

14<sup>th</sup>

**AICT**

ASIAN INTERVENTIONAL CARDIOVASCULAR THERAPEUTICS  
THE OFFICIAL CONGRESS OF APSIC

# FFR vs. iFR vs. RFR vs. QFR

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**Medistra Hospital,**  
**Jakarta, Indonesia**

Borobudur, biggest Buddhist temple in the world, Java, Indonesia

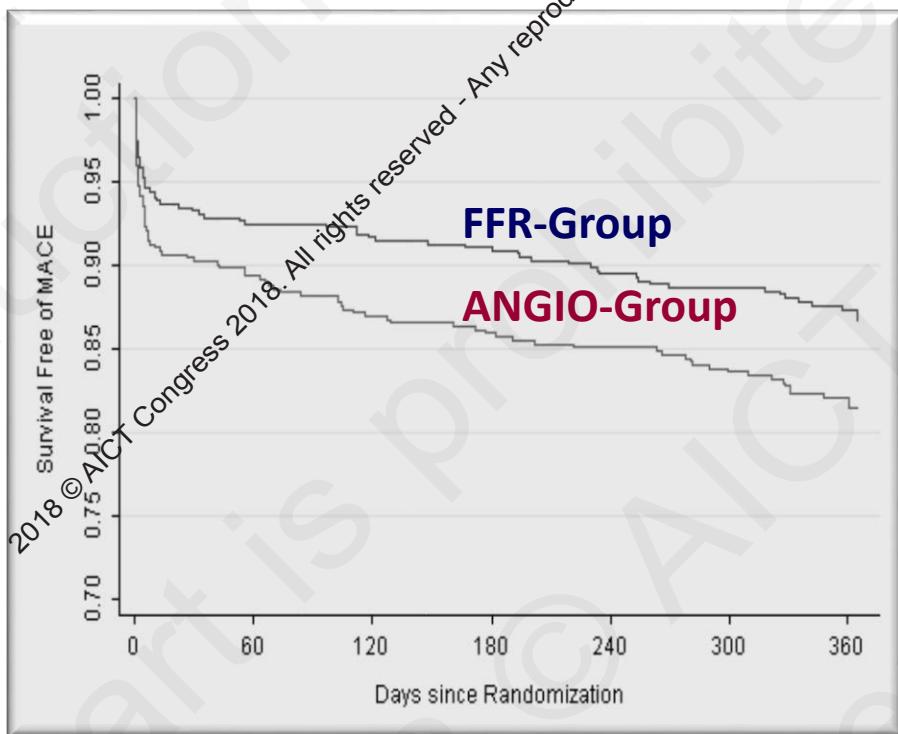
Speaker's name : **Teguh, SANTOSO**, Jakarta

I do not have any potential conflict of interest

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# FFR Guidance Superior To PCI With Angiography Alone



*The* **NEW ENGLAND**  
**JOURNAL of MEDICINE**

## Improves Outcomes <sup>1</sup>

- Reduces the risk of **MACE 28%**
- Reduces the risk of **Death & MI 34%**
- Results in **functional class** equal to or better than angio-guided PCI

## Makes Economic Sense <sup>2</sup>

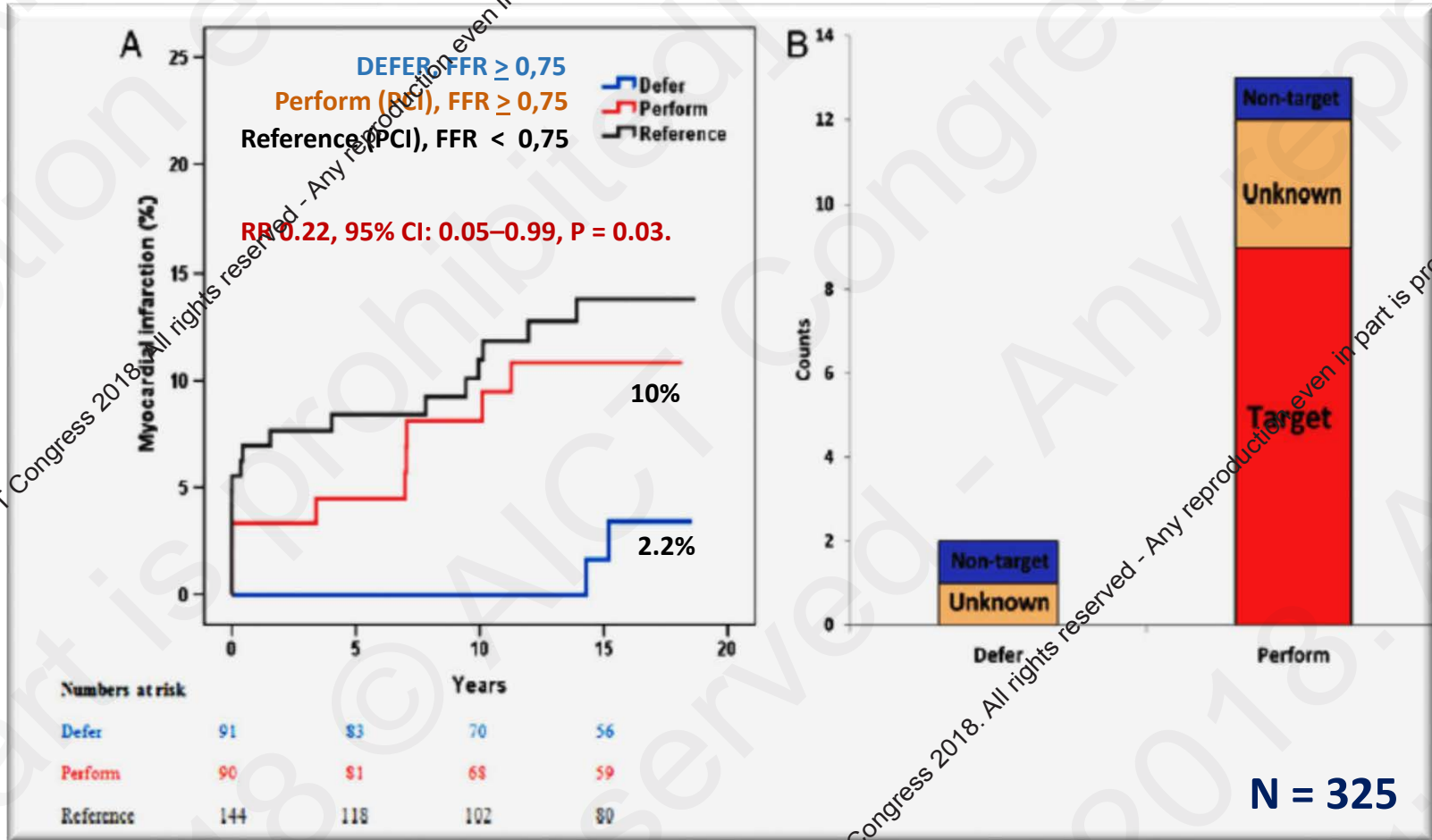
- 30% **fewer stents** used in FFR-guided arm
- **Saves \$675** per patient **at procedure time**
- **Saves >\$2000** per patient **at 12 months**
- Reduces **contrast usage**

1. Fearon W, New England Journal of Medicine, 360;3:213-224

2. Fearon WF et al. Circulation. 2010;122:2545-50

# DEFER Trial : 15-Year Follow-Up

Kaplan–Meier Of Myocardial Infarction (A) & Relation Of Myocardial Infarction With Study Vessel Territory (B).



Deferral of PCI of a functionally non-significant stenosis is associated with a favourable very long-term follow-up *without signs of late 'catch-up' phenomenon*

# FAME: 5 Year Results

- Stable CAD pts or atypical or no chest pain but ischemia on noninvasive testing
- With  $\geq 50\%$  stenosis in 1 major artery, considered for 1/2/3VD DES-PCI
- Excluded: 1. EF  $< 30\%$ , 2. prior CABG, 3. LM

(n = 1220)

FFR in all target lesions

Randomized Trial

Registry

$\geq 1$  stenosis with  
FFR  $\leq 0.80$  (n=888)

When all FFR  $> 0.80$   
(n=332)

Randomization 1:1

PCI + MT

73%

MT

27%

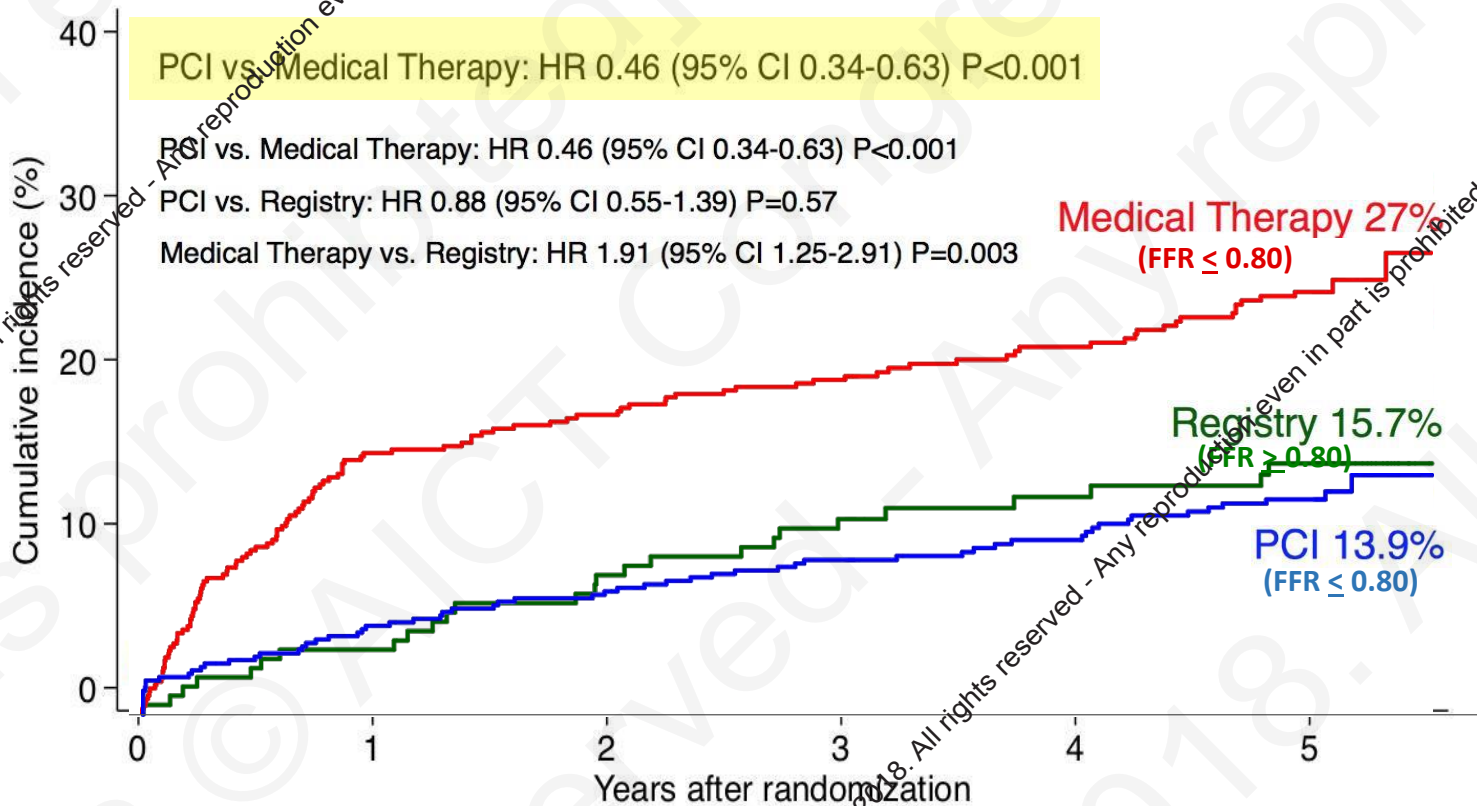
MT

50% randomly assigned to FU

Follow-up after 1, 6 months, 1, 2, 3, 4, & 5 years

# FAME: 5 Year Results

## Primary Endpoint (All Cause Death, MI, Or Urgent Revascularisation)



No. at risk

Medical Therapy

441

360

349

337

271

258

PCI

447

416

403

391

334

321

Registry

166

156

147

141

116

113

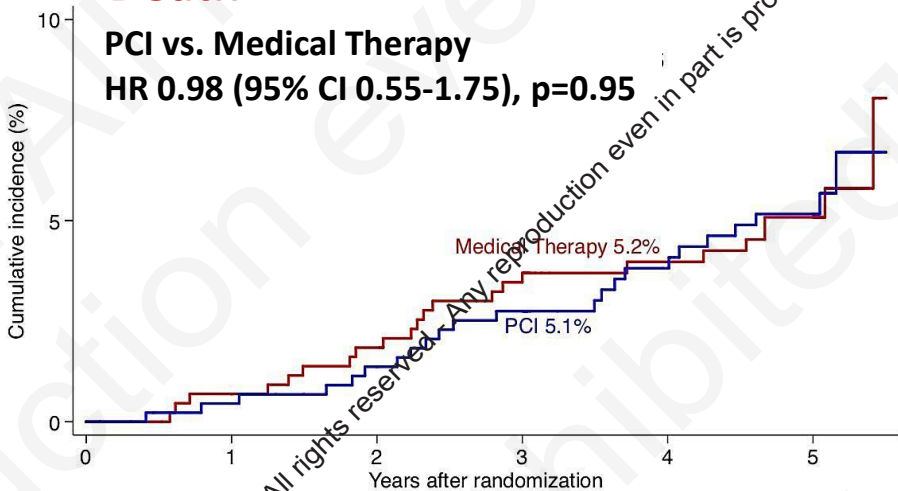
**N = 888**

# FAME: 5 Year Results

## Death

PCI vs. Medical Therapy

HR 0.98 (95% CI 0.55-1.75),  $p=0.95$

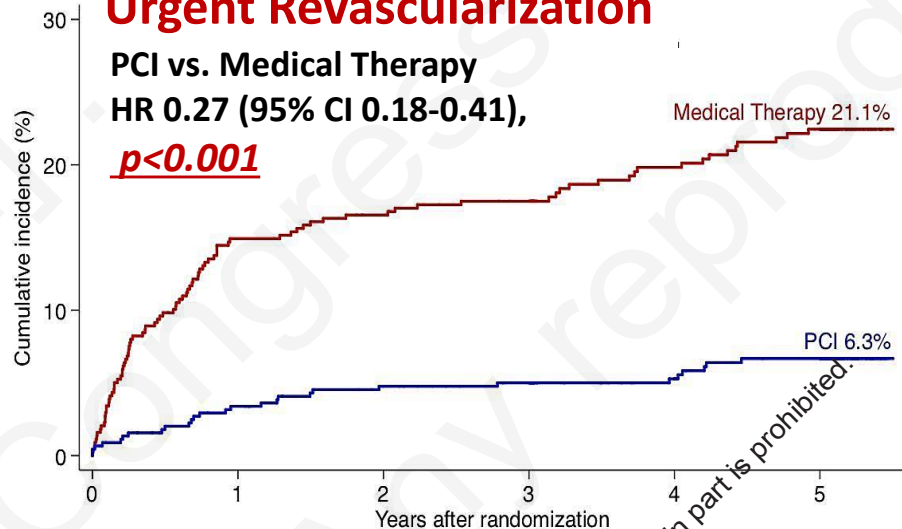


## Urgent Revascularization

PCI vs. Medical Therapy

HR 0.27 (95% CI 0.18-0.41),

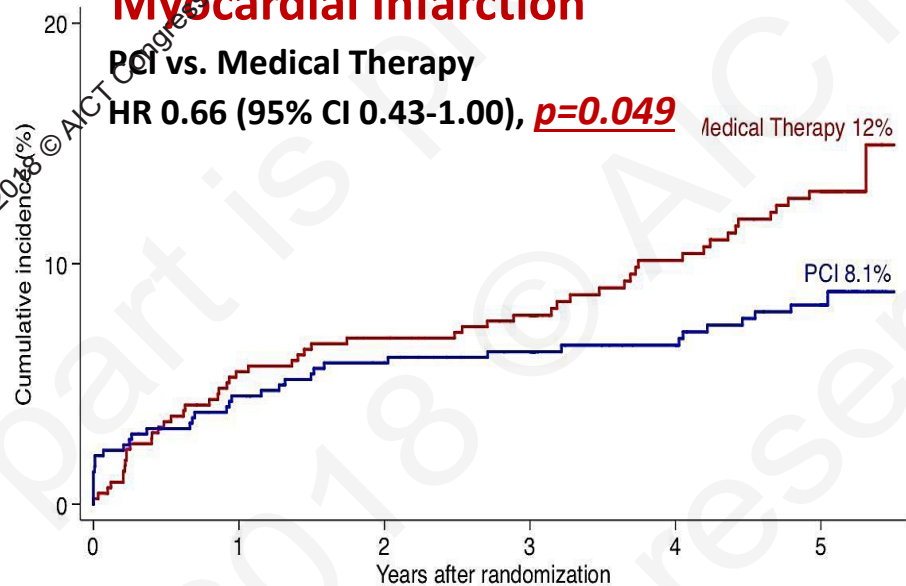
$p<0.001$



## Myocardial Infarction

PCI vs. Medical Therapy

HR 0.66 (95% CI 0.43-1.00),  $p=0.049$



Baseline

30 days

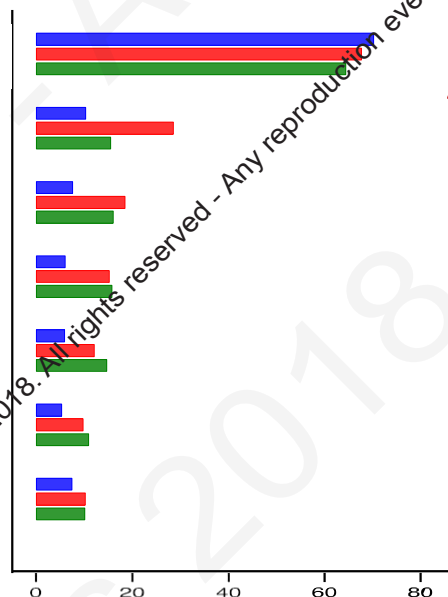
6 months

1 year

2 years

3 years

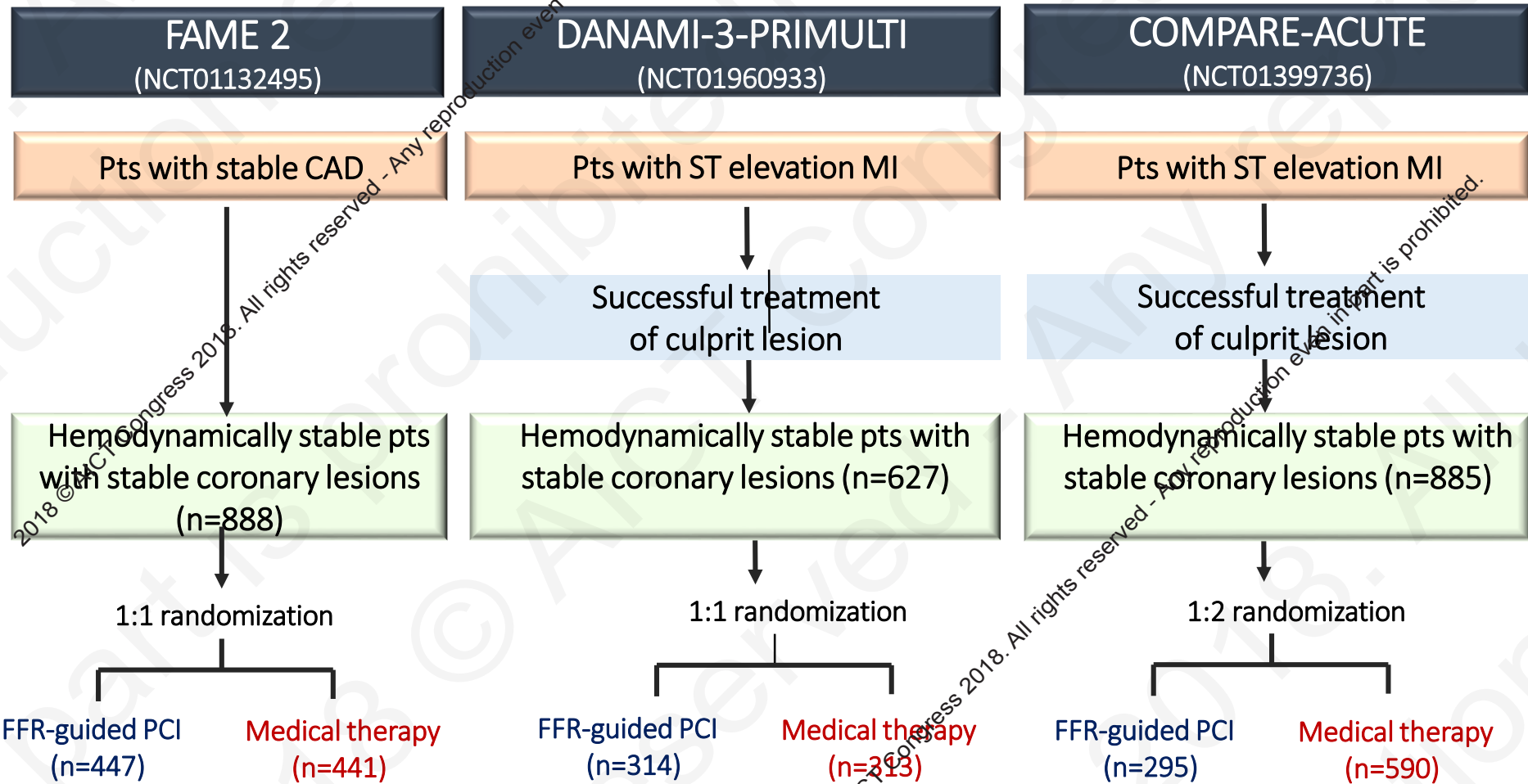
5 years



Pts with CCS II-IV (%)

**N = 888**

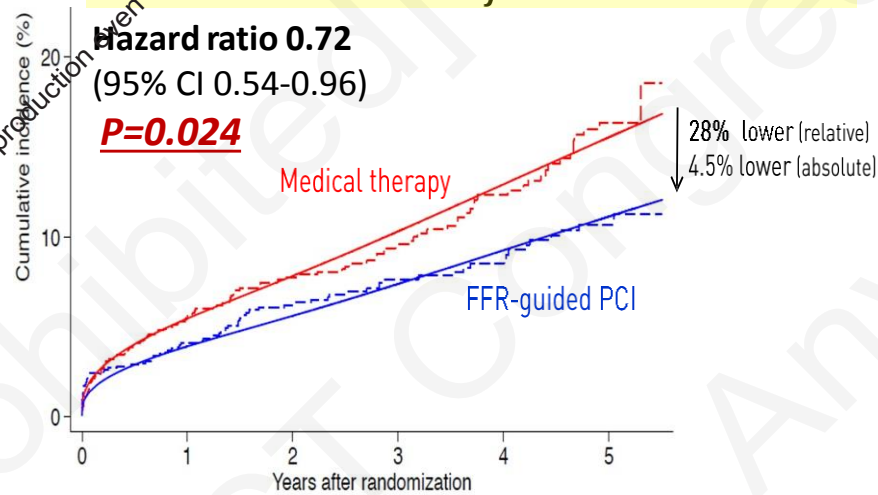
# A Pooled, Patient-Level Analysis of FAME 2, DANAMI-3-PRIMULTI & COMPARE-ACUTE



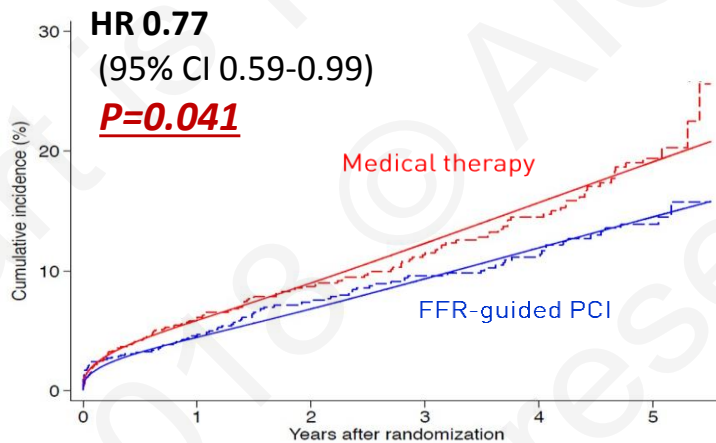


# A Pooled, Patient-Level Analysis of FAME 2, DANAMI-3-PRIMULTI & COMPARE-ACUTE

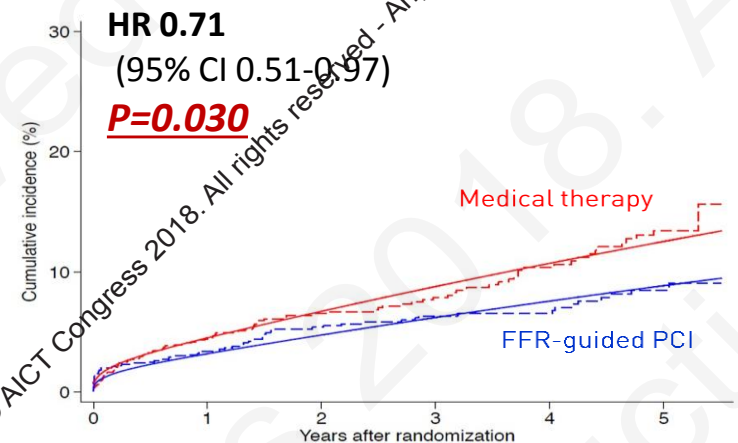
## Cardiac death or myocardial infarction



## All-cause death or myocardial infarction



## Myocardial infarction



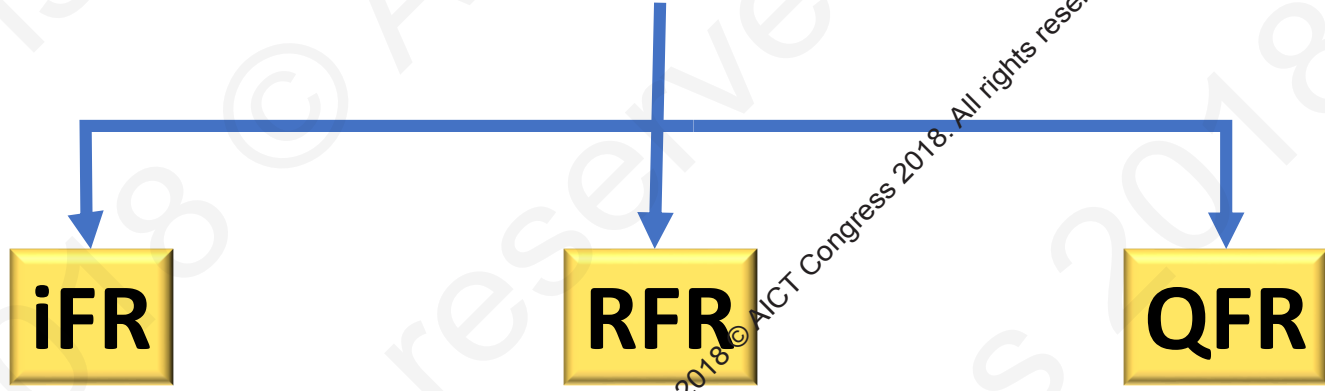
# FFR Measurement To Guide Revascularization Is A Class I Level A Indication (ESC Guideline),

***But It Is Not Widely Adopted***

- Procedural time (especially for multi-vessel assessment)
- Cost
- Discomfort or side effects from drugs
- Non-uniform adenosine response

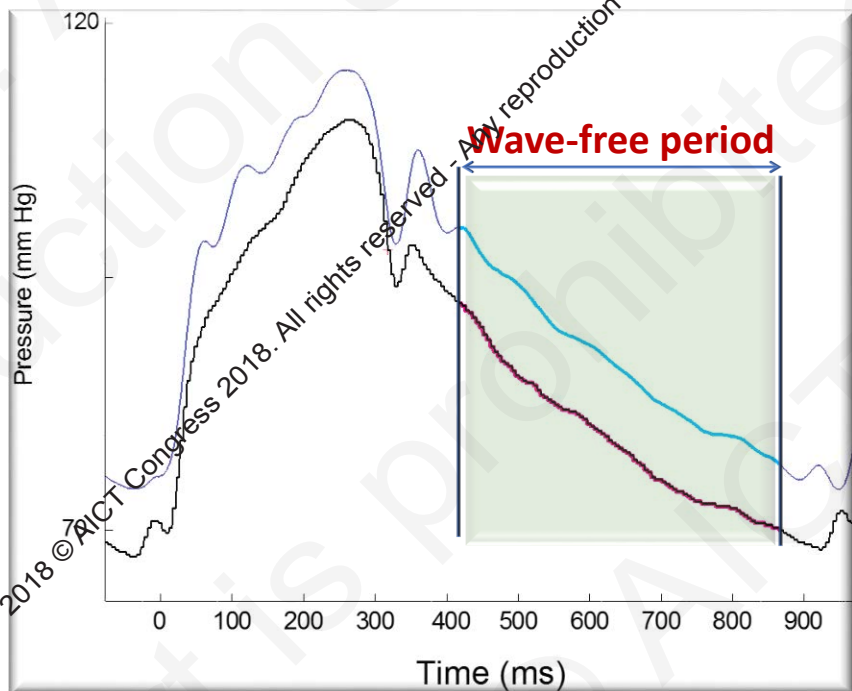


## Resting Indices

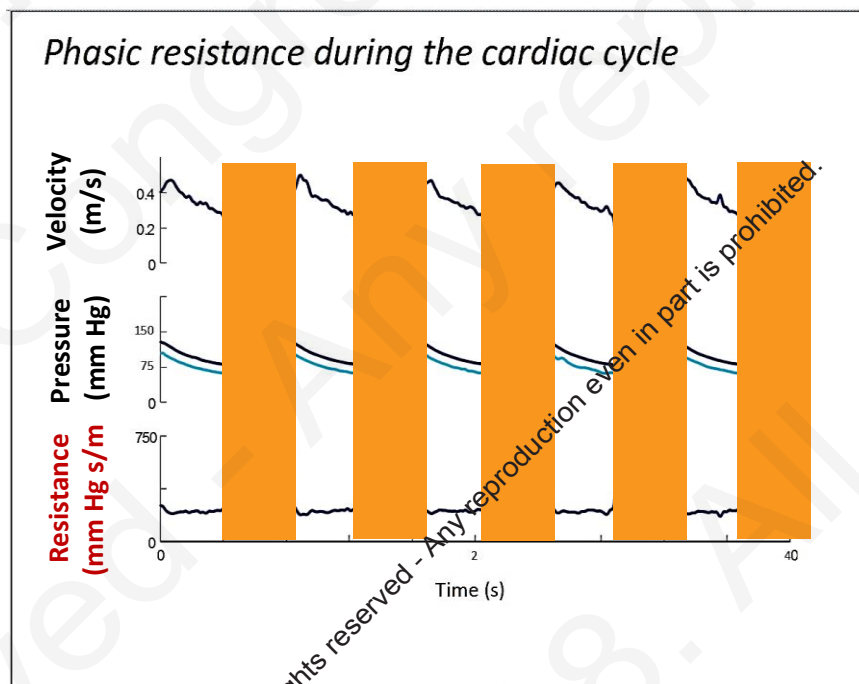


# iFR = Instantaneous Wave-Free Ratio

$$= \frac{Pd_{\text{wave free period}}}{Pa_{\text{wave free period}}}$$

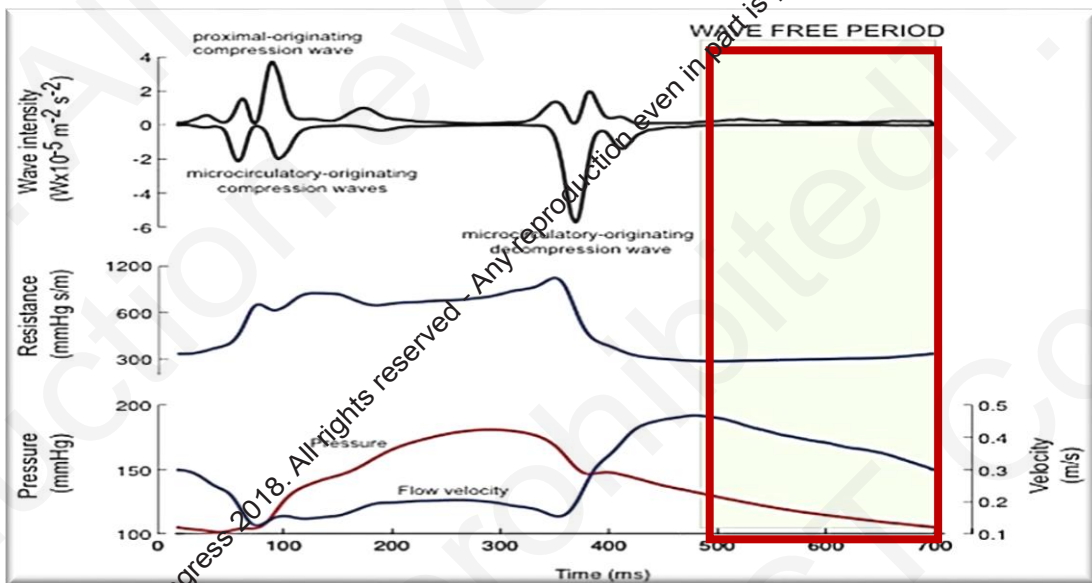


Pa  
Pd



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

# Concept of Wave-Free Period



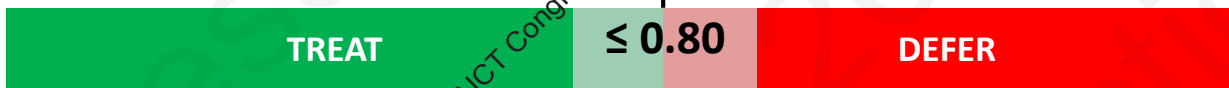
1. Noise from compression & suction waves is *minimized*
2. Resistance is constant so  $\Delta P$  is *proportional to  $\Delta Q$  (flow)*
3. Velocity is higher so *better power to discriminate*

**iFR**

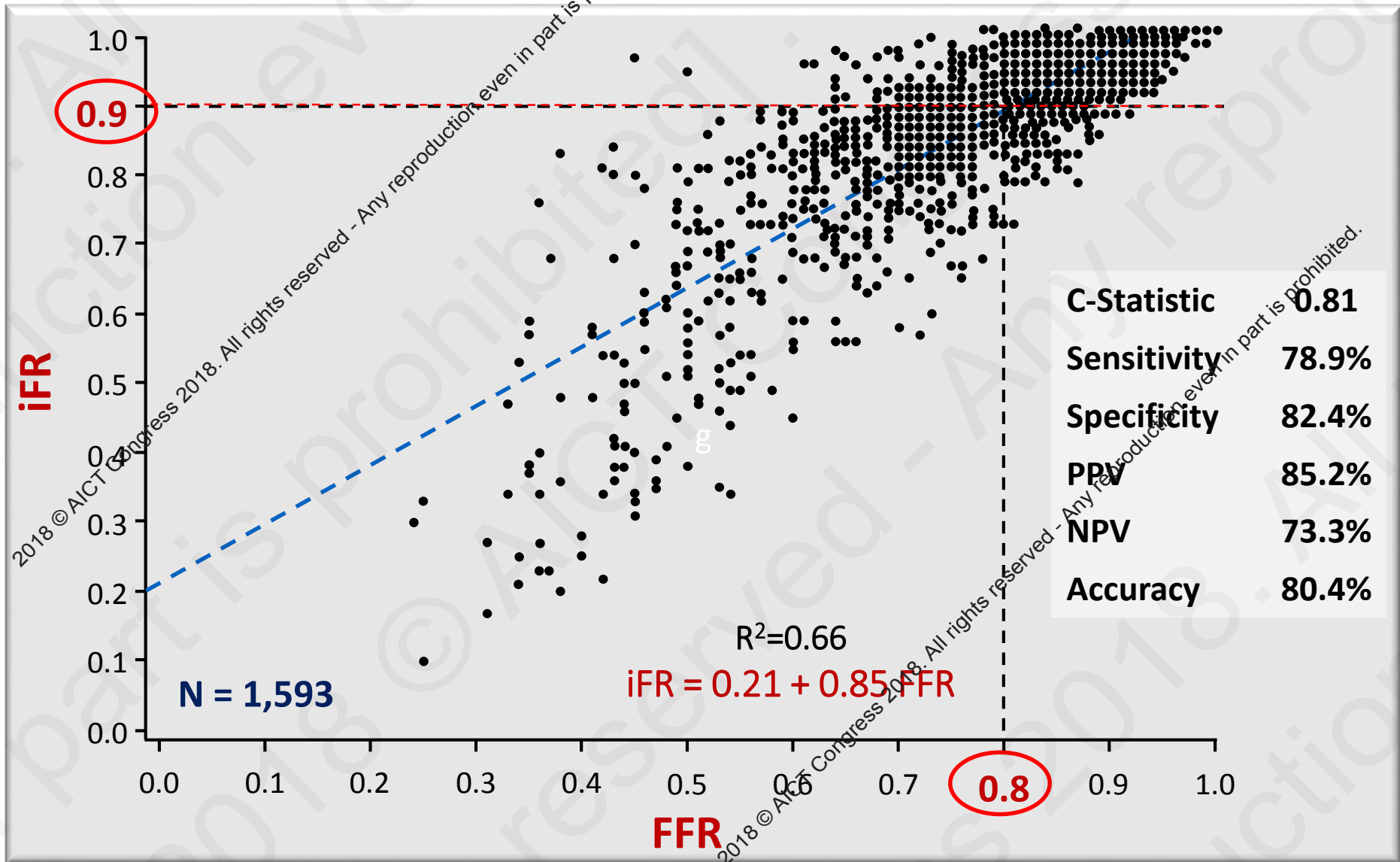


Clinical  
iFR & FFR  
Cut-points

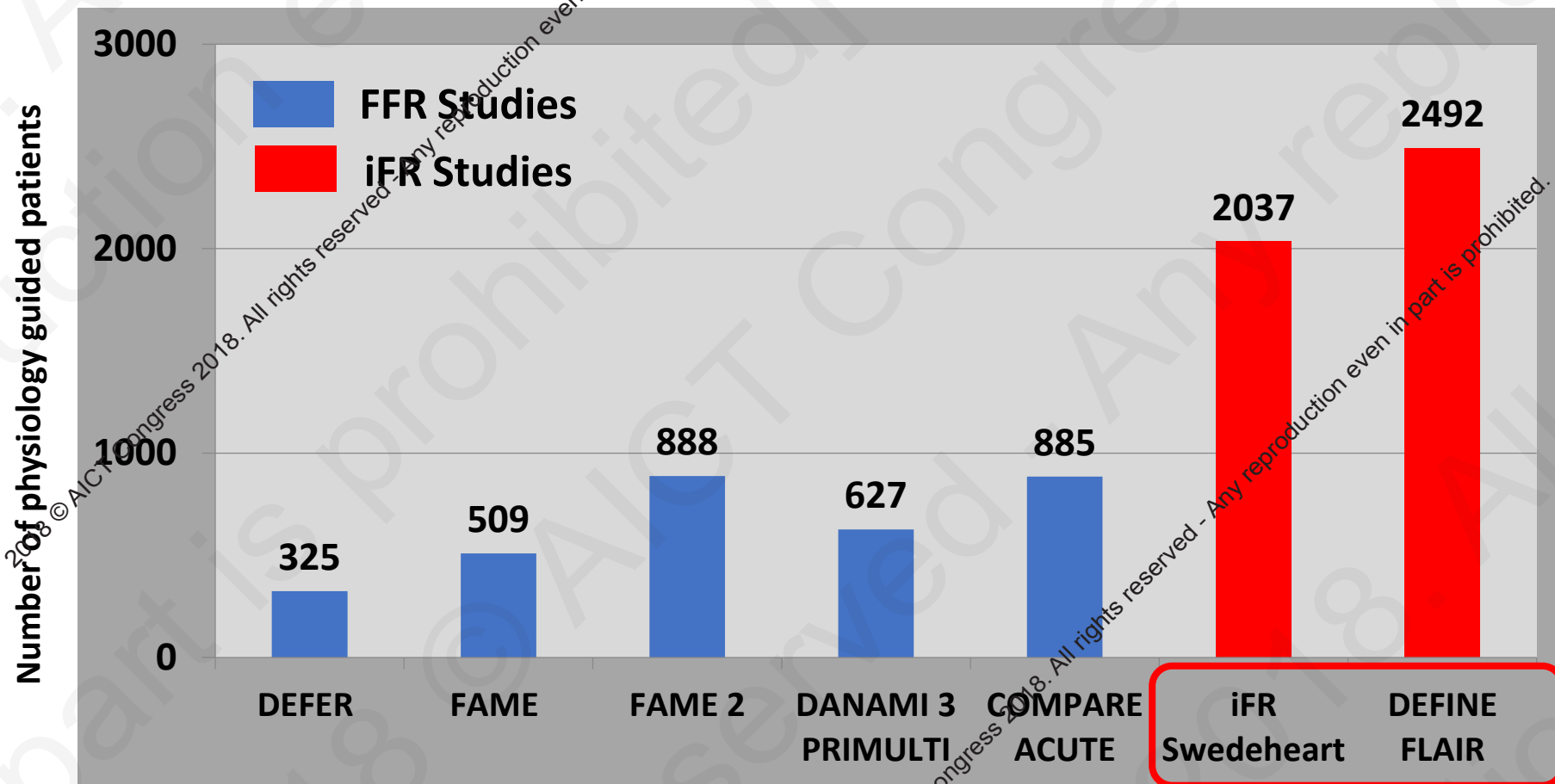
**FFR**



# RESOLVE - Correlation iFR vs. FFR



# Largest Global Physiology Studies Ever Performed



# DEFINE FLAIR

Intermediate lesion requiring physiological assessment in ACS : intermediate *non-culprit* lesion

N=2500, 1:1 Randomisation

**FFR**  
guided PCI

**iFR**  
guided PCI

FFR > 0.8  
Defer  
PCI

FFR ≤ 0.8  
Perform  
PCI

iFR > 0.89  
Defer  
PCI

iFR ≤ 0.89  
Perform  
PCI

30 day, 1, 2 and  
5yr follow-up

Patients with a clinical indication for physiology guided lesion assessment

N=2037, 1:1 Randomization

**iFR-guided**  
Revasc. (n=1019)

**FFR-guided**  
Revasc. (n=1018)

iFR > 0.89  
Defer  
Revasc.

iFR ≤ 0.89  
Perform  
Revasc.

FFR > 0.80  
Defer  
Revasc.

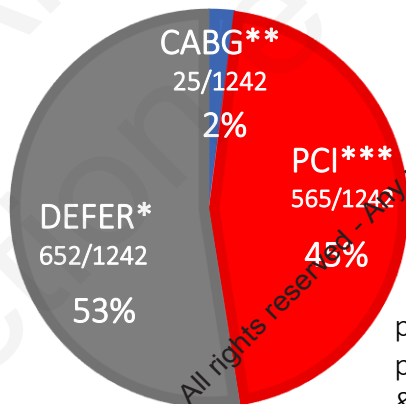
FFR ≤ 0.80  
Perform  
Revasc.

12-month Follow-up

# Treatment Allocation With iFR & FFR

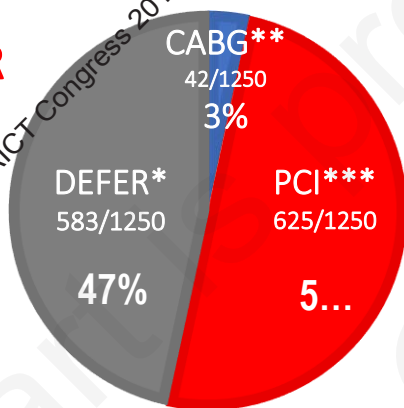
## DEFINE FLAIR

**iFR**

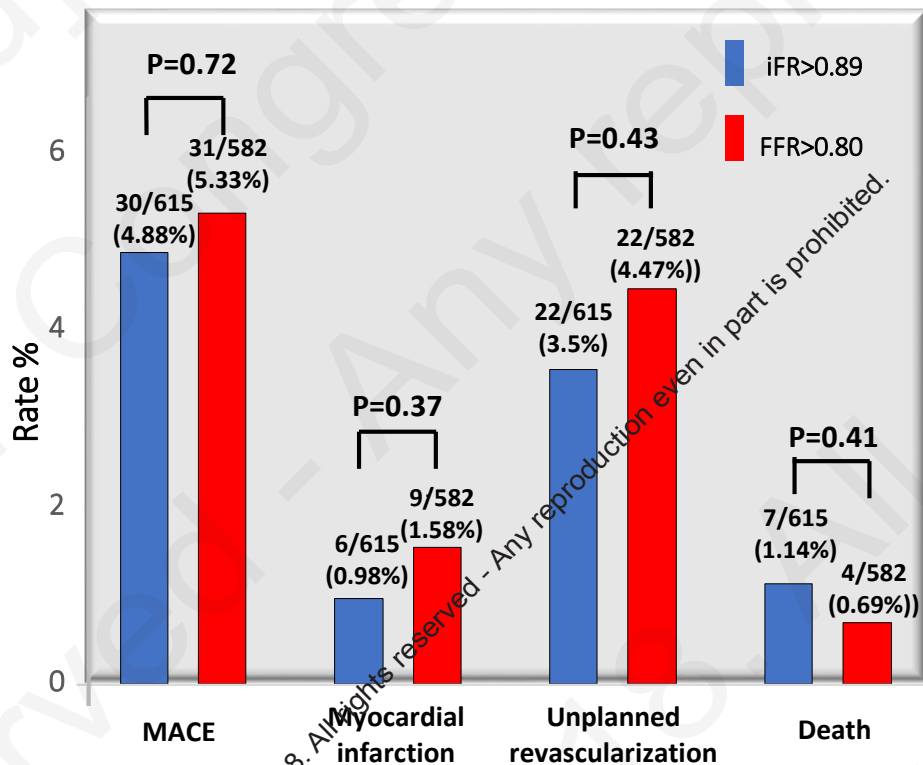


p for comparison between patients randomized to iFR & FFR

**FFR**



DEFER\* p=0.003  
 CABG\*\* p=0.04  
 PCI\*\*\* p=0.02



Significantly less revascularization with iFR

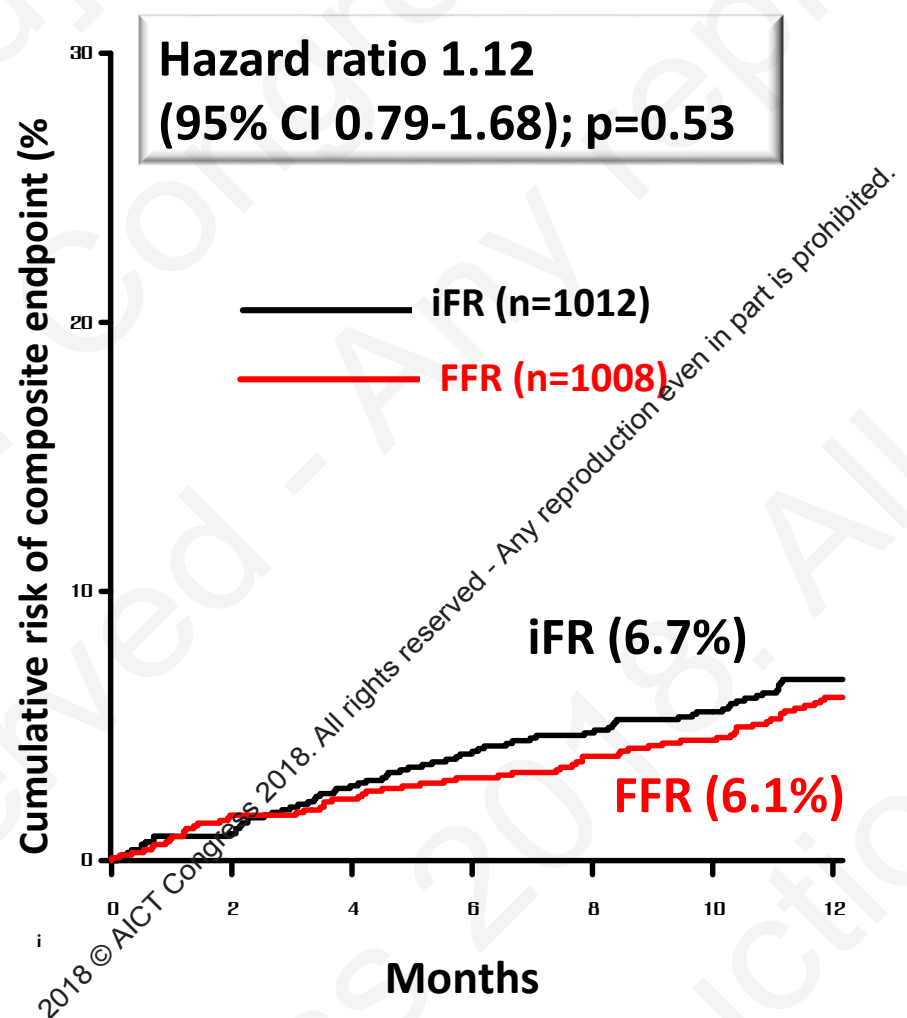
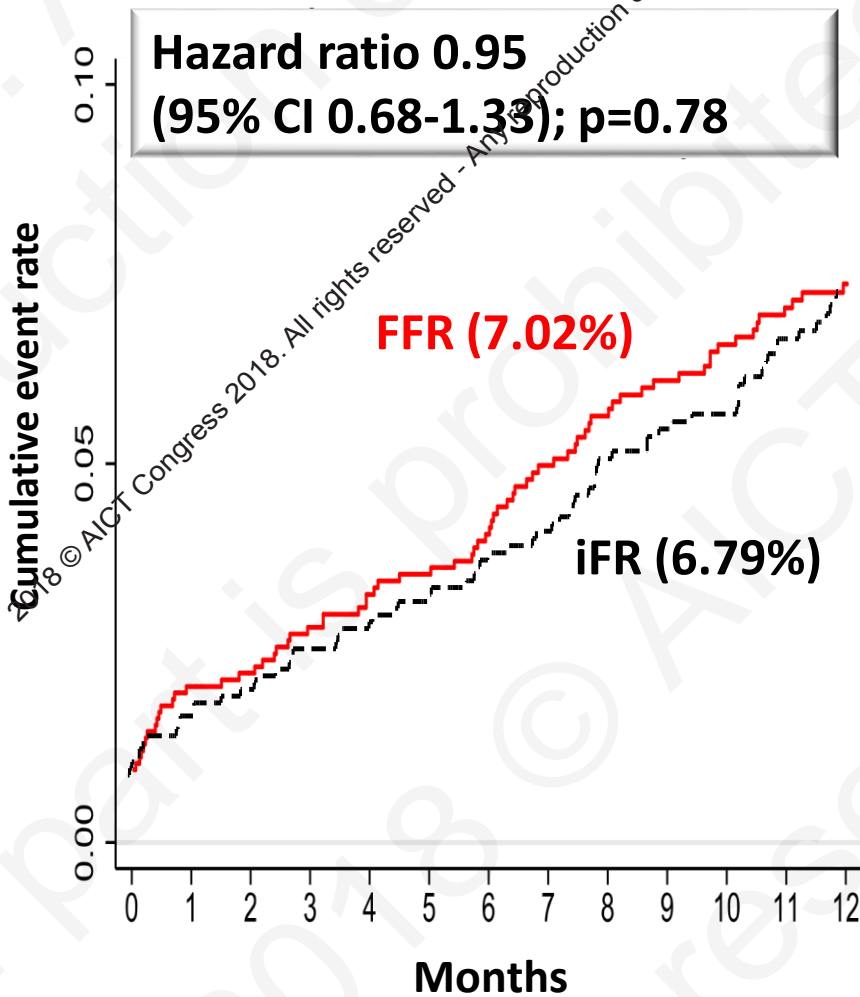
No increase in event rates in deferred pts



# Primary Endpoint (MACE)

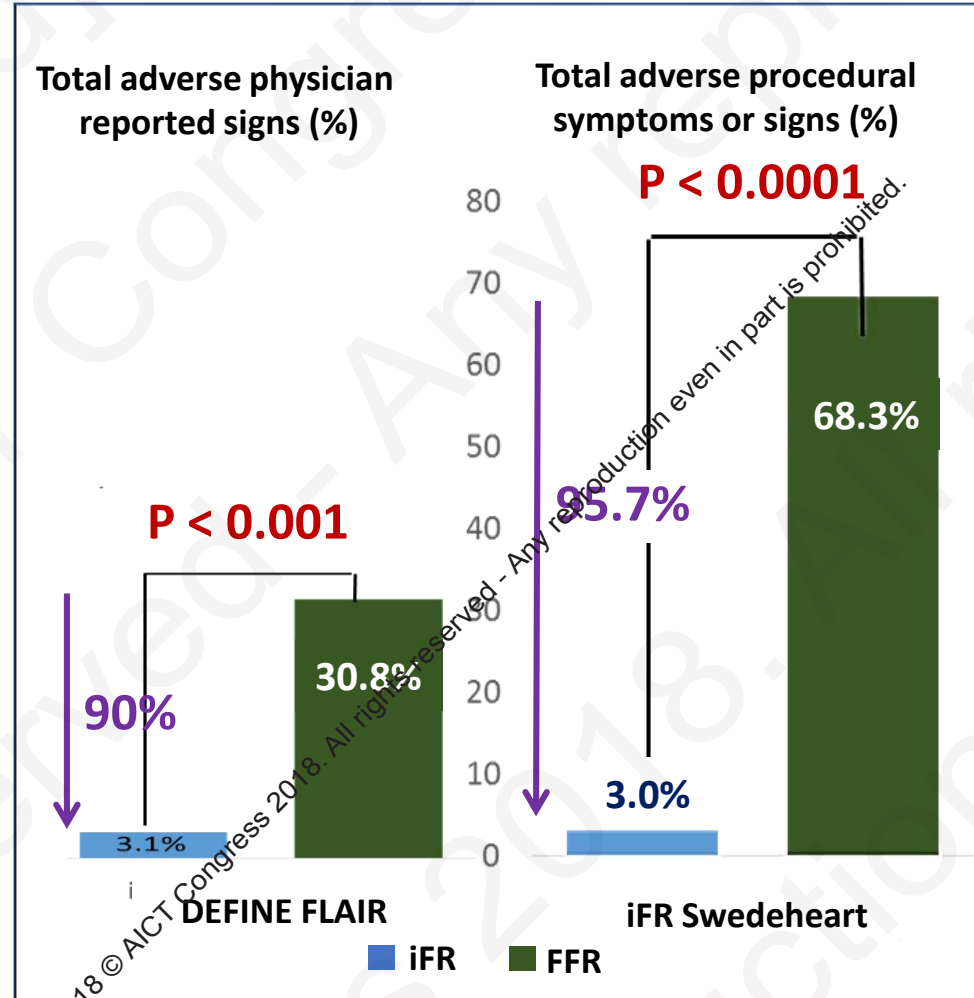
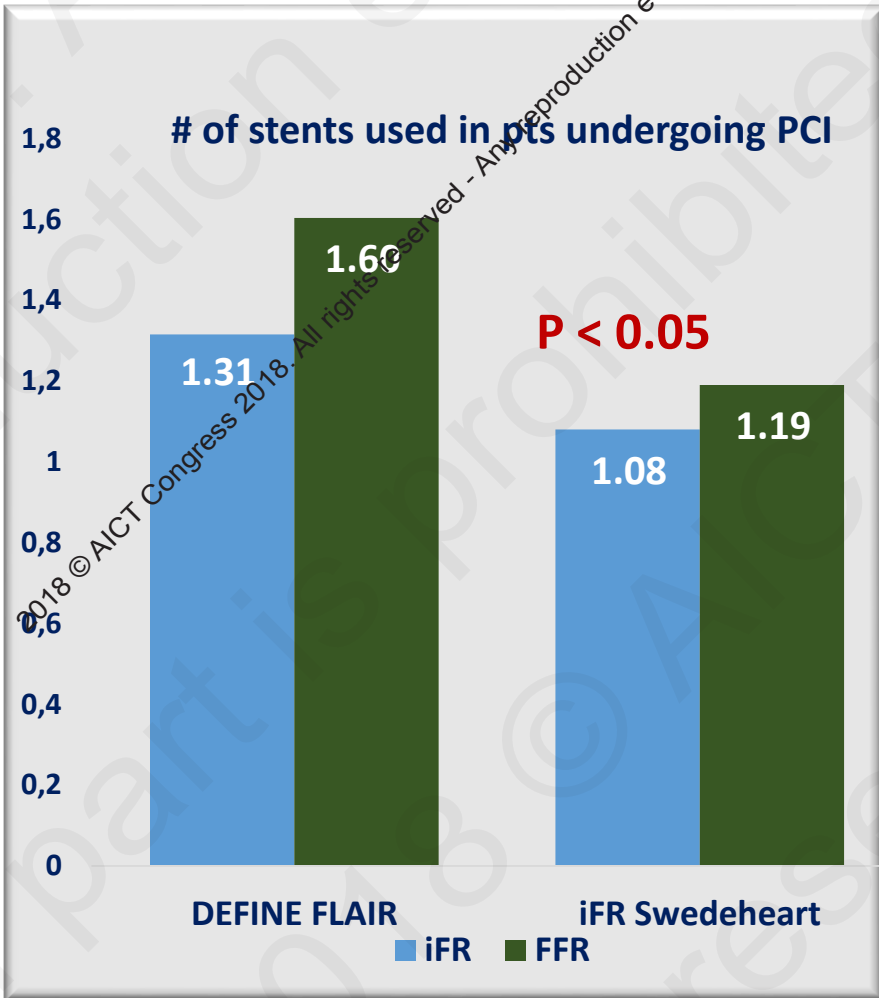
## Death, MI, Unplanned Revascularization

### DEFINE FLAIR



# An iFR-guided Strategy Led To A Significant Decrease In Stent Utilization & Patient Discomfort

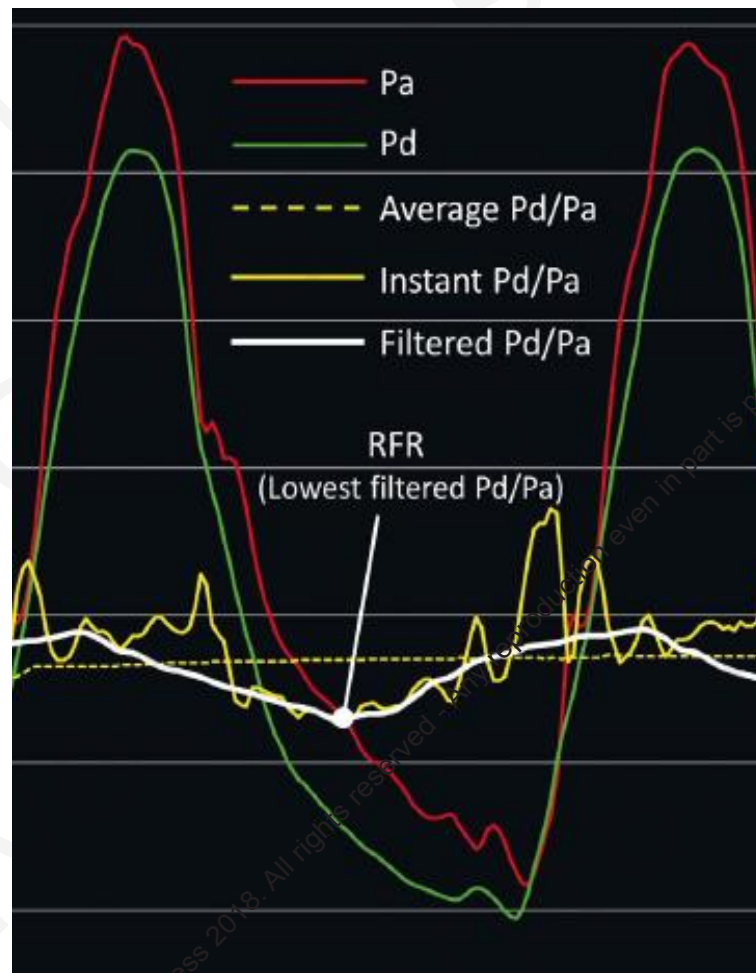
## DEFINE FLAIR



## RFR =

Point at which the relative difference in Pd & Pa is greatest (**lowest Pd/Pa ratio**) during the entire heart cycle

- Unbiased identification of lowest Pd/Pa in diastole or systole
- Independent of ECG
- No waveform landmark identification necessary
- Sensitive to small pressure changes during pullback
- High dynamic range

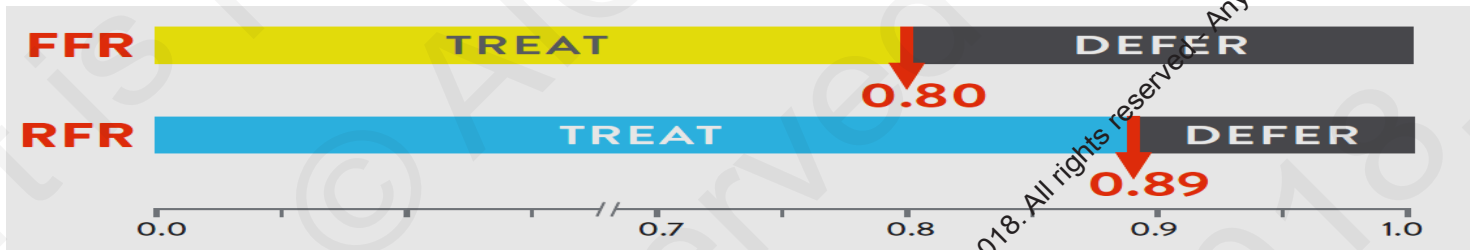
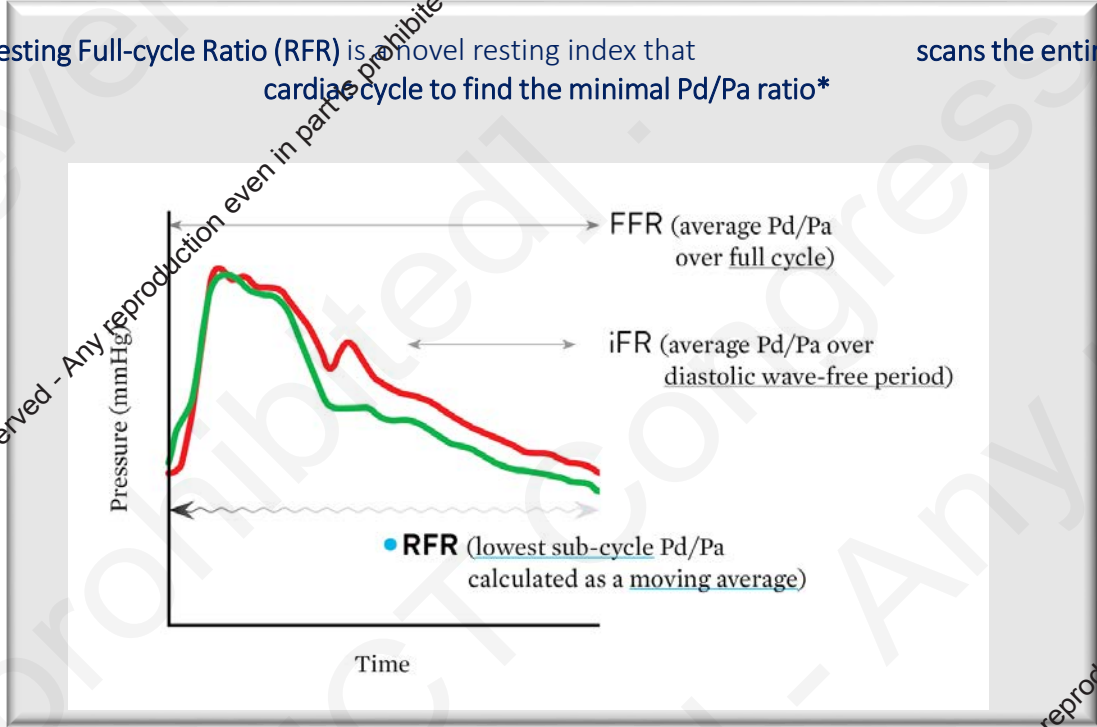


RFR is available on the QUANTIEN system with an easy workflow:

- No hyperemia required
- Clutter-free with the PressureWire X guidewire, the world's only wireless pressure guidewire<sup>1-5</sup>

# Resting Full-Cycle Ratio (RFR)

Resting Full-cycle Ratio (RFR) is a novel resting index that scans the entire cardiac cycle to find the minimal Pd/Pa ratio\*

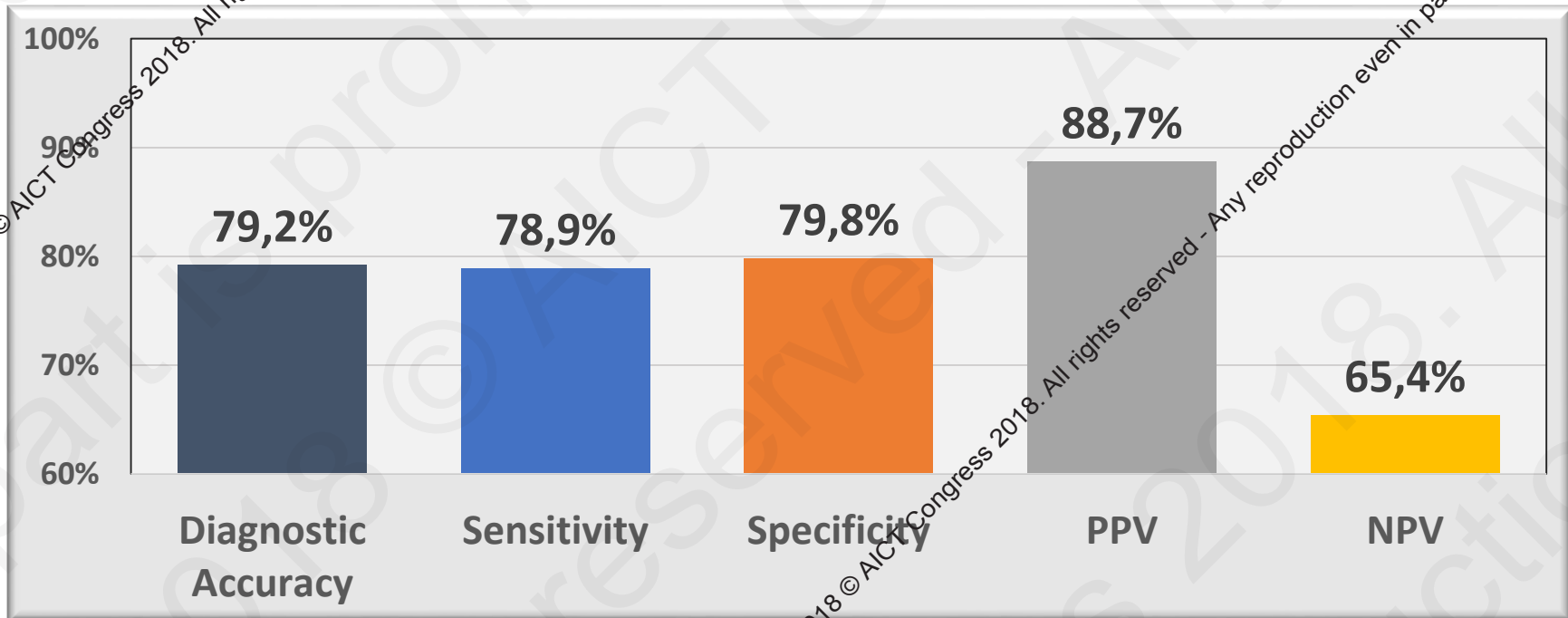


**Note that RFR has a different treatment thresholds than FFR<sup>5</sup>:**

- When **RFR ≤ 0.89**, treatment with PCI may be beneficial
- When **RFR > 0.89**, deferral of PCI may be beneficial

# ILUMIEN I + PREDICT Analysis Shows RFR is 79% Accurate vs FFR with a Cutoff of $\leq 0.89$

- A retrospective study of data from **historical (ILUMIEN I, PREDICT) studies comparing RFR to FFR** was presented at EuroPCR 2018
- The study included **299 patients and 313 lesions**
- RFR had **79.2% overall accuracy** compared with FFR, similar to other non-hyperemic pressure ratios

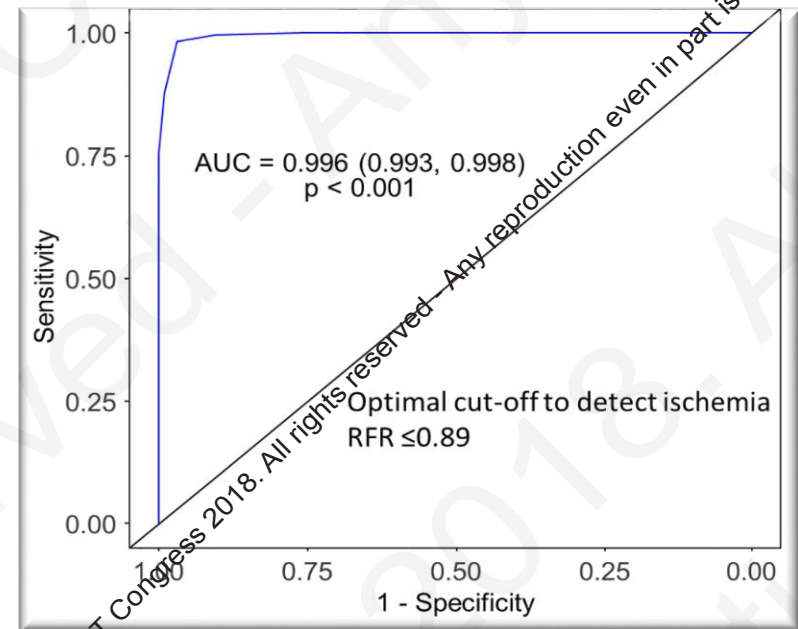
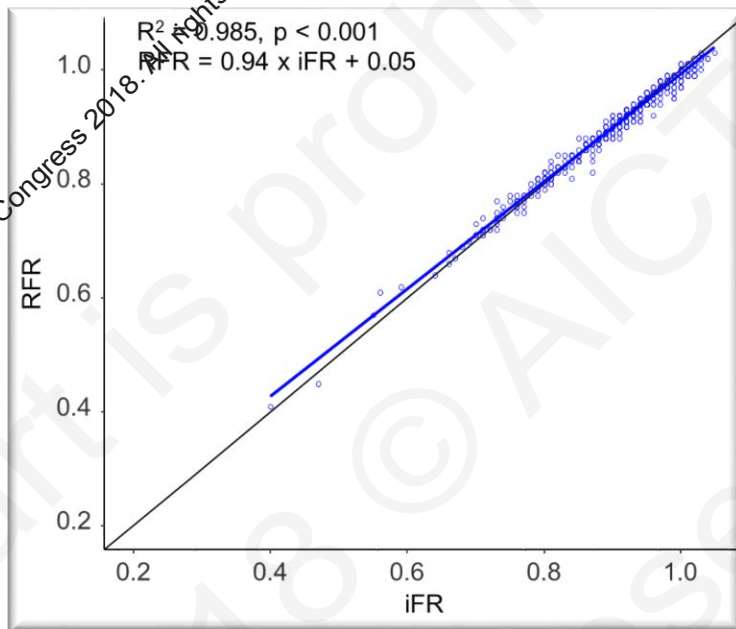


# Validate RFR Study

## A Head-to-Head Comparison Of RFR & iFR

- Retrospective study of data from historical (VERIFY-2, IRIS-FFR) studies.
- 651 RFR measurements made using genuine iFR waveforms performed with Philips wires (PrimeWire, Verrata) & proprietary software (Harvest).
- Primary endpoint: diagnostic accuracy of RFR vs iFR

	Accuracy	Sn	Sp	PPV	NPV	AUC
<b>RFR vs iFR</b>	<b>97.4%</b>	<b>98.2%</b>	<b>96.9%</b>	<b>94.5%</b>	<b>99%</b>	<b>99.6%</b>



**Equivalence testing (1% error margin):**

**RFR = iFR (mean difference -0.002; 95% CI -0.009 to 0.006, p=0.03)**

## Validate RFR<sup>1</sup> Shows *RFR is Comparable to iFR*

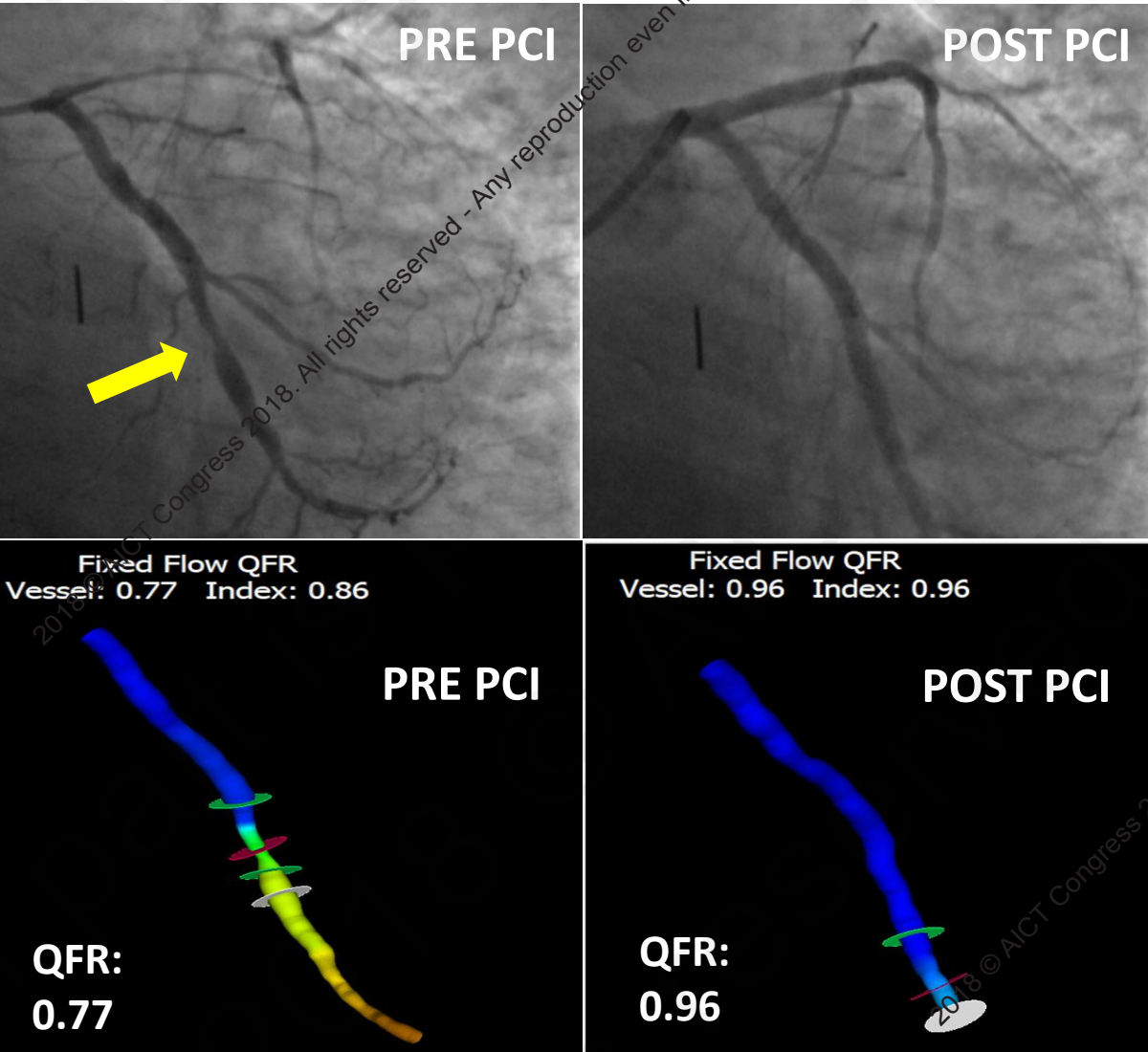
- RFR was **highly correlated to iFR** ( $R^2=0.99$ ,  $p<0.001$ )
- RFR was **diagnostically equivalent within 1 percent to iFR** ( $p=0.03$ ) using an identical cutoff value ( $\leq 0.89$ )
- While both tests lead to the **same clinical decision most of the time (accuracy=97.4%)**

### **However ....**

- **Retrospective analysis.**
- Use of **core laboratory** to eliminate artifacts and signal noise may **impact real-world agreement.**
- The **clinical benefits** of RFR has **not been fully investigated.**
  - Finding RFR outside of diastole is hypothesis-generating with the impact of this discovery unclear & requiring validation.

# Quantitative Flow Ratio (QFR)

Assessed From 3D Quantitative Coronary Angiography (QCA)



QFR is computed from:

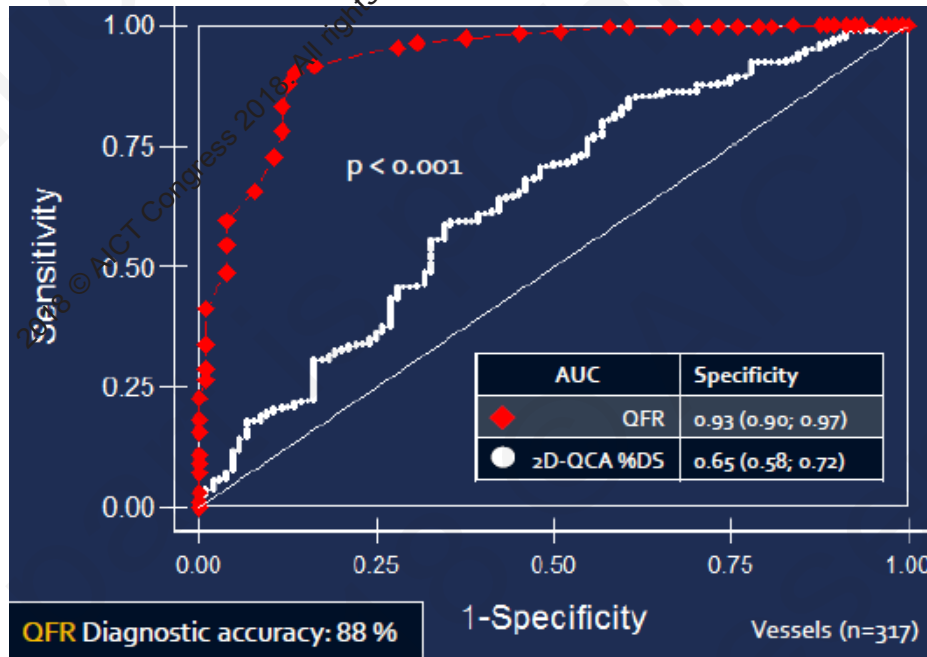
- lumen contours in two standard angiographic projections ( $>25^{\circ}$ )
- contrast flow velocity estimated by frame count during baseline conditions

- On-line & on-time
- Adenosine & wire free
- Pull back QFR curve & lesion QFR for prioritization in serial lesions
- Co-registration between angio & QFR

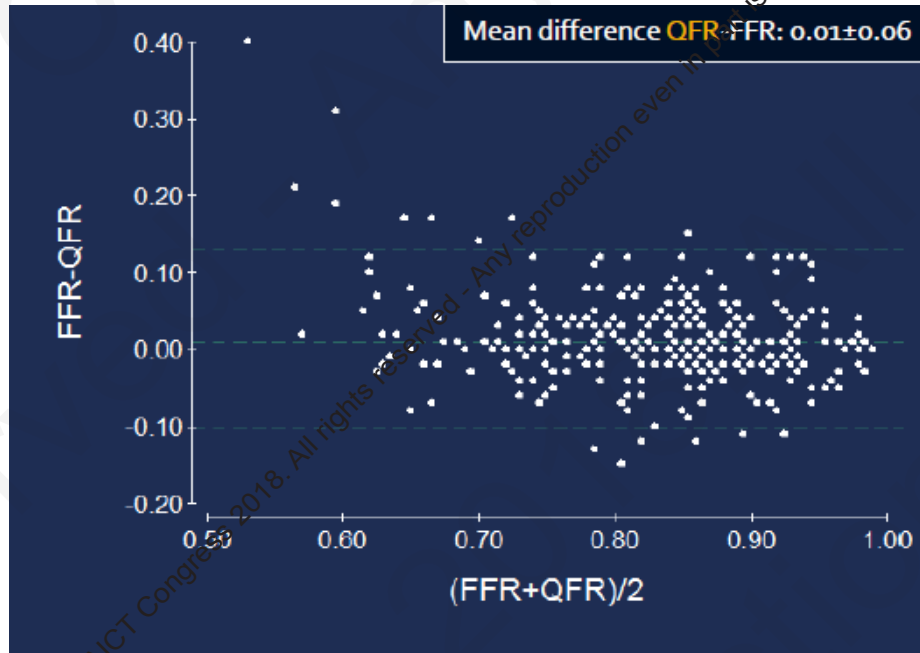


# Quantitative Flow Ratio (QFR) FAVOR II Europe-Japan

	Accuracy	Sn	Sp	PPV	NPV	AUC
QFR vs FFR	<b>88%</b>	<b>88%</b>	<b>88%</b>	<b>78%</b>	<b>94%</b>	<b>93%</b>
2D QCA vs FFR	--	46%	77%	48%	74%	65%



AOC is better with QFR vs. 2D QFR



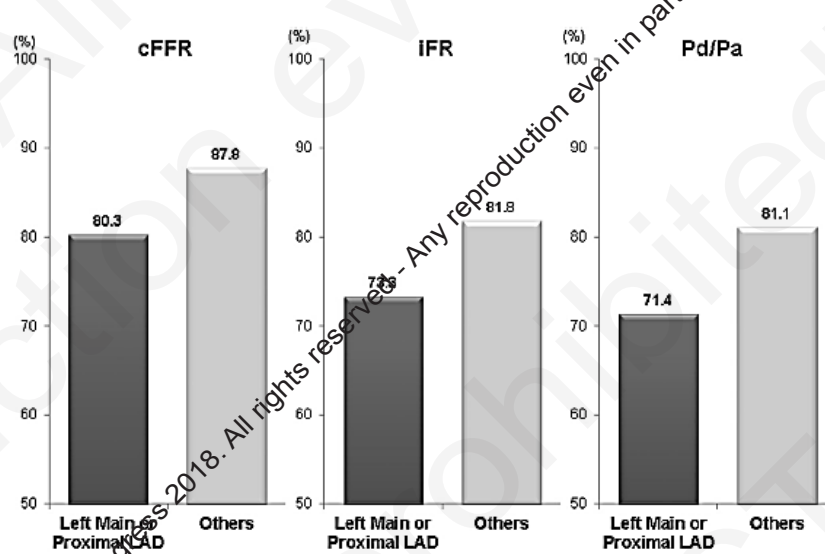
Bland-Altman Plot : Narrow 95% limit of agreement between FFR & GFR

# Despite The High Concordance Between FFR, iFR & QFR vs FFR,

## *Specific Mention Of The Differences Between Resting & Hyperemic Indices Are Warranted (1)*

1. **15-yr FU data** confirming the safety of deferring PCI based on an **FFR-guided** strategy are available <sup>1</sup>
2. RCTs have shown the superiority in **reducing death & MI** of an **FFR-guided** revascularization strategy compared to **angiographic** guidance <sup>2</sup>
3. RCTs have shown the superiority in reducing the need of **urgent revascularization** by an **FFR-guided** revascularization strategy compared to **medical therapy** <sup>3</sup>
4. In **proximal stenosis in large coronary arteries** (LM, pLAD), **iFR is discordant with FFR in up to 30% of pts** <sup>4</sup>

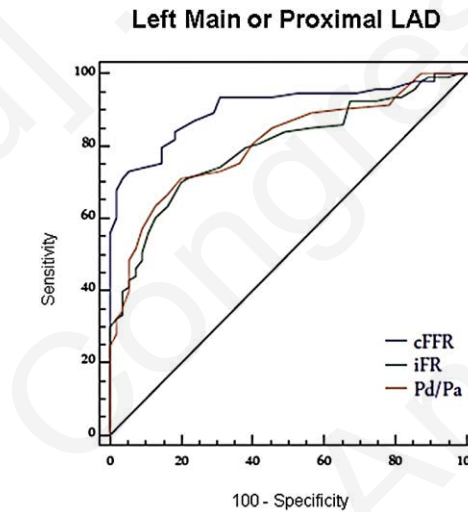
# Influence Of Lesion Location On Diagnostic Accuracy Of cFR & FFR



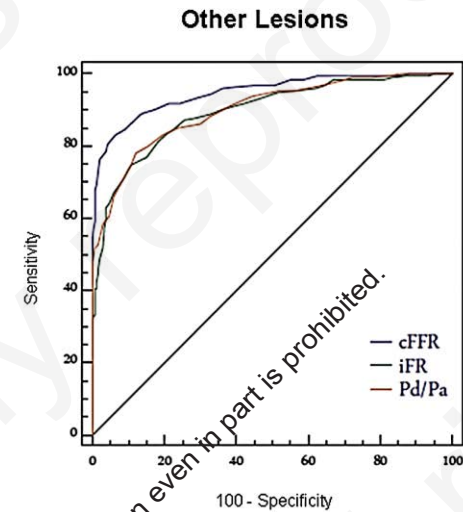
Sensitivity 80.3% vs. 87.8%,  $p = 0.17$   
Specificity 95.5% vs. 95.6%,  $p = 0.58$

Sensitivity 73.3% vs. 81.1%,  $p = 0.79$   
Specificity 62.5% vs. 82.4%,  $p = 0.001$

Sensitivity 71.4% vs. 81.1%,  $p = 0.62$   
Specificity 64.2% vs. 83.4%,  $p < 0.001$



cFFR AUC: 0.905 (0.846-0.947)  
iFR AUC: 0.795 (0.721-0.857)  
Pd/Pa AUC: 0.807 (0.734-0.867)  
 $\Delta$ AUC: 0.110 (0.061-0.160),  $p < 0.0001$   
 $\Delta$ AUC: 0.098 (0.050-0.147),  $p = 0.0001$



cFFR AUC: 0.948 (0.922-0.967)  
iFR AUC: 0.895 (0.862-0.923)  
Pd/Pa AUC: 0.901 (0.868-0.928)  
 $\Delta$ AUC: 0.053 (0.034-0.072),  $p < 0.0001$   
 $\Delta$ AUC: 0.047 (0.028-0.067),  $p < 0.0001$

		Accuracy	Sn	Sp	r	AUC
cFR	LM & pLAD	80.3%	71.0%	95.5%	0.889	90.5%
	Other lesions	87.8%	78.0%	95.6%	0.935	94.8%
iFR	LM & pLAD	73.3%	79.8%	62.5%	0.662	79.5%
	Other lesions	81.8%	81.1%	82.4%*	0.836	89.5%

***cFFR & iFR are less accurate in LM/pLAD*** vs. other lesion locations, likely related to the larger amount of myocardium supplied by LM/pLAD.

\*P=0.001

## Specific Mention Of The Differences Between Resting & Hyperemic Indices Are Warranted (2)

5. For **specific lesion subsets (i.e. LM, bifurcation)**, evidence for utility of the physiological assessment exist **only for FFR**<sup>5,6</sup>
6. The non-inferiority claims of iFR to FFR for 1-yr MACE in intermediate lesions clearly exist, this should be **clearly distinguished from equivalence**<sup>7,8</sup>:
  - The **event rates** in FAME (13.6%) were  $\approx 2x$  those reported in DEFINE-FLAIR & SWEDEHEART (6.5%), a reflection of the **higher SYNTAX score** (15-28 vs.  $< 15$ ), **lower mean FFR** (0.71 vs. 0.83), **greater proportion of MVD** (100% vs. 40%)
7. The benefit of **post-PCI physiological assessment** exists **only for FFR** as **submaximal hyperemia may potentially persist following PCI**, limiting the utility of resting indices<sup>9,10</sup>

5. Mallidi J, cs. Cathet Cardiovasc Interv 2015;86:12-8; 6. Koo BK, cs. Eur Heart J, cs. 2008;29:726-32;

7 Davies JE, cs. N Engl J Med 2017;376:1824-34; 8. Gotberg M, cs. N Engl J Med 2017;376:1813-23;

9. Agarwal SK, cs. JACC Cardiovasc Interv 2016;9:1022-31; 10. Piroth Z, cs. Circ Cardiovasc Interv 2017 Aug;10 (8).

# Conclusions

- Strong randomized clinical trial evidence that physiology based coronary revascularization by **FFR guidance improves clinical outcomes** (FAME, FAME II, DANAMI-3-PRIMULTI & COMPARE)
- **iFR** guided revascularization appears to be **non-inferior to FFR &** may help in **planning the PCI strategy** by increasing functional revascularization in stable angina patients & functional revascularization of non-culprit lesions in patients with STEMI & MVD avoiding additional procedures, including the use of adenosine
- **RFR** is diagnostically **equivalent to iFR** & is near identical with regards to diagnostic accuracy, sensitivity, specificity and AUC compared to iFR versus FFR. However, the **clinical benefits of RFR has not been fully investigated**
- **QFR is diagnostically also close to FFR**, but further validation study is required

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# AICT

ASIAN INTERVENTIONAL CARDIOVASCULAR THERAPEUTICS  
THE OFFICIAL CONGRESS OF APSIC

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Convention and Exhibition Centre (HKCEC)

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