What Events Happened in the Physiology Field in 2023?

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Physiology Field Issue in 2023

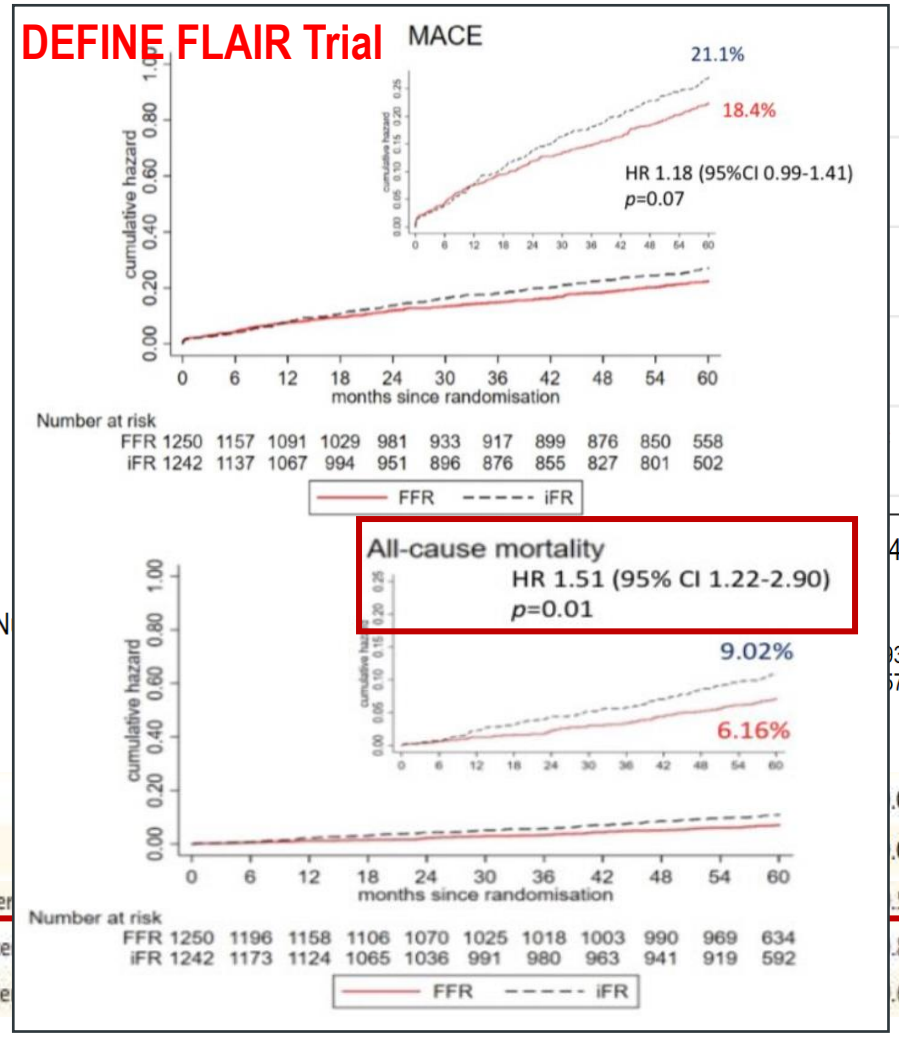
- Coronary revascularization guided by instantaneous wave-Free Ratio(iFR) compared with Fractional Flow Reserve(FFR) → How do we interpret the discordance between the two indices?

- Post-interventional physiological assessment to optimize immediate revascularization results → The evolving role of physiological assessment as a functional optimization tool.

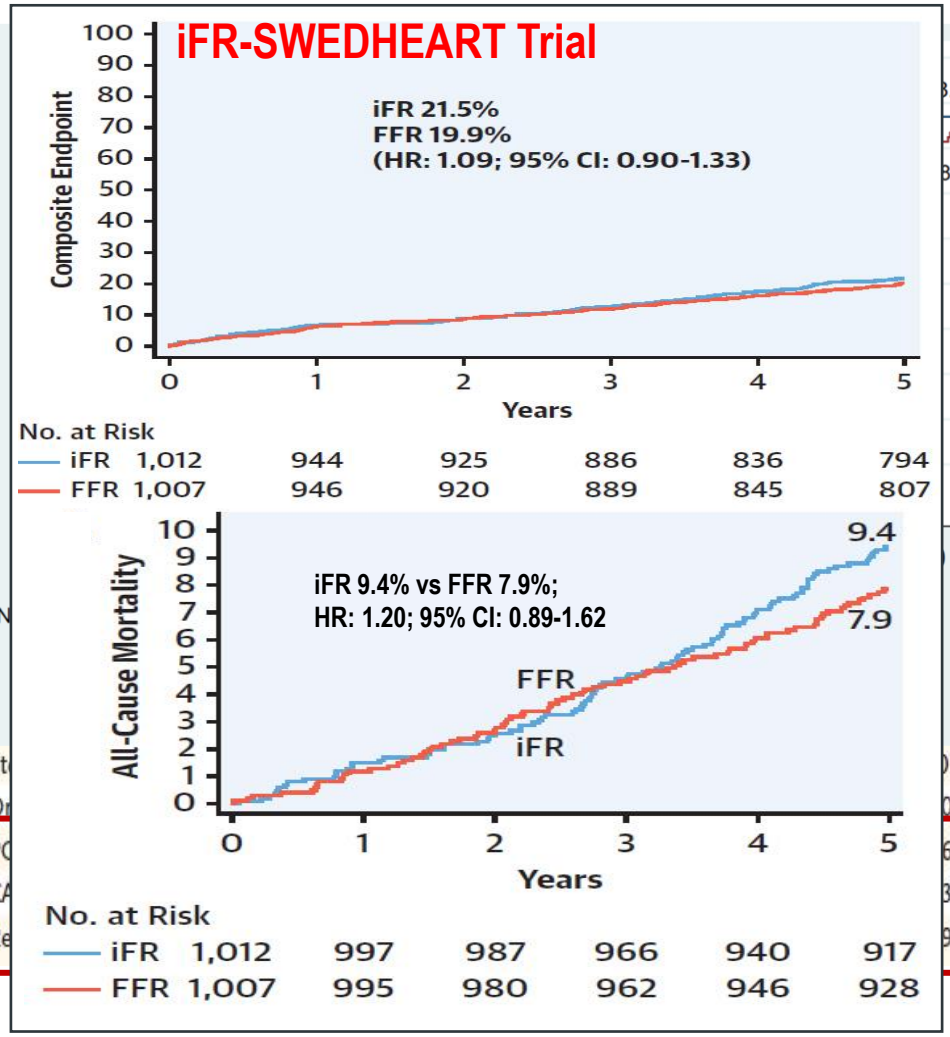
Comparing FFR with iFR guided revascularization

Non-Inferiority Trials for Clinical Outcome

DEFINE FLAIR Trial



iFR-SWEDHEART Trial



EUROPCR 2023

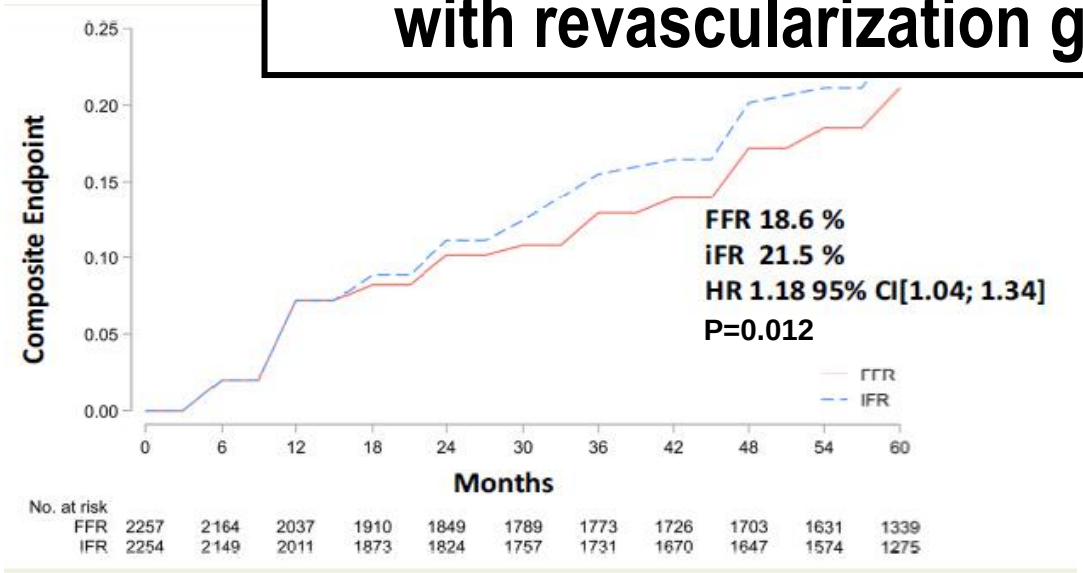
Götberg, MD et al. J Am Coll Cardiol 2022;79:965–974

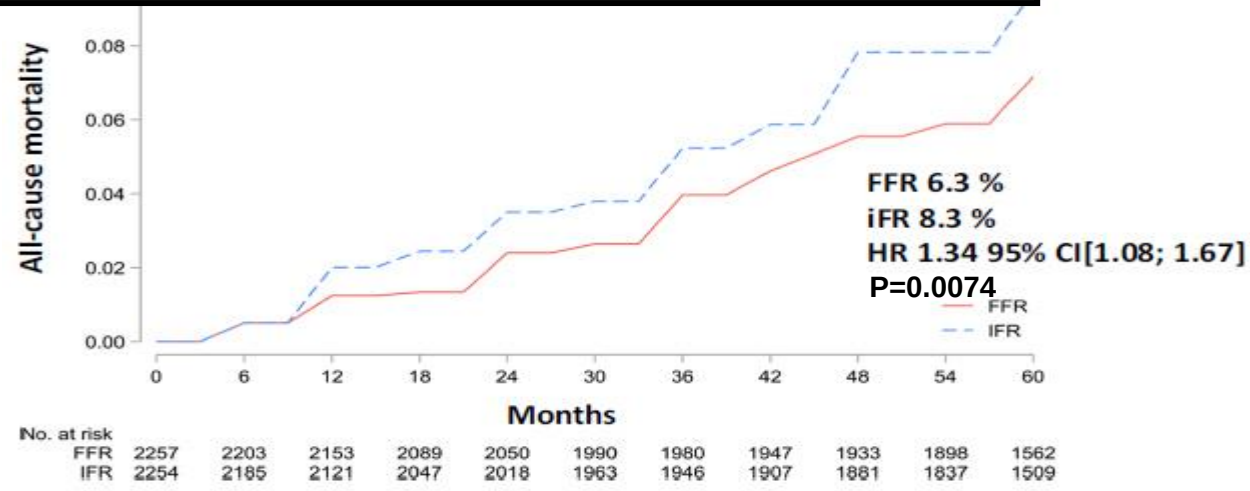
Comparing FFR with iFR guided revascularization

Study-level meta-analysis of the 5-year outcome data in iFR-SWEDEHEART and DEFINE-FLAIR

Procedure Data	iFR (N=2254)	FFR (N=2257)	RR [95%CI]	P vlaue
Revascularization performed	1126 (50%)	1236 (55%)	0.91 [0.86-0.96]	P=0.008
PCI	1008 (45%)	1081 (48%)	0.94 [0.75-0.99]	
CABG	118 (5%)	155 (7%)	0.86 [0.75-0.99]	

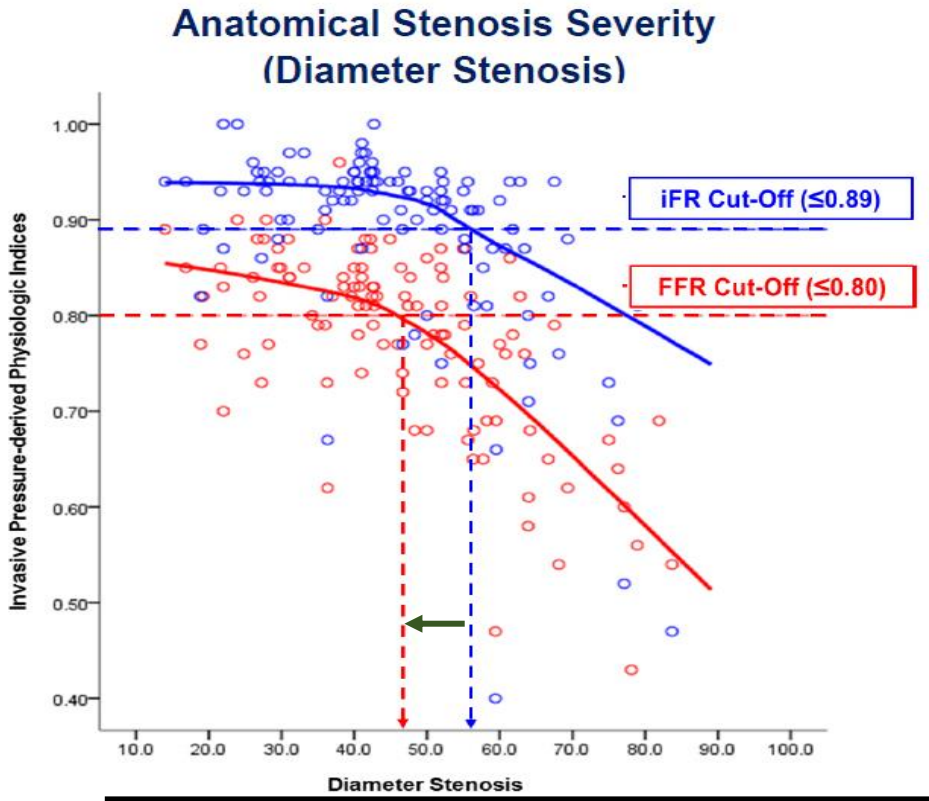
Five-year all-cause mortality and MACE rates were increased with revascularization guided by iFR compared to FFR.

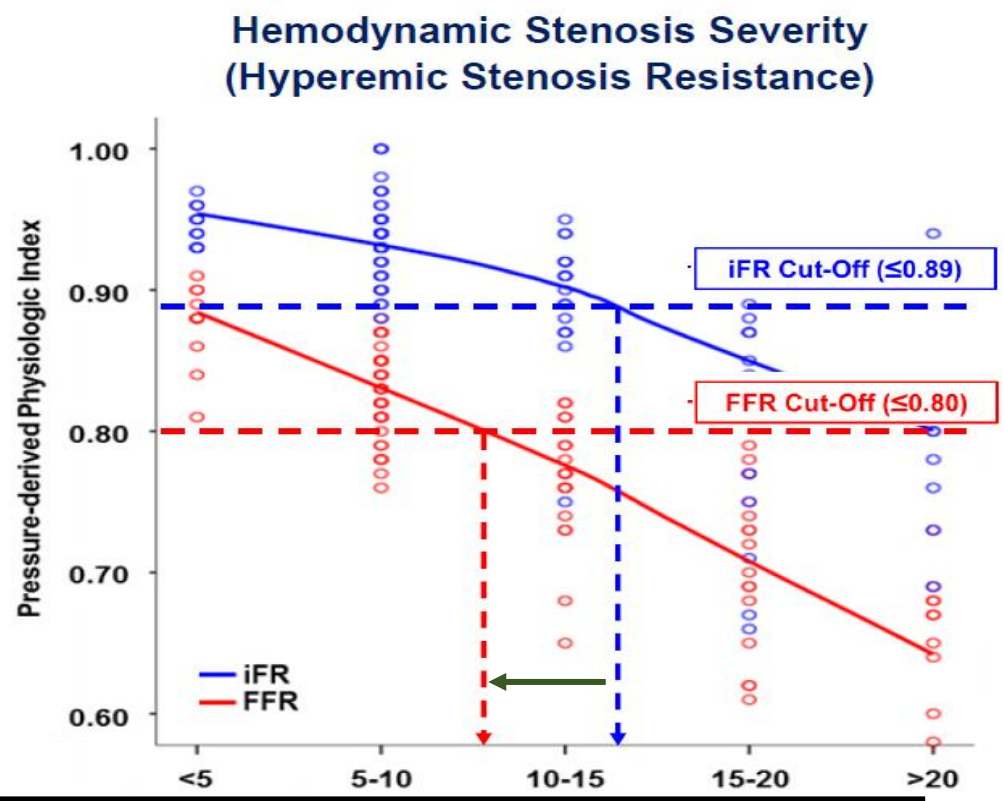




Fundamental Reason of Discordance

Stenosis Severity and Invasive Physiologic Indices





The iFR threshold from normal to abnormal was **crossed** at a slightly **more anatomically or hemodynamically severe stenosis** than FFR.
FFR showed **more sensitive** changes to worsening stenosis severity.

Lee JM, Koo BK, Circulation 2017

Discordance Between FFR & iFR

Clinical Outcomes of Patients With Discordance Between FFR and iFR

817vessel/573patier

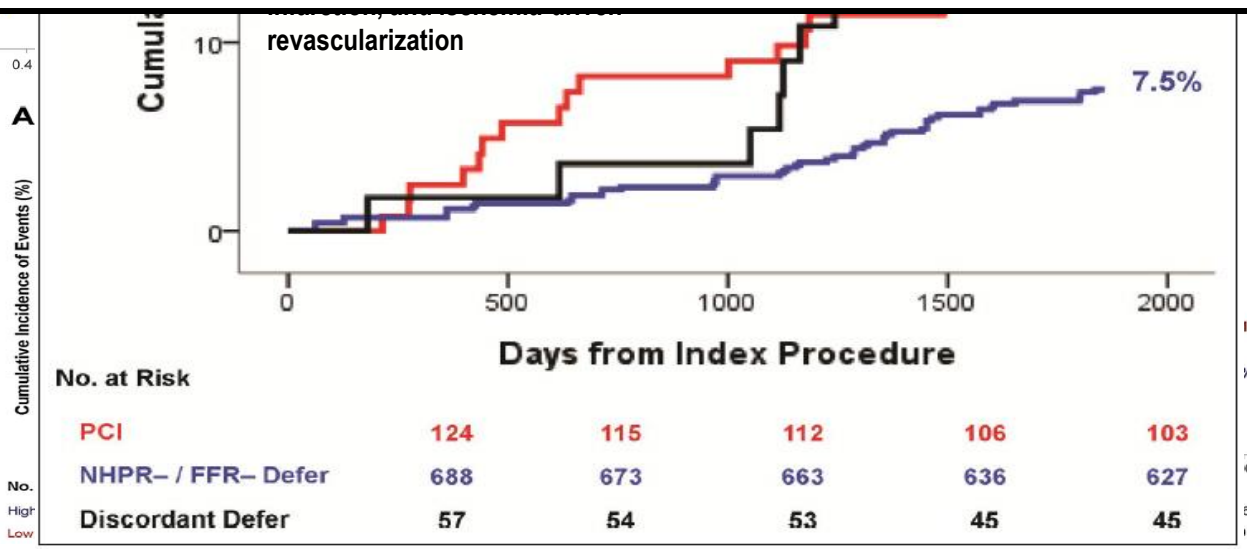
Comparison of 5-year clinical outcomes classified by NHPRs and FFR

Group	HR (95% CI)	P value
Revascularized Vessel	1.000 (Reference)	NA
NHPR(–) and FFR(–) Defer	0.478 (0.268-0.853)	0.013

any revascularization)

Adjusted	
95% CI)	p value
erence	NA
34-3.94)	0.820
38-3.38)	0.831
.17-5.16)	0.018

Deferred lesions with discordant results between NHPRs and FFR showed higher risk of 5-year VOCO than those with concordant negative.
Whether iFR can surrogate FFR will be concluded soon.



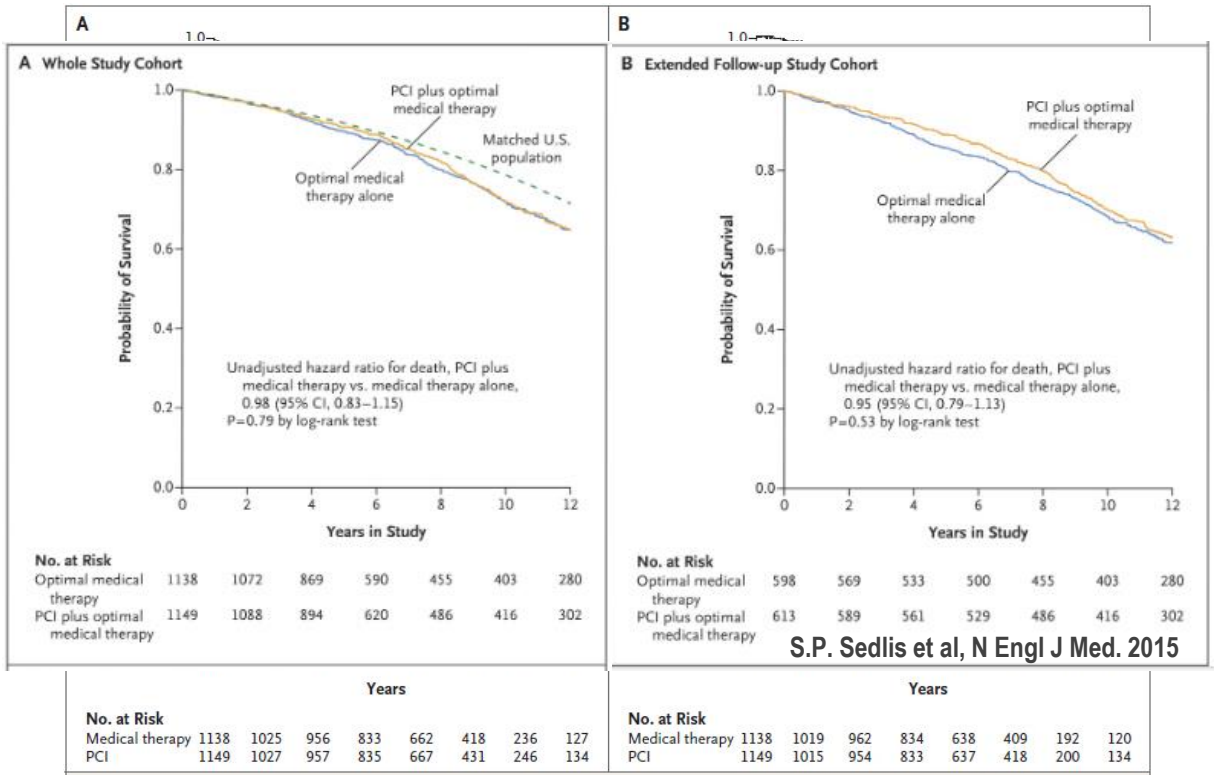
286
26
29
36

Lee SH at al, JACC Cardiovascular Intv. 2019

PCI has no benefit over OMT in SIHD

Courage trial, N= 2,287 (Median F/U 4.6Y)

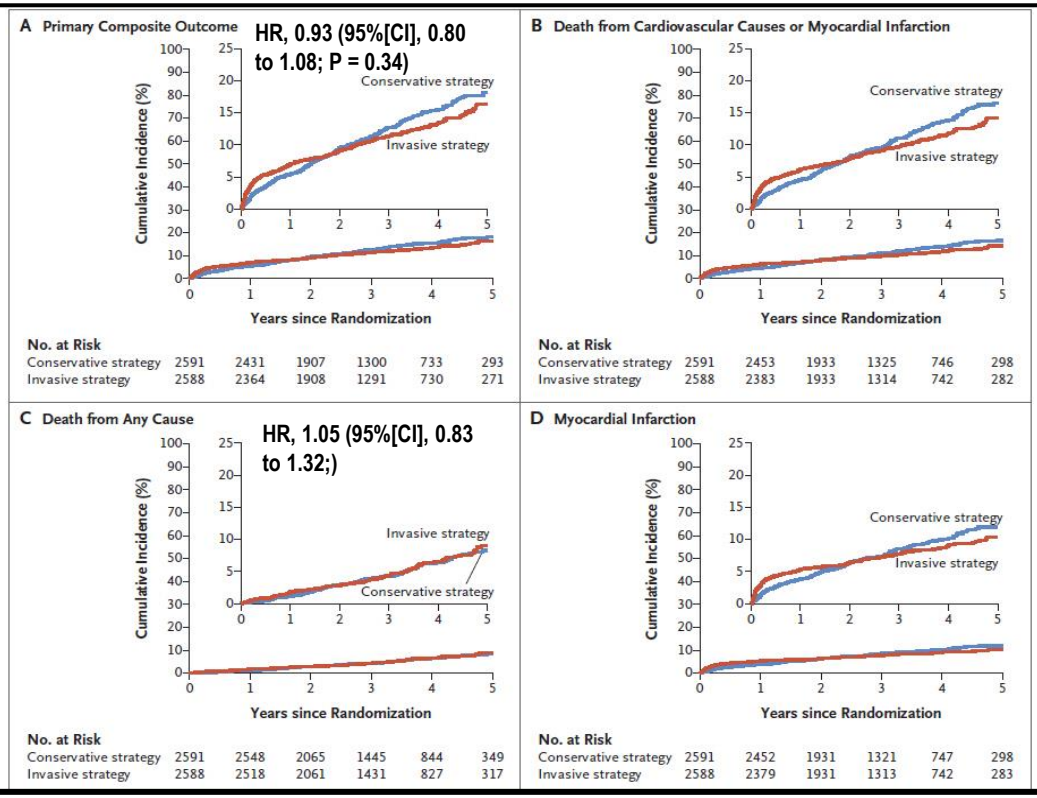
Enrollment Criteria is ≥70%(with ischemic evidence) or ≥80%(without ischemic evidence)



S.P. Sedlis et al, N Engl J Med. 2015

ISCHEMIA trial, N= 5,179 (Median F/U 3.2Y)

74% of Conservative strategy did not CAG, 20% of Invasive strategy did not revascularization.



As an initial management strategy in patients with SIHD,
PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to OMT.

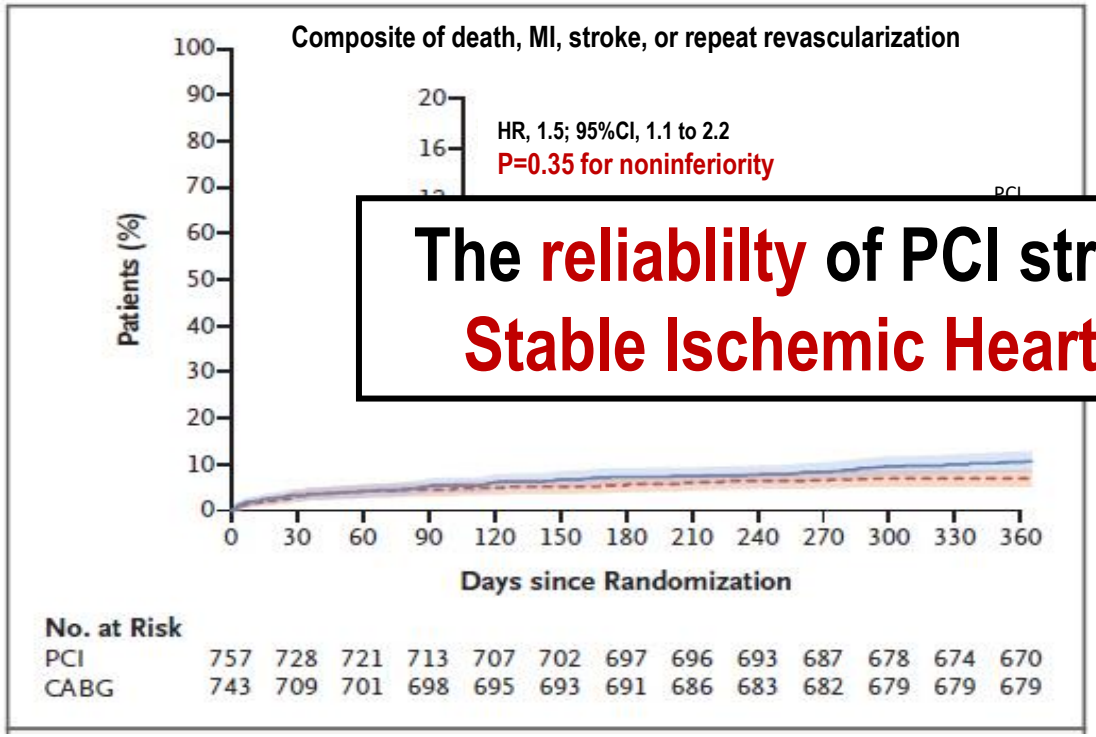
William E. Boden et al, N Engl J Med. 2007 April 12, 356:1503-1516

D.J. Maron et al, N Engl J Med. 2020 April 9, 382:1395-407

PCI has no benefit

FAME3 trial, N= 1,500 (FFR CR vs. Angiographic CABG)

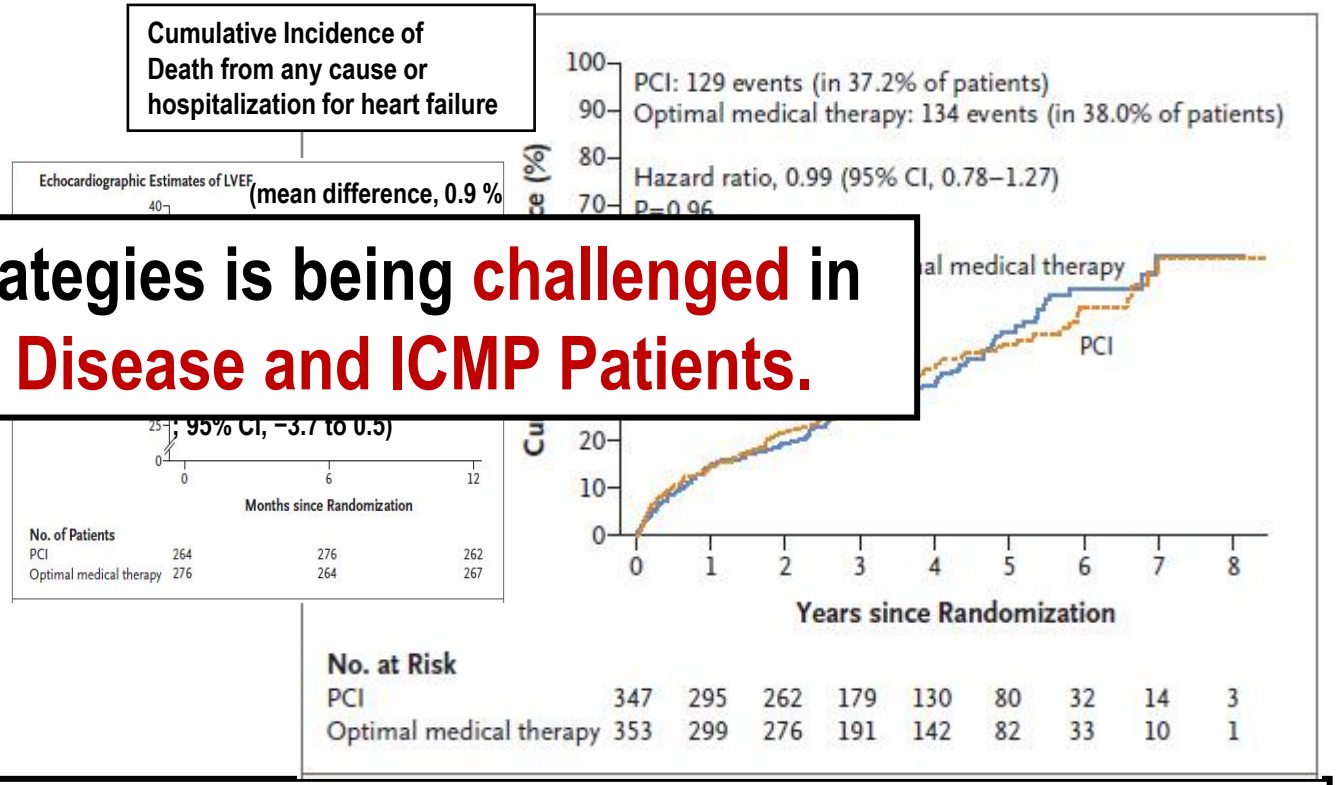
Enrollment Criteria Stenosis ≥50% in 3 Epicardial vessel or Major side Branch, no LM, PCI FFR ≤ 0.8



REVIVED-BCIS2 trial, N= 700 (Median F/U 41M)

PCI vs. OMT in Ischemic LV systolic dysfunction(LVEF 35% or less)

Cumulative Incidence of Death from any cause or hospitalization for heart failure



The reliablilty of PCI strategies is being challenged in Stable Ischemic Heart Disease and ICMP Patients.

In 3VDs patients, FFR-guided PCI was not found to be noninferior to CABG.
PCI did not result in a lower incidence of death from any cause or hospitalization for heart failure.

Fearon W et al, N Engl J Med. 2022; 386:128-37
Perera et al, N Engl J Med. 2022; 387:1351-60

Is it really a good validate?

Interventionists said, is Angiographic PCI enough to resolve ischemia?

Courage trial, N= 2,287 (Median F/U 4.6Y)

Enrollment Criteria is ≥70%(with ischemic evidence) or ≥80%(without ischemic evidence)

There was no mention of use of intravascular imaging, including the supplementary appendix.

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Characteristic	PCI (N=757)	CABG (N=743)
PCI characteristics		
Staged procedure — no./total no. (%)	166/750 (22.1)	NA
No. of stents	3.7±1.9	NA
Median total length of stents placed (IQR) — mm	80 (52–116)	NA
Intravascular imaging used — no./total no. (%)	87/744 (11.7)	NA

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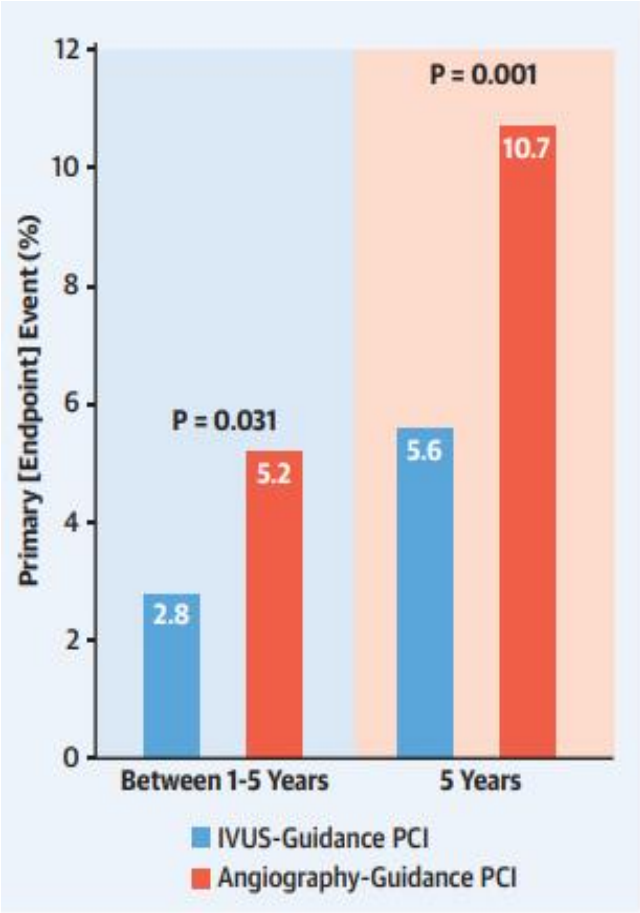
Fundamental Reason for Needs of Optimized PCI

Optimized PCI improved clinical outcomes

IVUS-XPL trial

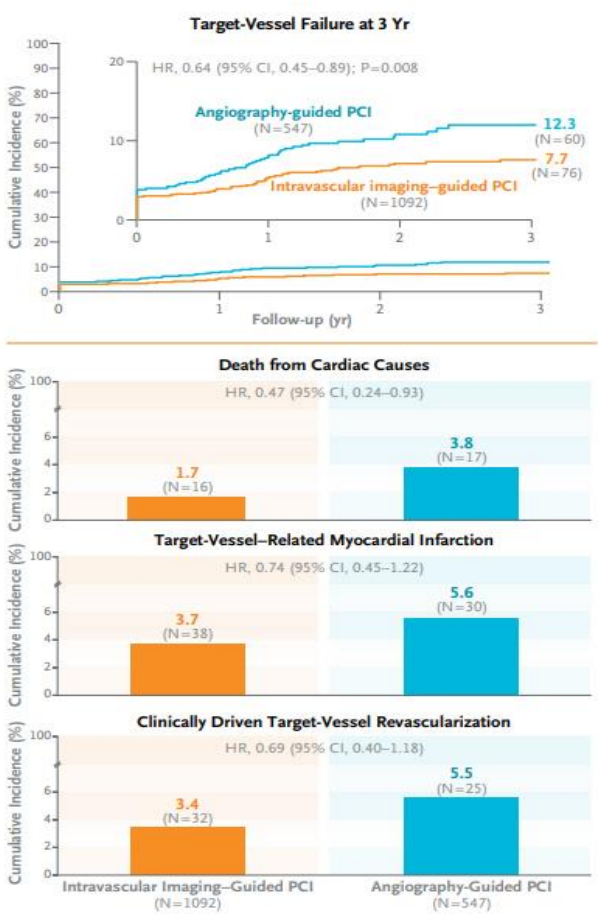
Angio vs. IVUS- guided PCI in Long lesion (≥ 28mm)



Hong SJ et al, J Am Coll Cardiol Intv. 2020;13(1):62-71

RENOVATE trial

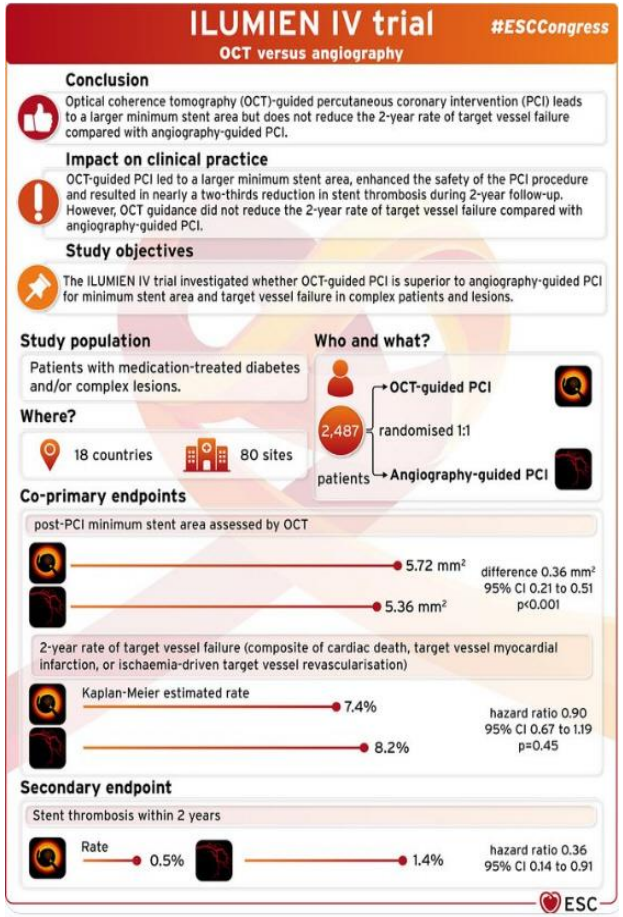
Angio vs. IVUS- guided PCI in Complex lesion



Lee JM et al, N Engl J Med. 2023; 388:1668-79

ILUMIEN IV trial

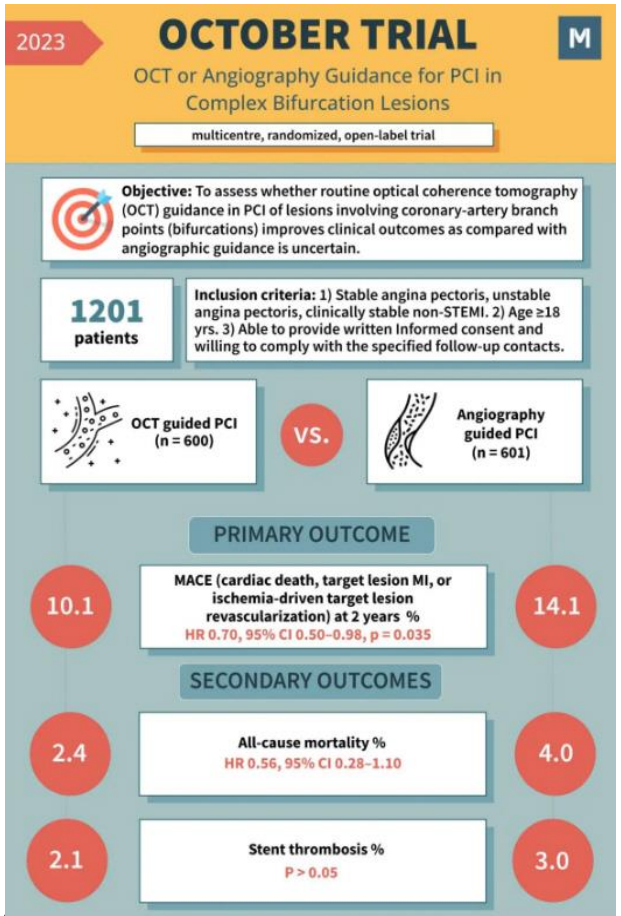
Angio vs. OCT- guided PCI



Ziad Ali et al, N Engl J Med. 2023; 389:1466-76

OCTOBER trial

Angio vs.OCT-guided PCI in Bifurcation lesion



Holm et al, N Engl J Med. 2023; 389:1477-87

How to Optimized PCI using FFR

FLAVOUR trial, N= 1,682 (FFR Guided 838 vs. IVUS Guided 844 in Intermediate Lesion, non-inferiority)

How to Define ischemia(=FFR) Vs.
How to Optimize PCI(=IVUS) ????

The initial aim of the trial was to prove th
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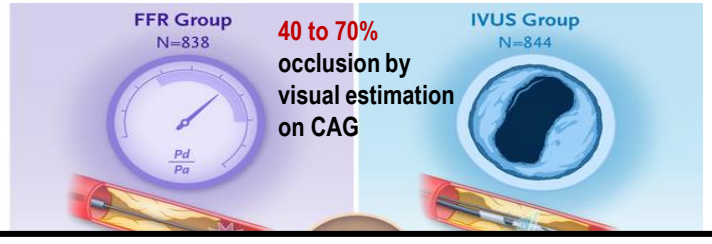
discrimi
interme

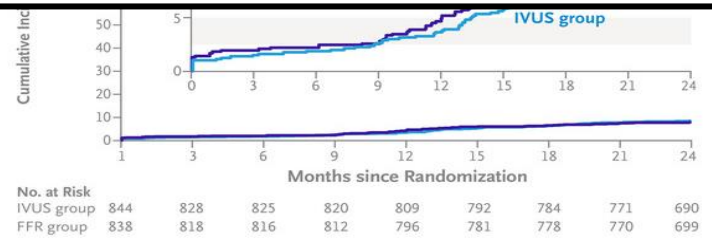
Published results of several studies showed that IVUS-guided stenting could further improve clinical outcomes

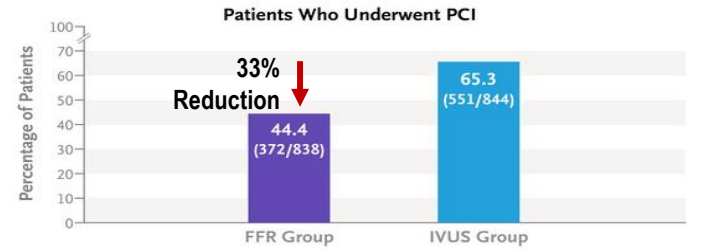
The trial aim modified to assess the non-inferiority of FFR-guided procedures in comparison with IVUS-guided procedures in 2017 → FFR can also optimize PCI as well as IVUS



No difference was observed in patient-reported outcomes between the **two strategies.**

PCI Optimization by FFR is as Reliable as IVUS in Intermediate Lesion.





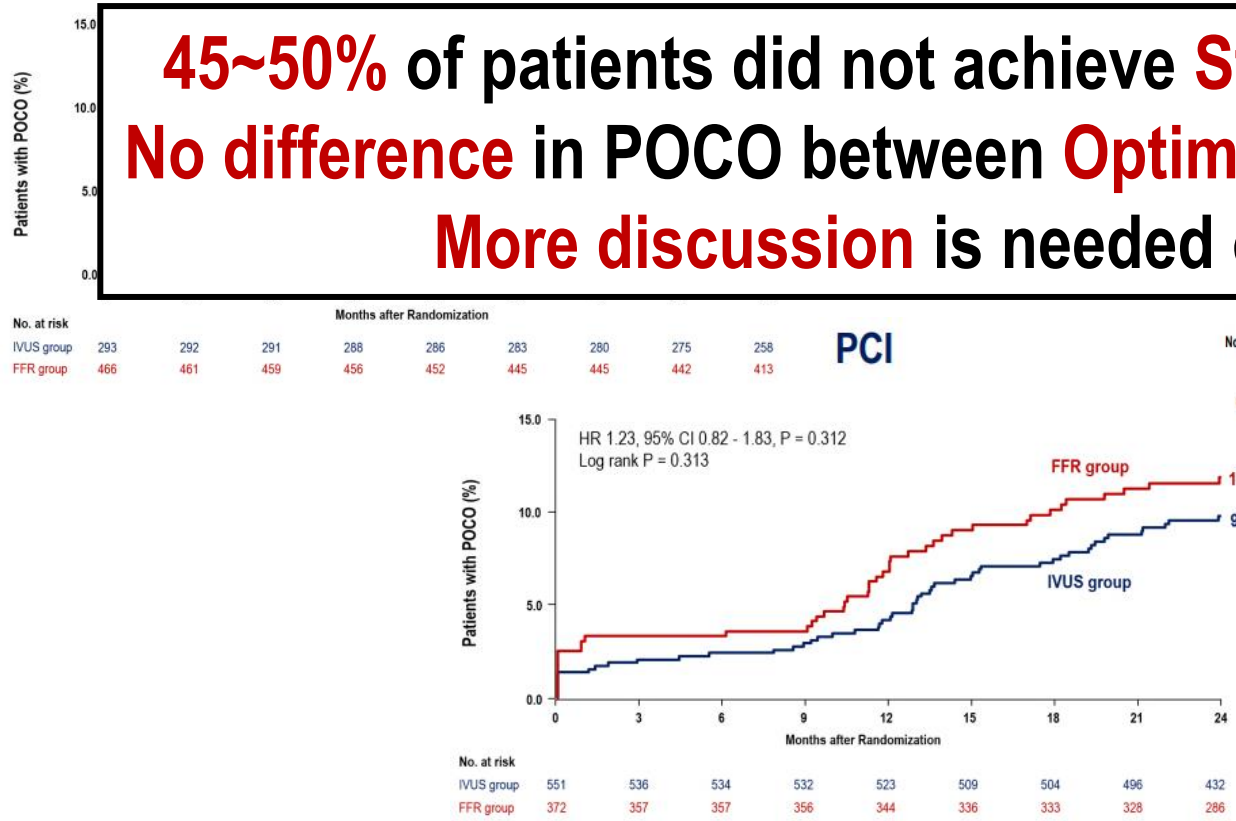
Group Criteria for Successful PCI
IVUS-guided PCI group
Plaque burden at stent edge ≤ 55% and minimal stent area ≥
area ≥
Post PCI ΔFFR at stent ([FFR at stent distal edge] – [FFR at stent proximal edge]) < 0.05

Characteristic	FFR Group	IVUS Group
Procedural outcome**		
Device success	305/305 (100)	525/526 (99.8)
Lesion success	305/305 (100)	525/526 (99.8)
Procedural success	305/305 (100)	525/526 (99.8)
IVUS findings		
Minimal stent area after PCI — mm²	—	7.0±2.2
FFR findings		
After PCI	0.88±0.06	—

Is it enough to Criteria of optimized PCI?

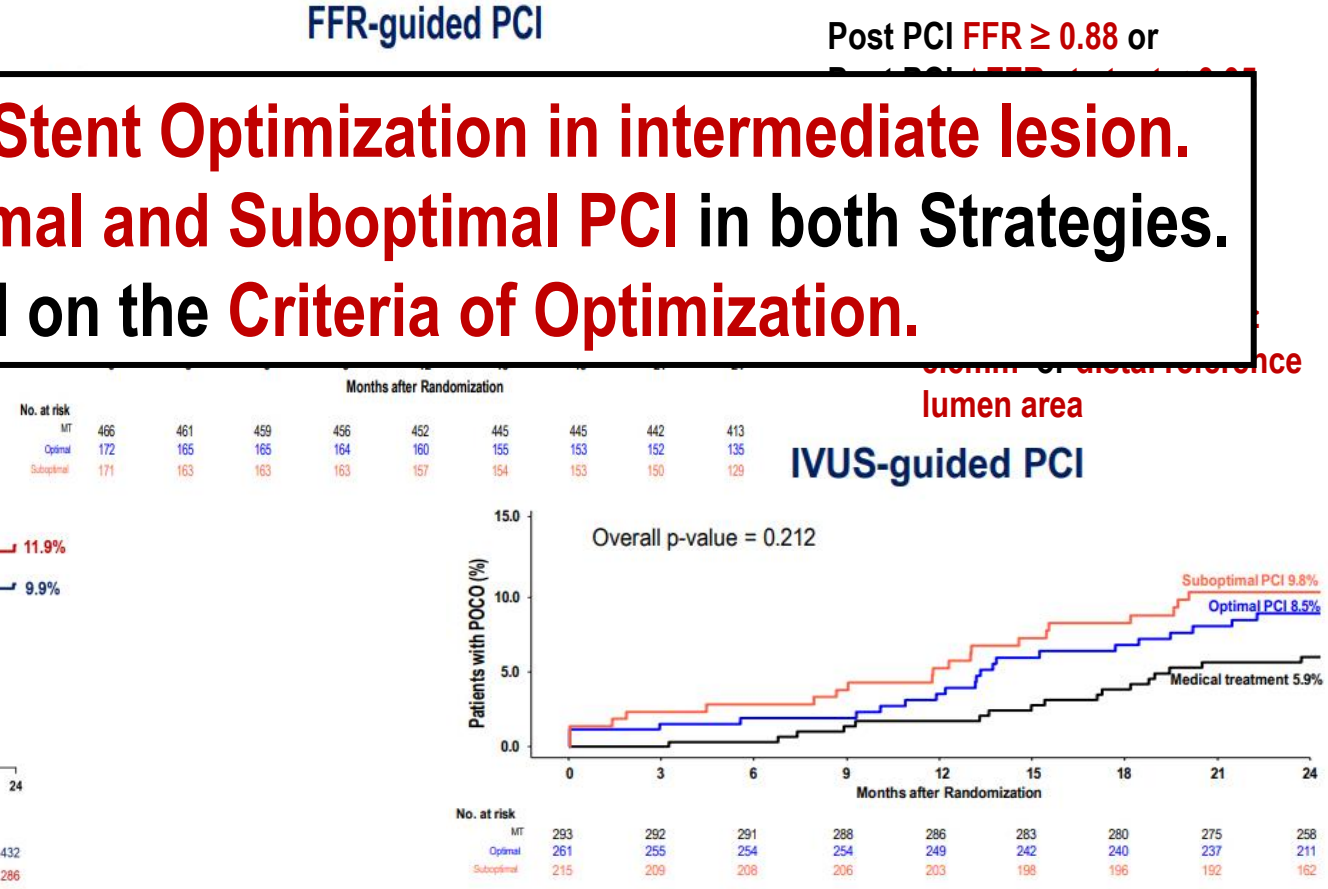
FLAVOUR trial, N= 1,682 (FFR Guided 838 vs. IVUS Guided 844 in Intermediate Lesion, **non-inferiority**)

Primary Outcome According to Treatment



Optimal PCI vs. Suboptimal PCI

Optimal PCI: **FFR-guided PCI 50%**, **IVUS-guided PCI 54.8%**



45~50% of patients did not achieve **Stent Optimization in intermediate lesion.**
No difference in POCO between **Optimal and Suboptimal PCI** in both Strategies.
More discussion is needed on the **Criteria of Optimization.**

Imaging-Guided Optimization Results in Complex PCI

RENOVATE-COMPLEX-PCI trial, N= 1,639 (Image 1092 vs. Angio 547 in Complex Lesion)

Stent Optimization Criteria by Intravascular Imaging

Stent Expansion

Visually residual angiographic dia. stenosis is <10% "AND"

→ Non-LM: In-stent MSA > 80% of the average reference lumen area

"OR" >5

→ LM:

stenosi

Stent A

No majo[illegible] longitudinal extension >1 mm) of the stent.

Edge Dissection

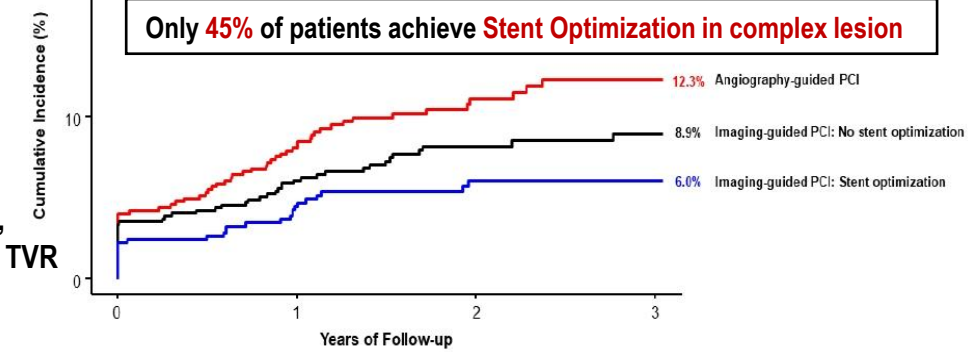
No major edge dissection in the proximal or distal 5 mm from the edge of the stent, extends to the medial layer with potential to provoke flow disturbances(defined as ≥60° of the circumference of the vessel at the site of a dissection or ≥3 mm in length of the dissection flap)

If any of above findings are identified, including additional post-dilatation of the stent or additional stent implantation is recommended.

Characteristics	Total (N=2438)	Imaging-guided PCI (N=1623)	Angiography-guided PCI (N=815)
Adjunctive non-compliant balloon used — no. (%)	1351 (55.4)	980 (60.4)	371 (45.5)
Size of adjunctive balloon — mm	3.5±0.6	3.5±0.6	3.5±0.5
Maximum inflation pressure — atm	18.9±4.6	18.7±4.6	19.2±4.6
Dimensions of devices — mm			

55% of patients did not achieve Stent Optimization in complex lesion.
Patients who achieved Stent Optimization reported better clinical outcome than patients who did not.

Only 45% of patients achieve Stent Optimization in complex lesion

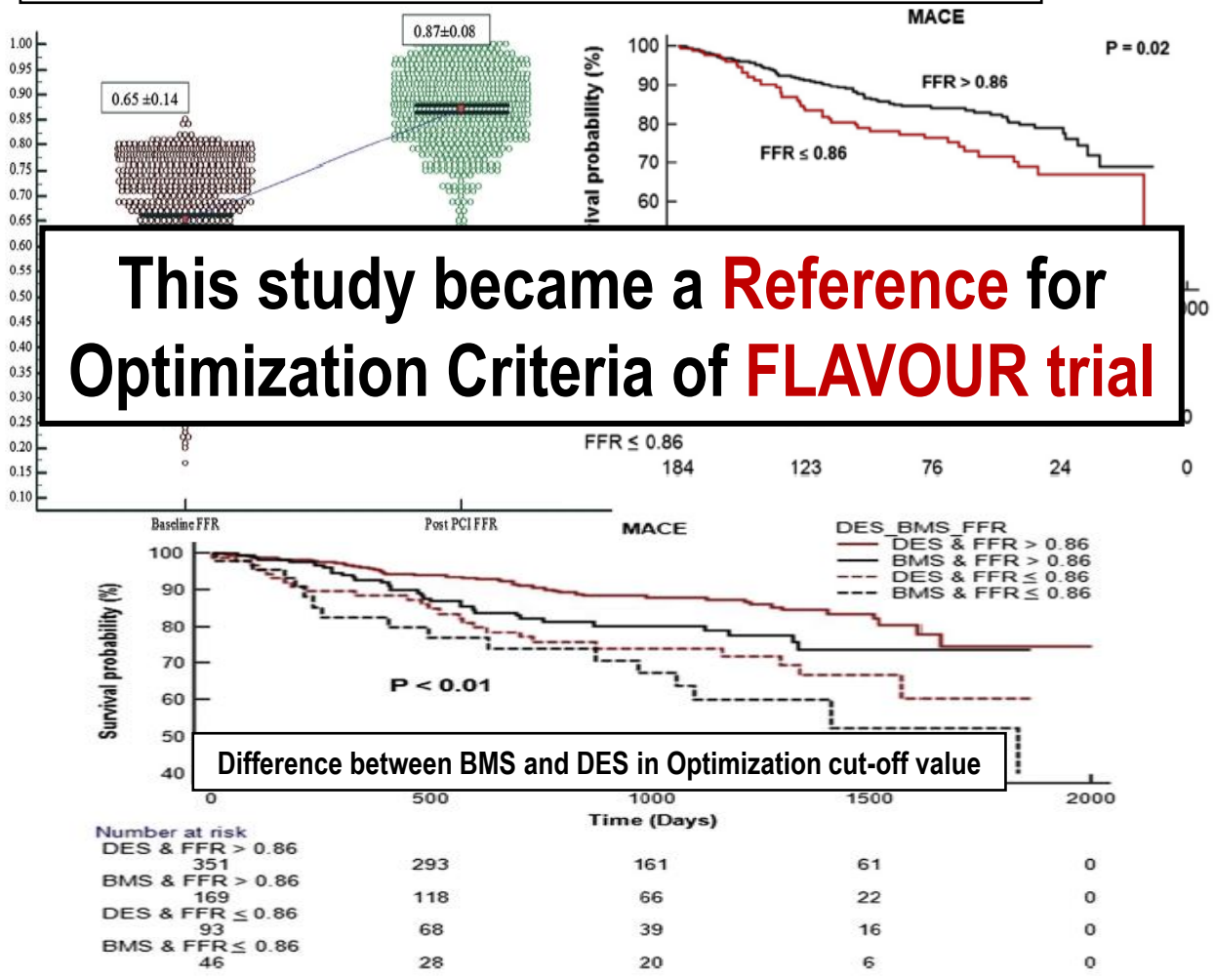


No. at Risk				
Angiography-guided PCI	547	496	267	120
Imaging-guided PCI: No stent optimization	596	556	307	152
Imaging-guided PCI: Stent optimization	496	467	260	103

What is the PCI Optimization by FFR

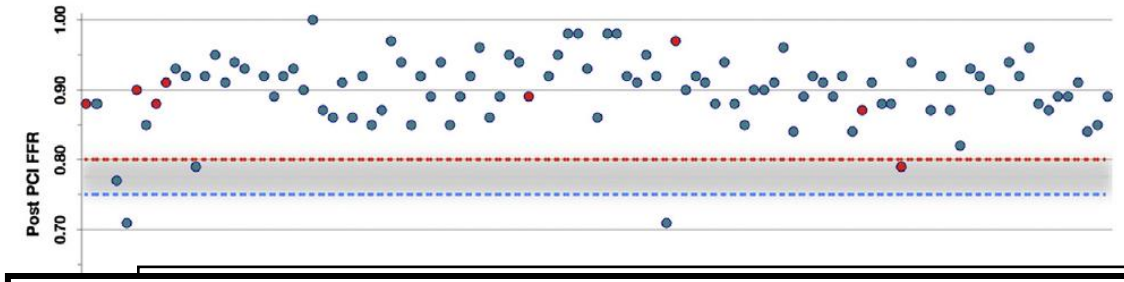
Association between post-stent FFR and clinical outcome

From 2009 to 2014, a total of 574 patients(664Lesions), post PCI FFR 0.87 ± 0.05

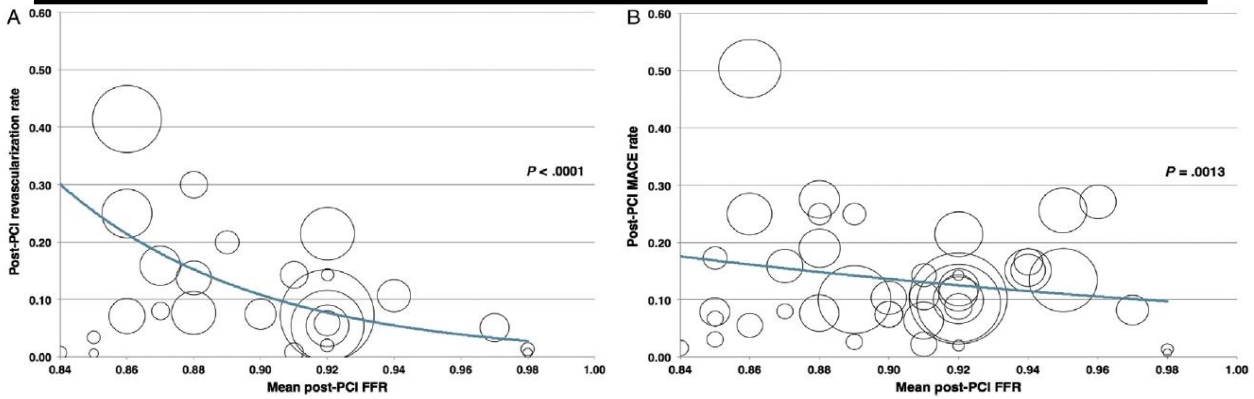


This study became a Reference for Optimization Criteria of FLAVOUR trial

Difference between BMS and DES in Optimization cut-off value



This study became a Reference for Optimization strategy of TARGET-FFR



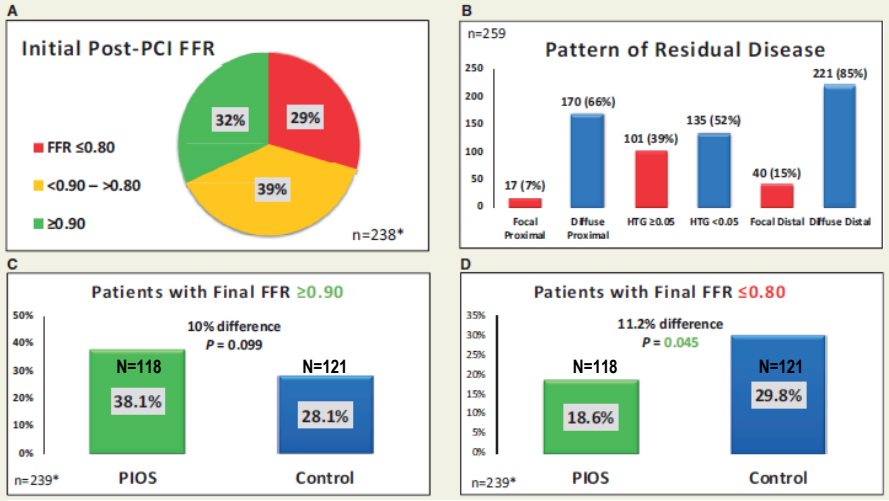
Post-PCI FFR ≥ 0.90 was associated with significantly lower risk of repeat PCI (OR 0.43, 95%CI 0.34-0.56, P = .0001) and MACE (OR 0.71, 95%CI 0.59-0.85, P = .0003)

Agarwal et al, J Am Coll Cardiol Intv 2016;9:1022–31
Rimac et al, Am Heart J 2017;183:1-9.

What is the PCI Optimization by FFR

Post-stenting FFR assessment for PCI optimization

TARGET-FFR→ single-centre, RCT, Post-PCI Pts. N=260
FFR-guided optimization(N=131) vs. standard angiography(N=129)
in achieving **final post-PCI FFR values ≥ 0.90**



Physiology-guided Incremental Optimization Strategy

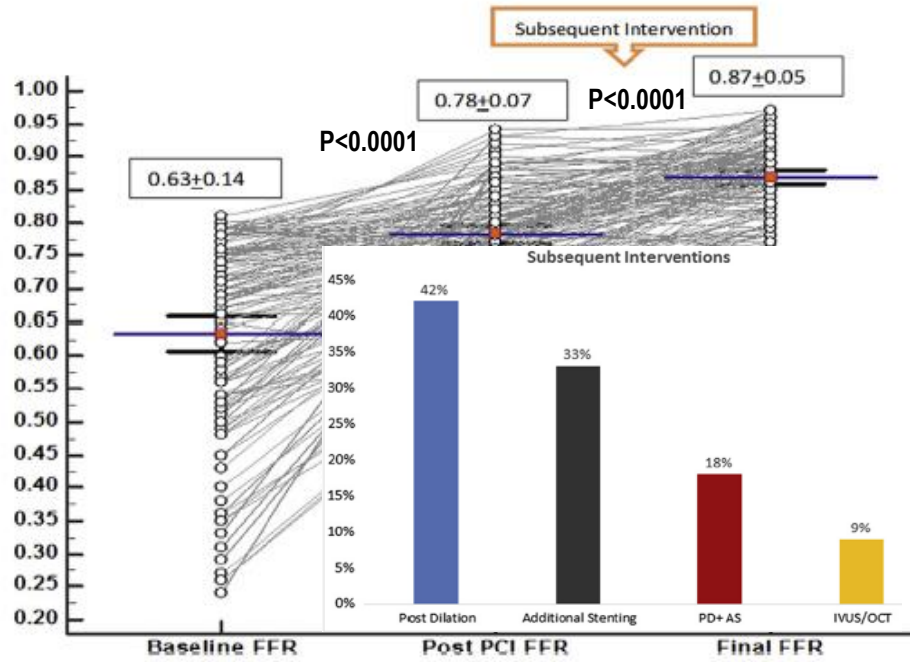
Hyperaemic trans-stent gradient ≥0.05: Post-dilate with larger NC balloon to 18atm. — **HTG ≥0.05**

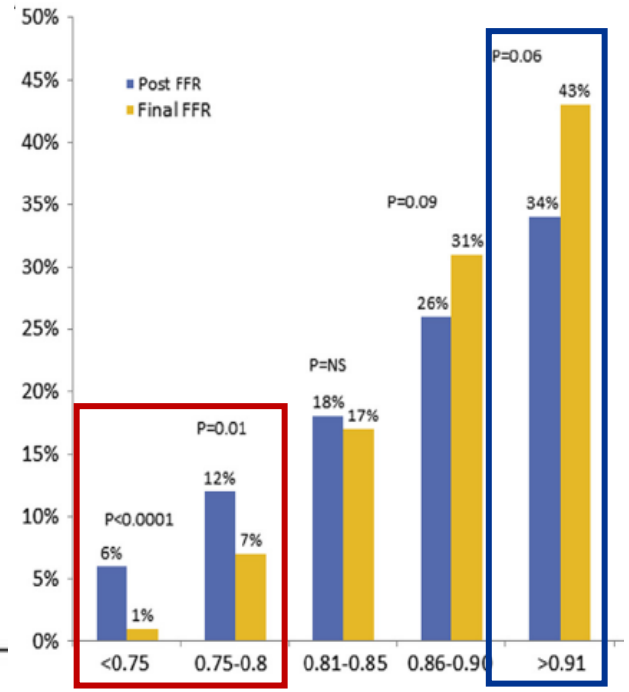
Repeat Pullback → Focal FFR increase ≥0.05 in an unstented segment <20mm: Deploy additional stent. — **Focal Step ≥0.05**

Repeat Pullback → FFR still <0.90: If either of the above criteria remain, option of further post-dilation or one more additional stent

Repeat Pullback → Result Accepted. Procedure Complete.

A total of 574 patients(664 Lesions), F/u 31±16m





Approximately 40% of patients had a physiologically Optimal result after PIOS-PCI(≥ 0.90). Over 70% of patients had a physiologically Optimal result after Subsequent Intervention(≥ 0.86). FFR-guided optimization strategy did reduce the proportion of patients with a final FFR ≤ 0.80.

D. Collison et al. European Heart Journal 2021; 42, 4656–4668
Agarwal et al, J Am Coll Cardiol Intv 2016;9:1022–31

Prognostic Impact of Post-PCI FFR

What is the Best cut-off of Post PCI FFR in 2nd generation DES

First Author, Year	Inclusion	F/u, Months	Post-PCI Index	Results
Ito et al, 2014	97 SIHD or ACS(nonculprit)	17.8(Median)	FFR ≤ 0.90	MACE 17% vs. 2%; p=0.02
				.001.
L				
Hwa				
Bomn				
Hoshino et al, 2019	201 SIHD with de novo LAD lesions	24	FFR < 0.86 D-index < 0.017/cm	VOCE log-rank p = 0.002 MACE log-rank p = 0.084
Hakeem et al, 2019	574 SIHD or ACS	30	FFR ≤ 0.86 Resting Pd/Pa ≤ 0.96	MACE FFR~ 23% vs. 17%; p = 0.02 MACE Resting Pd/Pa~ 24% vs.15%; p = 0.0006
Shin et al, 2020	588 SIHD or ACS (nonculprit)	24	FFR ≤ 0.80 Resting Pd/Pa ≤ 0.92	TVF FFR~ 10.3% vs. 2.5%; p < 0.001 TVF Resting Pd/Pa~ 6.2% vs. 2.5%; p = 0.029 FFR > 0.81 and Resting Pd/Pa > 0.93 were achieved in 81.5%, 63.1%
Diletti et al, 2021 FFR-SEARCH	959 SIHD or ACS	24	FFR < 0.90	MACE (HR, 1.08 [95% CI, 0.73–1.60]; *P*=0.707), TVR (HR, 1.91 [95% CI, 1.06–3.44]; *P*=0.030) FFR ≥ 0.91 was achieved in 58% of Patients

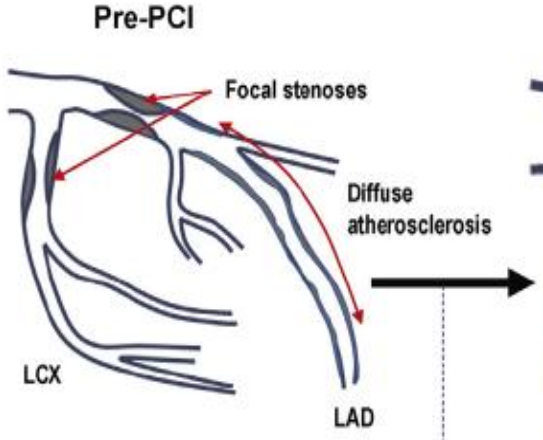
Several Post PCI Indices have been presented through many studies. However, there is controversy over what is the Best Cut-off Value. Low post-PCI FFR values were common after 2nd DES implantation, and were independently associated with future risk of TVF.

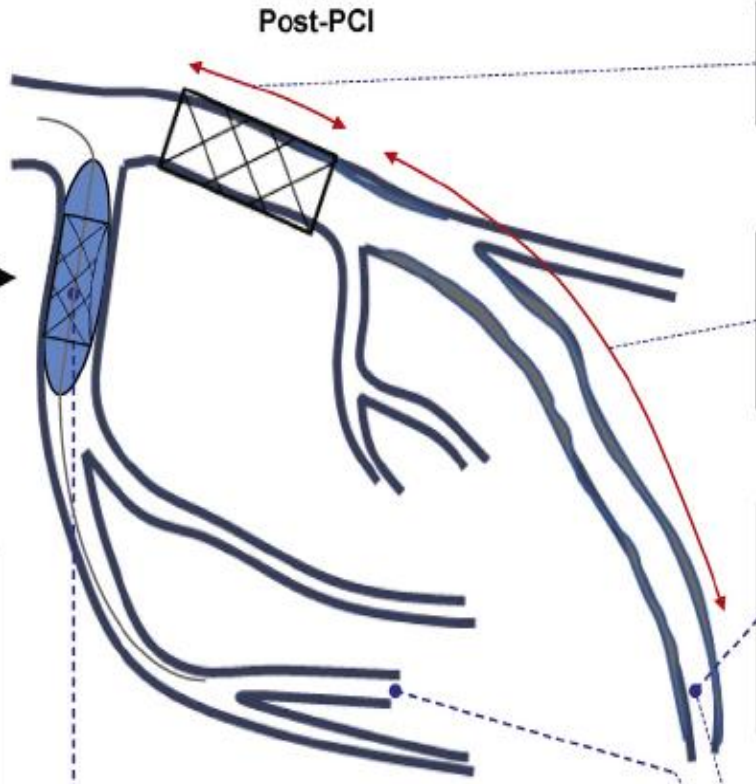
LEE JM et al. JACC: Asia 2021;1:14–36

Diletti et al, *Circ Cardiovasc Interv.* 2021;14:e009681

Physiologic Based Optimization of PCI

Current Evidence for Clinical Implications of Post-PCI FFR





FFR Gain After PCI

Δ FFR (absolute) or **Percent FFR increase (relative)** is significantly associated with angina severity, quality of life, and clinical outcomes.

- Higher Δ FFR was associated with greater improvement in angina severity and quality of life.
- Percent FFR increase had incremental prognostic value in addition to clinical risk factors and post-PCI FFR for target vessel failure.
- Optimal cut-off value of Δ FFR >0.18
- Optimal cut-off value of Percent FFR increase >15%

Post-PCI FFR - Suboptimal result

- IVUS or OCT can reveal potential mechanism of suboptimal post-PCI FFR.
- Adjunctive intervention can further improve post-PCI FFR.
- 9%-11% of diffuse atherosclerosis can be resulted in post-PCI FFR ≤0.80, even with high pressure inflation or additional stenting.

Trans-stent FFR gradient

- Independent predictor of MSA<5.5mm^2 (by IVUS).
- Associated with binary restenosis.
- Optimal cut-off value <0.04

Post-PCI FFR Step-up or D-index*

- Represents residual atherosclerotic disease.
- Associated with suboptimal post-PCI FFR.
- Presence of post-PCI FFR step-up associated with binary restenosis.
- Optimal cut-off value of D-index <0.017/cm

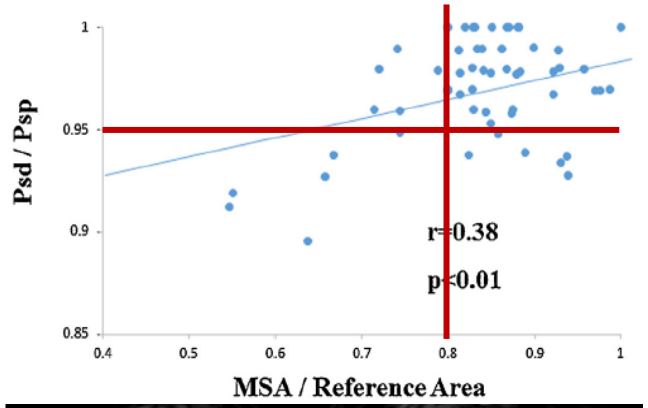
*D-index = FFR step-up amount / distance

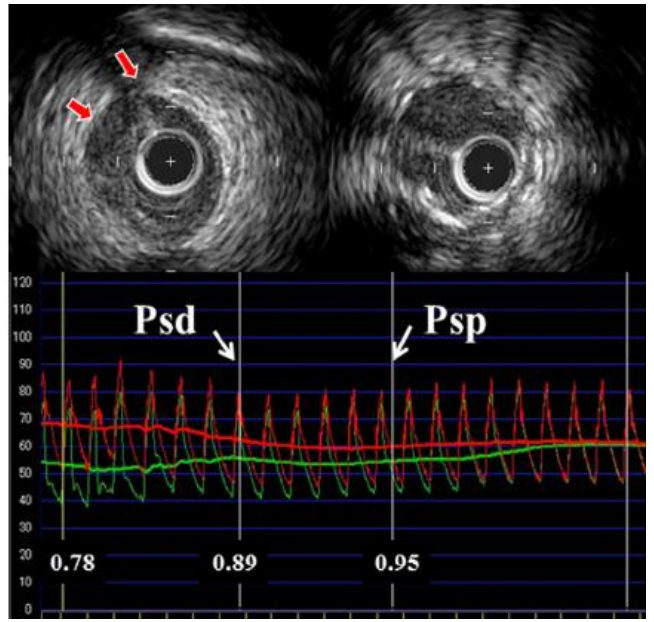
Post-PCI FFR – Prognostic Impact

- Post-PCI FFR cannot be approximated by angiographic residual diameter stenosis.
- Lower Post-PCI FFR is associated with higher risk of clinical events.
- Post-PCI FFR alone showed limited predictability for clinical events.
- Optimal cut-off value >0.84 to 0.96.

Post-PCI FFR - LAD vs. non-LAD

- Post-PCI FFR is significantly lower in LAD than non-LAD vessel despite similar angiographic stenosis.
- LAD is an independent predictor of low post-PCI FFR.
- Optimal cut-off value in LAD for clinical events was different in non-LAD.





LEE JM et al. JACC: Asia 2021;1:14–36

N. Tanaka et al. Journal of Cardiology 69 (2017) 613–618

Summary

We should understand fundamental difference of FFR and iFR.

It will soon concluded whether iFR can surrogate FFR and what is more reliable.

Post-PCI FFR can improved final revasculaization results by further optimizing procedure.

Physiology-guided optimization strategy(PIOS) did reduce the proportion of patients with a final FFR ≤ 0.80.

Low post-PCI FFR values were common after 2nd DES implantation, and were independently associated with future risk of TVF.

Thank You

For your attention

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