Fractional Flow Reserve After Coronary Intervention

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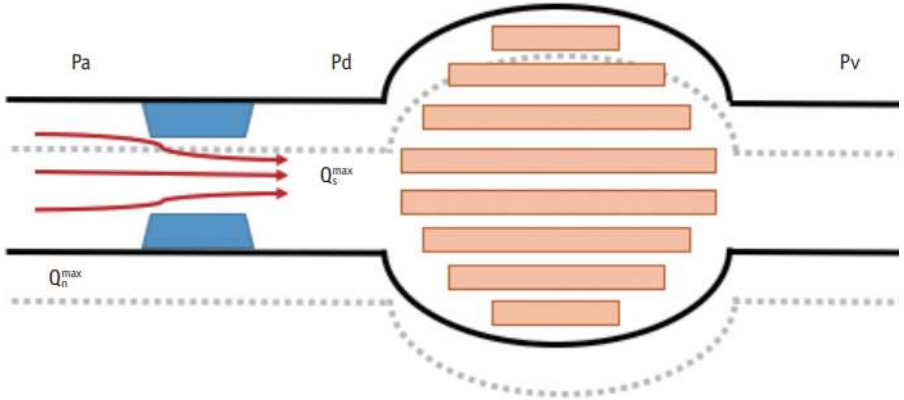
Disclosure

- I, **Doyeon Hwang**, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Fractional Flow Reserve

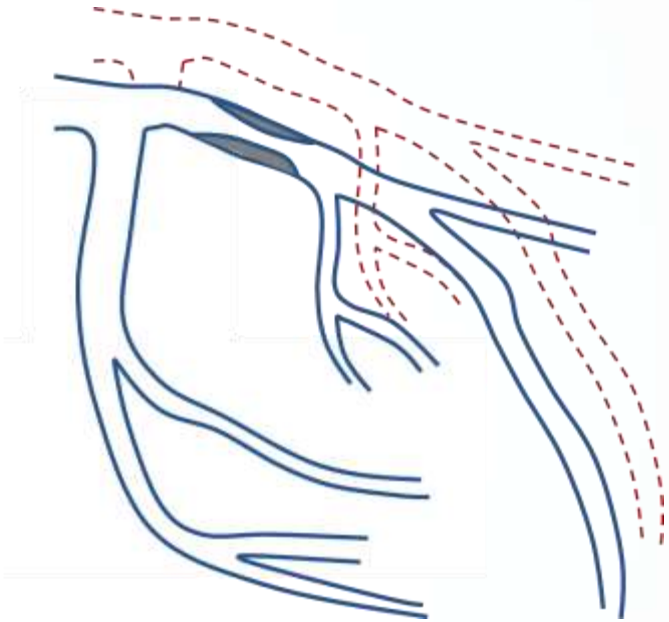
Surrogate marker for myocardial ischemia

Under Maximal Hyperemia



Q^{N}_{max}

Q^{S}_{max}



Q(flow)=Pressure/Resistance

$$FFR = \frac{\text{Maximum flow in presence of stenosis}}{\text{Normal maximum flow}} = \frac{Q^{S}_{max}}{Q^{N}_{max}} = \frac{(Pd-Pv)/R}{(Pa-Pv)/R} = \frac{\text{Distal Pr } (P_d)}{\text{Proximal Pr } (P_a)}$$

Hwang et al. Korean J Radiol. 2016;17(3):307-20.

Fractional Flow Reserve

Standard invasive physiologic index for guiding revascularization

- Robust scientific evidence
  - Various Major clinical trials (DEFER, FAME 1, FAME 2, FAMOUS-NSTEMI)
  - Around 5,000 studies has been published.

2018 European guideline

Recommendations on functional testing and intravascular imaging for lesion assessment

Recommendations	Class[a]	Level[b]
When evidence of ischaemia is not available, FFR or iwFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis.[15,17,18,39]	I	A
FFR-guided PCI should be considered in patients with multivessel disease undergoing PCI.[29,31]	IIa	B

2021 American guideline

Recommendations for the Use of Coronary Physiology to Guide Revascularization With PCI
Referenced studies that support the recommendations are summarized in Online Data Supplement 5.

COR	LOE	Recommendations
1	A	1. In patients with angina or an anginal equivalent, undocumented ischemia, and angiographically intermediate stenoses, the use of fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) is recommended to guide the decision to proceed with PCI.[1-6]
3: No benefit	B-R	2. In stable patients with angiographically intermediate stenoses and FFR >0.80 or iFR >0.89, PCI should not be performed.[7-10]

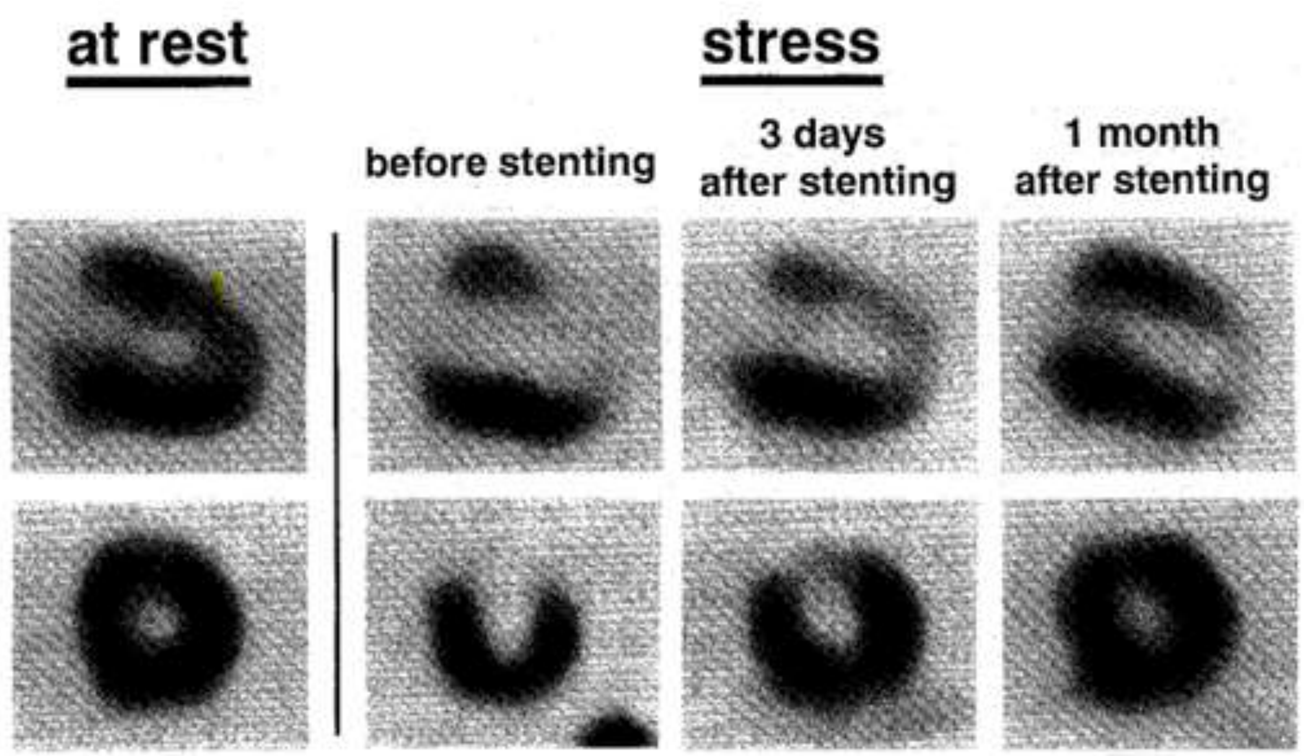
The clinical studies on FFR have been focused on its prognostic value and treatment decision-making before PCI.

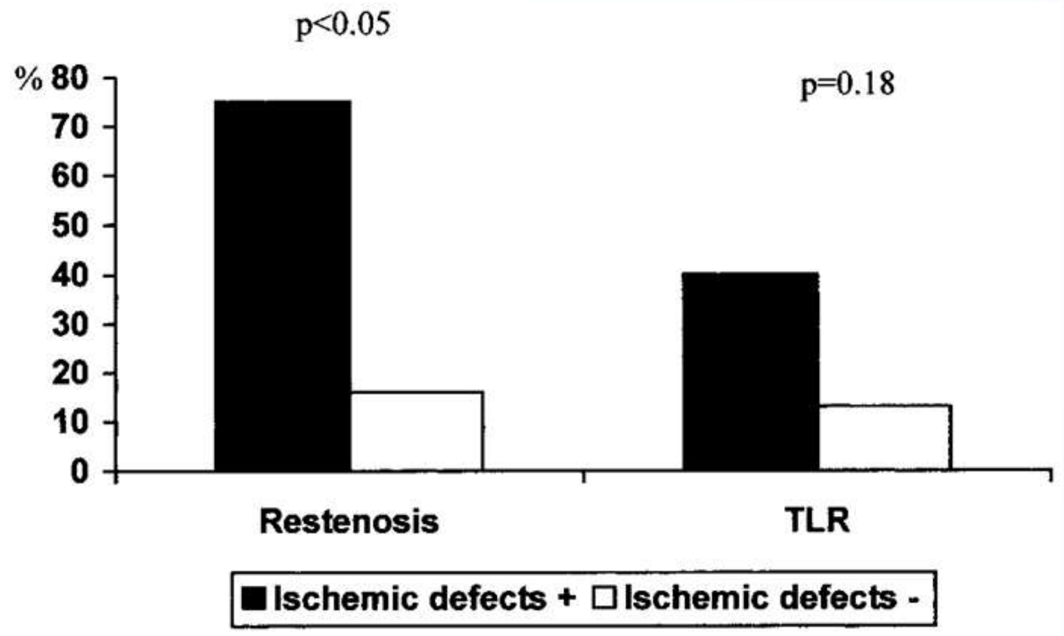
Eur Heart J. 2019;40(2):87-165.
Circulation. 2022;145(3):e4-e17.

Residual Myocardial Ischemia

Why Post-PCI FFR is important.

- Residual myocardial ischemia was often present after successful PCI.



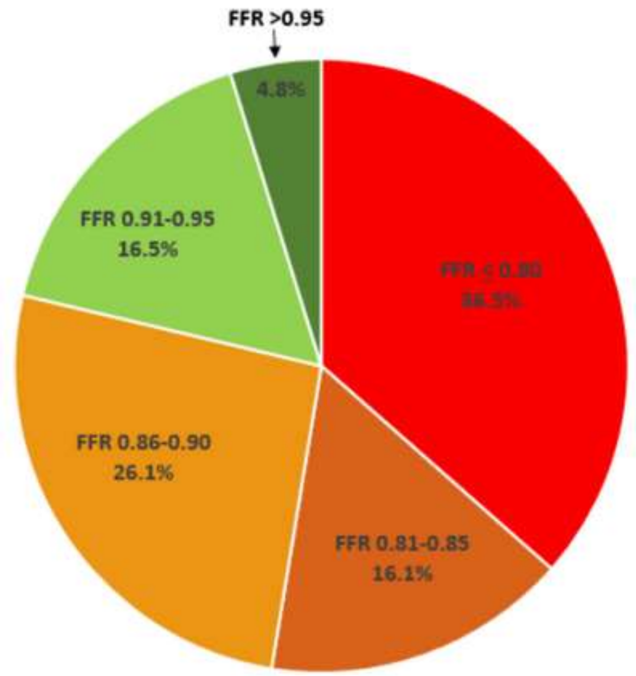


Nagaoka et al. Jpn Circ J. 1998;62(3):160-6.
Rodes et al. J Nucl Med. 2001;42(12):1768-72.

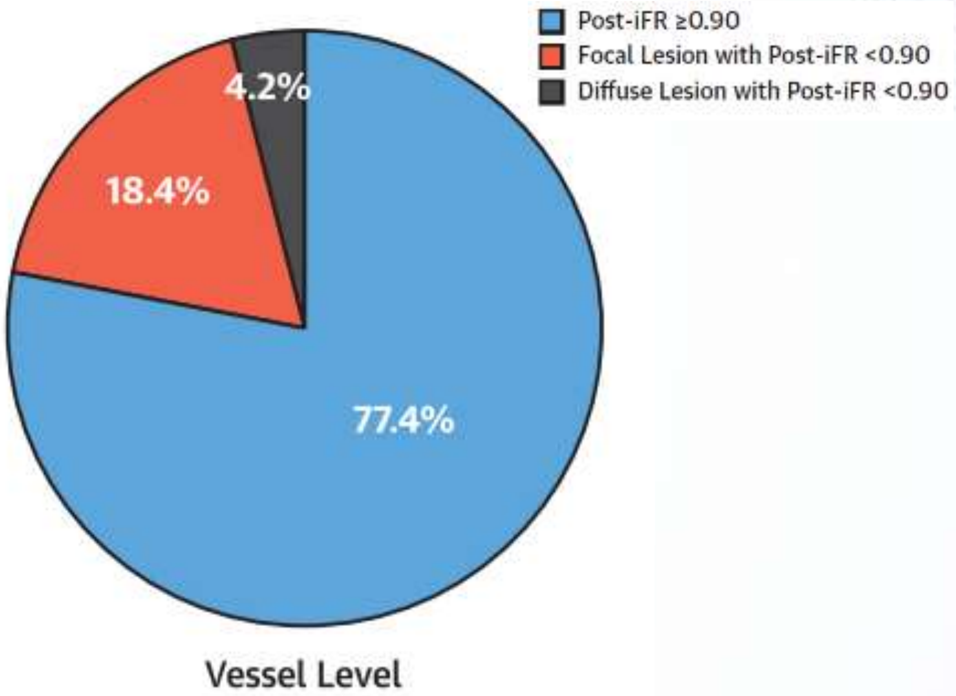
Residual Myocardial Ischemia

From Invasive Physiologic Assessment

From FFR Study



From iFR Study

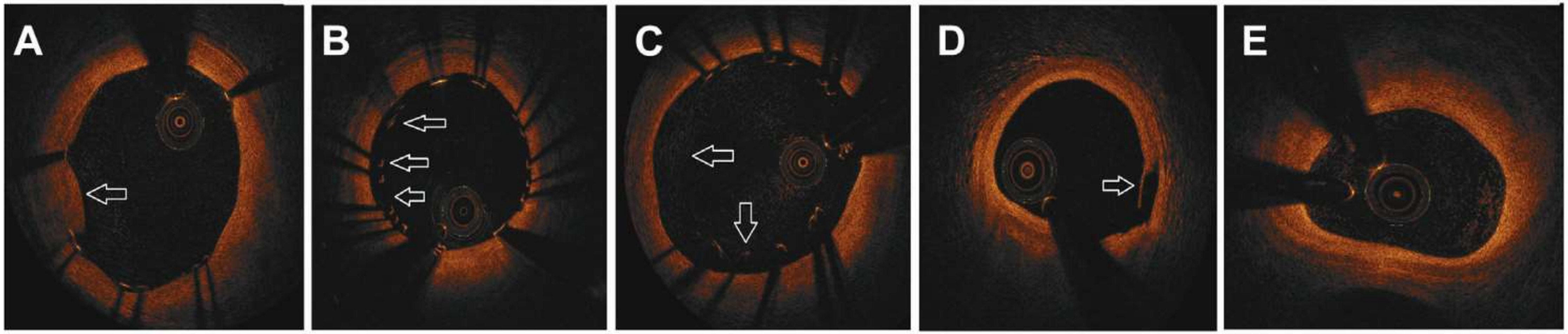


PCI does not guarantee optimal revascularization, i.e., restoration of normal epicardial conductance.

Uretsky et al. J Am Heart Assoc. 2020;9:e015073.
Patel et al. J Am Coll Cardiol Intv 2019;12:1991–2001.

Post-PCI FFR

- **Post-PCI FFR reflects the degree of maximum flow reduction due to residual disease burden in the coronary artery after revascularization.**
- **Suboptimal FFR after coronary stenting**



Plaque prolapse | Underexpansion and malapposition | Severe malapposition | Edge dissection | Residual plaque

Is suboptimal FFR after coronary stenting related to clinical outcomes?

Li et al. J Am Coll Cardiol Intv 2017;10:986–95.

FFR after Balloon Angioplasty

Usefulness of Fractional Flow Reserve to Predict Clinical Outcome After Balloon Angioplasty

G. Jan Willem Bech, MD; Nico H.J. Pijls, MD, PhD; Bernard De Bruyne, MD, PhD;
Kathinka H. Peels, MD; H. Rolf Michels, MD;
Hans J.R.M. Bonnier, MD, PhD; Jacques J. Koolen, MD, PhD

Background—After regular coronary balloon angioplasty, it would be helpful to identify those patients who have a low cardiac event rate. Coronary angiography alone is not sensitive enough for that purpose, but it has been suggested that the combination of optimal angiographic and optimal functional results indicates a low restenosis chance. Pressure-derived myocardial fractional flow reserve (FFR) is an index of the functional severity of the residual epicardial lesion and could be useful for that purpose.

Methods and Results—In 60 consecutive patients with single-vessel disease, balloon angioplasty was performed by use of a pressure instead of a regular guide wire. Both quantitative coronary angiography (QCA) and measurement of FFR were performed 15 minutes after the procedure. A successful angioplasty result, defined as a residual diameter stenosis (DS) <50%, was achieved in 58 patients. In these patients, DS and FFR, measured 15 minutes after PTCA, were analyzed in relation to clinical outcome. In those 26 patients with both optimal angiographic (residual DS by QCA ≤35%) and optimal functional (FFR ≥0.90) results, event-free survival rates at 6, 12, and 24 months were 92±5%, 92±5%, and 88±6%, respectively, versus 72±8%, 69±8%, and 59±9%, respectively, in the remaining 32 patients in whom the angiographic or functional result or both were suboptimal (P=0.047, P=0.028, and P=0.014, respectively).

Conclusions—In patients with a residual DS ≤35% and FFR ≥0.90, clinical outcome up to 2 years is excellent. Therefore, there is a complementary value of coronary angiography and coronary pressure measurement in the evaluation of PTCA result. (***Circulation*. 1999;99:883-888.**)

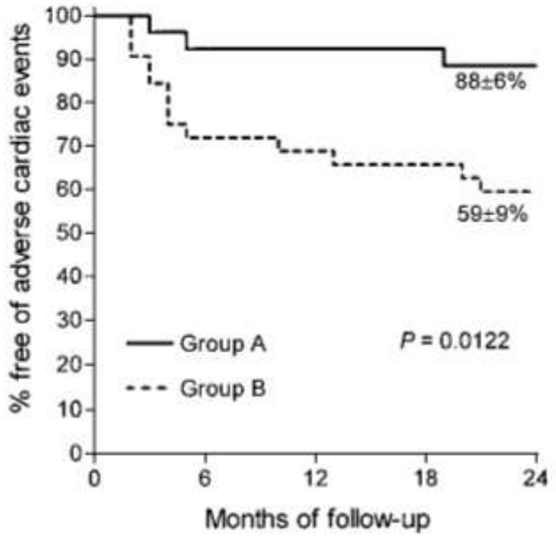


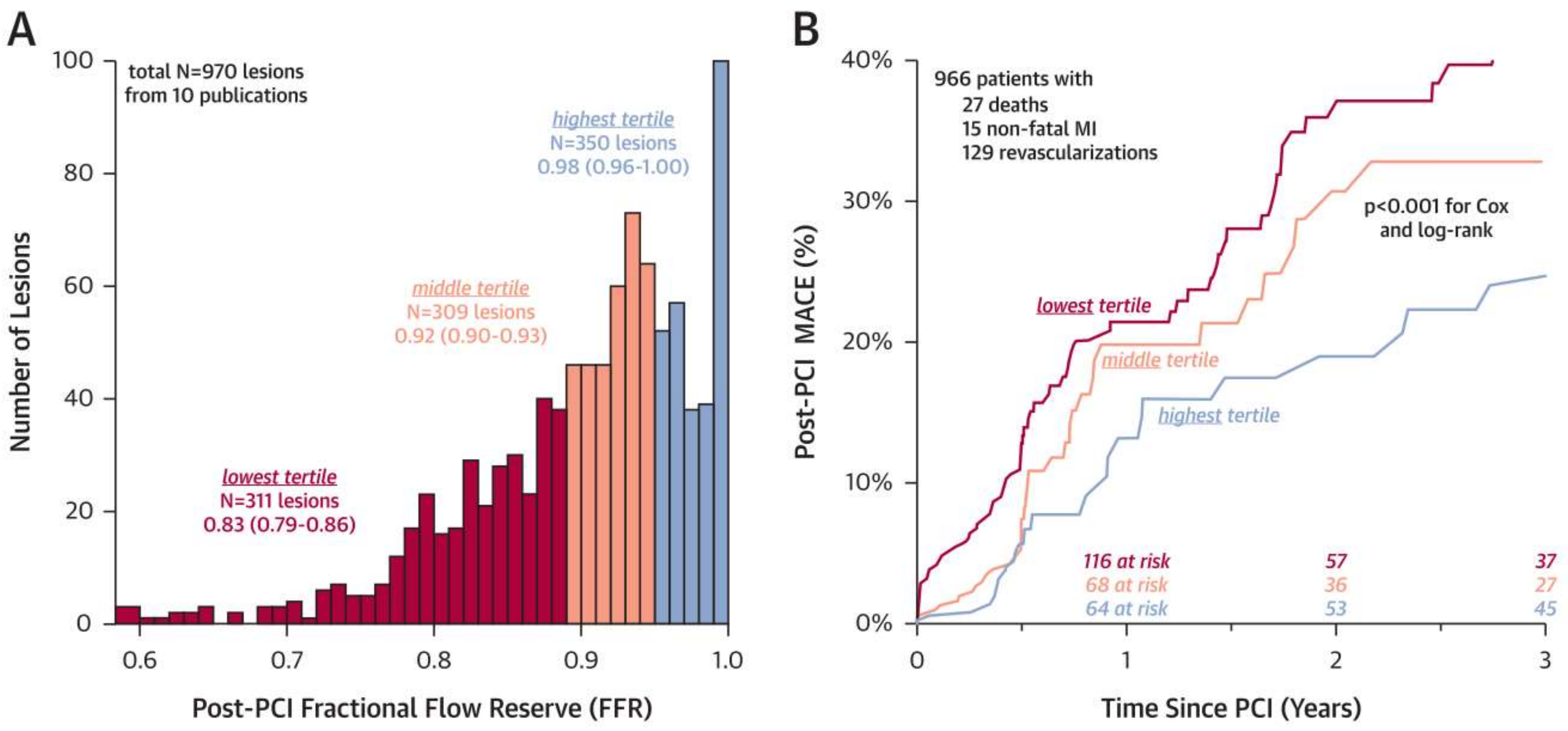
Figure 3. Event-free survival curves. Group A indicates 26 patients in whom both optimal angiographic (residual DS ≤35%) and optimal functional (FFR ≥0.90) results were obtained. Group B indicates remaining 32 patients in whom either angiographic or functional result or both were suboptimal.

60 patients who underwent balloon angioplasty
Primary outcome: Death, MI, UA, Repeat revascularization at 2 year
Optimal cut-off value of post-PCI FFR was 0.90.
Residual DS≤35% and FFR≥0.90 demonstrated excellent outcome.

Bech et al. Circulation. 1999 Feb 23;99(7):883-8.

Post-PCI FFR and Clinical Outcome

Patient level meta-analysis with 966 patients

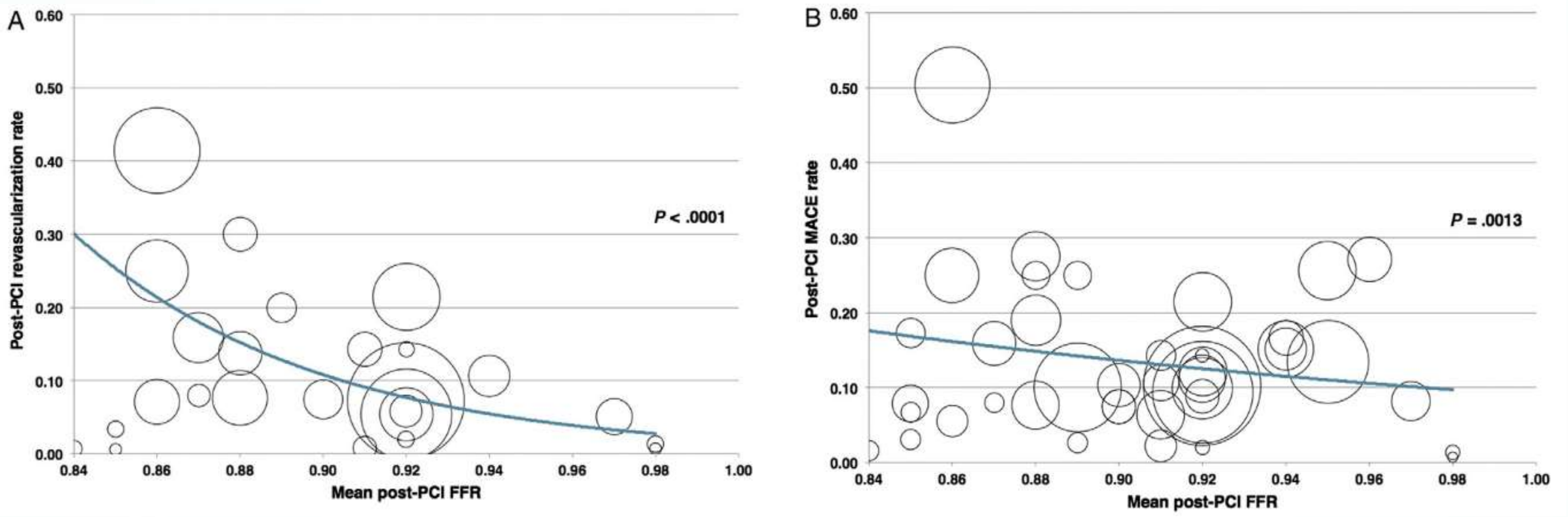


FFR measured after PCI showed an inverse relationship with events.

Johnson et al. J Am Coll Cardiol 2014;64:1641–1654.

Post-PCI FFR and Clinical Outcome

Study level meta-analysis



Meta-regression analysis indicated that higher post-PCI FFR values were associated with reduced rates of revascularization and MACE.

Rimac et al. Am Heart J. 2017 Jan;183:1-9.

Post-PCI FFR after DES Implantation

Table 1. Clinical data for post-PCI physiologic assessment after DES implantation

Study	Study population	Clinical outcome	Follow-up duration	Post-PCI physiologic Index	Cut-off value	Event rate or cumulative incidence (%) Post-PCI physiologic index: Low	High	p value
Leesar et al.	66 SIHD patients (BMS/DES)	Death, MI, TVR	2 years	FFR	0.96	28% (FFR <0.96)	6% (FFR ≥0.96)	0.02
Nam et al.	25 SIHD patients, 55 ACS patients (DES)	Death, MI, TVR	1 year	FFR	0.90	12.5% (FFR ≤0.90)	2.5% (FFR >0.90)	<0.01
Matsuo et al.	69 patients (BMS/DES)	TLR	6 months	FFR	0.79	FFR ≤0.79 vs FFR >0.79 (OR, 6.33; 95% CI, 0.75, 53.4)		0.09
Ito et al.	89 SIHD patients, 8 UA patients (DES)	Cardiac death, MI, stent thrombosis, TVR	17.8 months	FFR	0.90	17% (FFR ≤0.90)	2% (FFR >0.90)	0.02
Doh et al.	72 SIHD patients, 35 ACS patients (DES)	Death, TVMI, TVR	3 years	FFR	0.89	38.9% (FFR <0.89)	10.7% (FFR ≥0.89)	0.03
Reith et al.	66 SIHD patients (BMS/DES)	Death, MI, TLR	20 months	FFR	0.91	35.9% (FFR ≤0.91)	5.3% (FFR >0.91)	0.01
Agarwal et al.	574 SIHD or ACS patients (BMS/DES)	Death, MI, TVR	31 months	FFR	0.86	23% (FFR ≤0.86)	17% (FFR >0.86)	0.02
Kasula et al.	189 ACS patients (BMS/DES)	Death, MI, TVR	2.4 years	FFR	0.91	30% (FFR ≤0.91)	19% (FFR >0.91)	0.03
Li et al.	1,276 SIHD patients, 220 UA patients (DES)	Cardiac death, TVMI, TVR	3 years	FFR	0.88	12.3% (FFR <0.88)	6.1% (FFR ≥0.88)	0.002
Piroth et al.	639 patients from FAME I and FAME II (DES)	TV-Death, TVMI, TVR	2 years	FFR	0.92	8.7% (FFR <0.92)	4.2% (FFR ≥0.92)	0.011
Lee et al.	338 SIHD patients, 283 ACS patients (DES)	Cardiac death, TVMI, TVR	2 years	FFR	0.84	9.1% (FFR <0.84)	2.6% (FFR ≥0.84)	0.006
Hwang et al.	452 SIHD patients, 383 ACS patients (DES)	Cardiac death, TVMI, TVR	2 years	FFR	0.82 (LAD)	10.9% (FFR ≤0.82)	2.5% (FFR >0.82)	<0.001
					0.88 (non-LAD)	8.0% (FFR ≤0.88)	1.9% (FFR >0.88)	0.004
Hakeem et al.	574 SIHD or ACS patients (BMS/DES)	Death, MI, TVR	30 months	Pd/Pa	0.96 (Pd/Pa)	24% (Pd/Pa ≤0.96)	15% (Pd/Pa >0.96)	<0.001
				FFR	0.86 (FFR)	23% (FFR ≤0.86)	17% (FFR >0.86)	0.02
Van Bommel et al.	285 SIHD patients, 352 ACS patients	Death, MI, TVR	30 days	FFR	0.90	2.0% (FFR ≤0.90)	1.5% (FFR >0.90)	0.636
Azzalini et al.	50 SIHD patients, 15 ACS patients	Cardiac death, MI, TVR, readmission for angina	1 year	FFR	0.90	31.6% (FFR <0.90)	9.1% (FFR ≥0.90)	0.047
Hoshino et al.	201 SIHD patients with LAD lesion	Cardiac death, TVMI, TVR	24 months	FFR	0.86	FFR <0.86 vs. FFR ≥0.86 (HR, 2.11; 95% CI, 0.89, 5.03)		0.092
Shin et al.	309 SIHD patients, 279 ACS patients (DES)	Cardiac death, TVMI, TVR	24 months	Pd/Pa	0.92 (Pd/Pa)	6.2% (Pd/Pa ≤0.92)	2.5% (Pd/Pa >0.92)	0.029
				FFR	0.80 (FFR)	10.3% (FFR ≤0.80)	2.5% (FFR >0.80)	<0.001

ACS = acute coronary syndrome; BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; FFR = fractional flow reserve; HR = hazard ratio; LAD = left anterior descending artery; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease; TLR = target lesion revascularization; TVMI = target-vessel myocardial infarction; TVR = target vessel revascularization.

Higher post-PCI FFR was associated with better clinical outcomes.
Optimal cut-off value widely ranged from 0.79 to 0.96.
The differences in study population, definition of outcome, type of stent used and included vessels

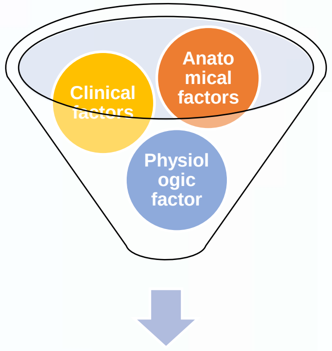
Hwang et al. Korean Circ J. 2021;51(3):189-201.

Post-PCI FFR for Future Event prediction

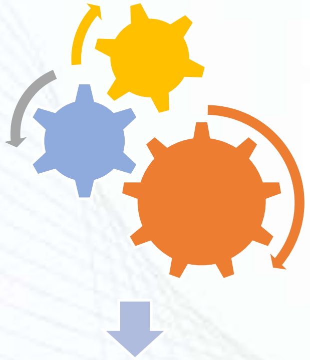
Risk model using Machine Learning technique

From International Post PCI FFR registry (N=2,200)

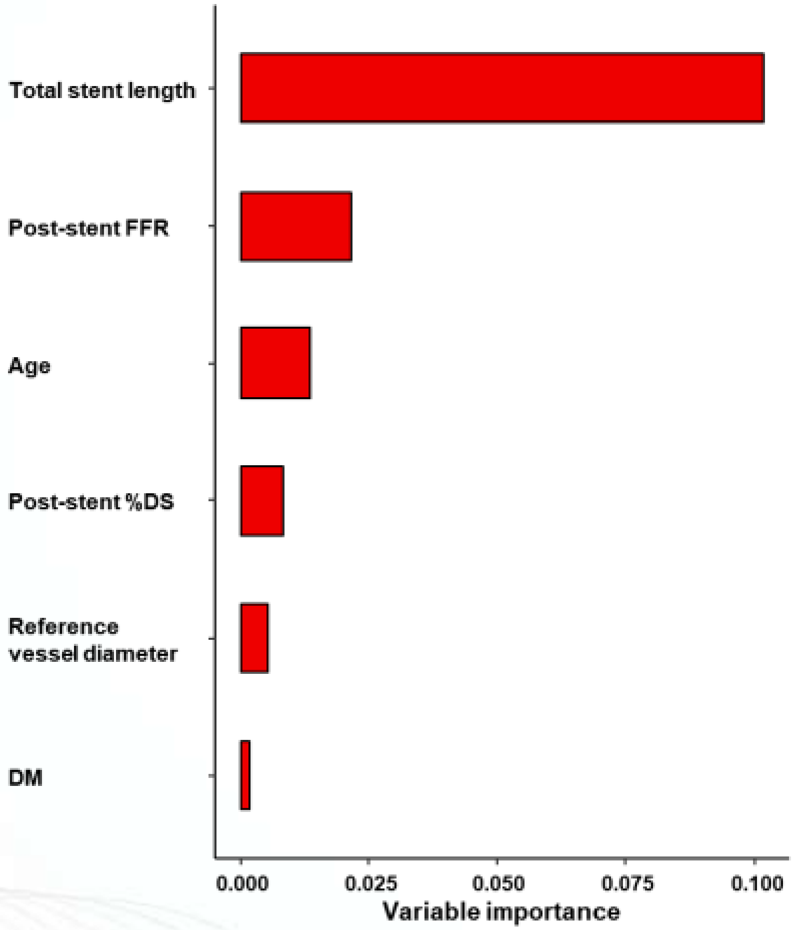
Associated variables

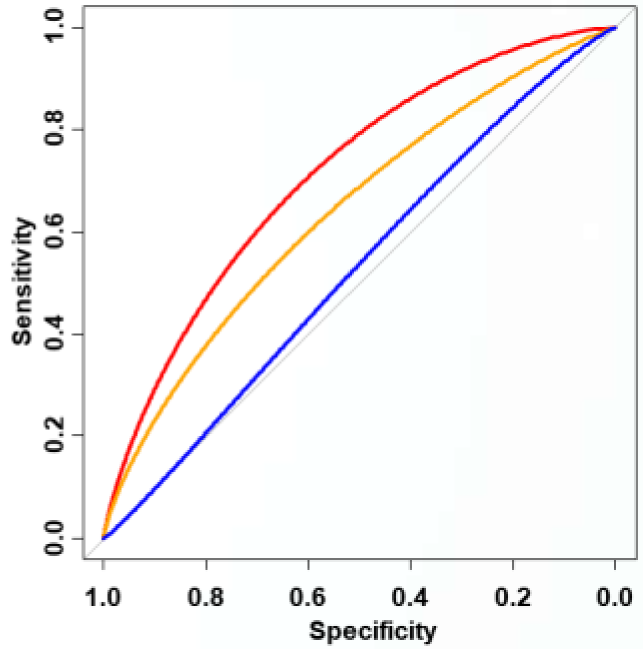


Machine learning



Risk prediction model

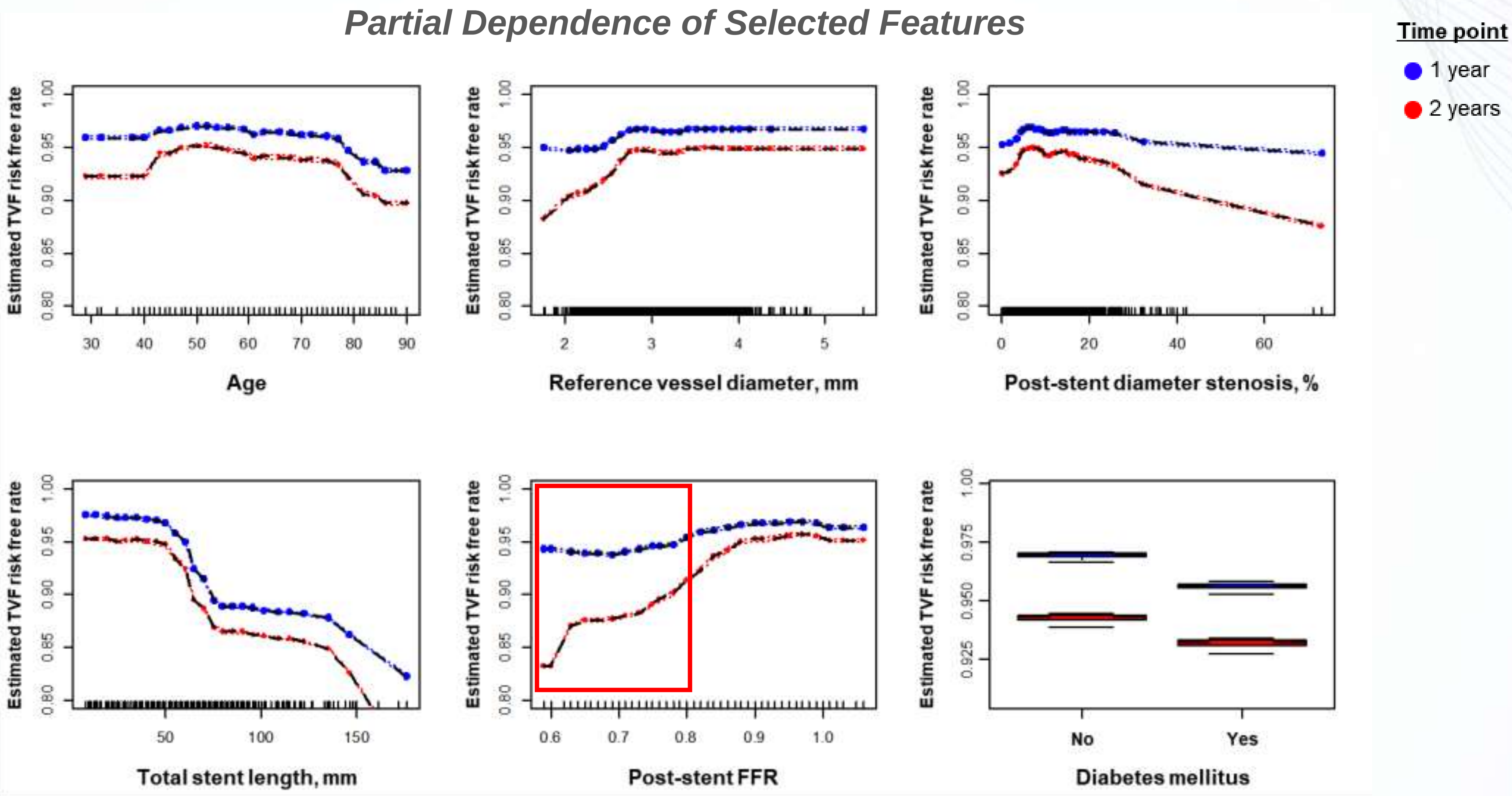




RSF model	C-index (95% CI)	p-value
Clinical, angiographic factors and post-stent FFR	0.72 (0.62-0.82)	Reference
Clinical and angiographic factors	0.65 (0.52-0.77)	0.045
Clinical factors	0.55 (0.41-0.59)	0.005

Hwang et al. JACC Cardiovasc Interv 2020;13:1639-50.

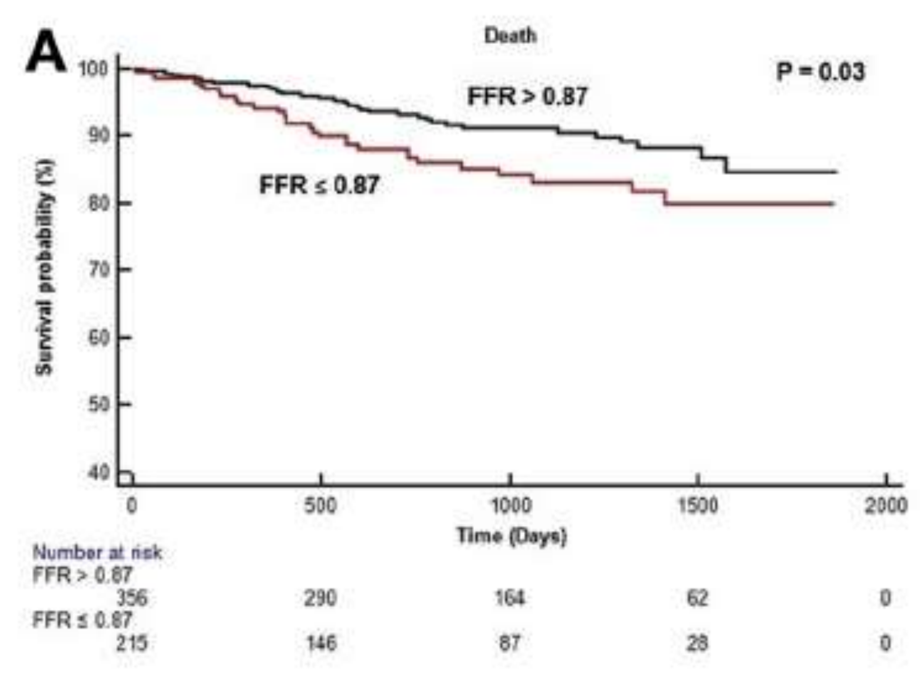
Post-PCI FFR for Future Event prediction



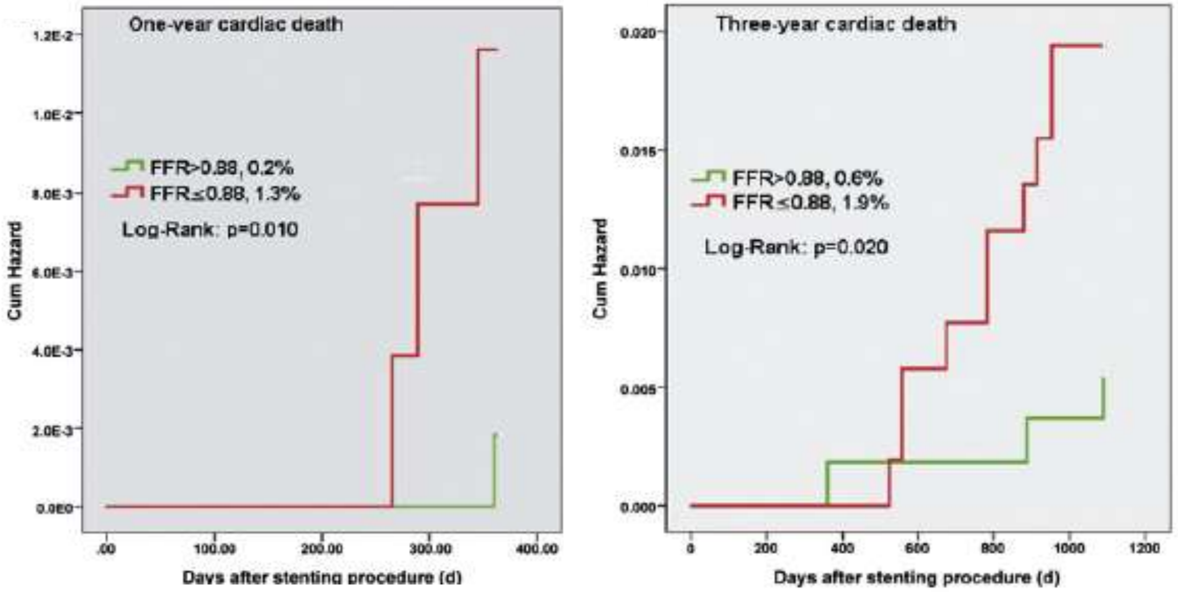
Hwang et al. JACC Cardiovasc Interv 2020;13:1639-50.

Post-PCI FFR and Hard Outcomes

Central Arkansas VA Health systems



DK-CRUSH VII

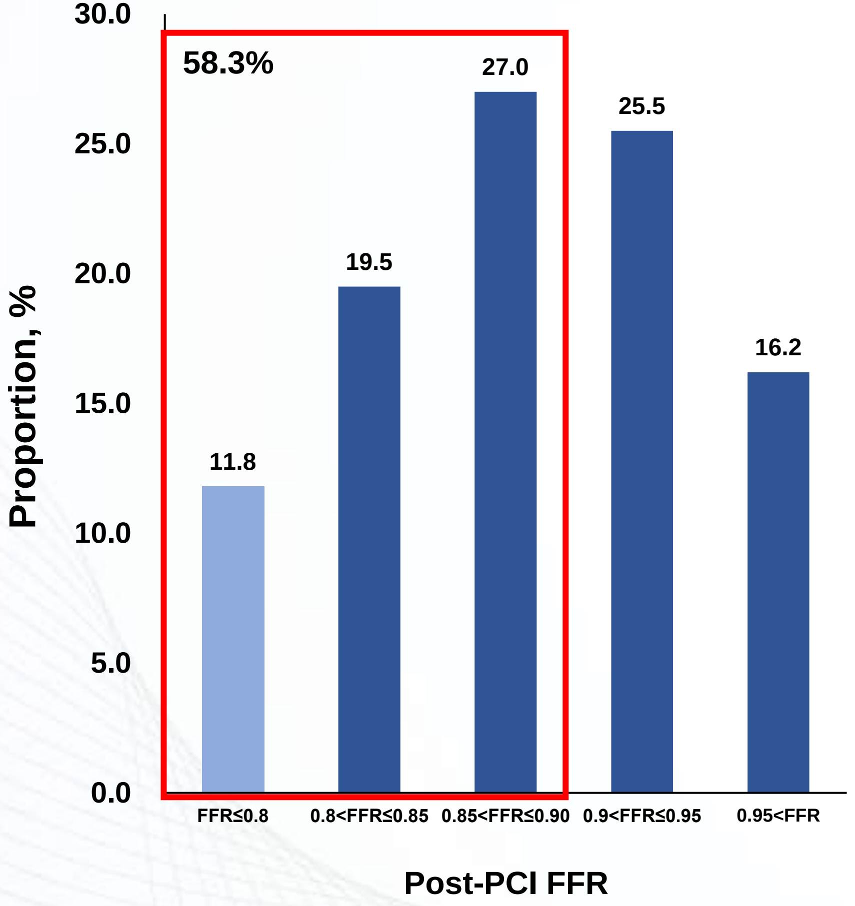


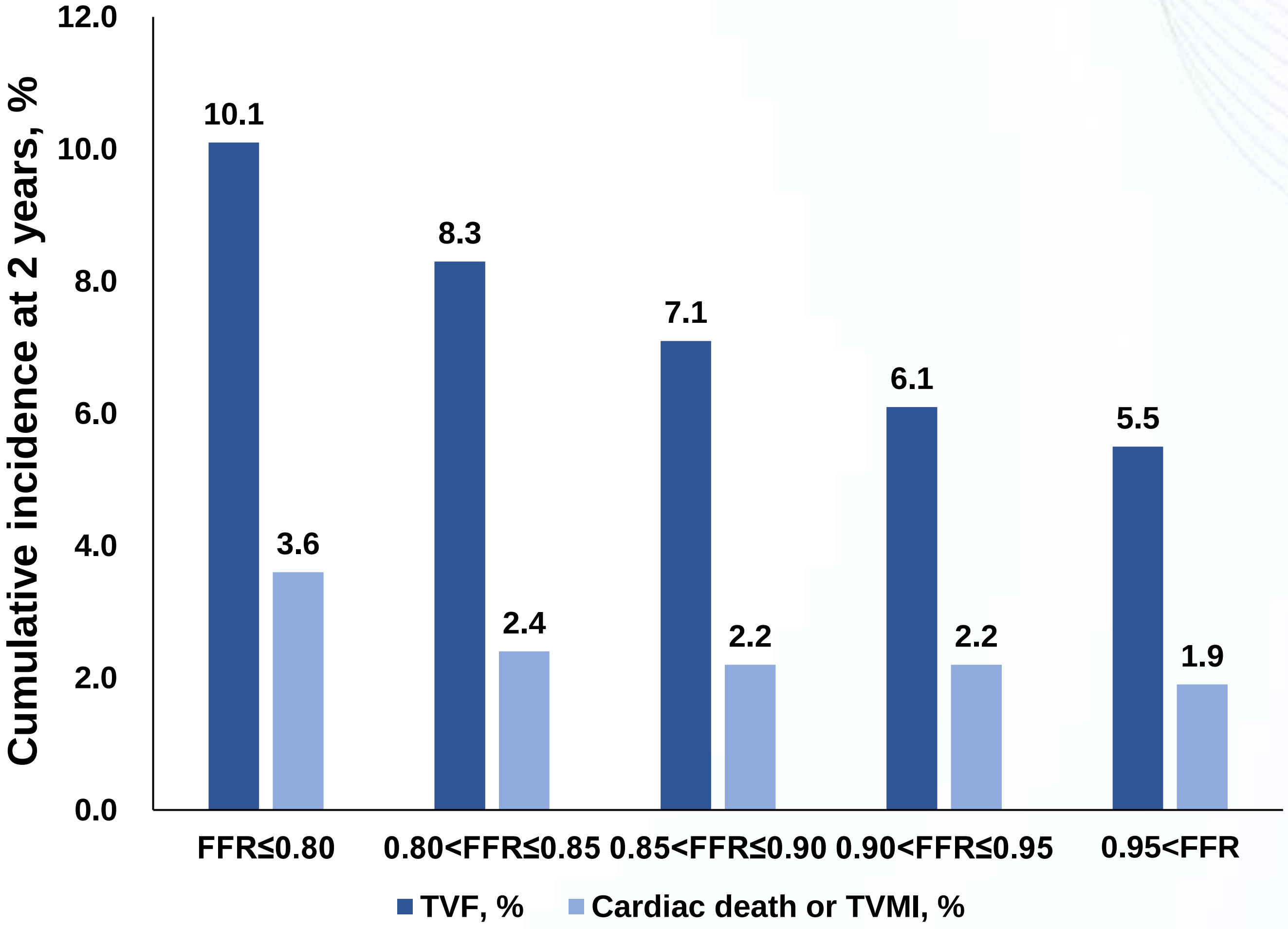
Two previous studies reported that patients with a lower post-PCI FFR value showed significantly higher rates of cardiac death or TVMI.

Agarwal et al. JACC Cardiovasc Interv 2016;9:1022–31
Li et al. JACC Cardiovasc Interv 2017;10:986–95

Updated Patient-level Meta-Analysis

POST-PCI FLOW study (5,277 patients with 5,869 vessels)



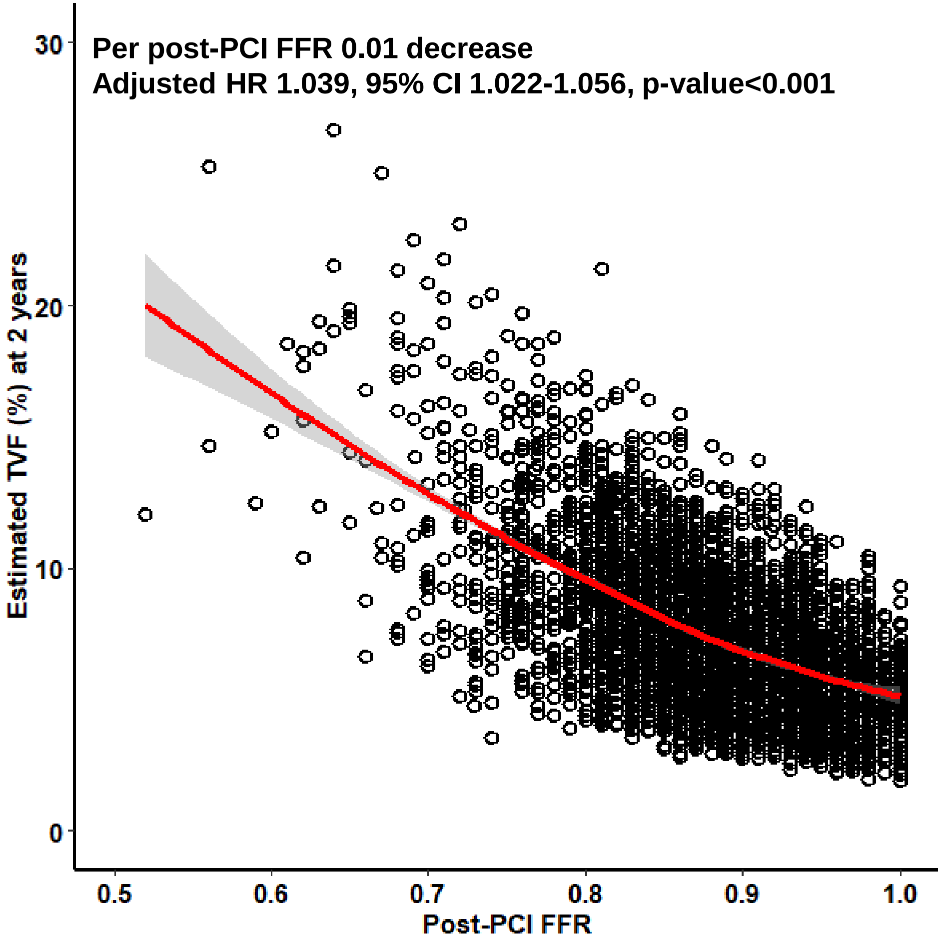


Hwang et al. JAMA Netw Open. 2022 Sep 1;5(9):e2232842.

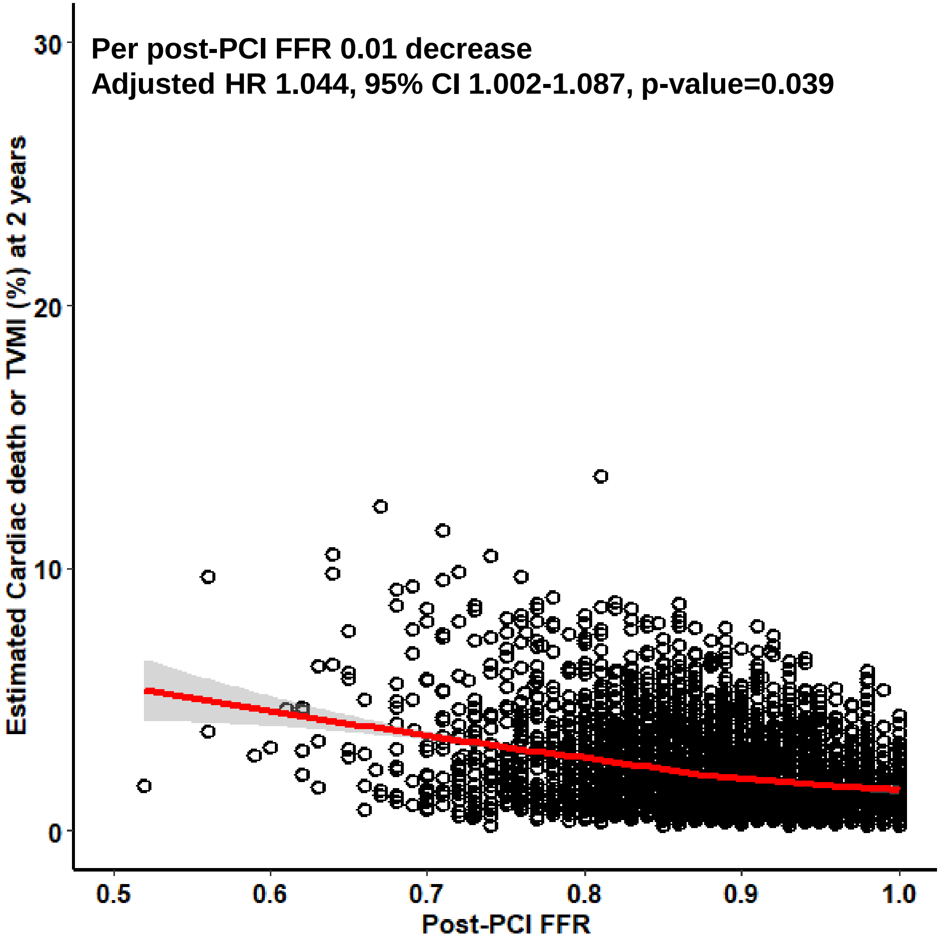
Updated Patient-level Meta-Analysis

POST-PCI FLOW study (5,277 patients with 5,869 vessels)

Target vessel failure



Cardiac death or TVMI



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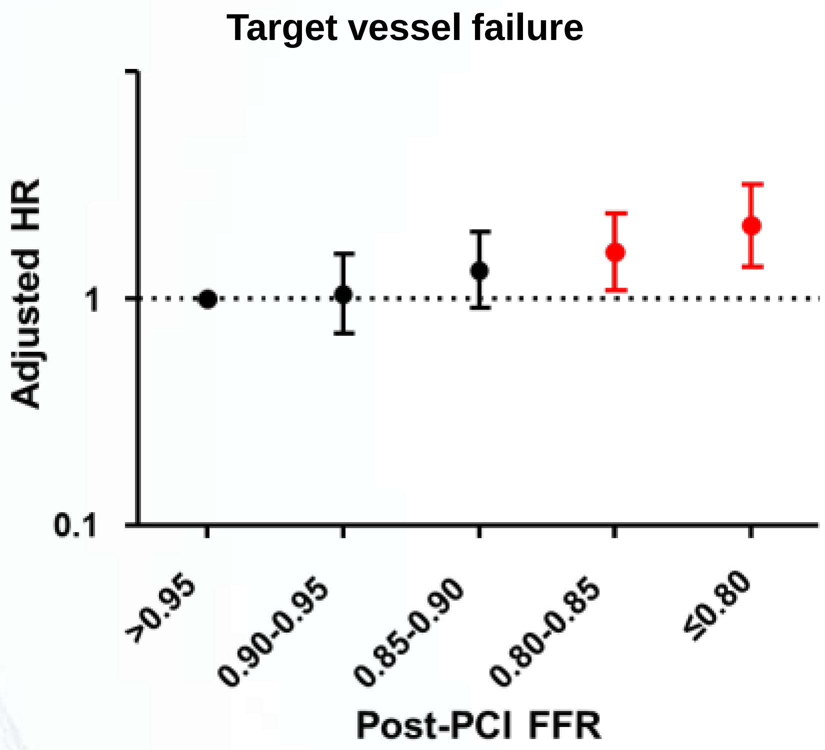
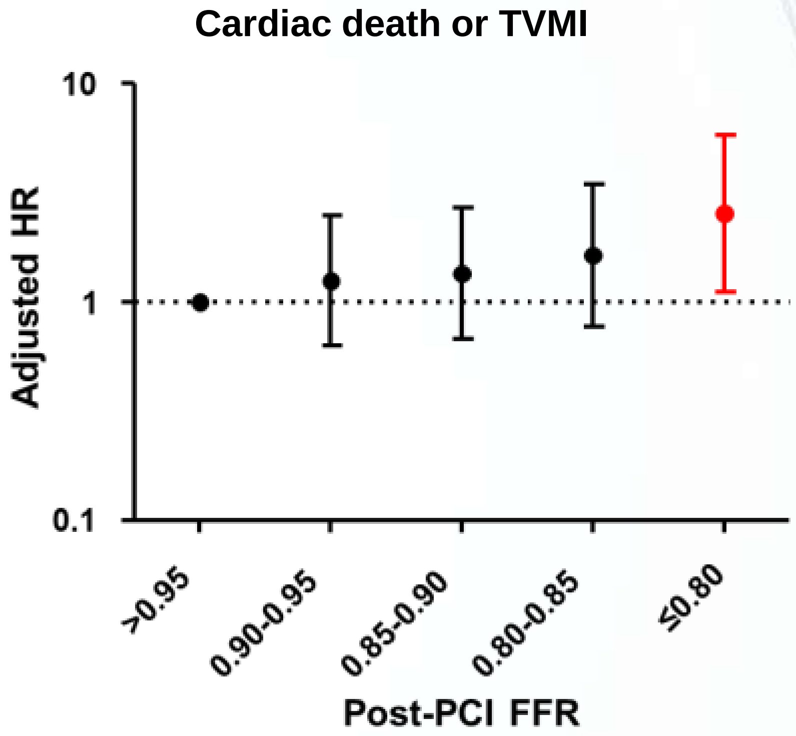
Updated Patient-level Meta-Analysis

POST-PCI FLOW study (5,277 patients with 5,869 vessels)





Target vessel failure		
0.95<Post-PCI FFR	Reference	
0.90<Post-PCI FFR≤0.95	1.052 (0.706-1.569)	0.80
0.85<Post-PCI FFR≤0.90	1.333 (0.911-1.950)	0.14
0.80<Post-PCI FFR≤0.85	1.604 (1.081-2.381)	0.02
Post-PCI FFR≤0.80	2.108 (1.385-3.209)	<0.001

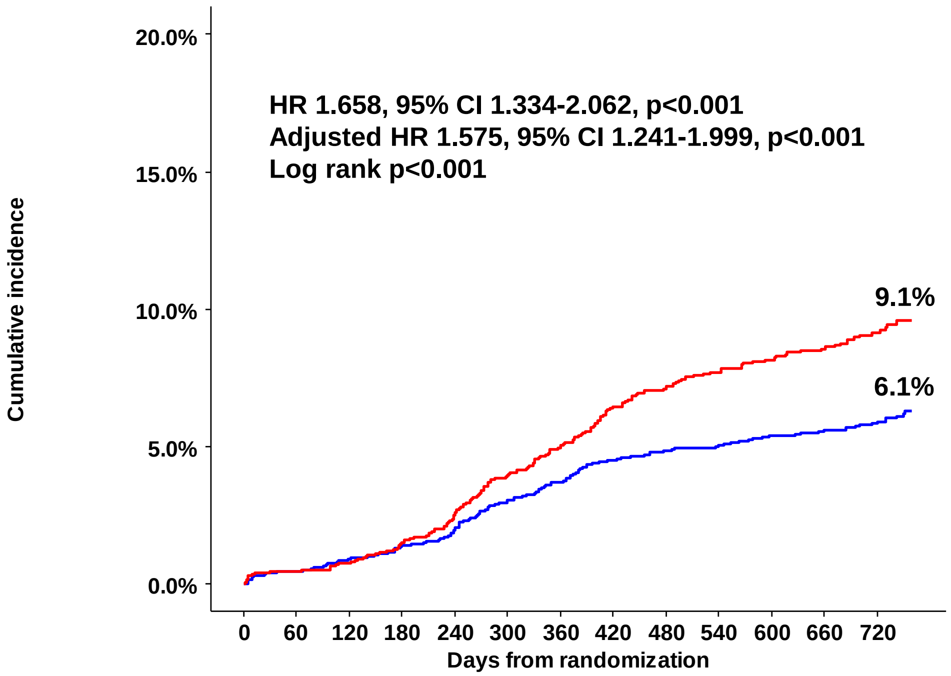
Cardiac death or TVMI		
0.95<Post-PCI FFR	Reference	
0.90<Post-PCI FFR≤0.95	1.255 (0.633-2.490)	0.52
0.85<Post-PCI FFR≤0.90	1.356 (0.681-2.700)	0.39
0.80<Post-PCI FFR≤0.85	1.636 (0.772-3.467)	0.20
Post-PCI FFR≤0.80	2.559 (1.116-5.867)	0.03

Hwang et al. JAMA Netw Open. 2022 Sep 1;5(9):e2232842.

Updated Patient-level Meta-Analysis

POST-PCI FLOW study (5,277 patients with 5,869 vessels)

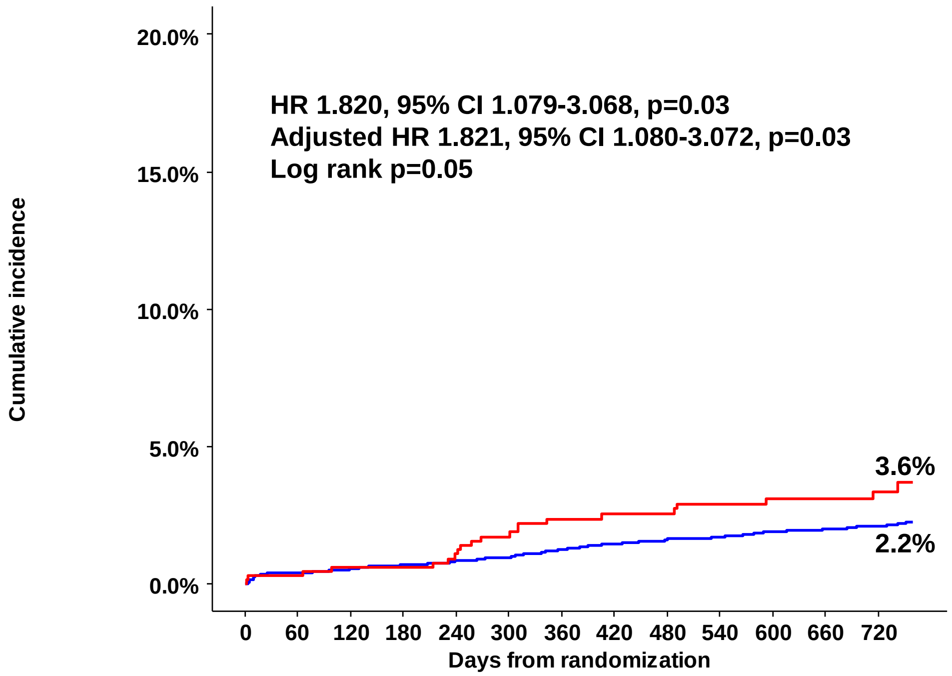
Target vessel failure



Number at risk

	0	60	120	180	240	300	360	420	480	540	600	660	720
Post-PCI FFR>0.86	3183	3159	3136	3114	3038	2946	2851	2703	2646	2601	2481	2417	2209
Post-PCI FFR<=0.86	2021	2003	1990	1967	1894	1849	1776	1639	1603	1571	1522	1480	1313

Cardiac death or TVMI



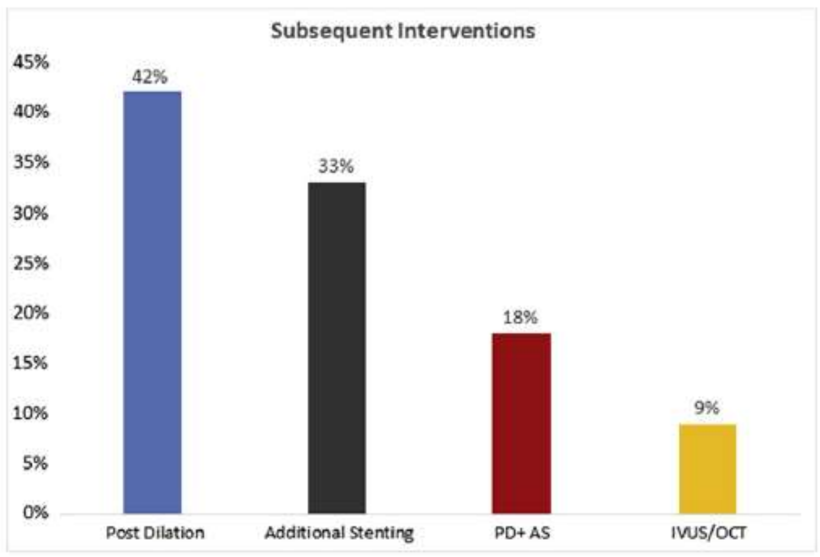
Number at risk

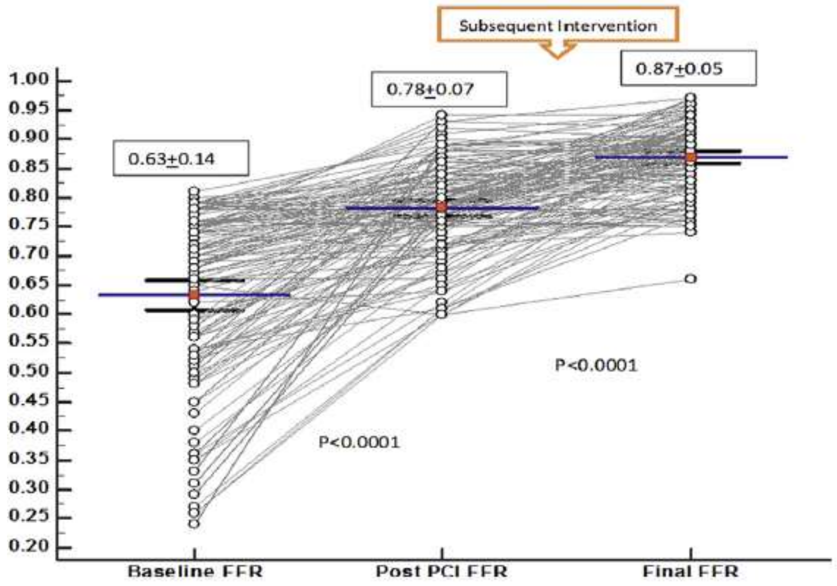
	0	60	120	180	240	300	360	420	480	540	600	660	720
Post-PCI FFR>0.80	4535	4500	4481	4457	4350	4263	4139	3919	3837	3776	3620	3535	3207
Post-PCI FFR<=0.80	669	663	656	652	631	620	594	553	549	535	518	499	445

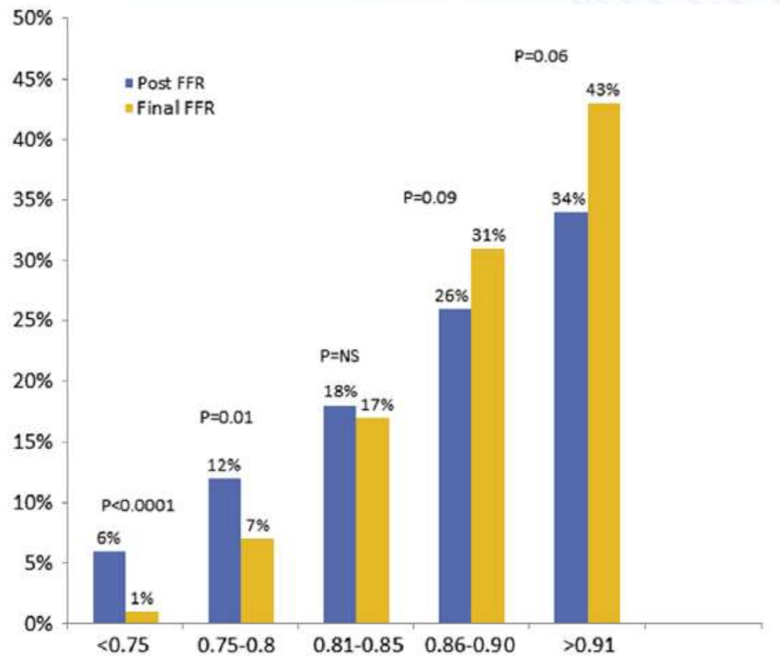
Hwang et al. JAMA Netw Open. 2022 Sep 1;5(9):e2232842.

Post-PCI FFR can be modifiable?

574 Patients with angiographically successful PCI





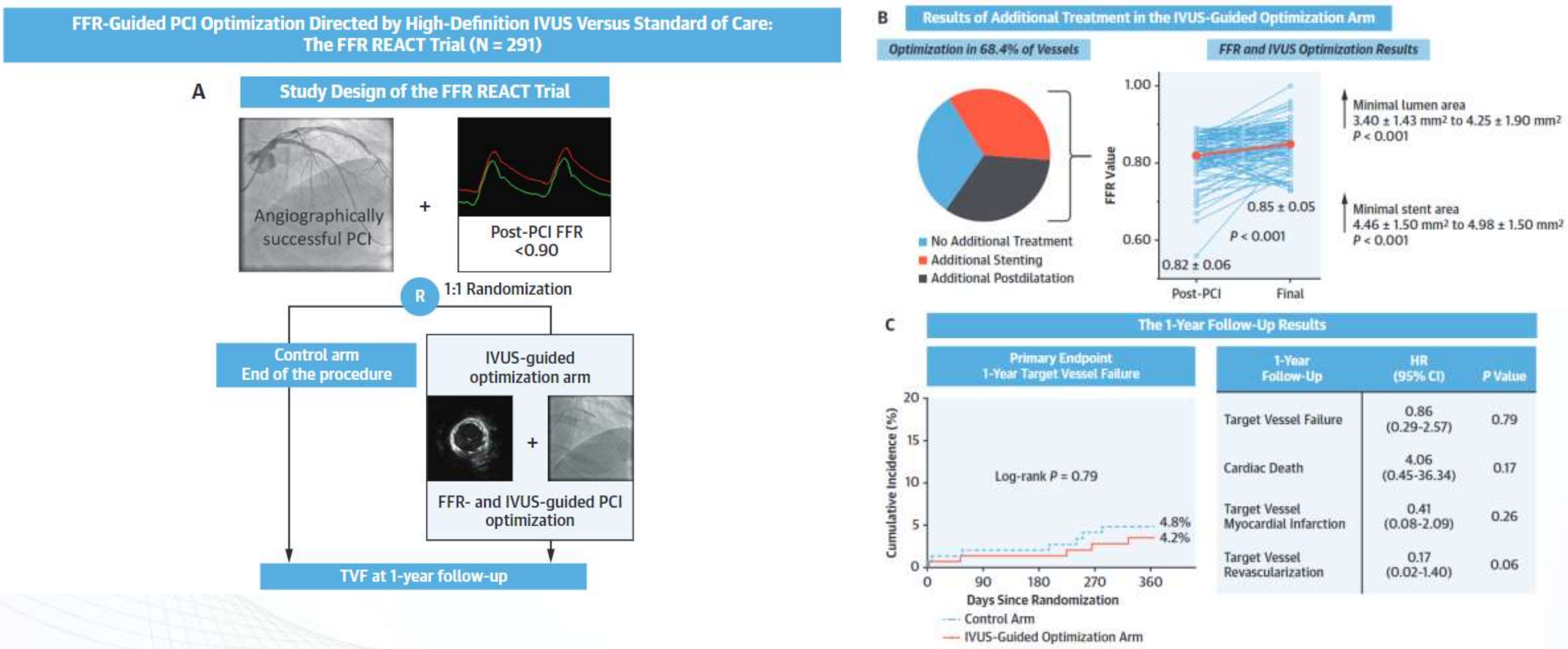


Subsequent intervention after PCI, post-PCI FFR increased from 0.78±0.08 to 0.87±0.06.

Agarwal et al. JACC Cardiovasc Interv. 2016;9(10):1022-31.

FFR-Guided PCI Optimization Directed by IVUS

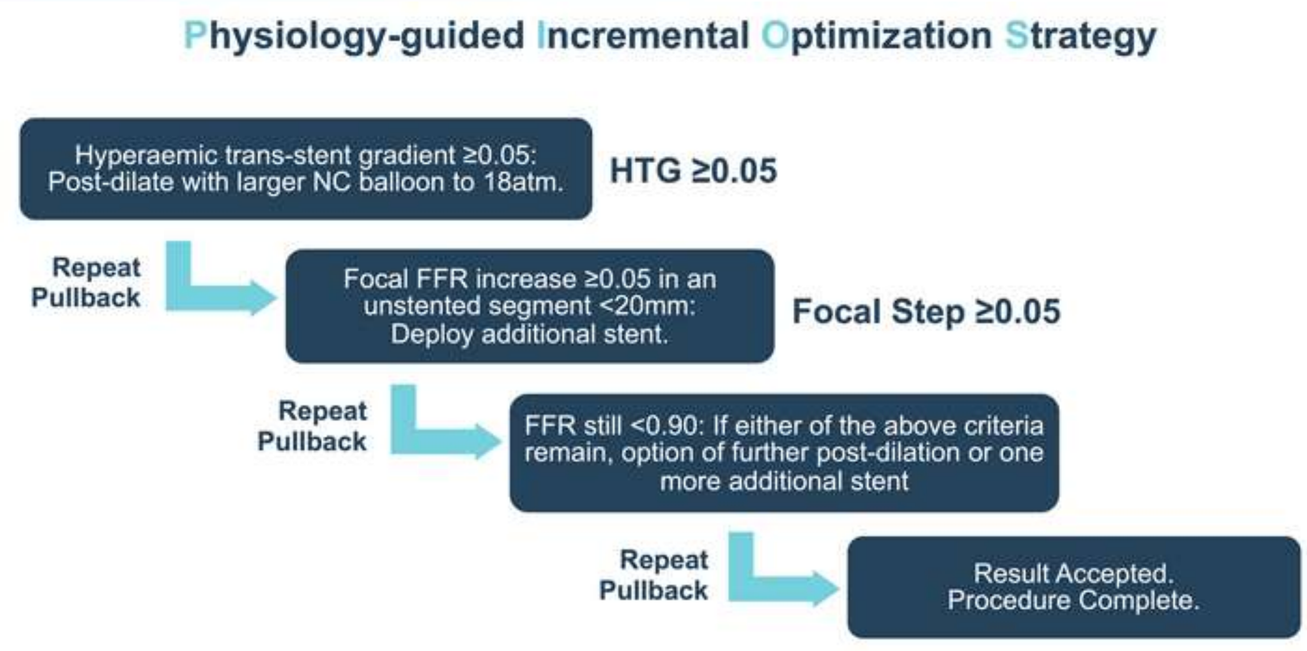
FFR REACT trial

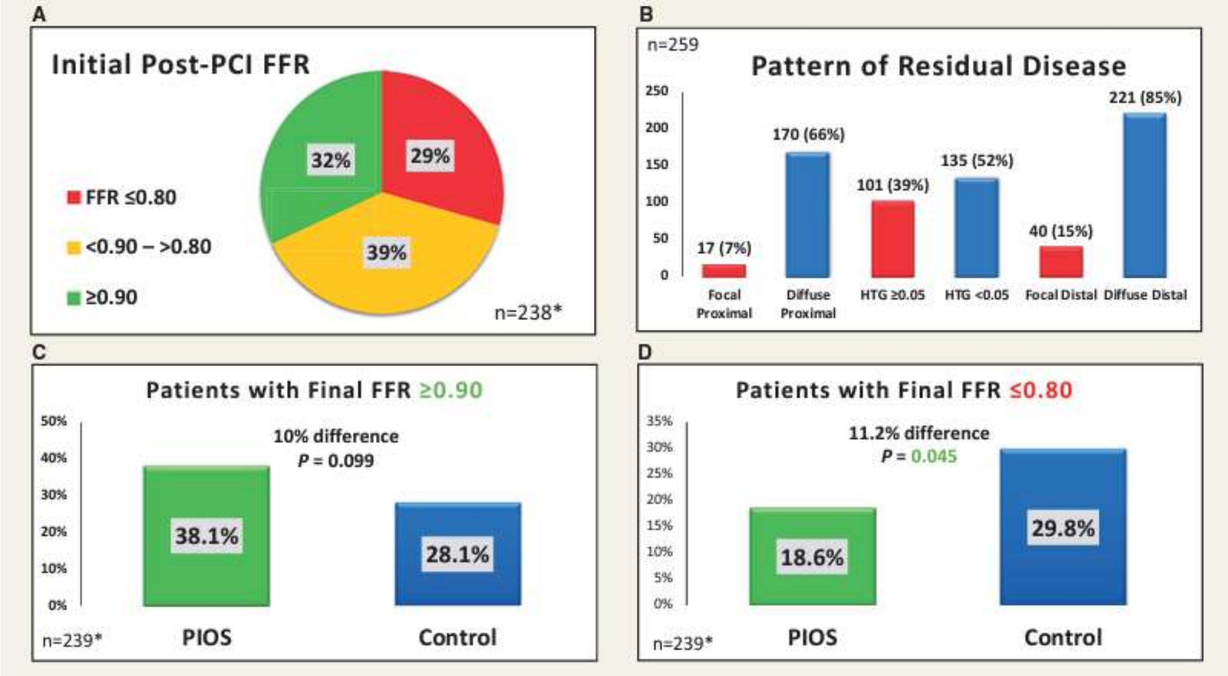


Neleman et al. JACC Cardiovasc Interv 2022;15:1595–1607

Post-PCI FFR-guided Optimization

TARGET-FFR trial

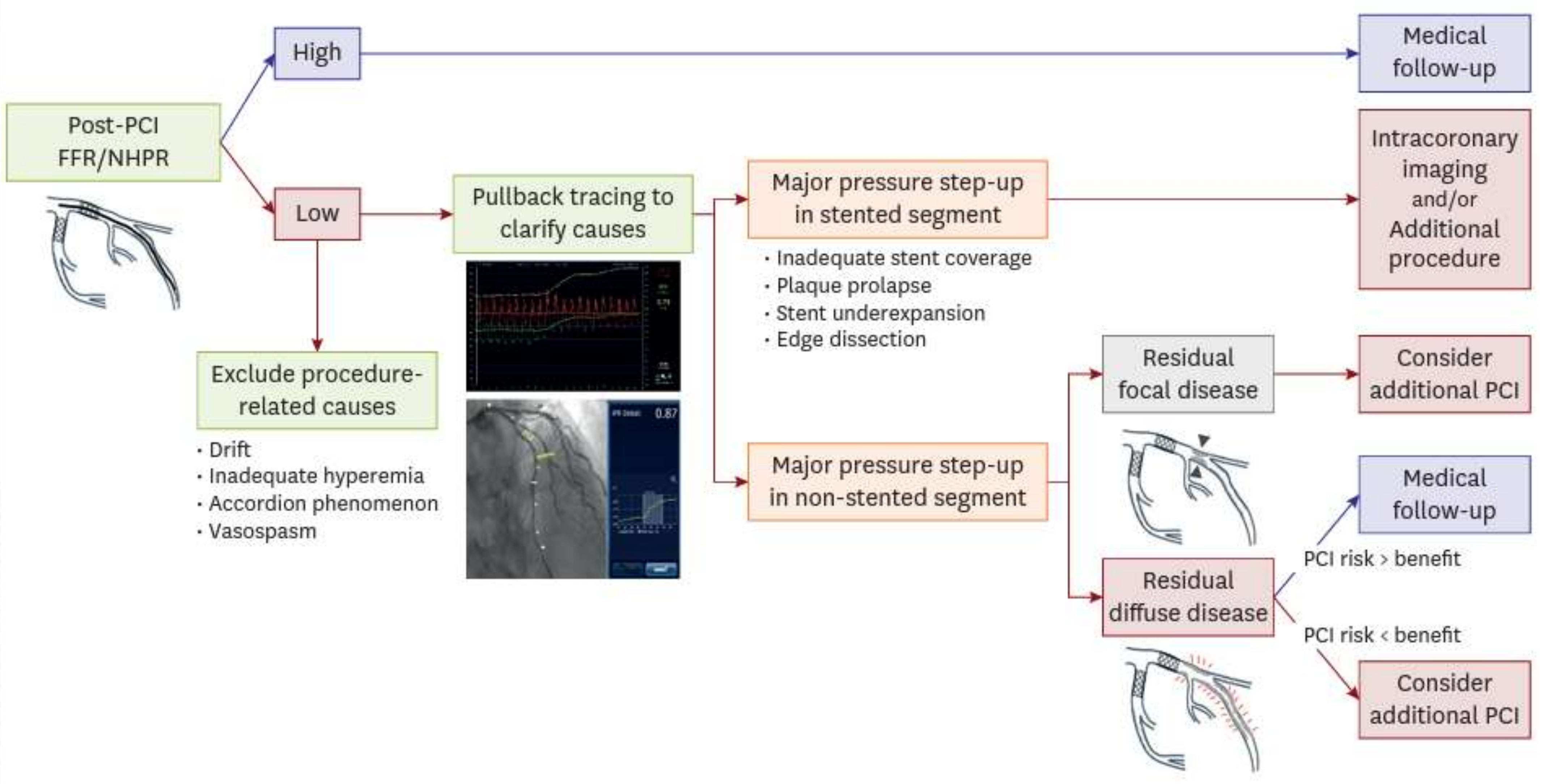




An FFR-guided optimization strategy did not significantly increase the proportion of patients with a final FFR ≥0.90, but did reduce the proportion of patients with a final FFR ≤0.80.

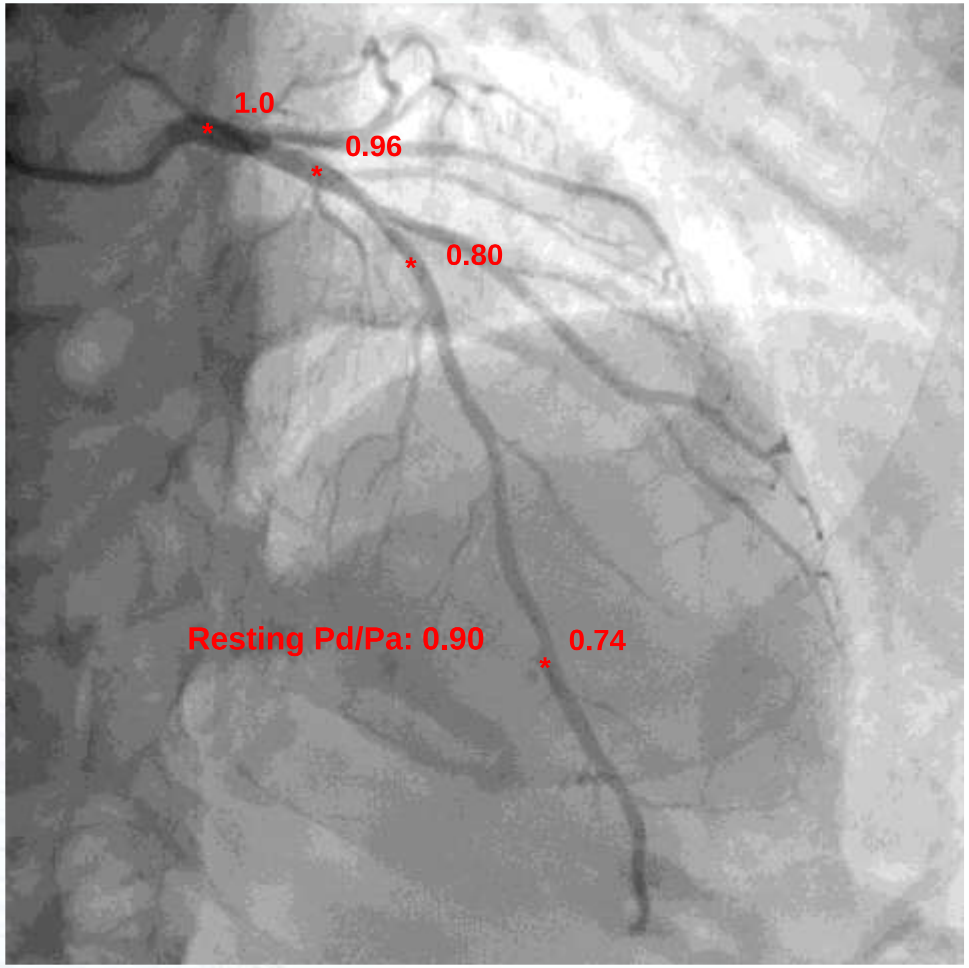
Collison et al. Eur Heart J. 2021 1;42(45):4656-4668.

PCI Optimization Strategy

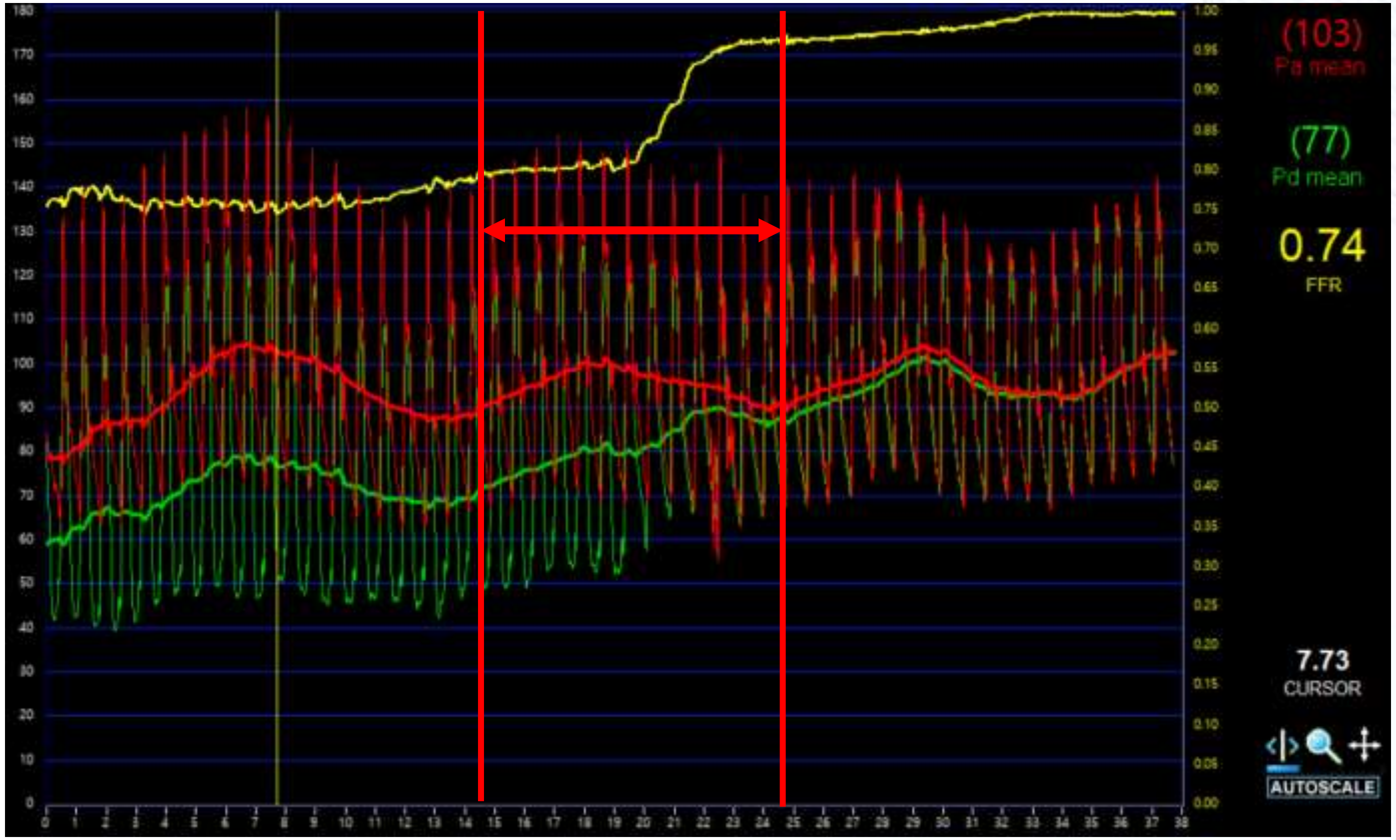


Hwang et al. Korean Circ J. 2021;51(3):189-201

Invasive functional test with FFR

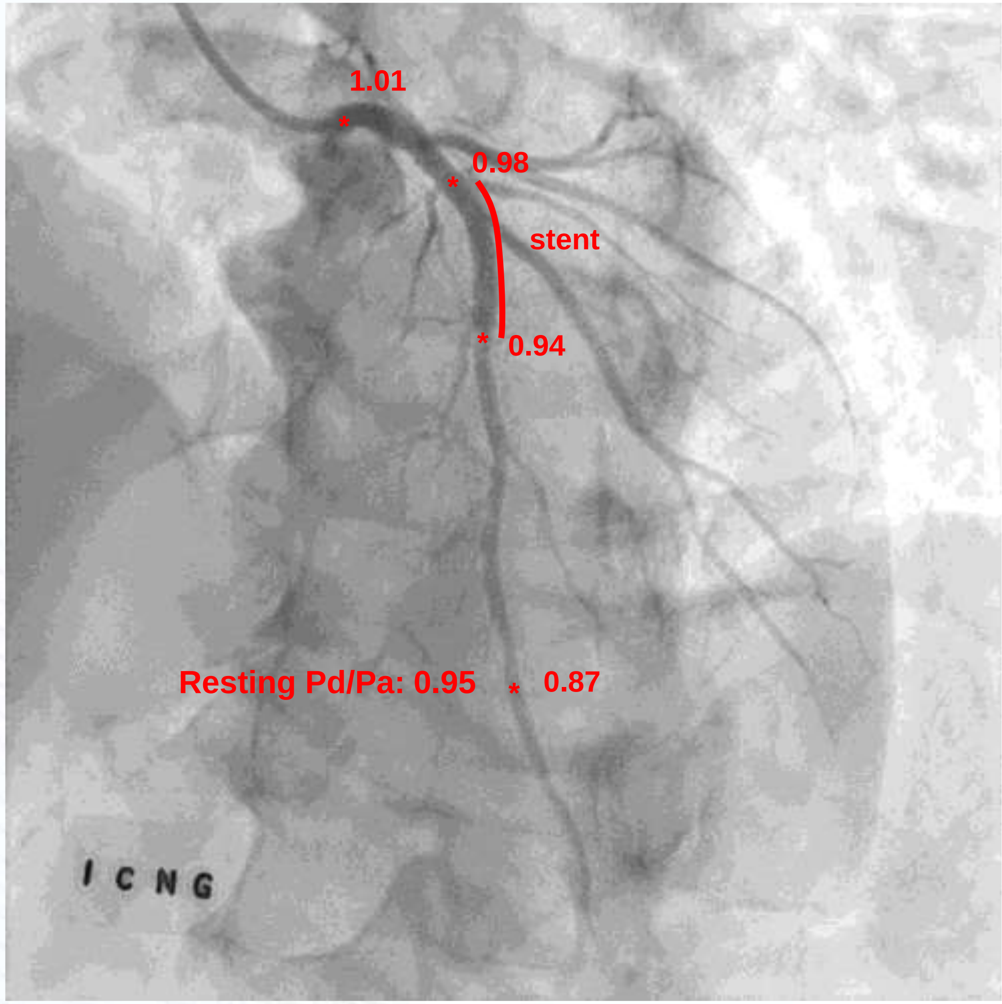


Delta FFR of disease segment: 0.16

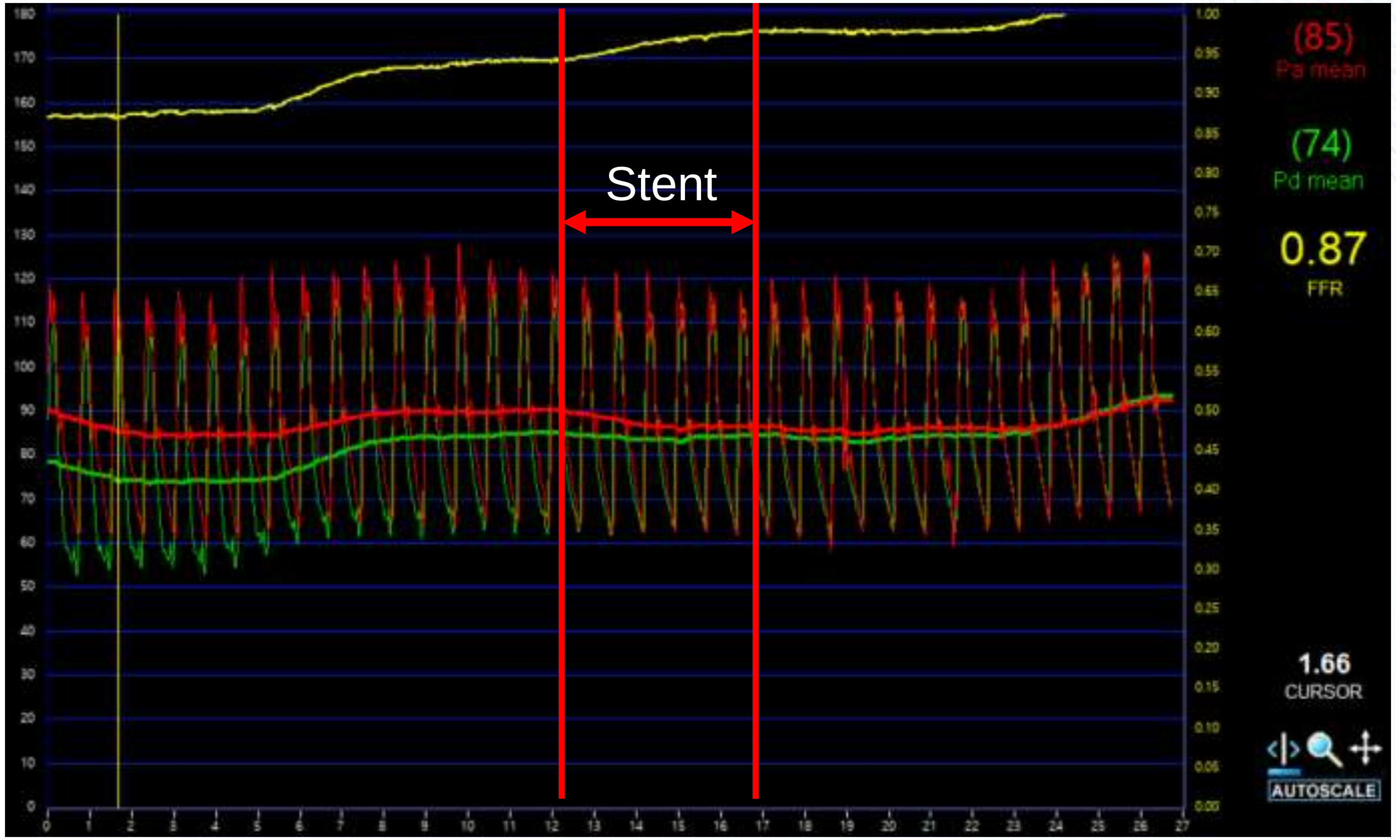


Mid LAD lesion needs to be treated.

Invasive functional test after PCI



Delta FFR of stented segment: 0.04



Summary

- Even after angiographically successful PCI, physiologically suboptimal PCI results are common and this can be evaluated by post-PCI FFR.
- Post-PCI FFR has a significant, non-linear, and inverse relationship with future adverse events, including hard outcomes.
- Post-PCI FFR can be used as a procedural quality metric.
- Post-PCI FFR measurement and comprehensive FFR pullback after PCI might reveal hidden problems and maximize the benefit of PCI.
- Intracoronary imaging is a good option for revealing these reasons and further optimization of PCI.