Physiologic Assessment of Coronary Artery Disease : Resting index : instantaneous wave-Free Ratio

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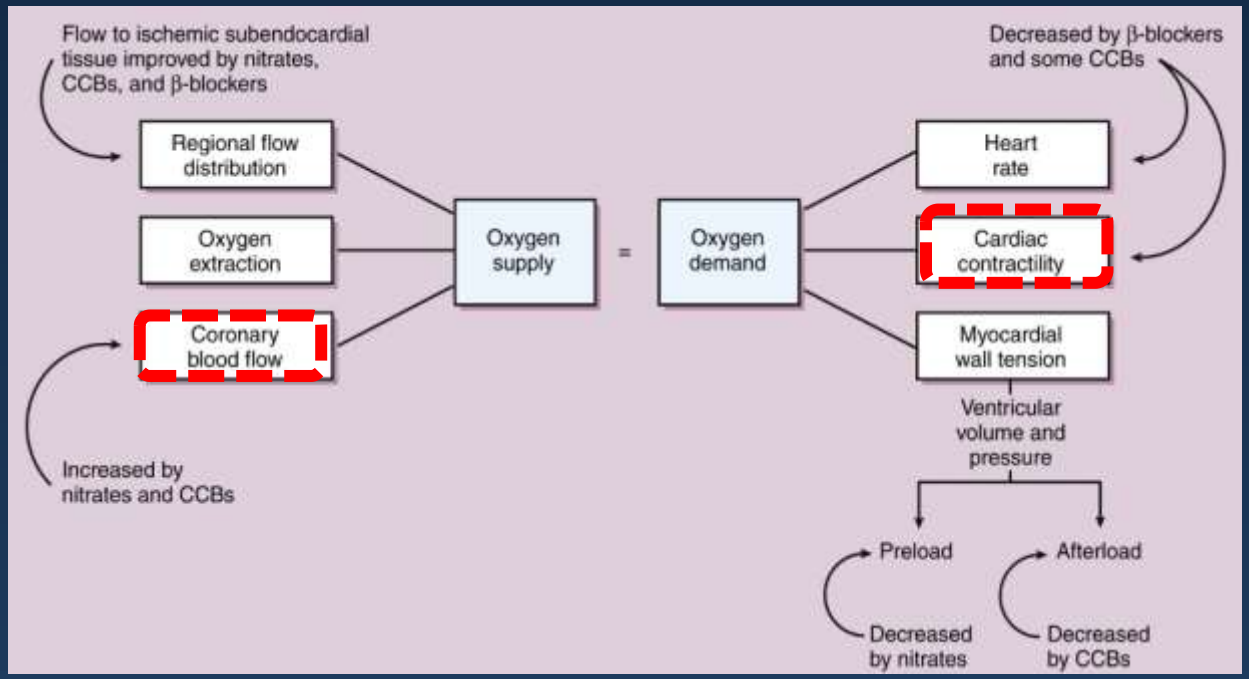
Functional measurements to assess significant coronary lesion : developed to define myocardial ischemia

Imbalance between oxygen demand and supply



- Defining minimal requirement of CBF to maintain contractility is needed
- Measuring required absolute coronary blood flow is impossible

- Coronary blood flow would determine the O2 supply
- Cannot measure O2 demand : CBF alone cannot define ischemia

Using Pressure to Get Flow

- Coronary pressure is simple to measure

$$P = Q \times R$$

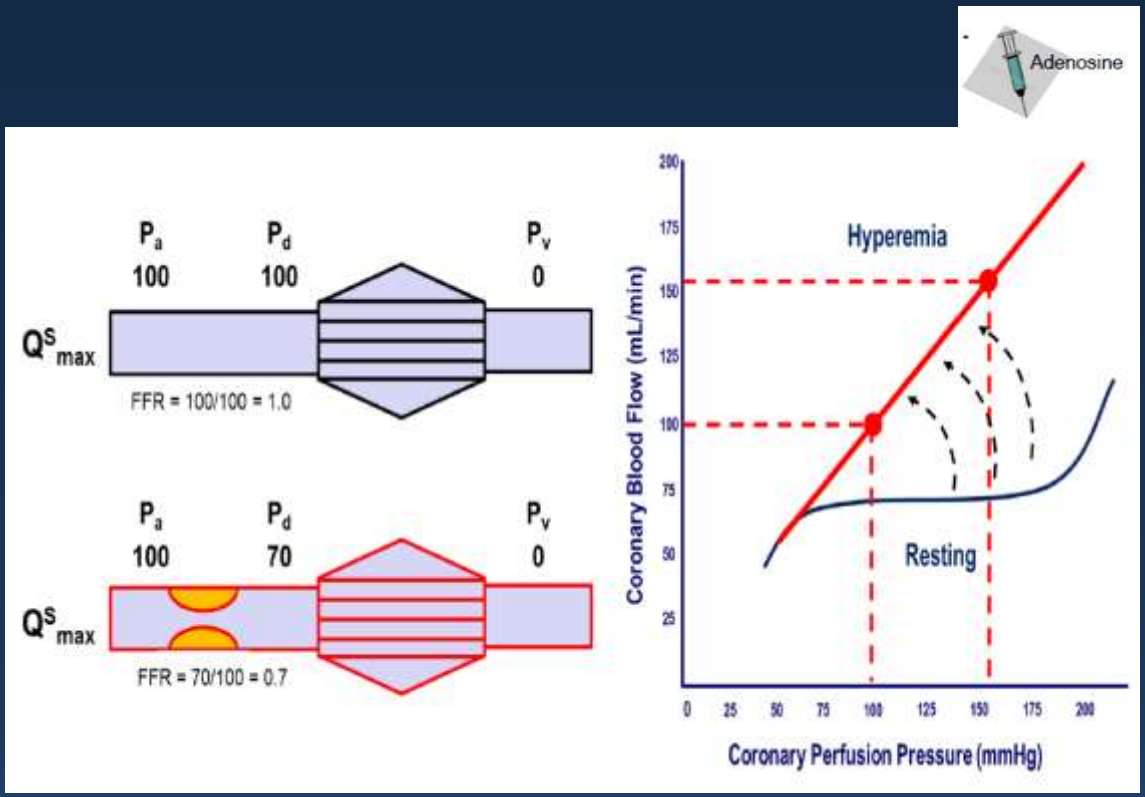
Pressure = Flow x Resistance

If, resistance is stable(constant)

Pressure ≈ Flow

Derived from Poiseuille's Law for Fluid Dynamics

FFR : To assume functional ischemia, indirectly

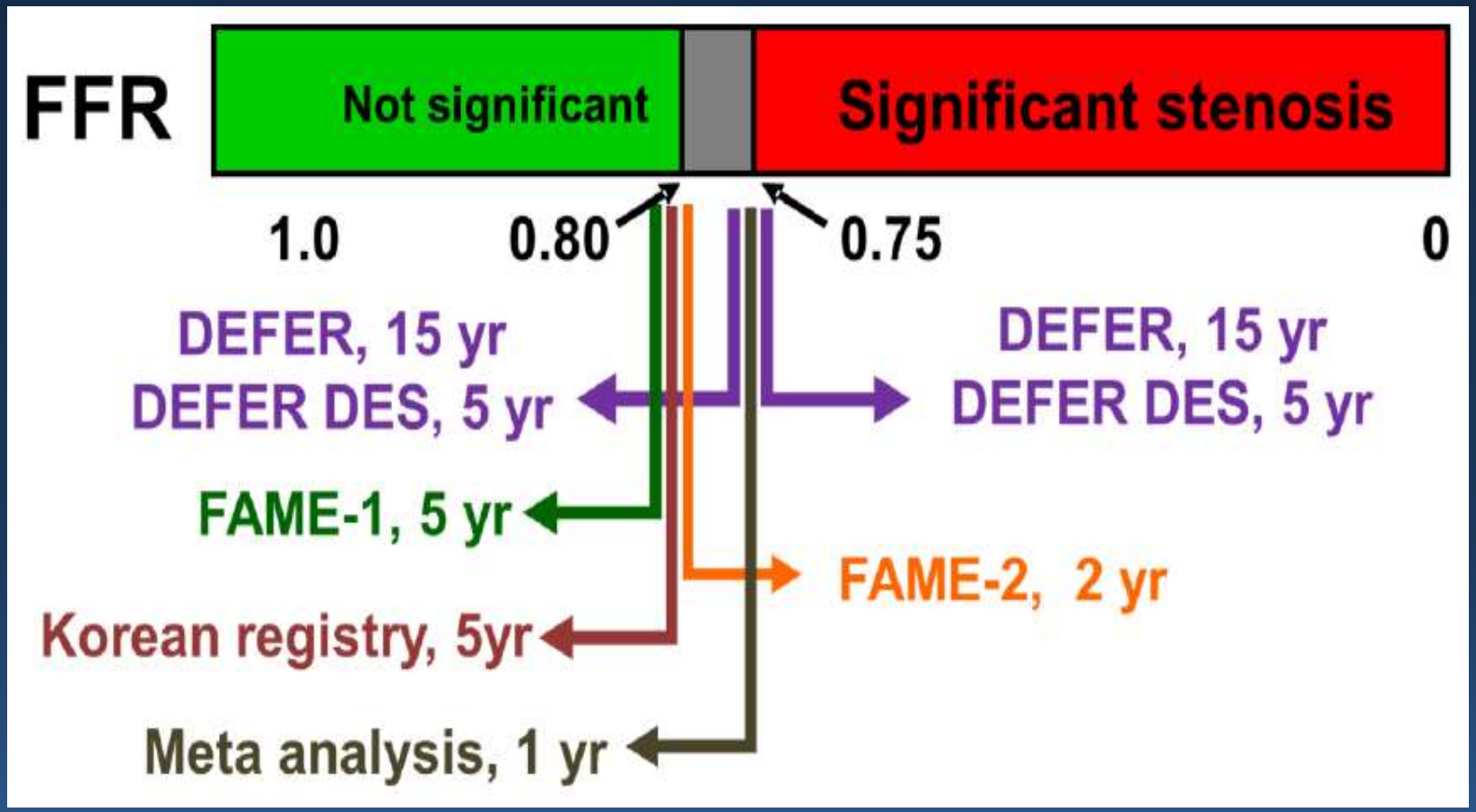


- We measure pressure drop between the stenosis during induced hyperemic condition
- Hyperemia
  - Minimized microvascular resistance by Adenosine / nicorandil

Lee JM, Koo BK, IPOP Textbook of Coronary Imaging and Physiology

Evidences of superiority of FFR guided PCI

- compare to Angiography guided PCI

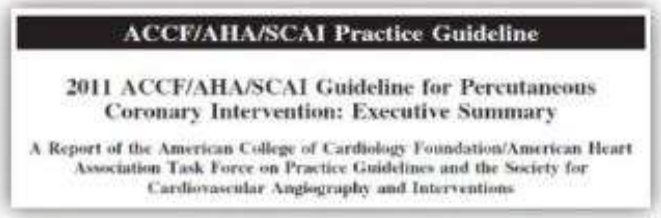


Guideline for PCI

Recommendations	Class[a]	Level[b]
FFR to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available.	I	A
FFR-guided PCI in patients with multivessel disease.	IIa	B

Upgrade

CLASS IIa Level of Evidence A: FFR is reasonable to assess angiographic intermediate coronary lesions (50% to 70% diameter stenosis) and can be useful for guiding revascularization decisions in patients with SIHD. (p32)



Poor adoption of FFR-guided PCI

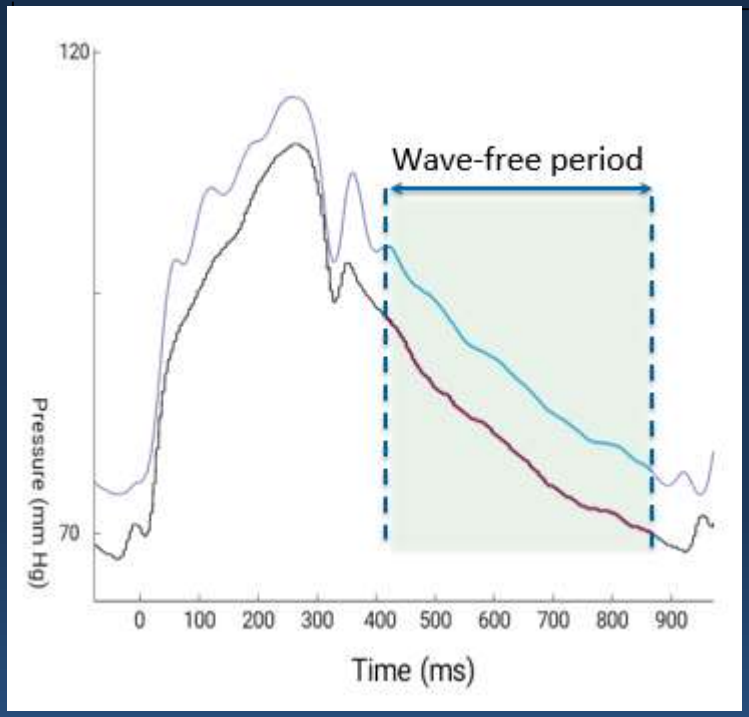
	2014 K-PCI (N = 44,967)	2009-2010 NCDR (N = 61,874)
Indications for PCI	All-comers	Intermediate stenoses
Use of FFR, n (%)	1,675 (3.72)	3,763 (6.1)
Use of IVUS, n (%)	12,846 (28.6)	12,589 (20.3)

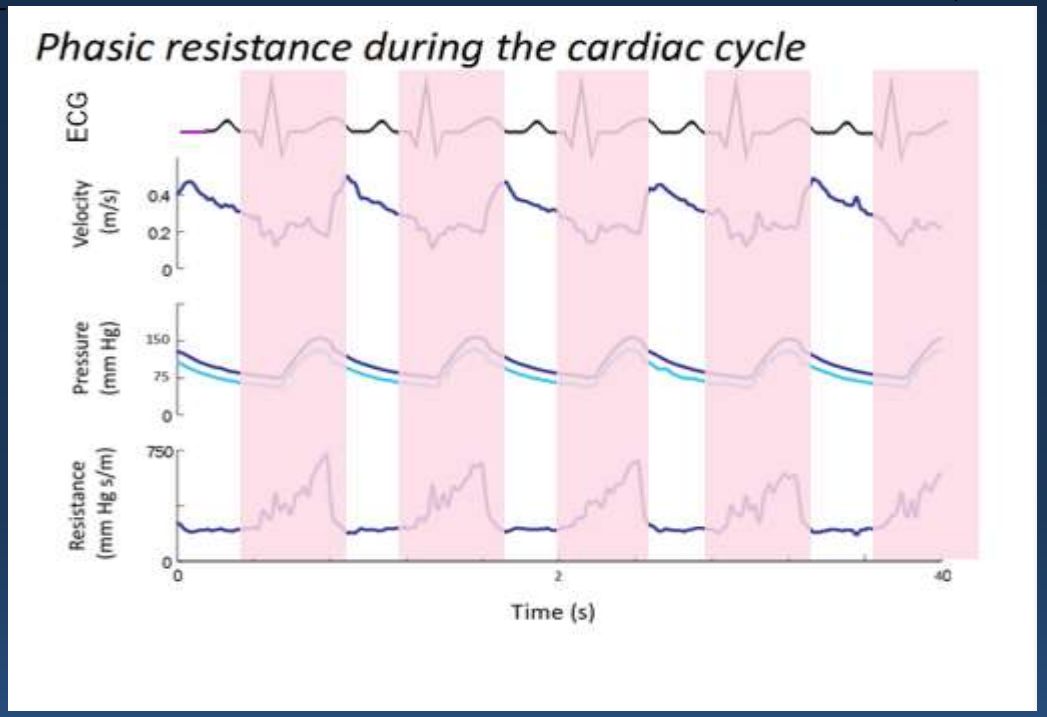
- 1.Interventional cardiologists still largely underestimate the advantage of physiology
- 2.Technical steps of FFR measurement must be carried out with precision
- 3.Substantial costs of pressure wires
- 4.Adenosine-mediated hyperemia: time-consuming, costly, alters systemic hemodynamics, side effects (AV conduction abnormalities, chest discomfort, etc.)

Jang JS *et al.* Korea Cir J 2017;43:328-40
Dattilo PB *et al.* J Am Coll Cardiol 2012;60:2337-9
de Waard GA *et al.* EuroIntervention 2017;13:450-8

instantaneous wave-Free Ratio (iFR)

Definition: Instantaneous pressure ratio, across a stenosis during the wave-free period, when ***resistance is naturally constant*** and ***minimized*** in the cardiac cycle

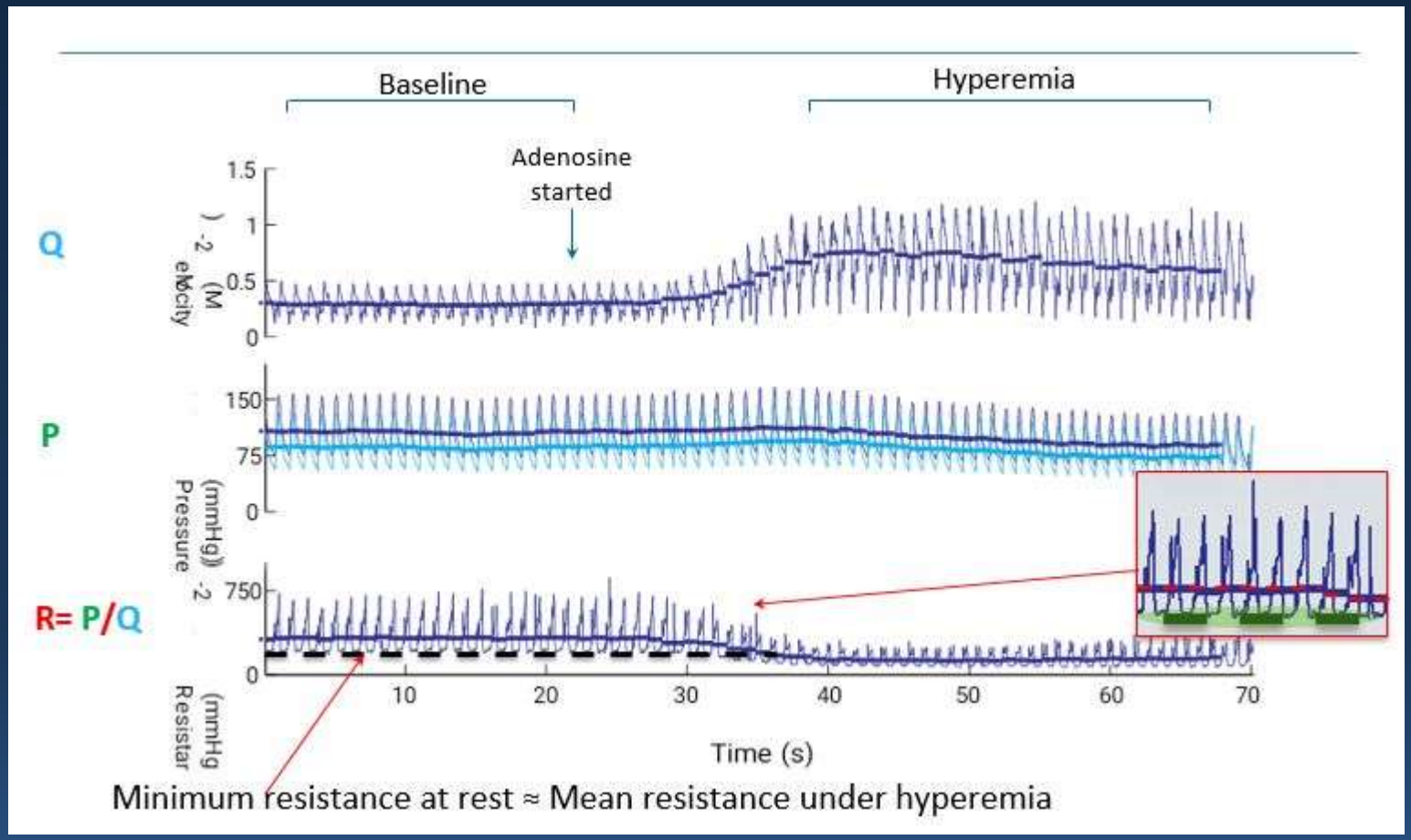




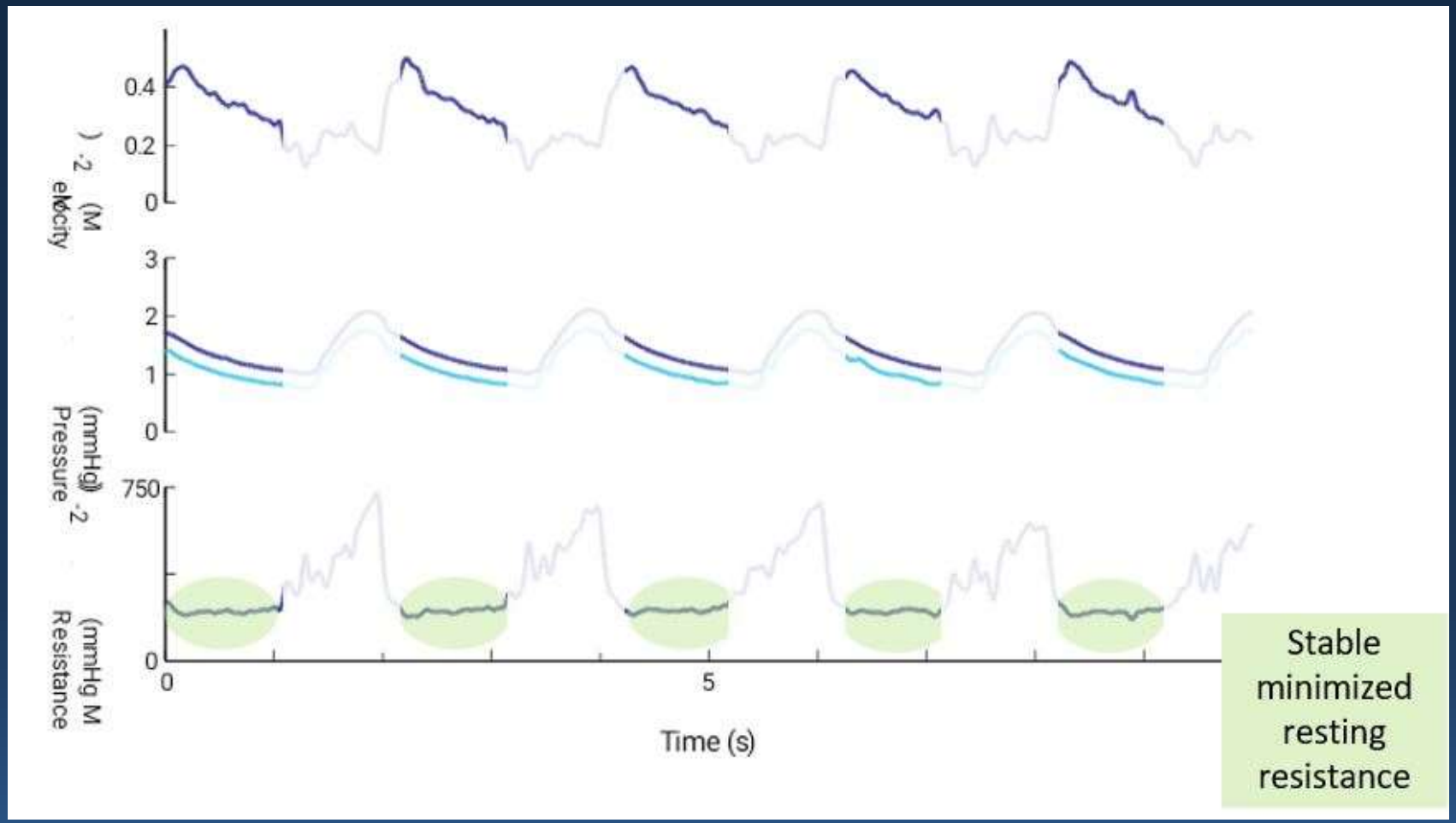
This wave-free period prevails over most 75% of the diastole and is the basis for iFR®- measurement.

Sen S, *et al.* Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity an alysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol*. 2012 Apr 10;59(15):13 92-402.

Change in hemodynamic variables with adenosine hyperemia



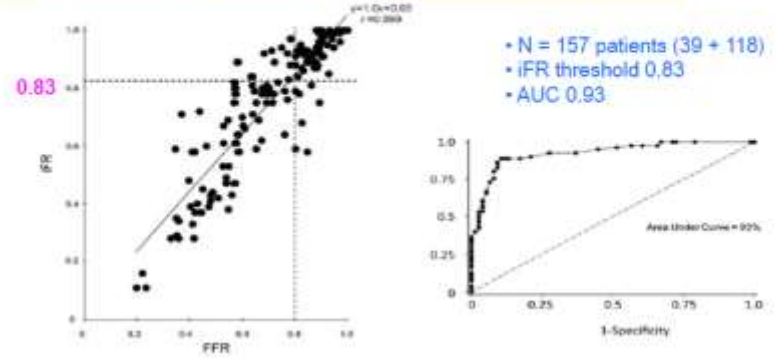
Minimum resistance (mid/late diastole) used to calculate iFR



Validation of iFR

Development and Validation of a New Adenosine-Independent Index of Stenosis Severity From Coronary Wave–Intensity Analysis

Results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) Study

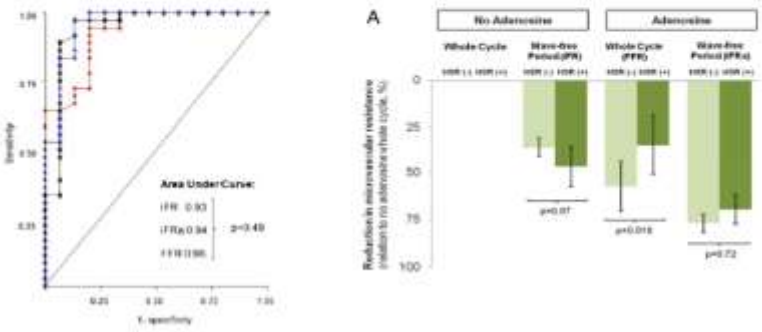


Sen& Davis et al JACC 2012

Diagnostic Classification of the Instantaneous Wave-Free Ratio Is Equivalent to Fractional Flow Reserve and Is Not Improved With Adenosine Administration

Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study)

hyperemic stenosis resistance (HSR) = (Pa –Pv) / Velocity vs iFR, FFR

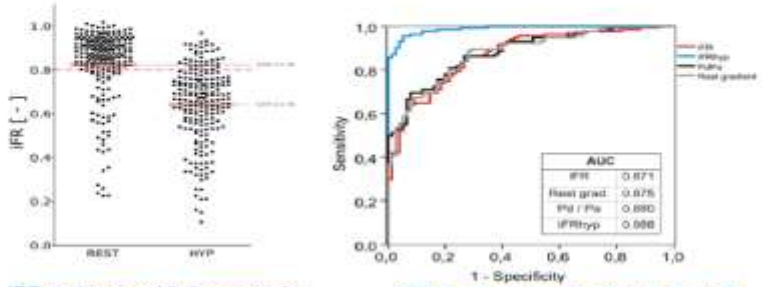


Sen& Davis et al JACC 2014

VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice)

A Multicenter Study in Consecutive Patients

- Prospective 206 Pts. + retrospective 500 recordingds



iFR reduces with hyperemia.

iFR is similar with simple Pd / Pa.

Nico Pijls et al JACC 2013

CLINICAL RESEARCH — Coronary Artery Disease

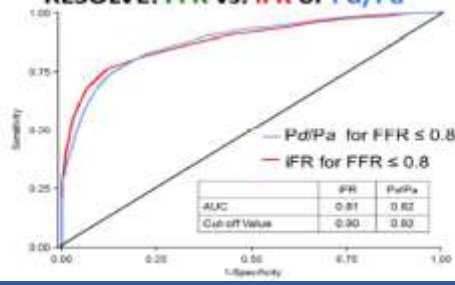
Multicenter Core Laboratory Comparison of the Instantaneous Wave-Free Ratio and Resting P_d/P_a With Fractional Flow Reserve

The RESOLVE Study

1768 patients, pooled analysis, core laboratory

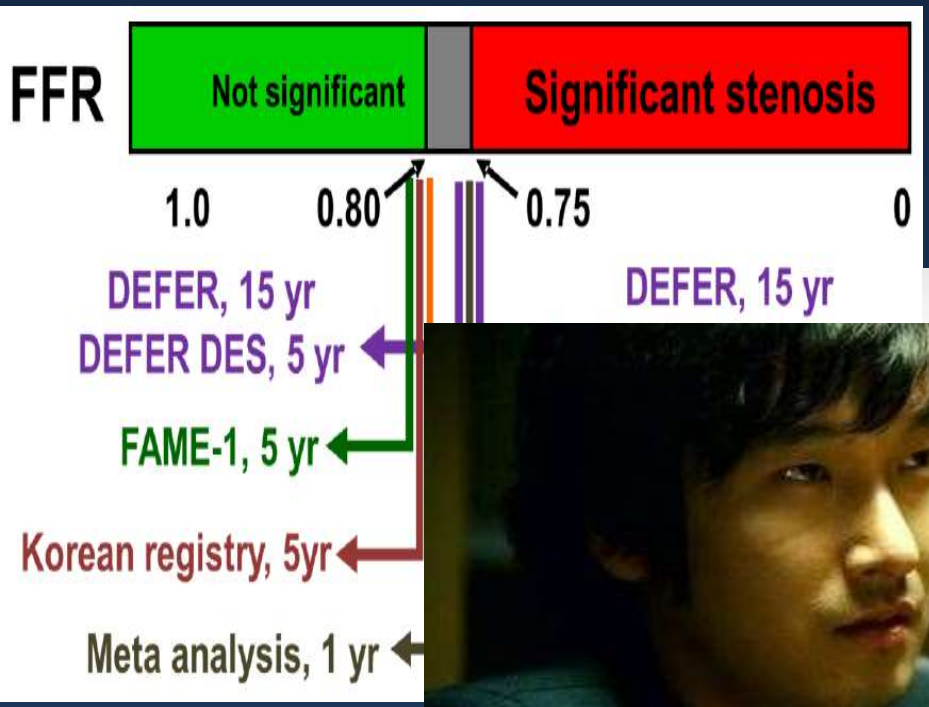
Classification match: 80%

RESOLVE: FFR vs. iFR or Pd/Pa

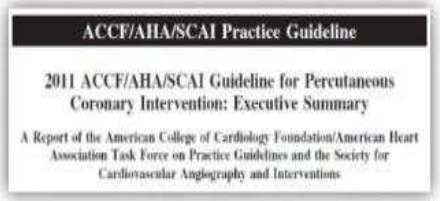


jeremias et al JACC 2013

Compared to FFR……



CLASS IIa Level of Evidence A: FFR is reasonable to assess angiographic intermediate coronary lesions (50% to 70% diameter stenosis) and can be useful for guiding revascularization decisions in patients with SIHD. (p32)



Two Randomized Controlled Tests

- 2 RCTs made evidence of iFR based PCI vs. FFR based PCI

ORIGINAL ARTICLE

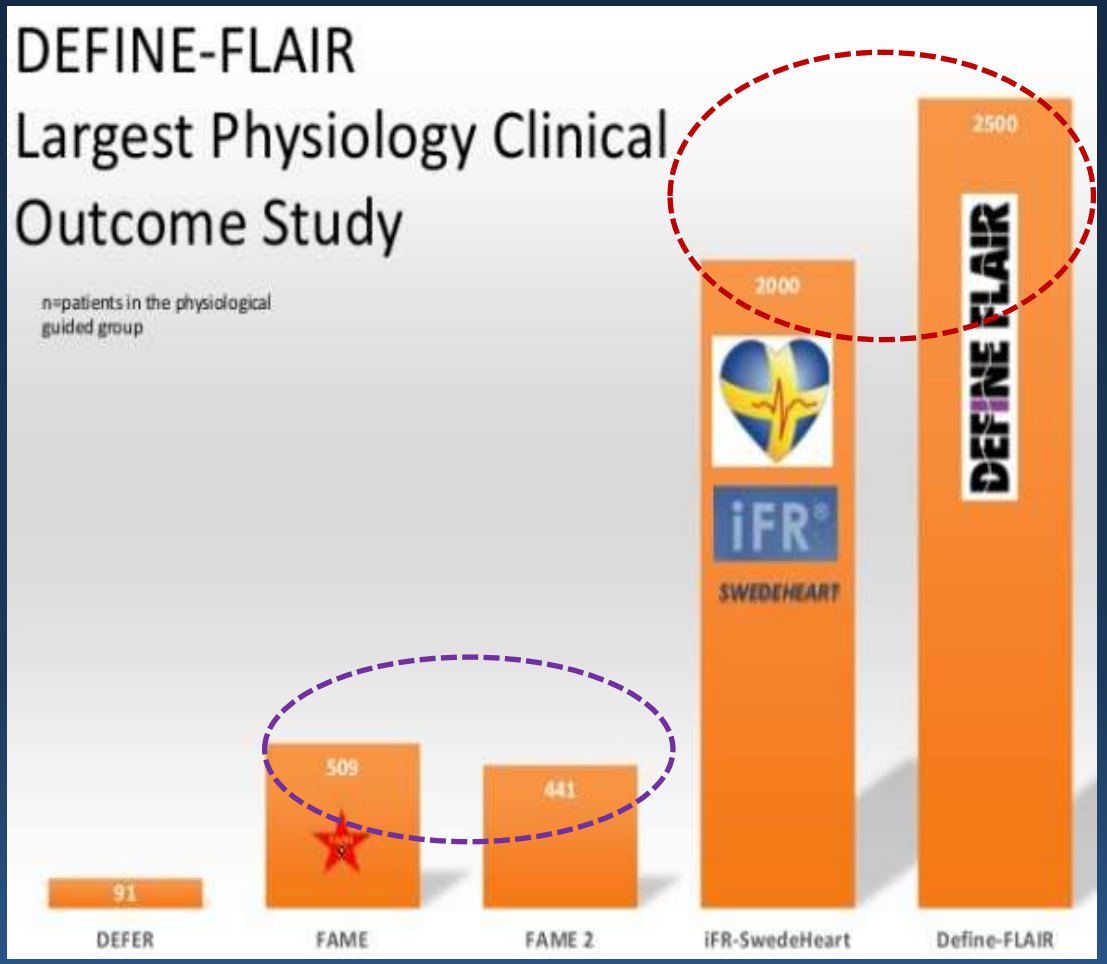
Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI

J.E. Davies, S. Sen, H.-M. Dehbi, R. Al-Lamee, R. Petraco, S.S. Nijjer, R. Bhindi, S.J. Lehman, D. Walters, J. Sapontis, L. Janssens, C.J. Vrints, A. Khashaba, M. Laine, E. Van Belle, F. Krackhardt, W. Bojara, O. Going, T. Härle, C. Indolfi, G. Niccoli, F. Ribichini, N. Tanaka, H. Yokoi, H. Takashima, Y. Kikuta, A. Erglis, H. Vinhas, P. Canas Silva, S.B. Baptista, A. Alghamdi, F. Hellig, B.-K. Koo, C.-W. Nam, E.-S. Shin, J.-H. Doh, S. Brugaletta, E. Alegria-Barrero, M. Meuwissen, J.J. Piek, N. van Royen, M. Sezer, C. Di Mario, R.T. Gerber, I.S. Malik, A.S.P. Sharp, S. Talwar, K. Tang, H. Samady, J. Altman, A.H. Seto, J. Singh, A. Jeremias, H. Matsuo, R.K. Kharbanda, M.R. Patel, P. Serruys, and J. Escaned

ORIGINAL ARTICLE

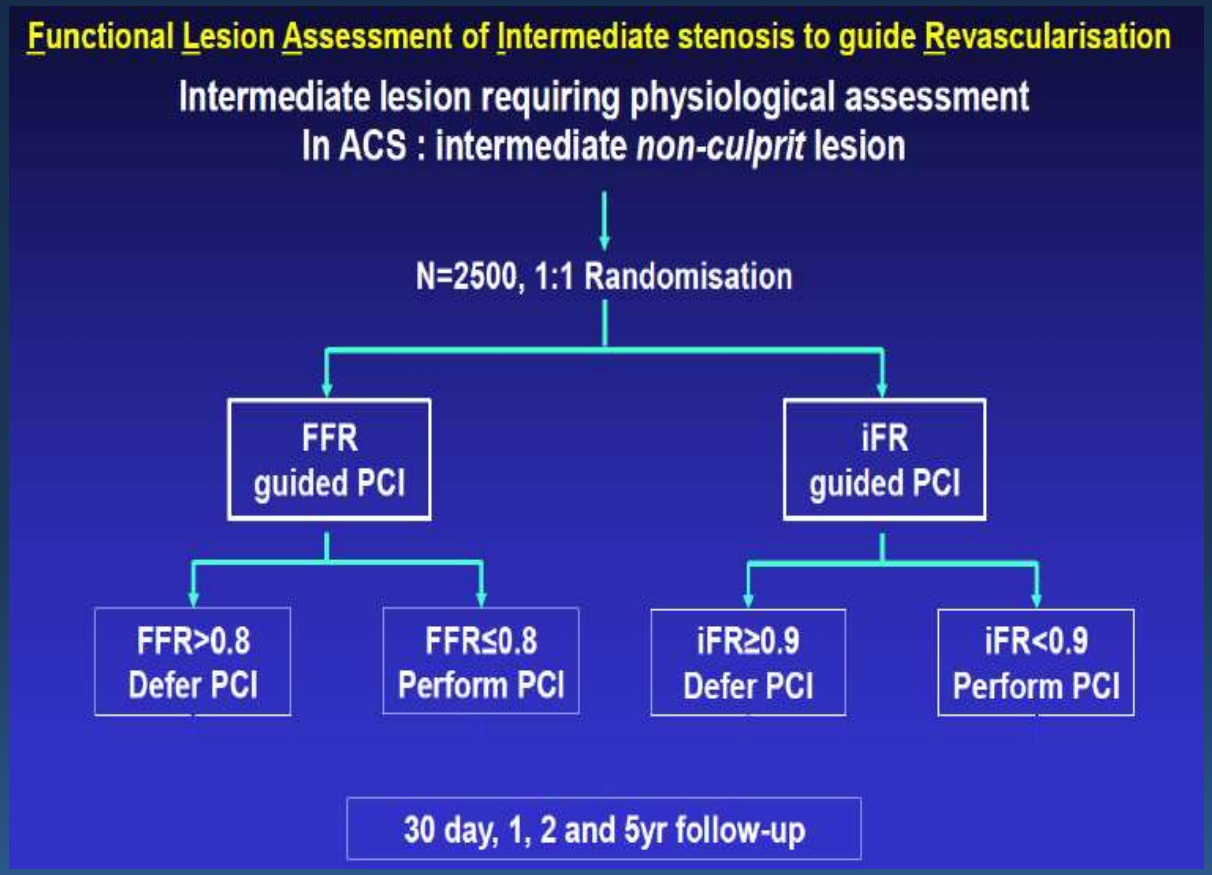
Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI

M. Götberg, E.H. Christiansen, I.J. Gudmundsdottir, L. Sandhall, M. Danielewicz, L. Jakobsen, S.-E. Olsson, P. Öhagen, H. Olsson, E. Omerovic, F. Calais, P. Lindroos, M. Maeng, T. Tödt, D. Venetsanos, S.K. James, A. Kåregren, M. Nilsson, J. Carlsson, D. Hauer, J. Jensen, A.-C. Karlsson, G. Panayi, D. Erlinge, and O. Fröbert, for the iFR-SWEDEHEART Investigators*



DEFINE FLAIR

Designed to prove the non-inferiority of iFR® in ACS patients with intermediate non-culprit lesion

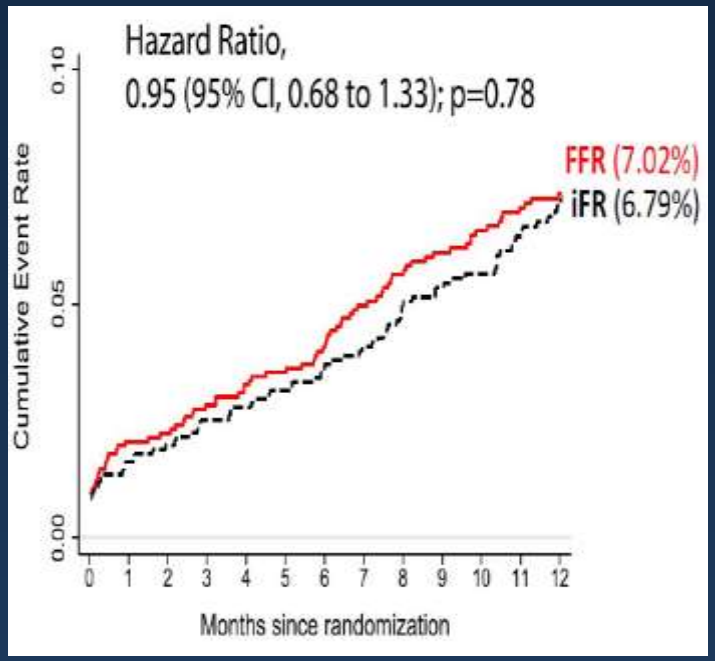


- Stable disease 81.7%, ACS 14.9%, STEMI(>24h) 3.5%
- Inclusion : 40~70% stenosis of the diameter on visual assessment
- Exclusion : patients with tandem stenosis separated more than 10mm

Primary endpoint : 1 year risk for DEFINE FLAIR

- MACE (Death, MI, Unplanned revascularization)

Variable	iFR Group (N=1242)	FFR Group (N=1250)	P Value†
Radial-artery approach — no. of patients (%)	896 (72.1)	888 (71.0)	0.54
Procedure time — min			
Median	40.5	45.0	0.001
Interquartile range	27.0–60.0	30.0–66.0	
Hyperemic agent administered — no. of patients (% of total no. who received a hyperemic agent)			
Total	NA	1608 (100)	
Intracoronary adenosine	NA	455 (28.3)	
Intravenous adenosine	NA	950 (59.1)	
Other agent	NA	203 (12.6)	
Multivessel disease — no. of patients (%)	505 (40.7)	519 (41.5)	0.66
Type of vessel evaluated — no. (% of total vessels evaluated)‡			
Total	1575 (100)	1608 (100)	0.58
Left anterior descending artery	844 (53.6)	845 (52.5)	0.56
Left circumflex artery	323 (20.5)	333 (20.7)	0.89
Right coronary artery	374 (23.7)	393 (24.4)	0.65
Other	33 (2.1)	31 (1.9)	0.74
Unknown	1 (0.1)	6 (0.4)	0.06
Total no. of vessels evaluated or treated‡	1879	1940	0.42
No. of vessels evaluated or treated per patient‡	1.51±0.76	1.55±0.80	0.42
Functionally significant lesions — no. (% of total vessels evaluated)§	451 (28.6)	557 (34.6)	0.004
≥1 Functionally significant lesions present — no. of patients (%)§	426 (34.3)	486 (38.9)	0.02



➢ confirming the non-inferiority of iFR® towards FFR.

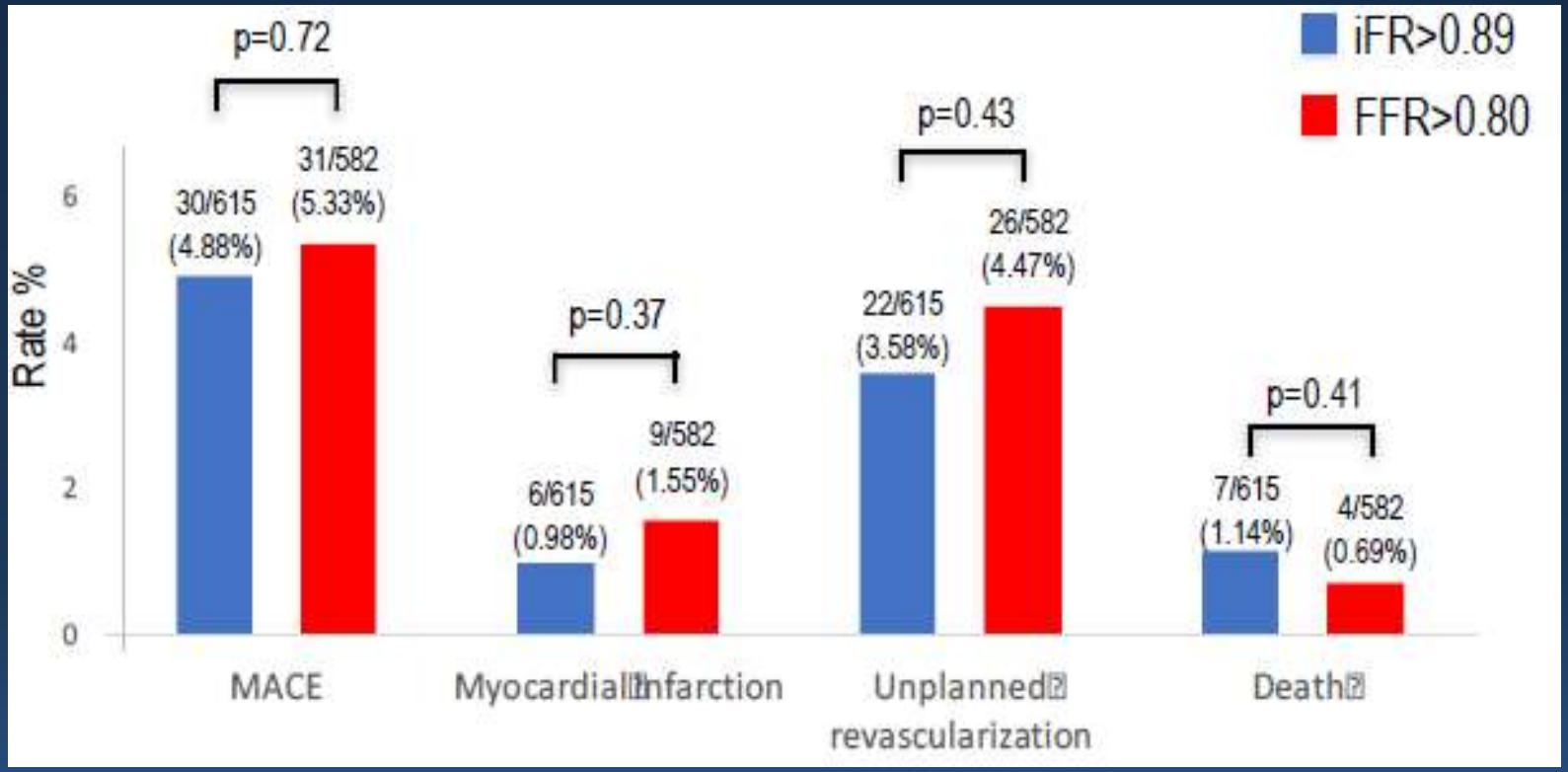
➢ Functionally significant lesions: more in FFR group

Davies et al. N Engl J med 2017; 376:1813-1823

In deferred population

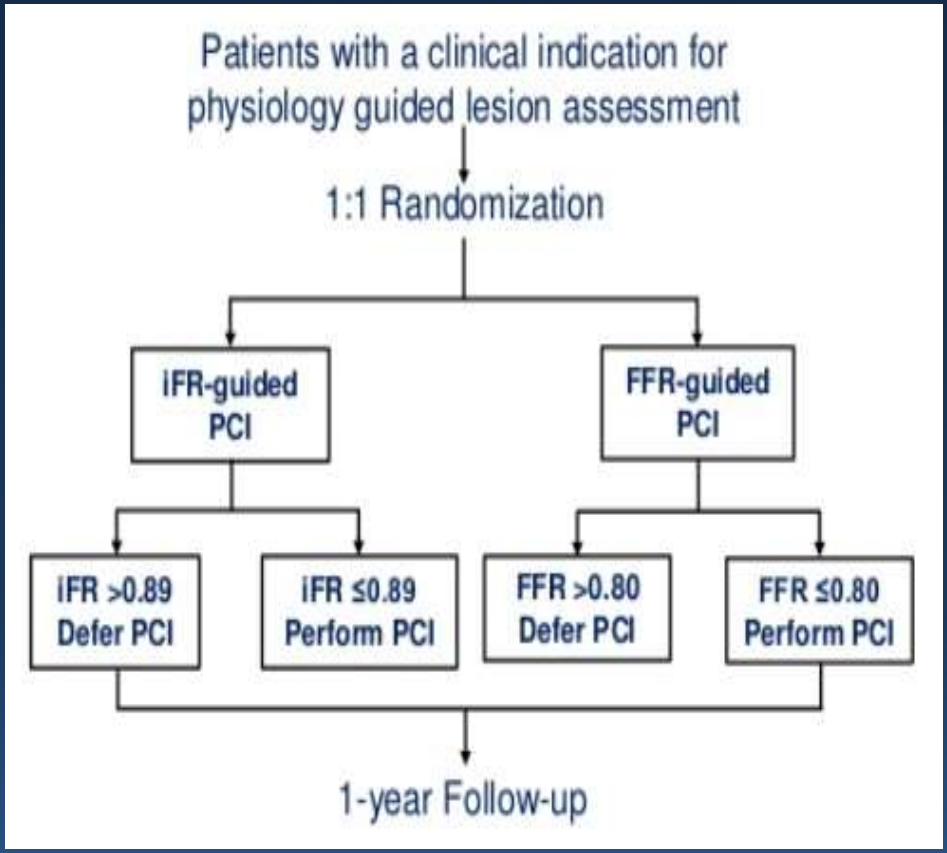
DEFINE FLAIR

In deferred patients at 12 months



Each outcomes also showed no significant difference between iFR and FFR

iFR-SWEDEHEART also examined the non-inferiority of iFR® with similar design



- Inclusion : SA or UA/NSTEMI, 30-80% stenosis grade
- 2000 patients, radnomized
- 13 centers in Sweden, Denmark

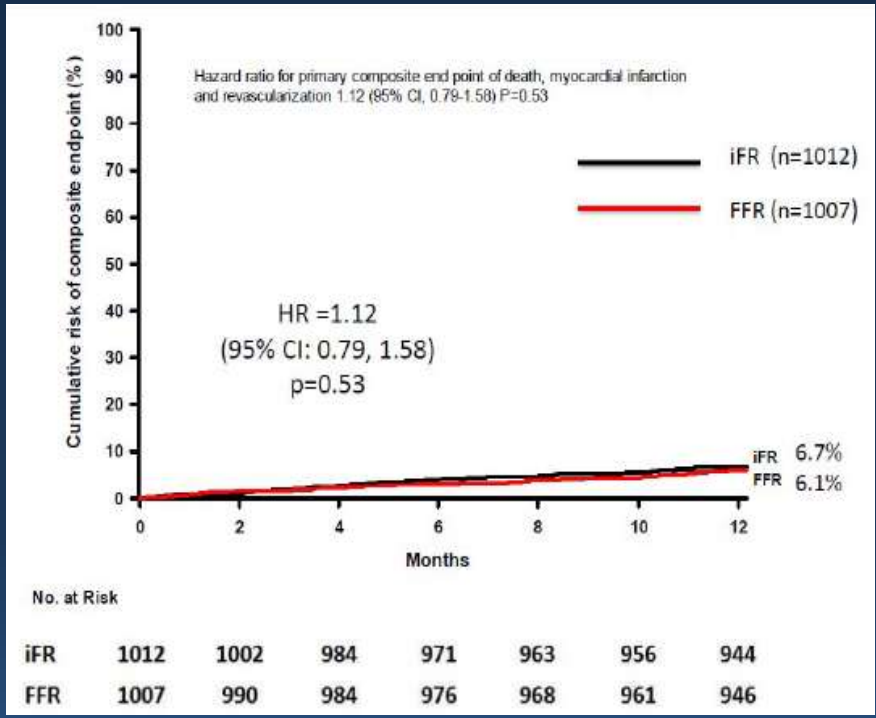
primary endpoint of 1 year MACE

MACE (Death, MI, Unplanned revascularization)

Characteristic	iFR Group (N=1012)	FFR Group (N=1007)	P Value
Radial-artery approach — no. of patients (%)	841 (83.1)	811 (80.5)	0.13
Contrast material used per patient — ml			0.10
Median	110	115	
Interquartile range	80–155	80–160	
Procedure time — min†			0.09
Median	50.8	53.1	
Interquartile range	13.8–87.8	18.1–88.1	
Fluoroscopy time — min			0.57
Median	10.5	10.2	
Interquartile range	6.3–16.8	6.5–16.0	
Intravenous adenosine administered — no. of patients (%)	NA	695 (69.0)	
Total no. of lesions evaluated	1568	1436	
No. of lesions evaluated per patient	1.55±0.86	1.43±0.70	0.002
Hemodynamically important lesions — no. (% of total lesions evaluated)‡	457 (29.1)	528 (36.8)	<0.001
No. of hemodynamically important lesions per patient‡	0.45±0.71	0.52±0.68	0.05
Mean iFR	0.91±0.10	NA	
Mean iFR in hemodynamically important lesions‡	0.80±0.13	NA	
Mean FFR	NA	0.82±0.10	
Mean FFR in hemodynamically important lesions‡	NA	0.72±0.08	
Lesion complexity according to the ACC–AHA class — no./total no. of treated lesions (%)§¶			0.73
A	61/915 (6.7)	73/980 (7.4)	
B1	304/915 (33.2)	320/980 (32.7)	
B2	284/915 (31.0)	300/980 (30.6)	
C	139/915 (15.2)	165/980 (16.8)	
Missing data	127/915 (13.9)	122/980 (12.4)	

More lesions evaluated in iFR, but fewer significant lesions

- Confirmed non–inferiority of iFR-method

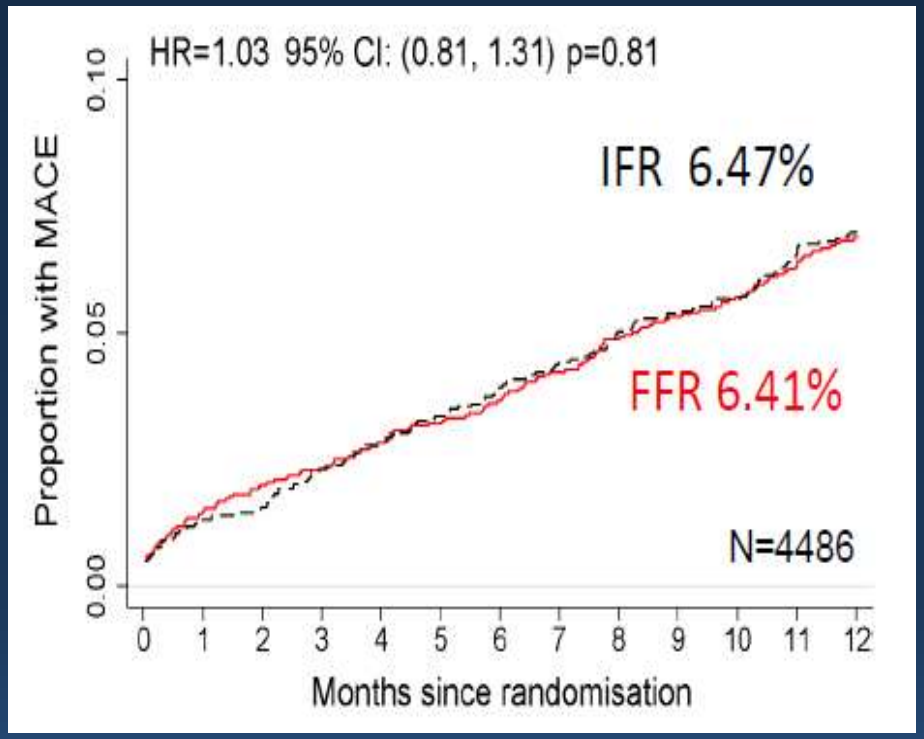


Gotberg et al. N Engl J med 2017; 376:1813-1823

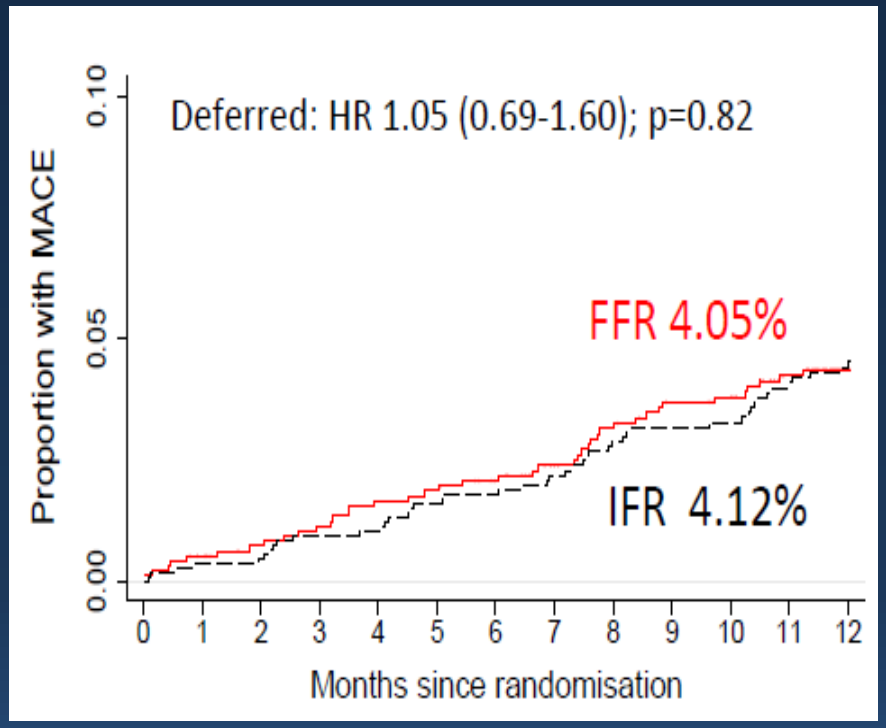
A Meta-analysis of 2 RCTs

- The MACE rate at 1 year

MACE in iFR and FFR guided revascularization



Outcomes in deferred population



- MACE : similar and low at 1year after decision making

MACE : similar and low rates at 1year after deferal

Javier et al. J Am Coll Cardiol Intv 2018;11:1437–49

A Meta-analysis of 2 RCTs

chest discomfort, dyspnea : Significantly more in the FFR-group

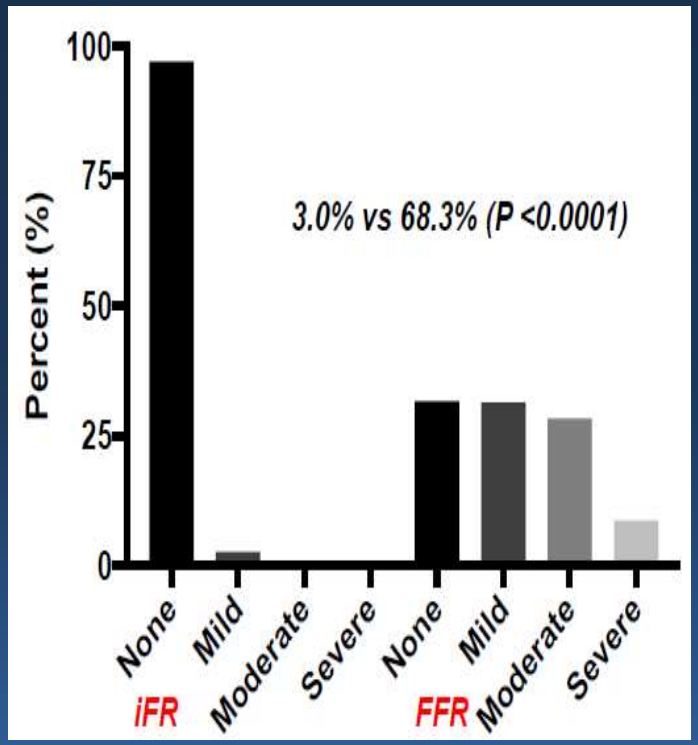
DEFINE FLAIR

Variable	iFR Group (N=1242)	FFR Group (N=1250)	P Value†
Patient-reported adverse procedural symptoms or signs — no. of patients (%)	39 (3.1)	385 (30.8)	<0.001
Patient-reported dyspnea — no. of patients (%)	13 (1.0)	250 (20.0)	
Patient-reported chest pain — no. of patients (%)	19 (1.5)	90 (7.2)	
Physician-reported adverse procedural signs — no. of patients (%)			
Heart-rhythm disturbance	2 (0.2)	60 (4.8)	
Significant hypotension	4 (0.3)	13 (1.0)	
Vomiting or nausea	1 (0.1)	11 (0.9)	
Ventricular arrhythmia or bronchospasm¶	1 (0.1)	8 (0.6)	
Other	4 (0.3)	38 (3.0)	

SWEDE HEART

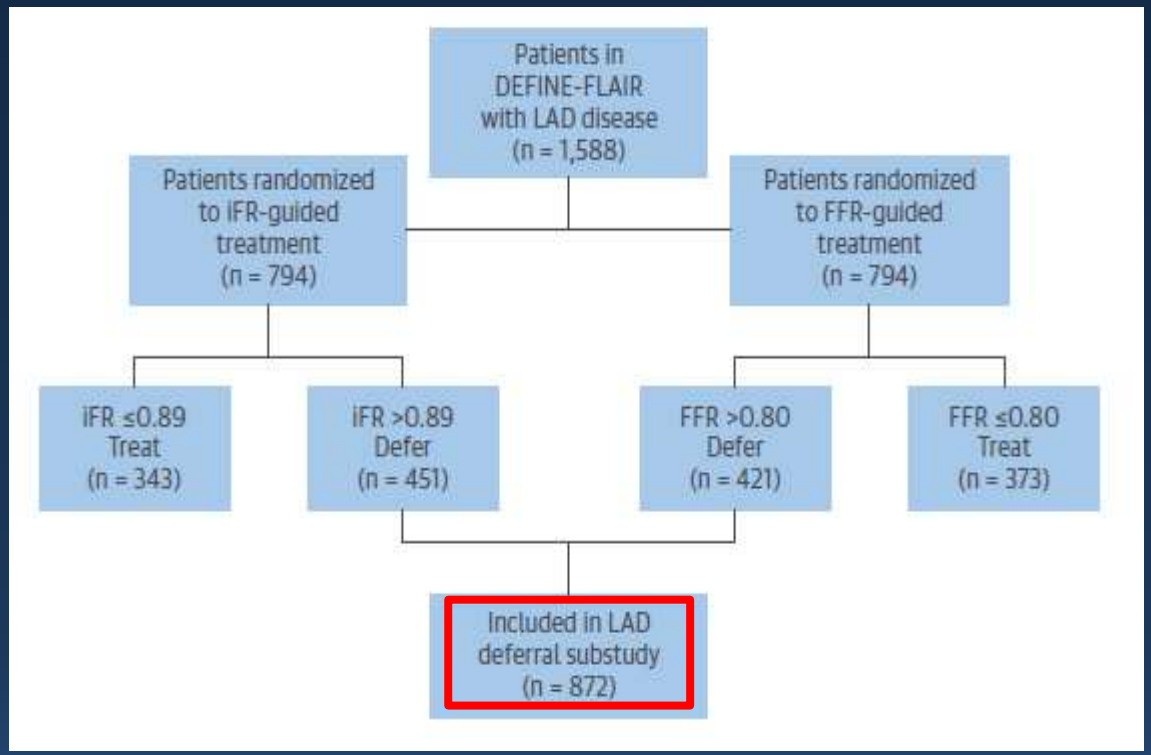
	iFR Group (N=1012)	FFR Group (N=1007)	Hazard Ratio (95% CI)	P Value
Chest discomfort during procedure				<0.001†
None	982 (97.0)	319 (31.7)		
Mild	26 (2.6)	316 (31.4)		
Moderate	2 (0.2)	285 (28.3)		
Severe	2 (0.2)	87 (8.6)		

- mainly because adenosine was not administered



Sub-study : safety of deferral in the LAD using FFR or iFR

DEFINE FLAIR

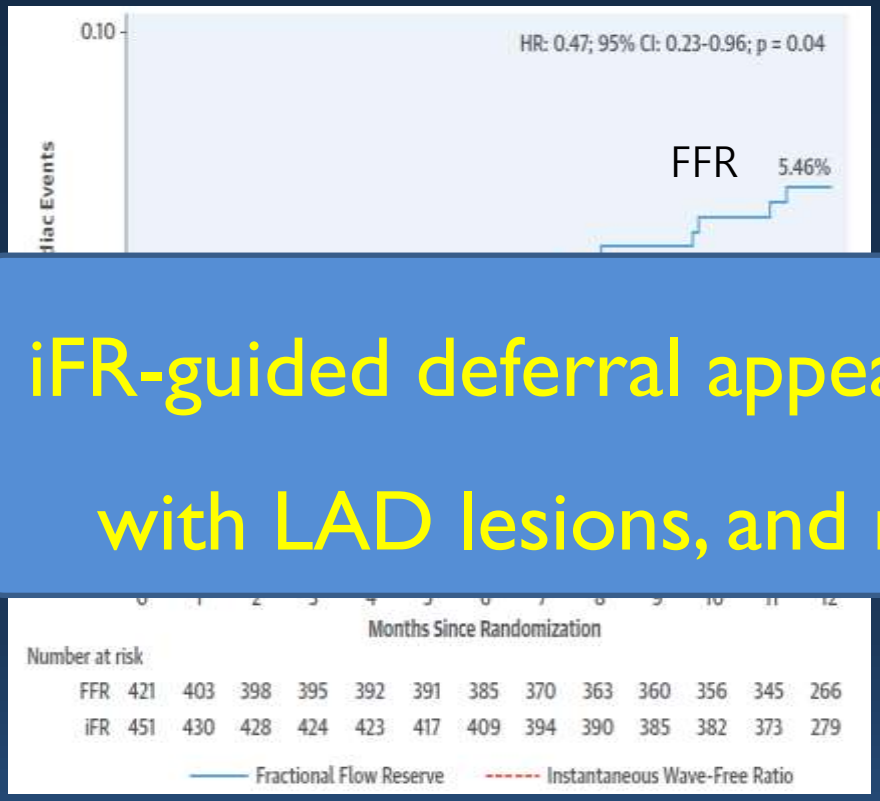


MACE : composite of cardiovascular death, myocardial infarction (MI), and unplanned revascularization at 1 year

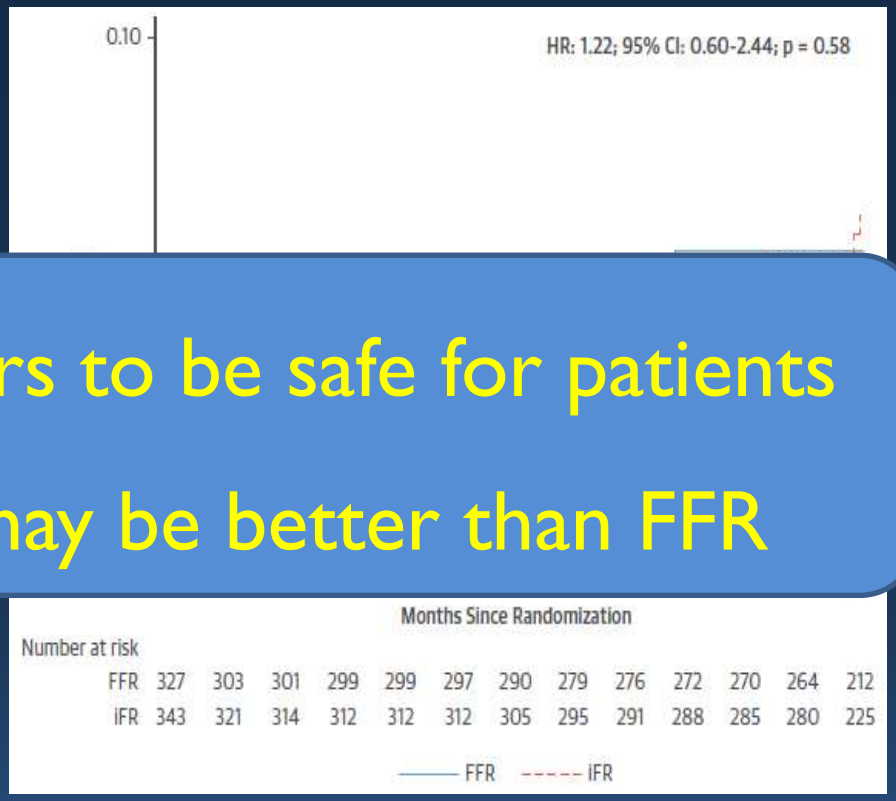
- Sayan Sen, Justin E. Davies et al. J Am Coll Cardiol 2019;73:444–53

Fate of Deferral of LAD by iFR or FFR

LAD-deferred patients



Non- LAD-deferred patients



iFR-guided deferral appears to be safe for patients with LAD lesions, and may be better than FFR

The event rate with iFR was significantly lower than with FFR in LAD deferred patients.

no difference by modality in non-lad deferred patients

The length of the procedure time

DEFINE FLAIR

Time saving was almost 4.5 minutes each.

Significantly shorter in the iFR group

Healthcare costs and outcomes with iFR and FFR

DEFINE FLAIR

Costs were estimated from a US healthcare payer perspective

	Mean difference (iFR – FFR) (95% CI)			
	Unadjusted		Adjusted [a]	
Healthcare costs (2017 US$ per patient) [a]				
Index procedure: assessment	-75	(-104 to -47) **	-76	(-105 to -48) **
Index procedure: angioplasty	-139	(-324 to 46)	-185	(-372 to 2)
Planned CABG	-294	(-628 to 40)	-332	(-665 to 0) *
Ambulatory care	-52	(-158 to 54)	-34	(-127 to 59)
Hospital care	-241	(-783 to 301)	-219	(-770 to 332)
Total cost	**-801**	**(-1483 to -119) ***	**-896**	**(-1537 to -255) ***
Health outcomes				
Number of MACE per patient [b]	0.002	(-0.031 to 0.033)	0.004	(-0.030 to 0.035)
QALYs per patient [c]	-0.003	(-0.017 to 0.010)	-0.003	(-0.017 to 0.010)

- micro-costing for the index catheterization and Medicare costs for subsequent revascularizations, ambulatory care, and adverse events
- iFR-guided approach led to an economic cost saving of estimated $896 per patient

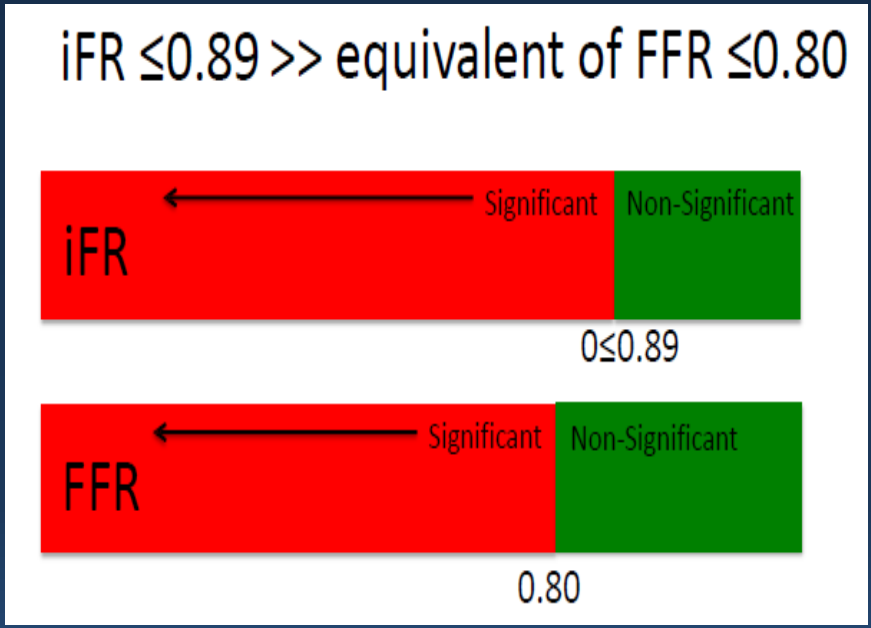
Healthcare costs and outcomes with iFR and FFR

iFR guided approach led to a cost saving (per patient up to 1 year)

	Scandinavian costs	U.S. Costs
iFR - Cost per patient:	$ 5 608	$ 13 110
FFR - Cost per patient:	$ 6 209	$ 14 071
iFR-guided approach Cost saving per patient:	*$ 601*	*$ 961*

New 2018 ESC guideline for myocardial revascularization

- Revascularization was indicated in both trials if FFR was ≤0.80 or if iFR was ≤0.89



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
IVUS should be considered to assess the severity of unprotected left main lesions.[35–37]	IIa	B

FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

Summary

- iFR values showed similar accuracy compared to FFR.

- Through 2 RCTs,
  - iFR guided intervention showed no inferior results compared with FFR guided intervention
  - Less procedure time & less chest discomfort in iFR group

- Meta-analysis & pooled analysis of 2 RCTs :
  - consistent outcome of non-inferiority and no difference of cumulative MACE incidence between ifr and ffr in deferred population
  - MACE events by ACS were more influenced in FFR-guided group

Summary

In recent sub-studies

- Deferred LAD
  - Clinical outcomes of deferred LAD (subgroup study) : iFR group showed better prognosis than FFR group (HR 0.47, P=0.04)
- Diabetes population
  - iFR-SWEDEHEAR : increased event rates among diabetic patients with FFR compared to iFR
  - DEFINE-FLAIR : No significant difference between iFR/FFR in MACE, More deferral occurred in iFR
- Costs
  - when compared to FFR, iFR was identified as more economically advantageous