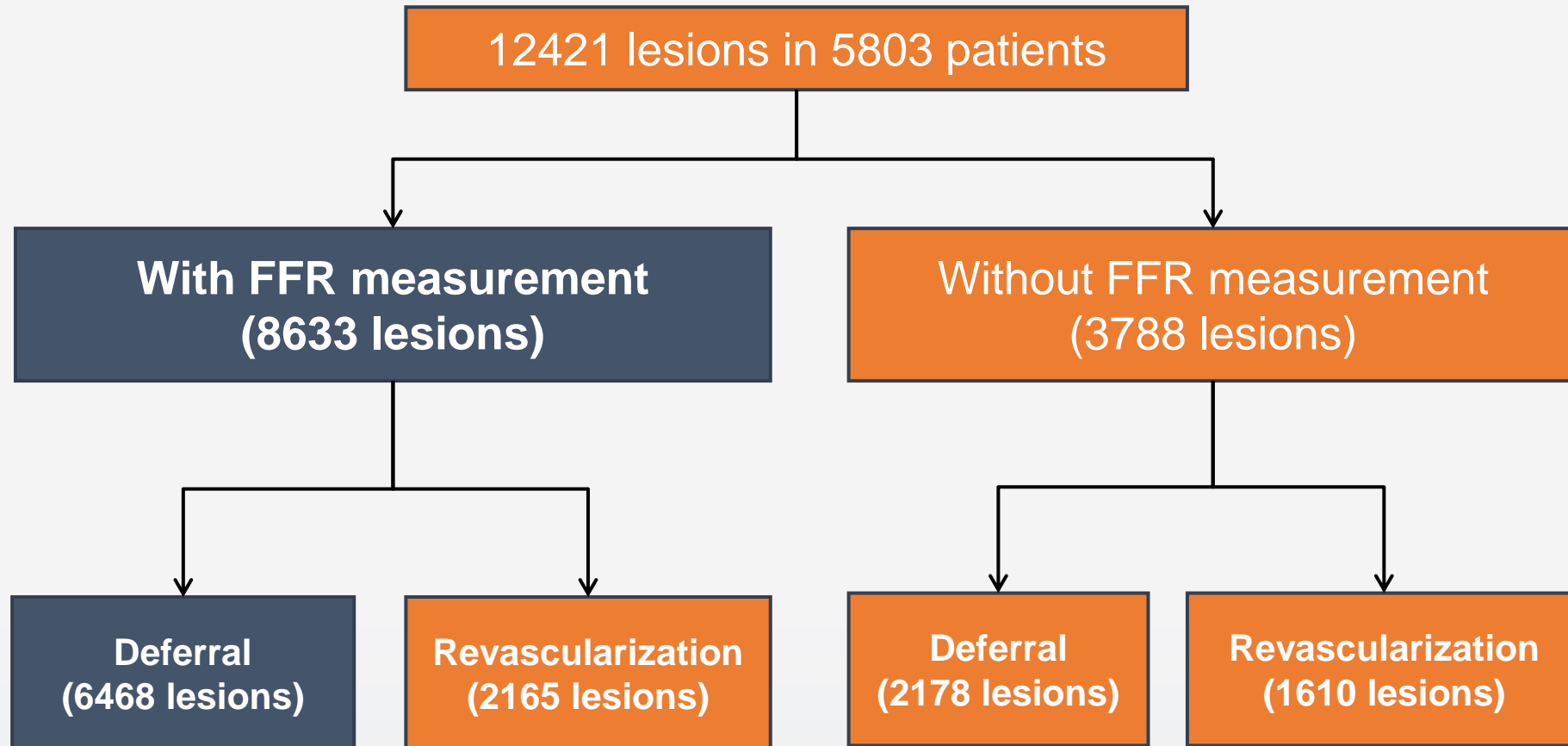
Numbers of late myocardial infarction and repeat revascularization of the stenoses in the fractional flow reserve (FFR) group initially deferred from stenting on the basis of FFR >0.80, and in stenoses in the FFR group that were stented because of FFR ≤0.80.

At 2 Years
Deferred Lesion Related

MI – **0.2%**
RR – 3.2%

J Am Coll Cardiol 2010;56:177–84

IRIS FFR Registry (2009.8-2015.8)



Patient Characteristics

**Stable Angina:
76.3%**

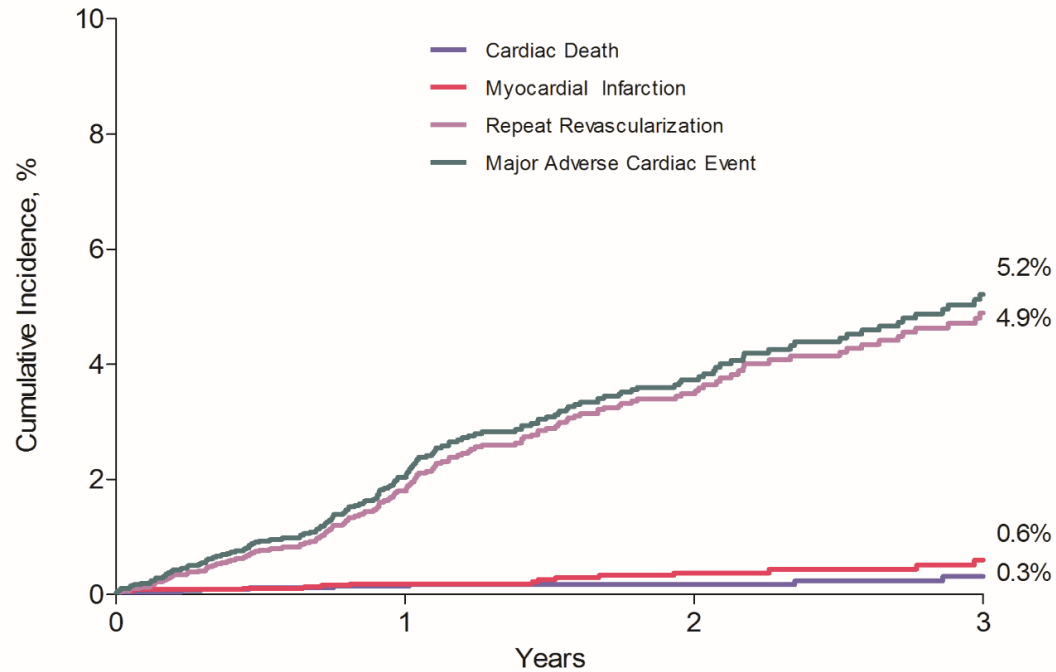
Variables	N=5846
Age	63.6±9.8
Sex (men)	4187 (71.6%)
Diabetes	1807 (30.9%)
Hypertension	3687 (63.1%)
Current smoker	1402 (24.0%)
Hyperlipidemia	3507 (60.0%)
Previous myocardial infarction	378 (6.5%)
Previous PCI	1138 (19.5%)
Previous stroke	345 (5.9%)
Chronic renal failure	119 (2.0%)
Chronic lung disease	125 (2.1%)
Peripheral artery disease	139 (2.4%)
Family history	600 (10.3%)

Lesion Characteristics

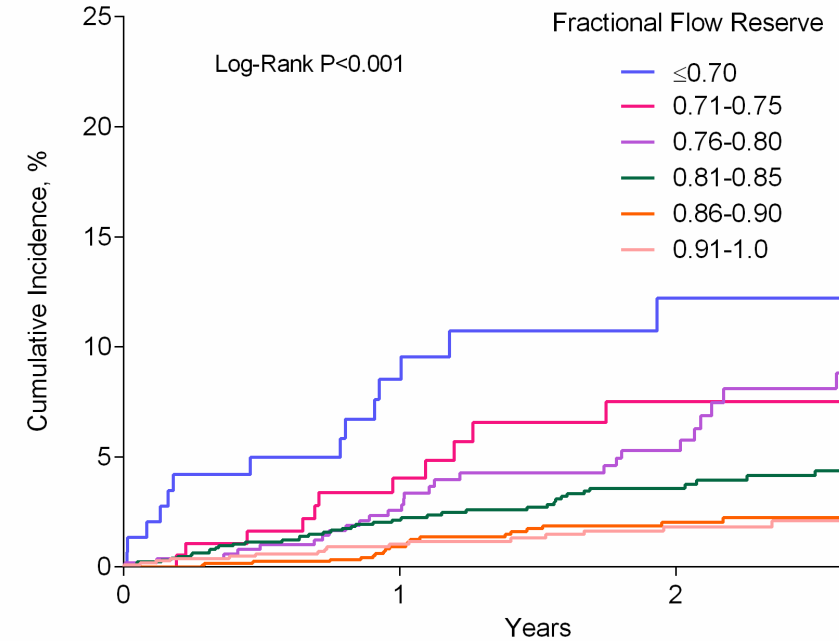
Variables	N=8633
Lesion territory	
Left main	345 (4.1%)
Left anterior descending artery	4372 (50.6%)
Left circumflex artery	2070 (24.0%)
Right coronary artery	1407 (16.3%)
ACC/AHA B2C lesion	4819 (55.8%)
Long lesion (>20mm)	3680 (42.6%)
Moderate to severe calcification	269 (3.1%)
Thrombus containing lesion	63 (0.7%)
Angiographic ulcerated lesion	55 (0.6%)
Diameter stenosis	
30-50%	2659 (30.7%)
50-70%	4057 (47.0%)
70-99%	1927 (22.3%)

Deferred Lesion Outcome

MI: **0.6 %** and RR: 4.9% at 3 years



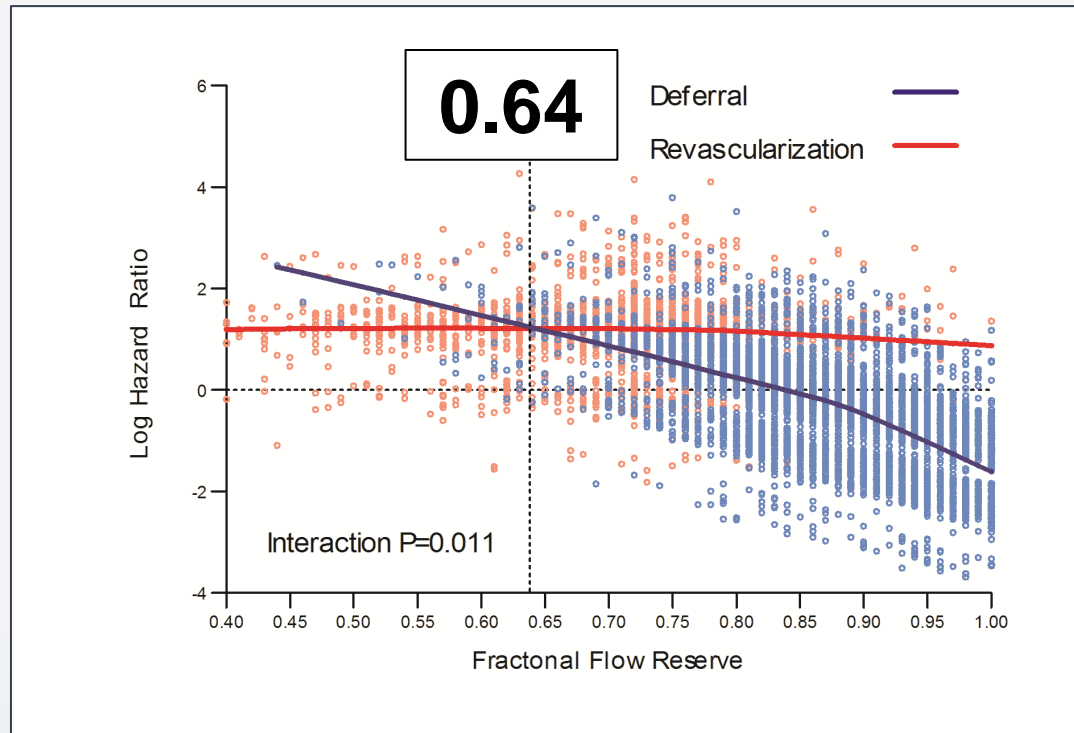
Cardiac Death	4608	3393	2069	1036
Myocardial Infarction	4608	3445	2107	1059
Repeat Revascularization	4608	3337	1998	987
Major Adverse Cardiac Event	4608	3333	1996	987



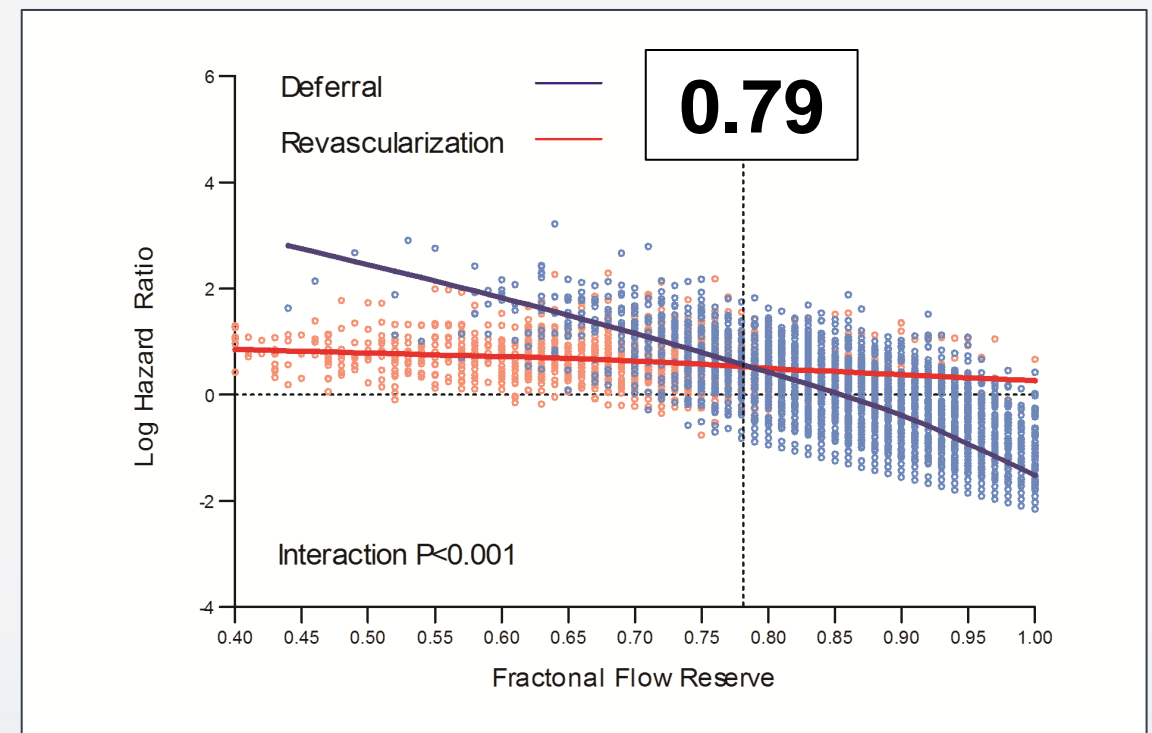
FFR Level	0	1	2	3
≤0.70	148	93	52	27
0.71-0.75	195	140	89	40
0.76-0.80	540	379	216	97
0.81-0.85	1320	953	601	309
0.86-0.90	1329	961	583	292
0.91-1.0	1076	784	482	222

Outcome Derived Revascularization Threshold of FFR

Cardiac Death or MI



Major Adverse Cardiac Events



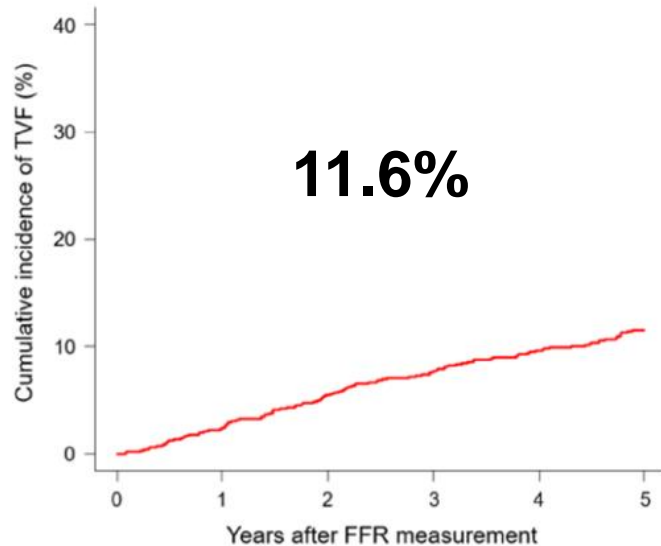
J-Confirm Registry at 5 Years

1263 patients with 1447 lesions from 28 Japanese centers.

TVF

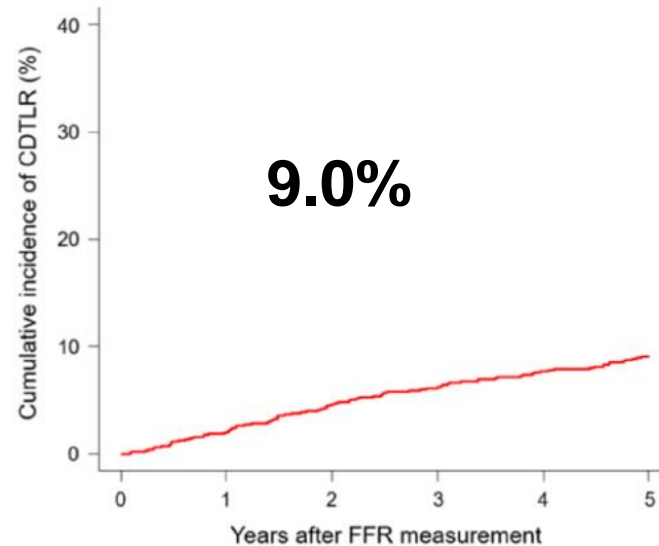
CD-TLR

TV-MI



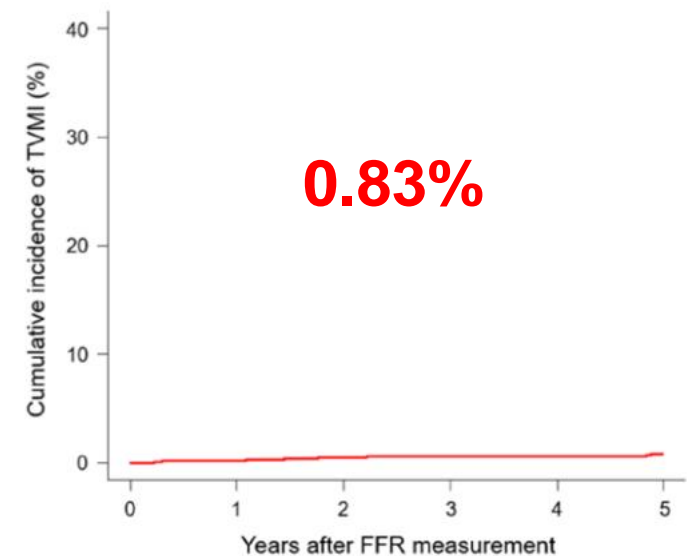
11.6%

Intervals	0	1 Year	2 Years	3 Years	4 Years	5 Years
N of lesions at risk	1447	1391	1306	1215	1133	829
Cumulative incidence	0.0%	2.4%	5.5%	7.6%	9.7%	11.6%



9.0%

Intervals	0	1 Year	2 Years	3 Years	4 Years	5 Years
N of lesions at risk	1447	1384	1289	1196	1113	817
Cumulative incidence	0.0%	2.0%	4.6%	6.2%	7.7%	9.0%



0.83%

Intervals	0	1 Year	2 Years	3 Years	4 Years	5 Years
N of lesions at risk	1447	1418	1366	1286	1210	889
Cumulative incidence	0.0%	0.21%	0.49%	0.57%	0.57%	0.83%

FLAVOUR Trial

TV-MI: **0.3%** at 1 Year

	IVUS group (n=901)			FFR group (n=919)			<i>P</i> value*
	Deferred (n=375)	Revascularized (n=526)	<i>P</i> value	Deferred (n=614)	Revascularized (n=305)	<i>P</i> value	
Vessel-oriented composite outcome†	14 (3.8%)	18 (3.5%)	0.81	25 (4.1%)	11 (3.6%)	0.72	0.77
Cardiac death	6 (1.6%)	5 (1.0%)	0.38	7 (1.2%)	1 (0.3%)	0.21	0.54
Target vessel MI	0 (0%)	2 (0.4%)	0.23	2 (0.3%)	1 (0.3%)	0.99	0.27
Target vessel revascularization	8 (2.2%)	12 (2.3%)	0.88	18 (3.0%)	10 (3.3%)	0.80	0.44
Target lesion revascularization	7 (1.9%)	8 (1.5%)	0.69	14 (2.3%)	7 (2.3%)	0.99	0.65

Circ Cardiovasc Interv. 2023;16:e013308

1-Year Outcomes of 8,579 Patients with Deferred Lesions

Data from IRIS-FFR, R3F, POST-IT, DEFINE FLAIR, SWEDEHEART

TABLE 2 Primary and Secondary Endpoints at 1 Year in Deferred Group According to Clinical Presentation (ACS Versus SAP)

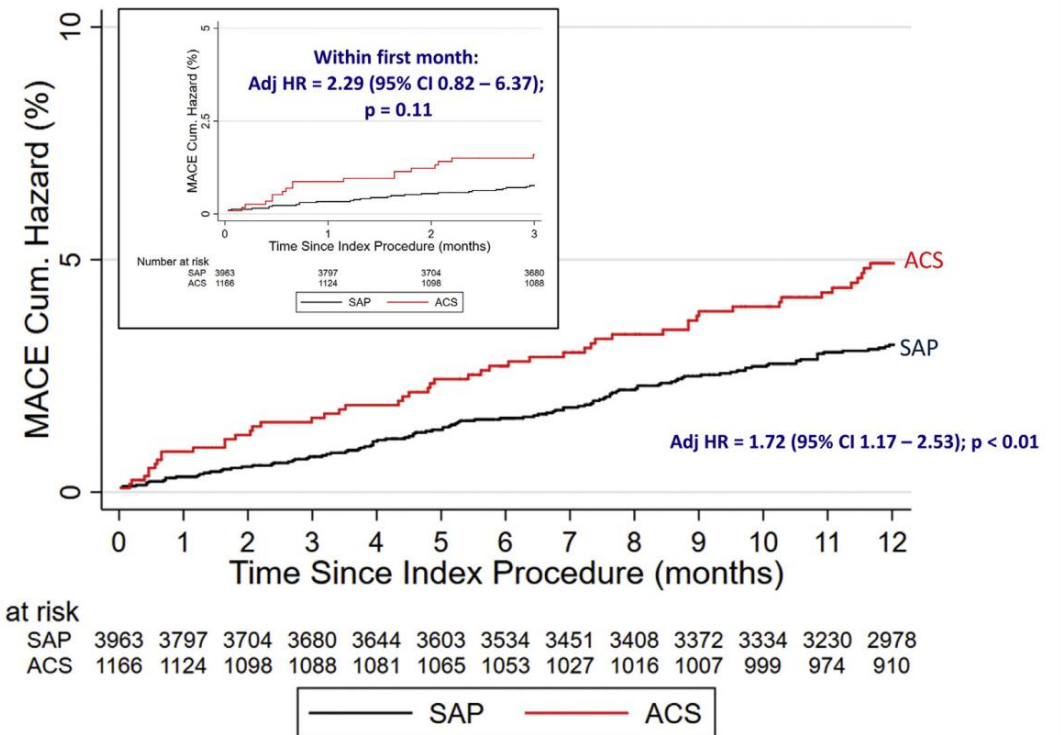
	ACS (n = 1,166)	SAP (n = 3,963)	Adjusted HR (95% CI)*	p Value
MACE	52 (4.46)	112 (2.83)	1.72 (1.17-2.53)	<0.01
Death	10 (0.86)	22 (0.56)	1.60 (0.68-3.79)	0.28
Myocardial infarction	10 (0.86)	18 (0.45)	1.80 (0.76-4.27)	0.18
Unplanned revascularization	39 (3.34)	81 (2.04)	1.81 (1.09-3.00)	0.02

Values are n (%). Results are presented for mixed-effect Cox models allowing for patients nested within studies, and a random effect for the effect of ACS versus SAP, in addition to fixed effects for the other covariates. *Adjusted for age, sex, diabetes, current smoking, hypertension, hyperlipidemia, and previous myocardial infarction.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); other abbreviations as in Table 1.

MI: **0.86%** in ACS and **0.45%** in sAP at 1 Year

FIGURE 2 Primary Endpoint: MACE in Deferred Group



Cumulative hazard curve for major adverse cardiac event(s) (MACE) after deferral on the basis of nonischemic fractional flow reserve >0.80 by clinical presentation. The inset depicts the same curve (adjusted hazard ratio [Adj HR] for clinical presentation of MACE) focusing on the first 3 months. ACS = acute coronary syndromes; CI = confidence interval; Cum. = cumulative; SAP = stable angina pectoris.

Deferred Lesion Intervention

721 patients with 882 coronary lesions

- **The rate of AMI** due to a previously deferred lesion within the first year after FFR assessment was **0.8%**.
- Of the 155 DLIs, 101 lesions (65%) underwent urgent revascularization: 30 DLIs (19%) were performed for AMI, of which 6 (4%) were for STEMI, and 24 (15%) were for NSTEMI.

Table 5 Multivariable predictors and 1-year β regression coefficients for freedom from DLI in the final^a model

	HR (95% CI)	P-value	β coefficients
Age (per 1-year increase)	0.98 (0.97–0.99)	0.005	−0.02075
Current/former smoker	1.49 (1.04–2.14)	0.03	0.39710
History of CAD or prior PCI	1.62 (1.05–2.49)	0.03	0.48086
Creatinine (per 1 mg/dL increase)	1.15 (1.08–1.22)	<0.001	0.13681
Multi-vessel CAD	1.68 (1.09–2.58)	0.02	0.51777
FFR value (per 0.05 unit decrease)	1.21 (1.03–1.42)	0.02	−3.81032

^aThe model was reduced using a stepwise variable selection technique. For prediction purposes, the 1-year baseline estimate of freedom from DLI for a patient with all covariates set to zero or to the reference group is 0.169. All abbreviations as shown in Tables 1 and 2.

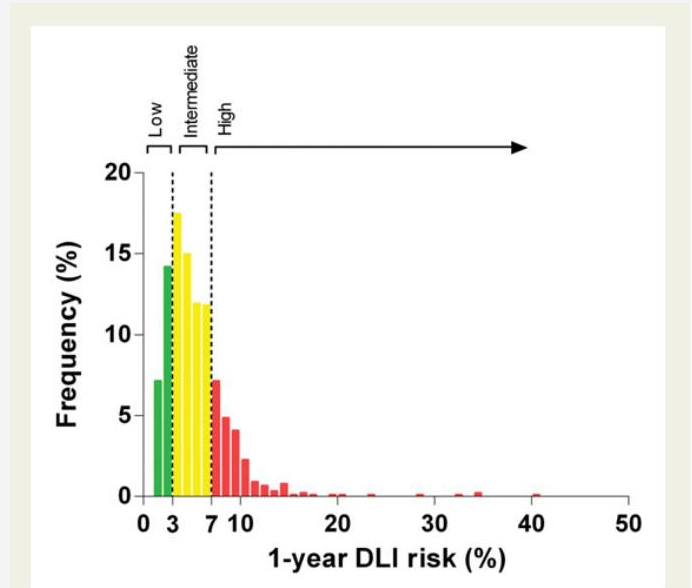


Figure 3 Variability in the predicted 1-year deferred lesion intervention risk using the final algorithm. The frequency of predicted 1-year deferred lesion intervention risk calculated using the final algorithm for each deferred lesion in the study, ranging from 1 to 40%. Deferred lesion intervention risk at 1 year was stratified into three categories based on quintiles of predicted risk: low (<3% = lowest quintile), intermediate (3–7% = 3 middle quintiles), and high risk (>7% = highest quintile).

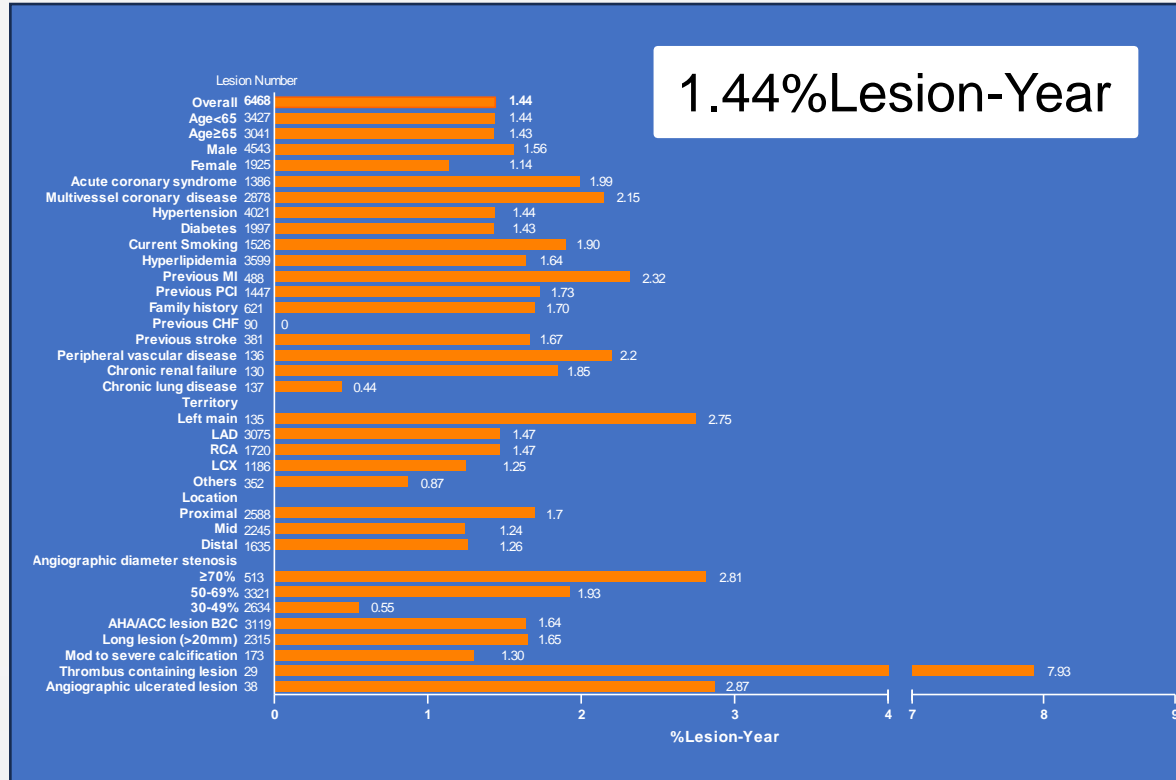
J-Confirm Registry at 5 Years

1263 patients with 1447 lesions from 28 Japanese centers.

Variables	Univariable				Multivariable*			
	HR	95% CI		P value	HR	95% CI		P value
FFR (per 0.01 decrease)	1.06	1.03	1.08	<0.001	1.05	1.02	1.08	<0.001
Hemodialysis	2.60	1.39	4.86	0.003	2.68	1.38	5.22	0.004
Target lesion of left main coronary artery	2.73	1.36	5.5	0.005	3.05	1.39	6.67	0.005
Male sex	1.41	0.89	2.22	0.14	1.73	1.02	2.94	0.044
Prior percutaneous coronary intervention	1.60	1.09	2.35	0.016	1.59	1.00	2.53	0.048
Target lesion of right coronary artery	1.29	0.90	1.84	0.16	1.43	0.96	2.14	0.08

IRIS FFR Registry (2009.8-2015.8)

Incidence Rate of Deferred Lesion Failure

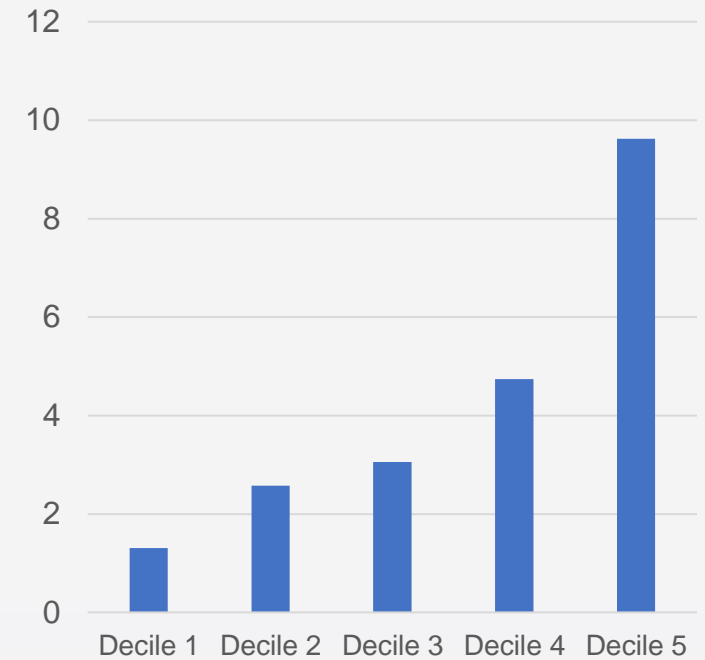
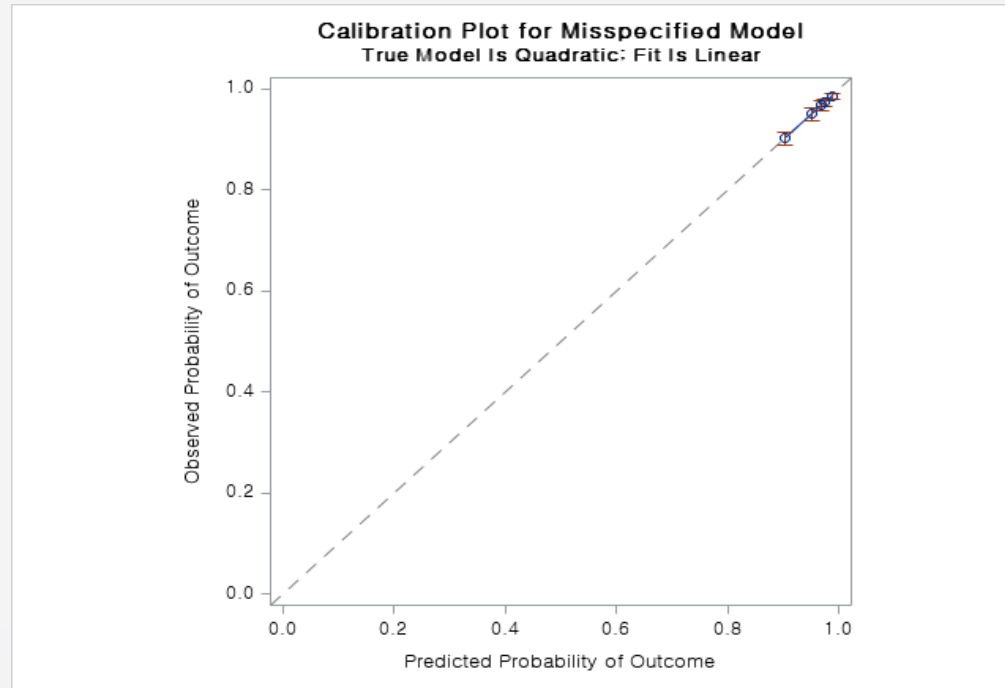


	HR (95% CI)	P value
FFR (by increase of 0.01)	0.94 (0.93-0.96)	<0.001
Multivessel CAD	1.66 (1.19-2.33)	0.003
Thrombus containing lesion	5.46 (1.98-15.0)	0.001
Diameter stenosis		<0.001
30-50%	1 (reference)	
50-70%	2.20 (1.41-3.44)	<0.001
>70%	2.50 (1.41-4.44)	0.002

IRIS FFR Registry (N=9737, 2010-2021):

DEFER SCORE for 5 Yr TV-MI (n=43, 0.4%) and TVR (n=406, 4.2%)

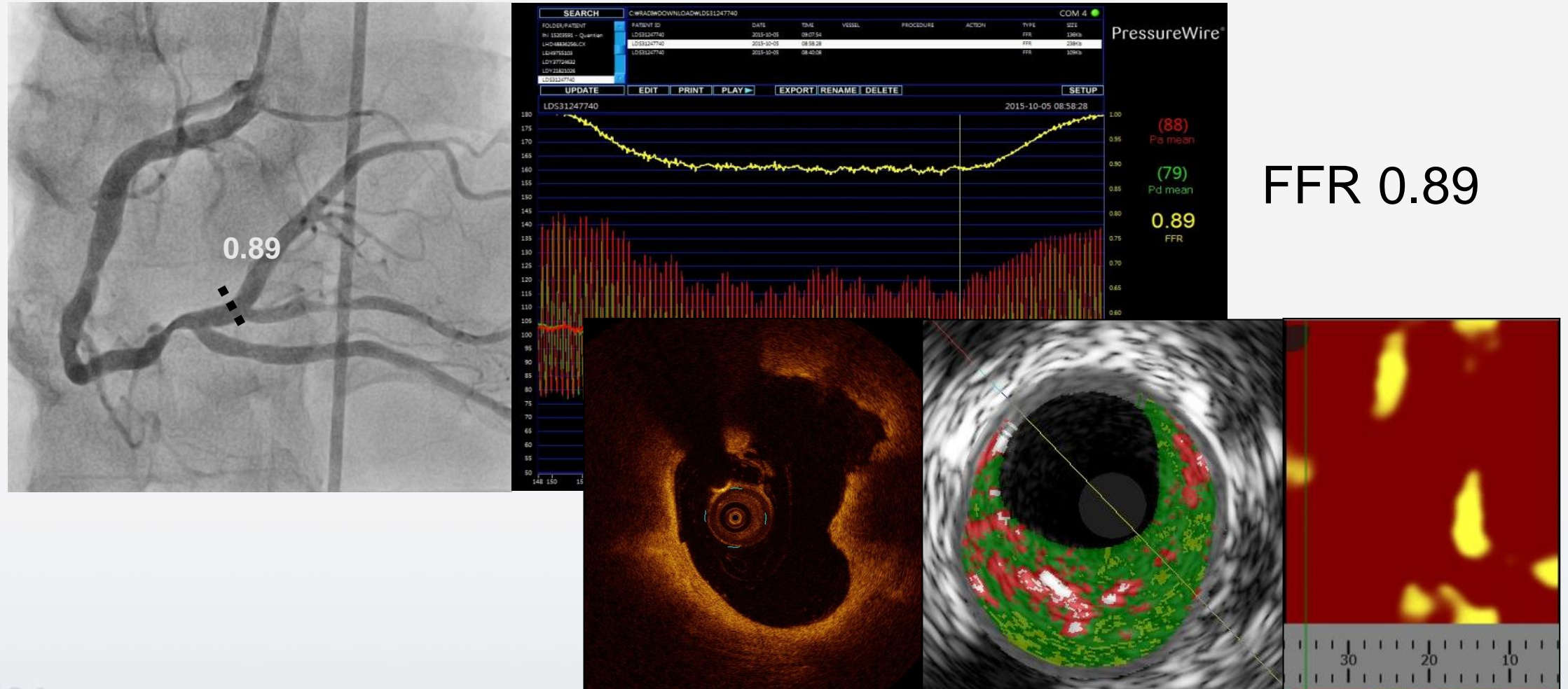
Variable		Score
Age	<60	4
	60-69	3
	70-79	2
	≥80	0
Smoking	Yes	1
	No	0
History of PCI	Yes	2
	No	0
Acute coronary syndrome	Yes	2
	No	0
Vessel_RCA	Yes	2
	No	0
Diameter stenosis	≥50%	3
	<50%	0
FFR	≤0.80	4
	0.81-0.85	2
	≥0.86	0



Unpublished Data

Counterargument

55 y/o male, Effort Chest Pain



Plaque Characteristics and Deferred Lesion (1)

High-Risk Plaque Characteristics

- Minimum lumen area <math><4\text{ mm}^2</math>
- Plaque burden $\geq 70\%$
- Low attenuating plaque
- Positive remodeling
- Napkin-ring sign
- Spotty calcification

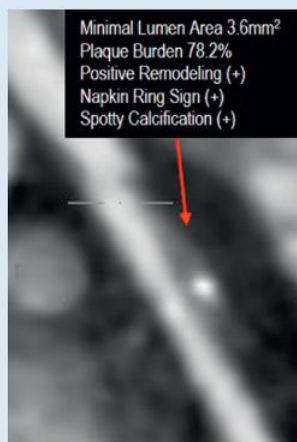


TABLE 3 Vessel-Oriented Clinical Outcomes According to FFR and HRPC Among Deferred Vessels

	FFR >0.80		p Value	FFR ≤0.80		p Value	Interaction p Value
	<3 HRPC*	≥3 HRPC		<3 HRPC	≥3 HRPC		
n	514/553 (92.9%)	39/553 (7.1%)		45/65 (69.2%)	20/65 (30.8%)		
Vessel-related ischemia-driven revascularization	2.7% (10)	12.6% (4)	0.002	13.1% (4)	17.2% (3)	0.545	0.017
Vessel-related myocardial infarction	1.8% (8)	2.7% (1)	0.613	0.0% (0)	5.0% (1)	0.143	0.942
Cardiac death	1.6% (6)	2.8% (1)	0.475	4.5% (1)	0.0% (0)	0.480	0.816
Vessel-oriented composite outcome†	4.3% (16)	15.0% (5)	0.004	17.0% (5)	17.2% (3)	0.754	0.031

Values are n/N (%) or % (n). The cumulative incidences of clinical outcomes were presented as Kaplan-Meier estimates. p values were log-rank or Breslow p value in survival analysis. *High-risk plaque characteristics: 1) plaque burden $\geq 70\%$; 2) MLA <math><4\text{ mm}^2</math>; 3) positive remodeling; 4) low attenuation plaque; 5) napkin ring sign; and 6) spotty calcification. For this analysis, 179 lesions with no measurable plaque exist by coronary CTA were included in the <math><3</math> HRPC group. †Vessel-oriented composite outcome included cardiac death, vessel-related myocardial infarction, or vessel-related ischemia-driven revascularization.

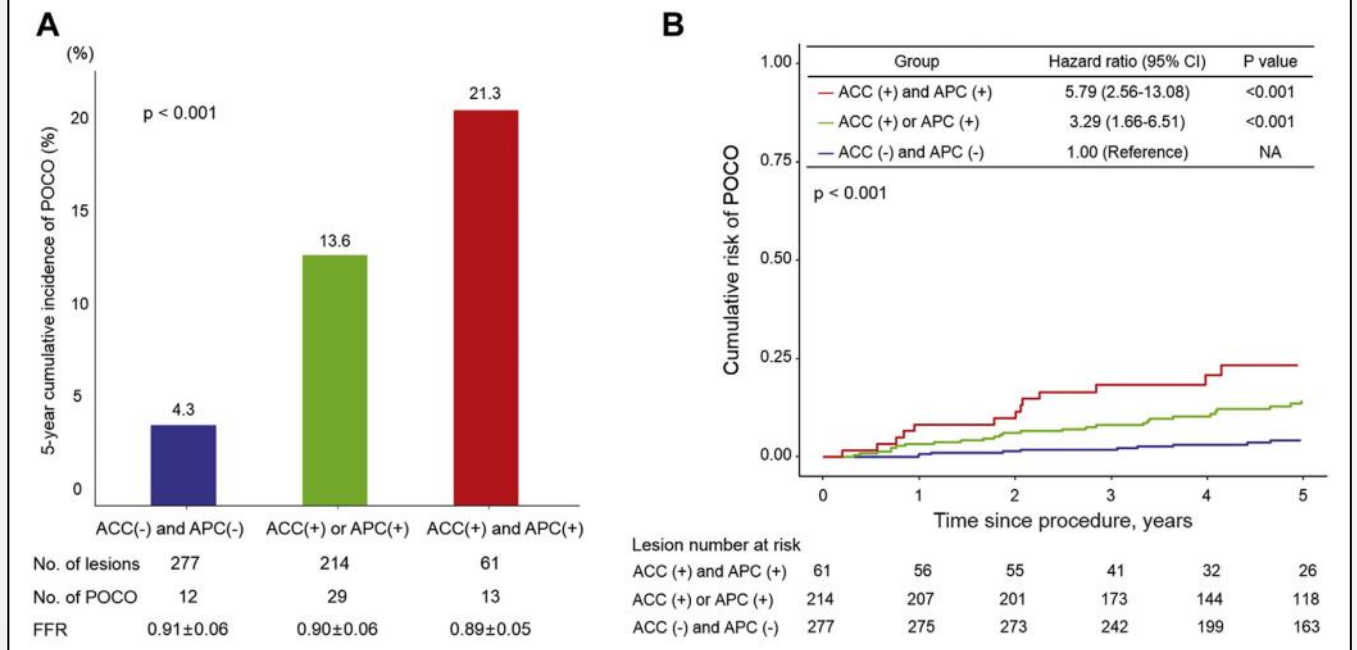
Abbreviations as in [Tables 1 and 2](#).

Plaque Characteristics and Deferred Lesion (2)

459 patients with 552 intermediate lesions with IVUS and FFR > 0.80

TABLE 3 Predictors for a POCO and VOCCO

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Predictors of POCO				
Diabetes mellitus	3.79 (2.08-6.90)	<0.001	3.50 (1.86-6.57)	<0.001
LVEF ≤40%	5.71 (1.94-16.86)	0.002	4.80 (1.57-14.63)	0.006
Positive remodeling	2.43 (1.30-4.56)	0.006	2.04 (1.03-4.03)	0.041
Plaque burden ≥70%	1.74 (1.06-2.87)	0.029		
Predictors of VOCCO				
Diabetes mellitus	3.64 (1.61-8.27)	0.002	3.34 (1.40-7.99)	0.007
Positive remodeling	3.14 (1.37-7.20)	0.007	2.56 (1.10-5.94)	0.029
Plaque burden ≥70%	2.02 (0.96-4.24)	0.064		



ACC = Adverse Clinical Characteristics, APC = Adverse Plaque Characteristics

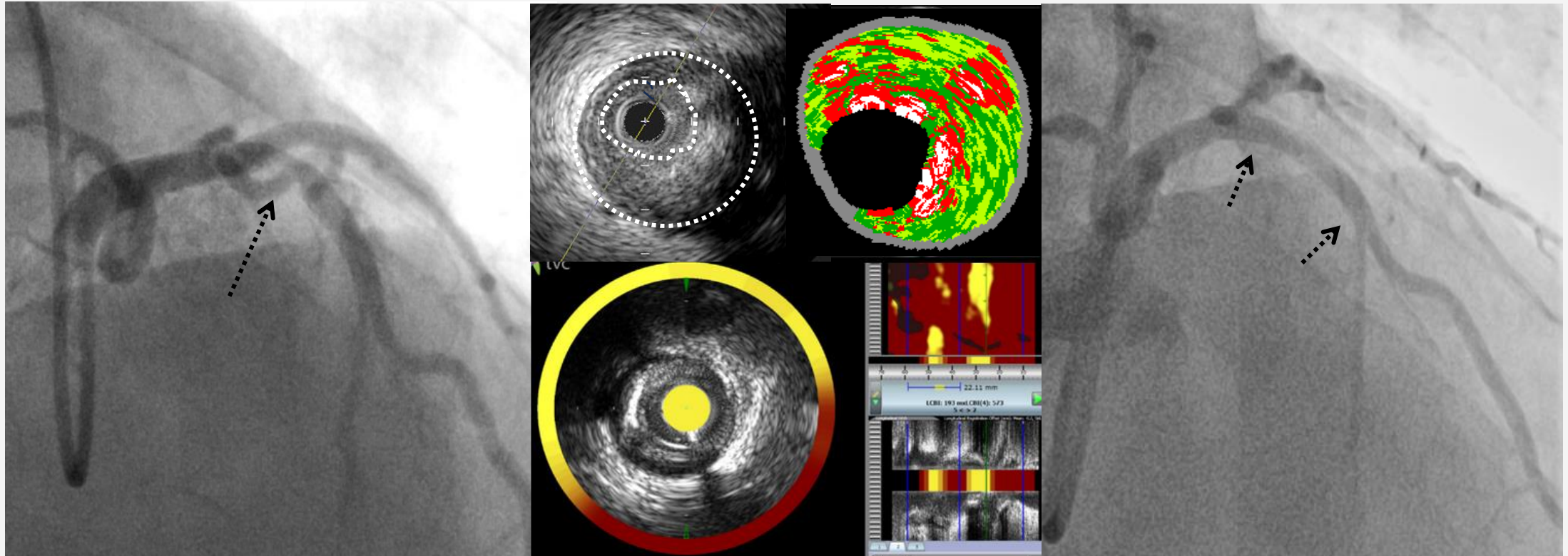
Coronary Stenosis (>50%) with Negative FFR (≥ 0.80) and meeting two of the following (Imaging defined VP)

1. $MLA \leq 4.0\text{mm}^2$
2. Plaque Burden $>70\%$
3. TCFA by OCT or RF-IVUS
4. Lipid-Rich Plaque by NIRS ($\max LCBI_{4\text{mm}} > 315$)

Preventive PCI + OMT
N=800

OMT alone
N=800

Primary endpoint : Target Vessel Failure at 2 years
(composite of death from cardiac cause, target-vessel MI, ischemic-driven target vessel revascularization, or unplanned hospitalization due to unstable or progressive angina)



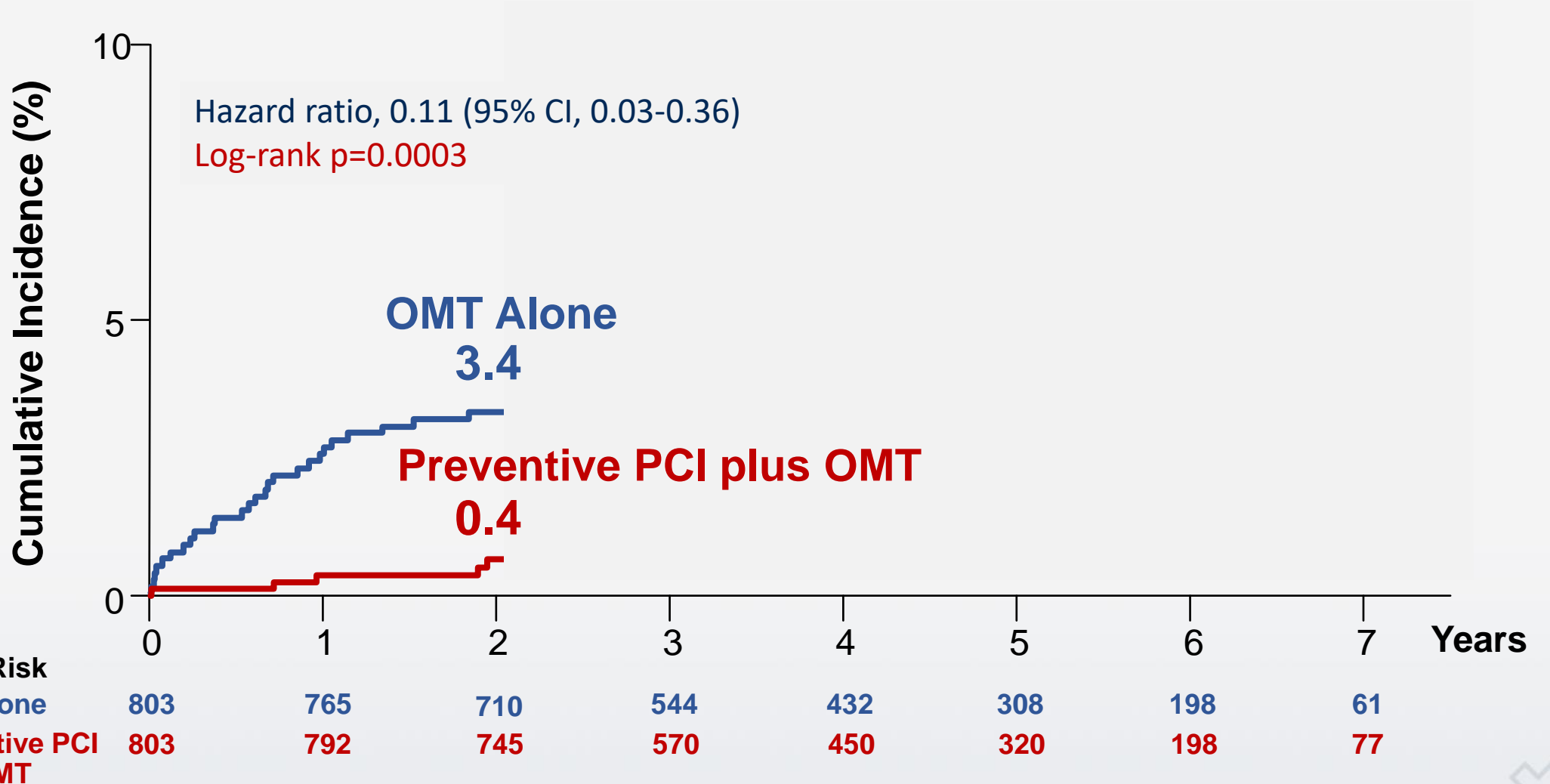
Diameter stenosis 70%,
FFR 0.83

MLA 2.11 mm²
Plaque burden 79%
TCFA by RF-IVUS
maxLCBI_{4mm} 573

Absorb (BVS)
3.5 mm x 18 mm

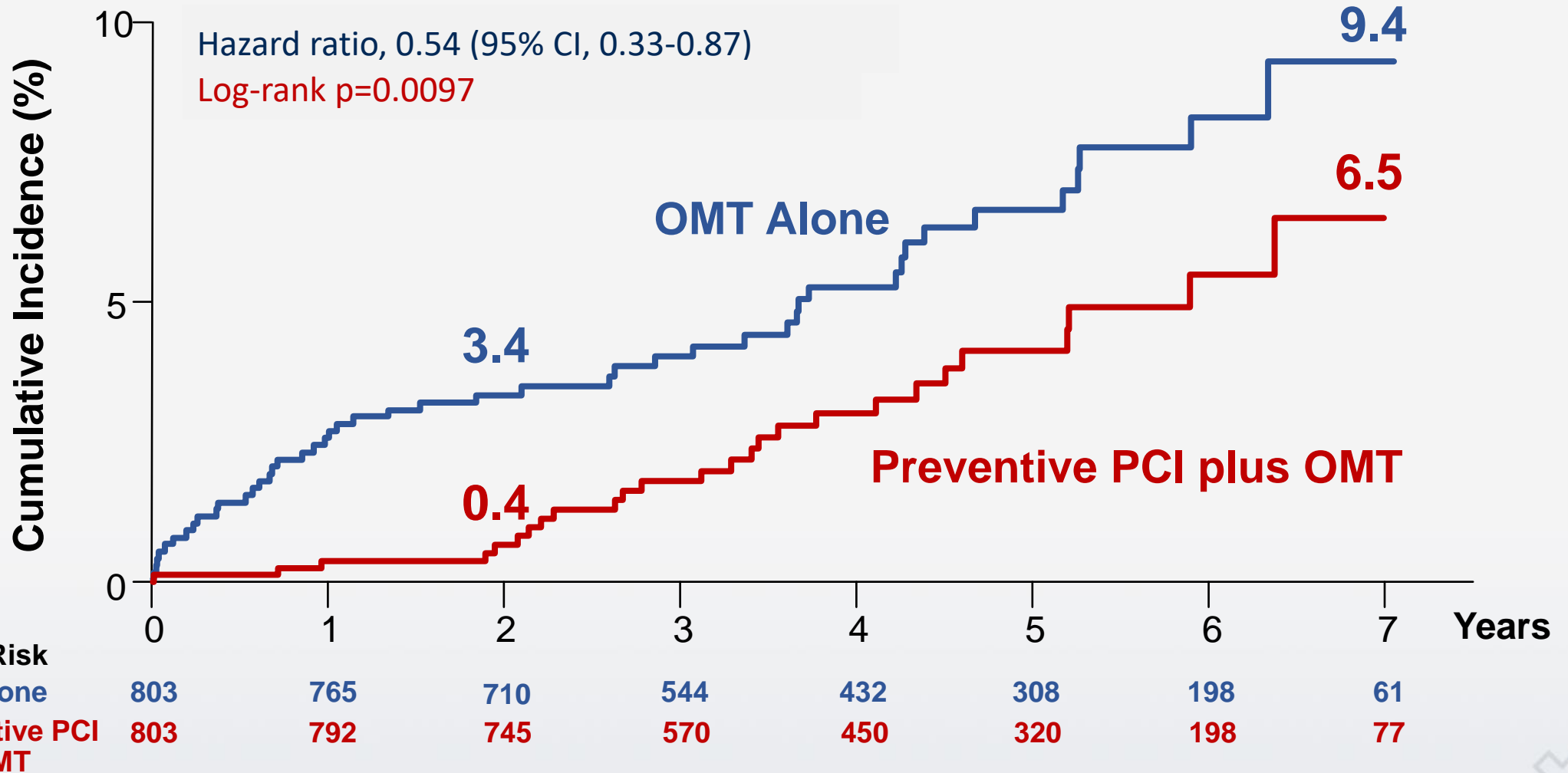
Primary Composite Outcome: Target Vessel Failure at 2 Year F/U

PREVENT



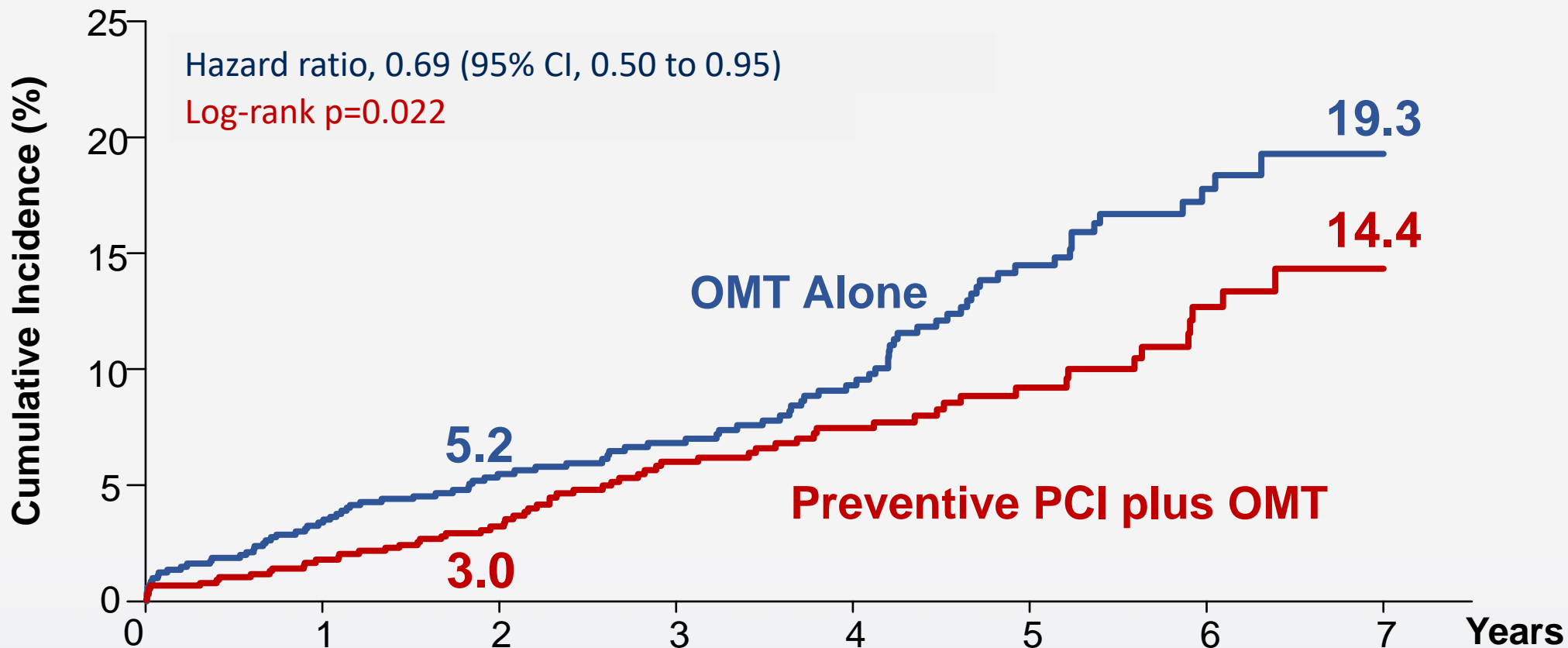
Primary Composite Outcome: Target Vessel Failure at 7 Year F/U

PREVENT



Patient-Oriented Composite Outcome: Death from Any cause, Any MI, or Any RR

PREVENT



No. at Risk	0	1	2	3	4	5	6	7
OMT Alone	803	761	700	536	424	297	190	58
Preventive PCI Plus OMT	803	781	728	551	431	302	187	72

Individual Components of the Primary Composite Outcome

PREVENT

Endpoints	Preventive PCI plus OMT (N=803)	OMT alone (N=803)	Difference in event rates (95% CI)	Hazard ratio (95% CI)
Primary composite outcome				0.54 (0.33 to 0.87)
At 2 years‡	3 (0.4%)	27 (3.4%)	-3.0 (-4.4 to -1.8)	0.11 (0.03 to 0.36)
At 4 years	17 (2.8%)	37 (5.4%)	-2.6 (-4.7 to -0.4)	
At 7 years	26 (6.5%)	47 (9.4%)	-2.9 (-7.3 to 1.5)	
Death from cardiac causes				0.87 (0.31 to 2.39)
At 2 years	1 (0.1%)	6 (0.8%)	-0.6 (-1.3 to 0.02)	
At 4 years	5 (0.8%)	7 (0.9%)	-0.1 (-1.1 to 0.9)	
At 7 years	7 (1.4%)	8 (1.3%)	0.1 (-1.4 to 1.5)	
Target-vessel related MI				0.62 (0.20 to 1.90)
At 2 years	1 (0.1%)	6 (0.8%)	-0.6 (-1.3 to 0.02)	
At 4 years	4 (0.6%)	7 (10%)	-0.3 (-1.3 to 0.6)	
At 7 years	5 (1.0%)	8 (1.4%)	-0.3 (-1.7 to 1.1)	

Event rates (%) shown are Kaplan–Meier estimates in the intention-to-treat population.

Individual Components of the Primary Composite Outcome

PREVENT

Endpoints	Preventive PCI plus OMT (N=803)	OMT alone (N=803)	Difference in event rates (95% CI)	Hazard ratio (95% CI)
<i>Ischemia-driven target-vessel revascularization</i>				0.44 (0.25 to 0.77)
At 2 years	1 (0.1%)	19 (2.4%)	-2.3 (-3.4 to -1.2)	
At 4 years	10 (1.7%)	29 (4.4%)	-2.7 (-4.6 to -0.8)	
At 7 years	17 (4.9%)	38 (8.0%)	-3.2 (-7.4 to 1.1)	
<i>Hospitalization for unstable or progressive angina</i>				0.19 (0.06 to 0.54)
At 2 years	1 (0.1%)	12 (1.5%)	-1.4 (-2.3 to -0.5)	
At 4 years	4 (0.7%)	16 (2.4%)	-1.7 (-3.0 to -0.4)	
At 7 years	4 (0.7%)	21 (4.9%)	-4.2 (-7.17 to -1.4)	

Summary

Simply,

- FFR 0.80 is very generous cut-off for “**DEFER**”.
- Deferred lesion related MI is very rare (<1%).
- “**DEFER**” is safe and good even after PREVENT trial.