Coronary Physiology: New Insights

FFR and iFR: WHERE DO WE STAND TODAY?

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Disclosure

- Institutional Research Grants from Abbott
- Consultang relations and fees from Abbott and Coroventis
- Minor equity in Philips, ASML, Heartflow, and General Electric
- Member of the Scientific Advisory Board of Heartflow
- Patents pending in the field of the Coronary Microcirculation and Aortic Valve Stenosis.

FFR and iFR: WHERE DO WE STAND TODAY?

First: *A Short Refresher*

Fractional Flow Reserve (FFR)

The FFR index (Fractional Flow Reserve) is based upon the two following principles:

- It is not resting flow, but ***maximum achievable flow*** which determines the functional capacity (exercise tolerance) of a patient

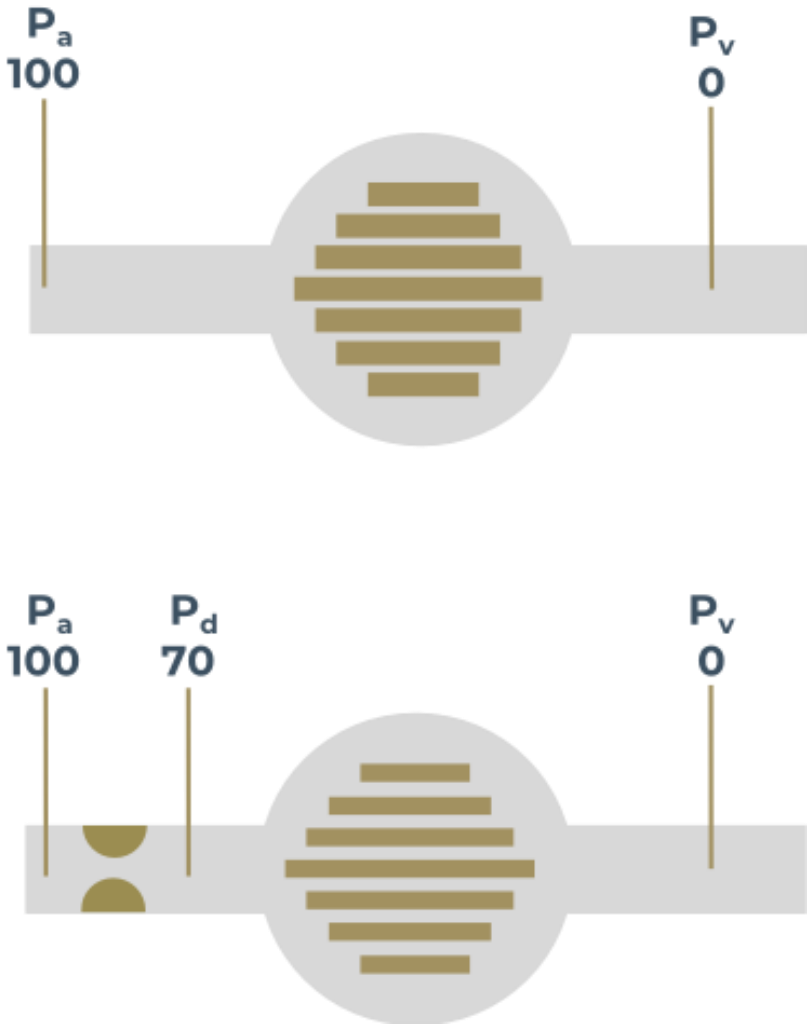
- At maximum vasodilation (corresponding with maximum hyperemia or with maximum exercise), blood flow to the myocardium is proportional to ***myocardial perfusion pressure (~hyperemic distal coronary pressure)***

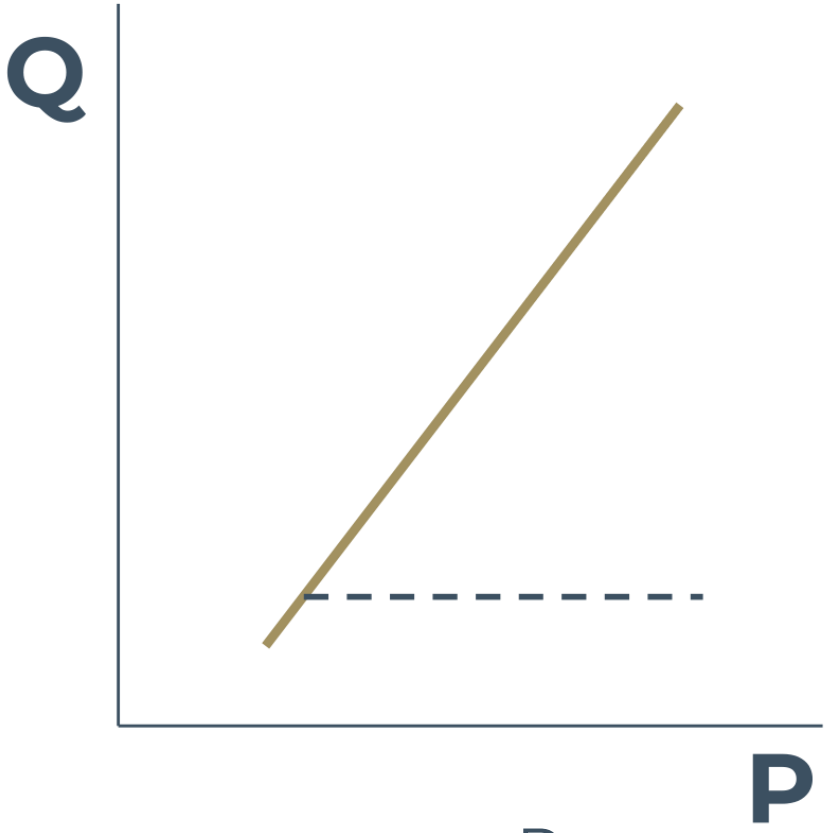
Consequently:

Fractional Flow Reserve is defined as maximum achievable blood flow in the presence of a coronary stenosis as a ratio to normal maximum flow

(i.e maximum flow in the hypothetical case that the artery were completely normal)

During maximal vasodilatation





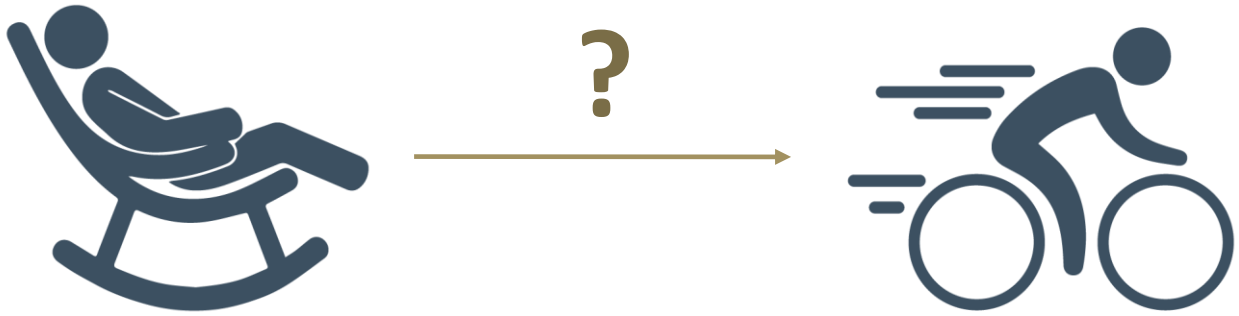
$$FFR_{myo} = \frac{P_d}{P_a}$$

$$= \mathbf{0.70}$$

- FFR is based upon a sound physiologic basis
- FFR has changed our practice in the catheterization laboratory and made us better understand the coronary circulation
- FFR solved the mismatch between coronary anatomy and physiology
- FFR has been validated in almost all clinical and angiographic conditions
- FFR has facilitated decision making for revascularisation and has ***improved outcome*** in many conditions

BUT: **To measure FFR, a pharmacological hyperemic stimulus is mandatory**

Is hyperemia mandatory?



A few words about hyperemia

- Intravenous infusion of ***adenosine*** or ATP
- Intracoronary injection of adenosine
- Single intravenous bolus of regadenoson (rapiscan®), approved January 2019
- Papaverine I.C

Side effects of adenosine are harmless and quickly transient and often overemphasized

(My own practice: two (2) serious side-effects in 15,000 procedures)

→ **IS HYPEREMIA A BIG DEAL?**

For Some it is, For Others Not

→ ***Anyway, it takes a few extra minutes and some extra costs***

key papers:
De Bruyne, Circulation 2003;107:1877-1883 , McGeoch, CCI 2008;71:198-204
FAME studies, VERIFY study, Fearon & Johnson, LBT PCR 2015

Instantaneous Wave-free Ratio (iFR)

- To overcome the necessity of administering an hyperemic stimulus, ***Davies et al*** proposed to use the ***resting Pd/Pa ratio*** during a particular part of the diastole. This was called ***iFR*** *(JACC 2011).*
- IFR was embraced enthusiastically because it made the ***procedure more simple***
- Two large (almost identical) RCT's (***DEFINE-FLAIR and SWEDE-HEART)*** were performed to show non-inferiority of iFR versus FFR
- One year results showed such non-inferiority of iFR compared to FFR

However……

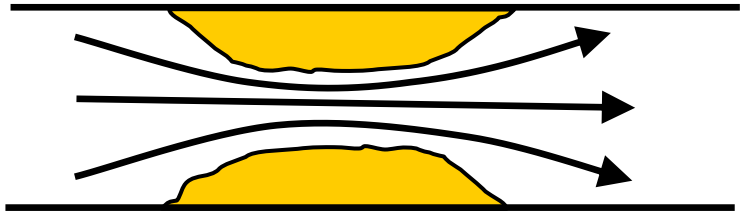
Problems Around iFR

- Concern about physiologic basis: a "*Wave-Free Period" did not exist* and a physiologic basis of iFR was missing
- Predicting hyperemic gradients from resting gradients is unreliable (*Poiseuille's law*)
- Serious problems with design and interpretation of ***DEFINE-FLAIR and SWEDE-HEART*** studies and ***high mortality with iFR guidance at 2 and 5 years***

Evt tekening toevoegen, van CVOI op USB stick

$\Delta P = f.Q + s.Q^2$

f = friction coefficient



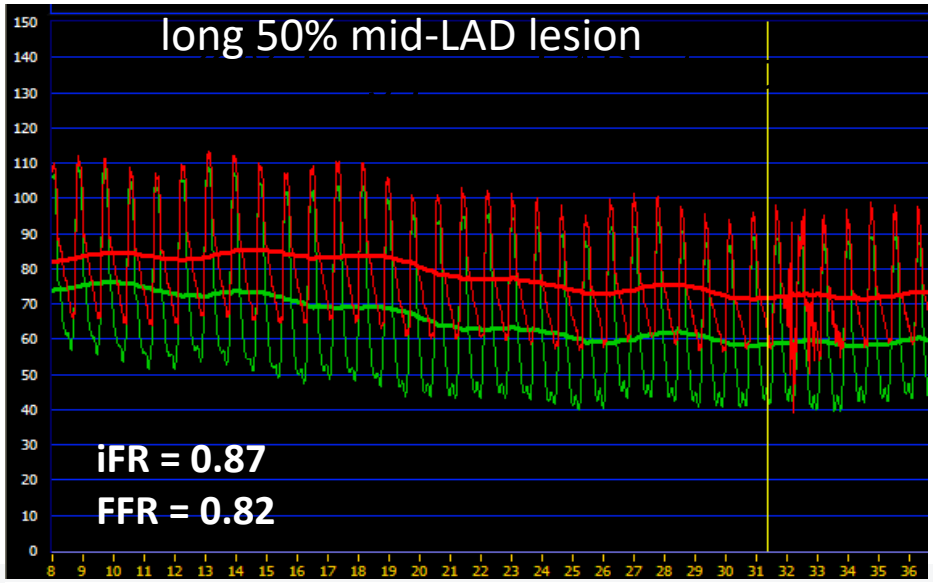
Moderate gradient at rest

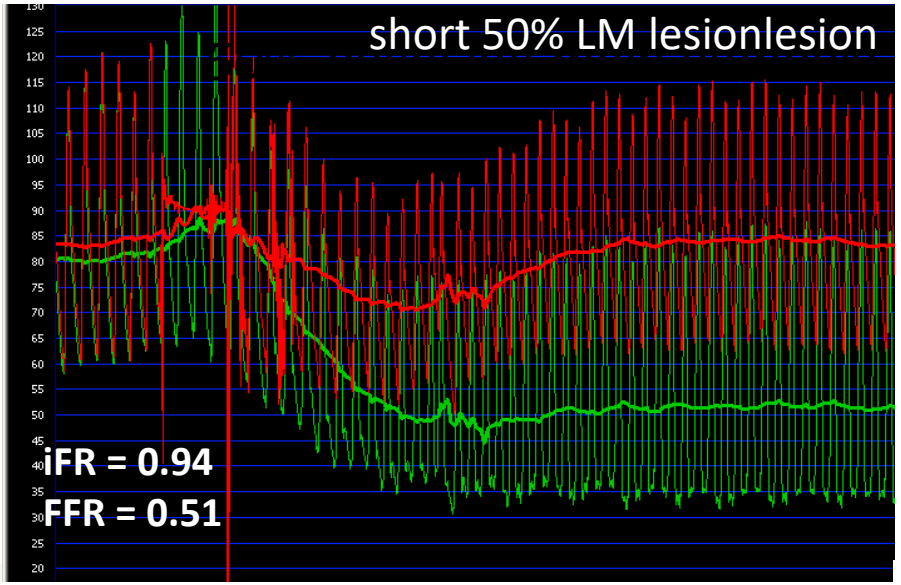
Moderate increment at hyperemia

S = separation coefficient

Small gradient at rest

Large gradient at hyperemia





→ **resting gradient cannot predict hyperemic gradient**

A closer look to DEFINE-FLAIR study and SWEDE-HEART:

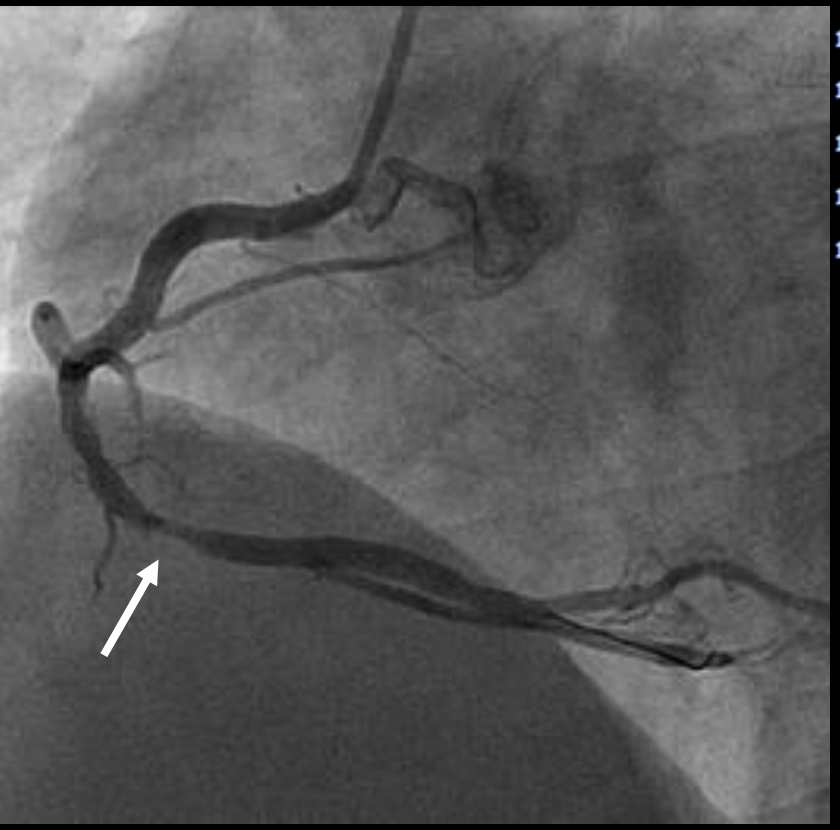
- ***low-risk populations:***
- single vessel disease in 58% of patients
- no PCI performed at all in 45% of patients
- average number of stents 0.7

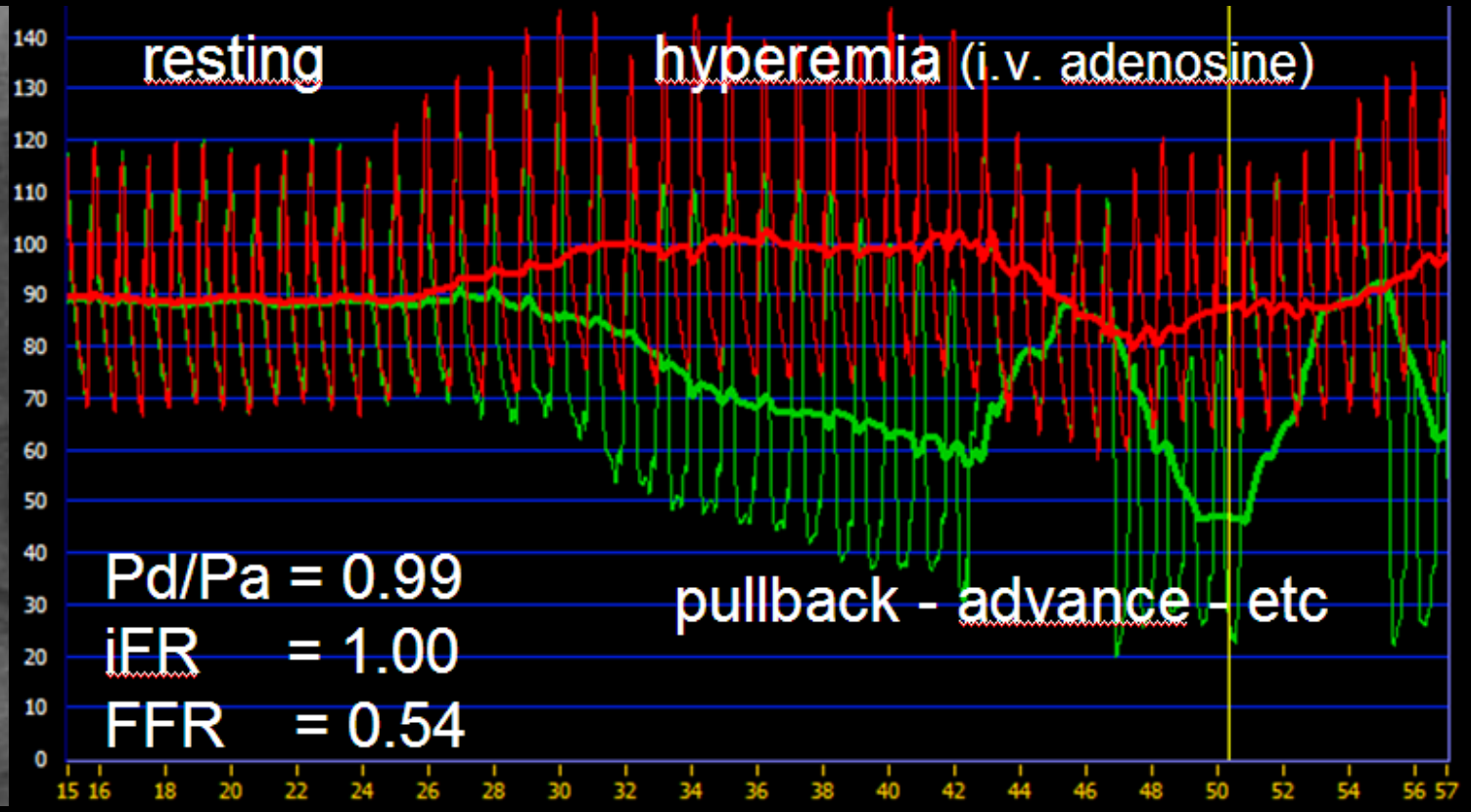
- ***Studies claimed to be "physiology-guided" but <u>first</u> an angiographic assessment was made and <u>only</u> if visual lesion severity was < 70%, iFR or FFR was measured***

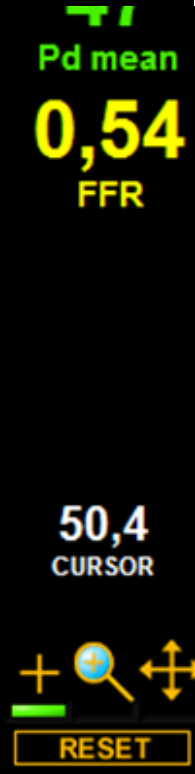
→ Almost 50% of all stents were placed without any physiologic measurement, just by eye-balling

→ Many ***false-negative iFR were excluded*** from analysis ***by design*** of the study and were actually analyzed as ***true-positives !!***

Young male, large RCA, 70% stenosis







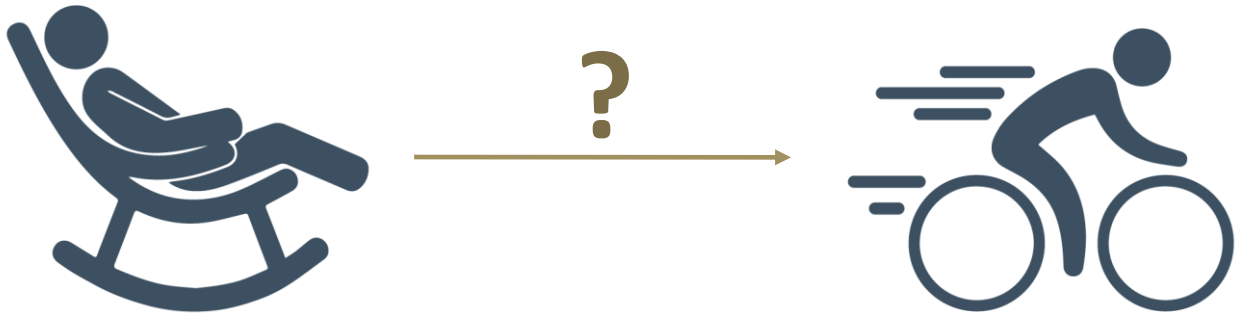
In this kind of patients in Define Flair and SwedeHeart randomization iFR vs FFR was not executed, thereby ***excluding false negative iFR***

A closer look to DEFINE-FLAIR study and SWEDE-HEART:

- This *bias was not recognized*, neither by the investigators, nor by the NEJM, nor by several guideline committees, nor by industries heavily promoting iFR and alternative equivalent NHPR's…..

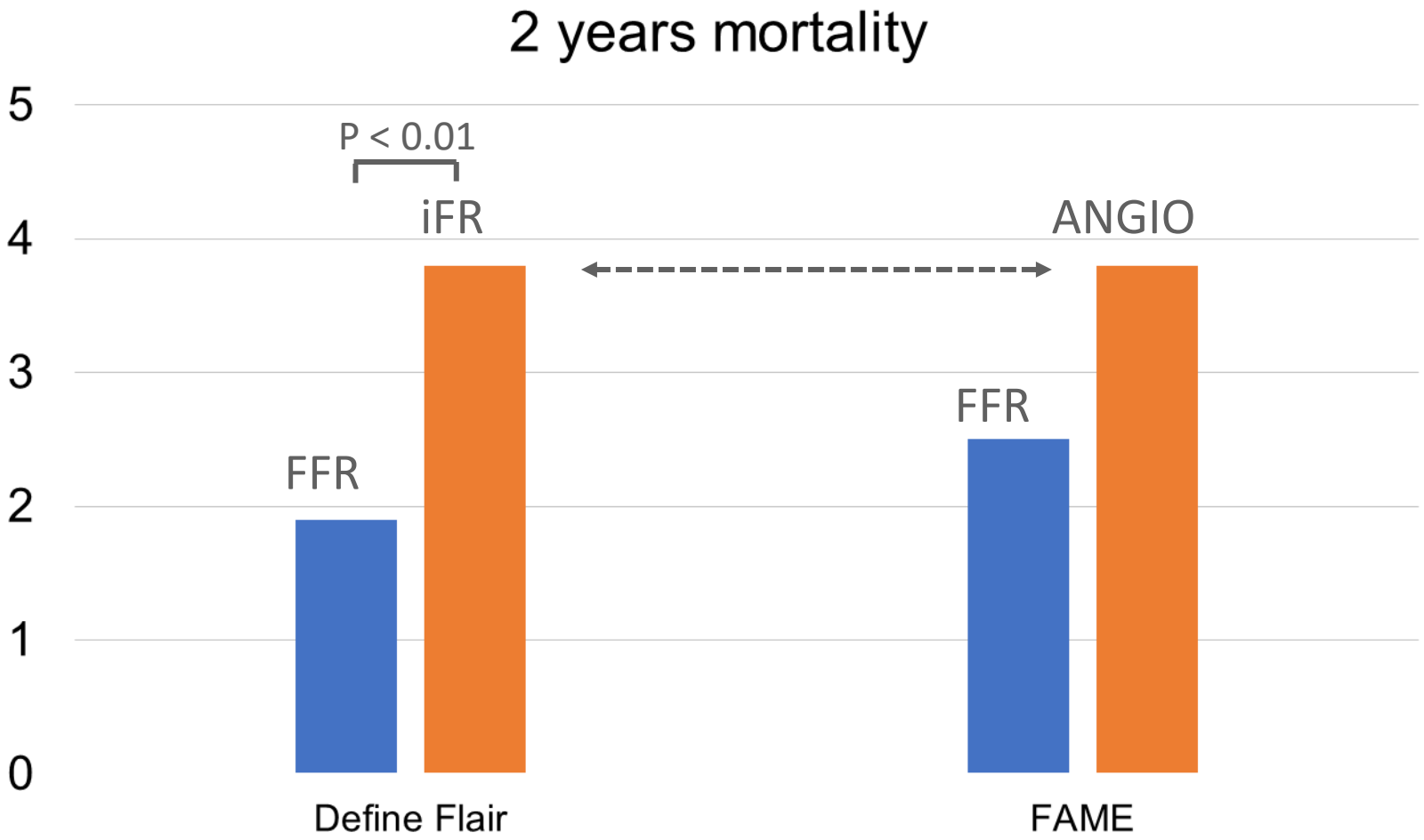
- ……and despite the low-risk study population and the bias in design of the study, the *non-inferiority was extended to all patients with coronary artery disease without additional RCT's*

Poor Outcome With iFR, despite Biased Study Design !



- After 2 years, mortality was significantly increased when using iFR instead of FFR and this difference further increased at 5 years, not only for mortality but also for MACE
- Mortality in the iFR –guided group in (low-risk) DEFINE-FLAIR study was as high as mortality in the Angio-guided group in the (high-risk) FAME study
- ***Recommendation of J American College of Cardiology and Europ Heart J to use FFR as gold standard and in particular not to use iFR in large coronary arteries, proximal stenosis, large perfusion territories.***
- This will be reflected in upcoming guidelines
- *Everything which has been said about iFR, also refers to **ALL** other so-called NHPR's*

2-year-mortality with iFR- guidance in low-risk
DEFINE-FLAIR population was twice as high as mortality with FFR
and was as high as in ***angio***-guided group in (high-risk) FAME population



adapted from Davies J, TCT 2019; Van Nunen, Lancet 2015;386;1853-1860; Eftekhari et al, EHJ 2024

AMERICAN COLLEGE of CARDIOLOGY

Instantaneous Wave Free Ratio vs. Fractional Flow Reserve

Nov 06, 2023

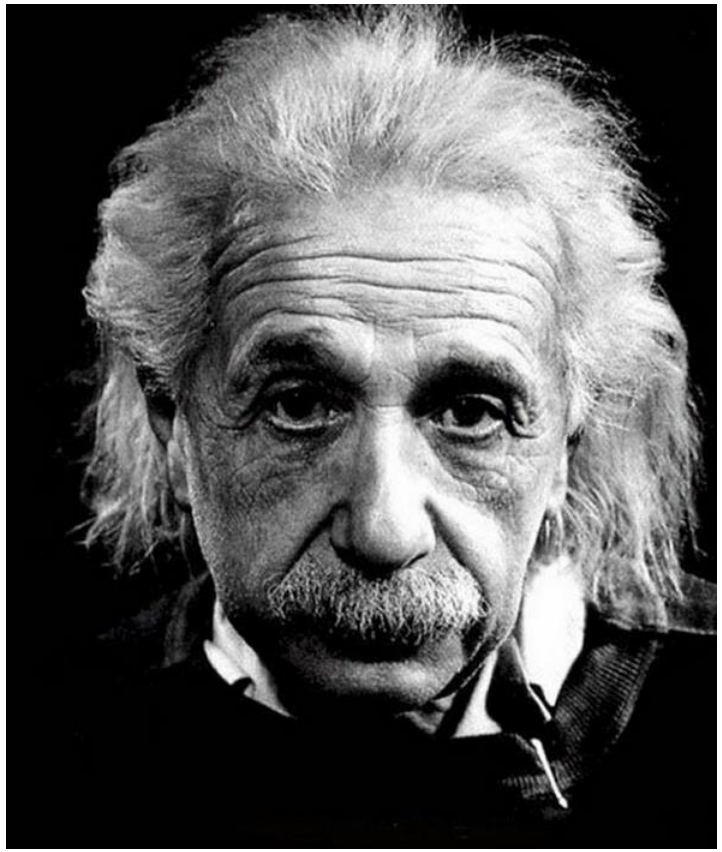
Quick Takes

- iFR-guided revascularization is associated with an increase in the composite of MACE (all-cause mortality, MI, or unplanned revascularization) and all-cause mortality alone compared to FFR-guided revascularization.
- Based on the current data, FFR-guided strategy should be the preferred option in proximal lesions in large coronary arteries with a large perfusion territory.
- Pending additional data, it is prudent to use nonhyperemic pressure indices judiciously and consider FFR-guided revascularization the gold standard strategy for intracoronary pressure measurement.

Recommendations in both EHJ and JACC 2023:

"Be cautious with iFR"

"Use FFR as gold standard"



Albert Einstein:

"Make It As Simple As Possible……..But Not Simpler"

FFR is simple !

Leaving Out Hyperemia and use of iFR / NHPR is obviously TOO Simple !

Conclusions: FFR vs iFR: Where Do We Stand

- Despite initial great enthusiasm about iFR / NHPR and leaving out ischemia,serious pitfalls became clear, both with respect to physiological background as well to clinical studies

- Unacceptably *high mortality / event rate with iFR* despite low risk populations in Define Flair and SwedeHeart studies

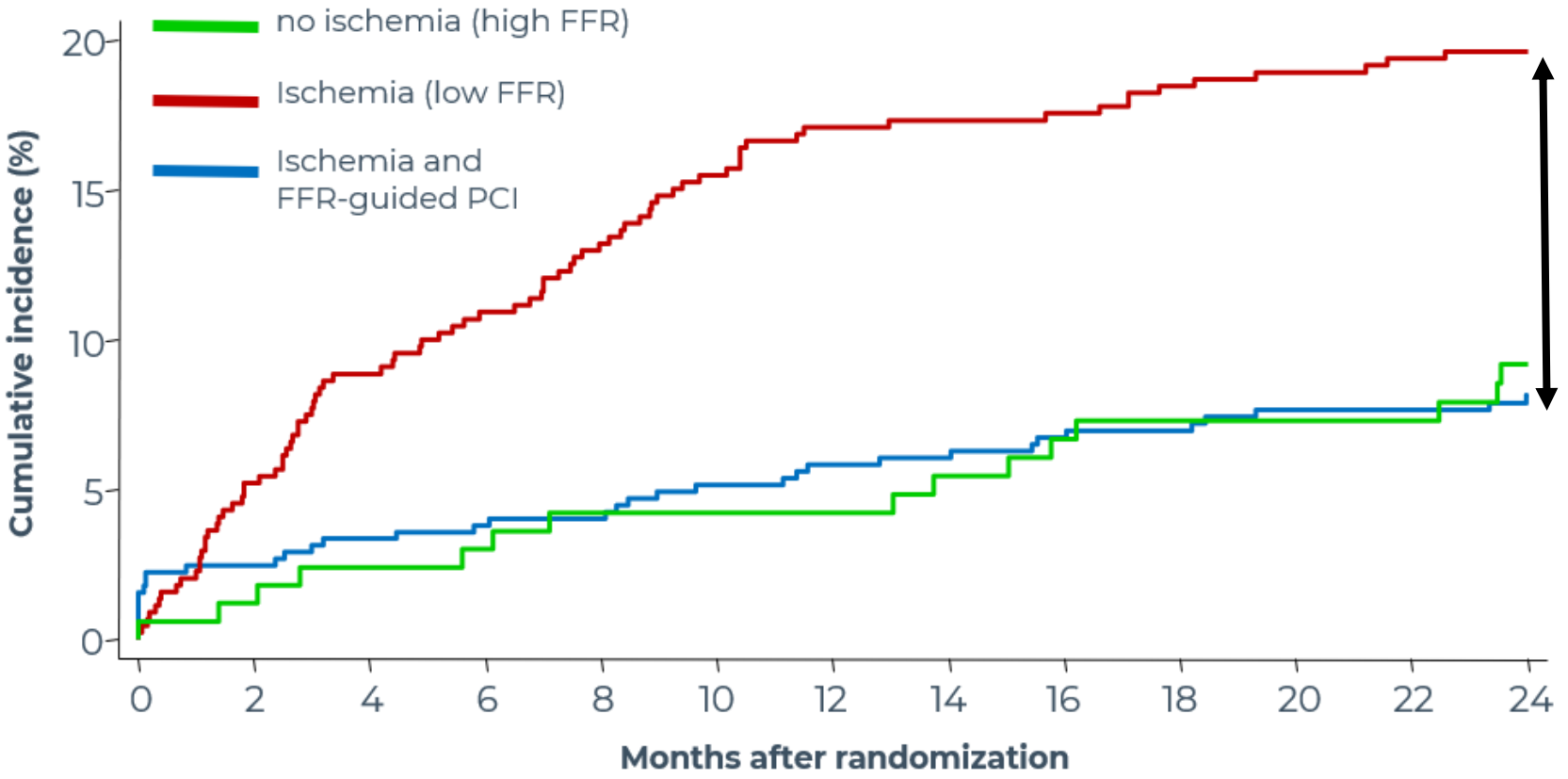
- Serious bias in Define Flair and SwedeHeart studies, too late (***or still not***) recognized by investigators, NEJM and other journals, by some guideline committees, and industries

- *Both JACC and EHJ recommendations 2023*: FFR guided strategy should be the preferred option in proximal lesions in large coronary arteries with a large perfusion territory. ***("if a truly relevant decision is at stake, use FFR")***

- **FFR-guided revascularization is the gold standard for intracoronary pressure measurement**

FAME 2: death, infarction, urgent revascularization

N = 1220



Benefit of FFR-guided PCI

No. at risk

MT	441	417	398	389	379	369	362	360	359	355	353	351	297
PCI+MT	447	434	429	426	425	420	416	414	410	408	405	403	344
Registry	166	164	162	160	157	157	156	153	151	150	150	150	122

De Bruyne et al, NEJM 2012, NEJM 2015; Xaplanteris et al, NEJM 2018