TCT Asia Pacific 2022

DON'T MESS UP: *Critics on FAME 3, FLOWER-MI, FUTURE, RIPCORD 2*

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CATHARINA-ZIEKENHUIS

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Potential conflicts of interest

I have the following potential conflicts of interest to report:

- Research contracts : *Abbott*
- Consulting: *Abbott, Heartflow (SAB)*
- Stockholder of a healthcare company: *Philips, GE, ASML, Heartflow*
- Other(s): *patents pending in the fields of coronary microcirculation and aortic valve stenosis*

Thomas Kuhn, 1965, “The Structure of Scientific Revolutions”

“Philosophers of science have repeatedly demonstrated that more than one theoretical model can always be placed upon any given set of scientific data”

Study to discuss: **“THE STUDY”**

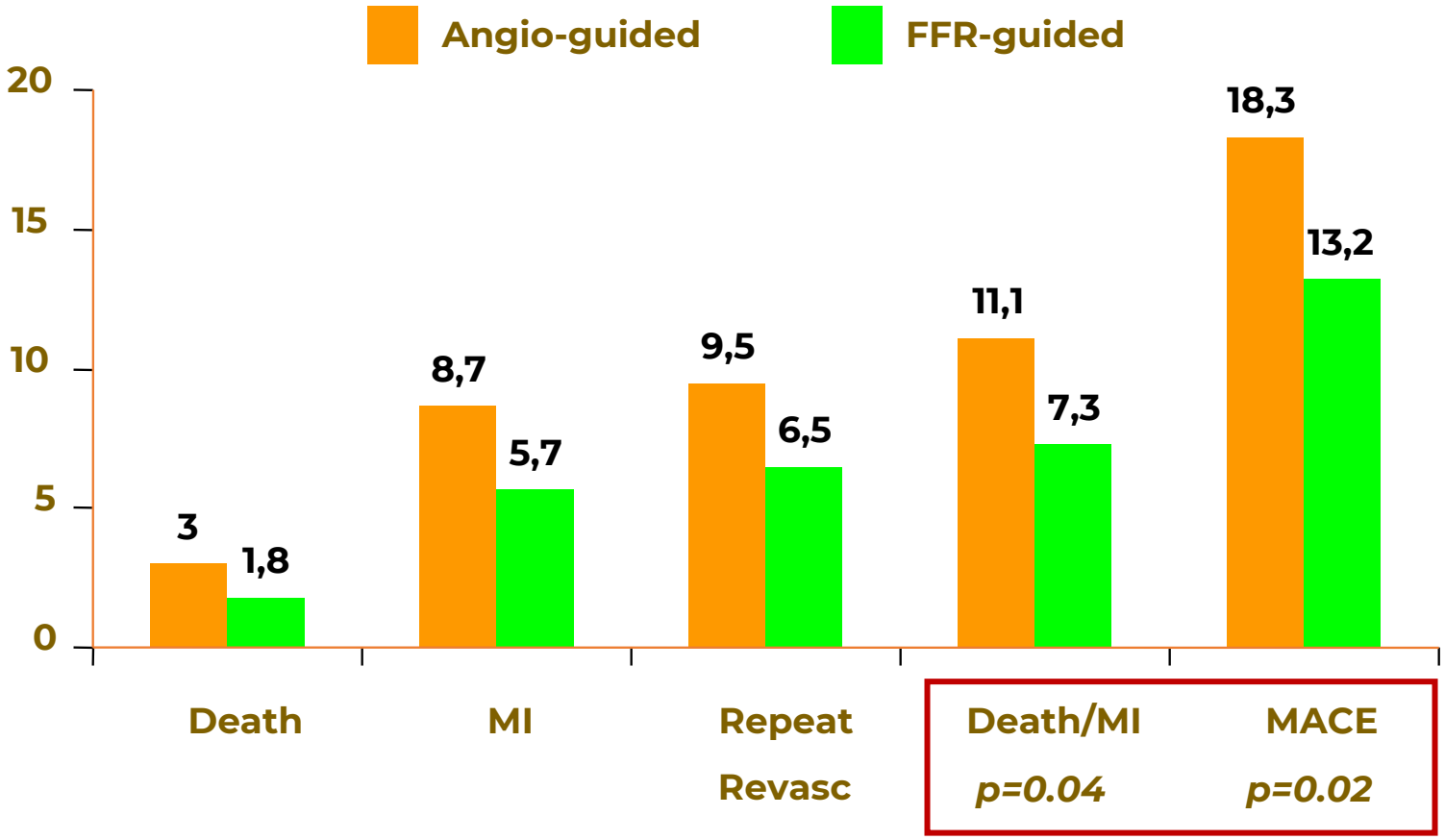
Comparable Study to which the respective study is compared: **“COMPARATOR”**

FFR – guided vs Angio- guided PCI in Multivessel Disease:

FUTURE vs FAME

	FAME-study (N= 1005) *(Tonino, NEJM 2009:360:213-224)*	FUTURE study (N= 927) *Rioufol, JACC 2021;78: 1875-85)*
Hypothesis	FFR-guided PCI in MVD is superior to standard, angio-guided PCI	FFR-guided PCI in MVD is superior to standard, angio-guided PCI
Primary Endpoint	Death, MI, revascularization at 1,2, 5 y	Idem + "unplanned revascularization"
Design	RCT in all-comers (***3 pat/center/month***)	RCT "all-comers" ***but < 1 pat/center/month***
Population	Moderate/high risk: 4 stenoses, 3 stents	moderate risk: 3 stenoses, 2 stents per pat.
Strong points	91% DES	95% DES
Weak points	***none***	***96 % staged procedures***, of which quite a number after 30 days and counted as event ! *poor adherence to study protocol:* ***FFR-value often neglected*** *(2.2 vs 2.1 stents per patient !)*
Outcome	***FFR-guided PCI superior to angio-guided PCI, also for all individual endpoints***	***equipoise for FFR-guidance vs standard***
Applicability for average population	**High: reduction of all adverse events with 30% at 1, 2 , and 5 years**	**limited because of serious limitations in design and performance**

FFR-guided vs Angio-guided PCI in Multivessel Disease: FAME study (N=1005) : one-year outcomes



Tonino ,NEJM 2009; Pijls, JACC 2011, Zimmermann, EHJ 2015

FFR – Guidance for Quality Of Life and Costs

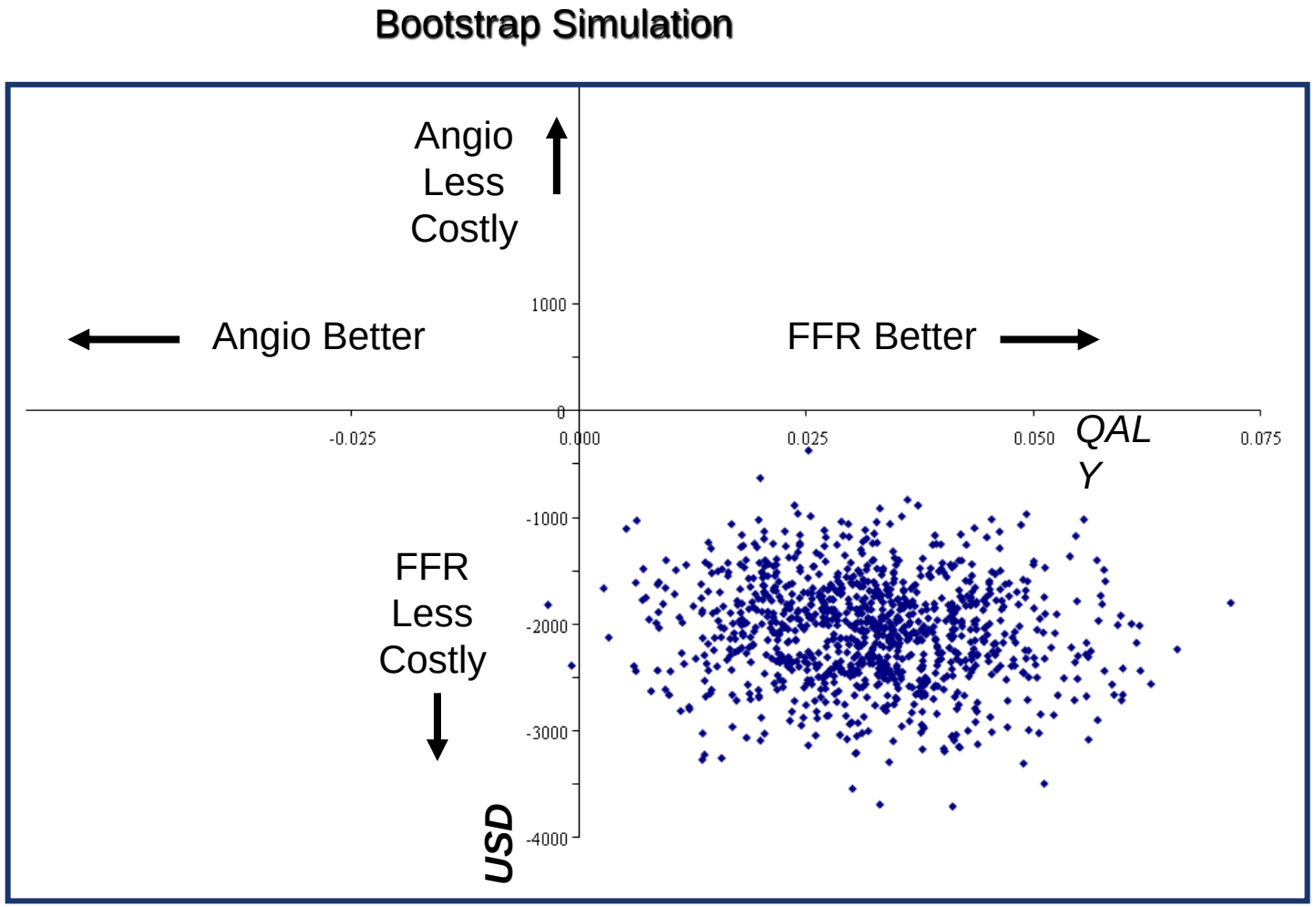
- **RIPCORD-2** *Stables, Circulation 2022*

  versus

- **FAME 1 -2 -3** *5 papers in NEJM 2009-2021 (Tonino, De Bruyne, Fearon)*
- **IRIS** *Ahn, Circulation 2017*

	FAME-study (N= 1000) *(Tonino, NEJM 2009:360:213-224)*	RIPCORD-2 study (N= 1100) *(Stables, Circulation 2022;146:687-698)*
Hypothesis	FFR-guided PCI in MVD is superior to standard, angio-guided PCI for outcome, ***but also for QOL and Costs***	Systematic use of FFR during angiography, is superior to regular angio with respect to ***QOL & costs***
Primary Endpoint	Death, MI, revascularization at 1,2, 5 y. ***Secondary endpoint***: QOL & costs at 1 year	Quality Of Life (QOL) and costs at 1year
Design	RCT	RCT
Population	***Moderate/high risk***: 4 stenoses, 3 stents 66 % of all lesions FFR-positive	***very low risk, mainly diagnostic population***. only 29% of lesions FFR-positive
Strong points	strong design	strong design
Weak points	***none***	***many (almost) normal arteries:*** If just one artery was >30%, all arteries were measured
Outcome	***FFR-guided PCI superior*** *to angio-guided PCI* ***also for QOL and Costs***	***equipoise for FFR-guidance vs standard angio with respect to QOL and costs***
Applicability for average population	high in patients with MVD and ***lesions 30-90%*** ***IRIS Registry: similar data (Ahn et al, Circ 2017)***	high: ***measure FFR mainly in vessels 30-90 %***

1 Year Economic Evaluation in FAME study: *The FAME study is one of those rare examples in today's Medicine, where a new method is not only better, but also more cost-effective!*



Fearon et al, Circulation 2010

COMPLETE REVASCULARISATION IN STEMI, INCLUDING NON-CULPRITS:

FFR-Guidance vs Angio-Guidance

RCT's

- **FLOWER-MI** *Puymirat, NEJM 2021*

  versus

- **COMPARE-ACUTE study** *Smits, NEJM 2017*
- **DANAMI/PRIMULTi study** *Engstrom, Lancet 2017*
- **FRAME Registry** *Hahn, ESC 2022*

	COMPARE-ACUTE study /DANAMI study/FRAME study *(Smit: NEJM 2017, Engstrom, Lancet 2017*	FLOWER-MI study (N=1171) *Puymirat, NEJM 2021;384:297-307*
Hypothesis	In PPCI for STEMI, FFR-guided complete revasc of non-culprits is superior to angio-guided procedure	In PPCI for STEMI, FFR-guided complete revasc of non-culprits is superior to angio-guided procedure
Primary Endpoint	Death, MI, urgent revasc at 1 year	Death, MI, urgent revasc at 1 year
Design	RCT in Acute STEMI (Compare & DANAMI)	RCT in acute STEMI
Population	STEMI + at least one non-culprit lesion >50%	STEMI + at least one non-culprit lesion >50%
Strong points	Excellent design, excellent adherence ***Randomization before anatomy was known***	Excellent design, excellent adherence
Weak points		- ***randomization áfter anatomy was known*** ***- In 16 % of all lesions → PCI without physiol***
Outcome	***Immediate FFR-guided PCI of non-culprits superior to angio-guidance***	***equipoise for FFR-guidance vs angio-guidance***
Applicability for average population	**Both studies favour complete revascularization in STEMI but Compare-Acute, DANAMI, and FRAME favour use of FFR , whereas FLOWER-MI does not**	

PCI vs CABG in 3-vessel disease

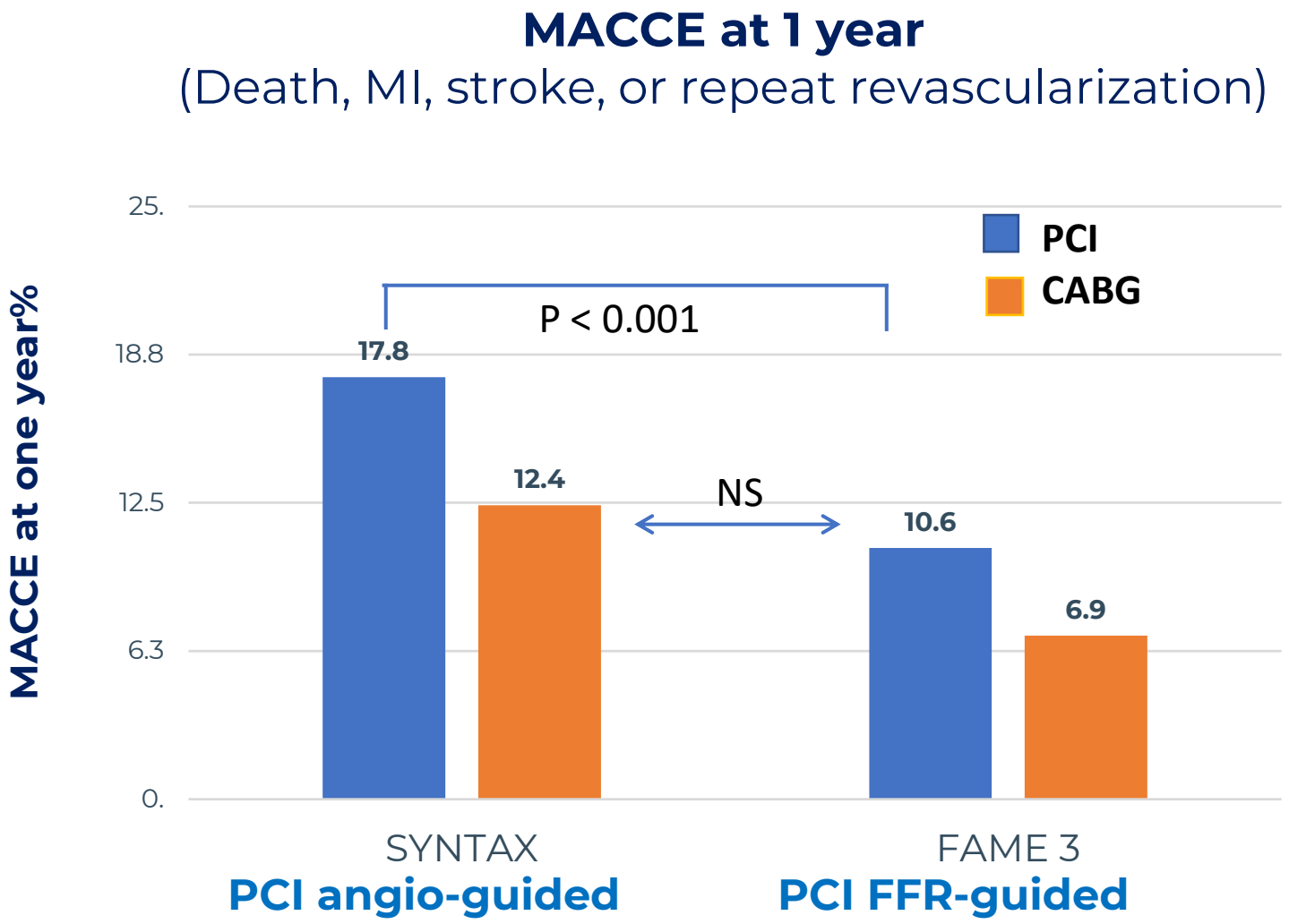
- **SYNTAX** *Serruys, NEJM 2009*

vs

- **FAME 3** *Fearon, NEJM 2021*

	SYNTAX study (N= 1800) *(Serruys, NEJM 2009)*	FAME-3 study (N= 1505) (*Fearon NEJM 2022)*
Hypothesis	Revascularization with DES in 3-VD is Non-inferior to bypass surgery	***FFR-guided*** Revascularization with DES in 3-VD is non-inferior to bypass surgery
Primary Endpoint	Death, MI, revascularization at 1,2, 5 y	Death, MI, revascularization at 1,2, 5 y
Design	RCT in 3-VD ***ánd in LM disease***	RCT in 3-VD
Population	high risk	high risk
Strong points	all-comers, 91% DES	all-comers, 91% DES
Weak points	***none***	***none***
Outcome	***CABG remains superior in high SYNTAX-score. PCI equivalent to CABG in low/medium SYNTAX score***	***CABG remains superior in high SYNTAX-score. PCI equivalent to CABG in low/medium SYNTAX score***
Applicability for average population	***high***	***highly Reduced mortality in both PCI ánd CABG groups***

SYNTAX and FAME-3 studies (optimal revascularisation in 3-VD)



Fearon et al. NEJM 2021 Serruys et al. NEJM 2009

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“Philosophers of science have repeatedly demonstrated that more than one theoretical model can always be placed upon any given set of scientific data”

……..but some data sets are stronger than others !!

Non-inferiority of NHPR's was investigated in 2 RCT'S:
DEFINE-FLAIR study and SWEDE-HEART:

- low-risk populations
- single vessel disease in 58% of patients
- no PCI at all-in 45% of patients
- average number of stents 0.7

- ***Studies claimed to be "physiology-guided" but <u>first</u> an angiographic assessment was made and <u>only</u> if visual lesion severity was < 70%, iFR or FFR was measured***

→ Almost 50% of all stents were placed without physiologic measurement, just by eye-balling

→ Most false-negative iFR excluded from analysis by design of the study

DEFINE FLAIR

Functional **L**esion **A**ssessment of
Intermediate stenosis to guide
Revascularization

iFR vs FFR for guiding coronary revascularization – DEFINE-FLAIR (2 year results)

Justin E Davies, MD, PhD on behalf of the DEFINE-FLAIR investigators

Hammersmith Hospital,

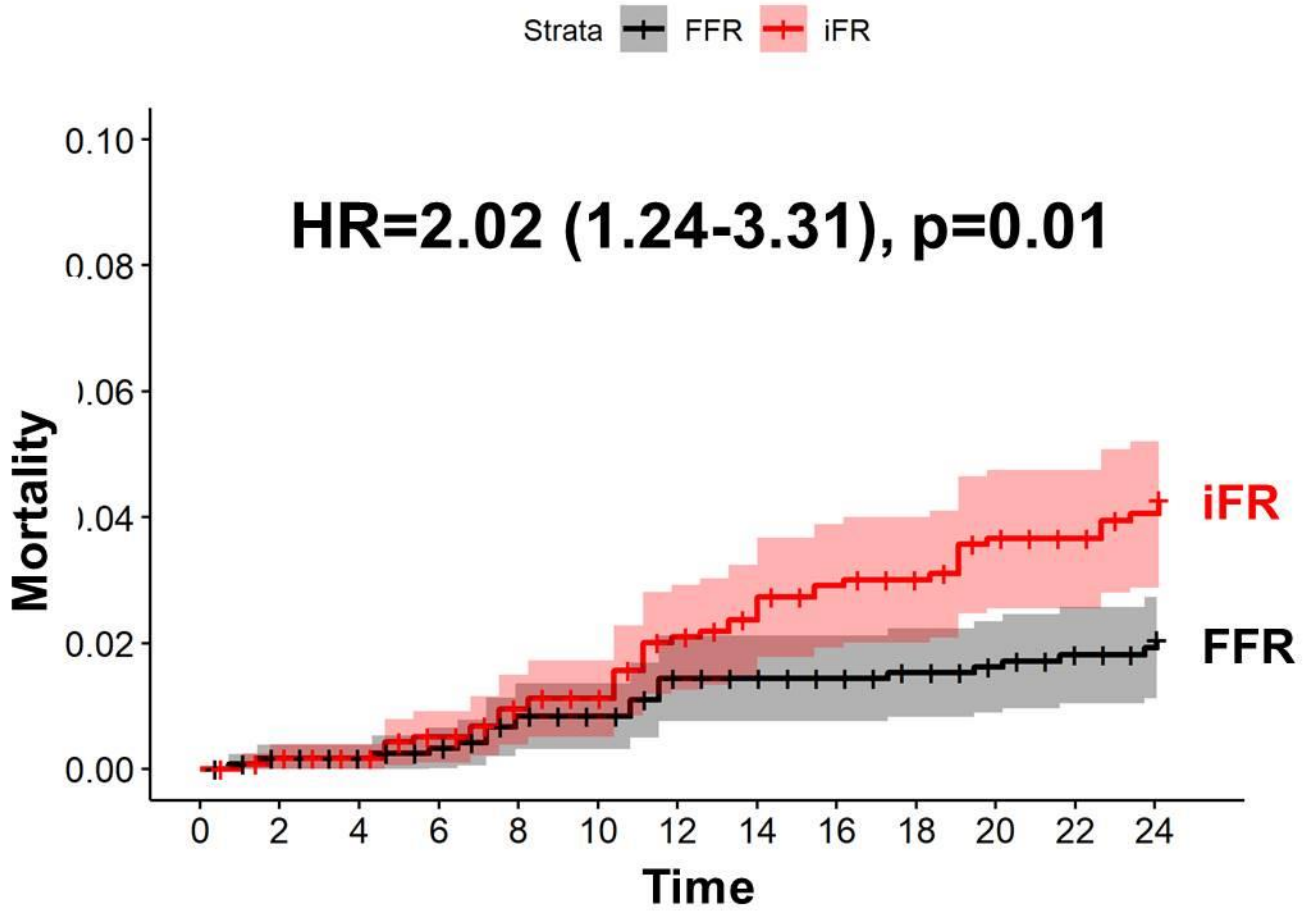
Imperial College London

Imperial College London

San Francisco, TCT 2019

DEFINE-FLAIR

Significantly Higher Two Year Mortality with iFR-Guided PCI



Adapted from Davies, et al. TCT 2019 by Takuya Mizukami, MD, PhD

FAME study Functional Class at 1 Year

	ANGIO-group N=496	FFR-group N=509	P-value
Patients without Event and free from Angina	326 (68)	360 (73)	0.07

Tonino, NEJM 2009:360:213-224

HYPEREMIA (FFR) vs NHPR (iFR, dPR, RFR, etc)

DEFINE-FLAIR *Davies, NEJM 2017*

SWEDE-HEART *Gotberg, NEJM 2017*

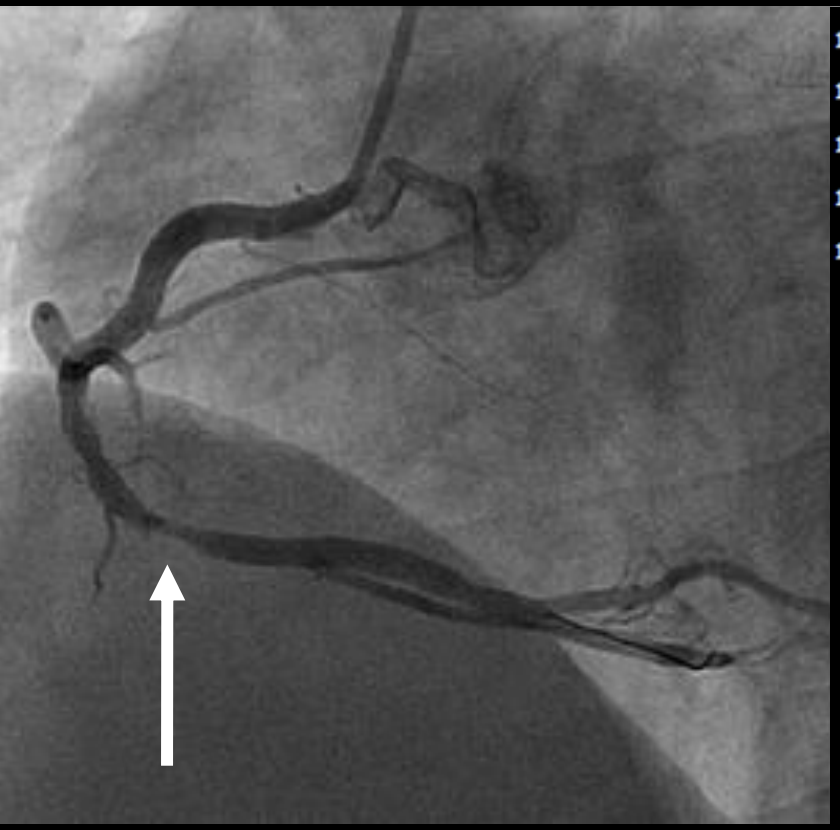
vs

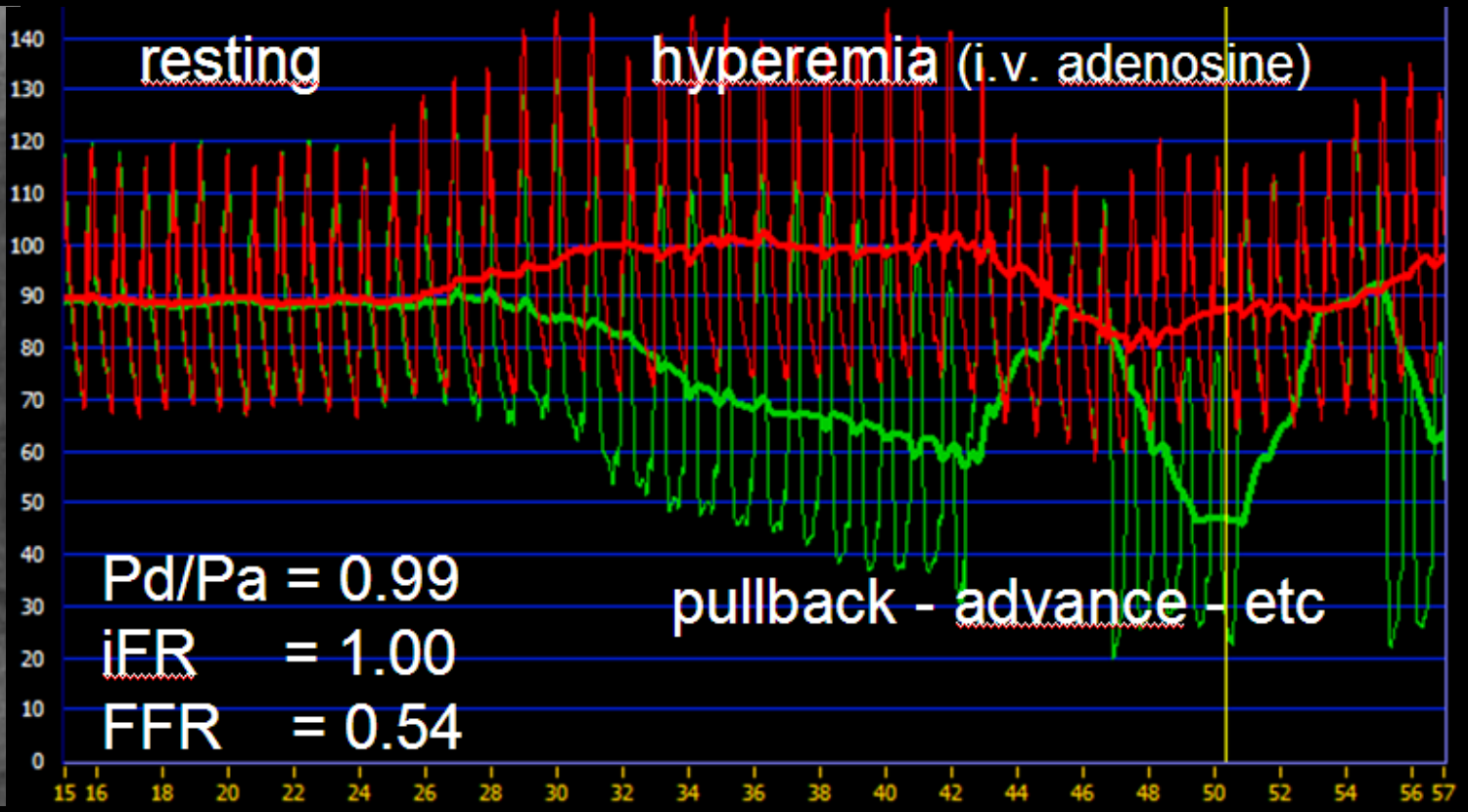
FAME *Tonino, NEJM 2009*

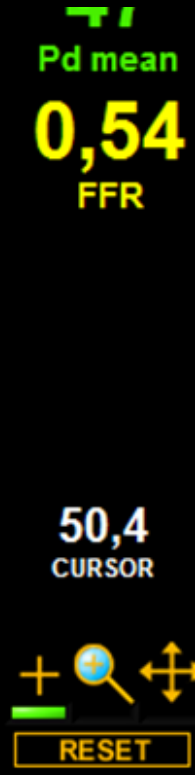
VERIFY *Berry, JACC 2012*

	FAME-study (N= 1000) *(Tonino, NEJM 2009:360:213-224)*	DEFINE FLAIR (N= 2492) *Davis, NEJM 2017, March 17th*
Hypothesis	FFR-guided PCI in MVD is superior to standard, angio-guided PCI	Instantaneous Flow Ratio (iFR) or NHPR are non-inferior to FFR with respect to outcome
Primary Endpoint	Death, MI, revascularization at 1,2, 5 y	Death, MI, revascularization at 1,2, 5 y
Design	RCT in all-comers	RCT "all-comers"
Population	Moderate/high risk: 4 stenoses, 3 stents	low risk population: ***0,7 stent per patient*** - ***56% Single vessel disease*** - ***no PCI at all in 45% of all patients***
Strong points	all-comers, 91% DES	***very large population***
Weak points		- ***50% of stented lesions in iFR/FFR group had no physiologic measurement performed*** - ***exclusion of many false-negatives by design***
Outcome	***FFR-guided PCI superior to angio-guided PCI, also for all individual endpoints***	***Non-inferiority for iFR guidance vs FFR guidance at 1 year*** ***Significant higher mortality in IFR group at 2 years***
Applicability for average population	***High*: reduction of all adverse events with 30% at 1, 2 , and 5 years**	***Caveat*. Mistrust negative iFR/ NHPR in proximal focal lesions and in high-risk patients**

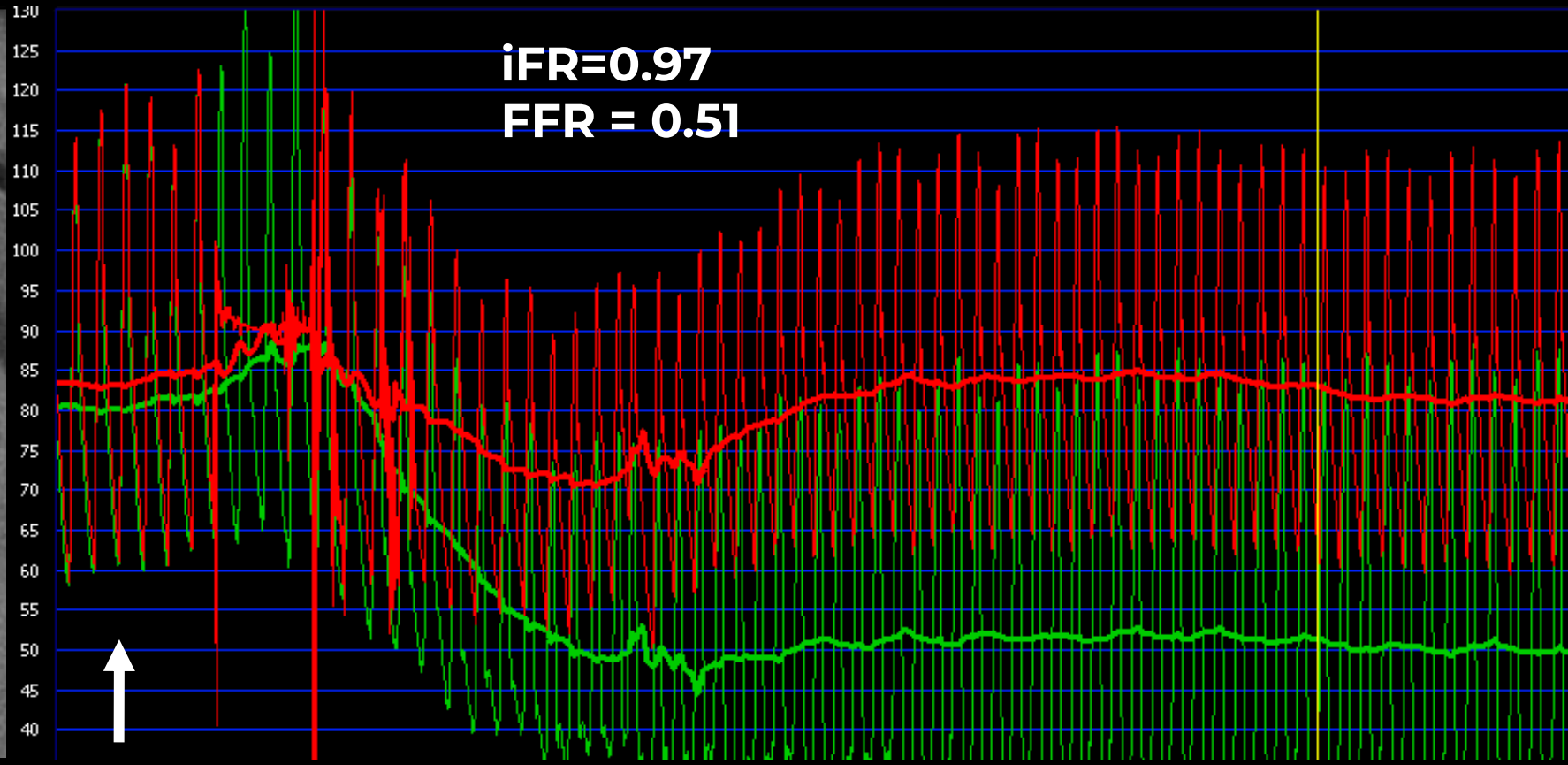
Young male, large RCA, focal lesion 70%





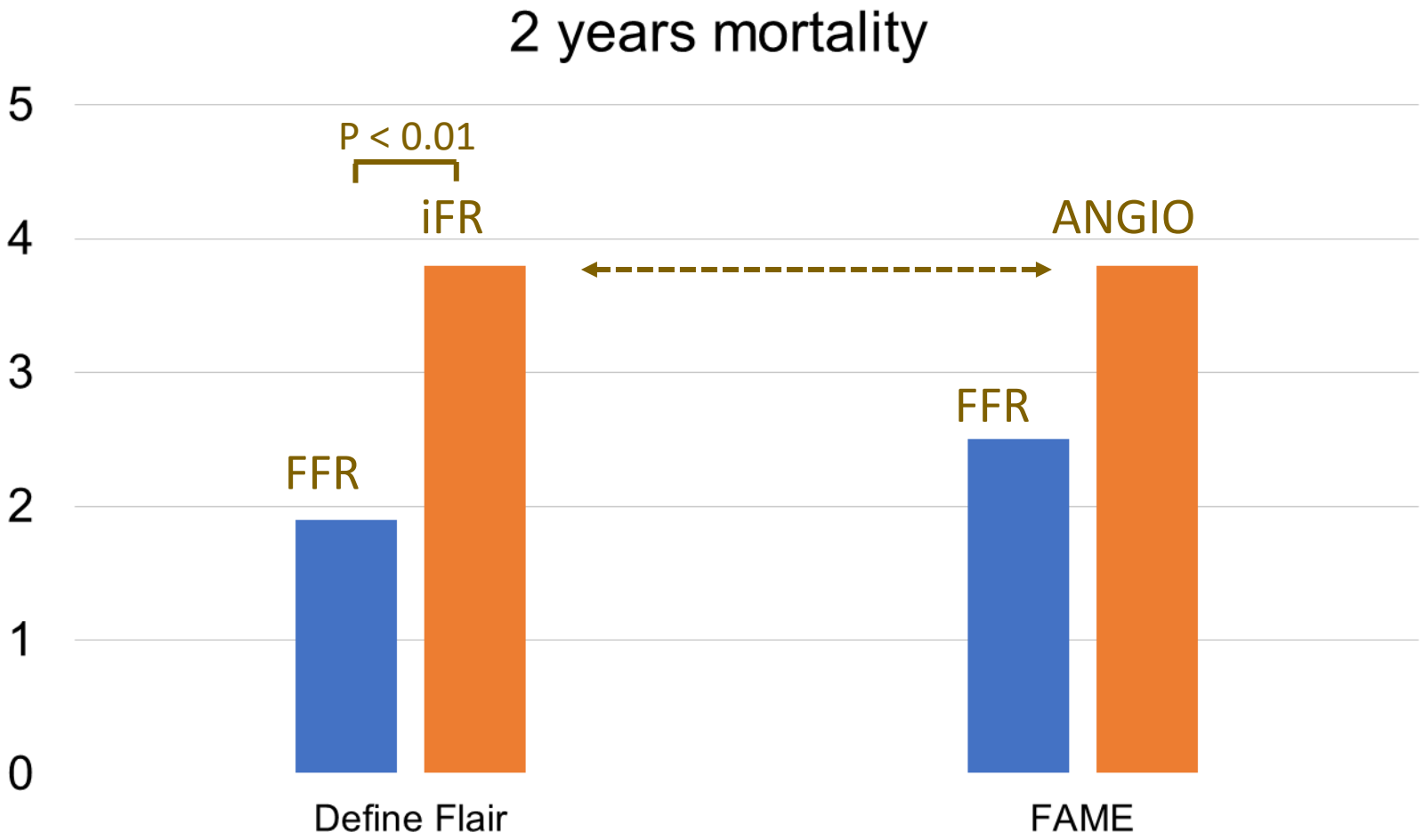


Middle-aged woman, short 50% LM stenosis



Rest hyperemia (i.v. adenosine)

2-year-mortality with iFR- guidance in low-risk DEFINE-FLAIR population, was twice as high as in FFR group (p<0.01) and equal to angio-guided group in complex FAME population



adapted from Davies J, TCT 2019; Van Nunen, Lancet 2015;386;1853-1860